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Development of a Practical and Scalable Synthesis of a Potent Selective Dual Antagonist for 5-HT2B and 5-HT7 Receptors

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ABSTRACT: Process research and development of a practical and scalable synthetic route toward compound (*S*)-**1** and compound (*R*)-**1**, which are potent selective dual antagonists for 5-HT2B and 5-HT7 receptors, respectively, is described. The medicinal chemistry route and second generation route were also unattractive for large-scale use for a variety of reasons. The new synthetic method does not require any purification by column chromatography for all steps and highly exothermic reactions. Additionally, we developed an efficient method of optical resolution in which each carboxylic acid isomer was separated with chiral amine in high yield and high enantiopurity. This highly efficient and scalable process was successfully demonstrated in the large scale synthesis of compound (*S*)-**1** and compound (*R*)-**1** in high enantiopurity.

INTRODUCTION

(*S*)-*N*-(Diaminomethylidene)-4′,5′-dihydro-3′*H*-spiro[fluorene-9,2′-furan]-2-carboxamide monohydrochloride (compound (*S*)-**1**, Figure 1) has a potent medicament for IBS, wherein

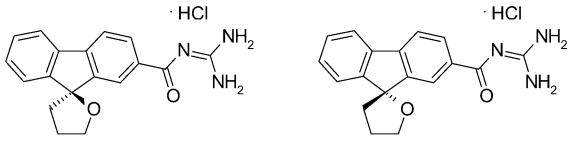

Figure 1. Structures of (*S*)-**1** and (*R*)-**1**.

the selective dual antagonist for 5-HT2B and 5-HT7 receptors comprises a selective dual antagonistic compound for 5-HT2B and 5-HT7 receptors having selective binding affinity for both 5-HT2B and 5-HT7 receptors.[1a] An enantioisomer (compound (*R*)-**1**, Figure 1) also has a potent same pharmacological effect.[1a] Additionally, these compounds have an advantage in that they have high affinity for serotonin receptor subtypes, particularly for 5-HT2B receptor and 5-HT7 receptor, and show excellent pharmacological effects in comparison with the conventional compounds which have only one of the antagonistic activities of 5-HT2B receptor and 5-HT7 receptor; this is useful as a prophylactic antimigraine agent having high safety and excellent effect.[1b] Herein, we report our efforts to develop an efficient synthetic route capable of being operated in a scale up synthesis of compound (*S*)-**1** for the first GMP delivery and compound (*R*)-**1** for a preclinical study campaign.

RESULT AND DISCUSSION

First Generation Synthetic Route (Medicinal Chemistry Synthetic Route). The medicinal chemistry synthetic route (first generation route) is shown in Scheme 1.

There were several drawbacks in the medicinal chemistry route (first generation route), and those are summarized below.

- Methyl protection of carboxylic acid should be avoided to produce a shorter synthetic route.
- The use of highly flammable and toxic BH_3−THF complex has a risk of provoking a dangerous operation on a large scale.
- Heating conditions of H_2O_2 in THF will be an unfavorable operation from the point of view of safety.
- The yield of optical resolution with cinchonidine was very low (16%). It was including the recovery from filtrate and following 8 times recrystallization of the cinchonidine salt to meet >99% ee.
- The overall yield was very low (4.2%).
- Purification using column chromatography in a final step is not an efficient method, and the use of chlorinated solvent in the final step is not favorable from the point of view of the environment, as well.

Second Generation Synthetic Route (Three-Hundred-Gram Scale Synthesis). Owing to the urgency with which we were required to provide material for further preclinical studies, we decided that chiral separation using the SMB method (simulated moving bed chromatography) should be better than an optical resolution method for the preparation of the 300 g campaign (Scheme 2). In this second generation route, the C−C bond formation method was improved; it was achieved using a Grignard reaction instead of a hydroboration−oxidation reaction, and the number of steps was shortened.

While the route was successfully used to prepare 350 g of (*S*)-**1** in good yield and high enantiopurity, it had many unattractive issues with regard to scale up synthesis for the 20 kg campaign. These are listed below.

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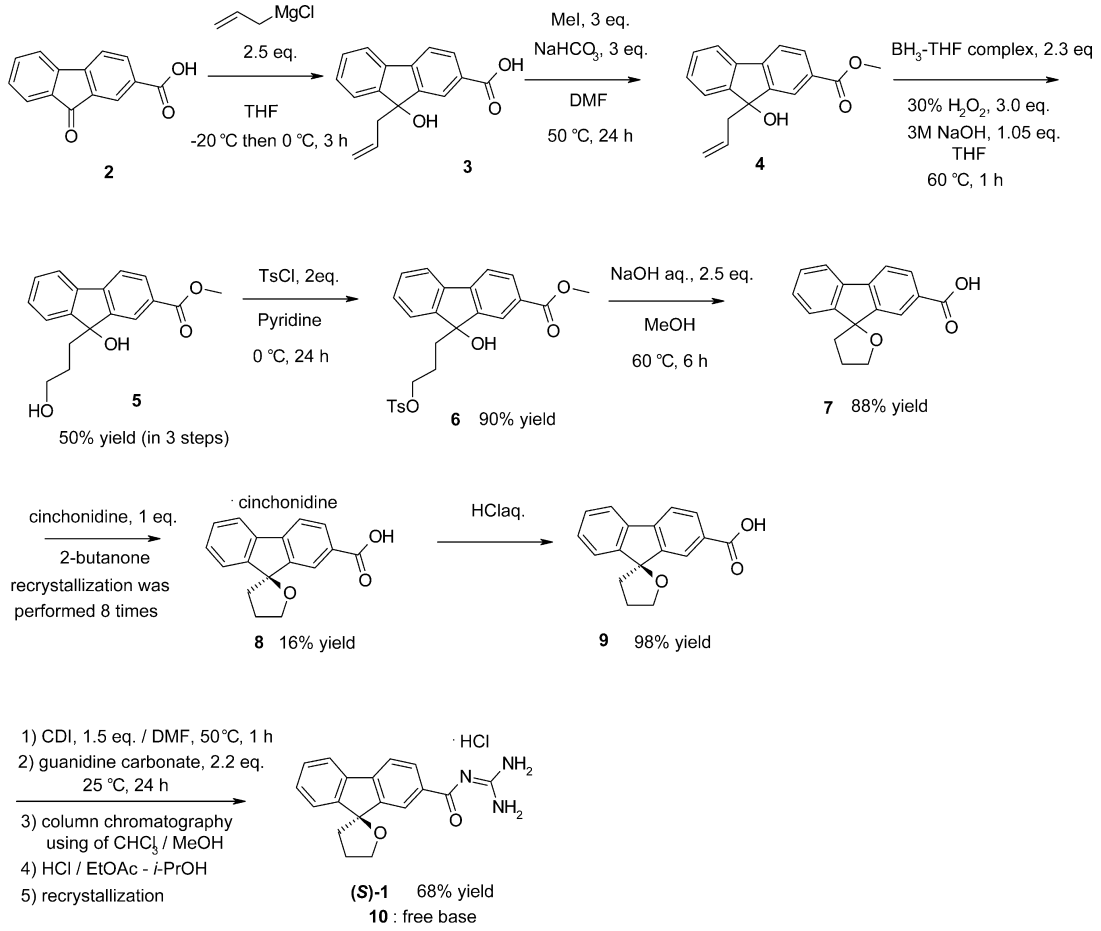
Scheme 1. First Generation Synthetic Route (Medicinal Chemistry Synthetic Route)



Chiral Separation Using SMB Chromatography[2] *in a Final Stage.* The chiral separation of racemate in the final stage was successful on the 1 kg scale. We could prepare the 99.7% ee sample for the precrinical study. The yield of the SMB chiral separation of **10** was 38%. However, it was estimated that it would be impossible to separate on a larger scale because of the low solubility and too expensive to separate for a 20 kg scale synthesis.[3]

Control of Grignard Reaction. This Grignard reaction was highly exothermic and was performed near or at the boiling temperature of THF solvent. Sudden initiation of the reaction occurred, and high heat release rate was observed, which could lead to vigorous boiling and to flooding in the vapor tube with risk of overpressure and explosion.[4]

Inefficient Method for the Spiro-Ring Formation. The second generation method for spiro-ring formation using an *O*-leaving group[5] was described in Scheme 3. The use of TsCl (2.1 equiv) gave a good conversion, but there were issues for scale up synthesis. For example, it was difficult to not only control the production of impurity A (typically 5%) but also prevent the formation of **14** that was caused by hydrolysis of the tosylate during the treatment with aqueous NaOH (typically 5%); both of these impurities were difficult to remove without SiO_2 column chromatography workup.

