is repeated in a second and third rat, depending on the activity found in the first rat. Compounds are considered active when blood pressure in one test SHR has been reduced to ≤116 mmHg or when the average of two test SHR has been reduced to ≤122 mmHg.

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Registry No. 1, 110551-96-7; 2, 110551-97-8; 3, 110551-98-9; 4, 110551-99-0; 5, 110552-00-6; 6, 110552-01-7; 7, 110552-02-8; 8, 110552-03-9; 8·HCl, 110552-96-0; 9, 110552-04-0; 10, 110552-05-1; 11, 110552-06-2; 12, 110552-07-3; 13, 110552-08-4; 14, 110552-09-5; 14·HCl, 110552-97-1; 15, 110552-10-8; 16, 110552-11-9; 17, 110552-12-0; 18, 110552-13-1; 19, 110552-14-2; 20, 110552-15-3; 20·HCl, 110552-98-2; 21, 110552-16-4; 22, 110552-17-5; 23, 110552-18-6; 24, 110552-19-7; 25, 110552-20-0; 26, 110552-21-1; 28, 110567-72-1; 29, 110552-23-3; 30, 110552-24-4; 31, 110552-25-5; 32, 110552-26-6; 33, 110552-27-7; 34, 110552-28-8; 34·HCl, 110552-99-3; 35, 110552-29-9; 32·HCl, 110553-00-9; 36, 110552-30-2; 37, 110552-31-3; 38, 110552-32-4; 38·2HCl, 110553-01-0; 39, 110552-33-5; 39·2HCl, 110553-02-1; 40, 110552-34-6; 40·2HCl, 110553-03-2; 41, 110552-35-7; 41·2HCl, 110553-04-3; 42, 110552-36-8; 42·2HCl, 110553-054; 43, 110552-37-9; 43·2HCl, 110553-06-5; 44, 110552-38-0; 45, 110552-39-1; 45·2HCl, 110553-07-6; 46, 110552-40-4; 47, 110552-41-5; 48, 110552-42-6; 49, 110552-43-7; 50, 110552-44-8; 50·2HCl, 110553-08-7; 51, 110552-45-9; 51·2HCl, 110553-09-8; 52, 110552-46-0; 52·2HCl, 110553-10-1; 53, 110552-47-1; 54, 110552-48-2; 55, 110552-49-3; 55·HCl, 110553-11-2; 56, 110552-50-6; 56·HCl, 110553-12-3; 57, 110552-51-7; 58, 110552-52-8; 59, 110552-53-9; 60, 110552-54-0; 61, 110552-55-1; 61·HCl, 110553-13-4; 62, 110552-56-2; 62·HCl, 110553-14-5; 63, 110552-57-3; 64, 110552-58-4; 64·HCl, 110553-15-6; 65, 110552-59-5; 65·HCl, 110553-16-7; 66, 110552-60-8; 67, 110552-61-9; 67·HCl, 110567-73-2; 68, 110552-62-0; 68·HCl, 110553-17-8; 69, 90259-60-2; 70, 90260-14-3; 71, 110552-63-1; 72, 110552-64-2; 73, 110552-65-3; 74, 110552-66-4; 75, 110552-67-5; 