A Practical Synthesis of (*S*)-(−)-Nadifloxacin: Novel Acid-Catalyzed Racemization of Tetrahydroquinaldine Derivative

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(*S*)-(−)-Nadifloxacin [(*S*)-(−)-9-fluoro-6,7-dihydro-8-(4-hydroxy-1-piperidyl)-5-methyl-1-oxo-1*H*,5*H*-benzo[*i*,*j*]quinolizine-2-carboxylic acid, (*S*)-(−)-OPC-7251], an antibacterial agent, was synthesized from (*S*)-(−)-5,6-difluoro-2-methyl-1,2,3,4-tetrahydroquinoline (DFTQ), which was prepared by the optical resolution of racemic DFTQ with 2,3-di-*O*-benzoyl-L-tartaric acid. Racemization of the undesired enantiomer [(*R*)-(+)-DFTQ] was studied in the presence of various acids and the best result was obtained in the case of methanesulfonic acid. The absolute configuration of (−)-nadifloxacin was determined as *S* by X-ray crystallographic analysis.

Key words (*S*)-(−)-nadifloxacin; antibacterial agent; optical resolution; acidic racemization; tetrahydroquinaldine

Nadifloxacin (**1**) shows potent activity against *Propionibacterium acnes* and has been commercialized as a liniment for acne.[1,2] Recently, Morita *et al.* achieved an asymmetric synthesis of **1** and they reported that the antibacterial activity of (−)-**1** was 60 to 250 times more potent than that of the (+)-isomer.[3] For further biological examination we needed to prepare large quantities of (−)-**1**, but their method using enantio-selective reduction of an acetylenic ketone seemed unsuitable for large-scale manufacturing due to difficulties in the handling of certain reagents. An alternative approach would be the optical resolution of a racemate, but since the yield can not exceed 50%, it is crucial to find a method to recycle the undesired enantiomer. We wish to describe here a practical synthesis of (*S*)-(−)-**1** by means of resolution and novel racemization of tetrahydroquinaldine derivatives (**2**) as a key reaction.

Results and Discussion

Preparation of 5,6-Difluoro-2-methyl-1,2,3,4-tetrahydroquinoline (2a) and 5-Bromo-6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (2b) The starting material 2-bromo-4,5-difluoroacetylaniline (**3**) was reacted with crotonaldehyde to obtain 8-bromo-5,6-difluoroquinaldine (**4**),[4] which was catalytically hydrogenated over palladium on carbon (Pd–C) to cleave the C–Br bond. The catalyst was changed to platinum on carbon (Pt–C), and ring hydrogenation was conducted to give **2a** in approximately 65% overall yield from **3**. The bromo analog **2b** was prepared from *p*-fluoroaniline according to the reported method.[1]

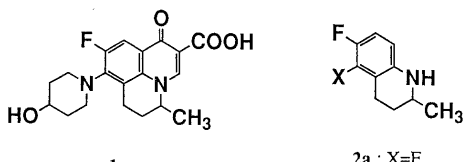

Chart 1

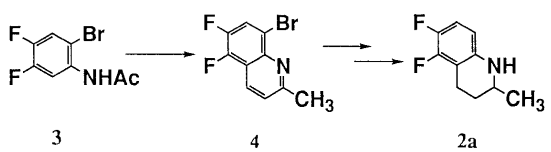

Chart 2

Optical Resolution of 2a and 2b The resolution of **2a** or **2b** was easily done by treating **2a** or **2b** with 2,3-di-*O*-benzoyl-L-tartaric acid (L-DBTA)[5] in ethyl acetate or 70% (v/v) aqueous MeOH, respectively, when (−)-**2a** or (−)-**2b** predominantly precipitated as the less soluble salt. After recrystallization from aqueous MeOH, the pure salt (*ca.* 100% de) was obtained in 35% [(−)-**2a**·L-DBTA salt] or 37% [(−)-**2b**·L-DBTA salt] yield, respectively. In the case of **2b**, the resolution was also accomplished with D-camphor-10-sulfonic acid (D-CSA),[5] and the desired diastereoisomeric salt of (−)-**2b** (99% de) was separated in 35% yield.