New Approach for 20 kg Scale Synthesis (Third-Generation). Under such circumstances, there has been a brisk demand for the development of an excellent production process for **1** with a higher overall yield that does not require column chromatography purification.

Our efforts were focused on designing a safe, scalable, and efficient synthesis of (*S*)-**1** (Scheme 4) that incorporates the following key points: (1) C−C bond formation using acetylide ion[6] with 9-oxo-9*H*-fluorene-2-carboxylic acid **2**; (2) a scalable synthetic method for spiro-ring formation under acidic conditions; and (3) optical resolution of racemate with commercially available chiral amine compound (establish a scalable optical resolution method).

We studied the new strategic approach to the 20 kg synthesis campaign of (*S*)-**1**. In the following sections, we would like to describe these results and discuss them.

C−C Bond Formation. To develop a suitable C−C bond formation, the reaction between compound **2** and non-protected propargyl alcohol **15** was attempted (Table 1). However, the reaction did not complete. This can be attributed to the higher acidity of the hydroxyl proton as compared to the acetylenic proton. If an additional quantity of base was used, another impurity formation was observed (HPLC). In this case, it was difficult to prepare the desired compound in high yield (entries 1−4). Next, we focused on a C−C bond formation with commercially available and inexpensive THP protected propagyl alcohol **17**. The use of DMF as a solvent gave better conversion compared with THF solvent. At 20 °C and above, the reaction did not complete (entries 5 and 6). On the other hand, addition of *t*-BuOK at −20 °C gave a good conversion and **18** was prepared in 92.8% yield (entry 7). This method was performed in a large scale synthesis campaign and gave 92.8 kg of **18**.

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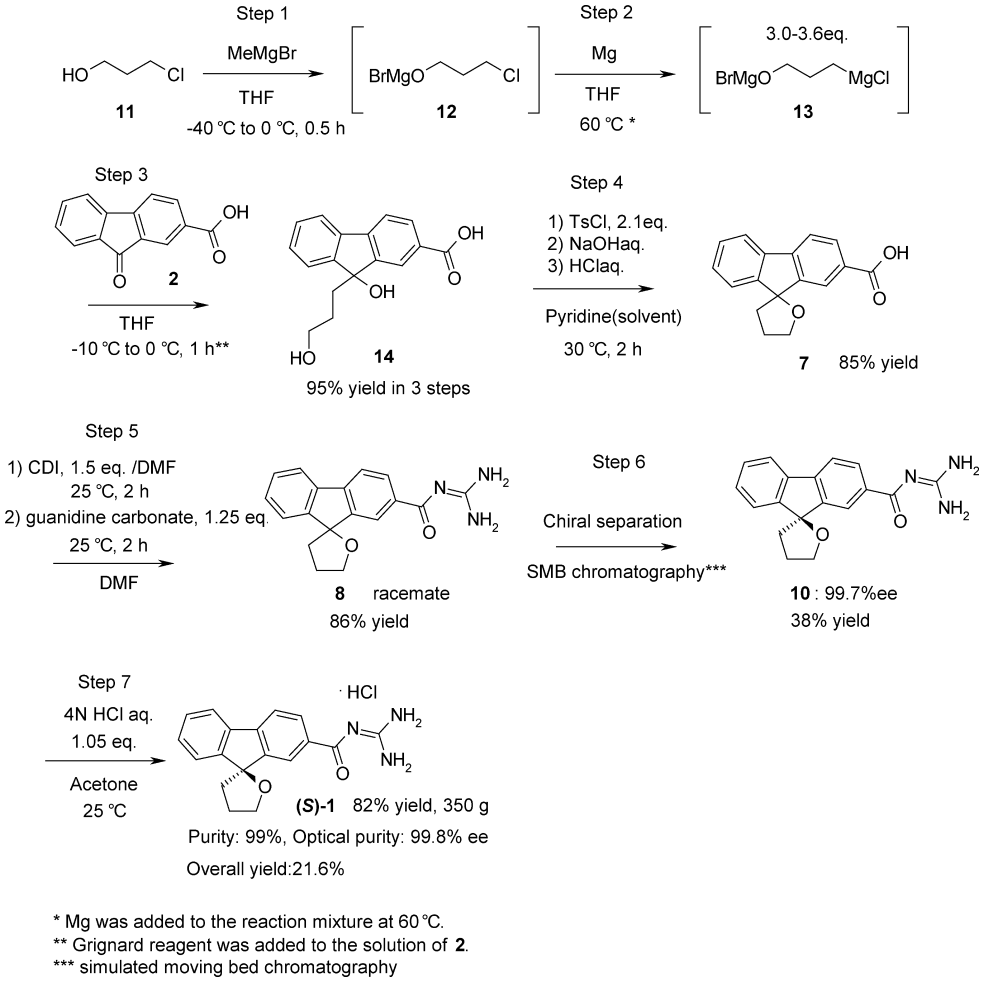
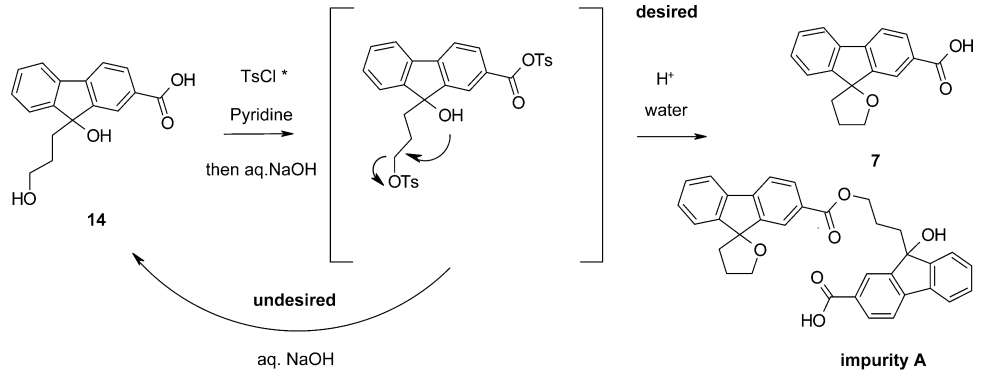
Scheme 2. Second Generation Synthetic Route (Three-Hundred-Gram Scale Synthesis)



Scheme 3. Spiro-ring Formation in the Second Generation Method



Reduction of Alkyne and Deprotection of Alcohol. Several methods were investigated in reduction of the alkyne step (Table 2). During this hydrogenation, we focused on the formation of impurity B. The hydrogenation of **18** (with H_2, Pd/C, and Et_3N in MeOH) gave 5% of impurity B (entry 1). The reaction conditions without Et_3N accelerated the formation of impurity B (entry 2). In this case, the carboxylic acid unit worked as an acid in this reaction. Next, catalytic hydrogen transfer reductions using ammonium[7] or potassium formate were attempted (entries 3 and 4). The use of potassium formate[8] with Pd/C in MeOH gave the best result. The level of impurity B was less than 2%. This might be due to the reduction of the benzyl alcohol moiety being suppressed by the high basicity of potassium formate.[9]

Intermediate **19** was used in the next step without purification and isolation. The following deprotection of THP

