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An Efficient Synthesis of a Key Intermediate towards (*S*)-(-)-Nadifloxacin

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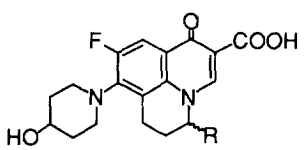
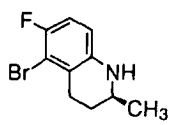
Abstract: An efficient and highly enantioselective synthesis of (*S*)-(-)-5,6-difluoro-2-methyl-1,2,3,4-tetrahydroquinoline (**4b**), a key intermediate in the synthesis of (*S*)-(-)-nadifloxacin (**2**), was carried out by using a cross-coupling reaction. Also α,β-acetylenic ketones **14a,b** underwent an asymmetric reduction using various chiral reagents to afford the corresponding propargylic alcohols **8a,b** in good yield and excellent enantiomeric excess, which can be easily converted to butanol **9**.

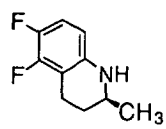
The quinolone carboxylic acid derivative (±)-9-fluoro-6,7-dihydro-8-(4-hydroxy-1-piperidyl)-5-methyl-1-oxo-1*H*,5*H*-benzo[*i,j*]quinolizine-2-carboxylic acid (Nadifloxacin, OPC-7251) (**1**), a new antibacterial agent, was synthesized by H. Ishikawa and co-workers.[1] It has a potent antibacterial activity against gram-positive bacteria, characteristically *Propionibacterium acnes*, and is characterized by a tricyclic structure with a methyl group at the C-5 of the benzo[*i,j*]quinolizine ring, thus proving a stereogenic center at C-5 position (Fig. 1). (*S*)-Nadifloxacin (**2**)[2] was 64 to 256 times more potent than **3**,[2] and approximately twice as active as **1** against gram-positive and gram-negative bacteria.[3] The intermediate (*S*)-5-bromo-6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (**4a**) has been prepared by resolution using (+)-10-camphorsulfonic acid by K. Hashimoto and co-workers.[2] This resolution method was wasteful since one of two enantiomers was useless, and therefore we have investigated the asymmetric synthesis of (*S*)-(-)-5,6-difluoro-2-methyl-1,2,3,4-tetrahydroquinoline (**4b**).



