Synthesis and Structure–Activity Relationships of 7-[3-(1-Aminoalkyl)pyrrolidinyl]- and 7-[3-1-aminocycloalkyl)pyrrolidinyl]-quinolone Antibacterials[1)]

Youichi KIMURA,* Shohgo ATARASHI, Masanobu TAKAHASHI, and Isao HAYAKAWA

Exploratory Laboratories I, Daiichi Pharmaceutical Co., Ltd., 1–16–13 Kitakasai, Edogawa-ku, Tokyo 134, Japan.
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A series of 7-[3-(1-aminoalkyl and 1-aminocycloalkyl)-1-pyrrolidinyl]quinolones have been prepared and their biological properties evaluated. Among them, 1-(*S*)-aminoalkyl derivatives exhibited potent antibacterial activities against gram-positive and gram-negative organisms. They had moderate lipophilicity and high aqueous solubility compared to their aminomethyl counterparts; *e.g.*, the 3-(1-aminoethyl)-1-pyrrolidinyl compound (83) showed superior pharmacokinetic properties to its aminomethyl counterpart (6).

Keywords quinolonecarboxylic acid; structure–activity relationship; pharmacokinetic property; antibacterial activity; 3-(1-aminoethyl)pyrrolidine; physicochemical property

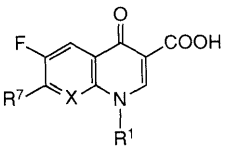
Quinolone antibacterial agents are clinically important therapeutic agents exemplified by norfloxacin (**1**),[2)] enoxacin (**2**),[3)] ofloxacin (**3**),[4)] and ciprofloxacin (**4**).[5)] These agents are characterized by a fluorine atom at C-6 and a basic alicyclic amine represented by piperazine at C-7 of a 1,4-dihydro-4-oxoquinoline nucleus.

The piperazinyl group at C-7 has recently been replaced by various pyrrolidines and the resulting compounds have greatly improved activity against gram-positive organisms compared to the C7-piperazinyl derivatives **1**—**4**. In particular, 3-aminomethylpyrrolidinyl derivatives and their *N*-ethyl analogues exhibit extremely potent activities against Gram-positive organisms. The 1-ethyl-7-[3-(ethylaminomethyl)-1-pyrrolidinyl]-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid, CI-934 (**5**),[6a)] is active *in vitro* and *in vivo* against gram-positive as well as gram-negative organisms, but shows relatively low activity against *Pseudomonas aeruginosa*. The corresponding *N*-desethyl analogue **6**[6a)] is reported to be more potent than CI-934 *in vitro* against various pathogens including *P. aeruginosa*, but the oral efficacy of **6** is less than that of CI-934. We suspected the reason to be the lower lipophilicity of **6** than CI-934, and so we designed compounds with increased lipophilicity with the aim of improving the oral efficacy of 3-aminomethylpyrrolidinyl derivatives while retaining their high level of activity.

It is known that secondary amino derivatives are transformed to toxic nitrosodialkylamines.[7)] To avoid this problem, we decided that the pyrrolidine ring side chain should contain a primary amino group. Primary amino derivatives, such as phenylethylamine, are reported to be deaminated by monoamine oxidase, but their analogues with α-substituents exhibit higher metabolic stability.[8)] Thus, we synthesized a series of 3-(1-alkylamino)- and 3-(1-aminocycloalkyl)pyrrolidinyl derivatives. After our work on this was completed, the synthesis of chiral 3-(1-aminoethyl)pyrrolidinyl derivatives by a different method was reported.[9)] Our paper deals with the synthesis and structure–activity relationships of a series of 7-[3-(1-aminoalkyl- and cycloalkyl)pyrrolidinyl]quinolones.

Chemistry

The compounds prepared for this study (Tables I and II) were synthesized by nucleophilic substitution of corresponding 6,7-difluoroquinolones **8**,[2)] **9**,[10)] **10**,[11)] and **11**[6c)] or 7-chloro-6-fluoro-1,8-naphthyridines **12**[12)] and **13**[13)] with appropriate pyrrolidine derivatives (method A). 8-Alkyloxy analogues **91** and **96**, and the 8-methyl analogue **92** were prepared by nucleophilic substitution of the borate complexes **14**,[14)] **15**,[15)] and **16**,[16)] respectively (method B). CI-934 (**5**), compound **6**, and PD-117558 (**7**) were prepared by the reported methods.[6a,b)]



compound	X	R^1	R^7	
1	CH	Et	–N NH	nolfloxacin
2	N	Et	–N NH	enoxacin
3			–N NMe	ofloxacin
4	CH	△	–N NH	ciprofloxacin
5	CF	Et	–N NHEt	CI-934
6	CF	Et	–N NH_2	
7	CF	△	–N NHEt	PD-117558

Chart 1

The synthetic routes to alkyl- and cycloalkyl-substituted 3-pyrrolidine methanamine derivatives are illustrated in Charts 3—6.

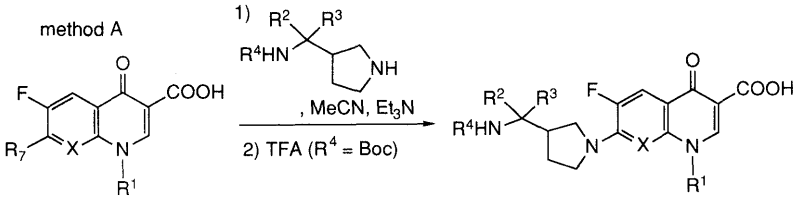
Diastereoisomers of 3-(1-*tert*-butoxycarbonylaminoethyl)pyrrolidine (**28a, b**) and 3-(1-*tert*-butoxycarbonylaminopropyl)pyrrolidine (**29a, b**) were prepared from the racemic carboxylic acid **17**.[17] Compound **17** was converted to the ketones **18** and **19**. The ketone **18** was reacted with hydroxylamine to give the oxime **20**. Hydrogenation of **20** and successive reaction with 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (Boc-ON) gave a diastereomeric mixture of carbamates **24a** and **24b**. They were separated by fractional recrystallization. The configurations of **24a** and **24b** were determined by X-ray analysis of **44a**. Compound **25a** and **25b** were prepared by the above procedure from **19**, and separated by HPLC. Hydrolysis of **24a** and **24b** with trifluoroacetic acid (TFA), followed by reduction with lithium aluminum hydride and successive reaction with Boc-ON gave **26a** and **26b**, respectively. Debenzylation of each isomer gave the desired pyrrolidines **28a** and **28b**. By using this procedure, compounds **29a** and **29b** were synthesized from **25a** and **25b**, respectively. Reduction of **24a** and **24b** with lithium aluminum hydride and subsequent debenzylation gave the N-methylamines **30a** and **30b**, respectively.

The 3-(1-amino-1-methylethyl)pyrrolidine (**37**) was prepared from 2-benzoylamino-2-methylpropanol (**31**) (Chart 4). Oxidation of **31** with pyridinum chlorochromate (PCC) gave the aldehyde **32**. Wittig–Horner reaction of **32** gave the α,β-unsaturated ester **33**. Reaction of **33** with nitromethane and 1,1,3,3,-tetramethylguanidine (TMG) gave the Michael adduct **34**. Hydrogenolysis of **34** with Raney nickel gave the pyrrolidone **35**. Reduction of **35** with lithium aluminum hydride and subsequent debenzylation gave **37**.

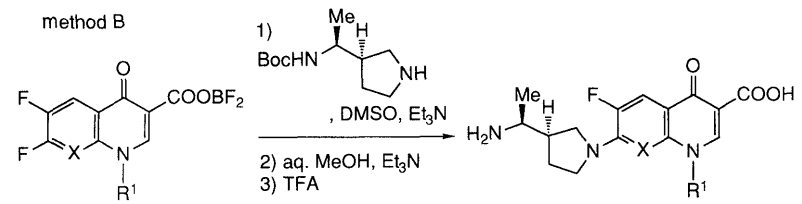
3-(1-Aminocyclopropyl)pyrrolidine (**43a**) and 3-(1-aminocyclobutyl)pyrrolidine (**43b**) were prepared from the amino acid derivatives **38a** and **38b**, respectively. Reduction of **38** with diisobutyl aluminum hydride gave the aldehyde **39**. Conversion of **39** to the pyrrolidone **42** was carried out by the procedure utilized for the preparation of **35** from **32**. Treatment of **42** with TFA, followed by reduction with lithium aluminum hydride gave **43**.

Optical resolution of **28a** and **28b** was carried out as described below (Chart 5). Compound **22a** was converted to diastereomeric amides **44a** and **44b** by reaction with *N*-tosyl-(*S*)-prolyl chloride.[18] They were separated by silica gel column chromatography. They were hydrolyzed and converted to the chiral 3-(1-*tert*-butoxycarbonylaminoethyl)pyrrolidines **47a** and **47b**, respectively, by the same procedure utilized for the preparation of the racemate **28a**. Enantiomers of **28b** (**47c** and **47d**) were prepared similarly. The absolute configuration of the *threo*-isomer **47a** was determined to be (3*R*, 1′*S*) by X-ray analysis of the intermediate **44a**.

(3*R*,1′*S*)-3-(1-*tert*-Butoxycarbonylaminoethyl)pyrrolidine (**47a**) was synthesized diastereoselectively from *N*-Boc-L-alanine (**48**) (Chart 6). Compound **48** was reacted with *N,N*′-carbonyldiimidazole (CDI) and then treated with ethyl magnesium-malonate[19] to give the β-ketoester **49**. Reduction of **49** with sodium borohydride, followed by reaction with methanesulfonyl chloride gave the methanesulfonate **51** as a mixture of diastereomers. The mixture was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give the α,β-unsaturated ester **52**. Michael addition of nitromethane to **52** proceeded diastereoselectively to give the *threo* isomer **53a** as the major product. When the reaction was carried out at 25 °C, the ratio of *threo*-**53a** and *erythro*-**53b** was 3 : 1. Diastereoselectivity was improved to 10 : 1 by carrying out the reaction at 5 °C. The ratios were determined by HPLC after conversion to



8: R^1 = Et, R^7 = F, X = CF
9: R^1 = c-C_3H_5, R^7 = F, X = CF
10: R^1 = c-C_3H_5, R^7 = F, X = CCl
11: R^1 = c-C_3H_5, R^7 = F, X = CH
12: R^1 = c-C_3H_5, R^7 = Cl, X = N
13: R^1 = 2,4-difluorophenyl, R^7 = Cl, X = N



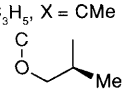
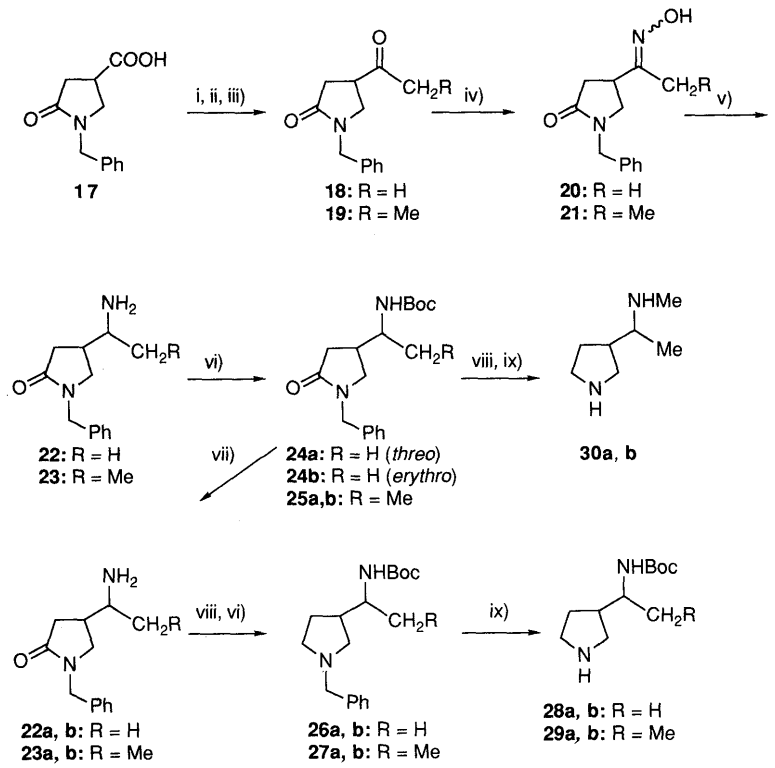
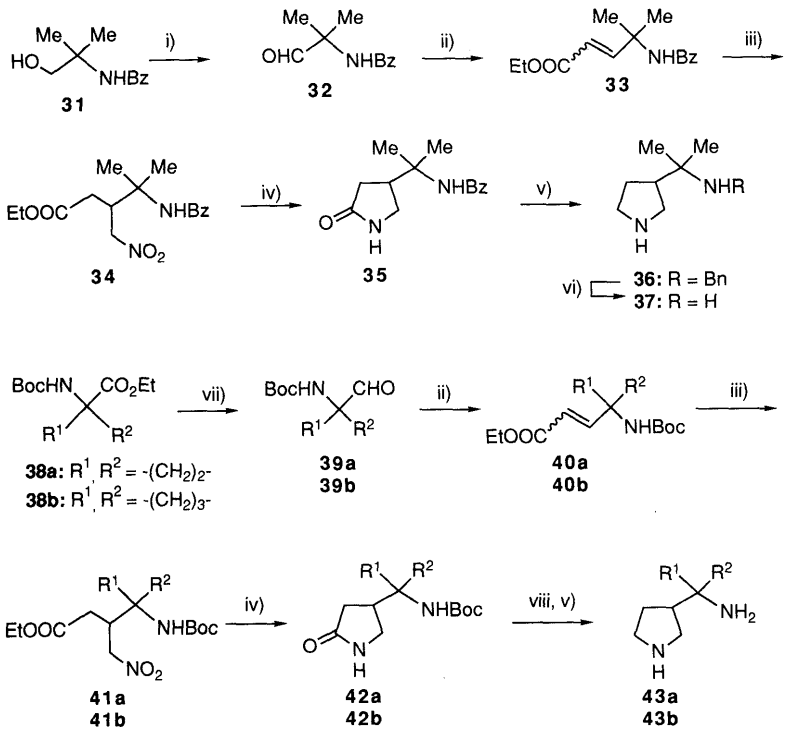
14: R^1 = c-C_3H_5, X = COMe
15: R^1 = c-C_3H_5, X = CMe
16: X, R^1 = 

