A PRACTICAL SYNTHESIS OF NOVEL RHO-KINASE INHIBITOR, (*S*)-4-FLUORO-5-(2-METHYL-1,4-DIAZEPAN-1-YLSULFONYL)-ISOQUINOLINE

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Abstract – A practical synthesis of novel Rho-kinase inhibitor, (*S*)-4-fluoro-5-(2-methyl-1,4-diazepan-1-ylsulfonyl)isoquinoline hydrochloride dihydrate (**1**) was achieved in a pilot-scale production. We have demonstrated the regioselective chlorosulfonylation of 4-fluoroisoquinoline in an one-pot reaction to afford 4-fluoroisoquinoline-5-sulfonyl chloride and the asymmetric construction of the (*S*)-2-methyl-1,4-diazepane moiety as key steps.

INTRODUCTION

A highly potent and selective Rho-kinase inhibitor, (*S*)-4-fluoro-5-(2-methyl-1,4-diazepan-1-ylsulfonyl)-isoquinoline hydrochloride dihydrate (**1**)[1] has been developed from Fasudil (**2**).[2,3] Both compounds have the same core structure of 5-(1,4-diazepan-1-ylsulfonyl)isoquinoline as shown in Figure 1. Fasudil has been recognized as a potent Rho-kinase inhibitor and clinically used for the treatment of cerebral vasospasm.[2] Furthermore the recent studies revealed that **2** could enhance memory and improve the prognosis of Alzheimer's patients,[3a] angina[3b] and pulmonary arterial hypertension.[3c] After exploring the chemical derivatives of **2**, the incorporation of fluorine atom at C4 position of isoquinoline moiety and the chiral attachment of the methyl group at C2' position of 1,4-diazepane moiety dramatically improved the pharmacological action. As can be seen, **1** showed much more potent and selective Rho-kinase inhibitory activity than Fasudil[1a] and would be potentially expected to cure the Cerebral Vascular Disorder.[1b] Especially, it is noteworthy that **1** can be effective on the ocular hypertension with intraocular pressure (IOP)-lowering activity and neuroprotection of retinal ganglion cells injured in glaucoma.[1a]
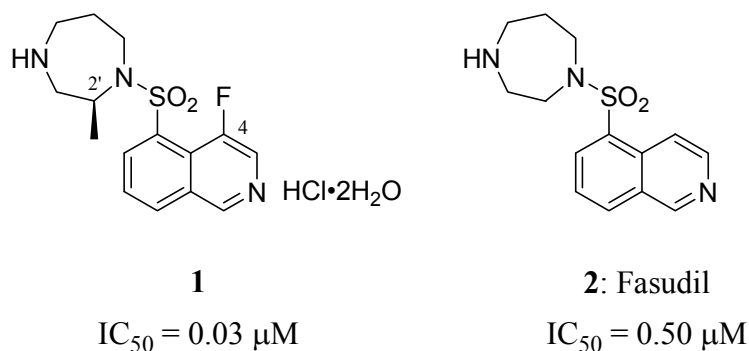
Figure 1. Structure and Activity of Rho-kinase inhibitors

As part of our drug research and development plans, we required the practical synthesis of **1** in multi-kilogram scale and be easily scalable to commercial scale. However, there are two major issues. First, we needed to develop a regioselective chlorosulfonylation reaction at C5 position of 4-fluoroisoquinoline. Second, we had to guarantee the stereochemical purity in (*S*)-2-methyl-1,4-diazepane moiety. Herein we disclose the synthesis of **1** starting from 4-fluoroisoquinoline at pilot-scale.