1 R = — **Nadifloxacin**
2 R = — **(*S*)-(-)-Nadifloxacin**
3 R = ····· **(*R*)-(+)-Nadifloxacin**



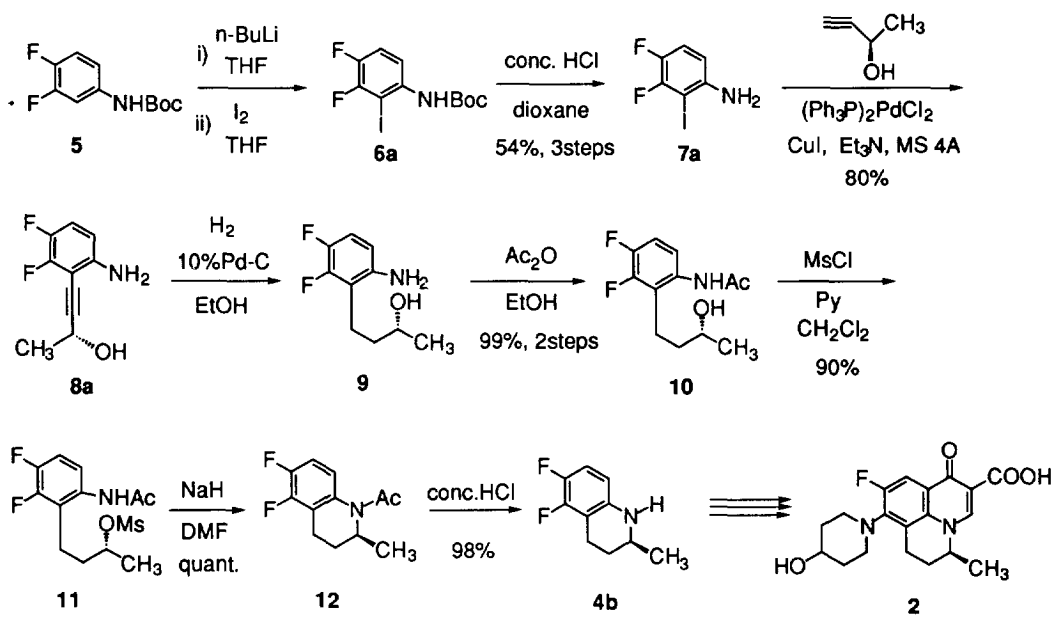
4a



4b

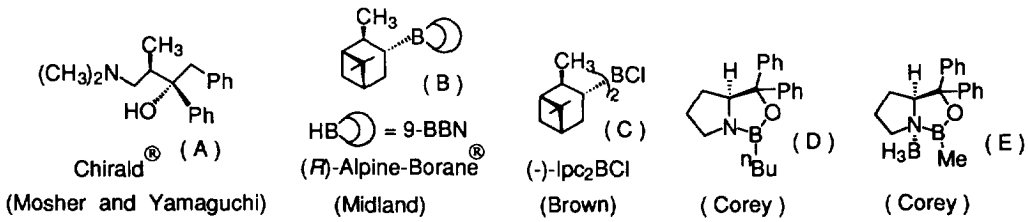
Fig. 1

We first planned to establish the stereogenic center of **4b** by a cross-coupling reaction[4] of 2-iodo-3,4-difluoroaniline (**7a**)[5] and (*R*)-3-butyn-2-ol.[6] (*S*)-(-)-5,6-Difluoro-2-methyl-1,2,3,4-tetrahydroquinoline (**4b**) was synthesized as shown in Scheme 1. A solution of N-(*tert*-butoxycarbonyl)-3,4-difluoroaniline (**5**)[5] in tetrahydrofuran (THF) was treated with n-butyllithium at -78℃ for 1.5 h to give a lithio derivative, which was reacted with iodine, followed by hydrolysis with concentrated HCl to afford **7a** in 54% yield. Palladium catalyzed cross-coupling reaction of the iodoaniline compound **7a** with (*R*)-3-butyn-2-ol in the presence of triethylamine and cuprous iodide afforded (*R*)-4-(2-amino-5,6-difluorophenyl)-3-butyn-2-ol (**8a**), $[\alpha]_D^{26}$ +18.8 (*c* 0.1, $CHCl_3$), in 80% yield. The butynol **8a** was hydrogenated with 10% palladium on charcoal (Pd - C) in EtOH to give the butanol **9**, which was acetylated with acetic anhydride in EtOH to give the acetanilide **10**, $[\alpha]_D^{28}$ +6.5 (*c* 0.1, MeOH), in 99% yield. Mesylation of the acetanilide **10** with methanesulfonyl chloride-pyridine in CH_2Cl_2 gave the mesyl compound **11**, $[\alpha]_D^{28}$ +62.3 (*c* 0.1, MeOH), in 90% yield, which was cyclized in the presence of sodium hydride (NaH) in N,N-dimethylformamide (DMF) to give (*S*)-1-acetyl-5,6-difluoro-2-methyl-1,2,3,4-tetrahydroquinoline (**12**), $[\alpha]_D^{26}$ +256.0 (*c* 0.1, MeOH), in quantitative yield. Hydrolysis of the acetyl compound **12** with concentrated HCl gave the desired compound **4b**, $[\alpha]_D^{26}$ -104.0 (*c* 0.1, MeOH), in 98% yield. The enantiomeric excess of the resulting **4b** was determined to be up to 99.8% ee by HPLC using ULTRON ES-CD column.



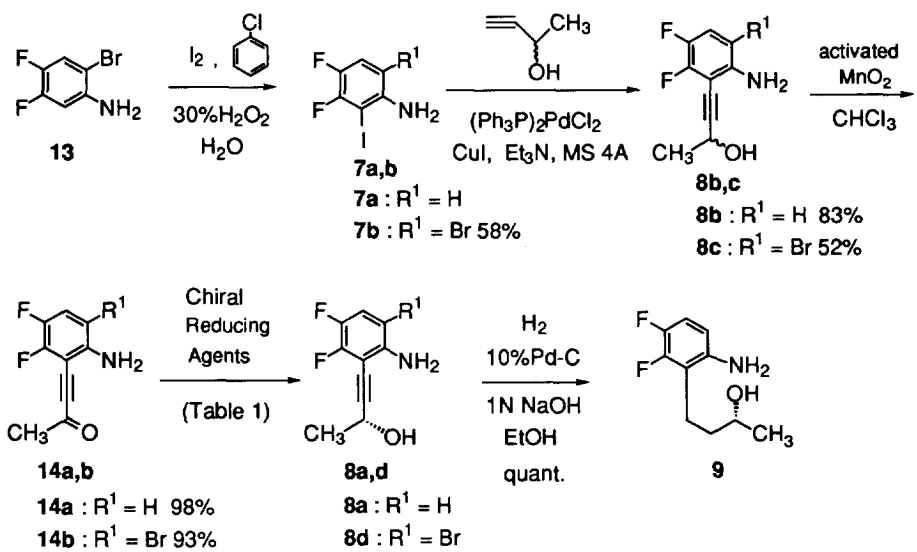
Scheme 1

In order to find the efficient synthesis of the butanol **9**, we investigated the asymmetric reduction of α,β-acetylenic ketones **14a,b** utilizing various chiral reagents (**A-E**).