Based on the X-ray crystallographic analysis of (−)-**2b**·D-CSA salt, the absolute configuration at the 2 position of (−)-**2b** was determined as *S*. A perspective molecular view of (−)-**2b**·D-CSA salt is shown in Fig. 1.

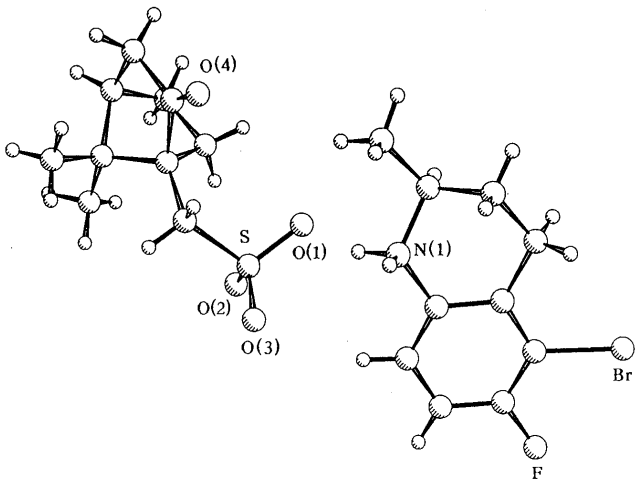

Fig. 1. A Perspective Molecular View of (*S*)-(−)-**2b**·D-CSA Salt

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Table 1. Degree of Racemization of (*R*)-(+)-**2a** after Heating with Various Acids[a]

Acid	Racemization (%)[b]	
	At 130 °C	At 160 °C
p-$CH_3C_6H_4SO_3H \cdot H_2O$	31	89
AcOH[c]	*ca.* 0	—
$BF_3 \cdot Et_2O$[d]	18	—
H_2SO_4	55	99
CF_3COOH	49	—
L-CSA $\cdot H_2O$	56	—
CF_3SO_3H	47	—
CH_3SO_3H	75	97

a) General procedure; A mixture of (*R*)-(+)-**2a** (55% ee) and 5% of the indicated acid was stirred at the indicated temperature for 2 h. After usual work-up, quantitatively recovered amine was directly subjected to HPLC measurement of enantiomer excess. *b*) Racemization (%) was calculated as follows: [initial optical purity (% ee) − final optical purity (% ee)] ÷ initial optical purity (% ee) × 100. *c*) The amine was refluxed in AcOH. *d*) Toluene was used as the solvent.

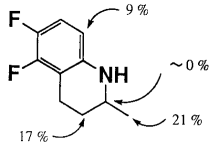

Chart 3. Extent of Deuteration after Heating **2a** with D_2SO_4

Racemization of Optically Active 2a and 2b From the industrial point of view, the recovered antipodal amines (*R*)-(+)-**2a** and (*R*)-(+)-**2b** (40—70% ee) can readily be racemized for re-resolution. It is known that optically active amines may racemize under basic conditions[6,7] and it was also reported that the racemization proceeds under the condition of dehydrogenation–hydrogenation equilibrium induced by some kinds of catalyst.[8] Based on these results, we sought the optimum conditions to racemize the amines **2a** and **2b**. The amine (*R*)-(+)-**2a** never racemized on heating, irrespective of the presence of base, whereas (*R*)-(+)-**2b** racemized completely after heating at 160 °C for 37 h. On heating with Pt–C, (*R*)-(+)-**2a** probably equilibrated with the dihydroquinoline, and a limited racemization (racemization degree: 69%) was actually observed, but about 30% of fully dehydrogenated quinoline derivative was also formed as a by-product.

In contrast, we found that in the presence of various acids the racemization of (*R*)-(+)-**2a** proceeded smoothly, as shown in Table 1. The racemization tended to be accelerated by a stronger acid or at a higher temperature, and its extent increased with a longer reaction time. After further optimization, the best result was obtained by heating with 0.2 eq of methanesulfonic acid at 120 °C for 7 h; thus, the racemization of (*R*)-(+)-**2a** was complete, affording racemic **2a** in 99% yield. Similarly, the racemization of (*R*)-(+)-**2b** was also complete upon heating with 0.2 eq of methanesulfonic acid at 160 °C for 3 h.