76, 90259-73-7; 77, 110552-68-6; 78, 110552-69-7; 78·2HCl, 110553-18-9; 79, 110552-70-0; 79·2HCl, 110553-19-0; 80, 110552-71-1; 81, 110552-72-2; 81·2HCl, 110553-20-3; 82, 110552-73-3; 83, 110552-74-4; 85, 110552-76-6; 86, 110552-77-7; 87, 110552-78-8; 88, 110552-79-9; $ClCO_2CH_2CH_3$, 541-41-3; $CH(OC_2H_5)_3$, 122-51-0; $CCH_3(OC_2H_5)_3$, 78-39-7; $CC_2H_5(OC_2H_5)_3$, 115-80-0; 2-$H_2NC_6H_4CONH(CH_2)_5$Imid, 110552-80-2; 2-$H_2NC_6H_4CONH(CH_2)_6$Imid, 110552-81-3; 2-$H_2NC_6H_4CONH(CH_2)_2CH(CH_3)$Imid, 110552-82-4; 2-$H_2N$-5-$ClC_6H_3CONH(CH_2)_{10}$Imid, 110552-83-5; 2-$H_2N$-4-$ClC_6H_3CONH(CH_2)_3$Imid, 110552-84-6; 2-$H_2N$-4-$ClC_6H_3CONH(CH_2)_6$Imid, 110552-85-7; 2-$H_2N$-3-$ClC_6H_3CONH(CH_2)_4$Imid, 110552-86-8; 2-$H_2N$-3-$ClC_6H_3CONH(CH_2)_6$Imid, 110552-87-9; 2-$H_2N$-3-$ClC_6H_3CONHCH_2CH(CH_3)CH_2$Imid, 110552-88-0; 2-$H_2N$-3-$ClC_6H_3CONH(CH_2)_2CH(CH_3)$Imid, 110552-89-1; 2-$H_2N$-5-$BrC_6H_3CONH(CH_2)_3$Imid, 110552-90-4; 2-$H_2N$-5-$BrC_6H_3CONH(CH_2)_4$Imid, 110637-22-4; 2-$H_2N$-5-$CH_3C_6H_3CONH(CH_2)_3$Imid, 110552-91-5; 2-$H_2N$-3-$CF_3C_6H_3CONH(CH_2)_4$Imid, 110552-92-6; 2-$H_2N$-3-$CF_3C_6H_3CONH(CH_2)_5$Imid, 110552-93-7; 2-$H_2N$-3-$CF_3C_6H_3CONH(CH_2)_6$Imid, 110552-94-8; 2-$H_2N$-3-$CF_3C_6H_3CONHCH_2CH(CH_3)CH_2$Imid, 110552-95-9; $H_2N(CH_2)_3$Imid, 5036-48-6; $H_2N(CH_2)_4$Imid, 67319-76-0; $H_2NCH_2CH(CH_3)CH_2$Imid, 93668-15-6; $H_2N(CH_2)_5$Imid, 78415-62-0; $H_2N(CH_2)_6$Imid, 78415-63-1; $H_2N(CH_2)_7$Imid, 68887-60-5; $H_2N(CH_2)_8$Imid, 78415-64-2; $H_2N(CH_2)_2CH(CH_3)$Imid, 93668-14-5; 2-H_2N-5-Cl-$C_6H_3CO_2H$, 635-21-2; 2-H_2N-5-Br-$C_6H_3CO_2H$, 5794-88-7; 2-H_2N-5-Cl-$C_6H_3CONH(CH_2)_4$Imid, 78-39-7; 2-H_2N-5-$ClC_6H_3CONH(CH_2)_4$Imid, 115-80-0; 2-H_2N-5-$BrC_6H_3CONHCH_2CH(CH_3)CH_2$Imid, 110613-11-1; isotoic anhydride, 118-48-9; 8-chloroisatoic anhydride, 63497-60-9; 7-chloroisatoic anhydride, 40928-13-0; 6-chloroisatoic anhydride, 4743-17-3; 6-bromoisatoic anhydride, 4692-98-2; 6-methylisatoic anhydride, 4692-99-3; thromboxane synthetase, 61276-89-9.