Scheme 2

Treatment of 2-bromo-4,5-difluoroaniline (**13**)[7] with iodine in the presence of 30% aqueous hydrogen peroxide (H_2O_2) and chlorobenzene in water according to the literature[8] afforded 6-bromo-3,4-difluoro-2-iodoaniline (**7b**) in 58% yield. Propargylic alcohol **8b,c** were prepared from a cross-coupling reaction of **7a,b** and (±)-3-butyn-2-ol by the same manner as described for the synthesis of **8a**. Oxidation of **8b,c** with activated manganese oxide in $CHCl_3$ gave the α,β-acetylenic ketones **14a,b** in excellent yield. Asymmetric reduction of the **14a,b** was carried out by use of various chiral reagents (**A-E**) as summarized in the Table 1.



Scheme 3

Table 1 Asymmetric Reduction of α,β-Acetylenic Ketones using Chiral Reducing Agents

Entry	Compd. No.	Red. Agent[a]	Solvent	Temp.(℃)	Time(h)	Yield(%)	ee(%)[b]	Config.[c]
1	**14a**	(B)	THF	rt	48	57	78	*R*
2	**14a**	(B)	THF	4	15	18	79	*R*
3	**14a**	(B)	Et_2O	4	15	20	80	*R*
4	**14a**	(C)	THF	4	20	0		
5	**14b**	(A)-$LiAlH_4$	Et_2O	-78	6	86	61	*R*
6	**14b**	(B)	THF	rt	20	64	95	*R*
7	**14b**	(C)	THF	4	20	89	95	*R*
8	**14b**	(D)-catechol-borane	$PhCH_3$	-15	20	33	8	*R*
9	**14b**	(E)	THF	rt	16	44	52	*R*

a) Various chiral reagents as shown in Scheme 2.

b) Enantiomeric purities were determined by HPLC analysis using ULTRON ES-OVM (**8a** : CH_3CN : 20 mM aqueous KH_2PO_4 = 3 : 97, **8d** : CH_3CN : 20 mM aqueous KH_2PO_4 = 8 : 92).

c) Configuration of the predominant isomer.

As far as we tried, reduction of **14b** using (-)-diisopinocampheylchloroborane ((-)-Ipc_2BCl, entry 7)[9] in THF gave the best results, which were 89% yield and 95% enantiomeric excess. The use of (*R*)-Alpine-Borane® (entry 6)[10] in THF was found to give **8d** in 64% yield and 95% enantiomeric excess. Reduction of **14b** using Chirald®-lithium aluminum hydride ($LiAlH_4$) (entry 5)[11] in diethyl ether (Et_2O) gave **8d** in 86% yield and 61% enantiomeric excess. Reduction of **14b** using Corey's reagents (entry 8 and 9)[12] in toluene or THF afforded **8b**, but the yields and enantiomeric excesses of the resulting **8d** were lower than the use of (-)-Ipc_2BCl or (*R*)-Alpine-Borane®. On the other hand, reduction of **14a** by use of (-)-Ipc_2BCl or (*R*)-Alpine-Borane® (entry 1 – 4) did not give satisfactory results. The differences in the asymmetric reductions are under investigation. Propargylic alcohol **8a,d** prepared by the asymmetric reduction were hydrogenated with 10 % Pd - C in 1N NaOH and EtOH to convert to butanol **9** in good yield.

In conclusion, we have established an efficient synthesis of (*S*)-(-)-5,6-difluoro-2-methyl-1,2,3,4-tetrahydroquinoline (**4b**) using a cross-coupling reaction of the iodoaniline **7a** and (*R*)-3-butyn-2-ol, and also the asymmetric reduction of α,β-acetylenic ketone **14b** with various chiral reagents gave **8d** in high enantiomeric excess.

Experimental Section

Melting points were determined with a Yamato MP-21 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO IR-810 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC-200 spectrometer. Mass spectra (MS) were obtained on a Shimadzu GCMS-QP-1000 instruments. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Silica gel (Merck Art

7734) was used for column chromatography. Preparative thin layer chromatography (PLC) was carried out on plates (20 x 20 cm, 0.5 mm, thickness) precoated with silica gel ($60F_{254}$, Merck Art 5744).

N-(*tert*-butoxycarbonyl)-3,4-Difluoro-2-iodoaniline (6a). A solution of n-butyllithium in hexane (1.6 M, 45 ml, 66 mmol) was added slowly to a solution of **5** (6.88 g, 30 mmol) in dry THF (80 ml) at -78℃ under a nitrogen atmosphere. After the mixture was stirred at -78℃ for 1.5 h, a solution of iodine (22.84 g, 90 mmol) in dry THF (100 ml) was added slowly at -78℃ and the reaction mixture was stirred at 4℃ for 3h, and then, saturated aqueous NH_4Cl (40 ml) was added the reaction mixture. After evaporation of the solvent, the residue was extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$ and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, AcOEt : hexane = 1 : 17) to give **6a** (10.0 g) as black crystals, which were used for next step though the purity of **6a** was a little poor. ^{1}H-NMR ($CDCl_3$) δ : 1.54 (9H, s), 6.77 (1H, broad s), 7.05 - 7.25 (1H, m), 7.75 - 7.95 (1H, m). MS *m/z* (%) : 355 (26, M^+), 299 (86), 255 (100), 172 (21), 128 (31), 127 (51), 126 (29), 100 (26).

