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Development of a Practical Synthesis of a Peripherally Selective Noradrenaline Reuptake Inhibitor Possessing a Chiral 6,7-Trans-disubstituted-1,4-oxazepane as a Scaffold

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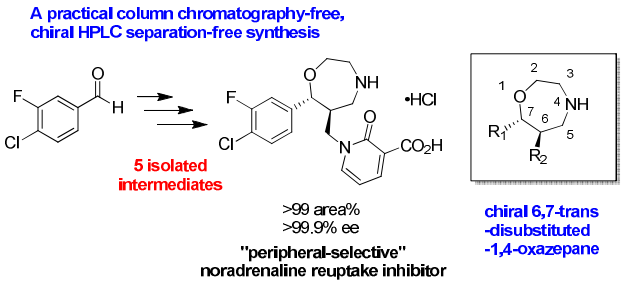


ABSTRACT:

A practical synthesis of a peripherally selective noradrenaline reuptake inhibitor that has a chiral 6,7-*trans*-disubstituted-1,4-oxazepane as a new class of scaffold is described. The amino alcohol possessing the desired stereochemistry was obtained with excellent dr and ee, starting from a commercially available aldehyde via Morita-Baylis-Hillman reaction, Michael addition, isolation as maleic acid salt, reduction, and diastereomeric salt formation with (+)-10-camphorsulfonic acid. The desired single stereoisomer obtained at an early stage of the synthesis was used for seven-membered ring formation in fully telescoped processes, providing the chiral 6,7-*trans*-disubstituted-1,4-oxazepane efficiently. In addition to controls of dr and ee of the chiral 1,4-oxazepane, and control of *N*,*O*-selectivity in S_N2 reaction of the intermediate mesylate with a pyridone derivative, finding appropriate intermediates that were amenable to isolation and upgrade of purity enabled a practical chiral HPLC separation-free, column chromatograph-free synthesis of the drug candidate with excellent chemical and optical purity in higher overall yield.

KEYWORDS: peripherally selective noradrenaline reuptake inhibitor, chiral 6,7-*trans*-disubstituted-1,4-oxazepane, optical resolution by diastereomeric salt formation, chiral HPLC separation/column chromatography-free synthesis, S_N2 reaction of 2-pyridone-3-carboxilic acid esters

INTRODUCTION

Noradrenaline reuptake inhibitors (NRIs) are known to have potential as medicines for patients with stress urinary incontinence.[1] In order to suppress adverse effects of centrally acting conventional NRIs,[2] development of "peripherally selective" NRIs as a new class of therapeutic agents for stress urinary incontinence has been pursued. Compound **1·HCl** was identified as a candidate for a peripherally selective NRI and has been developed by Takeda Pharmaceutical Company Limited.[3] The key structural feature of **1·HCl** is the chiral 6,7-*trans*-disubstituted-1,4-oxazepane core (Figure 1). Since this class of compounds has not attracted much attention as a scaffold for medicines so far, the number of reports of their syntheses has been limited.[3, 4] Therefore, the synthesis of **1·HCl** is intriguing not only for medicinal chemists, but also for organic chemists.

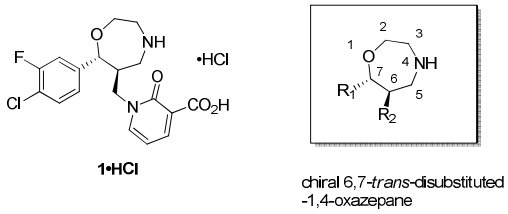
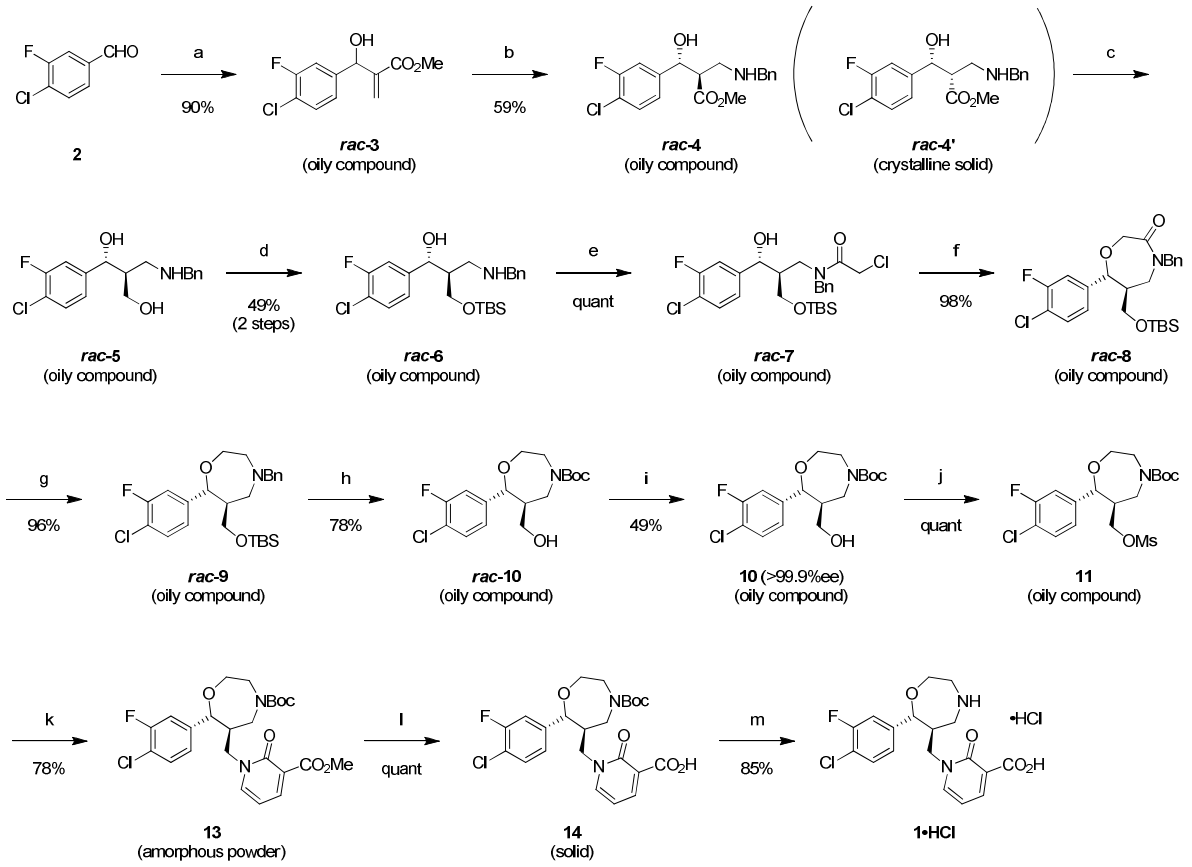


Figure 1. Structure of peripherally selective NRI **1·HCl**

The medicinal chemistry synthesis of **1·HCl** is shown in Scheme 1. A mixture of ***rac*-4** and ***rac*-4'** was prepared by Morita-Baylis-Hillman reaction of aldehyde **2** with methyl acrylate followed by Michael addition of benzyl amine, and the desired *trans* isomer ***rac*-4** was separated by column chromatography. The methyl ester of ***rac*-4** was reduced by $CaCl_2/NaBH_4$, and the resulting primary alcohol of ***rac*-5** was protected with TBS. The protected ***rac*-6** was reacted with

chloroacetyl chloride, and ring closure by addition of 1 M NaOH gave seven-membered lactam ***rac*-8**. Reduction of ***rac*-8** with $LiAlH_4/AlCl_3$ gave oxazepane ***rac*-9**, which was debenzylated with 1-chloroethyl chloroformate (ACE-Cl), and the resulting secondary amino group was protected with a Boc group. The obtained ***rac*-10** was optically resolved by HPLC using a chiral column to give the desired single enantiomer. The optically pure alcohol **10** was mesylated and reacted with methyl 2-oxo-1,2-dihydropyridine-3-carboxylate (**12a**) to give ester **13**. Hydrolysis of the methyl ester and subsequent deprotection of the Boc group by treatment with 4 M HCl in EtOAc gave **1·HCl**.

Scheme 1. Medicinal Chemistry Synthesis of **1·HCl** [a]

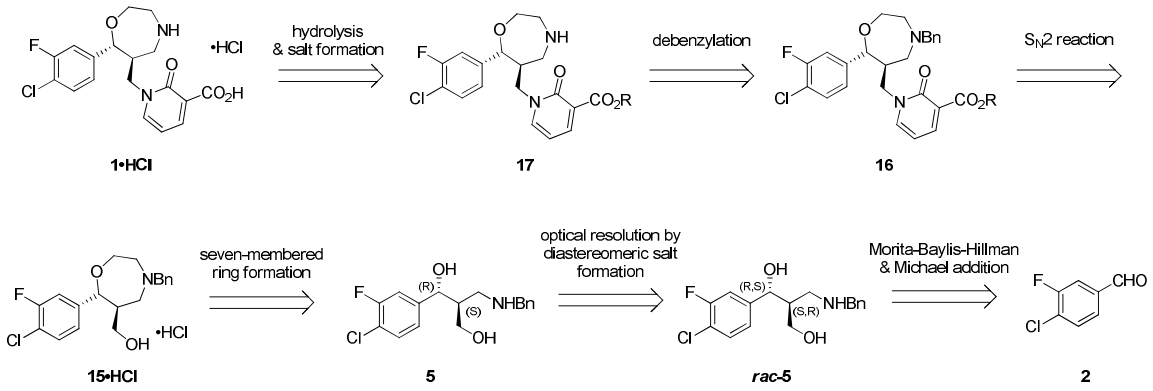


[a]Reagents and conditions: (a) methyl acrylate, DABCO, MeCN, rt; (b) $BnNH_2$, Et_3N, MeOH, rt; (c) $CaCl_2$, $NaBH_4$, THF, EtOH, 0 °C to rt; (d) TBSCl, Et_3N, imidazole, DMAP, THF, 0 °C to rt; (e) chloroacetyl chloride, Et_3N, THF, 0 °C to rt; (f) 1 M NaOH, THF, 0 °C to rt; (g) $LiAlH_4$, $AlCl_3$, THF, 0 °C to rt; (h) (1) 1-chloroethyl chloroformate, MeCN, rt, (2) 1 M HCl, MeOH, 80 °C, (3) Boc_2O, Et_3N, 0 °C to rt; (i) optical resolution by HPLC; (j) MsCl, Et_3N, THF, 0 °C to rt; (k) methyl 2-oxo-1,2-dihydropyridine-3-carboxylate **12a**, K_2CO_3, 1,2-dimethoxyethane, 80 °C; (l) 2 M NaOH, EtOH, 30 °C; (m) 4 M HCl in EtOAc, rt.