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 (Ofloxacin)†

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A short and efficient synthesis, starting with (*R*)- and (*S*)-alaninol, of the two optical antipodes of the quinolone antimicrobial agent ofloxacin has been devised. Testing in vitro of the products against a range of bacteria and in an assay system incorporating purified DNA gyrase from different bacterial species demonstrates that the *S*-(−) enantiomer is substantially the more active.

Recently there has been great interest in preparing and testing the enantiomers of drugs that exert their pharmacological action via specific receptors or enzymes. In favorable cases this has been shown to result in enhanced selectivity, greater potency, and fewer side effects.[1]

Among the quinolone antimicrobial agents, relatively few fused tricyclic analogues have been found to possess outstanding antibacterial activity.[2] Some of the more prominent exceptions are flumequine (**1**),[3] methylflumequine (S-25930) (**2**),[3] and ofloxacin (**3**)[4-6] (Chart I). Recently their optically active enantiomers have been separated and isolated through high-performance column chromatogra-

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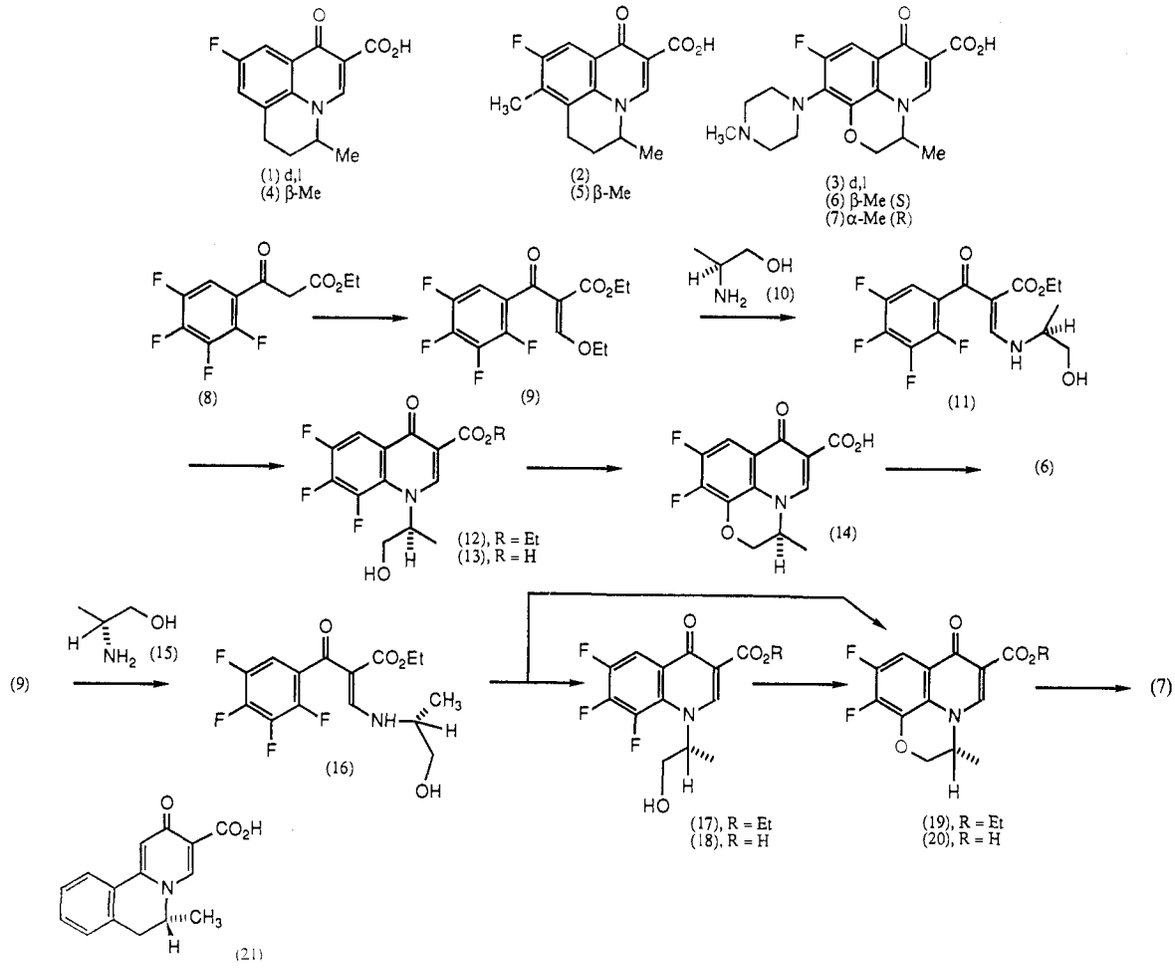
Chart I