Chart 2



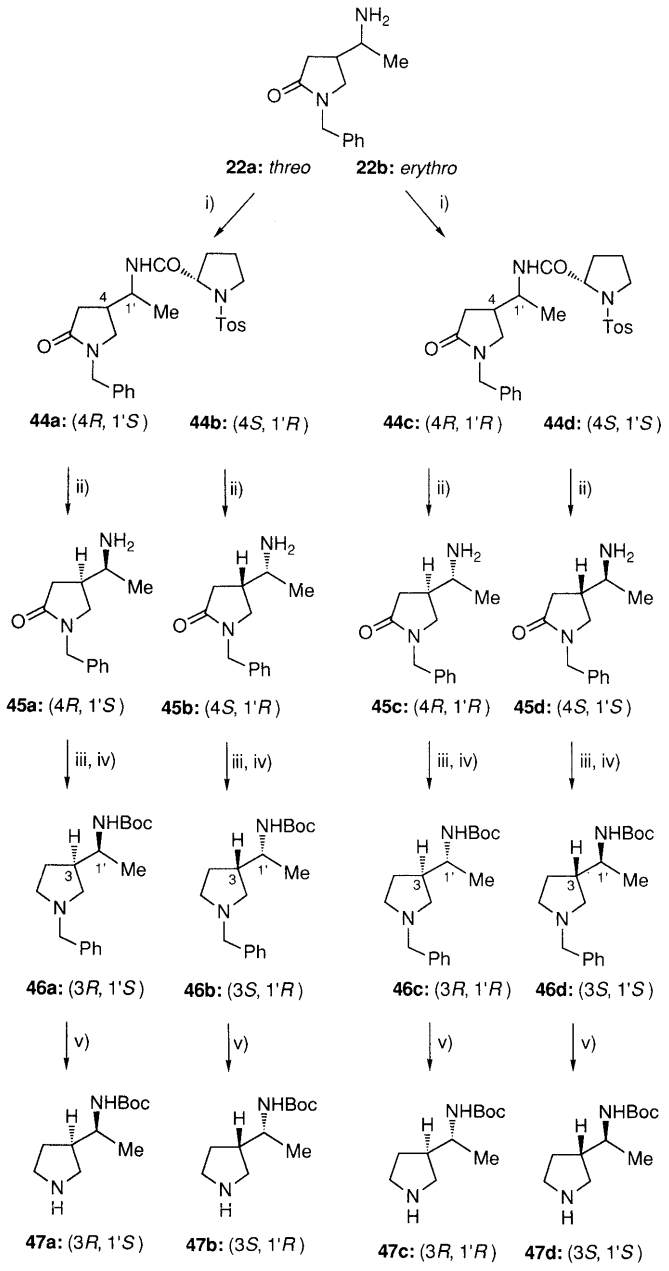
i) $SOCl_2$; ii) $Mg(OEt)_2$, $RCH(CO_2Et)_2$ (R=H or Me); iii) H^+; iv) $NH_2OH \cdot HCl$, Py; v) H_2, Ra-Ni; vi) Boc-ON; vii) TFA; viii) $LiAlH_4$; ix) H_2, Pd-C

Chart 3



i) PCC; ii) $Ph_3P{=}CHCOOEt$; iii) $MeNO_2$, TMG; iv) H_2, Ra-Ni; v) $LiAlH_4$
vi) H_2, Pd-C; vii) DIBAL; viii) TFA

Chart 4



i) N-Ts-(s)-PrCl; ii) NaOH; iii) $LiAlH_4$; iv) Boc-ON; v) H_2, Pd-C

Chart 5

55a and **55b**. Hydrogenolysis of the mixture of **53a** and **53b**, followed by benzylation gave a mixture of **55a** and **55b**. The major isomer **55a** was isolated by fractional recrystallization. The minor isomer **55b** was isolated by HPLC. Compound **55a** was identical with the compound derived from **45a** by *tert*-butoxycarbonylation. The minor isomer **55b** was hydrolyzed with TFA to give (4*S*,1'*S*)-4-(1-aminoethyl)-1-benzyl-2-oxopyrrolidine (**45d**), which was identical with the compound prepared by optical resolution of **22b** (Chart 5). Thus, the configuration of **47d** was determined to be (3*S*,1'*S*). The configurations of **47b** and **47c** were determined to be (3*S*,1'*R*) and (3*R*,1'*R*), respectively.

Enantiomers of 3-(1-*tert*-butoxycarbonylaminopropyl)-pyrrolidine (**29b**) were prepared similarly from chiral

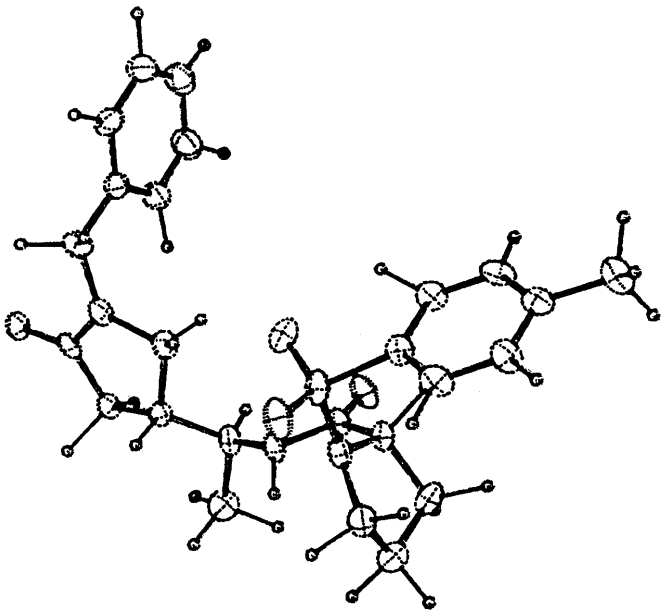


Fig. 1. Crystal Structure of **44a**

N-Boc-2-aminobutyric acids (**56a** and **56b**). Compounds **63a** and **63b** were obtained from **56a** and **56b**, each as a sole product. The ^{1}H-NMR spectra of **63a** and **63b** were identical with that of **23b**. This result suggested that the Michael reaction proceeded highly diastereoselectively. Compounds **63a** and **63b** were converted to enantiomers of **29b** (**65a** and **65b**, respectively).

Results and Discussion

In order to evaluate the effect of a substituent introduced at the methylene spacer between the pyrrolidine ring and amino group, the antibacterial activities of racemic 6,8-difluoroquinolones **66**—**82** were determined (Table III). The data for CI-934 (**5**),[6a] compound **6**,[6a] and PD-117558 (**7**)[6b] are included for comparison. Variation of the substituent at the methylene spacer influenced the activity, and the effect was remarkable with N_1-ethylquinolones. Introduction of a methyl or an ethyl group provides diastereoisomers (giving compounds **66**—**71**), and the effects of the alkyl groups on the activity varied between diastereoisomers. The *threo*-isomer of 3-(1-aminoethyl)pyrrolidine **67** retained the activity of **6** against gram-negative bacteria and displayed a 2- to 4-fold increase in activity against gram-positive bacteria. The *erythro*-isomer **66** was more than 2-fold less potent than **67**. Similarly, the 1-aminopropyl analogue **69** was 2—8 times more active than its diastereoisomer **68**. Compound **69** was 2—4 fold more potent than **6** against gram-positive bacteria, but 2-fold less active against *P. aeruginosa*. *N*-Methylation of **66** and **67** (giving **70** and **71**) resulted in a significant overall decrease of activities. The dimethyl analogue **72** and the cyclopropyl analogue **73** were as potent as **6** against gram-positive organisms, but 4-fold less potent against *P. aeruginosa*.

Similar results were obtained with the N_1-cyclopropyl derivatives **74**—**82**. The 1-aminoethyl analogue **75** displayed 2—8 times more potent activity compared with the 1-ethylaminomethyl analogue PD-117558 (**7**). The

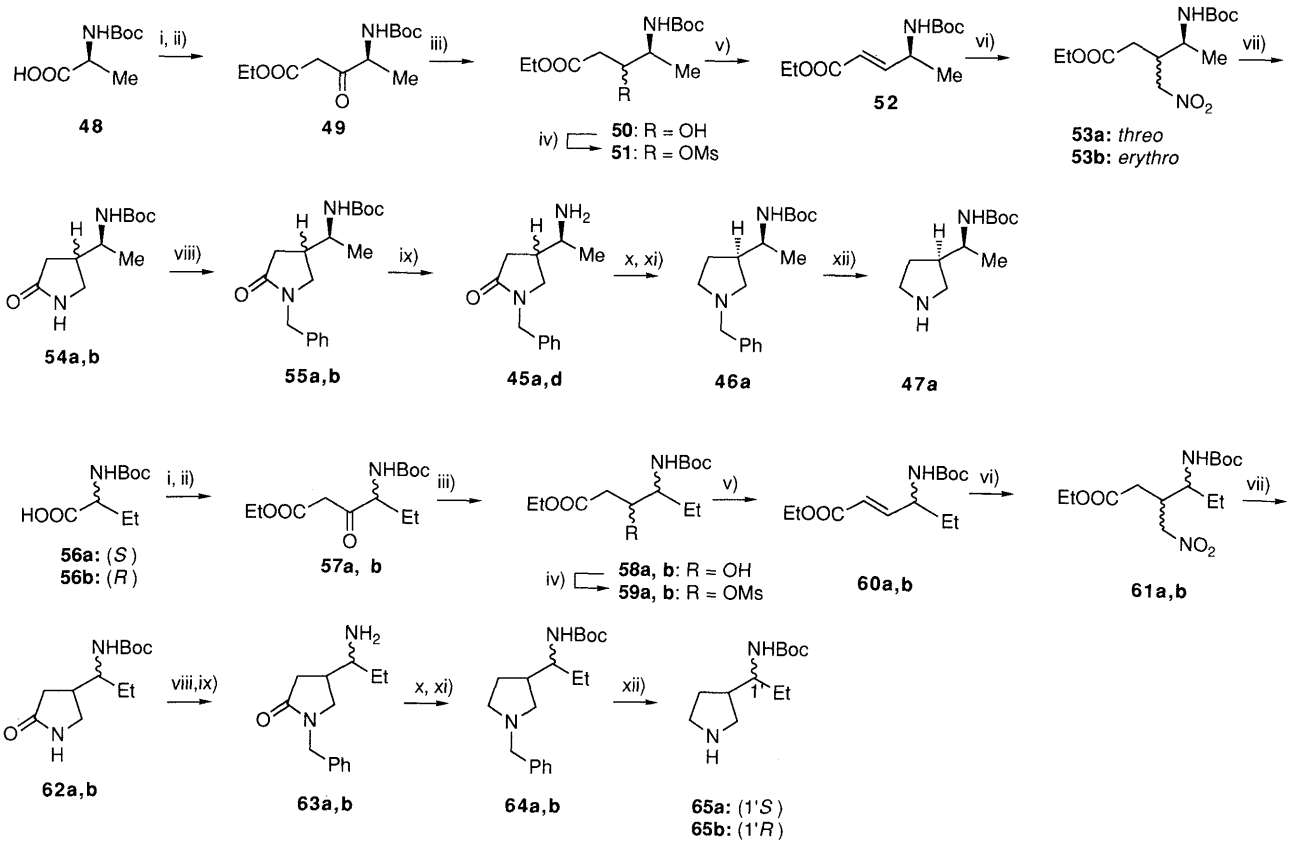


Chart 6

N-methyl analogue **79** was 2-fold less potent than **75**, but the loss of activity was not as significant as that of the N_1-ethyl analogue **71**. Introduction of sterically bulky groups tends to decrease activity against gram-negative bacteria (see results with *Serratia marcescens* and *Proteus vulgaris* for **80**—**82**).

