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ASYMMETRIC SYNTHESIS OF (*S*)-4,5-DIFLUORO-2-METHYLINDOLINE

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ABSTRACT : (*S*)-4,5-Difluoro-2-methylindoline (*S*)-**11** was synthesized effectively by asymmetric reduction of *N*-[(*R*)-*N*-*p*-tolylsulfonyl]prolinyl-2-(2-oxo)propyl-3,4-difluoroanilide **4b** followed by successive methylsulfonylation and intramolecular cyclization.

Nadifloxacin (OPC-7251, Fig. 1) is highly potent, broad-spectrum new quinolone antibacterial agent and has asymmetric carbon.[1] Its (*S*)-isomer is more active than its (*R*)-isomer and the range is from 32- to 1000-fold.[2] Although nadifloxacin shows potent antibacterial activity against gram-positive bacteria, its antibacterial activity against gram-nagative bacteria including *Pseudomonas aeruginosa* which become a serious problem in chemotherapy for its resistance to most of antibacterial agents is slightly weak. As a result of our efforts to find more active quinolone anti-infectives, we prepared (*R*,*S*)-9-cyclic amino-8-fluoro-1, 2-dihydro-2-methyl-6-oxo-6*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic acids (*R*,*S*)-**1**.[3] Some of them had more potent activity against gram-nagative bacteria including

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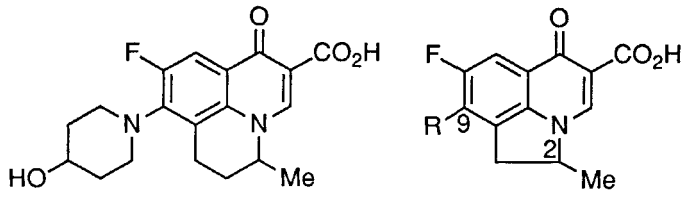


