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Development of Large-Scale Synthesis using a Palladium-Catalyzed Cross-Coupling Reaction for an Isoquinolone Derivative as a Potent DPP-4 Inhibitor

Misayo Sera,* Makoto Yamashita, Yuujirou Ono, Takashi Tabata, Eigo Muto, Takashi Ouchi, and Hiroyuki Tawada

Chemical Development Laboratories, CMC Center, Takeda Pharmaceutical Company Limited, 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532-8686, Japan

ABSTRACT: An efficient large-scale synthesis of a novel DPP-4 inhibitor **1**, an isoquinolone derivative bearing an aminomethyl group at the 3-position and carbamoylmethoxy group at the 6-position, is described. We have developed an effective and convenient synthetic method utilizing a key intermediate possessing a cyano group at the 3-position and a halogen atom at the 6-position. The key reaction, the insertion of an oxygen atom at the 6-position of isoquinolone was achieved by a cross-coupling reaction using 6-bromoisoquinolone and sodium *tert*-butoxide (^{t}BuONa) in the presence of $Pd(OAc)_2$ and *rac*-BINAP as a catalyst to afford 6-*tert*-butoxyisoquinolone in good yield. The cyano group at the 3-position was hydrogenated in the presence of Raney nickel to give the aminomethyl moiety of compound **1**. The synthetic route has been successfully applied to multikilogram-scale preparations in good yield and high quality.

INTRODUCTION

Dipeptidyl peptidase-4 (DPP-4) inhibitors have been used as a new class of antidiabetic drugs.[1] DPP-4 is an enzyme that inactivates incretin hormones, such as glucagon-like peptide 1 (GLP-1) which stimulates insulin secretion. Therefore, the inhibition of DPP-4 leads to increase insulin secretion from the pancreas.

Compound **1**[2] has been developed as a candidate for a DPP-4 inhibitor and is an isoquinolone derivative bearing an aminomethyl group at the 3-position and a carbamoylmethoxy group at the 6-position (Figure 1). The 6-position oxygen substituted

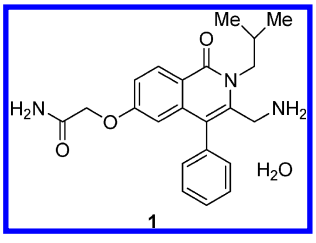

Figure 1. DPP-4 inhibitor **1**.

isoquinolone structure has been reported as a useful skeleton for several kinds of biologically active compounds. For example **2**,[3] as a potassium channel inhibitor, and **3**,[4] as a Rho-kinase inhibitor, have been researched for the treatments of cardiac diseases (Figure 2). Therefore, it is important to establish an efficient synthesis for the 6-position oxygen substituted isoquinolone derivatives.

The compound **1** was initially synthesized by the complicated route to introduce an aminomethyl group at the 3-position and a carbamoylmethoxy group at the 6-position of an isoquinolone ring, as shown in Scheme 1. However, this route had the following severe issues for a scale-up synthesis: (1) an expensive

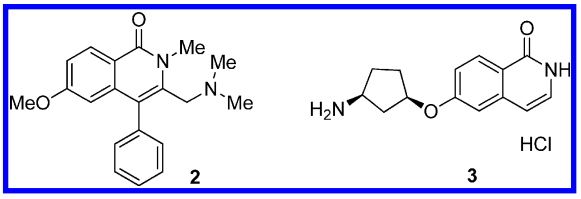

Figure 2. Isoquinolone derivatives as drug candidates.

and noncommercially available starting material **4** for the manufacturing process, (2) a linear route using a tedious protection−deprotection process in 16 steps and poor overall yield (5%), with an especially low yield for the final step, (3) several preparations requiring column chromatography. In this manuscript, we describe an alternative effective synthetic route that was developed for the large-scale manufacturing process.

Our retrosynthetic approach to **1** identified the isoquinolone derivative **12** as the key intermediate, containing a cyano group as a precursor of the aminomethyl group at the 3-position and a hydroxyl group or halogen at the 6-position (Scheme 2). It was assumed that **12** would be obtained by cyclization of **13**. When R was halogen, investigation of a C−O bond formation reaction between an arylhalide and an alcohol would be required to introduce an oxygen atom at the 6-position.