In an effort to support early-stage development of this new class of drug candidate, we initiated development of a practical synthesis of **1·HCl**. Our synthetic strategy is described in Scheme 2. The most obvious synthetic challenge was to determine a means to construct the two neighboring stereocenters on the seven-membered ring. In order to establish a practical synthesis of **1·HCl**, a facile synthesis of the chiral 6,7-*trans*-disubstituted-1,4-oxazepane that does not rely

on optical resolution by HPLC and column chromatographic separation was required. We planned to obtain the desired enantiomer by optical resolution utilizing diastereomeric salt formation. It is known that optical resolution at an early step is generally preferable from a standpoint of cost and efficiency.[5] Considering possible epimerization at the stereocenter adjacent to the methyl ester of **4** during the reduction to **5**, we strived to obtain a diastereomeric salt of **5** with a chiral acid that gives the desired (1*R*, 2*S*) stereoisomer of **5**. It was envisioned that the stereocenters of **5** would be retained without epimerization until the final product, judging from structures of intermediates and chemical transformations in downstream processes. Having the single stereoisomer in hand, preparation of the seven-membered ring was elaborated.

Scheme 2. Retrosynthetic analysis of **1·HCl**



In addition to the synthesis of the chiral 6,7-*trans*-disubstituted-1,4-oxazepane, another challenge existed for establishing a scalable synthesis of **1·HCl**; isolation and purification of intermediates were problematic, because most of the intermediates are oily compounds as described in scheme 1. In the course of investigation into the seven-membered ring formation, alcohol **15** was identified as a new intermediate that could be isolated as HCl salt (**15·HCl**) with

good purity. We expected that the reaction of **15·HCl** with a 2-pyridone-3-carboxylic acid ester would give **16**, and debenzylation followed by hydrolysis would give **1**. Whereas the medicinal chemistry synthesis changed the protecting group for the amino group from a Bn group to a Boc group and conducted deprotection at the last step, our synthetic route was thought to be more straightforward and would also provide potential opportunities to isolate **16** and/or **17** as a salt utilizing the amino group in **16**/**17**. Herein we describe process development of a practical synthesis of the chiral 6,7-*trans*-disubstituted-1,4-oxazepane and a strategy toward establishing a scalable synthesis of **1·HCl**.

RESULTS AND DISCUSSION

Preparation of 5·(+)-CSA. The synthesis of chiral amino alcohol **5** is summarized in Scheme 3. Although it is known that Morita-Baylis-Hillman reaction is generally a rather slow reaction,[6] the reaction of aldehyde **2** with methyl acrylate in MeOH using 0.5 equiv of DABCO as a catalyst proceeded relatively quickly, reaching >90% conversion in 17 h, and gave ***rac*-3** in 92% yield. After extraction with EtOAc, washing with brine, and solvent switch, ***rac*-3** was used for the next reaction without isolation.[7]

For Michael addition of benzylamine to ***rac*-3**, several solvents were screened to improve *trans*/*cis* ratio.[8] The solvent screening showed that MeOH was the best solvent, and gave ***rac*-4** in 72:28 dr at room temperature. When the reaction temperature was decreased to 0 °C, dr increased up to 82:18.[9] Interestingly, other screened solvents (EtOH, 2-propanol, MeCN, toluene, EtOAc, DMSO, *N*,*N*-dimethylacetamide, pyridine, triethylamine) all gave the *cis* isomer as the major product (41:59 to 20:80 dr). Isolation of ***rac*-4** without chromatographic separation required investigation, because ***rac*-4** is an oily compound and the undesired *cis* isomer ***rac*-4'** is

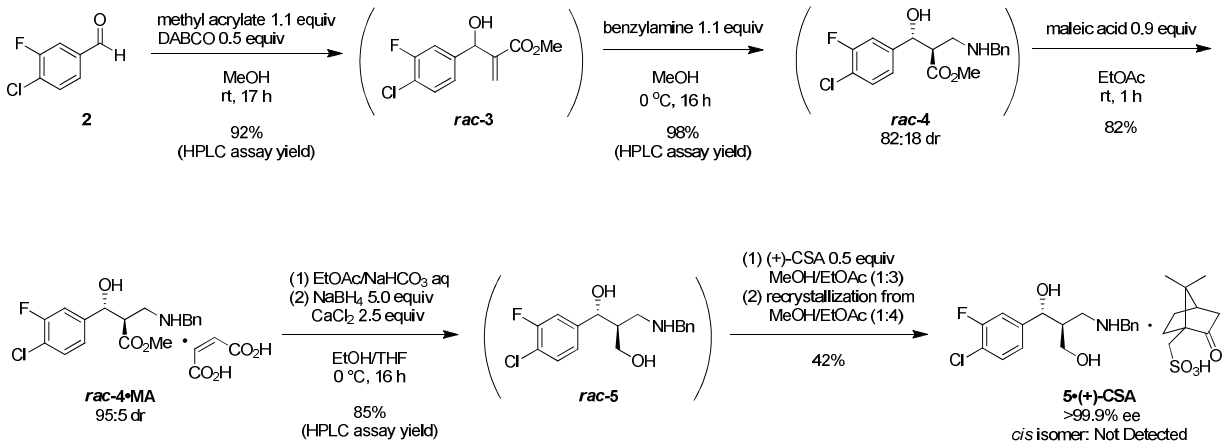
a crystalline solid. Screening of acids showed that maleic acid (MA) formed a good salt with ***rac*-4** in EtOAc to give a white solid, and isolation of the salt was effective for purging the *cis* isomer ***rac*-4'**. Compound ***rac*-4** was isolated as maleic acid salt (***rac*-4·MA**) in 80% yield with 95:5 dr from ***rac*-3**. Fortunately, the remaining *cis* isomer was confirmed to be removed in the later optical resolution step.

After salt break with EtOAc/aqueous $NaHCO_3$ and solvent switch to THF, free ***rac*-4** was subjected to reduction utilizing $Ca(BH_4)_2$ generated *in situ* from $CaCl_2$ and $NaBH_4$ in EtOH/THF.[10,11] In this reaction, the order of addition of reagents was found to be crucial. When 5.0 equiv of $NaBH_4$ was added portionwise to 2.5 equiv of $CaCl_2$ in EtOH/THF, $Ca(BH_4)_2$ was properly generated and addition of a THF solution of ***rac*-4** to the mixture gave ***rac*-5** in 85% yield. In contrast, when $CaCl_2$ was added to $NaBH_4$ in EtOH/THF, vigorous gas evolution and rapid exotherm were observed. Probably due to failure of generation of $Ca(BH_4)_2$, addition of a THF solution of ***rac*-4** to this mixture gave ethyl ester of ***rac*-4** as the main product, which would be formed by transesterification, and ***rac*-5** as the minor product, respectively. On completion of the reaction led by addition of reagents in the proper order, the reaction mixture was quenched by sequential addition of MeOH, H_2O and 2 M HCl. The pH of the reaction mixture was adjusted to 7–8 by addition of 8 M NaOH, and insoluble salts were filtered off. After solvent switch to EtOAc, washing with 5% aqueous $NaHCO_3$ and brine, and concentration, the obtained ***rac*-5** was used for the optical resolution without isolation.

More than 150 chiral acids were screened for the optical resolution of ***rac*-5**, revealing that inexpensive (+)-10-camphorsulfonic acid ((+)-CSA) was a good resolving agent for the desired stereoisomer (1*R*, 2*S*)**-5**. The obtained ***rac*-5** in MeOH/EtOAc (1:3) was treated with 0.5 equiv of (+)-CSA, and the generated diastereomeric salt **5·(+)-CSA** was isolated by filtration. The crude

product (typically 75–80% ee) was recrystallized from MeOH/EtOAc (1:4) to give **5·(+)-CSA** in 42% yield with >99.9% ee. The *cis* isomer was removed during the isolation of **5·(+)-CSA** and was not detected in the obtained **5·(+)-CSA**.

Scheme 3. Synthesis of **5·(+)-CSA**[a]



[a]For the synthesis of ***rac*-4·MA**, the amounts of reagents were calculated based on the amount of **2**. For the synthesis of **5·(+)-CSA**, the amounts of reagents were calculated based on the amount of ***rac*-4·MA**.

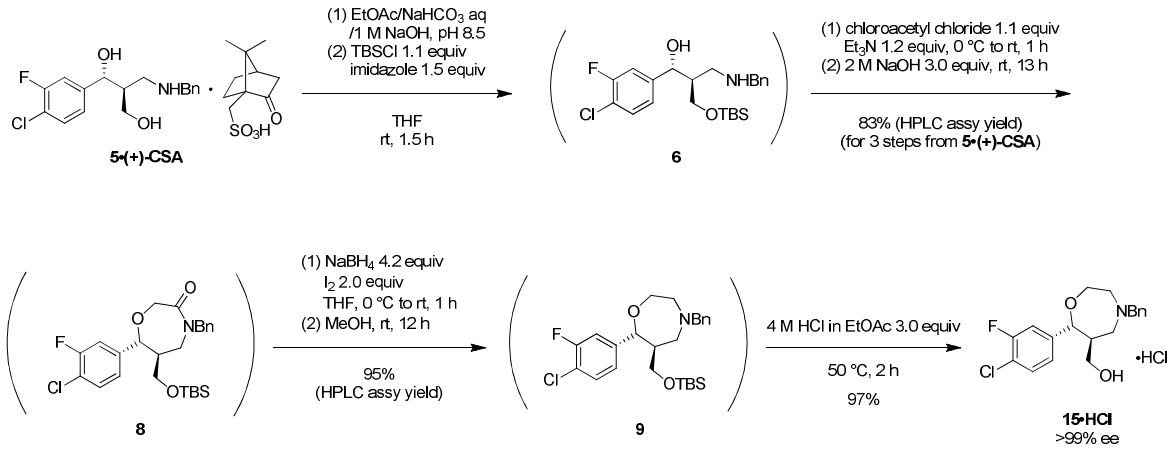
Preparation of 15·HCl. With the single stereoisomer in hand, seven membered-ring formation was investigated (Scheme 4). After salt brake of **5·(+)-CSA**, free **5** was treated with TBSCl in the presence of imidazole for protection of the primary alcohol. Following extraction with EtOAc, washing with brine, and solvent switch to THF, the crude **6** was reacted with chloroacethyl chloride in the presence of triethylamine. Addition of 3.0 equiv of 2 M NaOH to this mixture in one pot provided lactam **8** in 83% yield for 3 steps from **5·(+)-CSA**. Lactam **8** was used for the next reaction after workup (pH adjustment to 8–9 by addition of 1M HCl, extraction with EtOAc, washing with brine, and solvent switch to THF) without isolation.