phy of their appropriate esters.[3,7] It has been shown that, in the cases of flumequine (**1**) and methylflumequine (**2**), the *S* enantiomers **4** and **5** are more active than the *R* antipodes and the racemates, suggesting that the methyl group at C-3 should be above the plane of the molecule, when drawn in the customary way, for optimal antibacterial activity. (−)-Ofloxacin is about 8–128 times more active than (+)-ofloxacin and twice as active as the racemate against both Gram-negative and Gram-positive bacteria.[7] The published route adopted for the preparation of the enantiomers of ofloxacin is rather lengthy, and the absolute configuration of the products cannot be determined from the method of preparation. After our work on developing a chiral synthesis was completed, a similar synthesis was reported which, though involving achiral reactants, was recognized as being suitable in principle for preparation of the desired antipodes.[8] Consequently, we report herein our findings which embody the realization of this objective and which allow the unequivocal assignment of absolute configuration to the more active antipode.

Starting with readily available (*S*)-(+)-2-amino-1-propanol (**10**) and (*R*)-(−)-2-amino-1-propanol (**15**), the synthesis led efficiently to (*S*)-(−)-ofloxacin (**6**) and (*R*)-(+)-ofloxacin (**7**), respectively, and subsequent biotesting demonstrated that the *S* antipode was the more active both in bacteria and in cell-free enzyme assays.

Chemistry. Condensation of ethyl (2,3,4,5-tetrafluorobenzoyl)acetate (**8**) with triethyl orthoformate by refluxing in acetic anhydride produced ethyl 2-(ethoxymethylene)-3-oxo-3-(2,3,4,5-tetrafluorophenyl)propionate (**9**). Unstable intermediate **9** was reacted in situ with (*S*)-(+)-2-amino-1-propanol (**10**) (Aldrich Chemical Co.) in an addition–elimination sequence to afford (+)-ethyl 2-[[[(*S*)-1-hydroxyprop-2-yl]amino]methylene]-3-oxo-3-(2,3,4,5-tetrafluorophenyl)propionate (**11**) in 57% yield. On cyclization with sodium hydride in dimethyl sulfoxide at room temperature, compound **11** afforded ethyl 1,4-dihydro-1-[1(*S*)-(hydroxymethyl)ethyl]-4-oxo-6,7,8-trifluoroquinoline-3-carboxylate (**12**) in 59% yield. Ester **12**, on heating with aqueous potassium hydroxide in tetrahydrofuran, afforded (−)-9,10-difluoro-3(*S*)-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid (**14**) in 70% yield, through intermediate carboxylic acid **13**. On condensation with *N*-methylpiperazine by heating in pyridine, this acid yielded (−)-9-fluoro-3(*S*)-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid (**6**) [(−)-(*S*)-ofloxacin]. The absolute configuration of (−)-(*S*)-ofloxacin is rendered certain by this preparation sequence from (*S*)-alaninol.[9]

Repetition of this reaction sequence with (*R*)-(−)-2-amino-1-propanol (**15**) (prepared from (*R*)-alanine by reduction of its ethyl ester,[10] by lithium aluminum hydride reduction in ether[11]) afforded (+)-9-fluoro-3(*R*)-methyl-

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Table I. Antimicrobial Activities

		microorganism: MIC,[a] μg/mL														
no.	Sa(A)	Sa	Se	Ml	Sb	Sa(C)	Sp(E)	Sf	Sp	Ec(A)	Ec	Ea	Kp	Pa(A)	Pa	A
3	0.2	0.39	0.39	3.1	1.56	1.56	0.78	0.78	0.39	0.05	0.1	0.2	0.05	0.39	0.1	0.39
6	0.15	0.30	0.30	1.21	1.21	1.21	0.46	0.46	0.26	0.07	0.04	0.07	<0.04	<0.04	0.07	0.30
7	4.8	9.75	4.8	>9.75	>9.75	>9.75	>9.75	>9.75	>9.75	1.21	9.75	9.75	1.21	9.75	1.21	9.75

