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Development of a Practical and Scalable Synthetic Route to YM758 monophosphate, a Novel I_f Channel Inhibitor

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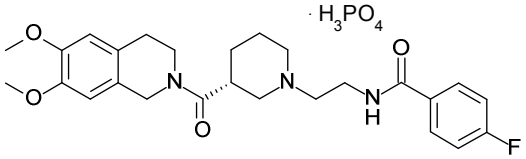
Abstract

A novel, practical, and efficient synthesis of (-)-*N*-{2-[(*R*)-3-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)piperidino]ethyl}-4-fluorobenzamide monophosphate (YM758 monophosphate, **(*R*)-1·H_3PO_4** (Figure 1) is described. The target molecule **(*R*)-1** has a potent I_f current channel inhibitor. Medicinal chemistry synthetic routes were very long and suffered from extensive use of chlorinated solvents and silica-gel column chromatography. A number of steps in the medicinal chemistry route were also unattractive for large-scale synthesis due to some reasons for example the use of unstable intermediates. An important objective of a new synthetic route was avoidance of such a use of unstable intermediate, and it was achieved by the discovery of an important 4,5-dihydrooxazole intermediate **19** and ring-opening *N*-alkylation of chiral amine with **19** under acidic condition. The new procedure does not require any purification by column chromatography for all steps. Overall yield was significantly improved from 14 or 34% to 49% compared to that of the medicinal synthetic routes. This

highly efficient process was successfully demonstrated at a pilot-scale operation, yielding 36.5kg of **(*R*)-1·H_3PO_4**.

Introduction

YM758 monophosphate **(*R*)-1·H_3PO_4** has an inhibitory action for I_f current and shows a strong and specific activity selectively lowering a heart beat and decreasing oxygen consumption of heart muscle in a selective manner whereby it is useful as a preventive and / or treating agent for diseases of circulatory system such as ischemic heart diseases (e.g., angina pectoris and myocardial infarction), congestive heart failure, arrhythmia, etc.[1] Herein, we describe our efforts to develop a practical, scalable approach to **(*R*)-1·H_3PO_4** which was demonstrated in a large-scale synthesis for the first GMP delivery. [1g, 1h]



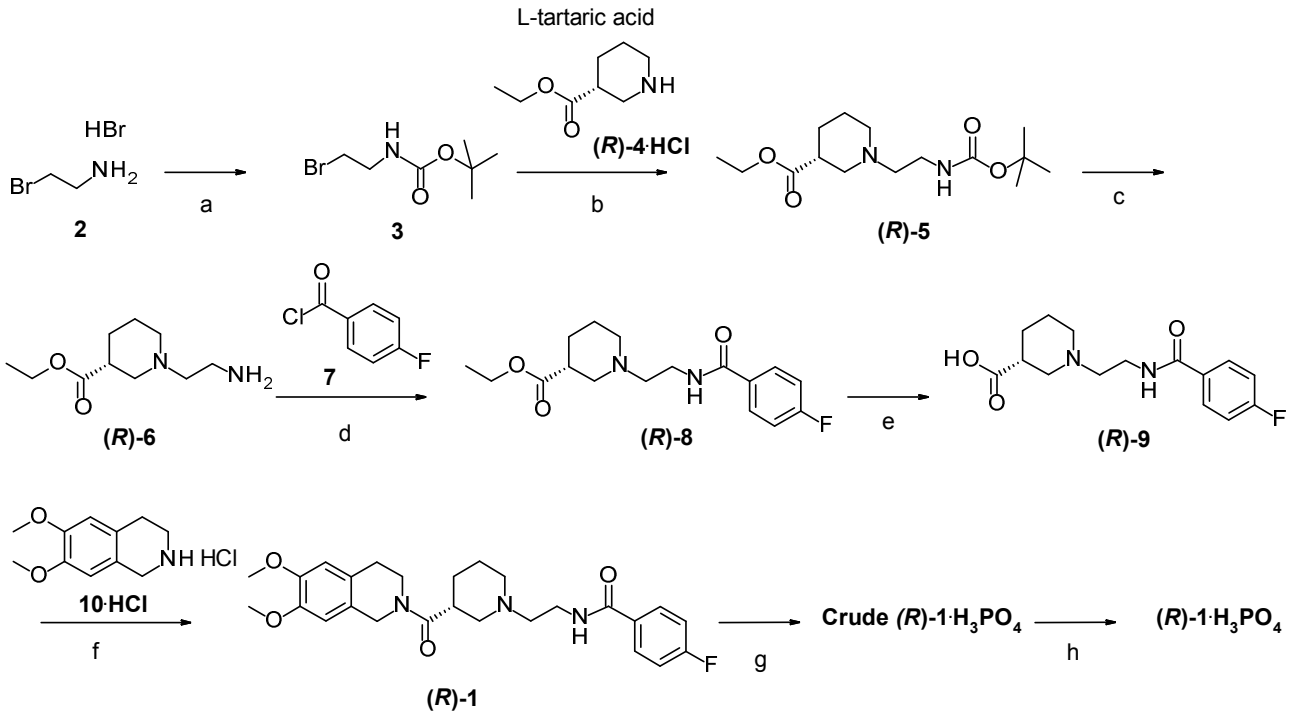
YM758 monophosphate
(*R*)-1·H_3PO_4

Figure 1. Structure of **(*R*)-1·H_3PO_4**

Medicinal Chemistry Synthetic Route A

The synthetic route to **(*R*)-1·H_3PO_4** used in *Medicinal Chemistry Synthetic Route A* was long, linear and involved unstable intermediates (Scheme 1). [1g,1h] These issues for a large-scale synthesis are described below.