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Scheme 4. New Synthetic Strategy for Compound (*S*)-1

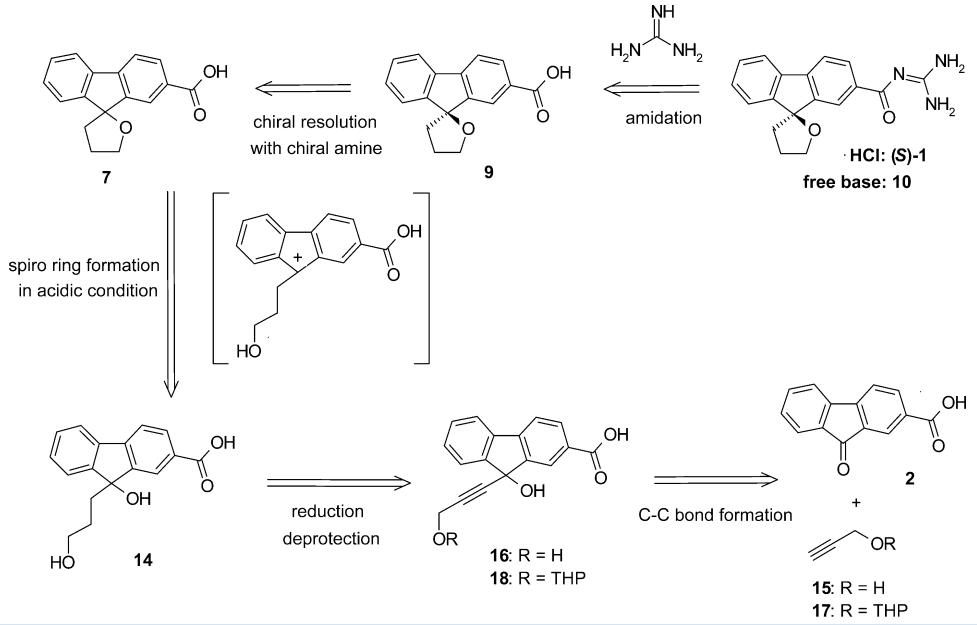
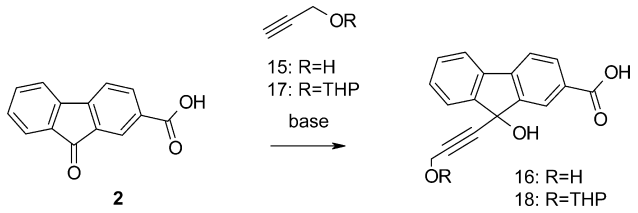


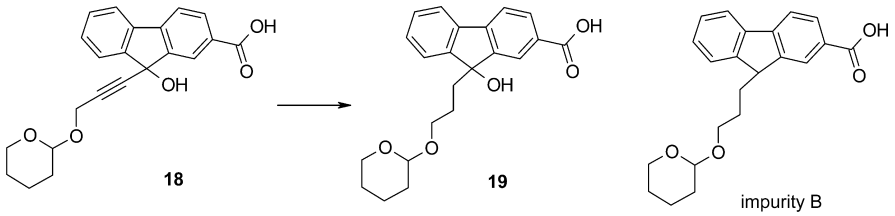
Table 1. C−C Bond Formation with Propagyl Substrates



entry	R (equiv)	base (equiv)/solvent	temp (°C)	HPLC yield of **16** or **18**[b] (%)
1	H (1.0)	*t*-BuOK (2 + 2)/DMF	0−25	48
2	H (1.0)	*t*-BuOK (2 + 2)/THF	0−25	21
3	H (1.0)	KOH (2 + 2)/THF	0−25	49
4	H (1.0)	NaH (2 + 2)/THF	0−25	2
5	THP (1.05)	*t*-BuOK (2.1)/THF	20−40	74
6	THP (1.05)	*t*-BuOK (2.1)/DMF	20−40	94
7[a]	THP (1.05)	*t*-BuOK (2.1)/DMF	−20 to 0	99.5

[a] *t*-BuOK was added to a DMF solution of **2** and **17** at −20 °C. Isolated yield was 92.8%. [b] Determined by HPLC methods A and B (see Experimental Section).

Table 2. Reduction of Alkyne[a]



entry	conditions	**18**/**19**[c]	impurity B[c] (%)
1	H_2, Et_3N (× 1 mol), 2 h[b]	ND/94	5
2	H_2, Et_3N (none), 1 h[b]	ND/92	8
3	ammonium formate (× 8 mol), 2 h	ND/96	4
4	potassium formate (× 8 mol), 2 h	ND/98	<2

[a] Catalyst, 10%Pd/C(M), Kawaken Fine Chemicals Co., Ltd.; solvent, MeOH; reaction temp, 25 °C. [b] Under atmospheric pressure. [c] Determined by HPLC methods A and B.

using a catalytic amount of 38 wt % HCl in MeOH gave 64.1 kg of diol compound **14** in excellent yield in a first scale up synthesis (88.7% yield in 2 steps from compound **18**).

Spiro-ring Formation. In the initial medicinal chemistry route, the spiro-ring formation under acidic conditions was given[1a,b] (Scheme 5). However, in these cases, about 16% of

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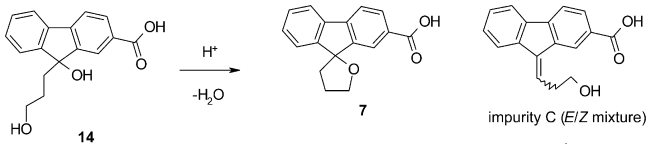
Scheme 5. Spiro-ring Formation under Acidic Conditions



eliminated impurity C was observed, and it was difficult to remove impurity C without SiO_2 column chromatographic purification. We thought that if we could prevent the formation of eliminated impurity C, the spiro-ring synthesis under acidic conditions[10] would be better because of the difficulties of the leaving group methods in a large scale synthesis as shown above.

As shown Table 3, the use of combination acid and a low-polarity solvent such as toluene did not give good resluts; impurity C was observed over 10% (entries 1−5). Also, AcOH or HCO_2H as a solvent did not give good results (entries 6 and 7). On the other hand, a polar solvent such as aqueous *i*-PrOH or *t*-BuOH could prevent the formation of impurity C, but esterificated byproduct was detected (entries 8−10). To reduce the level of impurity C, we focused on the solvent with characteristics of (1) high water solubility and (2) high boiling point aprotic solvent (no esterification).

And so we selected diglyme as a solvent and tried the cyclization reaction (entry 11). As we expected, this condition worked well; the level of impurity C was <1% in a reaction mixture. After the completion of the reaction, the target intermediate **7** was isolated in 88−90% yield simply by adding water to the reaction mixture. The purity of isolated compound **7** was 99% (HPLC), and it contained <1% of impurity C (<0.5% *E*/*Z* each other). Thereafter, 52.4 kg of compound **7** was prepared in a first scale up synthesis (87.7% yield).

Optical Resolution of Racemate. For the 20 kg manufacturing campaign, we challenged the optical resolution with the chiral amine approach. Both enantiomers had already been separated in high enantiopurity by medicinal chemists by using chiral amine. (*S*)-Carboxylic acid **9** was separated as a cinchonidine salt, and (*R*)- carboxylic acid **21** was separated as a brucine salt (Scheme 6).