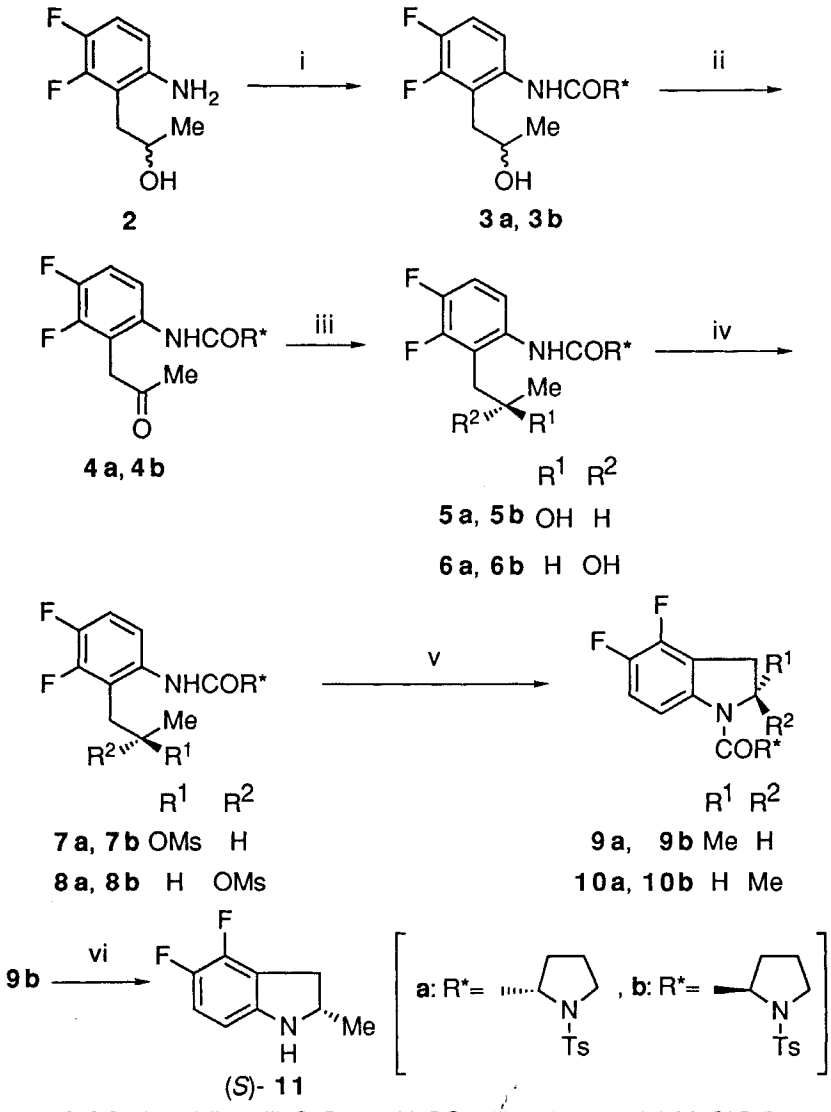
Fig. 1

Pseudomonas aeruginosa than nadifloxacin. Since (*R*,*S*)-**1** had asymmetric carbon similarly to nadifloxacin, it was expected that its (*S*)-isomer was more active than its (*R*)-isomer. Although (*S*)-nadifloxacin could be obtained by optical resolution of 5-bromo-6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline,[4] we couldn't get (*S*)-**1** by that of (*R*,*S*)-**11** corresponding to tetrahydroquinoline.

From this viewpoint, we attempted a stereocontrolled and straightfoward synthesis of (*S*)-**1** which was expected as the active isomer. However, most of previous syntheses of 2-substituted indolines have led to racemic compounds and could not give optically active derivatives without resolution.[5] Herein we report an effective asymmetric synthesis of (*S*)-**11**, a key intermediate of (*S*)-**1**, *via* diastereoselective reduction of **4b**.

First, we prepared **4a** [(*S*)-isomer of **4b**] (Scheme 1) and examined its asymmetric reduction. Amino group of anilinoalcohol **2**[6] was acylated with (*S*)-*N*-(*p*-tolylsulfonyl)prolinyl chloride to give anilide **3a** in 93% yield. Oxidation of **3a** with CrO_3 / aq. H_2SO_4 led to ketone **4a** in 99% yield. Diastereoselective reduction of **4a** was tested with several reductants (Table 1). Resulting alcohols **5a** and **6a** were transformed into *N*-[(*S*)-*N*-*p*-tolylsulfonyl]prolinylindolines **9a** and **10a** by successive treatment with methanesulfonyl chloride and potassium carbonate. Unfortunately, absolute configuration of major isomer **10a** was asigned to be *R* by X-Ray analysis (Fig. 2).

In this way, this diastereoselective reduction provided undesired alcohol **6a** which gave less active (*R*)-**1** predominantly. Therefore, we prepared **4b** and



i) ClCOR*/pyridine, ii) CrO_3/aq. H_2SO_4, iii) reductant, iv) MsCl/TEA, v) K_2CO_3/acetone, vi) KOH/MeOH-THF

Scheme 1

Table 1. Diastereoselective reduction of **4a**.

Entry	Reductant	Solvent	Temp.(℃)	Method[a]	**5a** : **6a**[b]
1	$NaBH_4$	THF	-18	A	36 : 64
2	$LiAlH_4$	THF	-70	A	15 : 85
3	BH_3	THF	r.t.	B	48 : 52

[a] Method A: Solution of **4a** was added to reductant; Method B: Reductant was added to solution of **4a**

[b] Ratio of **5a** and **6a** was determined by 90 MHz **^{1}H NMR**.[7]

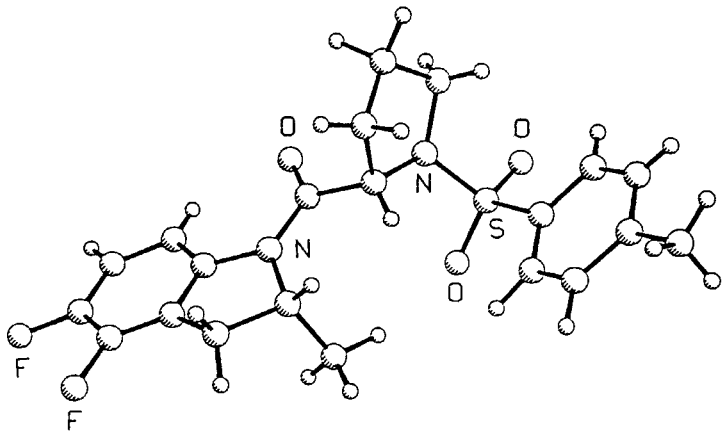


Fig. 2 The Molecular Structure of **10a**

Table 2. Diastereoselective reduction of **4b**.