In the medicinal chemistry synthesis, reduction of the amide group of lactam **8** was conducted using $AlCl_3/LiAlH_4$, which is known to generate AlH_3.[12] It was reported that this reduction system generally has a weaker reducing potency compared to $LiAlH_4$, and the use of $AlCl_3/LiAlH_4$ instead of $LiAlH_4$ for the reduction of **8** effectively prevented generation of a dechlorinated byproduct, which was difficult to remove in downstream processes. Considering safety issues related to the use of $LiAlH_4$ on a large scale, application of an alternative reagent for $AlCl_3/LiAlH_4$ was sought. When Red-Al was used for the reaction, the reduction did not proceed. Surprisingly, the use of Red-Al (4.0 equiv) with $AlCl_3$ (1.0 equiv) made the reaction proceed and gave oxazepane **9** in 91% yield in a small scale reaction. However, this combination of reagents showed poor reproducibility, forcing us to give up this reagent system. Finally, $NaBH_4/I_2$ reagent system[13] was adopted for the reduction of **8** instead of an expensive BH_3·THF solution. A solution of 2.0 equiv of I_2 in THF was added dropwise at 0 °C over 2 h to the solution of **8** and 4.2 equiv of $NaBH_4$ in THF. The reaction reached full conversion in 1 h, after being warmed to room temperature without generation of the dechlorinated byproduct.[14] The reaction was completely quenched by dropwise addition of MeOH and stirring the mixture for 12 h at room temperature. Oxazepane **9** was extracted with EtOAc, and washed with water, brine, and 5% aqueous $NaHCO_3$.

Since **9** is also an oily compound and was found to be difficult to isolate, we decided to convert **9** to another isolable intermediate in order to purge impurities generated during the seven-membered ring formation. We found that treatment of the obtained EtOAc solution of **9** with 3.0 equiv of 4 M HCl in EtOAc at 40–50 °C for 2 h gave **15·HCl** as a white solid, which was easily isolated by filtration. Although the synthesis of **15·HCl** from **5·(+)-CSA** was achieved through fully telescoped processes, **15·HCl** was isolated in good yield (total 76%) with good

purity (>98 area%, >99% ee, dechlorinated byproduct<0.1 area%) as a result of the extensive study.

Scheme 4. Synthesis of **15·HCl**[a]

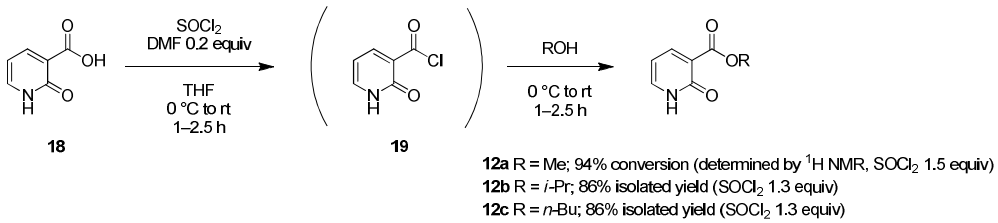


[a]For the synthesis of **8**, the amounts of reagents were calculated based on the amount of **5·(+)-CSA**. For the synthesis of **15·HCl**, the amounts of reagents were calculated based on the amount of **8** (HPLC assay yield).

Preparation of 2-pyridone-3-carboxilic acid esters 12a–12c. Preparation of 2-pyridone-3-carboxilic acid methyl ester **12a** was then examined. We first tried to synthesize compound **12a** by treating 2-hydroxy-3-pyridinecarboxylic acid **18** in refluxing MeOH in the presence of a catalytic amount or 1.0 equiv of H_2SO_4; however, the reaction stalled around 50–80% conversion.[15] Next, **12a** was synthesized by the reaction of MeOH with acid chloride **19** converted from **18** using $SOCl_2$ and a catalytic amount of DMF (Scheme 5).[16] Although the reaction proceeded well and reached 94% conversion, workup was found to be difficult due to high solubility of **12a** in water. Thus, we decided to synthesize isopropyl ester **12b**[17] and *n*-butyl ester **12c,** which were expected to have relatively low solubility in water. As expected,

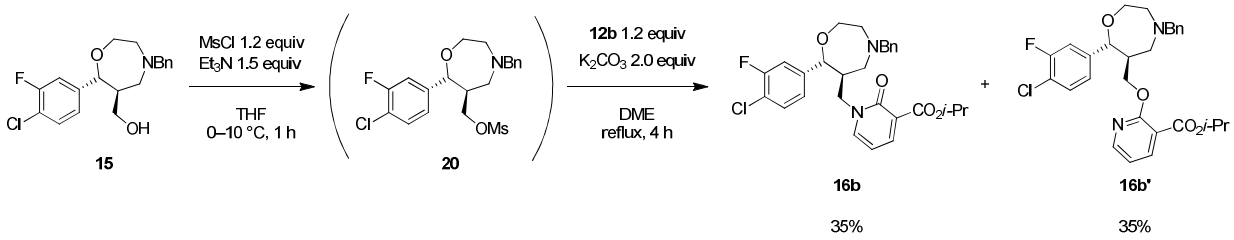
compounds **12b** and **12c** were amenable to extraction with EtOAc and washing with water/brine. After workup, compounds **12b** and **12c** were crystallized from EtOAc/*n*-heptane or *n*-heptane to provide **12b** and **12c** in 86% yield and 86% yield, respectively.

Scheme 5. Synthesis of **12a**–**12c**



Preparation of 1·HCl. As a preliminary experiment, 2-pyridone-3-carboxilic acid isopropyl ester **12b** was reacted with mesylate **20**, which was converted from alcohol **15,** using 1,2-dimethoxyethane (DME) as the solvent (Scheme 6). In this reaction, both the nitrogen atom and the oxygen atom of **12b** reacted with mesylate **20** to give **16b** and *O*-isomer **16b'** in 35% yield and 35% yield, respectively.[18]

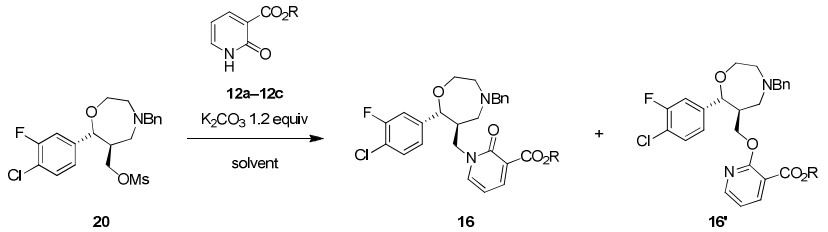
Scheme 6. Preliminary experiment for the synthesis of **16**



In order to increase the *N*, *O*-selectivity for the S_N2 reaction with mesylate **20**, 2-pyridones-3-carboxilic acid esters **12a**–**12c**, solvents and temperatures were screened (Table 1).[19] The ester

group of the 2-pyridones did not largely affect the *N*, *O*-selectivity. Among the screened solvents, MeCN was found to be the best solvent for the reaction (entry 1–6). Also, when the reaction temperature was decreased to 25–40 °C, the *N*, *O*-selectivity increased (entries 8, 9). Finally, the reaction was conducted in MeCN at 25–40 °C to give the desired product **16** in 75–77% yields after column chromatographic separation (entries 9–11).

Table 1. S_N2 reaction of mesylate **20** with 2-pyridone-3-carboxilic acid esters **12a**–**12c**



Entry	R =	solvent	temp (°C)	time (h)	**16**:**16'** (HPLC area% ratio)	yield (%)
1	Me	DME[a]	60	2	2.6:1	-
2	Me	DMAc[b]	60	2	4.8:1	-
3	Me	DMSO	60	2	6.7:1	-
4	Me	THF	60	2	2.7:1	-
5	Me	toluene	60	2	2.9:1	-
6	Me	MeCN	60	2	7.9:1	-
7	Me	MeCN	80	1	6.2:1	-
8	Me	MeCN	40	3	10.4:1	-
9	Me	MeCN	25	16	11.6:1	77
10	*i*-Pr	MeCN	40	2	10.0:1	75
11	*n*-Bu	MeCN	40	2	9.2:1	77

[a]1,2-dimethoxyethane. [b]*N*,*N*-dimethylacetamide.