3,4-Difluoro-2-iodoaniline (7a). Concentrated HCl (30 ml) was added to a solution of **6a** (10.0 g) in dioxane (100 ml) and the mixture was stirred at 70℃ for 30 min. After evaporation of the solvent, the residue was poured into 10% aqueous NaOH and extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$ and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, AcOEt : hexane = 1 : 10) and recrystallized from hexane to give **7a** (5.42 g, 54 %) as colorless needles , mp 58 ℃. ^{1}H-NMR ($CDCl_3$) δ : 4.09 (2H, broad s), 6.40 - 6.55 (1H, m), 6.90 - 7.10 (1H, m). IR (KBr) : 3414, 1491, 1261, 842, 801 cm^{-1}. MS *m/z* (%) : 255 (100, M^+), 129 (90), 127 (71), 101 (51), 75 (21). *Anal.* Calcd for $C_6H_4F_2I$ N : C, 28.26; H, 1.58; N, 5.49. Found : C, 27.81; H, 1.62; N, 5.40.

(*R*)-4-(2-Amino-5,6-difluorophenyl)-3-butyn-2-ol (8a). A mixture of **7a** (0.38 g, 1.5 mmol), (*R*)-3-butyn-2-ol (0.21 g, 3 mmol), CuI (14 mg, 0.075 mmol), $(Ph_3P)_2PdCl_2$ (53 mg, 0.075 mmol) and molecular sieves 4A (0.3 g) in Et_3N (20 ml) was stirred at 60℃ for 1.5 h under a nitrogen atmosphere. The insoluble materials were removed by filtration and washed with CH_2Cl_2; the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, AcOEt : hexane = 1 : 3) to give **8a** (0.24 g, 80 %) as pale brown crystals, which were 100% ee by HPLC analysis using ULTRON ES-OVM (CH_3CN : 20 mM aqueous KH_2PO_4 = 3 : 97) and recrystallized from AcOEt - hexane to give pure **8a** (100 % ee) as pale brown needles, mp 73 - 74℃. $[\alpha]_D^{28}$ + 18.8 (*c* 0.1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ : 1.69 (3H, d, *J* = 6.44 Hz), 2.03 (1H, d, *J* = 5.22 Hz), 4.13 (2H, broad s), 4.84 (1H, quint, *J* = 6.44 Hz), 6.30 - 6.45 (1H, m), 6.85 - 7.05 (1H, m). IR (KBr) : 3300, 1618, 1502, 1255, 1118, 1054, 900, 815 cm^{-1}. MS *m/z* (%) : 197 (100, M^+), 182 (34), 180 (46), 179 (74), 164 (47), 154 (47), 153 (58), 127 (97), 126 (42), 125 (45). *Anal.* Calcd for $C_{10}H_9F_2NO$: C, 60.91; H, 4.60; N, 7.10. Found : C, 60.77; H, 4.64; N, 6.99.

(*R*)-4-(6-Amino-2,3-difluorophenyl)-2-butanol (9). A mixture of **8a** (0.20 g, 1 mmol), 10 % Pd - C (20 mg) in EtOH (10 ml) was stirred at room temperature under atmospheric pressure of hydrogen until the theoretical amount of hydrogen (45 ml) had been absorbed. The catalyst was removed by filtration and the

filtrate was concentrated *in vacuo* to give **9** (0.20 g, 100 %) as white crystals, which were used for the next step without further purification. ^{1}H-NMR ($CDCl_3$) δ : 1.22 (3H, d, J = 6.16 Hz), 1.50 - 1.85 (3H, m), 2.65 - 2.80 (2H, m), 3.60 - 3.85 (1H, m), 3.80 (2H, broad), 6.30 - 6.45 (1H, m), 6.75 - 6.90 (1H, m). MS *m/z* (%) : 201 (32, M^+), 168 (31), 154 (29), 143 (30), 142 (100).

(*R*)-4-(6-Acetylamino-2,3-difluorophenyl)-2-butanol (10). To a solution of Ac_2O (0.2 ml, 2 mmol) in EtOH (10 ml) was added **9** (0.20 g, 1 mmol) and the mixture was stirred at room temperature overnight. The solvent was evaporated off and the residue was dissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed with water and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2 : MeOH = 100 : 1) to give **10** (3.85 g, 99 %) as a pale yellow solid, which was 100 % ee by HPLC analysis using CHIRALCEL OJ (hexane : isopropanol : diethylamine = 950 : 50 : 1). The solid was recrystallized from AcOEt - hexane to give pure **10** (3.56 g, 92 %, 100 % ee) as colorless needles, mp 106.5 - 107 ℃. $[\alpha]_D^{26}$ + 6.5 (*c* 0.1, MeOH). ^{1}H-NMR ($CDCl_3$) δ : 1.26 (3H, d, J = 6.14 Hz), 1.60 - 2.00 (2H, m), 2.15 (3H, s), 2.65 - 3.00 (2H, m), 3.50 - 3.75 (1H, m), 6.90 - 7.10 (1H, m), 7.60 - 7.75 (1H, m), 8.86 (1H, broad). IR (KBr) : 3400, 3272, 1655, 1538, 1502, 1445 cm^{-1}. MS *m/z* (%) : 243 (11, M^+), 184 (26), 183 (23), 182 (28), 168 (48), 156 (22), 154 (45), 143 (44), 142 (100). *Anal.* Calcd for $C_{12}H_{15}F_2NO_2$: C, 59.25; H, 6.22; N, 5.76. Found : C, 59.31; H, 6.08; N, 5.86.