RESULTS AND DISCUSSION

In our retrosynthetic analysis (Scheme 1), we set out to synthesize the intermediate **3** and verify that the absolute stereochemistry at the C2' position would be retained to form the enantiomerically pure (*S*)-2-methyl-1,4-diazepane moiety. Intramolecular cyclization of the sulfonamide alcohol (**3**) would afford **1** by a Mitsunobu reaction. The precursor of **3** could be identified the combination of **4** and readily available (*S*)-2-aminopropanol by the disconnection bond between C3' position and N4' position. The sulfonamide
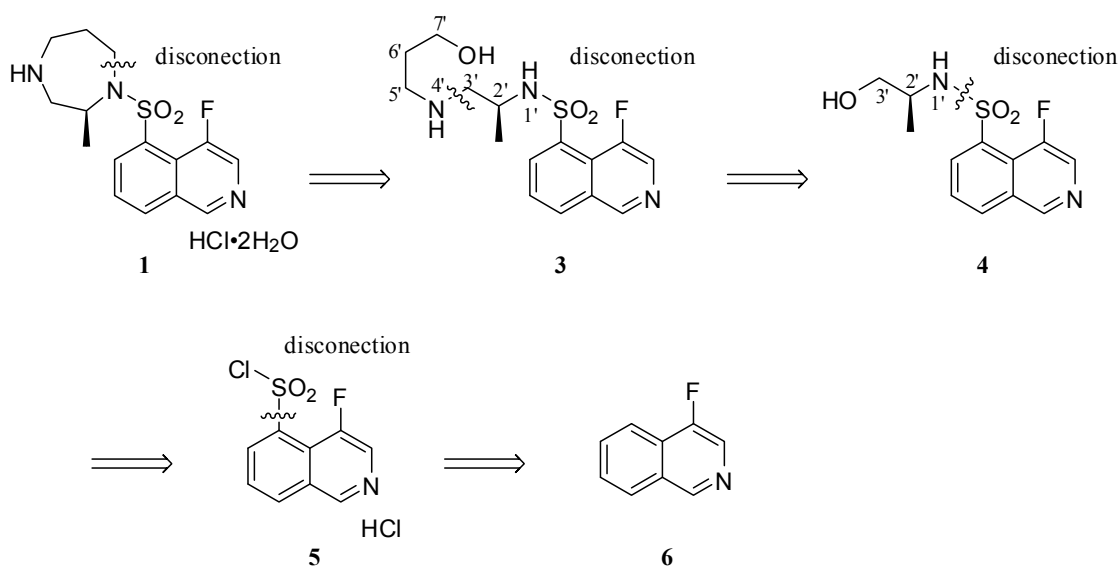
**Scheme 1**. Retrosynthetic analysis of **1**

alcohol (**4**) can be easily prepared from 4-fluoroisoquinoline-5-sulfonyl chloride (**5**). An efficient chlorosulfonylation of 4-fluoroisoquinoline (**6**)[4] is the most important issue to provide **5**.

Although several methods for synthesis of **5** were previously reported, these syntheses were not amenable due to many steps, low yields, troublesome purifications and tedious reaction conditions (e.g., diazonium salt intermediates).[5] Accordingly, we needed to establish the reproducible synthesis of **5** from **6** that is applicable for a large-scale production. In order to prepare **5**, we investigated a variety of reaction condition on the regioselective sulfonylation of **6** and its efficient purification.

Some methods for the synthesis of arylsulfonychlorides from the corresponding aromatics have been achieved by stepwise sulfonylation and subsequent chlorination with phosphorus pentachloride, phosphorus oxychloride, thionyl chloride,[6] or directly with chlorosulfuric acid,[6a,7] or treatment with a combination of sulfinic acid and NCS.[8] These methodologies have been already applied to some isoquinolines.[6b,6c,7b]

We attempted to transform **6** into **7** with a combination of concd H_2SO_4 and SO_3 to produce fuming sulfuric acid *in situ* (Table 1). The initial conditions by applying 2.2 eq of concd H_2SO_4 and 8.6 eq of SO_3 took 18 h at 30 °C to complete (Table 1, Entries 1, 2). While the quantity of concd H_2SO_4 accelerated the reaction (Entries 1 - 3), the low concentration of SO_3 decreased the reaction rate and the regioselectivity between the C5 position and the C8 position (Entries 4, 5). The presence of ca. 2 eq of concd H_2SO_4 seemed to be favorable in the sulfonylation reaction conditions. Using a vast excess of SO_3, the sulfonylation yield was improved for the desired **7** at 0 °C to 15 °C for 4 h (Entries 6 - 8). However, these conditions were unsuitable for a large-scale production, since the bulk amounts of concd H_2SO_4 make it difficult and expensive to neutralize for waste disposal compared to Entry 2. In addition, it was too difficult to stir the viscous reaction mixtures under these conditions. On the other hand, heating the reaction to 50 °C facilitated the stirring, but eroded the regioselectivity (Entry 9). We also investigated the influences of added Lewis Acids on the sulfonylation reaction in combination with concd H_2SO_4 and SO_3 system. Unfortunately, the separate addition of 1 eq of $MgCl_2$, $AlCl_3$, $ZnCl_2$, or H_3BO_3 decreased the yield of **7** (Entries 10 - 13). Half of equivalent of $FeCl_3$ or $AgNO_3$ had no impact on the yield of **7** (Entries 14, 15), but $FeCl_3$ did afford the highest regioselectivity in the reaction. In the procedure on a large-scale production, the handling of **6** was found to be troublesome because of its low melting point.[4]

Then we investigated the HSO_4^- salt of **6** for easy handling in the sulfonylation reaction. Remarkably, we found that the HSO_4^- salt of **6** was very effective in the reaction providing high yield as shown in Entry 16 with decreased H_2SO_4 equivalents and good regioselectivity. As the result, we selected the best conditions as Entry 16 and Entry 2 as a second choice for the sulfonylation of **6**.