[a] The MIC values were determined by the usual 2-fold agar dilution method using brain–heart infusion agar.[12] The microorganisms chosen for inclusion in the tabel are the following: Sa(A) = *Staphylococcus aureus* ATCC 6538 P; Sa = *Staphylococcus aureus* 45; Se = *Staphylococcus epidermis* 3519; Ml = *Micrococcus luteus* 9341; Sb = *Streptococcus bovis* A 5169; Sa(C) = *Streptococcus agalactiae* CMX 508; Sp(E) = *Streptococcus pyogenes* EES 61; Sf = *Streptococcus facecium* ATCC 8043; Sp = *Streptococcus pyogenes* 2548; Ec(A) = *Escherichia coli* JUHL; Ec = *Escherichia coli* H560; Ea = *Enterobacter aerogenes* ATCC 13048; Kp = *Klebsiella pneumoniae* 8045; Pa(A) = *Pseudomonas aeruginosa* K 799/WT; Pa = *Pseudomonas aeruginosa* K 799/61; A = *Acinetobacter* sp. CMX 669.

Table II. Inhibition Constants (K_i)[a] against DNA Gyrase Isolated from *M. luteus* and from *E. coli*

compd	K_i, μg/mL, from given source of DNA gyrase	
	M. luteus	*E. coli*
3	84	1.6
6	36	0.9
7	105	27
norfloxacin (control)	72	1.0

[a] K_i values were calculated from a Dixon plot of reciprocal velocity vs. inhibitor concentration.[13]

10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7*H*-pyrido-[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic acid (**7**) [(+)-(*R*)-ofloxacin] through **16**, **17**, **18**, **20**, and a minor cyclized intermediate **19**. The isolation of **19** suggests that the cyclization of the dihydrobenzoxazine ring takes place in part during heating of the sodium hydride–dimethyl sulfoxide reaction, which majorly leads to **17**.

Biological Evaluation. In previously published work,[7] (−)-ofloxacin has been reported to be more potent in vitro than (+)-ofloxacin by 8–128-fold, depending upon the species of microorganism used. Our findings (Table I) lead to a closely similar range of activity (8–125-fold). With a complete bioassay system utilizing DNA gyrase purified from *Escherichia coli*, the enantiopreference was 30-fold (Table II) whereas against *E. coli* JUHL the ratio was only 3-fold while against the H560 strain the ratio was 125-fold. Clearly it is always dangerous to generalize from a small sample set, but these findings suggest that chiral preference of the enzyme can either be exaggerated or diminished by cellular penetration factors. Enantiopreference by the *Micrococcus luteus* enzyme system is 3-fold while the preference in the intact microorganism is 8-fold.

On balance, the benefits to a patient that might be achieved by administration of the more active enantiomer as opposed to use of the racemate of ofloxacin must be judged by balancing the economic factors and the enantioperferences, if any, of biopharmaceutical parameters and the various side effects. These factors remain to be established. Nonetheless, it is interesting from a molecular biological standpoint to see that the same enantiopreference is seen in the ofloxacin and flumequine series. On the other hand, the opposite absolute stereochemistry has been reported for the more active enantiomer in the different ring system represented by 6(*R*)-methyl-6,7-dihydro-2-oxo-2*H*-benzo[*a*]quinolizine-3-carboxylic acid (Ro 15-0650) (**21**).[14]