(*R*)-2-[4-(6-Acetylamino-2,3-difluorophenyl)butyl] Methanesulfonate (11). Methanesulfonyl chloride (5.9 ml, 76 mmol) was added to a stirred and ice-cooled solution of **10** (4.62 g, 19 mmol) in CH_2Cl_2 (90 ml) and pyridine (9.2 ml, 114 mmol) and the reaction mixture was stirred at room temperature overnight. The mixture was poured into 1N HCl (10 ml) and extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$ and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, CH_2Cl_2 : MeOH = 60 : 1) and recrystallized from AcOEt - hexane to give **11** (5.47 g, 90 %) as colorless needles, mp 101 - 102℃. $[\alpha]_D^{28}$+ 62.3 (*c* 0.1, MeOH). ^{1}H-NMR ($CDCl_3$) δ : 1.47 (3H, d, J = 6.43 Hz), 1.80 - 2.15 (2H, m), 2.20 (3H, s), 2.70 - 2.95 (2H, m), 3.08 (3H, s), 4.85 - 5.00 (1H, m), 6.95 - 7.10 (1H, m), 7.50 - 7.60 (1H, m), 7.54 (1H, broad s). IR (KBr) : 3254, 1657, 1530, 1506, 1328, 1183 cm^{-1}. MS *m/z* (%) : 321 (1, M^+), 279 (2), 226 (15), 225 (12), 184 (22), 183 (50), 182 (43), 168 (51), 154 (50), 142 (100). *Anal.* Calcd for $C_{13}H_{17}F_2NO_2S$: C, 48.59; H, 5.33; N, 4.36. Found : C, 48.64; H, 5.45; N, 4.36.

(*S*)-1-Acetyl-5,6-difluoro-2-methyl-1,2,3,4-tetrahydroquinoline (12). Sodium hydride (60 % dispersion in mineral oil, 0.83 g, 20.8 mmol) was added to a stirred and ice-cooled solution **11** (5.14 g, 16 mmol) in DMF (70 ml) and the reaction mixture was stirred for 2.5 h at room temperature. The reaction mixture was poured into ice-water and extracted with AcOEt - benzene (5 : 1). The extracts were dried over $MgSO_4$ and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, AcOEt : hexane = 4 : 5) to give **12** (3.60 g, quant.) as yellow oil. $[\alpha]_D^{26}$ + 256.0 (*c* 0.1, MeOH). ^{1}H-NMR ($CDCl_3$) δ : 1.11 (3H, d, J = 6.60 Hz), 1.52 (1H, broad s), 2.17 (3H, s), 2.10 - 2.35 (1H, m), 2.35 - 2.60 (1H, m), 2.85 - 3.00 (1H, m), 4.85 (1H, broad s), 6.80 - 7.15 (2H, m). IR (KBr) : 2970,

2930, 1665, 1501, 1373, 1305, 1267, 1214 cm^{-1}. MS *m/z* (%) : 226 (18), 225 (23, M^+), 183 (29), 168 (100), 166 (13).

(*S*)-5,6-Difluoro-2-methyl-1,2,3,4-tetrahydroquinoline (4b). A mixture of concentrated HCl (20 ml) and **12** (1.47 g, 6.5 mmol) was refluxed with stirring for 4 h. 10 % Aqueous NaOH (15 ml) was added to the reaction mixture at 0℃ and diluted with water. The mixture was extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$ and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, AcOEt : hexane = 1 : 6) to give **4b** (1.16 g, 98 %, 99.8 % ee) as colorless oil. $[\alpha]_D^{26}$ - 104.0 (*c* 0.1, MeOH). ^{1}H-NMR ($CDCl_3$) δ : 1.21 (3H, d, *J* = 6.26 Hz), 1.40 - 1.60 (1H, m), 1.85 - 2.05 (1H, m), 2.50 - 2.80 (1H, m), 2.80 - 2.95 (1H, m), 3.25 - 3.40 (1H, m), 3.65 (1H, broad s), 6.10 - 6.20 (1H, m), 6.65 - 6.85 (1H, m). IR (KBr) : 3418, 2928, 1505, 1343, 1256, 920 cm^{-1}. MS *m/z* (%) : 183 (30, M^+), 168 (100), 166 (15), 153 (24), 148 (10).