To optimize the optical resolution method to prepare optically pure (*S*)-carboxylic acid **9**, several solvents were screened with cinchonidine (Table 4). The use of *i*-PrOH and *i*-PrOAc did not give crystals (entries 3 and 5), and MIBK

Table 3. Spiro-ring Formation under Acidic Conditions

				HPLC area %[g]			
entry	acid (equiv)	solvent	°C/h	**14**	**7**	impurity C[a]	comment
1	$TsOH·H_2O$ (1.0)	toluene	100/3	<1	79	16	
2	$TsOH·H_2O$ (0.1)	toluene	100/3	<1	82	14	
3	$TsOH·H_2O$ (0.1)	1,4-dioxane	100/3	82	8	10	
4	PPTS (0.1)	toluene	100/3	<1	71	25	
5	Amberlyst-15	toluene	100/3	<1	33	59	*c*
6	AcOH		80/3	30	42	10	
7	HCO_2H		80/3	<1	43	trace	*c*
8	H_2SO_4 (0.6)	*i*-PrOH/water (50/50)	100/37	1	89	5	*d*
9	MsOH (0.6)	*i*-PrOH/water (50/50)	100/65	2	84	6	*e*
10	H_2SO_4 (0.6)	*t*-BuOH/water (57/43)	100/44	<1	89	3	*f*
11	H_2SO_4 (0.6)	diglyme[b] (6 v/w) water (5 v/w)	93/24	<1	94	<1	

[a]Impurity C was calculated as an *E*/*Z* mixture. [b]Diglyme = diethyleneglycol dimethyl ether. [c]Complex mixture. [d]4% of isopropyl ester was observed. [e]6% of isopropyl ester was observed. [f]3% of *tert*-butyl ester was observed. [g]Determined by HPLC methods A and B.

Scheme 6. Optical Resolution of the Racemate of the Medicinal Chemistry Method

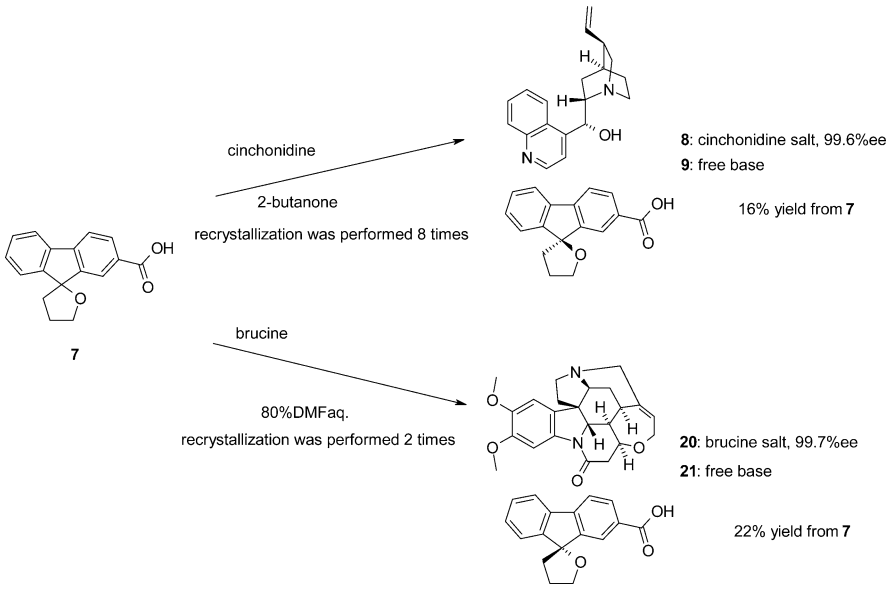


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Table 4. Solvent Screening for Cinchonidine Salt[a]

entry	solvent (v/w)	temp (°C)	yield (%) from 7	% ee[b]
1	MEK (10)	25	42	66
2	MIBK (15)	25	67	20
3	*i*-PrOH (10)	25	not crystallized	
4	EtOAc (10)	25	61	30
5	*i*-PrOAc (10)	25	not crystallized	
6	methyl propionate (10)	25	57	38
7	methyl propionate (20)	0	50	60

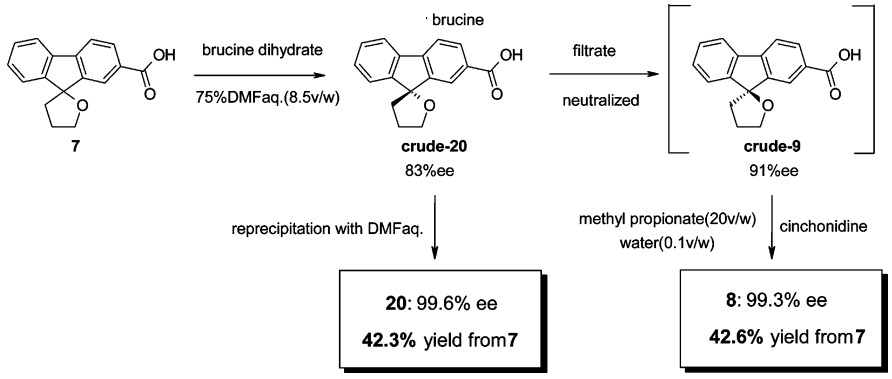
[a]Cinchonidine: 1 equiv. [b]Determined by HPLC method C (see the Experimental Section).

and EtOAc gave low enantioselectivity (entries 2 and 4). The use of methyl propionate gave the best result in this case (entry 7). However, this method was not perfect; cinchonidine salt formation and three times recrystallization of cinchonidine salt were required to meet the desired optical purity (>98% ee), and the yield was very low (24% from **7**).

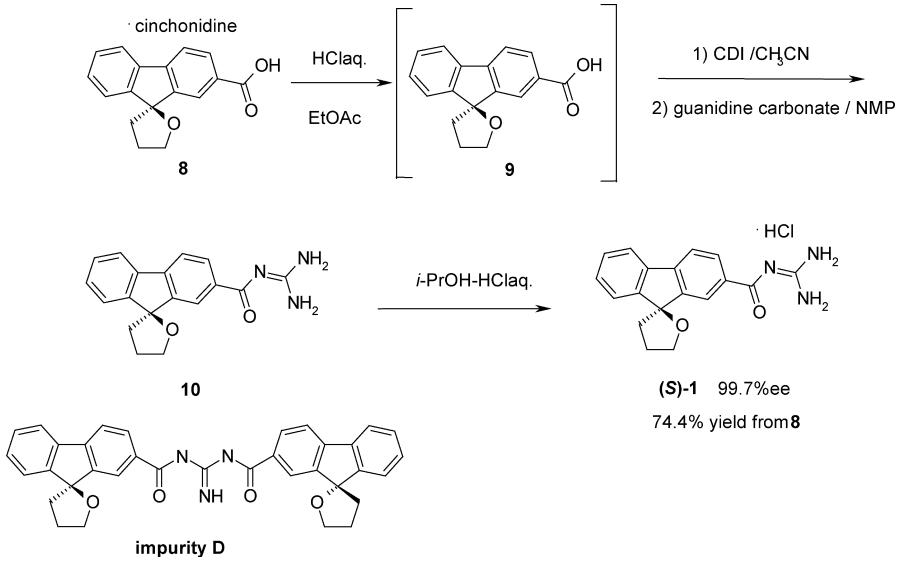
At that time, we were required to synthesize not only compound **9** but also compound **21** for preclinical study. And so, we focused on the medicinal chemistry methods. (*R*)-Carboxylic acid **21** was separated as a brucine salt in aqueous DMF solution in high optical purity, in good sequences. On the basis of these results, a new approach that cinchonidine salt formation for (*S*)-carboxylic acid **9** was performed using the filtrate of the brucine salt preparation for (*R*)-carboxylic acid **21** was attempted. The filtrate was treated with the EtOAc–aqueous hydrochloric acid, and brucine was removed in an aqueous layer. The organic layer that included **9** was concentrated. In this stage, the level of enantioisomer **21** was about 4–5% by HPLC analysis. The residue was dissolved in methyl propionate, and 0.5 equiv of cinchonidine (vs racemate **7**) was added. During the salt formation with cinchonidine, addition of a small amount of water (0.5% v/v of methyl propionate) gave a good result; the optical purity was increased to 99.4% ee. When crystallization was performed without water, optical purity was 97% ee and recrystallization was required once more to meet the desired optical purity. We guessed that the solubility of the optical isomer was increased by the addition of water. The crystalline morphology of **8** appeared to be the same compared with the sample derived from non-water adding conditions by XRD analysis. Finally, we succeeded in a first scale up for optical resolution and obtained 46.7 kg of **8** in high optical purity (99.3% ee, 42.6% yield from **7**, Scheme 7). Additionally, the crude brucine salt was purified in aqueous DMF two times and gave the optically pure brucine salt **20** (99.6% ee, 42.3% yield from **7**). The desired highly enantiopure carboxylic acid compounds were prepared in an overall yield of 85%.[11]

Completion of Synthesis. We describe here the completion of the synthesis for the final product (Scheme 8).