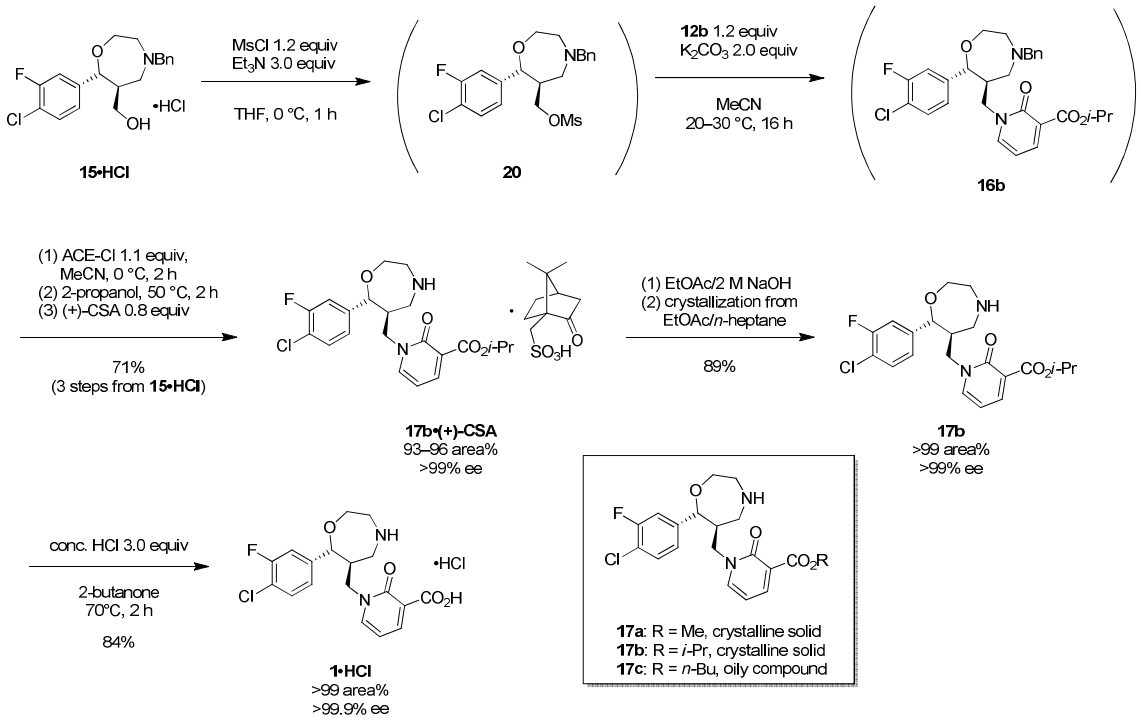
The obtained product **16** was found to be amorphous or an oily compound, which made it difficult to separate **16** from *O*-isomer **16'** without column chromatographic separation.[20] Thus, a mixture of **16** and **16'** was subjected to the next reaction without isolation, and an appropriate intermediate that was amenable to isolation and upgrade of purity was searched for in downstream processes (Scheme 7). In the modified procedure, **15·HCl** was directly converted to mesylate **20** without salt brake using 3.0 equiv of triethylamine and 1.2 equiv of MsCl, and used for the S_N2 reaction with **12b** after workup and solvent switch to MeCN. Debenzylation of **16b** was conducted using ACE-Cl[21], because debenzylation of **16b** using H_2 and a Pd catalyst gave the dechlorinated byproduct that was hard to remove. Following the reaction with 1.1 equiv of ACE-Cl in MeCN at 0 °C for 2 h, the resulting intermediate carbamate was decomposed by addition of 2-propanol with heating at 50 °C for 2 h to give **17b**. The solvent was switched to EtOAc, and the EtOAc solution of **17b** was washed with 5% aqueous $NaHCO_3$ and brine.

In spite of our effort to isolate **17b** as a crystalline solid, it was difficult to crystallize **17b** without column chromatographic purification, probably due to hindrance by several kinds of impurities, including the *O*-isomer and benzyl chloride liberated as a byproduct during the debenzylation.[22] At this point, we screened several acids for isolation of **17b** as a salt. Fortunately, we found that (+)-CSA formed a good salt with **17b** (**17b·(+)-CSA**) in EtOAc, enabling isolation of **17b**.[23] The obtained EtOAc solution of **17b** was treated with 0.8 equiv of (+)-CSA and the generated salt was collected by filtration, affording **17b·(+)-CSA** in 71% yield for 3 steps from **15·HCl** without residual *O*-isomer or benzyl chloride. To our delight, after salt brake of **17b·(+)-CSA**, it was possible to obtain free **17b** as a crystalline solid. Crystallization of **17b** from EtOAc/*n*-heptane was effective for upgrading **17b** (**17b·(+)·CSA**: 93–96 area%, **17b**: >99 area%), thereby allowing us to strictly control the purity of the final product.

We also prepared methyl ester **17a** and *n*-butyl ester **17c**. Whereas **17a** was a crystalline solid, **17c** was found to be an oily compound. Taking into account the easy workup for preparation of **12b**, isopropyl esters **12b**, **16b,** and **17b** were finally selected as the intermediates for the synthesis of **1·HCl**.

Successfully obtaining the penultimate intermediate **17b** with excellent purity, the end game was investigated. Although hydrolysis of the isopropyl ester of **17b** with aqueous NaOH in EtOH proceeded smoothly, extraction of **1** was found to be difficult due to low solubility of **1** in common organic solvents, which would be ascribed to zwitterionic nature of **1**. When we tried to crystallize **1** directly from the reaction mixture by adding hydrochloric acid and setting pH of the reaction mixture to the isocratic point, compound **1** unfortunately became oily product. Thus, we changed our strategy and tried to conduct the hydrolysis using hydrochloric acid in organic solvents, and to isolate the generated hydrochloric acid salt **1·HCl** by filtration. As a result of solvent screening, it was found that the hydrolysis of **17b** with 3.0 equiv of concentrated hydrochloric acid in 2-butanone proceeded well at 70 °C, and precipitation of the desired **1·HCl** was observed during the reaction. The reaction mixture was diluted with diisopropyl ether, and **1·HCl** was isolated by filtration in 84% yield with excellent chemical and optical purity (99.7 area%, >99.9% ee[24]). The optical purity of **5·(+)-CSA** was confirmed to be fully retained throughout the downstream processes as expected.

Scheme 7. Synthesis of **1·HCl** [a]



[a]For the synthesis of **17b·(+)-CSA**, the amounts of reagents were calculated based on the amount of **15·HCl**.

CONCLUSION

We have developed a practical synthesis of the potential peripherally selective NRI **1·HCl**. The chiral amino alcohol **5** that has the desired stereochemistry was successfully prepared from aldehyde **2** via Morita-Baylis-Hillman reaction, Michael addition, isolation as maleic acid salt, reduction, and diastereomeric salt formation with (+)-CSA with excellent dr and ee. Since the optical purity of **5·(+)-CSA** was fully retained until the final product, our strategy to set optical resolution at an early stage of the synthesis enabled effective preparation of **1·HCl**. The seven-membered ring was formed in the fully telescoped processes using the obtained **5·(+)-CSA**, which provided the chiral 6,7-*trans*-disubstituted-1,4-oxazepane efficiently. *N*,*O*-selectivity for

the S_N2 reaction of 2-pyridone-3-carboxylic acid ester **12b** with mesylate **20** was increased by optimizing the reaction conditions. In addition to the controls of dr, ee, and *N*,*O*-selectivity, finding appropriate intermediates (***rac*-4·MA**, **5·(+)-CSA**, **15·HCl**, **17b·(+)·CSA**, **17b**) that could be isolated and upgraded enabled a chromatographic/chiral HPLC separation-free synthesis of **1·HCl** with excellent chemical and optical purity. Also, as a result of our investigation, the overall yield was higher (11%) compared to the medicinal chemistry synthesis (6%). We believe that our practical synthesis is useful for preparation of chiral 6,7-*trans*-disubstituted-1,4-oxazepane derivatives and will contribute to studies on bioactivities of these compounds.

EXPERIMENTAL SECTION

All materials were purchased from commercial suppliers and used without any additional purification. Melting points were determined on a Stanford Research Systems OptiMelt MPA 100, and are uncorrected unless otherwise noted. ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER AVANCE 600 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are shown in ppm. HPLC analysis of the compounds and reaction monitoring was carried out on a Shimadzu LC-2010C_{HT}. High-resolution mass spectrometry (HRMS) data was obtained on a Shimadzu Prominence UFLC system with a Thermofisher LTQ Orbitrap Discovery. IR spectra were recorded on a Thermo Electron FT-IR Nicolet 4700 (ATR).

HPLC conditions. (A) Inertsil ODS-3 column, 5 μm, 250 mm × 4.6 mm i.d.; UV detector at 220 nm; isocratic elution with 50 mM aqueous KH_2PO_4 (pH 7.0) /MeCN (50:50) at 1.0 mL/min flow rate; column temperature: 25 °C. Retention times: **2** (13.7 min), ***rac*-3** (12.1 min), ***rac*-4·MA** (22.2 min), ***rac*-4'** (16.7 min).

(B) Inertsil ODS-3 column, 5 μm, 250 mm × 4.6 mm i.d.; UV detector at 220 nm; eluent: (A) 50 mM aqueous KH_2PO_4 (pH 7.0) /MeCN (80:20) (B) 50 mM aqueous KH_2PO_4 (pH 7.0) /MeCN (50:50); gradient: A:B 100:0 (0 min) – 80:20 (50 min) – 0:100 (60 min) – 0:100 (70 min); flow late at 1.0 mL/min; column temperature: 25 °C. Retention times: **5·(+)-CSA** (42.0 min), ***cis*-5** (40.3 min).

(C) Inertsil ODS-3 column, 5 μm, 150 mm × 4.6 mm i.d.; UV detector at 220 nm; Eluent: (A) 0.1% H_3PO_4 in H_2O (B) 0.1% H_3PO_4 in MeCN; gradient: A:B 90:10 (0 min) – 10:90 (10 min) – 10:90 (15 min); flow late at 1.3 mL/min; column temperature: 25 °C. Retention times: **12b** (4.9 min), **12c** (5.9 min), **15·HCl** (6.5 min), **16b** (7.6 min), **17b/17b·(+)-CSA** (6.6 min), **20** (7.2 min).

(D) Inertsil ODS-3 column, 5 μm, 150 mm × 4.6 mm i.d.; UV detector at 220 nm; eluent (A) 0.1% H_3PO_4 in H_2O (B) 0.1% H_3PO_4 in MeCN; gradient: A:B 90:10 (0 min) – 5:95 (7 min) – 5:95 (15 min); flow late at 1.3 mL/min; column temperature: 25 °C. Retention times: **6** (5.6 min), **7** (9.9 min), **8** (10.4 min), **9** (6.8 min).