6-Bromo-3,4-difluoro-2-iodoaniline (7b). To a suspension of 2-bromo-4,5-difluoroaniline (**13**) (4.16 g, 20 mmol), iodine (2.54 g, 20 mmol) and chlorobenzene (1.0 g) in water was added dropwise 30 % aqueous H_2O_2 (2.5 ml, 22 mmol) and the reaction mixture was stirred at 90℃ for 4 h. The reaction mixture was poured into ice-water and extracted with Et_2O. The extracts were dried over $MgSO_4$ and concentrated to dryness *in vacuo*. The residue was purified by column chromatography (silica gel; eluent, AcOEt : hexane = 1 : 15) and recrystallized from Et_2O - hexane to give **7b** (3.85 g, 58 %) as colorless needles , mp 38 ℃. ^{1}H-NMR ($CDCl_3$) δ : 4.56 (2H, broad), 7.25 - 7.45 (1H, m). IR (KBr) : 3320, 1610, 1584, 857 cm^{-1}. MS *m/z* (%) : 335 (100), 333 (100, M^+), 287 (26), 127 (53), 126 (51), 99 (32). *Anal.* Calcd for $C_6H_3BrIF_2N$: C, 21.58; H, 0.91; N, 4.19. Found : C, 21.86; H, 0.91; N, 4.23.

4-(2-Amino-5,6-difluorophenyl)-3-butyn-2-ol (8b). Compound **8b** (0.25 g, 83 %) was prepared by a synthetic procedure similar to that used for **8a** with **7a** (0.38 g, 1.5 mmol), (±)-3-butyn-2-ol (0.32 g, 4.5 mmol), $(Ph_3P)_2PdCl_2$ (53 mg, 0.075 mmol), CuI (14 mg, 0.075 mmol), molecular sieves 4A (0.20 g), and Et_3N (20 ml). Pale brown needles from AcOEt - hexane, mp 80 -82℃. ^{1}H-NMR ($CDCl_3$) δ : 1.59 (3H, d, *J* = 6.60 Hz), 2.13 (1H, broad s), 4.14 (2H, broad s),, 4.83 (1H, q, *J* = 6.60 Hz), 6.30 - 6.45 (1H, m), 6.80 - 7.00 (1H, m). IR (KBr) : 3400, 3300, 1608, 1503, 1250, 1109, 1050 cm^{-1}. MS *m/z* (%): 197 (100, M^+), 182 (29), 180 (42), 179 (65), 178 (21), 164 (35), 154 (38), 153 (45), 151 (34), 127 (70), 126 (32), 125 (32). *Anal.* Calcd for $C_{10}H_9F_2NO$: C, 60.91; H, 4.60; N, 7.10. Found : C, 60.98; H, 4.67; N, 7.10.

4-(2-Amino-3-bromo-5,6-difluorophenyl)-3-butyn-2-ol (8c). Compound **8c** (43 mg, 52 %) was prepared by a synthetic procedure similar to that used for **8a** with **7b** (0.10 g, 0.3 mmol), (±)-3-butyn-2-ol (42 mg, 0.6 mmol), $(Ph_3P)_2PdCl_2$ (6 mg, 0.009 mmol), CuI (1 mg, 0.006 mmol), molecular sieves 4A (50 mg), and Et_3N (4 ml). Colorless needles from AcOEt - hexane, mp 93 -94℃. ^{1}H-NMR ($CDCl_3$) δ : 1.60 (3H, d, *J* = 6.62 Hz), 2.00 (1H, d, *J* = 5.50 Hz), 4.54 (1H, broad s), 4.85 (1H, m), 7.20 - 7.30 (1H, m). IR (KBr) : 3325, 1605, 1488 cm^{-1}. MS *m/z* (%): 277 (35), 275 (36, M^+), 259 (36), 257 (35), 153 (100), 152 (37), 151 (34), 126 (32), 125 (45). *Anal.* Calcd for $C_{10}H_8BrF_2NO$: C, 43.50 ; H, 2.92 ; N, 5.07. Found

: C, 43.17; H, 2.76; N, 5.03.

4-(2-Amino-5,6-difluorophenyl)-3-butyn-2-one (14a). Activated manganese dioxide (1.04 g, 12 mmol) was added to a solution of **8b** (0.55 g, 2 mmol) in $CHCl_3$ (10 ml) and the mixture was stirred under reflux for 0.5 h. The mixture was cooled to about 25℃ and the insoluble materials were removed by filtration and washed with $CHCl_3$. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel; eluent, AcOEt : hexane = 1 : 4) and recrystallized from AcOEt - hexane to give **14a** (1.16 g, 98 %) as yellow needles. mp 138 - 139℃. ^{1}H-NMR ($CDCl_3$) δ : 2.49 (3H, s), 4.35 (2H, broad s), 6.80 - 6.95 (1H, m), 7.00 - 7.15 (1H, m). IR (KBr) : 3350, 2170, 1655, 1580, 1500, 1299, 1195 cm^{-1}. MS *m/z* (%) : 195 (74, M^+), 180 (100), 153 (16), 152 (32), 126 (28), 125 (65), 75 (17). *Anal.* Calcd for $C_{10}H_7F_2NO$: C, 61.54; H,3.62; N, 7.18. Found : C, 61.57; H, 3.83; N, 7.11.