Since the acidic racemization of simple amines has not often been reported, we tried deuterium exchange examination of optically active **2a** under heating in the presence of D_2SO_4. ^{1}H-NMR analysis showed that the racemized **2a** isolated in this experiment was partially deuterated at the 3, 8 and methyl positions (Chart 3). The

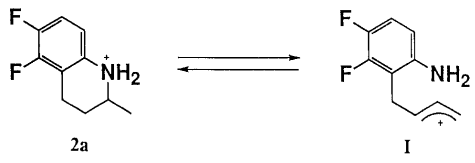

Chart 4

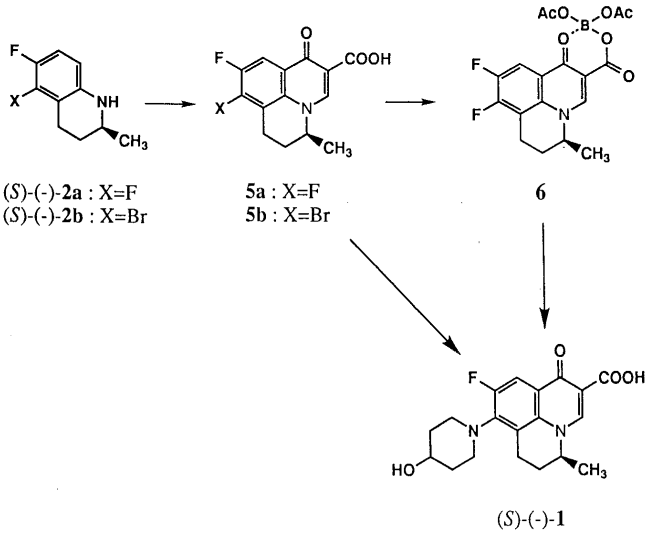

Chart 5

results strongly suggest that the racemization proceeds through the equilibrium between protonated **2a** and the cation I (Chart 4).

Derivatization of (*S*)-(−)-2a and (*S*)-(−)-2b to (*S*)-(−)-1 The obtained (*S*)-(−)-**2a** was reacted with diethyl ethoxymethylenemalonate (EMME), followed by heating with polyphosphoric acid at 130 °C for 1 h to give the acid compound (**5a**). Chelation of **5a** with boron triacetate followed by reaction with 4-hydroxypiperidine gave (*S*)-(−)-**1** in 60% yield from the (*S*)-(−)-**2a**·L-DBTA salt.[9] Similarly, (*S*)-(−)-**2b** also derived to the corresponding acid (**5b**), which was directly reacted with 4-hydroxypiperidine in hexamethylphosphoramide (HMPA) to afford (*S*)-(−)-**1** in 36% yield from the (*S*)-(−) **2b**·D-CSA salt. The product (*S*)-(−)-**1** obtained by both methods showed 100% ee, so no racemization occurred during the later process.

In conclusion, we have established a practical synthetic method for (*S*)-(−)-nadifloxacin **1** by applying a novel acidic racemization reaction to **2a** and **2b** as a key reaction. The present method is more suitable than the former method[3] for large-scale production of (*S*)-(−)-**1**.

Experimental

Optical rotations were measured at the Na D-line with a JASCO DIP-360 or Union Giken PM-101 polarimeter. Melting points were determined with a Yamato MP-21 melting point apparatus in an unsealed capillary tube without correction. Elemental analyses were performed with a Yanagimoto MT-5. ^{1}H-NMR spectra were measured with a Varian XL-200 spectrometer in $CDCl_3$ or DMSO-d_6 solution containing tetramethylsilane as an internal standard. HPLC was run with a Shimadzu LC-6A liquid chromatograph, equipped with Shimadzu SPD-6A and Shimadzu CR-6A units.

8-Bromo-5,6-difluoro-2-methylquinoline (4) A mixture of **3** (2.50 g, 0.010 mol), sodium *m*-nitrobenzenesulfonate (2.25 g, 0.010 mol), iron(III) sulfate heptahydrate (0.28 g, 0.1 mol), boric acid (2.72 g, 0.044 mol),