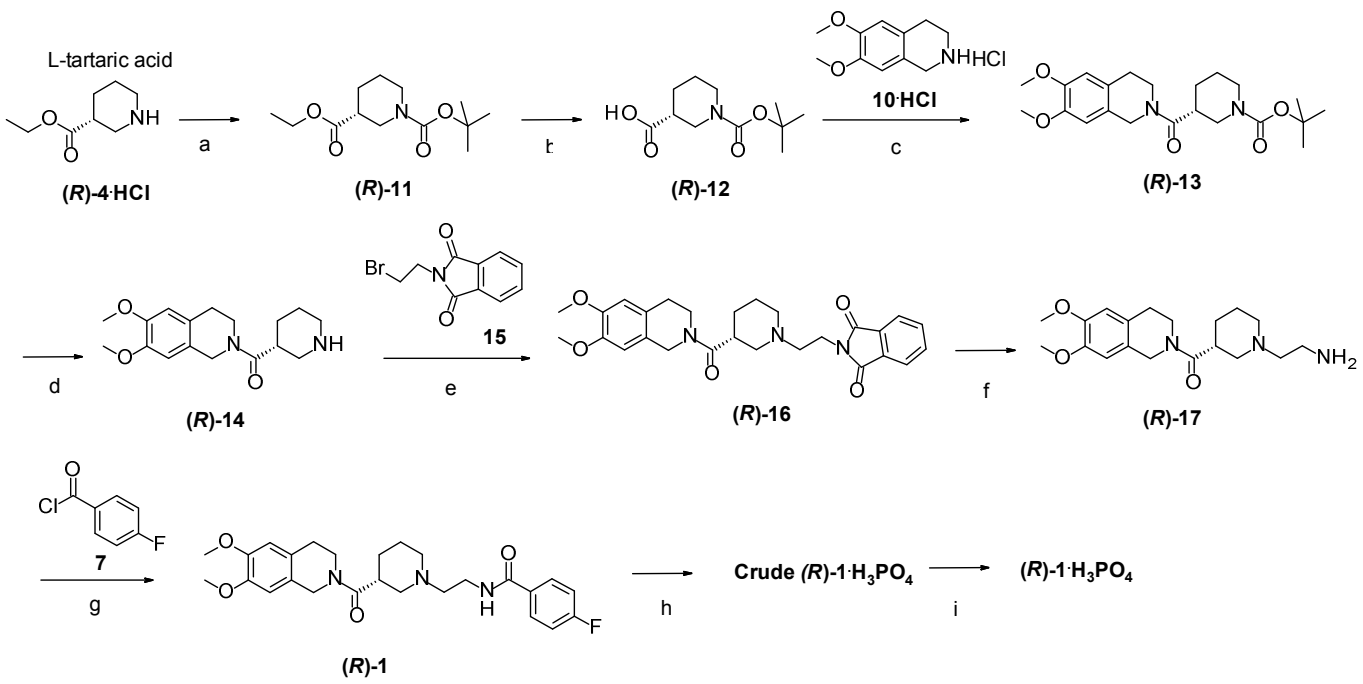
Scheme 1. *Medicinal Chemistry synthetic Route A* for **(*R*)-1·H_3PO_4** [a]



[a] Reagents and conditions: (a) Boc_2O, $NaHCO_3$, EtOAc-water, 50%; (b) aq. KOH, $CHCl_3$, then **3**, K_2CO_3, CH_3CN, 84%; (c) (1) 4M HCl/EtOAc, EtOH, (2) aq. KOH, $CHCl_3$, quantitative yield; (d) **7**, THF, $CHCl_3$, SiO_2 column chromatography, 57%; (e) (1) aq. NaOH, EtOH, (2) aq. HCl; (f) (1) **10·HCl**, aq. KOH, $CHCl_3$, (2) EDC·HCl, HOBt, DMF; (g) aq. H_3PO_4, EtOH, 93% in three steps; (h) recrystallization with EtOH/water, 74%. Overall yield: 16%.

Boc-protected bromoethylamine compound **3** was an unstable compound therefore it was easily decomposed during storage even at 5 °C in a lab-scale. Furthermore, as primary amine compound **(*R*)-6** was also an unstable compound, self-condensation occurred and an impurity was observed during vacuum concentration in a lab-scale. Additionally, protection and deprotection steps were inefficient way in a large-scale synthesis. Needless to say, it was an impractical manner that needed many steps to prepare **(*R*)-1·H_3PO_4** (total eight steps) and the overall yield was low (16%). Finally, the use of chlorinated solvents for extraction steps and purifying steps in SiO_2 column chromatography should be avoided from the point of view of environment as well.

Scheme 2. *Medicinal Chemistry synthetic Route B* for **(*R*)-1·H_3PO_4** [a]



[a] Reagents and conditions: (a) (1) aq. NaOH, (2) Boc_2O, 1,4-dioxane; (b) (1) aq. NaOH, EtOH, (2) aq. HCl, $CHCl_3$, 96% in two steps; (c) **10·HCl**, EDC·HCl, HOBt, Et_3N, THF, $CHCl_3$, SiO_2 column chromatography, quantitative yield; (d) (1) 4M HCl/EtOAc, (2) aq. NaOH, $CHCl_3$, 77%; (e) **15**, K_2CO_3, CH_3CN, $CHCl_3$, SiO_2 column chromatography, 92%; (f) 40% $MeNH_2$/MeOH, $CHCl_3$, SiO_2 column chromatography, 84%; (g) **7**, CH_3CN, $CHCl_3$, SiO_2 column chromatography then Al_2O_3 column chromatography; (h) aq. H_3PO_4, EtOH; (i) recrystallization with EtOH/water, 60% in three steps. Overall yield: 34%.

Some issues of *Medicinal Chemistry Route B* (Scheme 2) for a large-scale synthesis are described below. First, a protection of (***R***)-**4** and a deprotection of (***R***)-**13** were inefficient ways for a large-scale synthesis. Furthermore, since a waste product is resulted by deprotection, the use of phthalimide alkyl bromide **15** was an unattractive manner to install an amino unit. Second, since Boc protected amino acid (***R***)-**12** was a fragile compound, it was easily decomposed during storage even at 5 °C in a lab-scale. Third, a diacylated impurity was produced in the final benzoylation step and was difficult to purge into mother liquor. Finally, the use of chlorinated solvents for extraction step and purifying step in SiO_2 column chromatography should be avoided from the point of view of environment as well. Needless to say, it was not a practical way that needed many steps to prepare **(*R*)-1·H_3PO_4** (nine steps), the overall yield was low (34%). Against this background, we experienced strong demand for the development of a

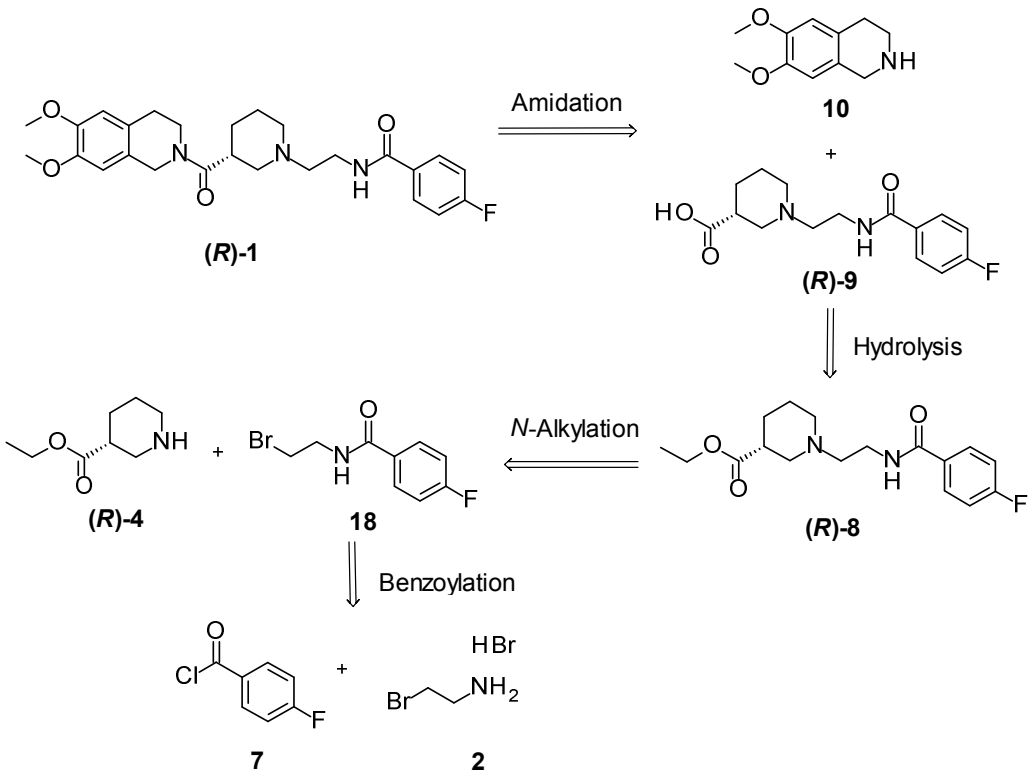
scalable production process for **(*R*)-1** with a higher overall yield that does not require column chromatography purification and unstable intermediates. To that end, we started to look for an alternative synthetic route of **(*R*)-1** and developed a new synthetic route for a first-scale up synthesis. In following sections, we describe details of our achievements.