Entry	Reductant	Solvent	Temp.(℃)	Method[a]	**5b** : **6b**[b]
1	$Zn(BH_4)_2$	THF	-18	A	64 : 36
2	$NaBH_4$	THF	-18	A	66 : 34
3	$LiAlH_4$	THF	-70	A	84 : 16
4	$LiAlH_4$	THF	-70	B	88 : 12
5	$LiAlH_4$	Et_2O	-70	B	75 : 25
6	BH_3	THF	r.t.	B	51 : 49

[a] Method A: Solution of **4b** was added to reductant; Method B: Reductant was added to solution of **4b**

[b] Ratio of **5b** and **6b** was determined by 90 MHz **^{1}H NMR**.[8]

examined its diastereoselective reduction. Thus, **2** was treated with (*R*)-*N*-(*p*-tolylsulfonyl)prolinyl chloride to furnish anilide **3b**. Oxidation of **3b** gave **4b**. Diastereoselective reduction of **4b** was tested with various reductants (Table 2). The best result was obtained when **4b** was reduced with $LiAlH_4$ in THF at -70℃ (Entry 4). Futhermore, trituration with 5% *i*-PrOH / *i*-Pr_2O raised ratio of alcohols **5b** and **6b** to 91 : 9 in 72% yield (based on **2**). Sequential treatment of **5b** and **6b** with methanesulfonyl chloride and potassium carbonate followed by recrystallization from MeCN provided *N*-[(*R*)-*N*-*p*-tolylsulfonyl]prolinylindoline **9b** as almost single isomer in 72% yield. **9b** was hydrolysed with KOH to give (*S*)-**11** in 95% yield.

Thus, we could obtain desired (*S*)-**11** effectively and selectively without optical resolution. Asymmetric synthesis of (*S*)-**1** having various substituents at 9-position is in progress.

EXPERIMENTAL

Melting points were taken on a Yanagimoto apparatus and are uncorrected. Infrared spectra were recorded on a JASCO IR-810 instrument. Proton nmr spectra were recorded with a Hitachi (90 MHz) spectrometer. The chemical shifts are reported in δ downfield from tetramethylsilane as an internal standard. The elemental analyses were run on a Yanaco CHN corder MT-3.

***N*-[(*S*)-*N*-*p*-Tolylsulfonyl]prolinyl-2-[2-(*R*,*S*)-hydroxy]propyl-3,4-difluoroanilide (3a)**: To a stirred solution of anilinoalcohol **2** (1.88 g, 0.010 mol) in 20 ml of CH_2Cl_2 were added pyridine (0.89 ml, 0.011 mol) and (*S*)-*N*-(*p*-tolylsulfonyl)prolinyl chloride (3.17 g, 0.011 mol) at -5℃. After stirring for 30 min, the mixture was washed successively with 10% HCl, water, 5% aqueous solution of $NaHCO_3$ and water and dried over $MgSO_4$. The solvent was removed and the residue was purified by column chromatography on silica-gel with CH_2Cl_2-EtOAc (9 : 1) to afford anilide **3a** (4.07 g, 93%) as colorless prisms, m.p. 160-163℃, $[\alpha]_D^{25}$=-156.6° ($CHCl_3$, c=0.99). ^1H NMR ($CDCl_3$): δ=1.23 and 1.45 (each d, *J*=6.3 Hz, 1.5 and 1.5 H, Me), 1.58-1.99 (m, 4H, $CHC\underline{H}_2C\underline{H}_2CH_2$), 2.46 (s, 3H, Me), 2.80-3.32 (m, 4H, $C\underline{H}_2CHOH$ and

CH_2N), 3.45-3.75 (m, 1H, C<u>H</u>OH), 3.92-4.52 (m, 2H, OH and CHCO), 7.05 (q, *J*=8.8 Hz, 1H, 5-H), 7.36 (d, *J*=8.0 Hz, 2H, Ts), 7.40-7.65 (m, 1H, 6-H), 7.75 (d, *J*=8.0 Hz, 2H, Ts), 10.15 and 10.22 (each br s, 0.5 and 0.5H, NH). Anal. Calcd. for $C_{21}H_{24}F_2N_2O_4S$: C, 57.52; H, 5.52; N, 6.39. Found: C, 57.23; H, 5.47; N, 6.35.