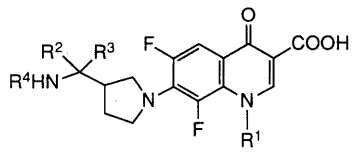
These results indicated that introduction of a methyl or ethyl group at the methylene spacer enhances activity against gram-positive bacteria, but sterically bulky substituents such as dimethyl, cyclopropyl, and cyclobutyl groups are unfavorable for anti-pseudomonal activities.

In order to estimate the effects of chirality, the antibacterial activities of chiral 3-(1-aminoalkyl)-1-pyrrolidinyl derivatives were compared (Table IV). The antibacterial activity of the optical isomers of 1-aminoethyl derivatives **83**—**86** varies remarkably, while there is little difference in activity *in vitro* between the enantiomers of the ethylaminomethyl analogue CI-934.[6c] The *in vitro* activities of chiral isomers show the following trend: **86** (3*S*,1′*S*) < **84** (3*S*,1′*R*) < **85** (3*R*,1′*R*) < **83** (3*R*,1′*S*). Compound **83** was 4- to 32-fold more potent than its antipode **84**, and was 2- to 4-fold more potent than the (*dl*)-aminomethyl analogue **6**. Of the two enantiomers of the 1-aminopropyl analogue **69**, (1′*S*)-**87** showed 4- to 64-fold more potent activity than its antipode **88**. Compound **87** was 2 times more potent than **83** against gram-positive and gram-negative organisms, but 2-fold less active than **83** against *P. aeruginosa*. These results clearly indicated that the stereochemistry of 3-(1-aminoalkyl)pyrrolidinyl derivatives has an important influence on the antibacterial activity.

The substituents at the N-1 and C-8 positions of the quinolone nucleus also affected the activity. N_1-Cyclopropyl-C_8-fluoro derivatives **89** and **97** are 2 to 4 times more potent than their N_1-ethyl analogues **83** and **87**, respectively. Variation of the C-8 substituent of **89** (giving compounds **90**—**92**) changed the activity in a narrow range, and the C_8-Cl analogue **90** was the most potent. The C_8-H analogue **93** was less active than **89**. Significant loss of gram-positive activities was observed with the naphthyridine derivatives **94** and **95**. The benzoxazine derivative **96** was 4-fold less active than the N_1-cyclopropyl derivative **89** and 2-fold less active than the N_1-ethyl analogue **83**. These data indicated that (1′*S*)-3-(1-aminoethyl and 1-aminopropyl)pyrrolidines are the preferred C-7 substituents for new quinolone antibacterials.

Aqueous solubilities and apparent partition coefficients of selected compounds are shown in Table V. The compounds tested (**66**—**97**) were more lipophilic than **6**, except **96**. The *P′* values of the compounds were related to the substituents at the C-7 and N-1 positions. The *P′* values of **67** and **83** were 3 times that of **6**, and the *P′*s of the N_1-cyclopropyl analogues **75** and **77** were 1.5 times those of **67** and **83**. The 3-(1-aminopropyl)pyrrolidinyl compounds **69** and **87** were more lipophilic than **67** and

TABLE I. Physical Properties of the 7-Substituted 6,8-Difluoroquinolones



Compound	R^1	R^2	R^3	Configuration	R^4	mp (°C)	Yield[a] (%)	Formula	Analysis (%) Calcd (Found)		
									C	H	N
66	Et	Me	H	*erythro*	H	212—215	44	$C_{18}H_{21}F_2N_3O_3 \cdot 1/4H_2O$	58.45 (58.40)	5.86 5.71	11.36 11.41)
67	Et	Me	H	*threo*	H	212—217	48	$C_{18}H_{21}F_2N_3O_3 \cdot 3/4H_2O$	57.06 (57.38)	5.99 6.06	11.09 11.05)
68	Et	Et	H	N.D.[b]	H	197—199	47	$C_{19}H_{23}F_2N_3O_3 \cdot 1/4H_2O$	59.44 (59.37)	6.17 5.89	10.95 10.68)
69	Et	Et	H	N.D.[c]	H	211—215	45	$C_{19}H_{23}F_2N_3O_3 \cdot 1/2H_2O$	58.75 (58.37)	6.23 5.89	10.82 10.68)
70	Et	Me	H	*erythro*	Me	208—211	47	$C_{19}H_{23}F_2N_3O_3 \cdot 1/2H_2O$	58.75 (58.46)	6.23 5.99	10.82 10.72)
71	Et	Me	H	*threo*	Me	276 (dec.)	45	$C_{19}H_{23}F_2N_3O_3 \cdot 1/2H_2O$	58.75 (58.54)	6.23 6.02	10.82 10.68)
72	Et	Me	Me		H	235—240	74	$C_{19}H_{23}F_2N_3O_3 \cdot H_2O$	57.42 (57.38)	6.34 6.07	10.57 10.47)
73	Et	$-(CH_2)_2-$			H	186—197	23	$C_{19}H_{21}F_2N_3O_3 \cdot H_2O$	57.71 (57.90)	5.86 5.81	10.63 10.49)
74	CP	Me	H	*erythro*	H	193—200	46	$C_{19}H_{21}F_2N_3O_3 \cdot 5/4H_2O$	57.06 (57.35)	5.92 5.81	10.51 10.42)
75	CP	Me	H	*threo*	H	201—204	42	$C_{19}H_{21}F_2N_3O_3 \cdot 1/4H_2O$	59.76 (59.65)	5.67 5.54	11.00 10.86)
76	CP	Et	H	N.D.[b]	H	166—168	45	$C_{20}H_{23}F_2N_3O_3 \cdot 3/2H_2O$	57.41 (57.56)	6.26 6.06	10.04 10.10)
77	CP	Et	H	N.D.[c]	H	205—208	46	$C_{20}H_{23}F_2N_3O_3 \cdot 1/4H_2O$	60.67 (60.34)	5.98 5.75	10.61 10.58)
78	CP	Me	H	*erythro*	Me	193—197	48	$C_{20}H_{21}F_2N_3O_3 \cdot 1/4H_2O$	60.67 (60.83)	5.98 5.78	10.61 10.61)
79	CP	Me	H	*threo*	Me	220—230	32	$C_{20}H_{21}F_2N_3O_3 \cdot 1/2H_2O$	59.99 (59.74)	6.04 5.79	10.49 10.45)
80	CP	Me	Me		H	227—230 (dec.)	36	$C_{20}H_{21}F_2N_3O_3 \cdot 1/2H_2O$	59.99 (60.02)	6.04 5.98	10.49 10.47)
81	CP	$-(CH_2)_2-$			H	227—230	27	$C_{20}H_{21}F_2N_3O_3 \cdot 3/2H_2O$	57.68 (57.31)	5.81 5.66	10.09 10.39)
82	CP	$-(CH_2)_3-$			H	245—250	45	$C_{21}H_{23}F_2N_3O_3 \cdot 5/4H_2O$	59.21 (59.28)	5.74 6.02	9.87 9.78)

a) Yields are those obtained from the coupling step to the final product, including deprotection when appropriate. *b*) Derived from **29a**. *c*) Derived from **29b**.

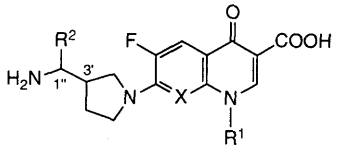
83, and their N_1-cyclopropyl analogues **77** and **97** had the highest lipophilicity of all the compounds tested. Lipophilicity of the compounds seems to be determined by the C_7-substituent and the quinolone nucleus.

Aqueous solubilities of the racemates **67** and **75** were as low as those of the parent compounds **6** and **7**, respectively. But the chiral compounds **83** and **89** exhibited higher aqueous solubility than their racemates **67** and **75**, respectively. In contrast, the racemates **69** and **77** were highly soluble in water compared to the chiral compounds **87** and **97**. Aqueous solubilities of naphthyridine **94** and benzoxazine **96** compounds were inferior to those of the corresponding 8-fluoroquinolones **83** and **89**.

The pharmacokinetic profiles of the selected compounds after oral administration (20 mg/kg) to rats are shown in Table VI. 8-Fluoro derivatives **80**, **83**, and **89** exhibited good oral absorbability. The peak plasma concentration (C_{max}) of **83** was about 3 times higher than that of **6**, and the area under the plasma level curve of **83** was superior to that of **6** (Fig. 2). The C_{max} values of the naphthyridine **94** and benzoxazine **96** were lower than that of **6**. These results suggested that adequate lipophilicity and good aqueous solubility are required for good oral absorbability.

In summary, 3-(1-aminoalkyl)pyrrolidinyl derivatives display enhanced activity against gram-positive organisms compared with 3-aminomethylpyrrolidinyl and 3-ethylaminomethylpyrrolidinyl analogues. The chirality of 3-(1-aminoethyl)pyrrolidinyl derivatives is quite important and the (3*S*,1′*R*)-isomer is the most active of all stereoisomers. Lipophilicity and aqueous solubility of the molecule, which depend on the combination of the C-7 substituent and the quinolone nucleus, largely determine the oral absorbability. Thus, introduction of substituents adjacent to the amine enhanced both the antibacterial activity and the oral absorbability.

TABLE II. Physical Properties of the Chiral 7-Substituted Quinolones



Compound	$R^{1a)}$	X	R^2	Chirality (3′,1″)	mp (°C)	Rotation[b] (solvent)	Yield[c] (%)	Formula	Analysis (%) Calcd (Found) C	H	N
83	Et	CF	Me	(*R*,*S*)	218	−221.0 (0.1 N HCl)	55	$C_{18}H_{21}F_2N_3O_3 \cdot 1/4H_2O$	58.45 (58.13)	5.86 5.90	11.36 11.44)
84	Et	CF	Me	(*S*,*R*)	219—222	+219.2 (0.1 N HCl)	61	$C_{18}H_{21}F_2N_3O_3 \cdot 1/4H_2O$	58.45 (58.61)	5.86 5.80	11.36 11.39)
85	Et	CF	Me	(*R*,*R*)	209—213	−185.2 (0.1 N NaOH)	64	$C_{18}H_{21}F_2N_3O_3 \cdot 1/4H_2O$	58.45 (58.75)	5.86 5.73	11.36 11.33)
86	Et	CF	Me	(*S*,*S*)	210—212	+182.3 (0.1 N NaOH)	62	$C_{18}H_{21}F_2N_3O_3 \cdot 1/4H_2O$	58.45 (58.81)	5.86 5.82	11.36 11.42)
87	Et	CF	Et	(1″*S*)	215—216	−164.2 (1 N NaOH)	64	$C_{19}H_{23}F_2N_3O_3 \cdot 1/2H_2O$	58.75 (58.70)	6.23 6.21	10.83 11.13)
88	Et	CF	Et	(1″*R*)	216—217	+153.6 (1 N NaOH)	59	$C_{19}H_{23}F_2N_3O_3 \cdot 1/4H_2O$	58.73 (59.13)	6.23 6.59	10.82 10.18)
89	CP	CF	Me	(*R*,*S*)	227—229	−250.0 (0.1 N HCl)	66	$C_{19}H_{21}F_2N_3O_3$	60.47 (60.37)	5.61 5.69	11.13 11.13)
90	CP	CCl	Me	(*R*,*S*)	198—220	−163.7 (0.1 N HCl)	59	$C_{19}H_{21}ClF_2N_3O_3 \cdot 1/2H_2O$	56.65 (56.58)	5.50 5.59	10.43 10.41)
91	CP	COMe	Me	(*R*,*S*)	188—190	−167.4 (0.1 N NaOH)	45	$C_{20}H_{24}FN_3O_3 \cdot 1/2H_2O$	60.29 (60.03)	6.32 6.45	10.55 10.39)
92	CP	CMe	Me	(*R*,*S*)	185—186	−163.0 (0.1 N NaOH)	75	$C_{20}H_{24}FN_3O_3 \cdot H_2O$	61.36 (61.58)	6.69 6.82	10.73 10.45)
93	CP	CH	Me	(*R*,*S*)	236—241	−47.6 (0.1 N NaOH)	69	$C_{19}H_{22}FN_3O_3$	63.50 (63.21)	6.17 6.35	11.69 11.55)
94	CP	N	Me	(*R*,*S*)	260—262	−8.54 (1 N NaOH)	64	$C_{18}H_{21}FN_4O_3 \cdot 3/2H_2O$	55.81 (55.92)	6.24 6.48	14.46 14.51)
95	DFP	N	Me	(*R*,*S*)	211—212	−14.0 (0.1 N NaOH)	54	$C_{21}H_{19}F_3N_4O_3$	58.33 (58.15)	4.43 4.49	12.96 12.94)
96			Me	(*R*,*S*)	242—244	−150.4 (0.1 N NaOH)	47	$C_{19}H_{22}FN_3O_4$	60.79 (60.50)	5.91 6.22	11.19 11.05)
97	CP	CF	Et	(1″*S*)	216—218	−174.1 (1 N NaOH)	63	$C_{20}H_{23}F_2N_3O_3 \cdot 1/4H_2O$	60.67 (60.63)	5.98 6.15	10.61 10.60)
98	CP	CF	Et	(1″*R*)	218—220	+174.5 (1 N NaOH)	60	$C_{20}H_{23}F_2N_3O_3 \cdot H_2O$	58.67 (58.57)	6.15 6.26	10.26 10.24)

a) CP stands for cyclopropyl group. DFP stands for 2,4-difluorophenyl group. *b*) Degrees. *c*) Yields are those obtained from the coupling step to the final product, including deprotection.