(E) Inertsil ODS-3 column, 5 μm, 150 mm × 4.6 mm i.d.; UV detector at 220 nm; eluent (A) 20 mM aqueous KH_2PO_4/MeCN (90:10) (B) 20 mM aqueous KH_2PO_4/MeCN (30:70); gradient; A:B 100:0 (0 min) – 0:100 (15 min) – 0:100 (20 min); flow late at 1.3 mL/min; column temperature: 25 °C. Retention times: **1** (7.1 min).

Chiral HPLC conditions. (A) Ultron ES-PhCD, 5 μm, 150 mm × 6.0 mm i.d.; UV detector at 210 nm; isocratic elution with 50 mM aqueous KH_2PO_4/MeCN (50:50) at 1.0 mL/min flow rate; column temperature: 25 °C. Retention times: **5·(+)-CSA** (8.4 min), ***ent*-5** (10.2 min).

(B) CHIRALPAK AS-RH, 5 μm, 150 mm × 4.6 mm i.d.; UV detector at 220 nm; isocratic elution with 20 mM aqueous NH_4HCO_3 (pH 9.0, adjusted by diethylamine) /MeCN (60:40) at

1.0 mL/min flow rate; column temperature: 25 °C. Retention times: **15·HCl** (22.8 min), ***ent*-15·HCl** (40.8 min).

(C) CHIRALPAK ZWIX (+), 3 μm, 250 mm × 3.0 mm i.d.; UV detector at 220 nm; isocratic elution with MeOH/MeCN/H_2O (49:49:2) /50 mM formic acid/25 mM diethylamine at 1.0 mL/min flow rate; column temperature: 25 °C. Retention times: **17b/17b·(+)-CSA** (47.0 min), ***ent*-17b/*ent*-17b·(+)-CSA** (50.7 min).

(D) CHIRALCEL OZ-RH, 5 μm, 150 mm × 4.6 mm i.d.; UV detector at 220 nm; isocratic elution with 50 mM aqueous KH_2PO_4 (pH 2.0) /MeCN (40:60) at 0.2 mL/min flow rate; column temperature: 25 °C. Retention times: ***N*-Boc 1** (28.1 min), ***ent*-*N*-Boc 1** (24.8 min).

Methyl (2*RS*,3*RS*)-2-[(Benzylamino)methyl]-3-(4-chloro-3-fluorophenyl)-3-hydroxypropanoate (2*Z*)-but-2-enedioate (1:1) (***rac*-4·MA**). To a mixture of 4-chloro-3-fluorobenzaldehyde **2** (200 g, 1.26 mol) and methyl acrylate (119 g, 1.39 mol) in MeOH (400 mL) was added DABCO (70.7 g, 631 mmol), and the mixture was stirred at 20–30 °C for 17 h. To the mixture were added EtOAc (2 L) and 10% aqueous NaCl (2 L), and the layers were separated. The organic layer was washed with 10% aqueous NaCl (1 L) and concentrated *in vacuo* to give methyl 2-[(4-chloro-3-fluorophenyl)(hydroxy)methyl]prop-2-enoate (***rac*-3**). To a solution of ***rac*-3** in MeOH (600 mL) was added dropwise benzylamine (149 g, 1.39 mol) in MeOH (200 mL) at 0 °C. After stirring at 0 °C for 16 h, EtOAc (2 L) and 10% aqueous NaCl (2 L) were added and the layers were separated. The organic layer was concentrated *in vacuo* to give methyl (2*RS*,3*RS*)-2-[(Benzylamino)methyl]-3-(4-chloro-3-fluorophenyl)-3-hydroxypropanoate (***rac*-4**). To the residue of ***rac*-4** was added dropwise maleic acid (131 g, 1.13 mol) in EtOAc (3 L), and the mixture was stirred at 20–30 °C for 1 h. The resulting solids were

collected by filtration, washed with EtOAc (1 L) and dried *in vacuo* at 50 °C to give ***rac*-4·MA** (436 g, 74%) as a white solid. HPLC purity: 94.7 area% (***rac*-4'**: 5.3 area%. HPLC condition A). A small portion of the product was recrystallized from MeOH/EtOAc (1:10) to obtain a sample for analysis. Mp 144–145 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.86 (br dd, J = 12.8, 2.6 Hz, 1H), 3.04–3.14 (m, 1H), 3.24 (br dd, J = 12.8, 9.8 Hz, 1H), 3.62 (s, 3H), 4.03–4.21 (m, 2H), 5.03 (br d, J = 4.5 Hz, 1H), 6.03 (s, 2H), 7.12–7.20 (m, 1H), 7.33 (br dd, J = 10.4, 1.3 Hz, 1H), 7.40 (s, 5H), 7.57 (br t, J = 7.9 Hz, 1H), 8.59 (br s, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 43.2, 49.5, 50.4, 52.2, 70.9, 114.4 ($^{2}J_{CF}$ = 21.1 Hz), 118.3 ($^{2}J_{CF}$ = 18.1 Hz), 123.2 ($^{3}J_{CF}$ = 3.0 Hz), 128.6 (2C), 128.9, 129.9 (2C), 130.4, 131.7, 135.9 (2C), 143.8 ($^{3}J_{CF}$ = 6.0 Hz), 157.0 ($^{1}J_{CF}$ = 246.1 Hz), 167.2 (2C), 170.8; IR (ATR) 3151, 2179, 1722, 1572, 1481, 1353, 1265, 1177, 1087, 1003, 983, 965, 921, 904, 863, 835, 755, 701, 569, 548, 527, 488 cm^{-1}; HRMS (ESI): $[M+H]^+$ calcd for $C_{18}H_{20}ClFNO_3$ (***rac*-4**), 352.1116; found, 352.1110.

[(1*S*, 4*R*)-(7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)]methanesulfonic Acid - (1*R*,2*S*)-2-[(Benzylamino)methyl]-1-(4-chloro-3-fluorophenyl)propane-1,3-diol (1:1) (5·(+)-CSA). To a suspension of ***rac*-4·MA** (100 g, 214 mmol) in EtOAc (1 L) was added 5% aqueous $NaHCO_3$ (1 L), and the mixture was stirred at 20–30 °C for 30 min. The layers were separated and the organic layer was concentrated *in vacuo* to give ***rac*-4**. To the resulting ***rac*-4** was added THF (400 mL). $CaCl_2$ (59.3 g, 534 mmol) was added to a mixture of THF (400 mL) and EtOH (400 mL), and the mixture was stirred at 20–30 °C for 1 h under N_2 flow. To this mixture was added portionwise $NaBH_4$ (40.5 g, 1.07 mol) at 0 °C, and the mixture was stirred for 30 min at this temperature under N_2 atmosphere. To this mixture was added dropwise the above prepared THF solution of ***rac*-4** at 0 °C, and the mixture was stirred at this temperature for 16 h under N_2 atmosphere. MeOH (500 mL) was added dropwise to the mixture at 0 °C, followed by addition

of H_2O (500 mL) and 2 M HCl (700 mL). To the mixture was added 8 M NaOH (100 mL), and pH of the mixture was adjusted to 7. After stirring for 30 min, the suspension was filtrated and washed with EtOAc (500 mL). The filtrate was concentrated *in vacuo* to remove organic solvents. To the resulting aqueous solution was added EtOAc (1 L), and the layers were separated. The aqueous layer was extracted with EtOAc (1 L), and the combined organic layer was concentrated *in vacuo*. To the residue were added EtOAc (500 mL) and 5% aqueous $NaHCO_3$ (500 mL), and the layers were separated. The organic layer was washed with 10% aqueous NaCl (500 mL) and concentrated *in vacuo* to give (1*RS*,2*SR*)-2-[(benzylamino)methyl]-1-(4-chloro-3-fluorophenyl)propane-1,3-diol (***rac*-5)**. To a solution of ***rac*-5** in MeOH (100 mL) and EtOAc (300 mL) was added (+)-CSA (24.8 g, 107 mmol). The mixture was stirred at 50 °C for 1 h, at 20–30 °C for 1 h and at 0–10 ºC for 1 h. The resulting solids were collected by filtration, washed with EtOAc (300 mL) and dried *in vacuo* at 50 °C to give crude **5·(+)-CSA**. To a solution of crude **5·(+)-CSA** in MeOH (400 mL) was added dropwise EtOAc (1.5 L) at 50 °C. The mixture was stirred at 50 °C for 1 h, at 20–30 °C for 1 h and at 0–10 ºC for 1 h. The resulting solids were collected by filtration, washed with EtOAc (300 mL) and dried *in vacuo* at 50 °C to give **5·(+)-CSA** (42.8 g, 36%) as a white solid. HPLC purity: 99.8 area% (HPLC condition B). Optical Purity: >99.9% ee (chiral HPLC condition A). Mp 180–181 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.74 (s, 3H), 0.93–1.13 (m, 3H), 1.19–1.35 (m, 2H), 1.80 (d, J = 18.1 Hz, 1H), 1.84 (dt, J = 11.1, 3.3 Hz, 1H), 1.89–1.97 (m, 1H), 2.04–2.14 (m, 1H), 2.23 (br dd, J = 18.1, 3.0 Hz, 1H), 2.38 (d, J = 14.7 Hz, 1H), 2.62–2.74 (m, 1H), 2.89 (d, J = 14.7 Hz, 1H), 2.94–3.06 (m, 2H), 3.30–3.33 (m, 1H), 3.44 (br dd, J = 10.8, 4.3 Hz, 1H), 4.08–4.25 (m, 2H), 4.66 (br d, J = 6.8 Hz, 1H), 5.03 (br s, 1H), 6.06 (br s, 1H), 7.16 (br d, J = 8.3 Hz, 1H), 7.30 (br d, J = 10.6 Hz, 1H), 7.38–7.45 (m, 3H), 7.47 (br d, J = 4.9 Hz, 2H), 7.56 (t, J = 8.1 Hz, 1H), 8.54 (br s, 2H); ^{13}C NMR (151 MHz,

DMSO-d_6) δ 19.5, 20.1, 24.1, 26.4, 42.1, 42.2, 44.4, 46.3, 46.7, 47.0, 50.4, 58.2, 60.2, 70.8, 114.6 ($^2J_{CF}$ = 21.1 Hz), 117.9 ($^2J_{CF}$ = 16.6 Hz), 123.5 ($^3J_{CF}$ = 3.0 Hz), 128.7 (2C), 128.9, 129.9 (2C), 130.3, 131.8, 145.7 ($^3J_{CF}$ = 6.0 Hz), 157.0 ($^2J_{CF}$ = 246.1 Hz), 216.3; IR (ATR) 3240, 2964, 1739, 1622, 1449, 1279, 1178, 1152, 1061, 1006, 964, 859, 823, 764, 747, 699, 615, 597, 583, 535, 523, 509, 408 cm^{-1}; HRMS (ESI): $[M+H]^+$ calcd for $C_{17}H_{20}ClFNO_2$ (**5**), 324.1167; found, 324.1163.