Results and Discussion

Our synthetic strategy

A new synthetic strategy was designed to improve some issues of *Medicinal Chemistry routes* (Scheme 3). Our new strategy is to introduce (*R*)-1-{2-[(4-fluorobenzoyl)amino]ethyl}piperidine-3-carboxylate **(*R*)-8** as an intermediate via *N*-alkylation of **(*R*)-4** with bromide **18b** without protection and deprotection.

Scheme 3. New Synthetic Strategy for **(*R*)-1** [a]



Synthesis of Bromo compound (18)

First, to prepare the benzoylated bromoethylamine compound **18**, some typical reaction conditions were investigated. As results, the use of organic base for example pyridine or Et_3N in organic solvent such as THF or CH_3CN gave poor conversion due to a poor solubility of 2-bromoethylamine hydrobromide in the organic solvents. Therefore, we attempted this reaction under Schotten-Baumann like conditions (Table 1).[2] As results, EtOAc gave the best HPLC yield of **18** (entry 1) in comparison with other solvents such as toluene, CH_3CN, MTBE and MIBK (entries 2 - 5).

Table 1. Synthesis of Bromo compound **18**[a]

entry	solvents	HPLC yield of **18**[b]
1	EtOAc–water	98%
2	Toluene–water	93%
3	CH_3CN–water	95%
4	MTBE–water	91%
5	MIBK–water	88%

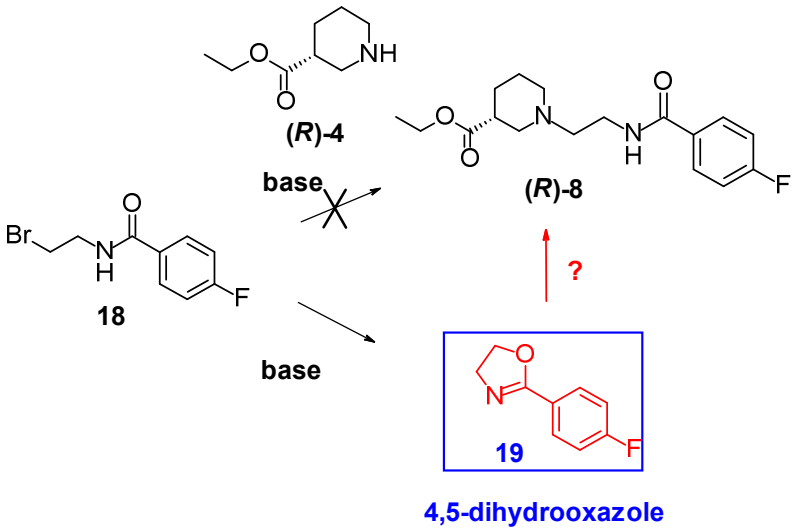
[a] K_2CO_3:**7** × 2mol., **2** :× 1.0 mol., reaction temp.:0 °C,

[b]:determined by HPLC method A (see Experimental Section).

Synthesis of (*R*)-8 (*N*-alkylation of (*R*)-4 with **18)**

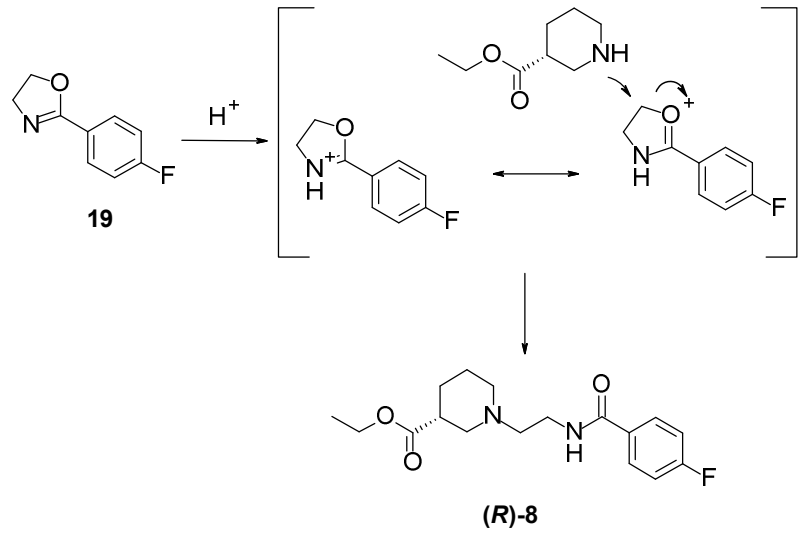
Next, *N*-alkylation reaction of **(*R*)-4** with **18** was investigated in various basic conditions, for example potassium carbonate, sodium hydroxide, sodium hydride, Et_3N, DBU and so on. As results, in many cases, **18** was converted to another compound smoothly, however, the desired alkylated compound **(*R*)-8** was not detected by LC-MS analysis. After NMR and Mass spectrum studies of this major product, we assigned that the structure of major product was 2-(4-fluorophenyl)-4,5-dihydrooxazole **19** as shown Scheme 4.[3]

Scheme 4. Main product of *N*-alkylation of **(*R*)-4** with **18** in a basic condition



At that time, we predicted that the ring opening *N*-alkylation of the 4,5-dihydrooxazole **19** in acidic condition would be able to work (Scheme 5).[4] It means that after protonation of nitrogen, α-position of oxygen was attacked by nucleophile, in this case **(*R*)-4**.