water (8.8 ml), and concentrated HCl (8.8 ml) was stirred for 0.5 h under reflux. Crotonaldehyde (1.23 ml, 0.015 mol) was added dropwise to the mixture at the same temperature and stirring was continued for 1 h under reflux. The insoluble matter was filtered off with the aid of Celite and the filtrate was poured into MeOH (35.5 ml). The solution was neutralized with 25% (w/v) aqueous NaOH, and cooled below 5 °C. The resultant precipitates were collected by filtration and washed with 50% (v/v) aqueous MeOH to give **4** (1.74 g, 67%). An analytical sample was obtained by recrystallization from hexane. mp 103 °C. *Anal.* Calcd for $C_{10}H_6BrF_2N$: C, 46.54; H, 2.34; N, 5.43. Found: C, 46.70; H, 2.37; N, 5.56. ^{1}H-NMR ($CDCl_3$) δ: 2.82 (3H, s, C2-CH_3), 7.42 (1H, d, J=8.7 Hz), 7.90 (1H, dd, J=9.8, 7.8 Hz), 8.31 (1H, d, J=8.7 Hz, C3-H).

(±)-5,6-Difluoro-2-methyl-1,2,3,4-tetrahydroquinoline (2a) A mixture of **4** (98.1 g, 0.380 mol), 5% Pd–C (50% wet) (1.96 g), and sodium acetate (31.2 g, 0.380 mol) in 90% (v/v) aqueous AcOH (589 ml) was hydrogenated at 50 °C under a hydrogen pressure of 1—5 atm. After the hydrogen absorption had ceased, the catalyst was filtered off and then 5% Pt–C (4.9 g) was added to the filtrate. The mixture was subjected to hydrogenation again at 50 °C under 1—5 atm of hydrogen. The catalyst was filtered off and the solvent was evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (200 ml) and washed successively with 5% (w/v) aqueous NaOH (200 ml) and brine. The CH_2Cl_2 solution was dried over $MgSO_4$ and evaporated *in vacuo* to give **2a** (67.5 g, 97%). An analytical sample was obtained by distillation; bp 76—79 °C (0.07 mmHg). mp 29 °C. *Anal.* Calcd for $C_{10}H_{11}F_2N$: C, 65.56; H, 6.05; N, 7.65. Found: C, 65.51; H, 5.99; N, 7.80. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, d, J=6.2 Hz, C2-CH_3), 1.38—1.58 (1H, m, C3-H), 1.87—2.00 (1H, m, C3-H), 2.54—2.73 (1H, m, C4-H), 2.76—2.92 (1H, m, C4-H), 3.20—3.36 (1H, m, C2-H), 3.63 (1H, br, NH), 6.12 (1H, ddd, J=8.8, 3.8, 1.8 Hz, C8-H), 6.74 (1H, ddd, J=8.8 Hz, C7-H).

(*S*)-5,6-Difluoro-2-methyl-1,2,3,4-tetrahydroquinolinium Hydrogen 2,3-Di-*O*-benzoyl-L-tartarate [(*S*)-(−)-2a · L-DBTA Salt] **2a** (50.0 g, 0.273 mol) was added to a stirred solution of L-DBTA (53.8 g, 0.150 mol) in AcOEt (100 ml) and the mixture was stirred at room temperature for 1 h. The resulting precipitates were collected by filtration and recrystallized from 60% (v/v) aqueous MeOH to give (*S*)-(−)-**2a** · L-DBTA salt (49.9 g, 35%) as colorless prisms. mp 172—176 °C. $[\alpha]_D^{20}$ −104° (c=1.0, MeOH), 100% ee as determined by HPLC [column, Urtlon ES-CD; eluent, 20 mM aqueous KH_2PO_4–CH_3CN (85:15)]. *Anal.* Calcd for $C_{28}H_{25}F_2NO_8$: C, 62.11; H, 4.65; N, 2.59. Found: C, 62.34; H, 4.43; N, 2.67. ^{1}H-NMR (DMSO-d_6) δ: 1.12 (3H, d, J=6.4 Hz, C2-CH_3), 1.25—1.45 (1H, m, C3-H), 1.78—1.95 (1H, m, C3-H), 2.52—2.82 (2H, m, C4-H), 3.15—3.50 (2H, m, C2-H, NH), 5.88 (2H, s, C<u>H</u>COOH), 6.23 (1H, ddd, J=8.8, 4.0, 1.8 Hz, C8-H), 6.88 (1H, ddd, J=8.8 Hz, C7-H), 7.60 (4H, t, J=7.2 Hz, C3-H of benzoyl), 7.74 (2H, t, J=7.2 Hz, C4-H of benzoyl), 8.02 (4H, d, J=7.2 Hz, C4-H of benzoyl), 13.70 (2H, br, COOH).