**Table 1.** Results of the Sulfonylation Reaction of Isoquinoline (**6**)
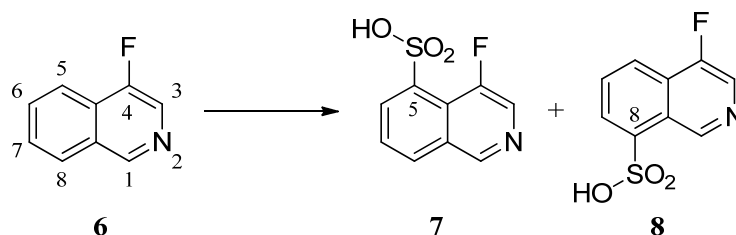
Entry	concd H_2SO_4 (eq)	SO_3 (eq)	Additive (eq)	Temp. (°C)	Time (h)	**6**[a] (%)	**7+8**[a] (%)	**7/8**[a]
1	2.2	8.6	-	30	3	49	51	1.8
2	2.2	8.6	-	30	18	1	98	1.5
3	-	9.0	-	30	22	43	48	1.5
4	4.3	8.4	-	30	22	54	30	1.4
5	8.8	8.4	-	30	22	75	14	1.1
6	2.2	12	-	0	4	4	96	2.1
7	2.1	17	-	30	4	0	99	1.8
8	6.6	17	-	15	4	8	92	1.9
9	2.2	7.1	-	50	48	9	91	1.3
10	2.2	8.6	$MgCl_2$ (1)	30	3	71	26	1.7
11	2.2	8.6	$AlCl_3$ (1)	30	3	67	33	1.8
12	2.2	8.6	$ZnCl_2$ (1)	30	3	41	58	1.9
13	2.2	8.6	H_3BO_3 (1)	30	3	63	35	1.9
14	2.2	8.6	$FeCl_3$ (0.5)	30	3	20	80	2.4
15	2.2	8.6	$AgNO_3$ (0.5)	30	3	10	65	2.1
16[b]	-	8.6	-	30	16	0	94	1.8

[a] Determined by HPLC. [b] No additional H_2SO_4 added but HSO_4^- salt (**6a**) was used.

Next, we developed a concise one-pot reaction for production of the sulfonyl chloride (**5**) *via* the corresponding sulfonic acid (**7**) prepared in a combination of concd H_2SO_4 and SO_3 from **6** and which was subsequently exposed upon $SOCl_2$ (Table 2). Our first attempt for a simple procedure was as follows. The 4-fluoroisoquinoline (**6**) in $SOCl_2$ was treated with a mixture of concd H_2SO_4 and SO_3. This reaction was failed and gave only a trace amount of **5** and **9** with the recovered **6** (63%) (Table 2, Entry 1). Accordingly, we conducted stepwise the sulfonylation of **6** with concd H_2SO_4 and SO_3 and subsequently the chlorination of the prepared **7** and **8** with $SOCl_2$ in one-pot reaction (Entry 2). The similar result was obtained by application of HSO_4^- salt of **6** (Entry 3). The ratio of **7** and **8** was not changed in the chlorination process. Satisfactory results were obtained to afford extra pure **5** in 41% and 39% yield after crystallization as the

HCl salt respectively. Fortunately, the 8-sulfonyl chloride (**9**) as by-product can be easily removed by filtration in the mother liquid during the crystallization procedure.

Table 2. One-Pot Sulfonylation and Chlorination Reaction from **6**
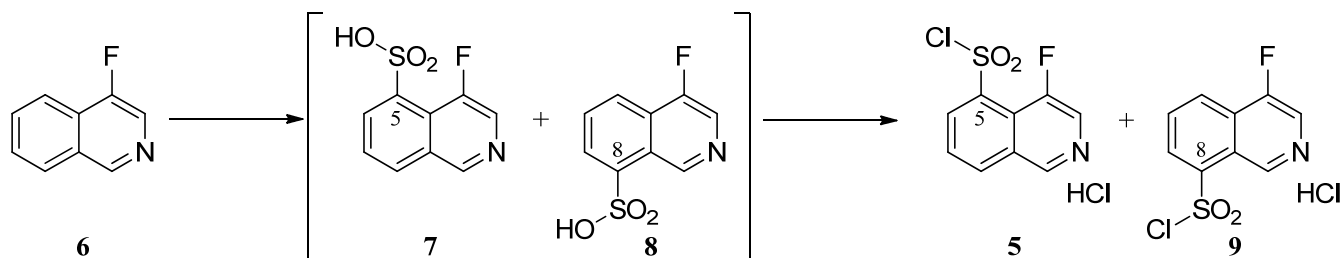
Entry	concd H_2SO_4 (eq)	SO_3 (eq)	Time (h)	6^a (%)	$7/8^a$	$SOCl_2$ (eq)	$5+9^b$ (%)	$5:9^c$
1^d	2.2	8.6	18	63	-	14	-	-
2^e	2.2	8.6	18	0	1.6	5.4	41	98 : 0.3
$3^{e,f}$	-	8.6	16	0	1.8	4	39	>99 : 0.4

[a] Determined by HPLC.