RESULTS AND DISCUSSION

Synthesis of Isoquinolone Derivatives by Ortho-Lithiation. First, we investigated the synthesis of the 2-benzoylbenzoic acid derivative **15** utilizing ortho-lithiation,[5] as shown in Scheme 3. Commercially available benzoic acid **14** was treated with 2 equiv of LiTMP (lithium 2,2,6,6-tetramethylpiperidide)[5b] at −78 °C followed by reaction with methyl

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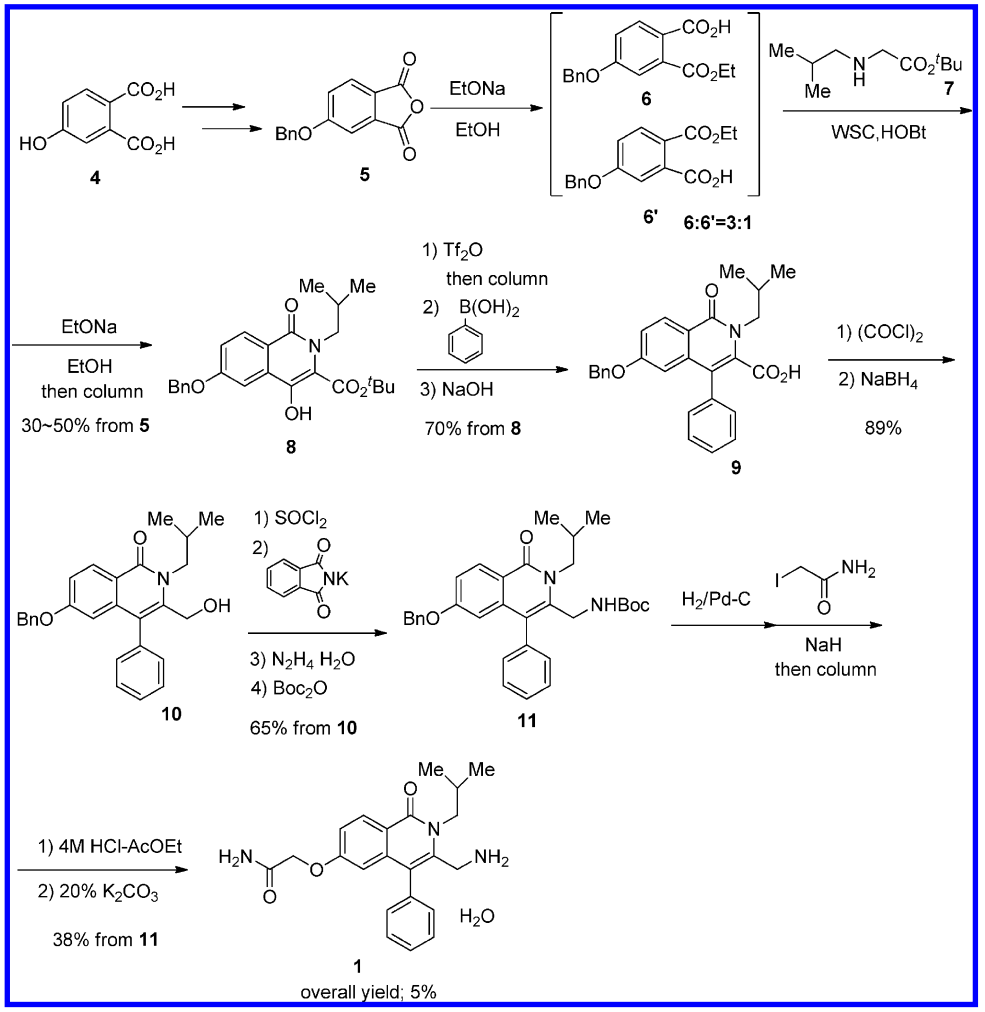
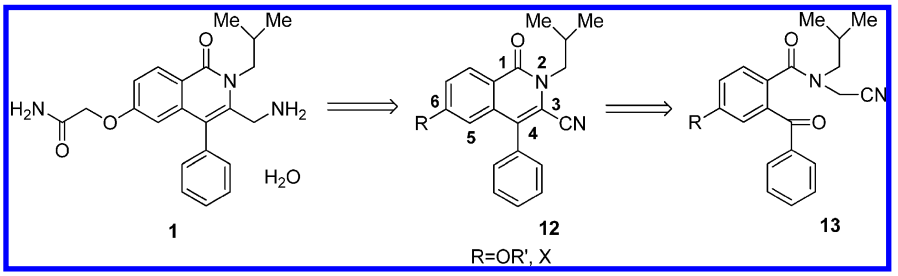
Scheme 1. Medicinal chemistry route