By treating (*S*)-(−)-**2a** · L-DBTA salt with aqueous NaOH, (*S*)-(−)-**2a** was quantitatively obtained as an oil. $[\alpha]_D^{20}$ −62.7° (c=1.0, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, d, J=6.2 Hz, C2-CH_3), 1.38—1.58 (1H, m, C3-H), 1.87—2.00 (1H, m, C3-H), 2.54—2.73 (1H, m, C4-H), 2.76—2.92 (1H, m, C4-H), 3.20—3.36 (1H, m, C2-H), 3.63 (1H, br, NH), 6.12 (1H, ddd, J=8.8, 3.8, 1.8 Hz, C8-H), 6.74 (1H, ddd, J=8.8 Hz, C7-H).

The mother liquor obtained in the above operations was combined, diluted with AcOEt and washed successively with aqueous NaOH and brine. The AcOEt solution was dried over $MgSO_4$ and evaporated *in vacuo* to give (*R*)-(+)-**2a** (24.1 g, 48%) as an oil. $[\alpha]_D^{21}$ +28.5° (c=1.0, MeOH) (45% ee).

(*S*)-5-Bromo-6-fluoro-2-methyl-1,2,3,4-tetrahydroquinolinium Hydrogen 2,3-Di-*O*-benzoyl-L-tartarate [(*S*)-(−)-2b · L-DBTA Salt] A solution of L-DBTA (0.72 g, 2.0 mmol) in 70% (v/v) MeOH (3.0 ml) was added to a stirred solution of **2b** (0.85 g, 3.5 mmol) in 70% (v/v) aqueous MeOH (5.5 ml) and the mixture was stirred for 15 min at room temperature. The resulting precipitates were collected by filtration and recrystallized from 70% (v/v) aqueous MeOH to give (*S*)-(−)-**2b** · L-DBTA salt (0.78 g, 37%) as colorless prisms. mp 183 °C. $[\alpha]_D^{20}$ −88.3° (c=1.0, MeOH), 99% ee as determined by HPLC [column, Urtlon ES-CD; eluent, 20 mM aqueous KH_2PO_4–CH_3CN (7:3)]. *Anal.* Calcd for $C_{28}H_{25}BrFNO_8$: C, 55.83; H, 4.18; N, 2.33. Found: C, 55.91; H, 4.21; N, 2.41. ^{1}H-NMR (DMSO-d_6) δ: 1.12 (3H, d, J=6.2 Hz, C2-CH_3), 1.30—1.49 (1H, m, C3-H), 1.84—1.96 (1H, m, C3-H), 2.55—2.80 (2H, m, C4-H), 3.13—3.28 (1H, m, C2-H), 3.35 (1H, br, NH), 5.88 (2H, s, C<u>H</u>COOH), 6.47 (1H, dd, J=8.8, 4.8 Hz, C8-H), 6.89 (1H, dd, J=8.8 Hz, C7-H), 7.61 (4H, t, J=7.2 Hz, C3-H of benzoyl), 7.75 (2H, t, J=7.2 Hz, C4-H of benzoyl), 8.03 (4H, d, J=7.2 Hz, C2-H of benzoyl), 13.50 (2H, br, COOH).

By treating (*S*)-(−)-**2b** · L-DBTA salt with aqueous NaOH, (*S*)-(−)-**2b** was quantitatively obtained as an oil. $[\alpha]_D^{20}$ −46.1° (c=1.0, MeOH). *Anal.* Calcd for $C_8H_{11}BrFN$: C, 49.20; H, 4.54; N, 5.74. Found: C, 49.37; H, 4.47; N, 6.07. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, d, J=6.0 Hz, C2-CH_3), 1.43—1.63 (1H, m, C3-H), 1.91—2.03 (1H, m, C3-H), 2.56—2.74 (1H, m, C4-H), 2.81—2.94 (1H, m, C4-H), 3.21—3.36 (1H, m, C2-H), 3.63 (1H, br, NH), 6.55 (1H, dd, J=8.8, 4.6 Hz, C8-H), 6.75 (1H, dd, J=8.8 Hz, C7-H).