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Dr. Tho Nguyen at Kansas University and are in the range of ±0.4% of the theoretical values. Optical rotations were measured at 589 nm by using a Perkin-Elmer Model 241 polarimeter using chloroform solvent unless otherwise stated. The IR spectra were determined by using a Perkin-Elmer IR-710B instrument. ^{1}H NMR spectra were obtained with a Varian FT-80A spectrometer with TMS as the internal standard and $CDCl_3$ as solvent. Electron-impact mass spectra (EIMS) and chemical-ionization mass spectra (CIMS) were determined with a Ribermag R10-10 mass speectrometer, and high-resolution mass spectra (HRMS) were determined with a ZAB VG mass spectrometer. Identical IR, NMR, and MS were obtained for the chiral analogue pairs. For pH determinations, pH strips (0–14) colorpHast, from Aldrich Chemical Co., Inc., Milwaukee, WI, were used. Silica gel 60F-254 precoated thin-layer chromatography plates (0.25 mm) for analytical purposes were purchased from E. M. Reagents, E. Merck, Cincinnati, OH. The solvent systems used were as follows: A, CH_2Cl_2–EtOAc, 3:2; B, CH_2Cl_2–EtOAc, 2:3; C, EtOAc; D, EtOAc–MeOH–HOAc, 4.5:0.4:0.1; and E, EtOAc–MeOH, 8.5:1.5.

(+)-Ethyl 2-[[[(*S*)-1-Hydroxyprop-2-yl]amino]-methylene]-3-oxo-3-(2,3,4,5-tetrafluorophenyl)propionate (**11**). A solution of ethyl (2,3,4,5-tetrafluorobenzoyl)acetate (**8**) (400 mg, 1.51 mmol) in acetic anhydride (0.9 mL) and triethyl orthoformate (0.5 mL, 444 mg, 3 mmol) was heated at 110 °C for 2 h. The reaction mixture was evaporated under high vacuum to leave an oily residue, which was diluted with toluene (2 mL) and concentrated. This process was repeated two more times to afford ethyl 2-(ethoxymethylene)-3-oxo-3-(2,3,4,5-tetrafluorophenyl)propionate (**9**) as an oil. To a stirred solution of **9** (without purification) in dry methylene chloride (5 mL) was added (*S*)-(+)-2-amino-1-propanol (**10**) (0.19 mL, 180 mg, 2.4 mmol) in CH_2Cl_2, and the reaction mixture was stirred at room temperature for 30 min (until TLC showed the absence of **8** in the reaction mixture; solvent system A). The reaction mixture was concentrated under reduced pressure to leave an oily residue, which was purified by preparative layer chromatography (silica gel, solvent system A) to afford an oil, **11**: 300 mg, 57%; $[\alpha]^{25}_D$ 25.3° (*c* 0.15); IR (Nujol) 3450 (OH and NH), 1670 (C=O), and 1620 (Ar) cm^{-1}; ^{1}H NMR δ 0.85 (t, 3 H, CH_2CH_3), 2.30 (br s, 1 H, O*H*), 3.35 (m, 4 H, CH_2OH and CH_2CH_3), 3.70 (m, 1 H, $CHCH_3$), 8.05 (dd, 1 H, J = 14 and 3 Hz, C_5-*H*), and 8.15 (s, 1 H, C_2-*H*); EIMS, m/z 349 (M^+), 318 ($M^+ - CH_2OH$), 272 ($M^+ - CH_2OH - OC_2H_5$), 177 ($C_6HF_4C{=}O$, base peak); HRMS calcd for $C_{15}H_{15}F_4NO_4$ m/z 349.09361, found 349.09409 (M^+).

(−)-Ethyl 1,4-Dihydro-1-[1(*S*)-(hydroxymethyl)ethyl]-4-oxo-6,7,8-trifluoroquinoline-3-carboxylate (**12**). To a stirred solution of **11** (190 mg, 0.544 mmol) in dry DMSO (3 mL) was added, in portions, NaH (50% mineral oil suspension, 24.5 mg, 1.02 mmol), and the reaction mixture was stirred at room temperature for 3 h (until TLC showed the absence of **11** in the reaction mixture; solvent system B). The reaction mixture was diluted with an excess of H_2O (20 mL) and was extracted from