***N*-[(*S*)-*N*-*p*-Tolylsulfonyl]prolinyl-2-(2-oxo)propyl-3,4-difluoroanilide (4a)**: A solution of CrO_3 (0.75 g, 7.5 mmol) in 30% aq. H_2SO_4 (2 ml) was added to a stirred solution of anilide **3a** (3.95 g, 0.009 mol) in acetone (36 ml) and the resulting mixture was stirred for 45 min at room temperature. After addition of *i*-PrOH (0.84 ml, 0.011 mol), the mixture was filtered and the filtrate was evaporated. The residue was dissolved in a mixture of CH_2Cl_2 and water. Aqueous phase was extracted twice with CH_2Cl_2, and the combined organic extracts were washed twice with water, then dried over $MgSO_4$. Evaporation of the solvent afforded ketone **4a** (3.89 g, 99%) as a brown solid, which was used in the next reaction without further purification. m.p. 149-152℃. ^{1}H NMR ($CDCl_3$): δ=1.50-2.32 (m, 4H, CHC<u>H</u>$_2$C<u>H</u>$_2$CH$_2$), 2.40 (s, 3H, MeCO), 2.47 (s, 3H, Ts), 3.00-3.37 (m, 1H, C<u>H</u>HN), 3.56-4.28 (m, 4H, C<u>H</u>HN, CH_2CO, CHCO), 7.09 (q, *J*=8.8 Hz, 1H, 5-H), 7.36 (d, *J*=7.5 Hz, 2H, Ts), 7.40-7.63 (m, 1H, 6-H), 7.75 (d, *J*=7.5 Hz, 2H, Ts), 8.98 (br s, 1H, NH).

Diastereoselective reduction of ketone (4a) with $LiAlH_4$ (Table 1, Entry 2): To a stirred suspension of $LiAlH_4$ (0.04 g, 0.001 mol) in THF (10 ml) was added dropwise a solution of ketone **8a** (0.44 g, 0.001 mol) in THF (5 ml) at -70℃. After stirring for 1 h, the mixture was poured into 10% HCl and ice-water, and aqueous layer was extracted twice with CH_2Cl_2. The combined extracts were washed twice with water and dried over $MgSO_4$. The solvent was evaporated to give a 15 : 85 mixture of the alcohols **5a** and **6a** (0.44 g, 100%) as a brown solid, which was used in the next reaction without further purification. m.p. 166-169℃. ^{1}H NMR ($CDCl_3$): δ=1.23 and 1.45 (each d, *J*=6.3 Hz, 0.45 and 2.55 H, Me), 1.58-2.32 (m, 4H, CHC<u>H</u>$_2$C<u>H</u>$_2$CH$_2$), 2.48 (s, 3H, Me), 2.80-3.32 (m, 4H, C<u>H</u>$_2$CHOH and CH_2N), 3.45-3.75 (m, 1H, C<u>H</u>OH), 3.97-4.51 (m, 2H, OH and

CHCO), 7.32 (q, *J*=8.8 Hz, 1H, 5-H), 7.36 (d, *J*=8.0 Hz, 2H, Ts), 7.40-7.65 (m, 1H, 6-H), 7.75 (d, *J*=8.0 Hz, 2H, Ts), 10.25 (br s, 1H, NH).