Scheme 5. Plausible mechanism of ring-opening *N*-alkylation in acidic conditions



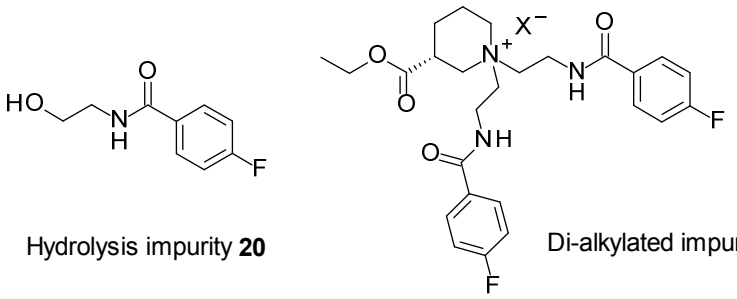
Under this hypothesis, we conducted reactions of 4,5-dihydrooxazole **19** and **(*R*)-4** under various acidic conditions. These results are shown in Table 2.

Table 2. Acid and solvent screening for ring-opening *N*-alkylation[a]

entry	conditions	**19** : **8**[b]	(***R***)-**8** : (***S***)-**8**[c]
1	4M HCl-EtOAc (1.05 eq.) / toluene, 1 day	62 : 38	-
2	*p*-TsOH monohydrate (1.05 eq) / toluene, 1 day	<1 : >99	99.3 : 0.7
3	AcOH (1.05 eq.) / toluene, 2 days	88 : 12	-
4	PPTS (1.05 eq.) / toluene, 2 days	<1 : >99	96.5 : 3.5
5	$MeSO_3H$ (1.05 eq.) / toluene, 2 days	12 : 88	99.3 : 0.7
6	TFA (1.05 eq.) / toluene, 2 days	11 : 89	97.3 : 2.7
7	*p*-TsOH monohydrate (1.05 eq.) / EtOAc, 2 days	64 : 36	-
8	*p*-TsOH monohydrate (1.05 eq.) / CH_3CN, 2 days	69 : 31	-

[a] Temperature: reflux of solvent, **(*R*)-4**: 1.2 equiv (>99.5% ee), [b] determined by HPLC method A (see experimental Section), [c] **(*S*)-8** : enamtiomer of **(*R*)-8**, determined by HPLC method B (see experimental Section).

A starting material **(*R*)-4** was purchased from supplier as a free base and its enantiopurity was more than 99.5% ee. As shown in Table 2, *p*-TsOH monohydrate gave the best yield in this reaction in comparison with any other acids (entry 2). Another sulfonic acid such as $MeSO_3H$ gave low yields of product due to the poor solubility of the methane sulfonic acid salt of **(*R*)-4** in toluene (entry 5). In contrast, the use of weak acid such as PPTS gave a full-conversion, however racemization occurred during the reaction and more than 3% of enantiomer **(*S*)-8** was observed by HPLC analysis (entry 4). Furthermore, AcOH did not give a full-conversion. As a solvent, toluene was the best because of the low-polarity and high boiling point, the reaction proceeded smoothly at approximately 110 °C. Other solvents such as EtOAc or CH_3CN gave a long reaction time due to a lower boiling point. Additionally we assigned two major impurities **20** and **21** in this reaction (Figure 2). Since the percentage of these impurities in a reaction mixture was less than 1% each other on HPLC, there was no critical issue to meet the desired purity of the final product.



Hydrolysis impurity **20** Di-alkylated impurity **21**

Figure 2. Structures of major impurities during *N*-alkylation

As described above, we developed a ring-opening *N*-alkylation condition. However, it was an imperfect way to prevent the racemization during the reaction to meet the desired quality (> 99.0% ee). To overcome the issue, understanding the cause of the racemization mechanism was necessary. Eventually, we considered that the main reason of racemization would be caused by the self-basicity of **(*R*)-4** under heating conditions. Therefore, to minimize racemization and accelerate the desired reaction rate, optimization of reaction conditions study was conducted as shown in Table 3.

Table 3. Optimization for *N*-alkylation [a]

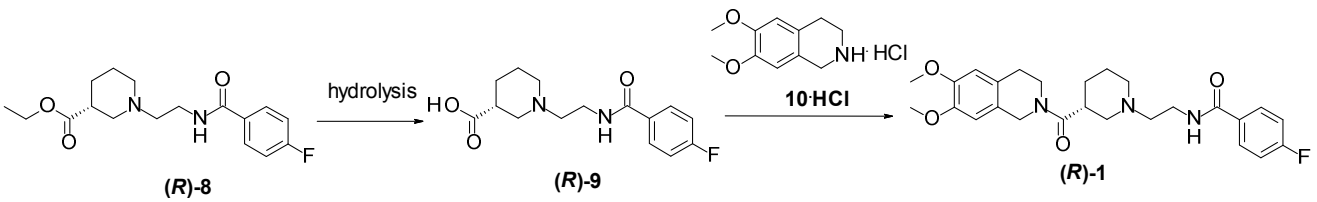
entry	*p*-TsOH monohydrate (equiv)	**(*R*)-4** (equiv)	time (h)	**19** : **8**[b]	**(*R*)-8** : **(*S*)-8**[c]
1	0.5	1.5	24	0.5 : 99.5	67.8 : 32.2
2	1.1	1.2	36	3 : 97	99.3 : 0.7
3	0.7	1.2	24	1.0 : 99	94.6 : 5.4
4	0.5	1.2	24	0.4 : 99.6	90.8 : 9.2
5	0.3	1.2	24	ND : 100	89.0 : 11.0
6	1.2	1.2	36	10 : 90	99.0 : 1.0
7	1.1	1.1	36	9 : 91	99.3 : 0.7
8	1.05	1.2	32	4 : 96	99.5 : 0.5

[a] reaction temperature: 110 °C, [b] determined by HPLC method A (see experimental Section), [c] determined by HPLC method B (see experimental Section).

To understand the reason of racemization, excess amount of **(*R*)-4** was used for this reaction (entry 1). As we expected, more than thirty percent of **(*S*)-8** enantiomer was observed on HPLC analysis. It means that the racemization might be happened by the self-basicity of **(*R*)-4**. To prevent the racemization, 1.1 equiv. of *p*-TsOH was charged in the reaction as a counter acid (entry 2). As a result, the racemization was improved at the level of <1%, however reaction rate was very slow, 3% of starting material **19** was remained even after 36-hours reaction. From these results, we considered that catalytic amount of acid might be better to accelerate the reaction rate. It was considered that the amine might be blocked by large amount of acids and the desired reaction would be prevented. Based on the hypothesis, catalytic amount of acid was used for this alkylation reaction as shown entries 3-5. As expected, the desired reaction was accelerated, in contrast, an unacceptable level of enantiomer **(*S*)-8** was observed. From these results, we could understand that the balance between amount of acid and reaction rate is clearly important for the scale-up synthesis. To solve these issues, we optimized the reaction conditions (entries 6-8). From these findings, we selected the condition of entry 8 as an optimal reaction condition for the first scale-up synthesis. Finally, we developed the practical procedure to afford desired **(*R*)-8**. 4,5-dihydrooxazole **19** was used in alkylation step without isolation and purification because it had enough quality after the phase separation (see experimental section).