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CH_2Cl_2 (4 × 10 mL). The combined CH_2Cl_2 layer was washed with H_2O (2 × 5 mL), dried (Na_2SO_4), and concentrated to leave a residue, which was again washed with H_2O (0.5 mL), and the resulting solid was crystallized from a mixture of CH_2Cl_2–ether to afford **12**: 105 mg; 59%; mp 170–175 °C; $[\alpha]^{25}_D$ −28° (*c* 0.2); IR (Nujol) 3450 (OH), 1700 (C=O), and 1620 (Ar) cm^{-1}; ^1H NMR δ 1.35 (t, 3 H, CH_2CH_3), 1.55 (s, 1 H, O*H*, exchangeable with D_2O), 4.15–4.65 (m, 4 H, CH_2OH and CH_2CH_3), 5.25 (m, 1 H, C*H*Me), 7.40 (dd, 1 H, *J* = 14 and 3 Hz, C_5-*H*), and 8.65 (s, 1 H, C_2-*H*); EIMS, *m/z* 329 (M^+), 298 ($M^+ - CH_2OH$). Anal. Calcd for $C_{15}H_{14}F_3NO_4 \cdot {}^1/_2H_2O$: C, 53.25; H, 3.47; N, 4.14. Found: C, 53.92; H, 3.34; N, 4.28.

(−)-9,10-Difluoro-3(*S*)-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic Acid (14). To a stirred solution of **12** (75 mg, 0.227 mmol) in THF (12 mL) was added a 10% aqueous solution of KOH (2 mL), and the reaction mixture was heated at 65–70 °C for 2 h (until TLC showed the absence of **12** in the reaction mixture; solvent system C and D). The reaction mixture was concentrated under reduced pressure to remove THF, and the resulting aqueous basic layer was acidified to pH 4–5 by the addition of dilute HOAc to afford a white precipitate, which was filtered and washed with H_2O and then with ether to afford **14** as a pure solid (45 mg, 70%): mp >280 °C dec; $[\alpha]^{25}_D$ −66.5° (*c* 0.1); IR (Nujol) 1700 (C=O) and 1610 (Ar) cm^{-1}; EIMS, *m/z* 281 (M^+), 253 ($M^+ - CO$), 237 ($M^+ - CO_2$); CIMS-CH_4, *m/z* 282 ($M^+ + 1$). Anal. C, H, N.

(−)-9-Fluoro-3(*S*)-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic Acid (6). To a stirred solution of **14** (94 mg, 0.33 mmol in pyridine (0.5 mL)) was added dropwise *N*-methylpiperazine (0.098 mL, 0.33 mmol), and the reaction mixture was heated to reflux at 120 °C for 12 h. The reaction mixture was concentrated under high vacuum to leave a residue, which was taken up in toluene (0.5 mL) and concentrated. This process was repeated three more times to afford solid **6** [(*S*)-(−)-ofloxacin] (100 mg, 83%): mp 188 °C; $[\alpha]^{25}_D$ −85° (*c* 0.2); IR (Nujol) 3400 (OH), 1750 (C=O), 1660 (C=O), and 1590 (Ar) cm^{-1}; ^1H NMR δ 8.00 (s, 1 H, C_4-*H*), 7.65 (d, 1 H, *J* = 9 Hz, C_8-*H*), 4.50 (m, 1 H, C*H*Me), 4.35 (br s, 2 H, OCH_2), 3.30 (m, 8 H, 4 × NCH_2), 2.50 (m, 8 H, 4 × NCH_2), 2.35 (s, 3 H, NMe), and 1.60 (d, 3 H, $CHCH_3$); EIMS, *m/z* 361 (M^+); CIMS-CH_4, *m/z* 362 ($M^+ + 1$); HRMS calcd for $C_{18}H_{20}F_3O_4$ *m/z* 361.14365, found 361.14525.