(*S*)-5-Bromo-6-fluoro-2-methyl-1,2,3,4-tetrahydroquinolinium D-Camphor-10-sulfonate [(*S*)-(−)-2b · D-CSA Salt] A suspension of D-CSA (340 g, 1.46 mol) in acetone (1.5 l) was added to a stirred solution of **2b** (600 g, 2.46 mol) in acetone (500 ml). The resulting precipitates were collected by filtration and recrystallized from EtOH to give (*S*)-(−)-**2b** · D-CSA salt (406 g, 35%) as colorless prisms. mp 224.5 °C. $[\alpha]_D^{20}$ −10.2° (c=1.0, MeOH), 99% ee as determined by HPLC. *Anal.* Calcd for $C_{20}H_{27}BrFNO_4S$: C, 50.42; H, 5.71; N, 2.94. Found: C, 50.21; H, 5.79; N, 3.02. ^{1}H-NMR (DMSO-d_6) δ: 0.74 (3H, s, CH_3C), 1.03 (3H, s, CH_3C), 1.20—1.44 (5H, m), 1.50—2.12 (5H, m), 2.17—2.33 (1H, m), 2.45—3.00 (6H, m), 3.42 (1H, m), 7.01 (1H, dd, J=8.7, 4.8 Hz, C8-H), 7.19 (1H, dd, J=8.7 Hz, C7-H).

(*S*)-8,9-Difluoro-5-methyl-6,7-dihydro-1-oxo-1*H*,5*H*-benzo[*i,j*]quinolizine-2-carboxylic Acid (5a) A mixture of (*S*)-(−)-**2a** (11.34 g, 61.9 mmol) and EMME (20.11 g, 93.0 mmol) was heated at 130 °C with stirring for 3 h and the reaction mixture was added dropwise to the pre-heated polyphosphoric acid (PPA, 31.36 g) at 130 °C. When the addition was complete, the mixture was stirred at the same temperature for 1 h. Then EtOH (170 ml), concentrated HCl (11.3 ml) and water (113 ml) were added, and the whole was refluxed for 1 h. After cooling, water (220 ml) was added to the mixture and the resulting precipitates were collected by filtration. The crystals were washed with water and dried to give **5a** (15.28 g, 88%). An analytical sample was obtained by recrystallization from DMF. mp 283 °C. $[\alpha]_D^{20}$ −52.3° (c=1.0, MeOH). *Anal.* Calcd for $C_{14}H_{11}F_2NO_3$: C, 60.22; H, 3.97; N, 5.02. Found: C, 60.33; H, 3.85; N, 5.07. ^{1}H-NMR (DMSO-d_6) δ: 1.41 (3H, d, J=6.8 Hz, C5-CH_3), 2.05—2.33 (2H, m, C6-H), 2.85—3.25 (2H, m, C7-H), 4.90—5.07 (1H, m, C5-H), 8.10 (1H, dd, J=10.4, 8.6 Hz, C10-H), 9.07 (1H, s, C3-H), 14.94 (1H, s, COOH).

(*S*)-8-Bromo-9-fluoro-5-methyl-6,7-dihydro-1-oxo-1*H*,5*H*-benzo[*i,j*]-quinolizine-2-carboxylic Acid (5b) A mixture of (*S*)-(−)-**2b** (202 g, 0.827 mol) and EMME (590 g, 2.73 mol) was heated at 130 °C with stirring for 24 h. PPA (590 g) was added dropwise at 110 °C, and the reaction mixture was further stirred at the same temperature for 0.5 h. It was poured into water and adjusted to pH 3 with 48% (w/v) aqueous NaOH. The resulting precipitates were collected by filtration and added to 0.7 N aqueous KOH (2.2 l). The mixture was refluxed for 1 h, and adjusted to pH 5 with concentrated HCl. The resulting precipitates were collected by filtration and recrystallized from DMF to give **5b** (188 g, 67%) as colorless prisms. mp 294 °C. $[\alpha]_D^{20}$ −165.0° (c=1.0, 1 N NaOH). *Anal.* Calcd for $C_{14}H_{11}BrFNO_3$: C, 49.44; H, 3.26; N, 4.12. Found: C, 49.45; H, 3.22; N, 4.21. ^{1}H-NMR (DMSO-d_6) δ: 1.39 (3H, d, J=6.6 Hz, C5-CH_3), 2.10—2.30 (2H, m, C6-H), 2.90—3.30 (2H, m, C7-H), 4.87—5.07 (1H, m, C5-H), 8.03 (1H, d, J=8.6 Hz, C10-H), 9.06 (1H, s, C3-H), 14.91 (1H, br, COOH).