End game

Scheme 6. Completion of synthesis



The procedure of hydrolysis of ethyl ester **(*R*)-8** was modified of original medicinal chemistry method. After the hydrolysis of ethyl ester with NaOH in aqueous ethanol and neutralized with aqueous HCl, several amide coupling agents with commercially available 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline monohydrochloride (**10·HCl)** were screened for amidation. Some results of the screening are described in Table 4. From these findings, EDC·HCl/HOBt in DMF with Et_3N gave the best reaction profile (entry 1). In contrast, CDI gave the poor conversion and racemization, unacceptable levels of enantiomer **(*S*)-1** was observed in the reaction mixture (entry 2). Furthermore, DPPA in the presence of Et_3N [5] gave clean reaction profile, however an enantiomer **(*S*)-1** was detected approximately 5% on HPLC analysis (entry 3). Finally, $SOCl_2$ (acid chloride method) gave a poor reaction profile by HPLC analysis (entry 4). In this case, the mild and water-resistant coupling reagent EDC·HCl gave the best yield without racemization.

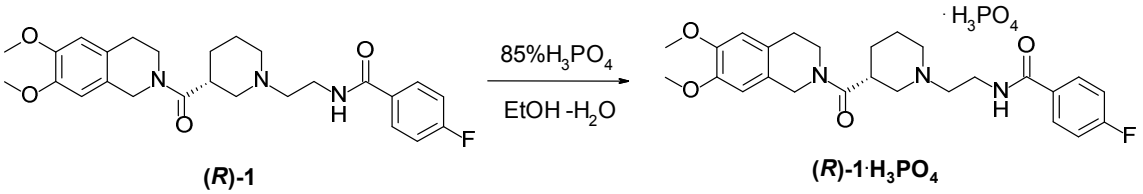
Table 4. Amide formation [a]

entry	conditions	**(*R*)-9**:**(*R*)-1** [b]	**(*S*)-1** (%) [c]
1	EDC·HCl (1.2 eq.), HOBt (0.3 equiv), Et_3N (1.0 equiv) / DMF	0.06 : 96.1	0.4
2	CDI (1.2 equiv), Et_3N (2.7 equiv) / DMF	31.1 :67.8	7
3	DPPA (1.2 equiv), Et_3N (2.7 equiv) / DMF	0.1 : 95.8	5
4	$SOCl_2$ (1.0 equiv) / then added to Et_3N (2.0 equiv), and **10**: 1 equiv/CH_3CN	multi peaks [d]	

[a] reaction was carried out at 0 °C and then 25 ºC, **10**: 1 equiv. [b] The ratio was determined by HPLC method C. [c] **(*S*)-1**: enamtiomer of **(*R*)-1**, determined by HPLC method D, [d] multi peaks were observed on HPLC analysis.

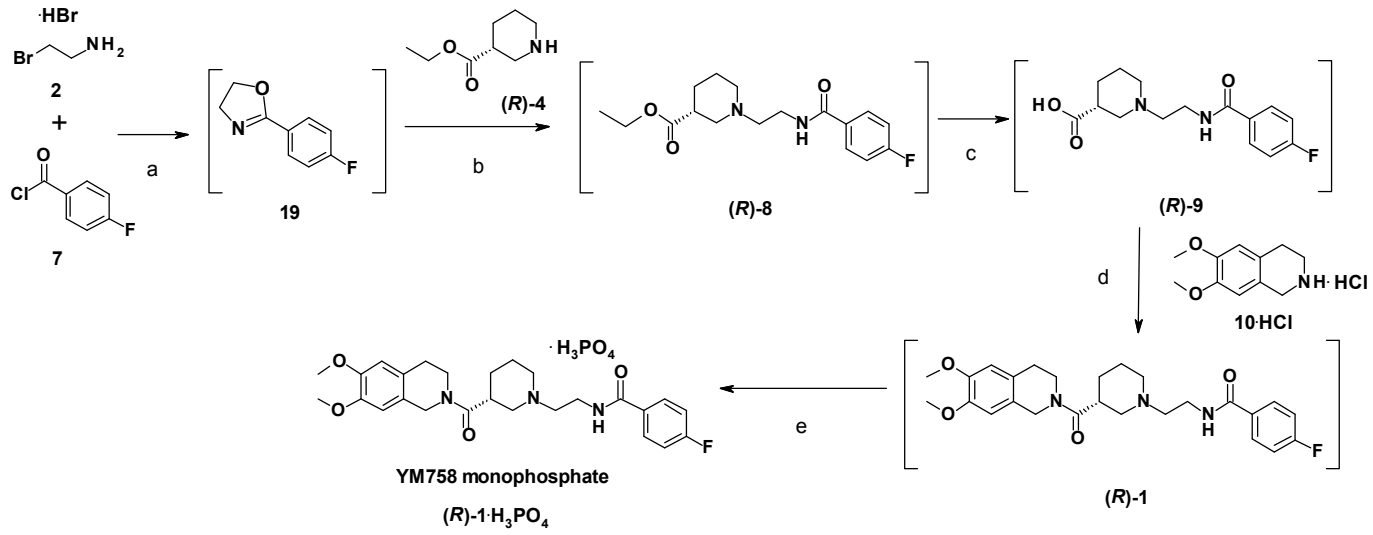
After the amidation, a free base **(*R*)-1** was converted to the monophosphate with 85 wt% phosphoric acid in aqueous ethanol (Scheme 7). The detailed salt formation procedure is described in the experimental section. Through the synthetic process for drug substance **(*R*)-1·H_3PO_4**, just final product was isolated as crystals. Any other intermediates were not isolated and not purified in this process. It means that we could well optimize the reaction conditions in every step for the preparation of the free base **(*R*)-1** and the final crystallization step has a robust purification method that could control the quality of final product. Though 0.4% of enantiomer **(*S*)-1** was detected in the free base **(*R*)-1**, it was well purged into the mother liquor and only 0.02% of **(*S*)-1** was observed in the drug substance (HPLC method D). In conclusion, we could prepare the high quality drug substance **(*R*)-1·H_3PO_4** in a first sale up synthesis (Scheme 8).

Scheme 7. Salt formation



(*R*)-1 (*R*)-1·H_3PO_4

Scheme 8. Summary of the new synthetic route [a]



[a] Reagents and conditions: (a) K_2CO_3, EtOAc-water, 5ºC then 50ºC; (b) *p*-TsOH·H_2O, toluene, reflux; (c) aq.NaOH, EtOH, water, < 25 °C; (d) EDC·HCl, HOBt, Et_3N, DMF, -4 to 4 °C; (e) aq. H_3PO_4, EtOH-water, 49% yield from **7**.