4-(2-Amino-3-bromo-5,6-difluorophenyl)-3-butyn-2-one (14b). Compound **14b** (1.27 g, 93 %) was prepared by a synthetic procedure similar to that used for **14a** with **8c** (1.27 g, 5 mmol) and activated manganese dioxide (3.92 g, 45 mmol) in $CHCl_3$ (40 ml). Yellow needles from AcOEt - hexane, mp 108 - 110 ℃. ^{1}H-NMR ($CDCl_3$) δ : 2.50 (3H, s), 4.76 (2H, broad s), 7.30 - 7.50 (1H, m). IR (KBr) : 3318, 2178, 1658, 1486, 1198 cm^{-1}. MS *m/z* (%) : 275 (63), 273 (64, M^+), 260 (99), 258 (100), 152 (49), 151 (67), 125 (45), 124 (38), 76 (34), 75 (36). *Anal.* Calcd for $C_{10}H_6BrF_2NO$: C, 43.82; H, 2.21; N, 5.11. Found : C, 43.67; H, 2.38; N, 5.11.

HPLC Analysis of 8b and 8c. Compound **8b** (1 mg) was dissolved in EtOH (1 ml) and 5 μl of the solution was subjected to HPLC analysis using ULTRON ES-OVM (i. d. 4.6 mm x 150 mm) (flow rate, 1.0 ml/min; eluent, CH_3CN : 20 mM aqueous KH_2PO_4 = 3 : 97, detection UV 254 nm). The chromatogram showed two peaks, and the retention times were 13.4 min (*S*-form) and 15.6 min (*R*-form). Also, compound **8c** (1 mg) was dissolved in EtOH (1 ml) and 5 μl of the solution was subjected to HPLC analysis using ULTRON ES-OVM (i. d. 4.6 mm x 150 mm) (flow rate, 1.0 ml/min; eluent, CH_3CN : 20 mM aqueous KH_2PO_4 = 8 : 92, detection UV 254 nm). The chromatogram showed two peaks, and the retention times were 12.9 min (*S*-form) and 16.1 min (*R*-form).

Asymmetric reduction of the ketone 14a with chiral reagents.

a) With B-isopinocampheyl-9-borabicyclo[3,3,1]nonane ((*R*)-Alpine-Borane®, B) (Table 1, entry 1). To a solution of **14a** (49 mg, 0.25 mmol) at 0 ℃ was added dropwise (*R*)-Alpine-Borane® (**B**, 0.5 M in THF, 0.7 ml, 0.35 mmol), and the reaction mixture was stirred at 0℃ for 1 h and at room temperature for 48 h. To the stirred reaction mixture was added 10% aqueous NaOH (2 ml) at 0℃. Then 30 % aqueous H_2O_2 (2 ml) was added at 0℃ and the reaction mixture was stirred at room temperature for 3 h. The mixture was extracted with Et_2O. The extracts were dried over $MgSO_4$ and concentrated to dryness *in vacuo*. The residue was purified by preparative thin layer chromatography (AcOEt : hexane = 2 : 1) to give **8a** (28 mg, 57 %, 78 % ee (*R*)) as yellow oil.

b) With B-isopinocampheyl-9-borabicyclo[3,3,1]nonane ((*R*)-Alpine-Borane®, B) (Table 1,

entry 2 and 3). Compound **14a** was reduced by the same manner as described above (entry 1); the reaction solvent, temperature, time, yield and configuration are given in Table 1.

Asymmetric reduction of the ketone14b with chiral reagents.

a) With (2*S*, 3*R*)-(+)-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol-Lithium Aluminum Hydride (Chirald®-$LiAlH_4$, A) (Table 1, entry 5). To a solution of $LiAlH_4$ - THF (1M solution, 0.27 ml, 0.264 mmol) was added dropwise a solution of (*R*)-Chirald® (**A**, 0.16 g, 0.576 mmol) in Et_2O (2 ml) at 0 ℃ under nitrogen atmosphere. The mixture was cooled to -78℃ and a solution of **14b** (60 mg, 0.22 mmol) in Et_2O (2 ml) was added dropwise to the reaction mixture. The mixture was stirred at -78℃ for 6 h and then 20 % aqueous citric acid (5 ml) was added. The mixture was gradually warmed to room temperature. The mixture was extracted with AcOEt. The extracts were dried over $MgSO_4$ and concentrated to dryness *in vacuo*. The residue was purified by preparative thin layer chromatography (AcOEt : hexane = 2 : 1) to give **8d** (52 mg, 86 %, 61 % ee (*R*)) as yellow powder.