Scheme 7. Improved Method of Optical Resolution



Scheme 8. Completion of the Synthesis



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To minimize the formation of bis-form impurity D to the level of 1%, the second generation synthetic method required use of a 14 vol/wt amount of DMF. After the completion of the reaction, it was necessary to remove the DMF under high vacuum, at high temperature evaporation for the isolation of desired compound **10**. In the medicinal chemistry method, impurity D was removed by column chromatography purification. Incidentally, the direct crystallization and phase separation was difficult. Needless to say, it was not a practical method in a large scale synthesis. To solve these issues, we investigated a new procedure, slow addition (5−8 h) of the carbonyl imidazole that was prepared from carboxylic acid **9** and CDI (carbonyldiimidazole) in CH_3CN to the suspension of guanidine carbonate in NMP, which gave 1% of impurity D in a reaction mixture. After the extraction with EtOAc, the desired free base **10** was prepared in a good purity. Compound **10** was used in the next step as a *i*-PrOH solution without isolation. After that, HCl salt formation was achieved in aqueous *i*-PrOH in a good procedure, and the crystal form was controlled perfectly. The details are described in the Experimental Section. The overall yield of (*S*)-**1** from **2** was 22.9%. Additionally, enantioisomer (*R*)-**1** (free base: **22**) was synthesized from **20** by using almost the same procedure, and the overall yield of (*R*)-**1** from **2** was 22.7%.

CONCLUSION

A new synthetic route has been developed for large-scale manufacture of the candidate drug compound (*S*)-**1**. The undesirable features of the medicinal chemistry route and the second generation synthesis method were avoided by employing a new C−C bond formation method, a new spiro-ring formation approach, and a practical optical resolution procedure. From 9-oxo-9*H*-fluorene-2-carboxylic acid (**2**) was manufactured 21 kg of compound (*S*)-**1** in 22.9% overall yield in safe operation. Impurities B, C, and D were controlled well at low levels during the hydrogenation of alkyne, spiro-ring formation, and amidation with guanidine carbonate. As a consequence, a highly optically pure drug substance (*S*)-**1** was prepared for GMP delivery and (*R*)-**1** was prepared for a preclinical study campaign.

EXPERIMENTAL SECTION

General. Starting materials, reagents, and solvents were obtained from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded in the specified deuterated solvent. Chemical shifts of ^{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual solvent (DMSO-d_6 2.50 ppm) or TMS. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet doublet, m = multiplet, and br = broad), coupling constant (Hz), and integration.

Chemical shifts of proton-decoupled ^{13}C NMR spectra are reported in ppm from the central peak of DMSO-d_6 (39.5 ppm) on the δ scale. IR spectra were performed by the KBr disk method (JP16). HPLC was performed using the HITACHI D-2500 or D-7500 system. The HPLC methods are described below. Glass-lined reactors were used in all steps, and a vacuum pump was used for concentration of organic layers.

HPLC Methods. Method A. YMC-Pack ODS-A, 5 μm, 4.6 mm × 150 mm column, elution 0.05% TFA aq/CH_3CN = 6/4, over 30 min, 1.0 mL/min, at 25 °C, with UV detection at 240 nm. **2**: 7.4 min, **18**: 10.5 min, DMF: 1.7 min, **14**: 2.6 min, **7**: 10 min, cinchonidine: 1.4 min, brucine: 1.6 min.

Method B. YMC-Pack ODS-A, 5 μm, 4.6 mm × 150 mm column, elution 0.05% TFA aq/CH_3CN = 4/6, over 30 min, 1.0 mL/min, at 25 °C, with UV detection at 240 nm. **2**: 2.9 min, **18**: 3.1 min, DMF: 1.6 min, double-bond intermediate: 3.4 min, **19**: 3.2 min, **14**: 1.8 min, **7**: 3.4 min, cinchonidine: 1.2 min, brucine: 1.3 min.

Method C. DAICEL CHIRALPAK AD-H, 5 μm, 4.6 mm × 250 mm column, elution *n*-hexane/EtOH/TFA = 2.55 L/0.45 L/3.0 g, over 60 min, 0.5 mL/min, at 25 °C, with UV detection at 240 nm. **9**: 15 min, **21**: 23 min.

Method D. YMC-Pack ODS-A, 5 μm, 4.6 mm × 150 mm column, elution 0.01 M K_2HPO_4 (adjust pH 7.0 by aq H_3PO_4)/CH_3CN = 7/3, over 60 min, 1.0 mL/min, at 25 °C, with UV detection at 240 nm. **9**, **21**: 3.3 min, **10**, **22**: 13 min, carbonyl imidazole intermediate: 50 min.

Method E. DAICEL CHIRALCEL OJ-RH, 5 μm, 4.6 mm × 150 mm column, elution 0.01 M K_2HPO_4 (adjust pH 7.0 by aq H_3PO_4)/CH_3CN = 75/25, over 30 min, 1.0 mL/min, at 40 °C, with UV detection at 305 nm. **22**: 10 min, **10**: 15 min.

9-Hydroxy-9-[3-(tetrahydropyran-2-yloxy)prop-1-yn-1-yl]-9*H*-fluorene-2-carboxylic Acid (18, Mixture of All Stereoisomers). A solution of 9-oxo-9*H*-fluorene-2-carboxylic acid (**2**) (61.5 kg, 274.3 mol) and (*RS*)-2-(prop-2-yn-1-yloxy)tetrahydropyran (**17**) (40.4 kg, 288.2 mol) in DMF (490 L) was cooled to −25 °C, and potassium *tert*-butoxide (64.7 kg, 576.6 mol) was added at −25 to 5 °C. The reaction mixture was aged for 0.5 h at 0 °C, after which time HPLC analysis indicated <1% starting material **2** remained (HPLC methods A and B). To the batch was added water (190 L), and 2 N aqueous HCl was added until pH 7. After that, EtOAc (750 L) and 2 N aqueous HCl were added to the batch (total amount of HCl was 1.1 equiv of potassium *tert*-butoxide). The separated aqueous layer was re-extracted with EtOAc (430 L). And the two organic layers were combined and washed with water (280 L) two times. The organic layer was concentrated *in vacuo*. After that, toluene (470 L) was added to the batch, and the resulting mixture was concentrated *in vacuo*. Toluene (890 L) and EtOAc (110 L) were added to the residue, and the solvent was distilled at atmospheric pressure to evaporate 420 L. The resulting slurry was cooled to 0−5 °C and aged for 12 h at 0−5 °C, and filtered and washed with toluene. The resulting wet cake was dried *in vacuo* at 70 °C to afford the desired **18** with a 98% purity, via HPLC methods A and B (92.8 kg, 92.8% yield).

FAB-MS (neg): 363.1. ESI-MS (pos): 365.2. ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.0 (1H, br), 8.15−8.20 (1H, m), 8.00−8.05 (1H, m), 7.85−7.92 (2H, m), 7.65−7.70 (1H, m), 7.42−7.50 (2H, m), 6.75 (1H, s), 4.67 (1H, s), 4.24 (1H, dd, J = 15.9, 2.1 Hz), 4.17 (1H, dd, J = 15.9, 2.8 Hz), 3.62−3.69 (1H, m), 3.30−3.37 (1H, m), 1.56−1.68 (2H, m), 1.39−1.47 (4H, m). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.9, (148.6, 148.5), (148.2, 148.1), (142.7, 142.6), (137.3, 137.2), (130.7, 130.5), 129.4, (128.8, 128.1), (125.2, 125.1), (124.6, 124.5), 121.1, 120.3, 96.3, (87.0, 86.9), (78.2, 78.1), 73.2, (61.2, 61.1), 53.8, 29.7, 24.8, 21.0, (18.8, 18.7). IR (KBr)/cm^{-1}: 3343, 2941, 1686, 1667, 1611, 1261, 1031. Mp: 160.1 °C (by DSC).