[(6*S*,7*R*)-4-Benzyl-7-(4-chloro-3-fluorophenyl)-1,4-oxazepan-6-yl]methanol Hydrochloride (1:1) (15·HCl). To a suspension of **5·(+)-CSA** (100 g, 180 mmol) in EtOAc (1 L) was added 5% aqueous $NaHCO_3$ (400 mL) and 1 M NaOH (200 mL), and pH was adjusted to 8.5–8.8. The mixture was stirred at 20–30 °C for 10 min, and the layers were separated. The organic layer was washed with 5% aqueous $NaHCO_3$ (300 mL) and 10% aqueous NaCl (300 ml) and concentrated *in vacuo* to give (1*R*,2*S*)-2-[(benzylamino)methyl]-1-(4-chloro-3-fluorophenyl)propane-1,3-diol (**5**). To a solution of **5** in THF (175 mL) were added imidazole (18.4 g, 270 mmol) and TBSCl (29.8 g, 198 mmol) under 15 °C, and the mixture was stirred at 20–30 °C for 1.5 h. To this solution were added EtOAc (500 mL) and 10% aqueous NaCl (500 mL), and the layers were separated. The organic layer was washed with 10 % aqueous NaCl (500 mL) and concentrated *in vacuo* to give (1*R*,2*S*)-3-(benzylamino)-2-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-1-(4-chloro-3-fluorophenyl)propan-1-ol (**6**). To a solution of **6** in THF (500 mL) was added triethylamine (21.9 g, 216 mmol). To this mixture was added dropwise chloroacethyl chloride (22.4 g, 198 mmol) at 0 °C, and the mixture was stirred at 20–30 °C for 1 h. To the mixture was added slowly 2 M NaOH (270 mL, 540 mmol), maintaining the temperature below 15 °C. After stirring at 20–30 °C for 13 h, 1 M HCl (320 mL) was added and pH was adjusted to 8–9. To the mixture was added EtOAc (500 mL), and the layers were separated. The organic layer was washed with 10%

aqueous NaCl (300 mL × 2) and concentrated *in vacuo* to give (6*S*,7*R*)-4-benzyl-6-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepan-3-one (**8**) (HPLC assay yield 83%, 71.4 g, 149 mmol). To a solution of **8** in THF (714 mL) was added $NaBH_4$ (23.7 g, 626 mmol) at 0 °C under N_2 atmosphere. To this mixture was added dropwise I_2 (75.6 g, 298 mmol) in THF (357 mL) at 0 °C over 2 h, and the mixture was stirred at 20–30 °C for 1 h under weak N_2 flow (**Caution.** H_2 was generated). The reaction was quenched by dropwise addition of MeOH (357 mL) at 20–30 °C, and the mixture was stirred at 20–30 °C for 12 h under weak N_2 flow. The mixture was concentrated *in vacuo*. EtOAc (710 mL) and H_2O (355 mL) were added, and the layers were separated. The organic layer was washed with H_2O (355 mL), 10% aqueous NaCl (355 mL), 5% aqueous $NaHCO_3$ (355 mL), 10% aqueous NaCl (355 mL) and concentrated *in vacuo* to give (6*S*,7*R*)-4-benzyl-6-({[*tert*-butyl(dimethyl)silyl]oxy}methyl)-7-(4-chloro-3-fluorophenyl)-1,4-oxazepane (**9**). To a solution of **9** in EtOAc (714 mL) was added 4 M HCl in EtOAc (112 mL, 447 mmol), and the mixture was stirred at 50 °C for 2 h. The mixture was cooled to 20–30 °C, and the resulting solids were collected by filtration and washed with EtOAc (142 mL × 3). The wet solids were suspended in MeCN (714 mL), and the mixture was stirred at 40–50 °C for 1 h, at 20–30 °C for 1 h and then filtrated. Wet solids were washed with MeCN (213 mL × 3) and dried *in vacuo* at 40 °C to give **15·HCl** (52.9 g, 76%) as a white solid. HPLC purity: 98.2 area% (HPLC condition C). Optical Purity: >99% ee (chiral HPLC condition B). Mp 239–242 °C; ^{1}H NMR (600 MHz, DMSO-d_6)[25] δ 2.55–2.65 (m, 0.25H), 3.04 (br dd, J = 10.4, 4.7 Hz, 1H), 3.08–3.22 (m, 2.5H), 3.25 (br d, J = 7.6 Hz, 2H), 3.38–3.47 (m, 1.5H), 3.49 (br s, 0.25H), 3.62 (br d, J = 13.2 Hz, 1H), 3.65–3.72 (m, 1H), 3.93 (br s, 0.25H), 4.11 (br dd, J = 13.0, 8.5 Hz, 1.25H), 4.36–4.53 (m, 2.5H), 4.58 (br d, J = 10.6 Hz, 1.25H), 4.97 (br s, 1.25H), 7.27 (br d, J = 7.9 Hz, 0.25H), 7.33 (br d, J = 7.9 Hz, 1H), 7.47 (br d, J = 3.4 Hz,

3.75H), 7.51–7.57 (m, 1.25H), 7.58–7.66 (m, 1.25H), 7.67–7.79 (m, 2.5H), 11.2 (br s, 0.25H), 11.4 (br s, 1 H); ^{13}C NMR (151 MHz, DMSO-d_6)[25] δ 41.8, 52.6, 54.8, 55.0, 55.9, 57.8, 60.0, 60.2, 60.3, 60.4, 63.1, 78.9, 81.2, 115.4 (d, $^2J_{CF}$ = 21.1 Hz), 116.2 (d, $^2J_{CF}$ = 21.1 Hz), 119.2 ($^2J_{CF}$ = 16.6 Hz), 124.7, 125.1 (d, $^3J_{CF}$ = 3.0 Hz), 128.8 (2C), 129.4, 130.2, 130.4, 130.7, 131.2, 131.4 (2C), 141.8 (d, $^3J_{CF}$ = 6.0 Hz), 142.7, 157.1 (d, $^1J_{CF}$ = 246.1 Hz). IR (ATR) 3268, 2929, 2614, 1581, 1490, 1428, 1107, 1060, 1017, 970, 954, 906, 851, 823, 764, 748, 698, 638, 570, 537, 516, 490, 418 cm^{-1}; HRMS (ESI): $[M+H]^+$ calcd for $C_{19}H_{22}ClFNO_2$ (**15**), 350.1323; found, 350.1312.

Propan-2-yl 2-Oxo-1,2-dihydropyridine-3-carboxylate (**12b**). To a solution of 2-hydroxy-3-pyridinecarboxylic acid **18** (5.00 g, 35.9 mmol) and DMF (525 mg, 7.19 mmol) in THF (50 mL) was added dropwise thionyl chloride (5.55 g, 46.7 mmol) at 0 °C, and the mixture was stirred at 20–30 °C for 2.5 h. The mixture was cooled to 0 °C, and 2-propanol (25 mL) was slowly added at this temperature. The mixture was warmed to 20–30 °C and stirred at this temperature for 2h. The mixture was cooled to 0–10 °C, and 4 M NaOH (40 mL) was slowly added and pH was adjusted to 8–9. To this mixture was added EtOAc (50 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (50 mL), and the combined organic layer was washed with 10% aqueous NaCl (10 mL × 2) and concentrated *in vacuo*. To the residue was added EtOAc (15 mL), and *n*-heptane (45 mL) was slowly added at 40–50 °C. The mixture was cooled to 0–10 °C and stirred for 1 h, and then filtrated. Wet solids were washed with EtOAc/*n*-heptane (1:5, 10 mL) and dried *in vacuo* at 50 °C to give **12b** (5.57 g, 86%) as a white solid. HPLC purity: 99.5 area% (HPLC condition C). Mp 95–97 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.25 (d, J = 6.4 Hz, 6H), 5.02 (dt, J = 12.7, 6.1 Hz, 1H), 6.19–6.33 (m, 1H), 7.65 (dd, J = 6.4, 2.3 Hz, 1H), 7.98 (dd, J = 7.2, 2.3 Hz, 1H), 12.1 (br s, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 21.6 (2C), 67.3, 104.2, 120.4, 140.9, 144.5, 159.4, 164.1; IR (ATR) 3580, 2973, 1715, 1635, 1601, 1556,

1376, 1269, 1232, 1166, 1104, 1063, 927, 887, 777, 731, 656, 580, 562, 538, 485 cm^{-1}; HRMS (ESI): $[M+H]^+$ calcd for $C_9H_{12}NO_3$, 182.0817; found, 182.0810.