Conclusions

In summary, a new practical synthetic route has been developed for large-scale synthesis of the **(*R*)-1·H_3PO_4** drug substance. Undesirable features of the Medicinal chemistry synthetic routes were conveniently avoided by employing a ring-opening *N*-alkylation of 4,5-difydrooxazole **19** with (*R*)-ethyl nipecotate **(*R*)-4**. In addition, an *N*-alkylation reaction between 4,5-difydrooxazoles and amines under acidic condition should be quite important methodology and suitable for large-scale synthesis. The original Medicinal Chemistry synthesis A and B were significantly shortened from nine synthetic steps to five and the overall yield was also considerably improved from 16% or 34% to 49%. Finally, the use of chlorinated solvents was eliminated, and no chromatographic purification was required for any of the stages. In a first scale-up synthesis campaign, we prepared the 36.5 kg of **(*R*)-1·H_3PO_4** under GMP conditions.

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 ($CHCl_3$ 7.26 ppm; DMSO-d_6 2.50 ppm) or TMS. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, 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 $CDCl_3$ (77.0 ppm), DMSO-d_6 (39.5 ppm) on the δ scale. IR spectra was performed KBr disk method (JP16). HPLC was performed using HITACHI D-2500 or D-7500 system. HPLC Methods were described below.

HPLC Methods.

Method A.

YMC-Pack ODS-A, 5μm, 4.6 mm × 150 mm column, elution 0.01M K_2HPO_4 (adjust pH 7.0 by aq. H_3PO_4)/CH_3CN = 6/4 ,over 60 min., 1.0mL/min., at 25 °C, with UV detection at 254 nm.

7: 23 min., **18**: 5.5 min., **19**: 6.2 min., **(*R*)-8**: 7.3 min., *p*-TsOH: 1.5 min., toluene: 20 min., **(*R*)-9**: 1.6 min.

Method B.

DAICEL CHIRALCEL OD-H, 5 μm, 4.6 mm × 250 mm column, elution *n*-hexane/EtOH / Et_2NH = 90/10/0.1, over 60 min., 0.5 mL/min., at 25 °C, with UV detection at 254 nm.

(*R*)-8: 11.3 min., **(*S*)-8**: 12.6 min.

Method C.

YMC-Pack ODS-A, 5 μm, 4.6 mm × 150 mm column, elution 0.1 M potassium hexafluorophosphate (adjust pH 2.0 by aq. H_3PO_4)/CH_3CN = 6/4 ,over 60 min., 1.0mL/min., at 25 °C, with UV detection at 254 nm.

DMF: 1.7 min., HOBt: 1.9 min., **10**: 2.7 min., **(*R*)-9**: 3.3 min., **(*R*)-1**: 9 min., toluene:20 min.

Method D.

DAICEL CHIRALPAK AD-RH, 5 μm, 4.6 mm × 150 mm column,

elution 20 mM Na_2HPO_4 -NaH_2PO_4 (pH7.0)/MeOH = 1 / 50, over 30 min., 1.0 mL/min., at 40 °C, with UV detection at 254 nm.

(*R*)-1: 6.6 min., **(*S*)-1**: 3.8 min.

***N*-(2-bromoethyl)-4-fluorobenzamide (18)**

To a solution comprising water (110 L) and potassium carbonate (36.8 kg, 266.3 mol) was added 2-bromoethylamine monohydrobromide **2** (27.3 kg, 133.2 mol) below –5 °C. To the reaction mixture was added EtOAc (100 L) followed by 4-fluorobenzoyl chloride **7** (21.1 kg, 133.1 mol) at 5 °C or lower temperature. The reaction mixture was agitated for 1 h; HPLC analysis subsequently indicated that < 1% of **7** remained (HPLC method A), and afforded **18** having a purity of 85.2% (HPLC method A). The reaction mixture was used next step without quenching. Analytical pure **18** was obtained by concentration in Labs.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.78 (1H, br), 8.05 – 8.10 (1H, m), 7.90 – 7.95 (1H, m), 7.45 – 7.51 (1H, m), 7.29 – 7.34 (1H, m), 4.84 (1H, t, J = 9.7 Hz), 4.13 (1H, t, J = 9.7 Hz), 3.48-3.68 (2H, m), ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.2, 163.9 (d, J_{CF} = 248.3 Hz), 129.9, 129.8, 116.8 (d, J_{CF} = 22.4 Hz),

115.3, 115.1, 41.3, 31.9, ESI-MS m/z: 246.1 (M^++1), IR (KBr) /cm^{-1}: 3305, 3097, 2972, 2900, 1640, 1506, 599.

2-(4-fluorophenyl)-4,5-dihydrooxazole (19)

The reaction mixture of **18** was heated at 45 to 52 °C and agitated for 4 h; HPLC analysis subsequently indicated that < 1% of **18** remained (HPLC method A). To the reaction mixture was added toluene (40 L). After the phase separation at 35 °C, the organic layer was washed with water (80 L) afforded **19** having purity 98% (HPLC method A) as a solution of toluene–EtOAc. The solution was used next step. Analytical pure **19** was obtained by concentration in Labs.

^{1}H NMR (400 MHz, DMSO-d_6): δ 7.89 – 7.95 (2H, m), 7.28 – 7.34 (2H, m), 4.41 (2H, t, J = 9.4 Hz), 3.96 (2H, t, J = 9.4 Hz), ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.8 (d, J_{CF} = 249.0 Hz), 162.0, 130.2, 130.1, 124.1 (d, J_{CF} = 3.0 Hz), 115.7, 115.5, 67.5, 54.4, FAB-MS m/z: 166 (M^++1), IR (KBr) /cm^{-1}: 3059, 2983, 2912, 1652, 1510, 1353, 1066, Anal. calcd for C_9H_8FNO: C,65.45; H,4.88; N,8.48; F,11.50, Found: C,65.27; H,4.79; N,8.33; F,11.29.

(*R*)-1-{2-[(4- fluorobenzoyl)amino]ethyl}piperidine-3-carboxylate ((*R*)-8)

To the toluene-EtOAc solution of **19** were added toluene (440 L), ethyl (*R*)-piperidine-3-carboxylate (***R*)-4** (25.1 kg, 159.7 mol) and *p*-toluenesulfonic acid monohydrate (26.6 kg, 139.8 mol), and the mixture was heated and the solvent was distilled at atmospheric pressure to evaporate 260 L and agitated under refluxing for approximately 32 h; HPLC analysis subsequently indicated that < 5% of **19** remained (HPLC method A). After the reaction mixture was cooled, EtOAc (260 L) and 4% (w/v) aqueous solution of $NaHCO_3$ (180 L) were added. After phase separation at 30 ºC, the organic layer was washed with a 4% (w / v) aqueous solution of $NaHCO_3$ (180 L) twice. The organic layer was concentrated *in vacuo* to give **(*R*)-8** having a purity of 86.7% (HPLC method A). This product was used next step without purification and isolation.

Analytical pure was obtained by crystallization as a following procedure. The solution of 61 g of crude product **(*R*)-8** in EtOAc (100 mL) was concentrated. To the residue were added diisopropyl ether (120 mL) and *n*-heptane (120 mL). The batch was heated and the resulted solution was cooled to – 4 ºC. The resulting slurry was aged for 12 h and then filtered, washed with a mixed solution of diisopropyl ether with *n*-heptane, and dried *in vacuo* at 40 °C to afford 53.31g of **(*R*)-8** (87.4% overall yield from 4-fluorobenzoyl chloride **7**). Enantiomer **(*S*)-8** was observed 0.6% by Chiral HPLC analysis (method B).