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were taken at 90 MHz with a JEOL FX-90 spectrometer and 400 MHz with a JEOL JNM-EX400 spectrometer. Chemical shifts are expressed in ppm (δ) with tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate as an internal standard. Optical rotations were measured at 589 nm with a Horiba SEPA-200 polarimeter. Solutions were dried over sodium sulfate. E. Merck Silica gel (230—400 mesh) was used for column chromatography. Thin-layer chromatography (TLC) was performed with Merck Silica gel 60 F254 TLC plates.

Synthesis of 3-(1-*tert*-Butoxycarbonylaminoalkyl)pyrrolidines (28a, b and 29a, b). 4-Acetyl-1-benzyl-2-pyrrolidone (18) A mixture of 1-benzyl-5-oxopyrrolidine-3-carboxylic acid (**17**)[18] (4.4 g, 20.3 mmol), thionyl chloride (10 ml, 0.139 mol), and dioxane (30 ml) was heated at 90—100 °C for 30 min. Concentration of the reaction mixture under reduced pressure gave 1-benzyl-5-oxopyrrolidine-3-carbonyl chloride as a mobile oil, which was dissolved in Et_2O (30 ml). To a solution of diethyl malonate (3.5 g, 21.9 mmol) in Et_2O (40 ml) was added magnesium ethoxide (2.5 g, 22.9 mmol). The reaction mixture was heated under reflux for 1.5 h and cooled to room temperature, then a solution of the acid chloride prepared as above was added dropwise and the whole was refluxed for 1 h. The reaction mixture was washed with dilute H_2SO_4, dried, and evaporated under reduced pressure. To the residue was added AcOH (10 ml), H_2O (45 ml), and H_2SO_4 (1 ml). The mixture was refluxed for 5 h, and then concentrated under reduced pressure. The residue was extracted with $CHCl_3$, and the extract was washed with 10% HCl and saturated $NaHCO_3$. The organic layer was dried and concentrated to dryness to give **18** (3.30 g, 76%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 2.2 (s, 3H), 2.66 (d, 2H, J=7.2 Hz), 3.0—3.6 (m, 3H), 4.32, 4.52 (each d, 1H, J=14 Hz, ABq), 7.29 (s, 5 H).

1-Benzyl-4-propionyl-2-pyrrolidone (19) According to the procedure described above, compound **19** was prepared from **17** and diethyl methylmalonate as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (t, 3H, J=7 Hz), 2.4—2.5 (m, 2H), 2.68 (d, 2H, J=9 Hz), 3.3—3.4 (m, 2H), 3.46 (dd, 1H, J=10, 6 Hz), 4.46 (ABq, 2H, J=15 Hz), 7.2—7.3 (m, 5H).

1-Benzyl-4-(1-hydroxyiminoethyl)-2-pyrrolidone (20) A mixture of **18** (3.3 g, 15.2 mmol) and hydroxylamine hydrochloride (2.5 g, 36.0 mol) in pyridine (15 ml) was heated at 90 °C for 5 h. The reaction mixture was diluted with H_2O (100 ml) and acidified with HCl. The mixture was extracted with CH_2Cl_2. The extract was dried and concentrated under reduced pressure. The crude product was chromatographed with MeOH–$CHCl_3$ (1 : 20) to give **20** (2.6 g, 74%) as crystals: mp 103—106 °C; ^{1}H-NMR ($CDCl_3$) δ: 1.8 (s, 3H), 2.62 (d, 2H, J=7.2 Hz), 2.9—3.6 (m, 3H), 4.44 (s, 2H), 7.28 (s, 5H).

1-Benzyl-4-(1-hydroxyiminopropyl)-2-pyrrolidone (21) According to

TABLE III. *In Vitro* Antibacterial Activity of Racemic 7-[(1-Amino-3-alkyl)-1-pyrrolidinyl]-6,8-difluoroquinolones

Compound	Minimum inhibitory concentration (μg/ml)									
	S. aureus 209P	*S. epidermidis* 56556	*S. pyogenes* G36	*S. faecalis* ATCC19433	*E. coli* NIHJ	*K. pneumoniae* Type 2	*P. vulgaris* 08601	*E. cloacae* 03400	*S. marcescens* 10100	*P. aeruginosa* 32104
66	<0.1	0.1	0.39	0.39	<0.1	0.2	0.2	0.1	0.2	0.39
67	<0.1	<0.1	<0.1	<0.1	<0.1	0.2	0.1	<0.1	0.1	0.2
68	0.1	0.2	1.56	0.78	<0.1	0.2	0.1	0.1	0.2	0.78
69	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	0.1	0.39
70	0.39	0.39	0.78	0.78	0.2	0.78	0.78	0.39	0.39	1.56
71	0.78	0.2	0.1	0.39	0.1	0.39	0.39	0.2	0.39	1.56
72	<0.1	<0.1	0.1	0.2	<0.1	0.2	0.2	0.1	0.39	1.56
73	<0.1	0.1	0.2	0.2	<0.1	0.2	0.2	<0.1	0.2	0.78
74	0.1	<0.1	0.1	0.1	<0.1	0.1	0.1	<0.1	0.2	0.78
75	0.006	0.025	0.013	0.05	0.006	0.025	0.013	0.013	0.05	0.1
76	<0.1	<0.1	0.2	0.2	<0.1	<0.1	<0.1	<0.1	0.1	0.39
77	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	0.2
78	<0.1	0.1	0.2	0.2	<0.1	0.1	0.1	<0.1	0.2	0.39
79	0.013	0.025	0.025	0.05	0.013	0.05	0.025	0.025	0.05	0.2
80	0.06	0.025	0.025	0.1	0.013	0.05	0.025	0.025	0.1	0.39
81	<0.1	<0.1	<0.1	0.2	<0.1	<0.1	0.1	<0.1	0.2	0.39
82	<0.1	<0.1	<0.1	0.1	<0.1	<0.1	0.1	<0.1	0.39	0.78
5	0.1	0.2	0.78	0.39	0.05	0.2	0.2	0.2	0.2	0.78
6	0.05	0.1	0.2	0.2	0.05	0.2	0.05	0.05	0.2	0.2
7	0.025	0.05	0.1	0.1	0.013	0.05	0.025	0.025	0.1	0.39

TABLE IV. *In Vitro* Antibacterial Activity of Chiral 7-[(1-Amino-3-alkyl)-1-pyrrolidinyl]-6,8-difluoro Derivatives

Compound	Minimum inhibitory concentration (μg/ml)									
	S. aureus 209P	*S. epidermidis* 56556	*S. pyogenes* G36	*S. faecalis* ATCC19433	*E. coli* NIHJ	*K. pneumoniae* Type 2	*P. vulgaris* 08601	*E. cloacae* 03400	*S. marcescens* 10100	*P. aeruginosa* 32104
83	0.013	0.025	0.05	0.1	0.013	0.1	0.025	0.025	0.1	0.2
84	0.1	0.39	1.56	0.78	0.1	0.78	0.1	0.2	0.39	0.78
85	0.05	0.1	0.78	0.39	0.025	0.2	0.05	0.05	0.2	0.39
86	0.2	0.39	6.25	1.56	0.1	0.39	0.1	0.2	0.39	1.56
87	0.013	0.013	0.025	0.05	0.006	0.05	0.025	0.013	0.05	0.39
88	0.2	0.39	6.25	3.13	0.1	0.39	0.1	0.2	0.39	1.56
89	<0.006	0.013	0.013	0.025	<0.006	0.025	0.013	0.006	0.05	0.1
90	<0.006	0.006	0.006	0.025	<0.006	0.013	0.006	0.006	0.025	0.1
91	0.006	0.013	0.013	0.05	0.013	0.025	0.013	0.025	0.05	0.1
92	<0.006	0.013	0.025	0.05	0.013	0.05	0.013	0.013	0.05	0.2
93	0.013	0.05	0.05	0.05	0.025	0.1	0.05	0.025	0.1	0.1
94	0.025	0.025	0.1	0.1	0.006	0.005	0.025	0.025	0.1	0.1
95	0.025	0.025	0.10	0.10	0.006	0.05	0.025	0.025	0.1	0.1
96	0.025	0.05	0.05	0.1	0.05	0.2	0.05	0.05	0.2	0.2
97	<0.006	0.006	0.006	0.025	<0.006	0.025	0.013	0.006	9.05	0.1
98	0.025	0.05	0.05	0.1	0.025	0.1	0.05	0.025	0.1	0.78
5	0.1	0.2	0.78	0.39	0.05	0.2	0.2	0.2	0.2	0.78
6	0.05	0.1	0.2	0.2	0.05	0.2	0.05	0.05	0.2	0.2
7	0.025	0.05	0.1	0.1	0.013	0.05	0.025	0.025	0.1	0.39

the procedure described above, compound **19** was converted to **21** (4.7 g, 64%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (t, 3H, J=7 Hz), 2.2—2.3 (m, 2H), 2.60 (m, 2H), 3.1—3.7 (m, 3H), 4.40 (ABq, 2H, J=13 Hz), 7.25 (m, 5H).

4-(1-Aminoethyl)-1-benzyl-2-pyrrolidone (22) Raney nickel (20 ml) was added to a solution of **20** (69.3 g, 0.298 mol) in MeOH (700 ml). The mixture was shaken under a hydrogen atmosphere at room temperature for 8 h. The catalyst was removed by filtration and the filtrate was concentrated to give **22** (64.0 g, 98%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.99, 1.06 (each d, 3H, J=7 Hz), 1.96 (s, 2H), 2.0—2.6 (m, 3H), 2.6—3.5 (m, 3H), 4.42 (s, 2H), 7.28 (s, 5H).

4-(1-Aminopropyl)-1-benzyl-2-pyrrolidone (23) According to the procedure described above, compound **21** was converted to **23** (2.8 g, quant.) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (t, 3H, J=7 Hz), 1.1—1.5 (m, 2H), 1.9—2.7 (m, 4H), 2.9—3.4 (m, 2H), 4.46 (ABq, 2H, J=16 Hz), 7.28 (m, 5H).

1-Benzyl-4-(1-tert-butoxycarbonylaminoethyl)-2-pyrrolidones (24a and 24b) 2-(*tert*-Butoxycarbonyloxyimino)-2-phenylacetonitrile (72.2 g, 0.293 mol) was added to a solution of **22** (64.0 g, 0.293 mol) in tetrahydrofuran (THF) (600 ml). The mixture was stirred for 70 min at room temperature, then concentrated under reduced pressure. The residue was dissolved in AcOEt (1 l) and washed with 0.2 N NaOH and saturated NaCl. The organic layer was dried and concentrated under reduced pressure. The residue was triturated with petroleum ether to give a mixture of **24a** and **24b** (67.0 g) as crystals. Fractional recrystallization of the crude product from isopropyl ether gave **24a** (12.9 g, 14%) and **24b** (23.7 g, 25%). *threo*-**24a**: mp 139—141 °C, ^{1}H-NMR ($CDCl_3$) δ: 1.09 (d, 3H, J=7 Hz), 1.42 (s, 9H), 2.1—2.6 (m,

TABLE V. Apparent Partition Coefficient and Aqueous Solubility of Selected Compounds

Compound	Solubility (μg/ml)	P' [a]	Compound	Solubility (μg/ml)	P' [a]
67	90	2.8	**69**	>12000	12.3
75	60	4.2	**77**	580	13.4
80	500	10.9	**83**	520	2.65
87	1200	12.0	**89**	195	4.64
94	80	5.05	**96**	46	0.63
97	100	15.8	**6**	104	0.83
5	400	4.15	**7**	40	7.27

a) Apparent partition coefficient; $CHCl_3$/0.1 M phosphate buffer (pH 7.4).

TABLE VI. Pharmacokinetic Profile of Selected Compounds after Oral Administration to Rats (20 mg/kg)[a]

	Compound					
	6	**83**	**89**	**80**	**94**	**96**
C_{max} (μg/ml)[b]	0.9	2.7	1.6	2.1	0.73	0.1
$t_{1/2}$ (h)[b]	0.76	2.53	2.55	2.42	3.57	N.D.
Urinary recovery (%)[b]	1.6	20	14	10.4	N.D.	N.D.

a) See Experimental. *b*) Mean values ($n=5$).