(*S*)-(*O*-*B*)-Diacetoxy-(8,9-difluoro-6,7-dihydro-1-oxo-1*H*,5*H*-benzo-[*i,j*]quinolizine-2-carboxy)borane (6) A mixture of boric anhydride (256 g, 3.68 mol), Ac_2O (2.53 l, 22.8 mol) and AcOH (1.15 l, 18.2 mol) was refluxed for 3 h. To the resulting yellow solution, **5a** (1870 g, 6.70 mol) was added and the mixture was refluxed for 2 h to give a brown suspension, which was diluted with toluene (10.0 l) and cooled to room temperature. The resulting precipitates were collected by filtration as the first crop and the filtrate was concentrated. The residue was triturated with toluene to give precipitates, which were collected by filtration as the second crop. The combined crops were dried to afford the crude **6** (2529 g, 93%). This crude material was used for the next step without further purification. ^{1}H-NMR ($CDCl_3$) δ: 1.62 (3H, d, J=6.9 Hz, C5-CH_3), 1.97 (3H, s, CH_3 of acetoxy), 2.06 (3H, s, CH_3 of acetoxy), 2.25—2.43 (2H, m, C6-H), 2.95—3.45 (2H, m, C7-H), 5.05—5.21 (1H, m, C5-H), 8.21 (1H, dd, J=8.8 Hz, C10-H), 9.32 (1H, s, C3-H).

(*S*)-9-Fluoro-6,7-dihydro-8-(4-hydroxy-1-piperidyl)-5-methyl-1-oxo-1*H*,5*H*-benzo[*i,j*]quinolizine-2-carboxylic Acid [(*S*)-(−)-1] From **6**: A mixture of **6** (1976 g, 4.85 mol) and 4-hydroxypiperidine (1473 g, 17.7

mol) in CH_3CN (9.9 l) was stirred at 50—60 °C for 4 h and concentrated. The residue was taken up in water (29.6 l) and the mixture was stirred at room temperature. The resulting precipitates were collected by filtration and added to a mixture of 3.5% (w/v) aqueous NaOH (18.3 l) and CH_3CN (7.9 l). The whole was stirred at room temperature until the suspension changed to a clear solution and then concentrated HCl (2.0 l) was added. The resulting precipitates were collected by filtration and recrystallized from 50% (v/v) aqueous EtOH to give (*S*)-(−)-**1** (1286 g, 74%).

From **5b**: A mixture of **5b** (80 g, 0.24 mol) and 4-hydroxypiperidine (120 g, 1.2 mol) in HMPA (640 ml) was stirred at 140 °C for 5 h, and the solution was concentrated *in vacuo*. The residual oil was treated with 2 N HCl (500 ml) and the precipitates were collected by filtration, recrystallized from EtOH and purified by silica gel column chromatography (eluent, CH_2Cl_2–MeOH) to give (*S*)-(−)-**1** (31.5 g, 36%) as a pale yellowish powder. An analytical sample was obtained by recrystallization from AcOEt–THF (9 : 1). mp 262 °C (dec.). $[\alpha]_D^{20}$ −314.0° (c=1.0, MeOH), 100% ee as determined by HPLC [column, TSK ODS-80Ts; eluent composition was 12% (v/v) aqueous CH_3CN (1 l) solution of KH_2PO_4 (0.801 g), $Na_2HPO_4 \cdot 12H_2O$ (0.838 g), β-cyclodextrin (9.99 g) and EDTA disodium salt (44 mg)]. *Anal.* Calcd for $C_{19}H_{21}FN_2O_4$: C, 63.32; H, 5.87; N, 7.77. Found: C, 63.10; H, 5.99; N, 7.81. ^{1}H-NMR (DMSO-d_6) δ: 1.42 (3H, d, J=6.8 Hz, C5-CH_3), 1.47—1.73 (2H, m, C3-H and C5-H of piperidine), 1.73—1.98 (2H, m, C3-H and C5-H of piperidine), 1.98—2.23 (2H, m, C6-H), 2.80—3.03 (2H, m, C2-H of piperidine and C7-H), 3.03—3.45 (4H, m, C2-H and C6-H of piperidine and C7-H), 3.60—3.80 (1H, m, C4-H of piperidine), 4.76 (1H, d, J= 4.0 Hz, OH of piperidine), 4.80—4.97 (1H, m, C5-H), 7.84 (1H, d, J=12.6 Hz, C10-H), 8.96 (1H, s, C3-H), 15.29 (1H, s, COOH).