***N*-[(*S*)-*N*-*p*-Tolylsulfonyl]prolinyl-2-[2-(*R*)-methylsulfonyloxy]-propyl-3,4-difluoroanilide (7a)** and ***N*-[(*S*)-*N*-*p*-tolylsulfonyl]prolinyl-2-[2-(*S*)-methylsulfonyloxy]propyl-3,4-difluoroanilide (8a)**: To a stirred solution of alcohols **5a** and **6a** (0.44 g, 0.001 mol) in CH_2Cl_2 (5 ml) were added methanesulfonyl chloride (0.085 ml, 0.0011 mol) and triethylamine (0.28 ml, 0.002 mol) at 0℃. The reaction mixture was stirred for 3 h, and poured into 10% HCl. The organic layer was washed with water and dried over $MgSO_4$. Evaporation of the solvent furnished mesylates **7a** and **8a** (0.51 g, 99%) as a pale yellow solid, which was used in the next reaction without further purification. m.p. 61-64℃. ^{1}H NMR ($CDCl_3$): δ=1.59 and 1.70 (each d, *J*=6.3 Hz, 0.45 and 2.55H, Me), 1.84-2.41 (m, 4H, $CHC\underline{H}_2C\underline{H}_2CH_2$), 2.47 (s, 3H, Ts), 2.81 (s, 3H, Ms), 3.00-3.52 (m, 3H, CH_2N, C<u>H</u>HCHOMs), 3.53-3.92 (m, 1H, CHOMs), 4.05-4.31 (m, 1H, C<u>H</u>HCHOMs), 4.75-5.22 (m, 1H, CHCO), 7.10 (q, *J*=8.8 Hz, 1H, 5-H), 7.37 (d, *J*=8.0 Hz, 2H, Ts), 7.40-7.63 (m, 1H, 6-H), 7.77 (d, *J*=8.0 Hz, 2H, Ts), 8.74 and 9.07 (each br s, 0.15 and 0.85H, NH).

***N*-[(*S*)-*N*-*p*-Tolylsulfonyl]prolinyl-2-(*R*)-methyl-4,5-difluoroindoline (10a)**: A suspension of mesylates **7a**, **8a** (0.51 g, 0.001 mol) and K_2CO_3 (0.28 g, 0.002 mol) in acetone (10 ml) and water (0.04 ml) was refluxed for 1 h. After evaporation of the solvent, the residue was dissolved with CH_2Cl_2 and water. Aqueous layer was extracted with CH_2Cl_2, and combined organic extracts were washed twice with water, dried over $MgSO_4$, and evaporated. EtOH was added to the residue and the resulting crystal was filtered to afford compound **10a** (0.27 g, 64%) as single isomer as colorless needles, m.p. 236-239℃, $[\alpha]_D^{20}$=-71.8° ($CHCl_3$, c=1.04). ^{1}H NMR ($CDCl_3$): δ=1.53 (d, *J*=6.3 Hz, 3H, Me), 1.73-2.36 (m, 4H, $CHC\underline{H}_2C\underline{H}_2CH_2$), 2.44 (s, 3H, Me), 2.70-3.00 (m, 1H, C<u>H</u>HN), 3.20-3.64 (m, 3H, C<u>H</u>HN, C<u>H</u>HC<u>H</u>Me), 4.35-4.68 (m, 1H, C<u>H</u>HCHMe), 4.68-4.95 (m, 1H, CHCO), 7.01 (q, *J*=8.8 Hz, 1H, 6-H), 7.29 (d, *J*=8.0 Hz, 2H, Ts), 7.65-7.89 (m, 1H, 7-H), 7.80 (d, *J*=8.0 Hz, 2H, Ts). Anal.

Calcd. for $C_{21}H_{22}F_2N_2O_3S$: C, 59.99; H, 5.27; N, 6.66. Found: C, 59.81; H, 5.44; N, 6.66.

***N*-[(*R*)-*N*-*p*-Tolylsulfonyl]prolinyl-2-[2-(*R*,*S*)-hydroxy]propyl-3,4-difluoroanilide (3b)**: Anilide **3b** was obtained by the similar way described for the preparation of **3a** as a brown solid except use of *N*-(*R*)-*N*-(*p*-tolylsulfonyl)-prolinyl chloride instead of (*S*)-chloride, which was used in the next reaction without further purification. m.p. 161-164℃. ^{1}H NMR ($CDCl_3$): δ=1.26 and 1.47 (each d, *J*=6.3 Hz, 1.5 and 1.5 H, Me), 1.55-2.34 (m, 4H, $CHCH_2CH_2CH_2$), 2.48 (s, 3H, Me), 2.55-3.36 (m, 4H, CH_2CHOH and CH_2N), 3.43-3.80 (m, 1H, CHOH), 4.01-4.55 (m, 2H, OH and CHCO), 7.08 (q, *J*=8.8 Hz, 1H, 5-H), 7.40 (d, *J*=8.0 Hz, 2H, Ts), 7.40-7.70 (m, 1H, 6-H), 7.78 (d, *J*=8.0 Hz, 2H, Ts), 10.21 and 10.38 (each br s, 0.5 and 0.5H, NH).