[b] Isolated yields as the HCl salt.

[c] After isolation by crystallization, the ratio of each compound was determined by HPLC.

[d] To a solution of **6** in $SOCl_2$ was added the solution of concd H_2SO_4 and SO_3.

[e] Sulfonylation and subsequently chlorination in one-pot stepwise reaction.

[f] HSO_4^- salt (**6a**) was used.

Thus obtained sulfonyl chloride **5** in one-pot reaction[9] was further utilized in the synthesis of our Rho-kinase inhibitor (**1**) as depicted in Scheme 2. Sulfonylamidation of **5** with (*S*)-2-aminopropanol gave the corresponding sulfonylamide (**4**) in 84% yield. Mesylation of **4** led to a mixture of the mesylate (**10**) and the aziridine intermediate (**11**).[10] *N*-Alkylation was carried out *in situ*, the mixture of **10** and **11** was directly treated with 3-aminopropanol to afford the desired **3** in a high yield. Two reaction pathways can be postulated for the nucleophilic attack on Site A or Site B of the aziridine. The ratio of the isomer **3b** to **3a** was greatly influenced by the reaction temperature. The desired addition (attacked from site A) was controlled by carrying out the reaction at low temperature.[11] However, we had to remove **3b** to the minimum at this stage. In order to avoid using the column chromatography separation especially in a large-scale production, we attempted to purify **3a** by way of a crystalline oxalate salt. As expected, the oxalate salt of **3a** was obtained as colorless crystals in 73% yield from **4**. Thus we succeeded in minimizing the amount of the contaminating isomer **3b** (attack from site B) to 0.3%.
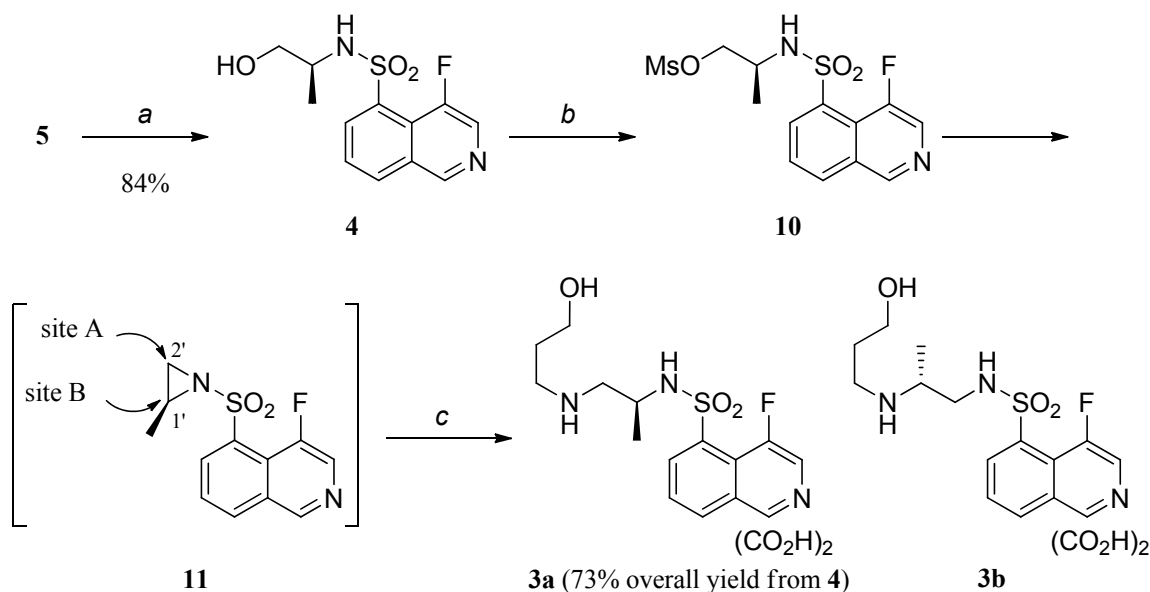
Scheme 2. Reagent and conditions; (a) (*S*)-2-aminopropanol, Et$_3$N, CH$_2$Cl$_2$, 20 °C. (*b*) MsCl, Et$_3$N, THF, 0 °C, then 3-aminopropanol was added, 25 °C. (*c*) (CO$_2$H)$_2$, aq. IPA, 75 °C, and cooled to 25 °C.