Butyl 2-Oxo-1,2-dihydropyridine-3-carboxylate (**12c**). To a solution of **18** (10.0 g, 71.9 mmol) and DMF (1.05 g, 14.4 mmol) in THF (100 mL) was added dropwise thionyl chloride (11.1 g, 93.5 mmol) at 0 °C, and the mixture was stirred at 20–30 °C for 2.5 h. The mixture was cooled to 0 °C, and *n*-butanol (30 mL) was slowly added at this temperature. The mixture was warmed to 20–30 °C and stirred at this temperature for 2.5 h. To the mixture were added EtOAc (100 mL) and 5% aqueous $NaHCO_3$ (10 mL), and the mixture was cooled to 0–10 °C. To the mixture was slowly added 4 M NaOH (45 mL), and pH was adjusted to 8–9. To this mixture were added EtOAc (100 mL) and H_2O (50 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (100 mL), and the combined organic layer was washed with 5% aqueous $NaHCO_3$ (50 mL) and concentrated *in vacuo*. To the residue was added *n*-heptane (60 mL), and the mixture was stirred at 20–30 °C for 10 min, and then filtrated. Wet solids were washed with *n*-heptane (40 mL × 2) and dried *in vacuo* at 50 °C to give **12c** (12.0 g, 86%) as a white solid. HPLC purity: 99.8 area% (HPLC condition C). Mp 84–85 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.97 (t, J = 7.4 Hz, 3H), 1.46 (sxt, J = 7.5 Hz, 2H), 1.65–1.83 (m, 2H), 4.31 (t, J = 6.6 Hz, 2H), 6.43 (br t, J = 6.6 Hz, 1H), 7.80 (br d, J = 4.5 Hz, 1H), 8.25 (dd, J = 7.2, 1.9 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 13.8, 19.2, 30.7, 65.0, 107.2 (br s), 119.1 (br s), 141.7 (br s), 145.4, 163.0, 164.9; IR (ATR) 3585, 2950, 1727, 1634, 1601, 1556, 1487, 1467, 1337, 1268, 1232, 1167, 1119, 1069, 948, 902, 812, 772, 729, 660, 585, 565, 535, 487, 444 cm^{-1}; HRMS (ESI): $[M+H]^+$ calcd for $C_{10}H_{14}NO_3$, 196.0974; found, 196.0965.

[(1*S*, 4*R*)-(7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)]methanesulfonic Acid - Propan-2-yl 1-{[(6*S*,7*R*)-7-(4-Chloro-3-fluorophenyl)-1,4-oxazepan-6-yl]methyl}-2-oxo-1,2-

dihydropyridine-3-carboxylate (1:1) (**17b·(+)-CSA**). To a suspension of **15·HCl** (29.0 g, 75.2 mmol) in THF (300 mL) was added triethylamine (22.8 g, 226 mmol), and the mixture was stirred at 20–30 °C for 1 h. To the mixture was added methanesulfonyl chloride (10.3 g, 90.2 mmol) at 0 °C, and the mixture was stirred at 0 °C for 1 h and concentrated *in vacuo*. To the residue were added EtOAc (300 mL) and 10 % aqueous NaCl (150 mL), and the layers were separated. The organic layer was washed with 10 % aqueous NaCl (150 mL) and concentrated *in vacuo* to give [(6*S*,7*R*)-4-benzyl-7-(4-chloro-3-fluorophenyl)-1,4-oxazepan-6-yl]methyl methanesulfonate (**20**). To a solution of **20** in MeCN (600 mL) were added **12b** (16.4 g, 90.2 mmol) and K_2CO_3 (20.8 g, 150 mmol), and the mixture was stirred at 20–30 °C for 16 h and concentrated *in vacuo*. To the residue were added EtOAc (600 mL) and 10 % aqueous NaCl (300 mL), and the layers were separated. The organic layer was washed with 10 % aqueous NaCl (300 mL) and concentrated *in vacuo* to give propan-2-yl 1-{[(6*S*,7*R*)-4-benzyl-7-(4-chloro-3-fluorophenyl)-1,4-oxazepan-6-yl]methyl}-2-oxo-1,2-dihydropyridine-3-carboxylate (**16b**). To a solution of **16b** in MeCN (300 mL) was added 1-chloroethyl chloroformate (11.8 g, 82.5 mmol) at 0 °C, and the mixture was stirred at 0 °C for 2 h and concentrated *in vacuo* to approximately 60 mL. To the solution was added 2-propanol (300 mL), and the mixture was stirred at 50 °C for 2 h and concentrated *in vacuo*. To the residue were added EtOAc (600 mL) and 5 % aqueous $NaHCO_3$ (150 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (300 mL), and the combined organic layer was washed with 10% aqueous NaCl (150 mL). To the organic layer was added (+)-CSA (14.0 g, 60.1 mmol) at 20–30 °C, and the solution was concentrated *in vacuo*. To the residue was added AcOEt (600 mL), and the mixture was stirred at 20–30 °C for 30 min. To the mixture was added dropwise *n*-heptane (300 mL), and the mixture was stirred at 20–30 °C for 30 min. The resulting solids were collected by filtration, washed with

EtOAc/*n*-heptane (2:1, 450 mL) and dried *in vacuo* at 50 °C to give **17b·(+)-CSA** (35.0 g, 71 % from **15·HCl**) as a white solid. HPLC purity: 95.9 area% (HPLC condition C). Optical Purity: >99% ee (chiral HPLC condition C). A small portion of the product was triturated with MeCN/EtOAc (1:1) to obtain a sample for analysis. Mp 207–209 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.75 (s, 3H), 1.05 (s, 3H), 1.25 (br d, J = 6.4 Hz, 6H), 1.27–1.35 (m, 2H), 1.80 (br d, J = 18.1 Hz, 1H), 1.85 (ddd, J = 11.6, 7.8, 4.0 Hz, 1H), 1.94 (br t, J = 4.2 Hz, 1H), 2.24 (dt, J = 18.1, 3.4 Hz, 1H), 2.40 (br d, J = 14.4 Hz, 1H), 2.62–2.73 (m, 1H), 2.89 (d, J = 14.7 Hz, 1H), 3.12 (br s, 1H), 3.15–3.22 (m, 2H), 3.23–3.32 (m, 2H), 3.69 (br dd, J = 13.2, 5.7 Hz, 1H), 3.76–3.87 (m, 1H), 3.91–4.10 (m, 2H), 4.54 (br d, J = 9.8 Hz, 1H), 5.00 (dt, J = 12.5, 6.2 Hz, 1H), 6.23 (br t, J = 6.8 Hz, 1H), 7.27 (br d, J = 6.8 Hz, 1H), 7.45–7.51 (m, 1H), 7.55 (br t, J = 8.1 Hz, 1H), 7.74 (br dd, J = 6.4, 1.9 Hz, 1H), 7.86 (dd, J = 7.2, 1.9 Hz, 1H), 8.90 (br s, 2H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 19.5, 20.1, 21.6 (2C), 24.1, 26.4, 40.7, 42.1, 42.2, 45.1, 46.7, 46.7, 47.1, 49.5, 58.2, 63.7, 67.6, 82.2, 104.3, 115.9 ($^2J_{CF}$ = 21.1 Hz), 119.1 ($^2J_{CF}$ = 18.1 Hz), 120.4, 125.1 ($^3J_{CF}$ = 3.0 Hz), 130.4, 141.1 ($^3J_{CF}$ = 6.0 Hz), 143.5, 144.0, 156.9 ($^1J_{CF}$ = 246.1 Hz), 158.4, 163.6, 216.3; IR (ATR) 3565, 3500, 2965, 1731, 1642, 1548, 1258, 1203, 1109, 1040, 968, 872, 758, 600, 534, 509, 419 cm^{-1}; HRMS (ESI): $[M+H]^+$ calcd for $C_{21}H_{25}ClFN_2O_4$ (**17**), 423.1487; found, 423.1481.

Propan-2-yl 1-{[(6*S*,7*R*)-7-(4-Chloro-3-fluorophenyl)-1,4-oxazepan-6-yl]methyl}-2-oxo-1,2-dihydropyridine-3-carboxylate (17b). To a suspension of **17b·(+)-CSA** (32.0 g, 48.9 mmol) in EtOAc (480 mL) was added 2 M NaOH (97.8 mL, 196 mmol), and the mixture was stirred at 20–30 °C for 10 min. The layers were separated, and the organic layer was washed with 5% $NaHCO_3$ (64 mL) and 10% aqueous NaCl (64 mL), and concentrated *in vacuo*. To the residue was added EtOAc (64 mL), and *n*-heptane (192 mL) was slowly added at 40–50 °C. The mixture

was gradually cooled to 0–10 °C, stirred for 1 h, and then filtrated. Wet solids were washed with EtOAc/*n*-heptane (1:5, 64 mL) and dried *in vacuo* at 50 °C to give **17b** (18.4 g, 89%) as a white solid. HPLC purity: 99.1 area% (HPLC condition C). Optical Purity: >99% ee (chiral HPLC condition C). Mp 123–124 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.33 (dd, J = 6.0, 3.0 Hz, 6H), 1.75 (br s, 1H), 2.66–2.75 (m, 1H), 2.80 (dd, J = 14.2, 3.2 Hz, 1H), 2.95–3.06 (m, 3H), 3.63 (ddd, J = 12.7, 9.3, 4.5 Hz, 1H), 4.05 (dd, J = 12.8, 5.3 Hz, 1H), 4.09–4.20 (m, 2H), 4.29 (d, J = 7.6 Hz, 1H), 5.04–5.35 (m, 1H), 6.13 (t, J = 6.8 Hz, 1H), 7.18 (dd, J = 8.3, 1.5 Hz, 1H), 7.23 (dd, J = 10.0, 1.7 Hz, 1H), 7.35 (t, J = 7.9 Hz, 1H), 7.42 (dd, J = 6.4, 2.3 Hz, 1H), 7.99 (dd, J = 7.2, 2.3 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.9 (2C), 46.7, 48.0, 51.7, 52.2, 68.5, 74.8, 84.7 ($^4J_{CF}$ = 1.5 Hz), 104.3, 114.8 ($^2J_{CF}$ = 21.1 Hz), 120.0 ($^2J_{CF}$ = 18.1 Hz), 121.7, 122.9 ($^3J_{CF}$ = 3.0 Hz), 130.7, 142.6, 143.4 ($^3J_{CF}$ = 6.0 Hz), 143.7, 158.0 ($^1J_{CF}$ = 249.2 Hz), 159.5, 164.0; IR (ATR) 3348, 2937, 1716, 1647, 1584, 1547, 1492, 1452, 1390, 1371, 1337, 1263, 1098, 1057, 967, 879, 810, 764, 750, 688, 628, 533, 456 cm^{-1}; HRMS (ESI): $[M+H]^+$ calcd for $C_{21}H_{25}ClFN_2O_4$, 423.1487; found, 423.1481.