Racemization of (*R*)-(+)-2a The best example of the racemization of recovered (*R*)-(+)-**2a** using CH_3SO_3H was as follows. A mixture of (*R*)-(+)-**2a** (64% ee) (100 g, 0.546 mol) and CH_3SO_3H (7.08 ml, 0.109 mol) was stirred at 120 °C for 7 h under N_2. The reaction mixture was diluted with AcOEt and washed successively with saturated aqueous $NaHCO_3$ and brine. The mixture was concentrated *in vacuo* to give **2a** (99.2 g, 99%). $[\alpha]_D^{21}$ 0° (c=1.0, MeOH). HPLC analysis showed over 95% purity which is sufficient for the resolution.

Racemization of Optically Active 2a with D_2SO_4 A mixture of (*S*)-(−)-**2a** (100% ee) (2.00 g, 11.0 mmol) and D_2SO_4 (0.54 g, 5.4 mmol) was stirred at 130 °C for 8 h under Ar. The mixture was diluted with CH_2Cl_2 and washed successively with 1 N NaOH and water. The CH_2Cl_2 solution was dried over $MgSO_4$ and evaporated *in vacuo* to give the racemate as an oil (1.53 g, 77%) with 13% ee as determined by HPLC [column, Urtlon ES-CD; eluent, 20 mM aqueous KH_2PO_4–CH_3CN (85 : 15)]. ^{1}H-NMR ($CDCl_3$) δ: 1.13—1.28 (*ca.* 2.1H,* m, C2-CH_3), 1.38—1.58 (*ca.* 0.8H,* m, C3-H), 1.87—2.00 (*ca.* 0.8H,* m, C3-H), 6.17 (*ca.* 0.9H,* ddd, J=8.8, 3.8, 1.8 Hz, C8-H). *: The integrated values of the indicated protons were decreased by deuterium exchange.

X-Ray Crystallographic Analysis of (*S*)-(−)-2b · D-CSA Salt The prism crystal used for the X-ray study had dimensions of approximately 0.80 × 1.00 × 1.00 mm. All data were obtained on a Rigaku AFC-5S automated four-circle diffractometer with graphite-monochromated Mo$K\alpha$ radiation. Final lattice parameters were obtained from a least-squares refinement using 25 reflections. Crystal data: $C_{20}H_{27}BrFNO_4S$, M_r=476.40, orthorhombic, space group $P2_12_12$, a=10.88 (6), b=28.26 (1), c=7.04(1) Å, V=2166(12) Å^3, Z=4, D_c=1.461 g/cm^3, $F(000)$=984 and μ (Mo$K\alpha$)=20.02 cm^{-1}. The intensities were measured using the $\omega/2\theta$ scan mode up to 50° in 2θ. The data were corrected for Lorentz and polarization factors, and absorption correction was applied. Of the 2241 independent reflections which were collected, 1170 reflections with $I>3\sigma$ (I) were used for the structure determination and refinement. The structure was solved using the program package TEXSAN.[10] All non-H atoms were found in the Fourier map, and H atoms at calculated positions were included for the structure calculation. Refinement by the full-matrix least-squares method with anisotropic temperature factors was carried out for non-H atoms. At final convergence, R=0.046, R_w=0.045, with $w=4F_O^2/\sigma^2(F_O)^2$, goodness of fit=1.61 and $(\Delta/\sigma)_{max}$= 0.01 for 253 parameters.[11] The minimum and maximum peaks in the final difference Fourier map were −0.30 and 0.31 eÅ^{-3}. Atomic scattering factors were taken from International Tables for X-ray Crystallography.[12] Computation was carried out on a Digital Micro VAX 3300.

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