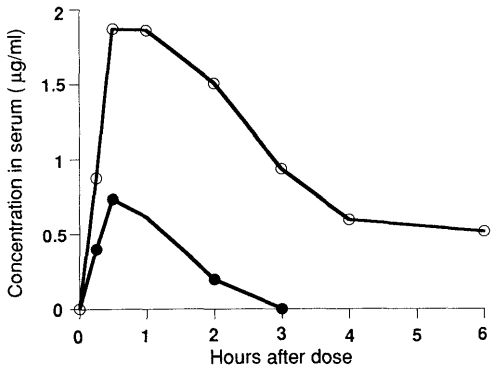


Fig. 2. Mean Plasma Concentrations of **83** (○) and **6** (●) after Oral Administration at 20 mg/kg to Rats ($n=5$)

2H), 2.8—3.4 (m, 2H), 3.4—3.8 (m, 1H), 4.1—4.4 (m, 1H), 4.48 (ABq, $J=16$ Hz), 7.37 (m, 5H). *erythro*-**24b**: mp 138 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (d, 3H, J=7 Hz), 1.42 (s, 9H), 2.2—2.7 (m, 2H), 2.9—3.5 (m, 2H), 3.5—3.9 (m, 1H), 4.3—4.5 (m, 1H), 4.46 (ABq, 2H, $J=16$ Hz), 7.35 (m, 5H).

1-Benzyl-4-(1-*tert*-butoxycarbonylaminopropyl)-2-pyrrolidones (25a and 25b) These compounds were synthesized from **23** by a similar procedure to that described for the synthesis of **24a** and **24b**, and separated by HPLC: Nucleosil 50-5 column (20×250 mm) (Senshu Kagaku Co., Ltd.). Solvent: AcOEt–THF (9:1). Flow rate: 6.6 ml/min. Retention time: 34 min for **25a**; 37 min for **25b**. Compound **25a**: mp 123—124 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (t, 3H, $J=7.5$ Hz) 1.1—1.6 (m, 2H), 1.40 (s, 9H), 2.1—2.6 (m, 3H), 2.9—3.7 (m, 3H), 4.1—4.4 (m, 1H), 4.43 (ABq, 2H, $J=16$ Hz), 7.28 (s, 5H). Compound **25b**: mp 114—117 °C; ^{1}H-NMR ($CDCl_3$) δ: 0.90 (t, 3H, $J=7.5$ Hz) 1.0—1.6 (m, 2H), 1.40 (s, 9H), 2.0—2.6 (m, 3H), 2.9—3.6 (m, 3H), 4.22 (ABq, 2H, $J=16$ Hz), 4.3—4.5 (m, 1H), 7.28 (s, 5H).

4-(1-Aminoethyl)-1-benzyl-2-pyrrolidones (22a and 22b) Compound **24a** (8.0 g, 25.1 mmol) was added portionwise to trifluoroacetic acid (TFA) (80 ml) under ice cooling. After the addition, the reaction mixture was stirred for 1 h at room temperature, then concentrated under reduced pressure. The residue was taken up in H_2O. The solution was neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was dried and concentrated to dryness to yield *threo*-**22a** (5.5 g, quant.) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (d, 3H, $J=7$ Hz), 1.24 (s, 2H), 2.0—2.6 (m, 3H), 2.6—3.0 (m, 1H), 3.0—3.5 (m, 2H), 4.45 (s, 2H), 7.28 (s, 5H). In the same way, compound **24b** was converted to *erythro*-**22b** (4.6 g, quant.). ^{1}H-NMR ($CDCl_3$) δ: 0.99 (d, 3H, $J=7$ Hz), 1.96 (s, 2H), 2.0—2.6 (m, 3H), 2.6—3.0 (m, 1H), 3.0—3.5 (m, 2H), 4.45 (s, 2H), 7.28 (s, 5H).

4-(1-Aminopropyl)-1-benzyl-2-pyrrolidones (23a and 23b) Following the procedure described for **22a**, compounds **25a** and **25b** were converted to **23a** (845 mg, 93%) and **23b** (800 mg, 88%). Compound **23a**: ^{1}H-NMR ($CDCl_3$) δ: 0.92 (t, 3H, $J=7$ Hz), 1.1—1.5 (m, 2H), 1.45 (s, 2H), 2.0—2.8 (m, 4H), 3.0—3.4 (m, 2H), 4.44 (ABq, 2 H, $J=16$ Hz), 7.28 (s, 5H). Compound **23b**: ^{1}H-NMR ($CDCl_3$) δ: 0.92 (t, 3H, $J=7$ Hz), 1.1—1.5 (m, 2H), 1.26 (s, 2H), 1.9—2.7 (m, 4H), 2.9—3.5 (m, 2H), 4.45 (ABq, 2H, $J=16$ Hz), 7.28 (s, 5H).

1-Benzyl-3-(1-*tert*-butoxycarbonylaminoethyl)pyrrolidines (26a and 26b) A solution of **22a** (480 mg, 2.21 mmol) in THF (30 ml) was treated with lithium aluminum hydride (500 mg, 13.2 mmol) and refluxed for 2 h. The reaction mixture was carefully treated with 2.0 ml of H_2O, and the grainy precipitate was removed by filtration. 2-(*tert*-Butoxycarbonyloxyimino)-2-phenylacetonitrile (540 mg, 2.19 mmol) was added to the filtrate, and the solution was stirred for 12 h. The reaction mixture was evaporated, and the residue was dissolved in AcOEt. This solution was washed with 0.5 N NaOH and H_2O. The organic layer was dried and concentrated to obtain a crude product, which was chromatographed with AcOEt–benzene (2:1) to give *threo*-**26a** (460 mg, 69%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (d, 3H, $J=7$ Hz), 1.44 (s, 9H), 1.6—3.0 (m, 8H), 3.60 (ABq, 2H, $J=16$ Hz), 5.45 (br s, 1H), 7.30 (s, 5H). In the same way, compound **22b** was converted to *erythro*-**26b** (520 mg, 73%). ^{1}H-NMR ($CDCl_3$) δ: 1.15 (t, 3H, $J=7$ Hz), 1.45 (s, 9H), 1.6—3.0 (m, 8H), 3.60 (ABq, 2H, $J=16$ Hz), 5.40 (br s, 1H), 7.30 (s, 5H).

1-Benzyl-3-(1-*tert*-butoxycarbonylaminopropyl)pyrrolidines (27a and 27b) Following the procedure described for **26a**, compounds **23a** and **23b** were converted to **27a** (840 mg, 77%) and **27b** (930 mg, 85%), respectively. Compound **27a**: ^{1}H-NMR ($CDCl_3$) δ: 0.88 (t, 3H, $J=8$ Hz), 1.3—2.0 (m, 4H), 1.45 (s, 9H), 2.1—2.9 (m, 5H), 3.3—3.5 (m, 1H), 3.58 (ABq, 2H, $J=13$ Hz), 4.7—4.9 (br, 1H), 7.30 (s, 5H). Compound **27b**: ^{1}H-NMR ($CDCl_3$) δ: 0.90 (t, 3H, $J=8$ Hz), 1.1—1.8 (m, 4H), 1.44 (s, 9H), 1.8—2.7 (m, 5H), 3.1—3.5 (m, 1H), 3.58 (ABq, 2H, $J=14$ Hz), 5.1—5.4 (br, 1H), 7.30 (s, 5H).

3-(1-*tert*-Butoxycarbonylaminoethyl)pyrrolidines (28a and 28b) A mixture of **26a** (460 mg 1.51 mmol), 50% aqueous 5% palladium on carbon (800 mg), and EtOH (20 ml) was shaken in a hydrogen atmosphere at 50 °C for 4 h. The catalyst was removed by filtration, and the filtrate was concentrated to give *threo*-**28a** (325 mg, quant.) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, d, $J=7$ Hz), 1.43 (s, 9H), 1.7—2.5 (m, 3H), 2.7—3.4 (m, 4H), 3.4—3.8 (m, 1H), 4.83 (d, 1H, $J=9$ Hz). In the same way, compound **26b** was converted to *erythro*-**28b** (420 mg, quant.). ^{1}H-NMR ($CDCl_3$) δ: 1.14 (d, 3H, $J=7$ Hz), 1.44 (s, 9H), 1.5—2.3 (m, 3H), 2.4—3.3 (m, 4H), 3.4—3.9 (m, 1H), 4.56 (d, 1H, $J=8$ Hz).

3-(1-*tert*-Butoxycarbonylaminopropyl)pyrrolidines (29a and 29b) Following the procedure described for **28a**, compounds **27a** and **27b** were converted to **29a** (320 mg, quant.) and **29b** (350 mg, quant.), respectively. Compound **29a**: ^{1}H-NMR ($CDCl_3$) δ: 0.95 (t, 3H, $J=7$ Hz), 1.25—1.4 (m, 1H), 1.44 (s, 9H), 1.5—1.7 (m, 2H), 1.9—2.0 (m, 1H), 2.15—2.3 (m, 1H), 2.65—2.75 (m, 1H), 3.0—3.25 (m, 3H), 3.45—3.55 (m, 1H), 4.42 (br d, 1H, $J=10$ Hz). Compound **29b**: ^{1}H-NMR ($CDCl_3$) δ: 0.95 (t, 3H, $J=7$ Hz), 1.30—1.50 (m, 1H), 1.44 (s, 9H), 1.53—1.65 (m, 1H), 1.70—1.90 (m, 1H), 2.05—2.15 (m, 1H), 2.38—2.50 (m, 1H), 3.03—3.13 (m, 1H), 3.25—3.60 (m, 4H), 4.67 (d, 2H, $J=9$ Hz).

3-(1-Methylaminoethyl)pyrrolidines (30a and 30b) A solution of **24a** (346 mg, 1.09 mmol) in THF (20 ml) was treated with lithium aluminum hydride (500 mg, 13.2 mmol), and the mixture was heated under reflux for 1.5 h. Then H_2O (0.5 ml), 15% NaOH (0.5 ml), and H_2O (1.5 ml) were added under ice cooling. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was mixed with EtOH (20 ml) and 50% aqueous 5% palladium on carbon (300 mg), and the mixture was shaken in a hydrogen atmosphere at 50 °C for 4 h. The catalyst was removed by filtration, and the filtrate was concentrated to give *threo*-**30a** (180 mg, quant.) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, d, $J=6$ Hz), 1.65—1.7 (m, 1H), 1.8—1.9 (m, 1H), 2.00 (q, 1H, $J=8$ Hz), 2.4—2.5 (m, 1H), 2.40 (3H, s), 2.55—2.65 (m, 1H), 2.85—3.0 (m, 2H), 3.05—3.15 (m, 1H). In the same way, compound **24b** was converted to *erythro*-**30b** (245 mg, quant.) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (d, 3H, $J=6$ Hz), 1.5—1.6 (m, 1H), 1.9—2.0 (m, 1H), 2.09 (q, 1H, $J=8$ Hz),

2.42 (s, 3H), 2.4—2.5 (m, 1H), 2.67 (dd, 1H, $J=11$ Hz, 8 Hz), 2.9—3.2 (m, 3H).

2-Benzoylamino-2-methylpropanal (32) A solution of 2-benzoylamino-2-methylpropanol (**31**) (19.3 g, 0.10 mol) in CH_2Cl_2 (50 ml) was added dropwise to a stirred suspension of pyridinum chlorochromate (32.3 g, 0.15 mol) in CH_2Cl_2 (200 ml), and the mixture was stirred for 20 h. Then Et_2O (200 ml) was added, and stirring was continued for 30 min. The precipitate was removed by decantation and the organic layer was passed through a Florisil column. The eluate was concentrated under reduced pressure, and the residue was chromatographed with $CHCl_3$–MeOH (10 : 1) to yield **32** (11.0 g, 58%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.56 (s, 6H), 6.8 (br s, 1H), 7.2—8.1 (m, 5H), 9.40 (s, 1H).

Ethyl 4-Benzoylamino-4-methyl-2-pentenoate (33) A solution of (carbethoxymethylene)triphenylphosphorane (8.0 g, 23.0 mmol) in CH_2Cl_2 (20 ml) was added dropwise to a solution of **32** (4.0 g, 20.1 mmol) in CH_2Cl_2 (60 ml). After the addition, the solution was stirred at room temperature for 6 h, then concentrated under reduced pressure. The residue was chromatographed with benzene–AcOEt (2 : 1) to obtain *cis*-**33** (0.7 g, 6.3%) and *trans*-**33** (4.5 g, 41%) as colorless powders. *cis*-**33**: ^{1}H-NMR ($CDCl_3$) δ: 1.20 (t, 3H, $J=7$ Hz), 1.72 (s, 6H), 4.02 (q, 2H, $J=7$ Hz), 5.78 (d, 1H, $J=12.6$ Hz), 6.36 (d, 1H, $J=12.6$ Hz), 7.25—7.95 (m, 5H). *trans*-**33**: ^{1}H-NMR ($CDCl_3$) δ: 1.34 (t, 3H, $J=7$ Hz), 1.60 (s, 6H), 4.24 (q, 2H, $J=7$ Hz), 6.2 (br s, 1H), 5.90 (d, 1H, $J=16.2$ Hz), 7.10 (d, 1H, $J=16.2$ Hz), 7.2—7.9 (m, 5H).