9-Hydroxy-9-[3-(tetrahydropyran-2-yloxy)propyl]-9*H*-fluorene-2-carboxylic acid (19, mixture of all stereoisomers). A solution of **18** (46.3 kg, 127.1 mol) in MeOH (400 L) was added potassium formate (85.5 kg, 1016 mol) and 10% Pd on carbon (6.95 kg, 50%-wet, M-type purchased from Kawaken Fine Chemicals Co., Ltd.) and the batch was stirring

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at 10 − 35 °C for 2 h, after which time HPLC analysis indicate <0.5% starting material **18** and <0.5% double-bond intermediate remained (HPLC method B). After that, the batch was added water (560 L) and filtered. The reaction vessel and lines filter were washed with MeOH (50 L, twice). The combined filtrate was filtered, via a <0.6 μm filter, into another vessel. The filtrate was distilled at atmospheric pressure to evaporate 585 L. After cooled to 25 °C, EtOAc (510 L) was added to the residue and then aqueous HCl (38 wt % HCl 79.2 kg in water 190 L) was added to the batch below 15 °C. After the phase separation, the organic layer was washed with water (93 L) twice. One more batch was conducted in the same manner. The organic later of first batch and second batch were combined and concentrated *in vacuo* to afford desired **19**, it was added MeOH (560 L). The solution was used next step without purification. Analytical pure **19** was obtained by concentration in laboratories.

FAB-MS (neg.); 367.1, ESI-MS (neg.); 367.0. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.89 (1H, br), 8.04 (1H, s), 7.94 − 7.99 (1H, m), 7.80−7.88 (2H, m), 7.50 − 7.54 (1H, m), 7.36 − 7.42 (2H, m), 5.70 (1H, s), 4.36 (1H, d, J = 12.2 Hz), 3.58 − 3.62 (1H, m), 3.40 − 3.43 (1H, m), 3.31 − 3.38 (1H, m), 3.08 − 3.17 (1H, m), 2.05 − 2.10 (2H, m), 1.58 − 1.65 (1H, m), 1.50 − 1.55 (1H,m), 1.25 − 1.47 (4H, m), 1.00 − 1.08 (2H, m). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.3, (150.5, 150.4), (149.9, 149.8), 143.6, 138.0, (130.0, 129.8), (128.8, 128.6), (124.4, 124.3), 123.7, 120.8, 119.8, (97.8, 97.7), 80.8, (66.5, 66.4), (61.2, 61.1), (36.7, 36.6), (30.2, 30.1), 24.9, (24.3, 24.2), 20.7, (19.2, 19.1), 14.0. IR (KBr)/cm^{-1}: 2944, 2870, 1714, 1685, 1613, 1261, 1021. Mp: 128.1 °C (by DSC).

(*RS*)-9-Hydroxy-9-(3-hydroxypropyl)-9*H*-fluorene-2-carboxylic Acid (14). To the solution of **19** in MeOH was added 38 wt % HCl (0.6 kg, 6.25 mol) at 20 °C, and the resulting mixture was aged for 2 h, after which time HPLC analysis indicate <1% starting material **19** remained (HPLC method B). After the addition of seed crystals of **14** (5g) and toluene (470 L) to the reaction mixture, the batch was concentrated *in vacuo*. To the residue was added toluene (560 L) and EtOAc (180 L), and the resulting slurry was stirred at 65 °C and then cooled to 0 °C. The batch was aged for 2 h at 0 °C and filtered and washed with toluene. The resulting wet cake was dried *in vacuo* at 70 °C to afford the desired **14** with a 98% purity, via HPLC methods A and B (64.1 kg, 88.7% yield in 2 steps).

FAB-MS (neg): 283.0. ESI-MS (neg): 282.8. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.88 (1H, br), 8.02 (1H, d, J = 1.3 Hz), 7.96 (1H, dd, J = 8.0, 1.6 Hz), 7.80−7.87 (2H, m), 7.50−7.53 (1H, m), 7.32−7.42 (2H, m), 5.67 (1H, s), 4.23 (1H, t, J = 5.2 Hz), 3.19 (2H, dd, J = 11.6, 6.4 Hz), 2.03 (2H, dd, J = 16.5, 7.0 Hz), 0.91−0.99 (2H, m). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.4, 150.7, 150.0, 143.6, 138.0, 130.0, 129.7, 128.8, 128.5, 124.4, 123.8, 120.8, 119.8, 80.9, 60.8, 36.7, 27.4. Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.78; H, 5.65. IR (KBr)/cm^{-1}: 3347, 3069, 2954, 1890, 1612, 1263, 1070. Mp: 222.6 °C (by DSC).

(*RS*)-4′,5′-Dihydro-3′*H*-spiro[fluorene-9,2′-furan]-2-carboxylic Acid (7). To a solution of **14** (63.8 kg, 224.4 mol) in diethyleneglycol dimethyl ether (diglyme, 380 L) was added water (319 L). After that, a 64% aqueous solution of sulfuric acid (8.5 kg, 55.5 mol) was added, and the batch was heated to 93 °C and aged for 24 h at the same temperature, after which time HPLC analysis indicate <2% starting material **14** remained (HPLC methods A and B). After that, to the batch was added water (829 L) at 80−90 °C. The resulting slurry was cooled to 25 °C and aged for 12 h, filtered, and washed with water. The resulting wet cake was dried *in vacuo* at 70 °C to afford the desired **7** with a 99% purity (52.4 kg, 87.7% yield). The level of each impurity C was <0.5% by HPLC analysis (HPLC methods A and B).

FAB-MS (pos): 267.1. FAB-MS (neg.): 265.1. ^{1}H NMR (500 M Hz, DMSO-d_6): δ 12.95 (1H, s), 8.00 (1H, s), 7.95−7.98 (1H, m), 7.82−7.87 (2H, m), 7.54−7.56 (1H, m), 7.35−7.44 (2H, m), 4.25 (2H, t, J = 6.6 Hz), 2.35−2.47 (2H, m), 2.27−2.33 (2H, m). ^{13}C NMR (100 M Hz, DMSO-d_6): δ 167.2, 150.3, 149.5, 143.3, 137.6, 130.4, 130.2, 129.2, 128.9, 124.3, 123.9, 120.9, 120.0, 88.9, 69.2, 37.1, 26.8. Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found: C, 76.65; H, 5.34. IR (KBr)/cm^{-1}: 2982, 2953, 2868, 2853, 1683, 1611, 1294, 1049. Mp: 230.1 °C (by DSC).

(9*R*)-8a-Cinchonan-9-ol Mono[(*S*)-4′,5′-dihydro-3′*H*-spiro[fluorene-9,2′-furan]-2-carboxylate] (8). To the solution of **7** (52.0 kg, 195.3 mol) in DMF (330 L) was added brucine dihydrate (92.5 kg, 214.9 mol). The batch was heated to 60 °C, and to the resulting solution was added water (42 L). After the addition of seed crystals **20** (21 g) and water (68 L) at 60 °C, the resulting slurry was cooled to 0 °C and aged for 12 h, filtered, and washed with DMF/water, 3:1 (89 L). The wet cake of **crude-20** was stored at 5 °C. To the filtrate was added EtOAc (780 L), and the resulting mixture was cooled to 5 °C. After that, a solution of 38 wt % HCl (34.3 kg) in water (150 L) was added to the batch below 15 °C. The separated aqueous layer was re-extracted with EtOAc (730 L). And these two organic layers were combined and washed with water (370 L, twice). The organic layer was concentrated *in vacuo* to afford desired **crude-9**. At this stage, the level of enamtioisomer **21** was 4.6% by HPLC analysis (method C). To the residue was added EtOAc (220 L), and the resulting mixture was concentrated *in vacuo*. To the resulting residue was added methyl propionate (1040 L). To the solution was added water (5.2 L) and cinchonidine (28.8 kg, 97.8 mol), and the resulting mixture was heated to 75 °C. After that, the solution was cooled to 70 °C, and seed crystals of **8** (26 g) were added. The batch was cooled to 30 °C and aged for 12 h. The resulting slurry was filtered and washed with methyl propionate. The wet cake was dried *in vacuo* at 70 °C to afford the desired **8** with a 99% purity, via HPLC methods A and B (46.7 kg, 42.6% yield from **7**). The level of enantioisomer **21** was 0.34% by HPLC analysis (HPLC method C).