After basifying of the oxalate salt of **3a** to afford the free amine (**3**) (Scheme 3), the intramolecular cyclization was conducted by treating **3** under Mitsunobu conditions.[12] The reaction proceeded smoothly to provide the desired product (**12**) in 90% yield (95% purity by HPLC). Finally, the purification of **1** was accomplished by the crystallization as the HCl salt in 73% yield over two steps (>99.9% ee). The crystalline **1** was sufficiently pure for GMP production and clinical use.
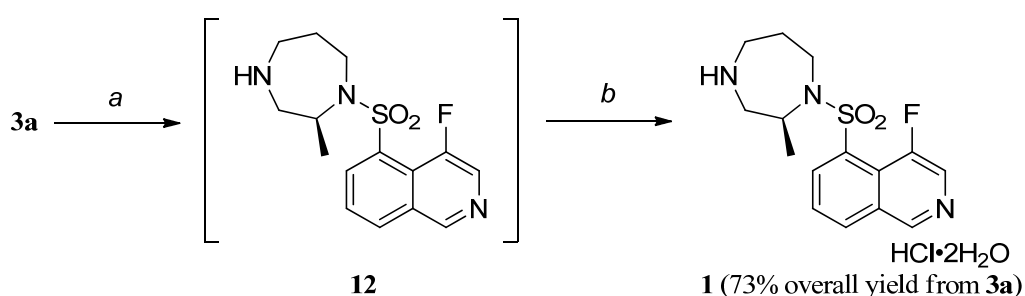
Scheme 3. Reagent and conditions; (*a*) K$_2$CO$_3$ aq., CH$_2$Cl$_2$, rt, followed DIAD, Ph$_3$P, toluene-THF, 25 °C. (*b*) concd HCl, acetone, 15 °C.

In conclusion, we have achieved the practical synthesis of novel Rho-kinase inhibitor, (*S*)-4-fluoro-5-(2-methyl-1,4-diazepan-1-ylsulfonyl)isoquinoline hydrochloride dihydrate (**1**) starting from 4-fluoroisoquinoline in a pilot-scale production. We developed and reported the concise one-pot chlorosulfonylation of 4-fluoroisoquinoline and the regioselective construction of the chiral 1,4-diazepane

by a Mitsunobu reaction intramolecular cyclization as the key steps. Application of **1** for the treatment of ocular hypertension is currently under study.

EXPERIMENTAL

General. All reactions were carried out under a N_2 atmosphere unless otherwise noted. Optical rotations were measured on a JASCO P-2200 polarimeter with sodium (D line) lamp. IR spectra were recorded on a Thermo Nicolet 370 FT-IR spectrometer. ^{1}H-NMR spectra and ^{13}C-NMR spectra were obtained on a JEOL JNM-AL 400 MHz spectrometer using $CDCl_3$ or DMSO-d_6 solvents with tetramethylsilane as internal standard unless otherwise noted. Mass spectra were obtained on a JEOL MS-BU20 mass spectrometer. Elemental analyses (C, H, N) were performed by Yanaco MT-5. Elemental analyses (Cl) were performed by Kyoto Electronics Manufacturing AT-510. Elemental analyses (S, F) were performed by Nippon Dionex ICS-1500. Melting points were determined in open glass capillaries on a Buchi B-545 melting point apparatus. The HPLC analyses were performed using Hitachi D-7000 equipment. The optical purity was determined by HPLC analysis (CHIRALPAK AD, Daicel Chemical Industries Limited).

4-Fluoroisoquinoline sulfate (6a)

To a solution of 4-fluoroisoquinoline (**6**)[4] (9.40 kg, 63.9 mol) in acetone (28 kg) was carefully and gradually added concd H_2SO_4 (6.58 kg, 67.1 mol) at $0 - 10$ °C, and the mixture was stirred at the same temperature for 2 h. The precipitated crystals were filtered, washed with acetone (22 kg), and dried under reduced pressure to yield **6a** (15.5 kg, 99%) as a colorless crystalline solid.: mp 166-167 °C; IR (KBr) 1659, 1617, 1601, 1558, 1506, 1407 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 8.09 (1H, t, $J = 7.9$ Hz), 8.25 (1H, t, $J = 7.9$ Hz), 8.31 (1H, d, $J = 7.9$ Hz), 8.60 (1H, d, $J = 7.9$ Hz), 8.87 (1H, d, $J = 3.7$ Hz), 9.74 (1H, s), 12.18 (2H, s); ^{13}C-NMR (DMSO-d_6) δ: 119.7 ($J = 3.3$ Hz), 122.2 ($J = 32.3$ Hz), 127.8 ($J = 14.9$ Hz), 128.8 ($J = 5.0$ Hz), 129.8, 131.0, 135.6, 146.5 ($J = 4.1$ Hz), 155.8 ($J = 256.6$ Hz); FABMS m/z 148 (M+H–H_2SO_4)$^+$; Anal. Calcd for $C_9H_8FNO_4S$: C, 44.08; H, 3.29; F, 7.75; N, 5.71. Found: C, 43.90; H, 3.31; F, 7.81; N, 5.73.