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.35 – 8.40 (1H, m), 7.85 – 7.95 (2H, m), 7.25 – 7.33 (2H, m), 4.05 (2H, q, J = 7.1 Hz), 3.35 (2H, dd, J = 13.3 Hz, 6.7 Hz), 2.85-2.90 (1H, m), 2.65-2.70 (1H, m), 2.45 – 2.51 (3H, m), 2.20 – 2.26 (1H, m), 2.05 – 2.10 (1H, m), 1.75 – 1.80 (1H, m), 1.60 – 1.65 (1H, m), 1.35 – 1.50 (2H, m), 1.16 (3H, t, J = 7.1 Hz), ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.3, 165.0, 162.5, 131.0, 130.9, 129.7 (d, J_{CF} = 9.0 Hz), 115.2, 115.0, 59.7, 57.0, 55.0, 53.2, 41.0, 36.9, 26.4, 23.9, 14.0, FAB-MS m/z: 323 (M^++1), IR (KBr) /cm^{-1}: 3344, 3060, 2952, 2813, 1733, 1683, 1548, 1503, 1291, 1228.

(*R*)-1-{2-[(4-fluorobenzoyl)amino]ethyl}piperidine-3- carboxylic acid ((*R*)-9)

To a solution of **(*R*)-8** in EtOH (260 L) was added water (64 L). After cooling, an aqueous of NaOH (8.0 kg of NaOH, 200 mol/ 90 L of water) was added to the batch and agitated at < 25 °C for 2 h; HPLC analysis subsequently indicated that < 1% of **(*R*)-8** remained (HPLC method A). Then the batch was added *conc*. hydrochloric acid (38 wt%) and pH was adjusted to pH 3.06. This solution was concentrated *in vacuo*. And the resulting residue was added toluene (190 L) and the mixture was concentrated *in vacuo.* To the residue was added toluene (190 L) followed by concentrating *in vacuo*. To the residue was added toluene (190 L) followed by concentrating *in vacuo* to give **(*R*)-9** having a purity of 90.4% (HPLC method A). Analytical pure **(*R*)-9** was obtained by concentration in Labs.

^{1}H NMR (400 MHz, DMSO-d_6, VT 90 °C): δ 8.74 (1H, br), 7.95 – 8.03 (2H, m), 7.20-7.27 (2H, m), 3.68 (2H, q, J = 5.9 Hz), 3.50 – 3.60 (1H, m), 3.41 – 3.49 (1H, m), 3.25 (1H, t, J = 6.0 Hz), 2.85 – 3.05 (4H, m), 1.79 – 2.05 (3H, m), 1.46 – 1.60 (1H, m), ^{13}C NMR (100 MHz, DMSO-d_6, VT 90 °C): δ 172.1, 165.2, 163.6 (d, J_{CF} = 247.8 Hz), 130.2, 129.5 (d, J_{CF} = 6.6 Hz), 114.8 (d, J_{CF} = 22.1 Hz), 114.4, 114.1, 55.5, 54.9, 52.2, 51.3, 33.7, 24.4, 20.9, FAB-MS m/z: 295 (M^++1), IR (KBr) /cm^{-1}: 3330, 3070, 2958, 2582, 1726, 1649, 1543, 1506.

(-)-*N*-{2-[(*R*)-3-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)piperidino]ethyl}-4-fluorobenzamide ((*R*)-1)

To a solution of **(*R*)-9** in DMF (200 L), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline monohydrochloride **10·HCl** (23.0 kg, 100.1 mol) was added. After cooling to 5 °C, triethylamine (10.1 kg, 99.8 mol) was added at <10 °C followed by the addition of HOBt (4.0 kg, 29.6 mol) and EDC·HCl (23.0 kg, 120.0 mol). The batch was agitated at –4 to 4 °C for one night (14 h); HPLC analysis subsequently indicated that < 2% of **10** remained (HPLC method C). To the batch were added water (64 L), EtOAc (380 L), and a 8%(w/v) aqueous solution of NaOH (105 L). After the phase separation, aqueous layer was extracted with EtOAc (190 L). The collected organic layer was washed with a 8%(w/v) aqueous solution of NaOH (130 L) two times and water (57 L). The resulting organic layer was washed with water (170 L) and the batch was concentrated *in vacuo* to afford **(*R*)-1** having a purity of 79% (HPLC method C). The resulting batch was added EtOH (140 L) and the resulting solution was used next step without purification. Analytical pure **(*R*)-1** was obtained by concentration in Labs.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 – 7.88 (2H, m), 7.11 (2H, t, J = 8.7 Hz), 6.95 (1H, br), 6.55 – 6.65 (2H, m), 4.62 (1H, br), 4.59 (1H, br), 3.85 (3H, s), 3.84 (3H, s), 3.75-3.82 (1H, m), 3.70 (1H, t, J = 5.8 Hz), 3.45-3.63 (2H, m), 2.85-2.95 (1H, m), 2.81 (1H, t, J = 5.8 Hz), 2.75 (1H, t, J = 5.8 Hz), 2.55-2.65 (2H, m) , 2.32-2.40 (1H, m), 2,18-2.25 (2H, m), 2.08-2.15 (1H, m), 1.75-1.87 (2H, m), 1.54-1.68 (2H, m), ^{13}C NMR (125 MHz, $CDCl_3$): δ 2 rotamers (172.9, 172.7), 166.4, 164.7 (d, J_{CF} = 253Hz), 2 carbons

(148.1, 148.0, 147.7), 130.9, 129.4, 129.3, 2 carbons (127.0, 125.6, 125.3, 124.3), 115.6, 115.4, 2 rotamers (111.8, 111.3), 2 rotamers (109.5, 108.9), 56.9, 2 carbons (56.0), 2 rotamers (55.9, 55.7), 53.6, 2 rotamers (47.1 ,44.1), 2 rotamers (43.3, 40.0), 2 rotamers (39.8, 39.5), 36.7, 2 rotamers (29.4, 27.9), 2 rotamers (27.6, 27.4), 24.9, HRMS (FAB-MS $[M+H]^+$, m/z), calcd for $C_{26}H_{32}FN_3O_4$ 470.2455, found 470.2459, IR (KBr) /cm^{-1}: 3366, 2939, 1640, 1518, 1503, 1226, 1160.