21: free base of **20**. FAB-MS (pos): 295.1 (cinchonidine), FAB-MS (neg); 265.2 (compound **9**). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.85 (1H, d, J = 4.6 Hz), 8.34 (1H, d, J = 8.6 Hz), 7.96−8.05 (3H, m), 7.82 (2H, t, J = 7.8 Hz), 7.73 (1H, t, J = 7.7 Hz), 7.53−7.61 (3H, m), 7.41 (1H, t, J = 7.5 Hz), 7.36 (1H, t, J = 7.3 Hz), 5.80−5.90 (1H, m), 5.43 (1H, d, J = 6.1 Hz), 5.00 (1H, d, J = 17.1 Hz), 4.95 (1H, d, J = 10.3 Hz), 4.22 (2H, t, J = 6.6 Hz), 3.31 (1H, br), 3.17 (1H, dd, J = 15.0, 8.0 Hz), 2.96 (1H, dd, J = 13.1, 9.8 Hz), 2.56−2.60 (4H, m), 2.22−2.43 (4H, m), 1.79 (1H, d, J = 3.1 Hz), 1.69−1.77 (3H, d, J = 8.0 Hz), 1.50 (1H, br). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.3, 150.2, 150.0, 149.5, 149.2, 147.8, 142.2, 141.5, 137.9, 132.9, 130.2, 129.7, 128.8, 126.3, 125.6, 124.3, 124.0, 123.8, 120.6, 119.6, 119.0, 114.6, 96.8, 88.9, 69.5, 69.3, 69.1, 60.2, 54.9, 41.8, 38.6, 37.1, 35.2, 27.2, 26.8, 26.3. IR (KBr)/cm^{-1}: 3197, 3071, 2972, 2946, 1613, 1373, 1268. Mp: 143.3 °C (by DSC).

(*S*)-*N*-(Diaminomethylidene)-4′,5′-dihydro-3′*H*-spiro-[fluorene-9,2′-furan]-2-carboxamide (10). A solution of 38 wt % HCl (16.5 kg,172 mol) in water (116 L) was added to a stirred suspension of **8** (46.0 kg, 82.0 mol) in EtOAc (700 L),

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keeping the temperature below 15 °C. The separated organic layer was washed with water (180 L) and then concentrated *in vacuo*. To the residue was added toluene (180 L), and the resulting mixture was concentrated *in vacuo*. To the residue **9** was added CH_3CN (180 L), and the resulting mixture was concentrated *in vacuo*. To the residue was added CH_3CN (110 L) and CDI (20.0 kg, 123.3 mol) at 20 °C, and the batch was stirred at 10−25 °C for 1 h, after which time HPLC analysis indicated <1% starting material **9** remained and >98% desired carbony imidazole intermediate (HPLC method D). After that, the solution was added for 8 h to a stirred suspension of guanigine carbonate (110.8 kg, 615 mol) in NMP (164 L) at 20 °C, followed by a wash of CH_3CN (20 L). And the batch was stirred at 20 °C for 12 h, after which time HPLC analysis indicated <3% starting material **9** remained (HPLC method D). After that, the batch was concentrated *in vacuo* to about 160 L. After that, EtOAc (650 L) and water (650 L) were added to the batch, the resulting aqueous layer was re-extracted with EtOAc (650 L), and these two organic layers were combined and washed with water (330 L) five times. The organic layer was concentrated *in vacuo*. After that, 2-propanol (260 L) was added to the residue and concentrated *in vacuo* to afford desired free base **10**, to which was added 2-propanol (710 L). The solution was used in the next step without purification.

Analytically pure **9** was obtained by concentration in our laboratories. Free carboxylic acid **9**: $[\alpha]_D^{20} = -4.91°$ (solvent: MeOH, 0.20 g/20 mL, 100 mm cell). Mp: 192.5 °C (by DSC). Free base **10**: FAB-MS (pos); 308.2. ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.17 (1H, s), 8.11 (1H, d, J = 7.8 Hz), 8.05 (2H, br), 7.76 (1H, d, J = 7.2 Hz), 7.73 (1H, d, J = 7.8 Hz), 7.53 (1H, d, J = 7.2 Hz), 7.38 (1H, t, J = 7.5 Hz), 7.32 (1H, t, J = 7.5 Hz), 6.70 (2H, br), 4.20−4.26 (2H, m), 2.34−2.44 (2H, m), 2.24−2.32 (2H, m). ^{13}C NMR (150 MHz, DMSO-d_6): δ 175.5, 163.0, 150.2, 148.6, 141.0, 139.1, 138.3, 129.4, 128.7, 128.4, 123.8, 123.7, 120.3, 119.0, 89.0, 60.0, 37.2, 26.8. IR (KBr)/cm^{-1}: 3335, 3198, 1634, 1567, 1272, 1610, 1045, 756, 658. Mp: 128.9 °C (by DSC).

(*S*)-*N*-(Diaminomethylidene)-4′,5′-dihydro-3′*H*-spiro-[fluorene-9,2′-furan]-2-carboxamide Monohydrochloride ((*S*)-1). A solution of **10** in 2-propanol was added via a 0.6 μm filter, into another vessel, followed by a wash of 2-propanol (50 L). After addition of water (8 L) to the solution, seed crystals (*S*)-**1** (26 g) were added to the batch at 35 °C. After that, a solution of 38 wt % HCl (8.24 kg, 85.9 mol) in water (15 L) was added via a 0.6 μm filter to the batch at 35 °C, and the resulting slurry was aged for 1 h at 35 °C. Next, the batch was heated to 65 °C and aged for 1 h. After that, the slurry was cooled to 25 °C and aged at the same temperature for 12 h. Before the filtration, the crystal form was checked by XRD analysis to meet the desired form. After that, the slurry was filtered, washed with 2-propanol, and dried in vacuo at 60 °C to give 21.0 kg of (*S*)-**1** having a purity of 99.1% (HPLC method D). Optical isomer **22** was observed to be 0.14% by Chiral HPLC analysis (HPLC method E), 74.4% yield from **8**. The overall yield was 22.9% from 9-oxo-9*H*-fluorene-2-carboxylic acid (**2**).

FAB-MS (pos); 308.0. ^{1}H NMR (600 MHz, DMSO-d_6): δ 12.26 (1H, s), 8.93 (2H, br), 8.58 (2H, br), 8.43 (1H, d, J = 1.8 Hz), 8.18 (1H, dd, J = 7.8, 1.8 Hz), 7.97 (1H, d, J = 7.8 Hz), 7.88 (1H, d, J = 6.6 Hz), 7.58 (1H, d, J = 7.2 Hz), 7.39−7.46 (2H, m), 4.35 (1H, dd, J = 14.4, 8.4 Hz), 4.22 (1H, dd, J = 14.4, 6.6 Hz), 2.50−2.58 (1H, m), 2.34−2.44 (2H, m), 2.26−2.32 (1H, m). ^{13}C NMR (150 MHz, DMSO-d_6): δ 167.2, 155.8, 150.5, 149.9, 144.3, 137.2, 130.3, 130.0, 129.6, 129.0, 124.0, 123.7, 121.2, 120.3, 88.9, 69.3, 37.0, 26.8. IR (KBr)/cm^{-1}: 3323, 3144, 1686, 1611, 1567, 1270, 1053, 738, 656. Anal. Calcd for $C_{18}H_{17}N_3O_2$·HCl. Calc: C (62.88%), H (5.28%), N (12.22%), Cl (10.31%). Found: C (62.82%), H (5.38%), N (12.16%), Cl (10.24%). Mp: 248.5 °C (by DSC). $[\alpha]_D^{20} = -9.04°$ (solvent: MeOH, 0.20 g/20 mL, 100 mm cell).