4-Fluoroisoquinoline-5-sulfonyl chloride hydrochloride (5)

To liquid sulfur trioxide (47.7 kg, 596 mol) was gradually added **6a** (15.8 kg, 64.4 mol) at 30 °C for 3 h and the resulting mixture was stirred at the same temperature for 16 h. To this reaction mixture was gradually added $SOCl_2$ (42.2 kg, 355 mol) at the same temperature for 3 h. The mixture was heated with stirring to 70 °C for 4h and allowed to cool to 20 °C. The reaction mixture was slowly added to a mixture of water (208 kg), NaCl (48 kg), ice (200 kg) and CH_2Cl_2 (320 kg) at a temperature of less than 5 °C. The organic layer was partitioned. The aqueous layer was extracted with CH_2Cl_2 (3 x 126 kg). The combined organic layers were washed with saturated brine (85 kg), $NaHCO_3$ (9 kg) in water (117 kg) and saturated brine (93 kg) and dried over anhydrous Na_2SO_4 (24 kg). Na_2SO_4 was filtered, washed with additional CH_2Cl_2 (210 kg) and combined. To this solution was slowly added 4 M HCl/EtOAc (18 kg) at 35 °C and the resulting

mixture was stirred at 35 °C for 1 h. The precipitated crystals were filtered, washed with CH_2Cl_2 (63 kg) and dried under reduced pressure to yield **5** (7.04 kg, 39%) as a colorless crystalline solid. The crystalline solids contained a trace amount of the C8-isomer (**9**) which was determined by HPLC (Ratio of **5** and **9** was 99.64:0.36).: mp 200-201 °C (decomp); IR (KCl) 2993, 2303, 2086, 1654, 1495, 1375, 1184 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 7.94 (1H, t, J = 7.8 Hz), 8.45-8.49 (1H, m), 8.67 (1H, dd, J = 7.8, 1.2 Hz), 8.77 (1H, d, J = 5.4 Hz), 9.62 (1H, s), 14.80 (1H, br s); ^{13}C-NMR (DMSO-d_6) δ: 124.2 (J = 13.4 Hz), 127.3 (J = 32.4 Hz), 129.2, 130.8, 130.9 (J = 3.8 Hz), 133.8, 142.4 (J = 5.7 Hz), 147.5 (J = 4.8 Hz), 155.0 (J = 268.0 Hz); ^{1}H-NMR (CDCl$_3$, as free base) δ: 7.84 (1H, t, J = 7.8 Hz), 8.40-8.44 (1H, m), 8.71 (1H, d, J = 4.4 Hz), 8.72 (1H, dd, J = 7.8, 1.5 Hz), 9.25 (1H, s); ^{13}C-NMR (CDCl$_3$, as free base) δ: 121.1 (J = 13.2 Hz), 126.6 (J = 1.7 Hz), 130.6, 134.5 (J = 28.1 Hz), 134.9, 135.7 (J = 1.7 Hz), 138.0 (J = 4.1 Hz), 149.2 (J = 5.8 Hz), 152.0 (J = 265.7 Hz); FABMS m/z 246 (M(as ^{35}Cl)+H–HCl)$^+$; Anal. Calcd for C$_9$H$_6$Cl$_2$FNO$_2$S: C, 38.32; H, 2.14; Cl, 25.13; F, 6.73; N, 4.96; S, 11.37. Found: C, 38.26; H, 2.09; Cl, 25.14; F, 6.58; N, 4.95; S, 11.34. Data for the intermediate (**7**): ^{1}H-NMR (DMSO-d_6) δ: 6.93 (1H, br s), 7.76 (1H, t, J = 7.8 Hz), 8.23-8.29 (1H, m), 8.49 (1H, dd, J = 7.8, 1.0 Hz), 8.52 (1H, d, J = 5.2 Hz), 9.28 (1H, s). Data for the intermediate (**8**): ^{1}H-NMR (DMSO-d_6) δ: 7.20 (1H, br s), 8.10 (1H, t, J = 7.8 Hz), 8.26 (2H, d, J = 7.8 Hz), 8.82 (1H, d, J = 3.4 Hz), 10.08 (1H, s).

(*S*)-4-Fluoro-*N*-(1-hydroxypropan-2-yl)isoquinoline-5-sulfonamide (4)