Ethyl 4-Benzoylamino-4-methyl-3-nitromethylpentanoate (34) A mixture of *trans*-**33** (2.0 g, 9.25 mmol) and 1,1,3,3-tetramethylguanidine (1.15 g, 10.0 mol) in nitromethane (110 ml) was stirred at room temperature for 20 h. The reaction mixture was concentrated and the residue was taken up in $CHCl_3$. The solution was washed with 0.5 N HCl and saturated NaCl, dried, and evaporated under reduced pressure. The residue was chromatographed with $CHCl_3$–MeOH (20 : 1) to give **34** (2.4 g, 98%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (t, 3H, $J=7$ Hz), 1.48 (s, 3H), 1.56 (s, 3H), 2.4—2.8 (m, 2H), 4.10 (q, 2H, $J=7$ Hz), 4.4—5.0 (m, 2H), 6.35 (br s, 1H), 7.2—7.9 (m, 5H). In the same way, *cis*-**33** was also converted to **34**.

4-(1-Benzoylamino-1-methylethyl)-2-pyrrolidone (35) A solution of **34** (810 mg, 2.51 mmol) in EtOH (40 ml) was shaken with Raney nickel (3 ml) under a hydrogen atmosphere at room temperature for 3 d. The catalyst was filtered off and the filtrate was concentrated. The residue was chromatographed with $CHCl_3$–MeOH (10 : 1) to give **35** (50 mg, 8%). ^{1}H-NMR ($CDCl_3$) δ: 1.46 (s, 6H), 2.1—2.6 (m, 2H), 2.8—3.8 (m, 3H), 5.96 (br s, 1H), 6.16 (br s, 1H), 7.2—8.0 (m, 5H).

3-(1-Benzylamino-1-methylethyl)pyrrolidine (36) A solution of **35** (780 mg, 3.17 mmol) in THF (20 ml) was treated with lithium aluminum hydride (800 mg, 21.1 mmol). The mixture was heated under reflux for 6 h, then carefully treated with H_2O (0.8 ml), 15% NaOH (0.8 ml), and H_2O (2.4 ml). The precipitate was filtered off and the filtrate was concentrated to dryness to leave a crude product, which was chromatographed with *n*-BuOH–AcOH–H_2O–AcOEt (1 : 1 : 1 : 1). The eluate was concentrated and the residue was dissolved in $CHCl_3$. This solution was washed with saturated $NaHCO_3$ and saturated NaCl. The organic layer was dried, and evaporated to give **36** (340 mg, 49%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (s, 6H), 1.8 (m, 2H), 2.3 (m, 4H), 2.9 (m, 4H), 3.72 (s, 2H), 7.28 (m, 5H), 7.25—7.3 (m, 2H).

3-(1-Amino-1-methylethyl)pyrrolidine (37) A mixture of **36** (200 mg, 0.916 mmol), palladium black (200 mg), 1 N HCl (3 ml), and MeOH (20 ml) was shaken in a hydrogen atmosphere at 25 °C for 18 h. The catalyst was filtered off, and to the filtrate was added 2 ml of 50% NaOH. The solution was distilled under reduced pressure to give **37** as an aqueous solution, which was used for the displacement reactions.

Synthesis of 4-(1-Amino-1-cycloalkyl)pyrrolidines (43a and 43b). Ethyl 1-*tert*-Butoxycarbonylaminocyclopropanecarboxylate (38a) A solution of 1-ethoxycarbonylcyclopropanecarboxylic acid (5.0 g, 31.6 mmol), diphenylphosphoryl azide (6.9 ml, 32.0 mmol), and Et_3N (4.5 ml, 32.0 mmol) in *tert*-BuOH (80 ml) was heated at 90—100 °C for 4 h. After concentration of the reaction mixture, the residue was dissolved in AcOEt, and this solution was washed with aqueous 5% citric acid, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried and concentrated to dryness to give **38a** (5.7 g, 79%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (m, 7H), 1.44 (s, 9H), 4.12 (q, 2H, $J=7$ Hz), 5.04 (br s, 1H).

Ethyl 1-*tert*-Butoxycarbonylaminocyclobutanecarboxylate (38b) According to the procedure described above, compound **38b** (12.1 g, 37%) was prepared from 1-ethoxycarbonylcyclobutanecarboxylic acid as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (q, 3H, $J=7$ Hz), 1.45 (s, 9H), 2.08 (m, 2H), 2.50 (m, 4H), 4.12 (q, 2H, $J=7$ Hz), 5.10 (br s, 1H).

1-*tert*-Butoxycarbonylaminocyclopropanecarbaldehyde (39a) A 1 M *n*-hexane solution of diisopropylaluminum hydride (46 ml) was added dropwise to a solution of **38a** (7.1 g, 31.0 mmol) in *n*-hexane (200 ml) at −65 °C under an argon atmosphere. The reaction mixture was stirred for 4 h at −65 °C, then warmed to room temperature and extracted with saturated aqueous $NaHSO_3$. The precipitate formed was removed by filtration. The filtrate was adjusted to pH 9 by adding 10% NaOH, and extracted with Et_2O. The organic layer was washed with H_2O, dried, and concentrated to gave **39a** (2.6 g, 40%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (m, 4H), 1.48 (s, 9H), 5.20 (br s, 1H), 9.20 (s, 1H).

1-*tert*-Butoxycarbonylaminocyclobutanecarbaldehyde (39b) According to the procedure described above, compound **38b** was converted to **39b** (1.26 g, 35%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (s, 9H), 2.04 (m, 2H), 2.45 (m, 4H), 5.24 (br s, 1H), 9.64 (s, 1H).

Ethyl 1-*tert*-Butoxycarbonylaminocyclopropanepropenoate (40a) Following the procedure described for **33**, compound **39a** was converted to **40a** (1.03 g, 67%) as a powder. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (t, 3H, $J=7$ Hz), 1.40 (s, 9H), 1.0—1.3 (m, 4H), 4.20 (q, 2H, $J=7$ Hz), 5.0 (br s, 1H), 5.80 (d, 1H, $J=18$ Hz), 6.28 (d, 1H, $J=18$ Hz).

Ethyl 1-*tert*-Butoxycarbonylaminocyclobutanepropenoate (40b) Following the procedure described for **33**, compound **39b** was converted to **40b** (725 mg, quant.) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (t, 3 H, $J=7$ Hz), 1.44 (s, 9H), 1.98 (m, 2H), 2.3 (m, 4H), 4.2 (q, 2H, $J=7$ Hz), 4.92 and 5.9 (each br s, 1H), 5.9 (d, 1H, $J=12$ Hz (cis) and 16 Hz (*trans*)), 6.72 (*cis*) and 7.16 (*trans*) (1H, $J=12$ Hz (*cis*), 16 Hz (*trans*)).

Ethyl 3-(1-*tert*-Butoxycarbonylaminocyclopropyl)-4-nitrobutanoate (41a) Following the procedure described for **34**, compound **40a** was converted to **41a** (960 mg, 75%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 0.85—0.95 (m, 4H), 1.30 (t, 3H, $J=7$ Hz), 1.47 (s, 9H), 2.25 (m, 1H), 2.6 (m, 2H), 4.16 (q, 2H, $J=7$ Hz), 4.6 (m, 2H), 5.0 (br s, 1H).

Ethyl 3-(1-*tert*-Butoxycarbonylaminocyclobutyl)-4-nitrobutanoate (41b) Following the procedure described for **34**, compound **40b** was converted to **41b** (750 mg, 80%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (t, 3H, $J=7$ Hz), 1.44 (s, 9H), 1.8—2.5 (m, 8H), 3.08 (m, 1H), 4.10 (q, 2H, $J=7$ Hz), 4.4—4.6 (m, 3H).

4-(1-*tert*-Butoxycarbonylamino-1-cyclopropyl)-2-pyrrolidone (42a) Following the procedure described for **35**, compound **41a** was converted to **42a** (320 mg, 44%). ^{1}H-NMR ($CDCl_3$) δ: 0.7—0.8 (m, 4H), 1.38 (s, 9H), 2.30 (m, 3H), 3.40 (m, 2H), 5.00 (br s, 1H), 5.80 (br s, 1H).

4-(1-*tert*-Butoxycarbonylamino-1-cyclobutyl)-2-pyrrolidone (42b) Following the procedure described for **35**, compound **41b** was converted to **42b** (430 mg, 86%). ^{1}H-NMR ($CDCl_3$) δ: 1.44 (s, 9H), 1.66—2.40 (m, 8H), 2.80—3.48 (m, 3H), 4.84 (br s, 1H). 6.0 (br s, 1H).

3-(1-Aminocyclopropyl)pyrrolidine (43a) To an ice-cold solution of anisole (0.6 ml, 5.52 mmol) in TFA (1.2 ml) was added **42a** (230 mg, 0.965 mmol), and the mixture was stirred at room temperature for 1 h. Then Et_2O was added, and the precipitate was collected by filtration and washed with Et_2O. This solid was suspended in THF (8 ml), then Et_3N (0.5 ml, 3.57 mmol) and lithium aluminum hydride (300 mg, 7.91 mmol) were added and the whole was refluxed for 18 h. The reaction mixture was carefully treated with H_2O (0.3 ml), 15% NaOH (0.3 ml), and H_2O (0.9 ml). The grainy precipitate was filtered off. The filtrate was mixed with 1 N HCl (3 ml) and concentrated to dryness. The residue was taken up in 3 ml of 50% NaOH, and the solution was distilled under reduced pressure to give **43a** as an aqueous solution, which was used in the displacement reactions.

3-(1-Aminocyclobutyl)pyrrolidine (43b) Following the procedure described for **43a**, compound **43b** was prepared from **42b** as an aqueous solution, which was used in the displacement reactions.

Synthesis of Chiral 3-(1-tert-Butoxycarbonylaminoethyl)-pyrrolidines (47a—d). 1-Benzyl-4-[1-[*N'*-*p*-toluenesulfonyl-2-(*S*)-pyrrolidinylcarbonylamino]ethyl]-2-pyrrolidones (44a and 44b) A mixture of (*S*)-*N*-*p*-toluenesulfonylproline (2.5 g, 9.3 mmol), thionyl chloride (2.1 ml), and benzene (20 ml) was refluxed for 5 h. The reaction mixture was evaporated to obtain the crude acyl chloride. The residue was dissolved in CH_2Cl_2 (15 ml), and this solution was added dropwise to a mixture of **22a** (3.55 g, 16.3 mmol), pyridine (1.3 ml, 16.3 mmol), and CH_2Cl_2 (15 ml). The reaction mixture was stirred for 24 h, then washed with 2 N HCl, H_2O, 2 N NaOH, and H_2O. The organic layer was dried and concentrated to dryness to give (*S*)-*N*-*p*-toluenesulfonylprolineamide as a mixture of diastereomers. The crude product showed two spots on TLC, *Rf* 0.26 (**44a**) and 0.29 (**44b**), using AcOEt. The mixture was separated by silica

gel column chromatography with AcOEt–MeOH (100 : 0—95 : 5) to give **44a** and **44b**, which were recrystallized from isopropyl ether. Compound **44a**: mp 126—132 °C, $[\alpha]_D$ −136.0° (c=0.350, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.15 (d, 3H, J=7 Hz), 1.40—1.19 (m, 4H), 2.00—2.80 (m, 3H), 2.45 (s, 3H), 3.00—3.40 (m, 2H), 3.4—3.8 (m, 2H), 4.45 (ABq, 2H, J=16 Hz), 6.88 (d, 1H, J=8 Hz), 7.39 (s, 5H), 7.44 (d, 2H, J=7 Hz), 7.69 (d, 2H, J=7 Hz). Compound **44b**: mp 96—98 °C; $[\alpha]_D$ −91.3° (c=0.515, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.19 (d, 3H, J=7 Hz), 1.40—1.80 (m, 3H), 1.80—2.20 (m, 2H), 2.44 (m, 3H). 2.28—2.80 (m, 2H), 3.00—3.40 (m, 3H), 3.40—3.70 (m, 1H), 3.90—4.20 (m, 2H), 4.50 (ABq, 2H, J=16 Hz), 6.88 (d, 1H, J=8 Hz), 7.28 (s, 5H), 7.44 (d, 2H, J=7 Hz), 7.70 (d, 2H, J=7 Hz).