Scheme 2. Retrosynthetic analysis of 1



benzoate, but the benzoylated compound **15** was not obtained (Scheme 3). Next, *o*-lithiation of amide **16**[5d] was investigated. When *n*-BuLi (2 equiv) was added to a solution of **16** in THF at −50 °C and quenched with D_2O, the deuterated derivative **20** was obtained in 24% yield. On the other hand, treatment of **16** with *n*-BuLi at 0 °C followed by reaction with D_2O gave compound **20** in quantitative yield (Scheme 4). The *o*-lithiated compound of amide **16** was stable, and the subsequent addition of methyl benzoate gave benzophenone **17**. However, alkylation of **17** with bromoacetonitrile failed to give **18** (Scheme 3).

Synthesis of 6-Haloisoquinolone Derivatives. Since the *o*-lithiation approach proved unsuccessful and the appropriate starting materials to synthesize 6-hydroxyisoquinolone are difficult to purchase, we designed an alternative synthetic route via a 6-haloisoquinolone (Scheme 5). Friedel−Crafts reaction of the commercially available acid anhydride **21** with benzene[6] in the presence of anhydrous aluminum chloride in *o*-dichlorobenzene afforded 4-bromobenzophenone **22**. The selectivity for the desired regioisomer was 2:1 (4-bromoisomer **22a**:5-bromoisomer **22b**) ratio, but the isomer **22a** was easily purified by crystallization from ethyl acetate and toluene in 47% yield in high quality (HPLC area % >99%). On the other hand, Grignard reaction of anhydride **21** with phenylmagnesium bromide[7] afforded a 1:1 ratio of regioisomer mixtures (**22a**, **22b**). Compound **25** was synthesized from **22a** by amidation and cyclization in excellent yield using the known procedures.[6c] On the basis of these results, the route B using Friedel−Crafts reaction was adopted to obtain the key intermediate **25** in 35% overall yield over two steps. Next, the key reaction to introduce

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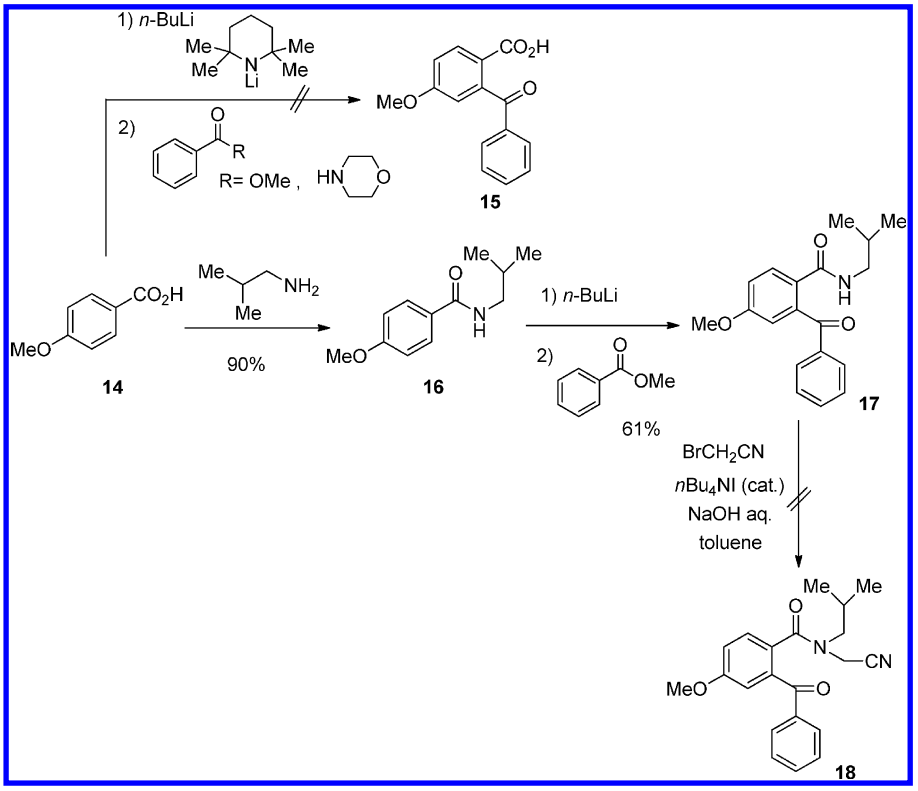
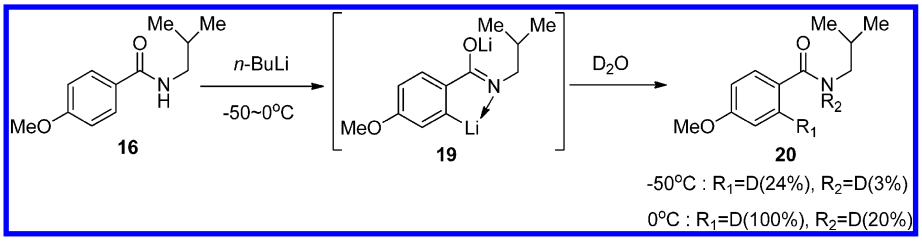
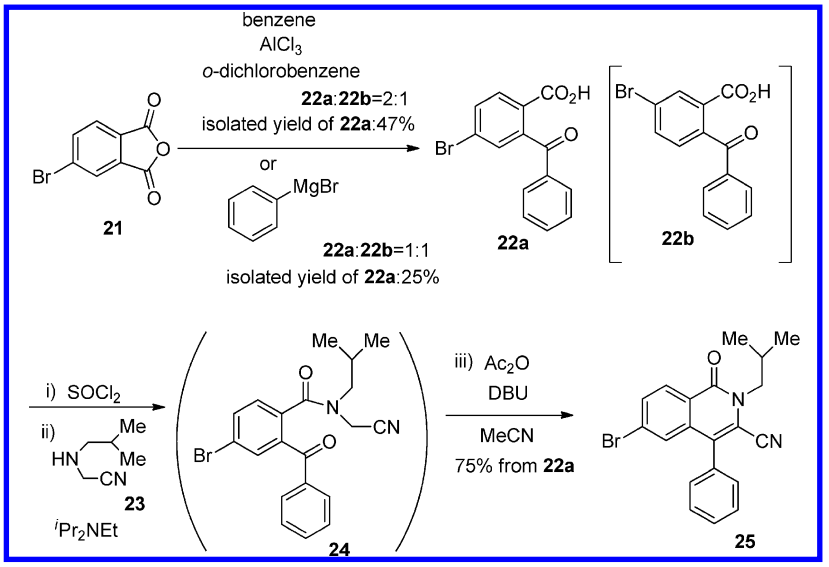
Scheme 3. Synthesis of isoquinolone derivatives (Route A)