To a solution of (*S*)-2-aminopropanol (2.08 kg, 27.7 mol) in CH_2Cl_2 (92 kg) was added Et$_3$N (6.30 kg, 62.3 mol) and the solution was cooled below –10 °C. To this mixture was gradually added **5** (7.04 kg, 25.0 mol) at –10 °C over 1 h. The resulting mixture was stirred at the same temperature for 30 min and allowed to stir at 20 °C for 18 h. After completion of the reaction, the mixture was diluted with additional CH_2Cl_2 (99 kg). The organic layer was washed with water (3 x 12 kg) and concentrated under reduced pressure. The residue was dissolved in IPA (36 kg) at 74 °C. The solution was allowed to cool to 25 °C and crystals were formed. The mixture was further cooled with stirring at 5 °C for 1 h. The precipitated crystals were filtered, washed with IPA (11 kg) and dried under reduced pressure at 40 °C to yield **4** (5.92 kg, 84%) as an off-white crystalline solid.: mp 149-151 °C; [α]$^{19}_D$ –18.36 (*c* 0.54, CHCl$_3$); IR (KBr) 3397, 3329, 3092, 1492, 1329, 1159, 1054 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ: 1.06 (3H, d, J = 6.3 Hz), 1.78 (1H, t, J = 5.1 Hz), 3.43-3.59 (3H, m), 5.34 (1H, t, J = 7.1 Hz), 7.77 (1H, t, J = 7.8 Hz), 8.23-8.28 (1H, m), 8.60 (1H, d, J = 5.4 Hz), 8.68 (1H, dd, J = 7.8, 1.2 Hz), 9.19 (1H, s); ^{13}C-NMR (CDCl$_3$) δ: 18.0, 51.8, 66.0, 121.8 (J = 12.4 Hz), 127.1, 130.8 (J = 2.5 Hz), 132.9, 133.0 (J = 29.8 Hz), 134.1 (J = 4.1 Hz), 134.9, 149.6 (J = 4.1 Hz), 152.8 (J = 259.9 Hz); FABMS m/z 285 (M+H)$^+$; Anal. Calcd for C$_{12}$H$_{13}$FN$_2$O$_3$S: C, 50.69; H, 4.61; F, 6.68; N, 9.85; S, 11.28. Found: C, 50.75; H, 4.49; F, 6.38; N, 9.93; S, 11.30.

(*S*)-4-Fluoro-*N*-[1-(3-hydroxypropylamino)propan-2-yl]isoquinoline-5-sulfonamide oxalate (3a)

To a solution of **4** (5.92 kg, 20.8 mol) in THF (65.1 kg) was added Et$_3$N (3.16 kg, 31.2 mmol) at 20 °C. To the mixture was gradually added MsCl (2.50 kg, 21.8 mol) at –10 °C for 35 min. The reaction mixture was stirred at 0 °C for 30 min and then 3-aminopropanol (6.26 kg, 83.3 mol) was added. The reaction mixture was allowed to warm to 25 °C and stirred for 20 h. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was diluted with CH$_2$Cl$_2$ (170 kg) and NaHCO$_3$ (1.00 kg) in water (12.0 kg). The organic layer was partitioned and concentrated under reduced pressure. The residue was dissolved in IPA (107 kg) and water (7.10 kg). To this solution was gradually added oxalic acid dihydrate (2.62 kg, 20.8 mol) in the solution of IPA (26.4 kg) and water (1.80 kg) at 70 °C for 35 min. The reaction mixture was allowed to cool to 25 °C and crystals were formed. The precipitated crystals were filtered, washed with IPA (23.3 kg) and dried under reduced pressure at 40 °C to yield **3a** (6.55 kg, 73%) as a colorless crystalline solid. The crystalline solids contained a trace amount of **3b** which was determined by HPLC (0.3%).: mp 176-177 °C; $[\alpha]^{19}_D$ –42.29 (*c* 0.54, DMSO); IR (KBr) 3287, 3080, 1717, 1589, 1332, 1164 cm^{-1}; ^{1}H-NMR (DMSO-*d$_6$*) δ: 0.89 (3H, d, *J* = 6.6 Hz), 1.66-1.77 (2H, m), 2.89-3.01 (4H, m), 3.46 (2H, t, *J* = 6.0 Hz), 3.59-3.69 (1H, m), 7.94 (1H, t, *J* = 7.8 Hz), 8.57 (2H, d, *J* = 7.8 Hz), 8.74 (1H, d, *J* = 4.9 Hz), 9.39 (1H, s); ^{13}C-NMR (DMSO-*d$_6$*) δ: 18.3, 28.5, 45.3, 46.7, 51.5, 58.2, 120.8 (*J* = 13.2 Hz), 127.6, 130.6 (*J* = 1.7 Hz), 132.5 (*J* = 28.1 Hz), 133.3, 134.1 (2C), 149.9 (*J* = 5.0 Hz), 152.1 (*J* = 263.2 Hz), 164.5 (2C); FABMS *m/z* 342 (M+H–(CO$_2$H)$_2$)$^+$; Anal. Calcd for C$_{17}$H$_{22}$FN$_3$O$_7$S: C, 47.33; H, 5.14; F, 4.40; N, 9.74; S, 7.43. Found: C, 47.37; H, 4.99; F, 4.26; N, 9.84; S, 7.37.