***N*-[(*R*)-*N*-p-Tolylsulfonyl]prolinyl-2-(2-oxo)propyl-3,4-difluoroanilide (4b)**: The same treatment described for the preparation of ketone **4a** afforded **4b** from **3b** as a brown solid, which was used in the next reaction without further purification. m.p. 149-152℃. ^{1}H NMR ($CDCl_3$): δ=1.50-2.40 (m, 4H, $CHCH_2CH_2CH_2$), 2.43 (s, 3H, MeCO), 2.48 (s, 3H, Ts), 3.04-3.39 (m, 1H, CHHN), 3.60-3.90 (m, 1H, CHHN), 3.95-4.36 (m, 3H, CH_2CO, CHCO), 7.15 (q, *J*=8.8 Hz, 1H, 5-H), 7.41 (d, *J*=7.5 Hz, 2H, Ts), 7.41-7.67 (m, 1H, 6-H), 7.75 (d, *J*=7.5 Hz, 2H, Ts), 9.06 (br s, 1H, NH).

Diastereoselective reduction of ketone (4b) with $LiAlH_4$ (Table 2, Entry 4): To a stirred solution of ketone **4b** (52.4 g, 0.12 mol) in THF (240 ml) was added $LiAlH_4$ (2.7 g, 0.07 mol) by portions with care at -70℃. After stirring for 1 h, the mixture was poured into 10% HCl and ice-water, and the aqueous layer was extracted twice with CH_2Cl_2. The combined extracts were washed twice with water and dried over $MgSO_4$. After evaporation of the solvent, the resulting solid was triturated with 5% *i*-PrOH / *i*-Pr_2O to give a 91 : 9 mixture of the alcohols **5b** and **6b** (37.9 g, 72% based on **2**) as a pale yellow solid, m.p. 172-173℃, $[\alpha]_D^{25}$=+164.3° ($CHCl_3$, c=1.00). ^{1}H NMR ($CDCl_3$): δ=1.26 and 1.47 (each d,

J=6.3 Hz, 0.27 and 2.73 H, Me), 1.55-2.34 (m, 4H, $CHCH_2CH_2CH_2$), 2.48 (s, 3H, Me), 2.55-3.36 (m, 4H, CH_2CHOH and CH_2N), 3.43-3.80 (m, 1H, CHOH), 4.01-4.55 (m, 2H, OH and CHCO), 7.08 (q, *J*=8.8 Hz, 1H, 5-H), 7.40 (d, *J*=8.0 Hz, 2H, Ts), 7.40-7.70 (m, 1H, 6-H), 7.78 (d, *J*=8.0 Hz, 2H, Ts), 10.21 (br s, 1H, NH). IR (KBr): ν=3380, 3250, 1671, 1348, 1161 cm^{-1}. Anal. Calcd. for $C_{21}H_{24}F_2N_2O_4S$: C, 57.52; H, 5.52; N, 6.39. Found: C, 57.68; H, 5.33; N, 6.22.

***N*-[(*R*)-*N*-*p*-Tolylsulfonyl]prolinyl-2-[2-(*R*)-methylsulfonyloxy]-propyl-3,4-difluoroanilide (7b)** and ***N*-[(*R*)-*N*-*p*-tolylsulfonyl]-prolinyl-2-[2-(*S*)-methylsulfonyloxy]propyl-3,4-difluoroanilide (8b)**: The same treatment described for the preparation of mesylate **7a** and **8a** furnished **7b** and **8b** from alcohol **5b** and **6b** as a pale yellow solid, which was used in the next reaction without further purification. m.p. 63-66℃. ^1H NMR ($CDCl_3$): δ=1.72 (d, *J*=6.3 Hz, 3H, Me), 1.80-2.35 (m, 4H, $CHCH_2CH_2CH_2$), 2.48 (s, 3H, Ts), 2.85 (s, 3H, Ms), 2.90-3.55 (m, 3H, CH_2N, CHHCHOMs), 3.60-3.93 (m, 1H, CHOMs), 4.05-4.31 (m, 1H, CHHCHOMs), 4.76-5.15 (m, 1H, CHCO), 7.14 (q, *J*=8.8 Hz, 1H, 5-H), 7.40 (d, *J*=8.0 Hz, 2H, Ts), 7.40-7.63 (m, 1H, 6-H), 7.83 (d, *J*=8.0 Hz, 2H, Ts), 9.12 (br s, 1H, NH).