Preparation of (*R*)-1. 2,3-Dimethoxystrychnidin-10-one Mono[(*R*)-4′,5′-dihydro-3′*H*-spiro[fluorene-9,2′-furan]-2-carboxylate] (20). To a solution of **crude-20** (1.32 kg of dry base, 2.0 mol, 83% ee) in DMF (9.24 L) was added water (1.32 L) at 60 °C and then to the solution was added seed crystals of **20** (1.3 g) and water (3.3 L) at 60 °C. The resulting slurry was aged at the same temperature for 0.5 h and cooled to 0 °C and aged for 2 h. The slurry was filtered and washed with DMF/water = 8/2 (2.64 L). This wet cake was dissolved in DMF (8.6 L). The solution was warmed to 60 °C, water (0.86 L) was added, and to the solution was added seed crystals **20** (1.3 g) and water (1.32 L) at 60 °C. The resulting slurry was aged at the same temperature and cooled to 0 °C and aged for 2 h. The slurry was filtered and washed with DMF/water = 8/2 (1.32 L). The wet cake was dried *in vacuo* at 70 °C to afford the desired **20** with a 99% purity, via HPLC methods A and B (1.1 kg, 42.3% yield from 7). The level of enantioisomer **9** was 0.2% by HPLC analysis (HPLC method C).

FAB-MS (pos): 395.2 (brucine). FAB-MS (neg): 265.3 (compound **21**). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.00 (1H, s), 7.98 (1H, d, J = 7.9 Hz), 7.81 (2H, t, J = 7.9 Hz), 7.65 (1H, s), 7.55 (1H, d, J = 7.3 Hz), 7.34−7.43 (2H, m), 6.99 (1H, s), 5.89 (1H, br), 4.27−4.31 (2H, m), 4.23 (2H, t, J = 6.6 Hz), 4.05 (2H, d, J = 6.4 Hz), 3.95 (1H, s), 3.78 (1H, d, J = 10.7 Hz), 3.74 (3H, s), 3.73 (3H, s), 3.65 (1H, d, J = 14.3 Hz), 3.10−3.16 (2H, m), 2.85−2.94 (1H, m), 2.59−2.80 (2H, m), 2.55−2.58 (1H, m), 2.25−2.48 (4H, m), 1.78−1.85 (2H, m), 1.34 (1H, d, J = 14.3 Hz), 1.24 (1H, d, J = 10.7 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.5, 168.0, 150.2, 149.3, 148.6, 145.8, 142.6, 139.4, 137.8, 135.5, 132.0, 130.3, 129.0, 128.9, 128.0, 124.3, 123.9, 123.6, 120.7, 119.7, 107.0, 100.5, 88.9, 76.7, 69.2, 63.6, 59.8, 59.0, 56.0 (2 carbons), 55.7, 51.8, 51.4, 49.6, 47.3, 41.6, 37.1, 30.7, 26.9, 25.9. Mp: 205.4 °C (by DSC).

(*R*)-*N*-(Diaminomethylidene)-4′,5′-dihydro-3′*H*-spiro-[fluorene-9,2′-furan]-2-carboxamide Monohydrochloride ((*R*)-1). A solution of 38 wt % HCl (0.334 kg, 3.48 mol) in water (11 L) was added to a stirred suspension of **20** (1.1 kg, 1.665 mol) in EtOAc (14.1 L), keeping the temperature below 15 °C. The separated organic layer was washed with water (4.4 L) and then concentrated *in vacuo*. To the residue was added toluene (3.7 L), and the resulting mixture was concentrated *in vacuo*. To the residue (**21**) was added CH_3CN (3.7 L), and the resulting mixture was concentrated *in vacuo*. To the residue was added CH_3CN (2.2 L) and CDI (405 g, 2.5 mol) at 20 °C, and the batch was stirring at 10−25 °C for 1 h, after which time HPLC analysis indicated <1% starting material **21** remained and >98% desired carbony imidazole intermediate (HPLC method D). After that, the solution was added for 8 h to a stirred suspension of guanigine carbonate (2.25 kg, 12.5 mol) in NMP (3.3 L) at 20 °C, followed by a wash of CH_3CN (0.45 L). And the batch was stirring at 20 °C for 12 h, after which time HPLC analysis indicated <3% starting material **21** remained (HPLC method D). After that, the batch was concentrated *in vacuo* to about 3.3 L. After that, EtOAc (13 L) and water (13 L) were added to the batch and the resulting aqueous layer was re-extracted with EtOAc (13 L). And the two organic layers were combined and washed with

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water (6.7 L) five times. The organic layer was concentrated *in vacuo*. After that, 2-propanol (5.1 L) was added to the residue and concentrated *in vacuo* to the afford desired free base **22**, to which was added 2-propanol (14.3 L). The solution was used in the next step without purification.

The solution of **22** in 2-propanol was added via a 1 μm filter into another vessel, followed by a wash of 2-propanol (1.0 L). After addition of water (162 mL) to the solution, the seed crystals (***R***)-**1** (0.51 g) were added to the batch at 35 °C. After that, a solution of 38 wt % HCl (167.1 g, 1.74 mol) in water (0.3 L) was added via a 1 μm filter to the solution at 35 °C, and the resulting slurry was aged for 1 h at 35 °C. Next, the batch was heated to 65 °C and aged for 1 h. After that, the slurry was cooled to 25 °C and aged at the same temperature for 1 h. Before the filtration, the crystal form was checked by XRD analysis. After that, the slurry was filtered and washed with 2-propanol and dried in vacuo at 60 °C to give 0.425 kg (74.3% yield from **20**) of (***R***)-**1** having a purity of 99.1% (HPLC method D). Optical isomer **10** was observed, 0.2% by Chiral HPLC analysis (HPLC method E). The overall yield was 22.7% from 9-oxo-9*H*-fluorene-2-carboxylic acid **2**.

Free carboxylic acid **21** (analytically pure **21** was obtained by concentration in our laboratories): $[\alpha]_D^{20}$ = +5.28° (solvent: MeOH, 0.20 g/20 mL, 100 mm cell).

Compound (***R***)-**1**. $[\alpha]_D^{20}$ = +8.77° (solvent: MeOH, 0.20 g/20 mL, 100 mm cell).

The analytical data of **21**, **22**, and (***R***)-**1** (mass, IR, ^{1}H NMR and ^{13}C NMR spectra) were in agreement with the above data (compounds **9**, **10**, and (***S***)-**1**).

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Notes

The authors declare no competing financial interest.

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(3) The SMB separation of **14** and **7** was also attempted. But it did not give efficient results in comparison with the separation of compound **8**.

(4) Actually, it had difficulty with controlling the reaction in the hundred-gram scale synthesis. In step 2, magnesium was added to the batch very carefully and slowly. It would be challenging to operate on scale-up synthesis. Magnesium: MSDS, Kanto Chemical Co., Inc.; mesh size, turning; not activated.

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(11) Compound **20** and **8** were easily converted to free carboxylic acid by treatment with aqueous HCl solution and extracted with EtOAc as shown in the Experimental Section. In a preliminary test, brucine and cinchonidine were recovered after the addition of an aqueous solution of NaOH to the resulting acidic aqueous layer.