(*S*)-4-Fluoro-5-(2-methyl-1,4-diazepan-1-ylsulfonyl)isoquinoline hydrochloride dihydrate (1)

To a solution of **3a** (6.55 kg, 15.2 mol) in CH$_2$Cl$_2$ (85.2 kg) was added a solution of K$_2$CO$_3$ (5.00 kg, 36.2 mol) in water (11.1 kg) at 20 °C. The reaction mixture was stirred at the same temperature for 1 h. The organic layer was partitioned and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 43.9 kg). The combined organic layers were concentrated under reduced pressure. The residue was dissolved in toluene (5.24 kg) and THF (5.90 kg). The solution was azeotropically evaporated to remove water under reduced pressure. The residue was dissolved in THF (93.7 kg). To this solution was added Ph$_3$P (5.12 kg, 19.5 mol) and a solution of DIAD (95%, 4.10 kg, 19.3 mol) in toluene (5.90 kg) at 20 °C. The resulting mixture was stirred at 25 °C for 30 min and then concentrated under reduced pressure. The residue was dissolved in CH$_2$Cl$_2$ (41.9 kg). To this mixture was added 1.05 M HCl solution (34.7 kg) at 10 °C. The aqueous layer was partitioned, washed with CH$_2$Cl$_2$ (46.5 kg) and stirred with activated carbon (0.33 kg) at 25 °C for 1 h. The mixture was filtered to remove the activated carbon. The activated carbon was washed with water (10.0 kg). The combined aqueous layers were cooled to 10 °C and neutralized with 8.3 M sodium hydroxide solution (7.86 kg) until pH>8 and then extracted with CH$_2$Cl$_2$ (3 x 21.0 kg). The combined organic layers were washed with water (13.0 kg) and concentrated under reduced pressure. The residue was dissolved in acetone (31.2 kg). To this solution was gradually added concd HCl (1.52 kg, 15.0 mol) at 10 °C. The

reaction mixture was stirred at 15 °C for 20 h and then cooled to 5 °C and stirred at the same temperature for 2h. The precipitated crystals were filtered, washed with acetone (8.80 kg) and dried under reduced pressure to yield **1** (4.41 kg, 73%, >99.9% ee) as a white crystalline solid.: mp 258-259 °C (decomp); $[\alpha]^{20}_D$ −8.82 (*c* 1.00, H_2O); IR (KCl) 3406, 2983, 2763, 1588, 1324, 1146, 1129 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 1.20 (3H, d, *J* = 6.6 Hz), 1.98-2.07 (2H, m), 3.06-3.16 (1H, m), 3.22-3.31 (2H, m), 3.35 (4H, s), 3.44 (1H, dd, *J* = 14.1, 4.4 Hz), 3.59-3.74 (2H, m), 4.37-4.47 (1H, m), 7.93 (1H, t, *J* = 7.8 Hz), 8.32 (1H, d, *J* = 7.8 Hz), 8.54-8.60 (1H, m), 8.72 (1H, d, *J* = 4.9 Hz), 9.39 (1H, s), 9.51 (2H, br s); ^{13}C-NMR (DMSO-d_6) δ: 16.6, 26.8, 42.9, 45.5, 50.3, 50.9, 120.9 (*J* = 12.4 Hz), 127.5, 130.7 (*J* = 1.7 Hz), 132.2, 132.5 (*J* = 27.3 Hz), 133.2 (*J* = 5.0 Hz), 133.3, 149.8 (*J* = 5.0 Hz), 152.0 (*J* = 264.0 Hz); FABMS *m/z* 324 (M+H–HCl–2H_2O)$^+$, Anal. Calcd for $C_{15}H_{23}ClFN_3O_4S$: C, 45.51; H, 5.86; Cl, 8.96; F, 4.80; N, 10.61. Found: C, 45.44; H, 5.65; Cl, 8.87; F, 4.68; N, 10.78.

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9. We investigated the other chlorosulfonylation conditions as follows. Attempts of the direct chlorosulfonylation of **6** with chlorosulfonic acid gave **5** as a minor product (13%) and the isomer (**9**) as the major product (24%) (by HPLC analysis). The separate use of the other strong acids such as $ClSO_3H$, CF_3SO_3H, or Nafion NR-50 instead of concd H_2SO_4 decreased the regioselectivity compared to the combination of H_2SO_4/SO_3 and $SOCl_2$. The direct electrophilic reaction of SO_2Cl_2 in the separate presence of Lewis acids such as $ClSO_3H$, $AlCl_3$, or Nafion NR-50 was unsuccessful and gave complex mixtures.

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11. The isomer **3b** was detected at various amounts in the following reaction conditions: 2.9% (at 0 °C and warmed to 25 °C for 12 h), 4.4% (at 20 °C for 12 h) and 5.4% (at 40 °C for 6 h). Although the complete suppression to produce **3b** was too difficult, we finally succeeded in diminishing the yield of **3b** from 2.9% to 0.3%. The methyl group at C1' position of aziridine ring serves as steric hindrance to control the nucleophilic attack of 3-aminopropanol toward site A rather than site B.

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