b) With B-isopinocampheyl-9-borabicyclo[3,3,1]nonane ((*R*)-Alpine-Borane®, B) (Table 1, entry 6). To a solution of **14b** (55 mg, 0.2 mmol) in THF at 0 ℃ was added dropwise (*R*)-Alpine-Borane® (**B**, 0.5 M in THF, 0.58 ml, 0.28 mmol) and the reaction mixture was stirred at the same temperature for 1 h and at room temperature for 20 h. To the stirred reaction mixture was added 10% aqueous NaOH (2 ml) at 0℃. Then 30 % aqueous H_2O_2 (2 ml) was added at 0℃ and the reaction mixture was stirred at room temperature for 3 h. The mixture was extracted with Et_2O. The extracts were dried over $MgSO_4$ and concentrated to dryness *in vacuo*. The residue was purified by preparative thin layer chromatography (AcOEt : hexane = 2 : 1) to give **8d** (35 mg, 64 %, 95 % ee (*R*)) as yellow powder.

c) With (-)-Diisopinocampheylchloroborane ((-)-Ipc_2BCl, C) (Table 1, entry 7). (-)-Ipc_2BCl (**C**, 71 mg, 0.22 mmol) was transferred to the flask under nitrogen atmosphere rapidly and dissolved in THF (2 ml). To the solution was added **14b** (55 mg, 0.2 mmol) in THF (3 ml) at 0℃. The reaction mixture was stirred at 4℃ for 20 h. To the stirred reaction mixture was added 10% aqueous NaOH (2 ml) at 0℃ Then 30 % aqueous H_2O_2 (2 ml) was added at 0℃ and the reaction mixture was stirred at room temperature for 3 h. The mixture was extracted with Et_2O. The extracts were dried over $MgSO_4$ and concentrated to dryness *in vacuo*. The residue was purified by preparative thin layer chromatography (AcOEt : hexane = 2 : 1) to give **8d** (49 mg, 89 %, 95 % ee (*R*)) as yellow powder.

d) With (*S*)-5,5-Diphenyl-2-butyl-3,4-propano-1,3,2-oxaborolidine (Corey's reagent, D) (Table 1, entry 8). To a solution of (*S*)-5,5-diphenyl-2-butyl-3,4-propano-1,3,2-oxaborolidine (**D**, 0.1M in THF 0.4 ml, 0.04 mmol) in toluene (2 ml) was added dropwise a solution of **14b** (55 ml, 0.20 mmol) in toluene (3 ml) at room temperature under nitrogen atmosphere. The mixture was cooled to -78℃ and catecholborane (1M in THF, 0.6 ml, 0.6 mmol) was added by syringe. The reaction mixture was stirred at -78 ℃ for 4 h and at -15℃ for 20 h. The mixture was acidified by addition of 20 % aqueous citric acid (2 ml) and extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$ and concentrated to dryness *in vacuo*. The

residue was purified by preparative thin layer chromatography (AcOEt : hexane = 2 : 1) to give **8d** (18 mg, 33 %, 8 % ee (*R*)) as yellow powder.

e) With (*S*)-5,5-Diphenyl-2-butyl-3,4-propano-1,3,2-oxaborolidine (Corey's reagent, E) (Table 1, entry 9). To a solution of (*S*)-5,5-diphenyl-2-butyl-3,4-propano-1,3,2-oxaborolidine (**E**, 1M solution, 0.3 ml, 0.3 mmol) in THF (3 ml) was added dropwise borane-THF (1M in THF, 0.33 ml, 0.33 mmol) at room temperature under a nitrogen atmosphere. The mixture was cooled to -78℃, and then Et_3N (33 mg, 0.33 ml) and a solution of **14b** (69 mg, 0.25 mmol) in THF (2 ml) were added by syringe. The mixture was stirred at room temperature for 16 h. The mixture was acidified by addition of 20 % aqueous citric acid (2 ml) and extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$ and concentrated to dryness *in vacuo*. The residue was purified by preparative thin layer chromatography (AcOEt : hexane = 2 : 1) to give **8d** (30 mg, 44 %, 52 % ee (*R*)) as yellow powder.

(*R*)-4-(6-Amino-2,3-difluorophenyl)-2-butanol (9). A mixture of **8d** (49 mg, 0.18 mmol), 10 % Pd - C (5 mg) in 1N NaOH (0.4 ml) and EtOH (8 ml) was stirred at room temperature under atmospheric pressure of hydrogen until the theoretical amount of hydrogen (15 ml) had been absorbed. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with water. The CH_2Cl_2 solution was dried over $MgSO_4$ and concentrated to give **9** (38 mg, 100%) as white crystals, which were used for the next step without further purification. ^{1}H-NMR ($CDCl_3$) δ : 1.22 (3H, d, J = 6.16 Hz), 1.50 - 1.85 (3H, m), 2.65 - 2.80 (2H, m), 3.60 - 3.85 (1H, m), 3.80 (2H, broad), 6.30 - 6.45 (1H, m), 6.75 - 6.90 (1H, m). MS *m/z* (%) : 201 (32, M^+), 168 (31), 154 (29), 143 (30), 142 (100).

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