(-)-*N*-{2-[(*R*)-3-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2- carbonyl)piperidino]ethyl}-4-fluorobenzamide monophosphate (YM758 monophosphate, (*R*)-1·H_3PO_4)

To the ethanolic solution of **(*R*)-1** was added EtOH (330 L). Then to the batch was added 85 wt% phosphoric acid (11.5 kg, 99.7 mol) and water (52 L) followed by heating. The resulting solution was filtered via a 1 μm filter, into another vessel. The filtrate was heated with stirring to 65 – 75 °C and cooled. The solution was added 30 g of **(*R*)-1·H_3PO_4** as seed crystals at 50 – 60 °C followed by cooling. And the resulting slurry was aged for 12 h at 0 – 5 ºC, filtered, washed with EtOH, dried *in vacuo* at 60 °C to afford 36.51 kg of **(*R*)-1·H_3PO_4** having a purity of 98.9% (HPLC method C). Optical isomer **(*S*)-1** was observed 0.02% by Chiral HPLC analysis (HPLC method D). Overall yield was 49% from 4-fluorobenzoyl chloride **7**.

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.70 (1H, br), 7.88 – 8.00 (2H, m), 7.27 (2H, t, J = 8.3 Hz), 6.86, 6.77 (1H, s in combination), 6.72 (1H, s), 4.63 (1H, ABq, J=16.0Hz)*, 4.50 (1H, ABq, J=16.8Hz) *, 3.71 (6H, s), 3.60 – 3.70 (2H, m), 3.40 – 3.57 (2H, m), 3.04 – 3.20 (3H, m), 2.60 – 2.82 (4H, m), 2.25 – 2.48 (2H, m), 1.60 – 1.85 (3H, m), 1.30 – 1.50 (1H, m), ^{13}C NMR (125 MHz, DMSO-d_6,): δ 2 rotamers (171.2, 171.1), 165.1, 163.8 (d, J_{CF} = 248 Hz), 147.4, 147.3, 130.6, 129.9, 129.8, 2 rotamers (126.2, 125.9), 125.0, 115.2, 115.0, 2 rotamers (111.9, 111.8), 2 rotamers (110.0, 109.9), 56.4, 55.5, 55.4, 2 rotamers (54.6, 54.4), 2 rotamers (52.6 ,52.5), 2 rotamers (46.1, 43.3), 2 rotamers (42.6, 39.4), 2 rotamers (37.3, 37.0), 35.5, 2 rotamers (28.6, 27.2), 2 rotamers (26.3, 26.1), 22.8, IR (KBr) /cm^{-1}: 3316,

3295, 3075, 2951, 2843, 2350, 1648, 1521, 1502, 1225, 1021, 1114, 962, 863, HRMS (FAB-MS $[M+H]^+$, m/z), calcd for $C_{26}H_{32}FN_3O_4$ (free base) 470.2455, found 470.2440, $[\alpha]_D^{20}$: -20.8° (solvent: water, 0.25 g/25 mL, 100 mm cell), Mp:206.7 °C (by DSC), Anal. calcd for $C_{26}H_{32}N_3O_4F \cdot H_3PO_4$: C, 55.02; H, 6.22; N, 7.40; F, 3.35; P, 5.46, Found: C, 55.01; H, 6.15; N, 7.43; F, 3.29; P, 5.44.

*It is made two protons in total integration.

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NOTES

The authors declare no competing financial interest.

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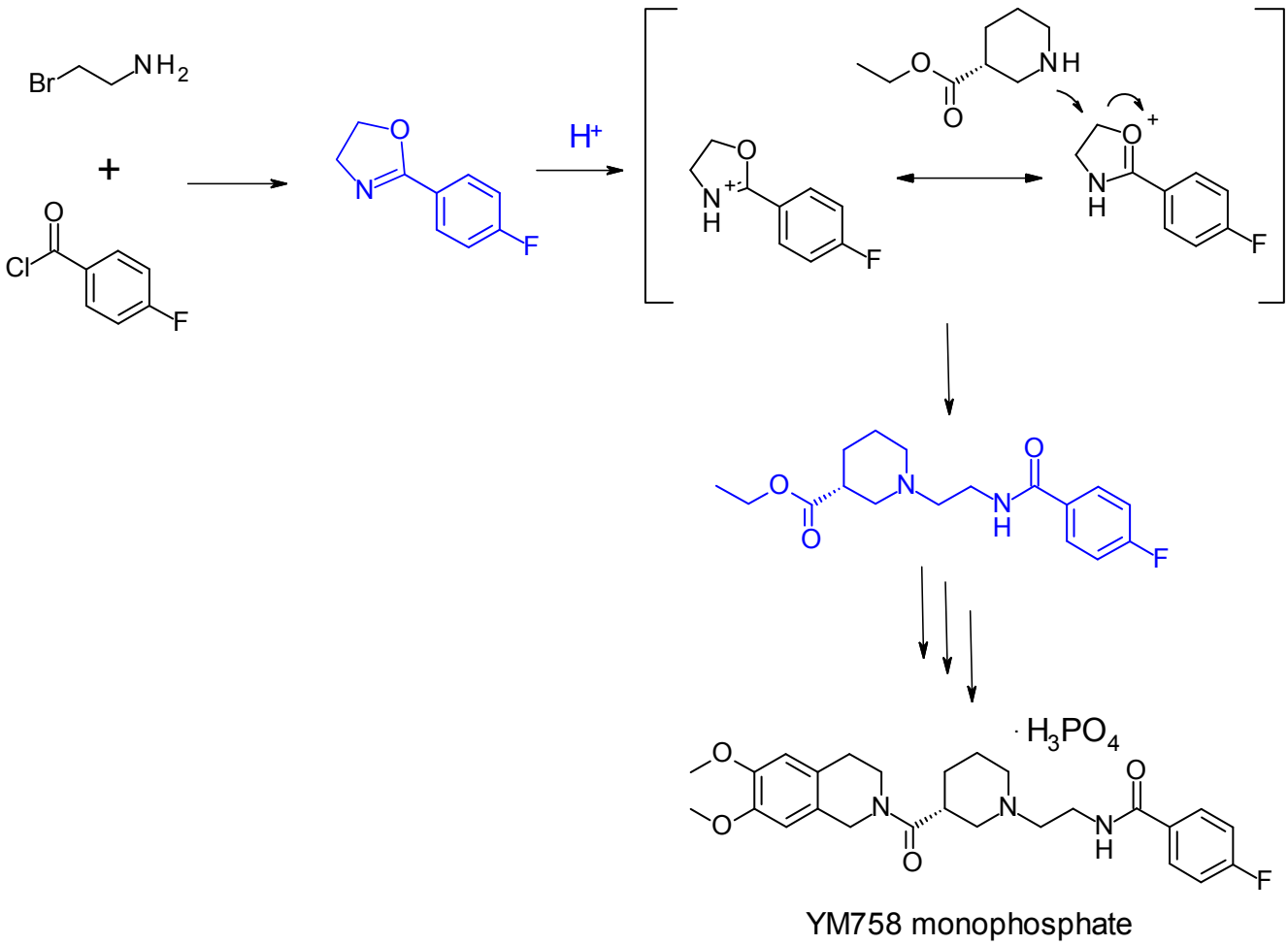
Synopsis of TOC



YM758 monophosphate