***N*-[(*R*)-*N*-*p*-Tolylsulfonyl]prolinyl-2-(*S*)-methyl-4,5-difluoroanilide (9b)**: Mesylates **7b** and **8b** (41.3 g, 0.08 mol) were treated with K_2CO_3 (16.6 g, 0.12 mol) according to similar method described for the preparation of **10a**. The residue was added to MeCN instead of EtOH and the resulting mixture was refluxed for 30 min. After cooling, precipitate was filtered to afford compound **9b** (24.1 g, 72%) as single isomer as colorless needles, m.p. 237-238℃, $[\alpha]_D^{25}$=+71.4° ($CHCl_3$, c=1.02). ^1H NMR ($CDCl_3$): δ=1.53 (d, *J*=6.3 Hz, 3H, Me), 1.76-2.38 (m, 4H, $CHCH_2CH_2CH_2$), 2.45 (s, 3H, Me), 2.65-3.00 (m, 1H, CHHN), 3.20-3.65 (m, 3H, CHHN, CHHCHMe), 4.36-4.70 (m, 1H, CHHCHMe), 4.70-4.92 (m, 1H, CHCO), 7.02 (q, *J*=8.8 Hz, 1H, 6-H), 7.31 (d, *J*=8.0 Hz, 2H, Ts), 7.65-7.95 (m, 1H, 7-H), 7.82 (d, *J*=8.0 Hz, 2H, Ts). IR (KBr): ν=1670, 1349, 1157 cm^{-1}. Anal. Calcd. for $C_{21}H_{22}F_2N_2O_3S$: C, 59.99; H, 5.27; N, 6.66. Found: C, 59.86; H, 5.33; N, 6.60.

(*S*)-4,5-Difluoro-2-methylindoline [(*S*)-**11**]: To a stirred solution of KOH (15.7 g, 0.28 mol) in MeOH (120 ml) was added a solution of coupound **9b** (23.6 g, 0.056 mol) in THF (120 ml), and the resulting mixture was refluxed for 2.5 h. After evaporation of the solvent, the residue was dissloved in a mixture of toluene and water. The organic extract was washed with water (×3), and dried over Na_2SO_4. Evaporation of the solvent and distillution gave indoline (*S*)-**11** (9.0 g, 95%) as a colorless oil, b.p. 90℃ (4 mmHg). ^1H NMR ($CDCl_3$): δ=1.29 (d, *J*=6.3 Hz, 3H, Me), 2.66 (dd, *J*=7.6 and 15.8 Hz, 1H, 3-H), 3.21 (dd, *J*=7.6 and 15.8 Hz, 1H, 3-H), 3.60 (brs, 1H, NH), 3.90-4.17 (m, 1H, 2-H), 6.24 (dd, *J*=3.2 and 8.8 Hz, 1H, 7-H), 6.78 (q, *J*=8.8 Hz, 1H, 6-H). Anal. Calcd for $C_9H_9F_2N$: C, 63.90; H, 5.38; N, 8.28. Found: C, 63.72; H, 5.35; N, 8.42. Optical purity of this compound was determined by HPLC analysis.[9]

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7. Chemical schift of $-CH_2CH(OH)\underline{CH}_3$ of **5a** and **6a** was 1.23 and 1.45 ppm, respectively.
8. Chemical schift of $-CH_2CH(OH)\underline{CH}_3$ of **5b** and **6b** was 1.47 and 1.26 ppm, respectively.
9. HPLC: Yanaco L-4000S Pump. M-315 at 254 nm connected to Shimadzu C-R6A CHROMATOPAC. Col. CHIRALCEL OD, 4.6$\phi \times$250mm. Solvent system (v / v): n-Hexane : EtOH = 99 : 1, flow rate 0.5 ml / min.

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