(*R*)-(−)-2-Amino-1-propanol (15). Synthon **15** ($[\alpha]^{25}_D$ −23° (*c* 2.0, absolute EtOH)) was prepared in 61% yield from (*R*)-alanine (Aldrich) by LAH reduction of its ethyl ester as reported[9,10] for the preparation of (*S*)-(+)-2-amino-1-propanol (**10**) from (*S*)-alanine.

(−)-Ethyl 2-[[[(*R*)-1-Hydroxyprop-2-yl]amino]-methylene]-3-oxo-3-(2,3,4,5-tetrafluorophenyl)propionate (16). Compound **16** was prepared in 53% yield, as an oil, as described for the preparation of **11**, except for the use of (*R*)-alaninol (**15**) as a reactant: $[\alpha]^{25}_D$ −25° (*c* 0.35); HRMS calcd for $C_{15}H_{15}F_4NO_4$ *m/z* 349.09361, found 349.09375 (M^+).

(+)-Ethyl 1,4-Dihydro-1-[1(*R*)-(hydroxymethyl)ethyl]-4-oxo-6,7,8-trifluoroquinoline-3-carboxylate (17) and (+)-Ethyl 9,10-Difluoro-3(*R*)-methyl-7-oxo-2,3-dihydro-7*H*-pyrido-[1,2,3-*de*]-1,4-benzoxazine-6-carboxylate (19). Compound **17** was prepared from **16** by following the procedure given above for the conversion of **11** to **12**. The reaction product, on purification by preparative layer chromatography over silica gel (solvent system E) and on crystallization from a mixture of CH_2Cl_2–ether, afforded **17** as the major product (42%): mp 170–175 °C; $[\alpha]^{25}_D$ 29° (*c* 0.25); EIMS, *m/z* 329. Anal. C, H, N.

The minor product **19** was isolated in 12% yield: mp 252 °C; $[\alpha]^{25}_D$ 66° (*c* 0.15); IR (Nujol) 1740 (C=O) and 1620 (Ar) cm^{-1}; ^1H NMR δ 1.35 (m, 3 H, CH_2CH_3), 1.60 (d, 3 H, $CHCH_3$), 4.35 (m, 1 H, C*H*Me), 4.40 (m, 4 H, CH_2O, CH_2CH_3), 7.80 (dd, 1 H, *J* = 14 and 3 Hz, C_8-*H*), and 8.35 (s, 1 H, C_4-*H*); EIMS, *m/z* 309 (M^+), 264 ($M^+ - OC_2H_5$), 237 ($M^+ - CO_2C_2H_5$, base peak); CIMS-CH_4, *m/z* 310 ($M^+ + 1$). Anal. C, H, N.

(+)-9,10-Difluoro-3(*R*)-methyl-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic Acid (20). From 17. Following the procedure described for the conversion of **12** to **14**, we prepared **20** in 63% yield: mp >280 °C dec; $[\alpha]^{25}_D$ 65° (*c* 0.2); EIMS, *m/z* 281 (M^+); CIMS-CH_4, *m/z* 282 ($M^+ + 1$). Anal. C, H, N.

From 19. Acid **20** was prepared in 55% yield from **19** by following the procedure described for the conversion of **12** to **14**. The product was identical in all respects with an authentic sample.

(+)-9-Fluoro-3(*R*)-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-2,3-dihydro-7*H*-pyrido[1,2,3-*de*]-1,4-benzoxazine-6-carboxylic Acid (7). Enantiomer **7** [(*R*)-(+)-ofloxacin] was prepared in 64% yield from **20** by using the procedure described for the conversion of **14** to **6** [(*S*)-(−)-ofloxacin]: mp 185 °C; $[\alpha]^{25}_D$ 84° (*c* 0.15); IR (Nujol) superimposable with that of **6**; EIMS, *m/z* 361 (M^+); CIMS-CH_4, *m/z* 362 ($M^+ + 1$); HRMS calcd for $C_{18}H_{20}FN_3O_4$ *m/e* 361.14365, found 361.14276.

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