1-Benzyl-4-[1-[*N'*-*p*-toluenesulfonyl-2-(*S*)-pyrrolidinylcarbonylamino]ethyl]-2-pyrrolidone (44c and 44d) According to the procedure described above, compounds **44c** and **44d** were prepared from **22b** and separated by silica gel column chromatography with $CHCl_3$–MeOH (95 : 5). Compound **44c**: *Rf* 0.40; recrystallized from isopropyl ether, mp 128.6—130.4 °C, $[\alpha]_D$ −123.0° (c=0.530, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ:1.10 (d, 3H, J=6.8 Hz), 1.51—1.66 (m, 3H), 2.04—2.09 (m, 1H), 2.29—2.34 (m, 1H), 2.45 (s, 3H), 2.38—2.52 (m, 2H), 3.03 (dd, 1H, J=6.8, 9.8 Hz), 3.11—3.18 (m, 1H), 3.29—3.33 (m, 1H), 3.51—3.56 (m, 1H), 3.98 (dd, 1H, J=8.3, 2.9 Hz), 4.02—4.07 (m, 1H), 4.38—4.49 (ABq, 2H, J=14.7 Hz), 4.44 (ABq, 2H, J=14.7 Hz), 6.77 (d, 1H, J=8.8 Hz), 7.22—7.37 (m, 7H), 7.71 (d, 2H, J=8.3 Hz). Compound **44d**: *Rf* 0.33; recrystallized from isopropyl ether, mp 128.6 °C; $[\alpha]_D$ −125.0° (c=0.248, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.31 (d, 3H, J= 6.8 Hz), 1.50—1.70 (m, 3H), 2.03—2.10 (m, 1H), 2.30—2.35 (m, 1H), 2.45 (s, 3H), 2.30—2.34 (m, 1H), 2.38—2.52 (m, 2H), 3.03 (dd, 1H, J=9.7, 7.3 Hz), 3.11—3.18 (m, 1H), 3.31 (dd, 1H, J=9.7, 8.3 Hz), 3.51—3.56 (m, 1H), 3.96—3.99 (m, 1H), 4.02—4.07 (m, 1H), 4.44 (ABq, 2H, J=14Hz), 6.77 (d, 1H, J=9.3 Hz), 7.19—7.37 (m, 7H), 7.71 (d, 2H, J=8.3 Hz).

Chiral 4-(1-Aminoethyl)-1-benzyl-2-pyrrolidones (45a—d) A mixture of **44a** (1.08 g, 2.30 mmol), NaOH (10 ml), and EtOH (30 ml) was heated under reflux for 3 h. The reaction mixture was concentrated under reduced pressure, and the residue was extracted with $CHCl_3$. The extract was dried and concentrated to give **45a** (480 mg, 96%). In the same way, compounds **44b—d** were converted to **45b** (430 mg, 93%), **45c** (254 mg, 68%) **45d** (536 mg, 77%), respectively. The ^{1}H-NMR spectra of these compounds were identical with those of the corresponding racemates. Specific rotations were as follows: (4*R*,1′*S*)-**45a**: $[\alpha]_D$ −4.60° (c=2.00, $CHCl_3$); (4*S*,1′*R*)-**45b**: $[\alpha]_D$ +4.40° (c=2.00, $CHCl_3$); (4*R*,1′*R*)-**45c**: $[\alpha]_D$ −14.27° (c=1.84, $CHCl_3$); (4*S*,1′*S*)-**45d**: $[\alpha]_D$ +15.6° (c=2.47, $CHCl_3$).

Chiral 1-Benzyl-3-(1-*tert*-butoxycarbonylaminoethyl)pyrrolidines (46a—d) To a suspension of lithium aluminum hydride (500 mg, 13.2 mmol) in THF (35 ml) was added **45a** (480 mg, 2.20 mmol), and the mixture was heated under reflux for 24h. The reaction mixture was carefully treated with H_2O (2.0 ml), and the grainy precipitate was removed by filtration. 2-(*tert*-Butoxycarbonyloxyimino)-2-phenylacetonitrile (540 mg, 2.19 mmol) was added to the filtrate, and the solution was stirred for 12 h. The reaction mixture was evaporated, and the residue was dissolved in AcOEt. This solution was washed with 0.5 N NaOH and H_2O. The organic layer was dried and concentrated to give a crude product, which was chromatographed with AcOEt–benzene (2 : 1) to give **46a** (285 mg, 41%) as an oil. In the same way, compounds **45b—d** were converted to **46b** (196 mg, 28%), **46c** (424 mg, 76%), **46d** (567 mg, 76%), respectively. Specific rotations were as follows: (3*R*,1′*S*)-**46a**: $[\alpha]_D$ −9.80° (c=2.00, $CHCl_3$); (3*S*,1′*R*)-**46b**: $[\alpha]_D$ +9.63° (c=1.80, $CHCl_3$); (3*R*,1′*R*)-**46c**: $[\alpha]_D$ −6.34° (c=1.83, $CHCl_3$); (3*S*,1′*S*)-**46d**: $[\alpha]_D$ +6.38° (c=2.73, $CHCl_3$).

Chiral 3-(1-*tert*-Butoxycarbonylaminoethyl)pyrrolidines (47a—d) A mixture of **46a** (460 mg, 1.51 mmol), 50% aqueous 5% palladium carbon (800 mg), and EtOH (20 ml) was shaken in a hydrogen atmosphere at 50 °C for 4 h. The catalyst was filtered off, and the filtrate was concentrated to give **47a** (320 mg, quant.), which was used without purification for the displacement reactions. In the same way, compounds **46b, c** were converted to **47b, c**.

Diastereoselective Synthesis of Chiral 3-(1-*tert*-Butoxycarbonylaminoalkyl)pyrrolidines (47a, 65a, and 65b). Ethyl 4-(*S*)-*tert*-Butoxycarbonylamino-3-oxopentanoate (49) A mixture of magnesium (1.32 g, 54.3 mmol), CCl_4 (4 ml), and EtOH (23 ml) was stirred for 2 h, then a solution of ethyl hydrogen malonate (15.8 g, 91.8 mmol) in THF (80 ml) was added and the whole was stirred for 0.5 h. The solution was concentrated to dryness, and the residue was dissolved in THF (115 ml). *N,N'*-Carbonyldiimidazole (11.4 g, 70.3 mmol) was added to a solution of L-*N*-Boc-alanine (**48**) (12.5 g, 66.1 mmol) in THF (155 ml). The mixture was stirred at room temperature for 0.5 h, then the solution of the magnesium salt prepared above was added dropwise. The whole was stirred for 1 h at 25 °C and the solvent was removed under reduced pressure. The residue was partitionated between benzene and aqueous 10% citric acid, and the organic layer was separated, washed with H_2O, and dried. Concentration of the solution gave **49** (15.8 g, 90%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (t, 3H, J=7 Hz), 1.35 (d, 3H, J=7 Hz), 1.45 (s, 9H), 3.35 (s, 2H), 4.20 (q, 2H, J=7 Hz), 4.25 (br s, 1H), 4.9—5.2 (m, 1H).

Ethyl 4-(*S*)-*tert*-Butoxycarbonylamino-3-hydroxypentanoate (50) Sodium borohydride (1.20 g, 31.7 mmol) was added to an ice-cold solution of **49** (15.5 g, 58.8 mmol) in EtOH (80 ml). The reaction mixture was stirred for 1 h, H_2O (100 ml) was added, and the EtOH was evaporated off under reduced pressure. The residue was extracted with $CHCl_3$, dried, and concentrated to give **50** (14.4 g, 92%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (d, 3H, J=7 Hz), 1.22 (t, 3H, J=7 Hz), 1.40 (s, 9H), 2.30—2.55 (m, 2H), 3.10—3.50 (m, 1H), 3.50—3.90 (m, 1H), 4.12 (q, 2H, J=7 Hz), 4.60—4.90 (m, 1H).

Ethyl 4-(*S*)-*tert*-Butoxycarbonylamino-3-methanesulfonyloxypentanoate (51) Methanesulfonyl chloride (8.0 g, 69.8 mmol) was added to a solution of **50** (14.5 g, 55.5 mmol), and the mixture was stirred for 18 h at 25 °C, poured onto ice and extracted with benzene. The extract was washed with 10% aqueous citric acid and H_2O. The organic layer was dried and concentrated to dryness to give **51** (18.4 g, 98%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (d, 3H, J=7 Hz), 1.28 (t, 3H, J=7 Hz), 1.45 (s, 9H), 2.64—2.74 (m, 2H), 3.06 (s, 3H), 3.70—4.00 (m, 1H), 4.18 (q, 2H, J=7 Hz), 4.60—4.90 (m, 1H), 5.00—5.30 (m, 1H).

Ethyl 4-(*S*)-*tert*-Butoxycarbonylamino-2-pentenoate (52) 1,8-Diazabicyclo[5.4.0]undec-7-ene (8.3 g, 54.5 mmol) was added to a solution of **51** (18.4 g, 55.7 mmol) in $CHCl_3$ (100 ml) and the mixture was stirred for 3 h at room temperature, washed with aqueous 10% citric acid and H_2O, dried, and concentrated under reduced pressure. The residue was chromatographed with AcOEt–MeOH (95 : 5) to give **52** (10.3 g, 78%) as an oil. $[\alpha]_D$ −26.0° (c=1.20, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (d, 3H, J=7 Hz), 1.28 (t, 3H, J=7 Hz), 1.45 (s, 9H), 4.19 (q, 2H, J=7 Hz), 3.90—4.80 (m, 2H), 5.89 (dd, 1H, J=17, 2 Hz), 6.88 (dd, 1H, J=17, 5 Hz).

Ethyl 4-(*S*)-*tert*-Butoxycarbonylamino-3-nitromethylpentanoate (53) 1,1,3,3-Tetramethylguanidine (1.5 g, 13.0 mmol) was added to a solution of **52** (10.3 g, 42.3 mmol) in nitromethane (50 ml) and the mixture was stirred for 2 d, then concentrated under reduced pressure. The residue was dissolved in $CHCl_3$, and this solution was washed with 10% aqueous citric acid and H_2O. The organic layer was dried and concentrated to dryness to give a mixture of **53a** and **53b** (12.3 g, 95%) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (d, 3H, J=7 Hz), 1.27 (t, 3H, J=7 Hz), 1.44 (s, 9H), 2.40—2.54 (m, 2H), 2.60—2.90 (m, 1H), 3.70—3.96 (m, 1H), 4.16 (q, 2H, J=7 Hz), 4.00—4.30 (br, 1H), 4.52 (d, 2H, J=6 Hz). The ratio of **53a** and **53b** was determined to be 3 : 1 by HPLC after conversion to **55**. When this reaction was carried out with 0.1 mol eq of TMG at 5 °C for 7 d, the ratio of **53a** and **53b** was 10 : 1.

4-(1-(*S*)-*tert*-Butoxycarbonylaminoethyl)-2-pyrrolidone (54) A solution of **53** (45.6 g, 0.150 mol) in MeOH (800 ml) was hydrogenated over Raney nickel (30 ml). The catalyst was filtered off and the filtrate was concentrated. The residue was treated with EtOH to give crystals, which were recrystallized from AcOEt to give a mixture of **54a** and **54b** (20.7 g, 61%): ^{1}H-NMR ($CDCl_3$) δ: 1.16 (d, 3H, J=7 Hz), 1.44 (s, 9H), 2.04—2.56 (m, 2H), 3.16—3.46 (m, 2H), 3.46—3.80 (m, 1H), 4.32—4.46 (br, 1H), 6.70—6.90 (br, 1H).

(4*R*,1′*S*)-1-Benzyl-4-(1-tert-butoxycarbonylaminoethyl)-2-pyrrolidone (55a) Following the procedure described for **24a** and **24b**, compound **45a**, which was prepared by optical resolution, was converted to **55a** (340 mg, 68%) as crystals: mp 129—131 °C; $[\alpha]_D$ −32.46° (c=0.308, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{26}N_2O_3$: C, 76.90; H, 8.23; N, 8.80. Found: C, 76.82; H8.14; N, 8.95.

(4*R*,1′*S*) and (4*S*,1′*S*)-1-Benzyl-4-(1-*tert*-butoxycarbonylaminoethyl)-2-pyrrolidone (55a and 55b) A solution of **54** (1.14 g, 5.00 mmol) in DMF (30 ml) was treated with 50% NaH (240 mg, 6.00 mmol). The mixture was stirred for 0.5 h, then benzyl chloride (633 mg, 5.00 mmol) was added and stirring was continued for 24 h at room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in AcOEt (50 ml) and benzene (50 ml). This solution was washed with H_2O, dried, and concentrated. The residue was recrystallized twice from isopropyl ether to give **55a** (460 mg, 42%), which was identical

with the material prepared by optical resolution of **22a** as above. Compound **55b** was obtained from the mother liquid by preparative HPLC. HPLC: Nucleosil 50-5 column (20 × 250 mm) (Senshu Kagaku Co., Ltd.); solvent: AcOEt–THF (95 : 5); flow rate, 5 ml/min; retention time, 52.5 min for **55a**; 46.5 min for **55b**. Compound **55a**: mp 129—130 °C; $[\alpha]_D$ −31.5° (c = 0.590, $CHCl_3$).