1-{[(6*S*,7*R*)-7-(4-Chloro-3-fluorophenyl)-1,4-oxazepan-6-yl]methyl}-2-oxo-1,2-dihydropyridine-3-carboxylic Acid Hydrochloride (1:1) (1·HCl). To a solution of **17b** (5.00 g, 11.8 mmol) in 2-butanon (25 mL) was added hydrochloric acid (36% solution, 3.59 g, 35.5 mmol), and the mixture was stirred at 70 °C for 2 h. The mixture was cooled to 20–30 °C and diisopropyl ether (12.5 mL) was slowly added. The mixture was cooled to 0–10 °C and stirred for 3 h, and then filtrated. Wet solids were washed with 2-butanon (10 mL × 2) and dried *in vacuo* at 50 °C to give **1·HCl** (4.14 g, 84%) as a white solid. HPLC purity: 99.7 area% (HPLC condition E). Optical purity of **1·HCl** was determined after being converted to the *N*-Boc derivative. A small portion of **1·HCl** (10 mg) in H_2O (0.5 mL) was treated with 1.5 equiv of

Boc_2O (7.9 mg) in the presence of 3.0 equiv of NaOH (1 M NaOH 72 μL) at 25 °C for 3 h. The mixture was diluted with MeCN and analyzed by HPLC. Optical Purity: >99.9% ee (chiral HPLC condition D). Mp 261–262 °C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 3.09–3.18 (m, 1H), 3.20–3.43 (m, 4H), 3.77–3.88 (m, 1H), 3.96 (br dd, J = 13.2, 5.7 Hz, 1H), 4.04 (dt, J = 13.8, 4.2 Hz, 1H), 4.17 (br dd, J = 13.6, 7.6 Hz, 1H), 4.59 (br d, J = 9.1 Hz, 1H), 6.66 (t, J = 7.0 Hz, 1H), 7.27 (br dd, J = 8.3, 1.1 Hz, 1H), 7.47 (br dd, J = 10.4, 1.3 Hz, 1H), 7.54 (br t, J = 8.1 Hz, 1H), 8.10 (dd, J = 6.4, 1.9 Hz, 1H), 8.26 (dd, J = 7.2, 1.9 Hz, 1H), 9.59 (br s, 2H), 14.2 (br s, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 40.5, 44.9, 46.5, 50.0, 63.9, 82.1, 108.4, 116.0 ($^2J_{CF}$ = 21.1 Hz), 116.7, 119.3 ($^2J_{CF}$ = 18.1 Hz), 125.1 ($^3J_{CF}$ = 4.5 Hz), 130.4, 140.9 ($^3J_{CF}$ = 7.6 Hz), 145.1, 145.2, 156.8 ($^1J_{CF}$ = 247.6 Hz), 163.6, 164.4; IR (ATR) 2925, 2693, 1725, 1625, 1563, 1484, 1445, 1379, 1293, 1206, 1126, 1097, 1064, 1003, 934, 868, 856, 820, 783, 771, 627, 538, 521, 459, 411 cm^{-1}; HRMS (ESI): $[M+H]^+$ calcd for $C_{18}H_{19}ClFN_2O_4$ (**1**), 381.1017; found, 381.1009.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

^{1}H and ^{13}C NMR spectra of compounds ***rac*-4·MA**, **5·(+)-CSA**, **15·HCl**, **15**, **12b**, **12c**, **17b·(+)-CSA**, **17b** and **1·HCl** (PDF)

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Notes

The Authors declare no competing financial interest.

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17. Compound **12b** was reported in references 16b and 16c without spectroscopic data.

18. Data for **16b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.32 (d, J = 6.0 Hz, 6H), 2.54–2.65 (m, 2H), 2.71–2.76 (m, 1H), 2.76–2.80 (m, 1H), 2.85 (br dd, J = 12.8, 1.5 Hz, 1H), 3.56–3.64 (m, 2H), 3.65–3.76 (m, 2H), 4.04 (dt, J = 12.8, 2.8 Hz, 1H), 4.21 (dd, J = 12.7, 5.1 Hz, 1H), 4.41 (d, J = 6.8 Hz, 1H), 5.19 (spt, J = 6.2 Hz, 1H), 5.90–5.94 (m, 1H), 6.84 (dd, J = 6.6, 2.1 Hz, 1H), 7.17 (dd, J = 8.1, 1.7 Hz, 1H), 7.22 (dd, J = 10.2, 1.9 Hz, 1H), 7.28–7.32 (m, 1H), 7.32–7.35 (m, 1H), 7.35–7.38 (m, 4H), 7.92 (dd, J = 7.0, 2.1 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 21.9 (2C), 45.0, 52.8, 53.9, 59.5, 63.9, 68.4, 71.8, 84.0, 104.1, 114.9 ($^{2}J_{CF}$ = 22.7 Hz), 119.9 ($^{2}J_{CF}$ = 22.7 Hz), 121.5, 122.9 ($^{3}J_{CF}$ = 4.5 Hz), 127.5, 128.6 (2C), 129.2 (2C), 130.6, 139.1, 142.5, 143.2 ($^{3}J_{CF}$ = 6.0 Hz), 143.6, 157.9 ($^{1}J_{CF}$ = 249.2 Hz), 159.4, 164.0. HRMS (ESI):

$[M+H]^+$ calcd for $C_{28}H_{31}ClFN_2O_4$, 513.1956; found, 513.1954. Data for **16b'**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.34 (d, *J* = 6.0 Hz, 6H), 2.45 (br dd, *J* = 7.6, 3.8 Hz, 1H), 2.66–2.75 (m, 1 H), 2.81 (br d, *J* = 12.5 Hz, 1H), 2.92 (br dd, *J* = 13.4, 2.5 Hz, 1H), 3.15 (br dd, *J* = 13.2, 2.3 Hz, 1H), 3.56 (br d, *J* = 12.8 Hz, 1H), 3.65–3.74 (m, 2H), 4.03–4.10 (m, 1H), 4.14–4.19 (m, 1H), 4.21–4.29 (m, 1H), 4.45 (br d, *J* = 8.3 Hz, 1H), 5.16–5.24 (m, 1H), 6.90 (dd, *J* = 7.6, 4.9 Hz, 1H), 6.94–7.01 (m, 1H), 7.10 (t, *J* = 7.6 Hz, 2H), 7.13 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.24–7.33 (m, 4H), 8.08 (dd, *J* = 7.4, 2.1 Hz, 1H), 8.20 (dd, *J* = 4.9, 2.3 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 22.0 (2C), 47.0, 55.1, 59.3, 63.8, 66.3, 68.4, 72.5, 83.1, 114.6, 115.0 ($^2J_{CF}$ = 21.1 Hz), 116.3, 119.7 ($^2J_{CF}$ = 18.1 Hz), 123.1 ($^3J_{CF}$ = 3.0 Hz), 126.8, 128.0 (2C), 129.0 (2C), 130.4, 139.2, 141.1, 144.2 ($^3J_{CF}$ = 6.0 Hz), 150.2, 158.0 ($^1J_{CF}$ = 249.2 Hz), 161.6, 164.4. HRMS (ESI): $[M+H]^+$ calcd for $C_{28}H_{31}ClFN_2O_4$, 513.1956; found, 513.1946.

19. K_3PO_4 and triethylamine were also used for the reaction. K_3PO_4 gave a comparable result to that of K_2CO_3. When triethylamine was used, the reaction was slow and >10% of the substrate remained even after 4 h.

20. We screened several acids to isolate **16b** as a salt. Although oxalic acid and fumaric acid formed a salt with **16b**, salt formation with these acids was not effective for removing **16b'**.

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22. When **17b** was stored as a crude oily product after workup and concentration, a slight increase of the amount of **16b** was observed. This was probably due to the reaction of **17b** with the liberated benzyl chloride. Addition of (+)-CSA to the EtOAc solution of **17b** after workup effectively suppressed the generation of **16b** by protonating the nitrogen atom of **17b**.

23. Though fumaric acid also formed a salt with **17b**, the salt formation was not effective for upgrading purity.

24. Optical purity of **1·HCl** was determined after being converted to the corresponding *N*-Boc derivative.

25. ^{1}H NMR spectrum of **15·HCl** appeared as a pair of two conformers (ca. 4:1) at room temperature, with many signals overlapped. The ^{1}H NMR spectrum measured at 72 °C and 92 °C gave broad signals due to coalescence of the two conformers. These results imply that some kind of restricted bond-rotation or ring-flip may occur in **15·HCl** at room temperature. ^{13}C spectrum of **15·HCl** at room temperature was likewise complicated, and some of the ^{13}C signals corresponding to the minor conformer, indicated with underlines, were too small to be analyzed. On the other hand, free **15** showed simple ^{1}H and ^{13}C NMR spectra at room temperature, which suggests that free **15** appears as one conformer due to rapid exchange between the two conformers at room temperature and supports the structure of **15**. Data for free **15**: ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.02–2.11 (m, 1H), 2.48–2.54 (m, 1H), 2.56–2.66 (m, 1H), 2.84 (br d, J = 3.0 Hz, 2H), 3.32 (d, J = 6.0 Hz, 2H), 3.51 (ddd, J = 12.4, 9.3, 2.5 Hz, 1H), 3.59–3.69 (m, 2H), 3.89 (dt, J = 12.7, 3.5 Hz, 1H), 4.39 (d, J = 8.3 Hz, 1H), 4.47–4.72 (m, 1H), 7.20–7.28 (m, 2H), 7.30–7.37 (m, 4H), 7.39 (dd, J = 10.6, 1.5 Hz, 1H), 7.53 (t, J = 7.9 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 48.9, 55.7, 57.8, 61.8, 62.7, 69.7, 81.5, 115.0 (d, $^{2}J_{CF}$ = 21.1 Hz), 117.8 (d, $^{2}J_{CF}$ = 18.1 Hz), 123.9 (d, $^{3}J_{CF}$ = 3.0 Hz), 126.8, 128.1 (2C), 128.6 (2C), 130.2, 139.2, 145.4 (d, $^{3}J_{CF}$ = 6.0 Hz), 156.9 (d, $^{1}J_{CF}$ = 246.1 Hz).