(4*R*,1′*S*) and (4*S*,1′*S*)-4-(1-Aminoethyl)-1-benzyl-2-pyrrolidone (45a and 45d) Following the procedure described for **22a**, compounds **55a** and **55b** were converted to **45a** (12.8 g, quant.) and **45d** (156 mg, quant.), respectively. Compound **45a**: $[\alpha]_D$ −4.78° (c = 1.83, $CHCl_3$). Compound **45d**: $[\alpha]_D$ +15.4° (c = 2.10, $CHCl_3$).

(*S*)- and (*R*)-Ethyl 4-*tert*-Butoxycarbonylamino-3-oxohexanoate (57a and 57b) Following the procedure described for **49**, compounds **56a** and **56b** were converted to **57a** (11.9 g, 88%) and **57b** (12.1 g, 92%), respectively. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (t, 3H, J = 7 Hz), 1.28 (t, 3H, J = 7 Hz), 1.44 (s, 9H), 1.4—2.1 (m, 2H), 3.54 (s, 2H), 4.22 (q, 2H, J = 7 Hz), 4.9—5.2 (m, 1H).

(4*S*)- and (4*R*)-Ethyl 4-*tert*-Butoxycarbonylamino-3-hydroxyhexanoate (58a and 58b) Following the procedure described for **50**, compounds **57a** and **57b** were converted to **58a** (8.27 g, 69%) and **58b** (10.0 g, 82%), respectively: ^{1}H-NMR ($CDCl_3$) δ: 0.95 (t, 3H, J = 7 Hz), 1.27 (t, 3H, J = 7 Hz), 1.45 (s, 9H), 1.3—1.8 (m, 2H), 2.44—2.60 (m, 2H), 2.7—3.2 (m, 1H), 3.3—3.7 (m, 1H), 3.9—4.1 (m, 1H), 4.17 (q, 1H, J = 7 Hz), 4.4—4.8 (br, 1H).

(4*S*)- and 4(*R*)-Ethyl 4-*tert*-Butoxycarbonylamino-3-methanesulfonyloxyhexanoate (59a and 59b) Following the procedure described for **51**, compounds **58a** and **58b** were converted to **59a** (9.74 g, 91%) and **59b** (12.8 g, 99%), respectively. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (t, 3H, J = 7 Hz), 1.28 (t, 3H, J = 7 Hz), 1.45 (s, 9H), 1.3—1.8 (m, 2H), 2.6—2.9 (m, 2H), 3.05 (s, 3H), 3.5—3.9 (m, 1H), 4.18 (q, 2H, J = 7 Hz), 4.2—4.8 (m, 1H), 4.96—5.24 (m, 1H).

(4*S*)- and (4*R*)-Ethyl 4-*tert*-Butoxycarbonylamino-2-hexenoate (60a and 60b) Following the procedure described for **52**, compounds **59a** and **59b** were converted to **60a** (7.15 g, quant.) and **60b** (8.94 g, 96%), respectively. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (t, 3H, J = 7 Hz), 1.30 (t, 3H, J = 7 Hz), 1.46 (s, 9H), 1.3—1.0 (m, 2H), 4.0—4.4 (m, 1H), 4.22 (q, 2H, J = 7 Hz), 5.96 (d, 1H, J = 16 Hz), 6.92 (dd, 1H, J = 16, 5 Hz). (*S*)-**60a**: $[\alpha]_D$ −15.1° (c = 0.88, $CHCl_3$). (*R*)-**60b**: $[\alpha]_D$ +16.5° (c = 1.24, $CHCl_3$).

(4*S*)- and (4*R*)-Ethyl 4-*tert*-Butoxycarbonylamino-3-nitromethylhexanoate (61a and 61b) Following the procedure described for **53**, compounds **60a** and **60b** were converted to **61a** (7.70 g, 87%) and **61b** (10.3 g, 93%), respectively. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (t, 3H, J = 7 Hz), 1.26 (t, 3H, J = 7 Hz), 1.44 (s, 9H), 1.2—1.5 (m, 2H), 2.44—2.60 (m, 2H), 2.7—3.0 (m, 1H), 3.5—3.9 (m, 1H), 4.20 (q, 2H, J = 7 Hz), 4.3—4.6 (br s, 1H), 4.54 (d, 2H, J = 6 Hz).

4-(1-(*S*)- and (*R*)-*tert*-Butoxycarbonylaminopropyl)-2-pyrrolidone (62a and 62b) Following the procedure described for **54**, compounds **61a** and **61b** were converted to **62a** (4.30 g, 73%) and **62b** (5.50 g, 70%), respectively. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (t, 3H, J = 7 Hz), 1.28 (t, 3H, J = 7 Hz), 1.45 (s, 9H), 1.3—1.7 (m, 2H), 2.4—2.6 (m, 2H), 2.7—3.0 (m, 1H), 3.45—3.95 (m, 1H), 4.17 (q, 2H, J = 7 Hz), 4.1—4.3 (m, 1H), 4.49 (d, 2H, J = 6 Hz). (1′*S*)-**61a**: mp 165—171 °C. (1′*R*)-**61b**: mp 163—170 °C.

4-(1-(*S*) and (*R*)-Aminopropyl)-1-benzyl-2-pyrrolidone (63a and 63b) Following the procedure described for the preparation of **45a** from **54**, compounds **62a** and **62b** were converted to **63a** (3.21 g, 76%) and **63b** (3.59 g, 68%), respectively. The ^{1}H-NMR spectra of these compounds were identical with that of **23b**. (1′*S*)-**63a**: $[\alpha]_D$ +0.84° (c = 2.61, $CHCl_3$). (1′*R*)-**63b**: $[\alpha]_D$ −0.90° (c = 1.11, $CHCl_3$).

1-Benzyl-3-(1-(*S*)- and (*R*)-*tert*-butoxycarbonylaminopropyl)pyrrolidine (64a and 64b) Following the procedure described for **26a**, compounds **63a** and **63b** were converted to **64a** (2.85 g, 47%) and **64b** (3.20 g, 48%), respectively. The ^{1}H-NMR spectra of these compounds were identical with that of **27b**. (1′*S*)-**64a**: $[\alpha]_D$ −30.4° (c = 1.11, $CHCl_3$). (1′*R*)-**64b**: $[\alpha]_D$ +30.3° (c = 1.28, $CHCl_3$).

3-(1-(*S*)- and (*R*)-*tert*-Butoxycarbonylaminopropyl)pyrrolidine (65a and 65b) Following the procedure described for **28a**, compounds **64a** and **64b** were converted to **65a** (1.65 g, quant.) and **65b** (1.82 g, quant.).

General Method A. *threo*-7-[3-(1-Aminoethyl)-1-pyrrolidinyl]-1-ethyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic Acid (67) A mixture of 1-ethyl-6,7,8-trifluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (**8**) (166 mg, 0.59 mmol), **28a** (160 mg, 0.75 mmol), Et_3N (150 mg, 1.48 mmol) in acetonitrile (10 ml) was refluxed for 3 h, then concentrated under reduced pressure. To the residue was added H_2O. The solid was collected by filtration, washed with EtOH and Et_2O, and dissolved in TFA (5 ml). This solution was stirred for 0.5 h at room temperature and concentrated. Water was added to the residue, and the solution was washed with $CHCl_3$. The aqueous layer was neutralized with aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried and concentrated to give a crude product. Recrystallization of the crude product from EtOH–NH_4OH gave 105 mg (48%) of **67**, mp 212—217 °C; ^{1}H-NMR (NaOD) δ: 1.11 (d, 3H, J = 7 Hz), 1.40 (t, 3H, J = 7 Hz), 1.4—1.7 (m, 1H), 1.9—2.2 (m, 2H), 2.80 (q, 1H, J = 7 Hz), 3.4—3.9 (m, 4H), 4.35 (m, 2H), 7.63 (dd, 1H, J = 16, 2 Hz), 8.23 (s, 1H). *Anal.* Calcd for $C_{18}H_{21}F_2N_3O_3 \cdot 3/4H_2O$: C, 57.06; H, 5.99; N, 11.09. Found: C, 57.38; H, 6.06; N, 11.05. By using this procedure the compounds in Tables I and II were prepared from appropriate pyrrolidines and 7-halogenated quinolones **12—16**.

General Method B. 10-[3-(*R*)-(1-(*S*)-Aminoethyl)-1-pyrrolidinyl]-9-fluoro-3-(*S*)-methyl-2,3-dihydro-7-oxo-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-3-carboxylic Acid (96) A mixture of 300 mg (0.912 mmol) of borate complex **16**, 790 mg (3.69 mmol) of **47a**, 500 mg (4.94 mmol) of Et_3N, and 6 ml of dimethyl sulfoxide (DMSO) was stirred for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was taken up in 1 ml of Et_3N and 50 ml of 90% MeOH, and the mixture was refluxed for 12 h, then evaporated. The residue was extracted with $CHCl_3$, and the extract was washed with aqueous 10% citric acid and H_2O. The organic layer was dried and concentrated under reduced pressure. The residue was taken up in 10 ml of TFA and the solution was stirred for 0.5 h, then evaporated. The residue was dissolved in 1 N NaOH, and the solution was neutralized to pH 7.5 with aqueous HCl, and extracted with $CHCl_3$. The extract was dried and evaporated. The residue was purified by recrystallization from EtOH to obtain 160 mg (47%) of **96**, mp 242—244 °C; ^{1}H-NMR (NaOD) δ: 1.10 (d, 3H, J = 6 Hz), 1.48 (d, 3H, J = 6 Hz), 1.4—1.6 (m, 1H), 1.9—2.1 (m, 2H), 2.7—2.8 (m, 1H), 3.3—3.5 (m, 3H), 3.6—3.7 (m, 1H), 4.2—4.3 (m, 1H), 4.4—4.5 (m, 1H), 4.5—4.6 (m, 1H), 7.46 (d, 1H, J = 14 Hz), 8.35 (s, 1H); $[\alpha]_D$ −150. 4° (c = 0.230, 0.1 N NaOH). *Anal.* Calcd for $C_{19}H_{22}FN_3O_4$: C, 60.79; H, 5.91; N, 11.19. Found: C, 60.50; H, 6.22; N, 11.05. By using this procedure, compounds **90** and **91** were prepared from the borate complexes **14** and **15**, respectively.

Determination of Apparent Partition Coefficients The apparent partition coefficients of the compounds tested in this study were measured according to the method reported previously.[22]

Determination of Aqueous Solubility About 400 μg of the sample (a μg) was dissolved in 0.1 N NaOH (50 ml) and the maximum UV absorption of the solution was measured [A_1]. A suspension of the sample in water (*ca.* 10 ml) was stirred for 0.5 h, and filtered. A 3 ml aliquot of the filtrate was dissolved in 3 ml of 0.2 N NaOH. A portion (1 ml) of the solution was diluted with 0.1 N NaOH to obtain 50 ml of 0.1 N NaOH solution. The maximum UV absorption of the solution was measured [A_2]. The aqueous solubility, S, was calculated from the relation $S = a \times [A_2]/[A_1]$

***In Vitro* Antibacterial Activity** The minimal inhibitory concentration (MIC) of a test compound was determined according to the standard method[20] by a serial two-fold dilution method using Muller–Hinton broth (Difco Laboratories, Detroit, Mich.). The inoculum size was approximately 10^5 cfu/ml. The MIC of a compound was defined as the lowest concentration that prevented visible growth of bacteria after incubation at 37 °C for 18 h.[22]

Pharmacokinetic Studies Plasma and urine levels in rats were determined by microbiological assay. Compounds were administered in solution by oral gavage (five per group). Blood samples were obtained at 0.5, 1, 3, 4, 5, and 6 h after dosing. Urine was collected 0—4, 4—8, 8—24 h after dosing. Plasma levels and urinary excretion of the test compounds were determined by an agar plate system. The test organism was *Bacillus subtilis* ATCC6051.[21]

X-Ray Crystallographic Analysis of 44a[23] A colorless, needle-shaped crystal of $C_{25}H_{31}N_3O_4S$ (M.W. 469.6) having approximate dimensions of 0.2 × 0.2 × 0.3 mm was grown from isopropyl ether. The lattice parameters and intensities were measured on a Philips four-circle X-ray autodiffractometer with monochromated Cu K_α radiation using the θ-2θ scan technique. The compound crystallized in orthorhombic space group $P212121$ with cell dimensions a = 16.1848 Å, b = 16.9019 Å, c = 9.5000 Å, V = 2598.81 Å^3. For Z = 4 and F.W. = 430.55, the calculated density was 1.205 g/cm^3. The structure was solved by the direct method with the program MULTAN 78. The final R value was 0.0598. A perspective view of the molecule is shown in Fig. 1.

Supplementary Material Tables of final atomic positional parameters,

atomic thermal parameters, and bond lengths and angles of compound **44a** are available. Ordering information is given on the masthead page.

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22) Determination of antibacterial activities and pharmacokinetics was performed by the Microbiology and Pathology Group of these Laboratories.
23) The X-ray crystal structure analysis of **42a** was performed by K. Yamazaki of the Drug Metabolism & Analytical Chemistry Research Center of Daiichi Pharmaceutical Co., Ltd.