Scheme 4. Deuteration study of 16



Scheme 5. Synthesis of isoquinolone derivatives (Route B)



an oxygen atom at the 6-position of the isoquinolone ring was examined.

C−O Bond Formation by a Palladium-Catalyzed Cross-Coupling Reaction. Although several methods for C−O bond

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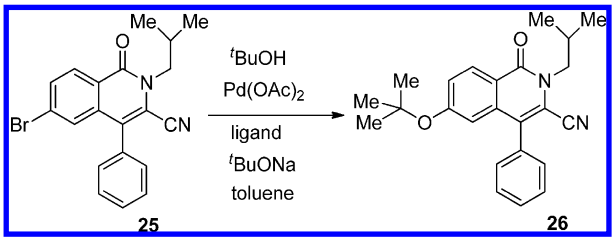
formation with an aromatic ring have been reported, such as direct nucleophilic substitution reactions,[8] and copper-[9] or palladium-catalyzed[10] cross-coupling reactions, we first investigated palladium-catalyzed C−O bond formation of aryl halides with alcohols (alkoxides), as reported by Buchwald et al. and Hartwig et al. They reported that this C−O bond formation is a useful and powerful method for obtaining aryl ethers and also oxygen-containing heterocycles via intramolecular C−O bond formation, whereas it was not well-known to apply this method to heterocyclic compounds except halopyridines.[11]

In order to apply palladium-catalyzed C−O bond formation reaction to bromoisoquinolone **25**, suitable conditions for the reaction of **25** with ^{t}BuONa were investigated because the *tert*-butoxy group as an oxygen source could be easily used to give the hydroxyl group. To establish an appropriate catalyst system for this substrate, first, several ligands were screened in the presence of $Pd(OAc)_2$ as a catalyst (Table 1). The desired product **26** was not obtained using monophosphines (runs 1−5). Biphenyl-based electron-rich bulky monophosphine ligands (runs 6, 7) displayed moderate efficiency, and bis(phosphine), especially BINAP (run 8) was found to be the best ligand, giving **26** in nearly quantitative yield.[12]

Table 1. Screening of ligands[a]

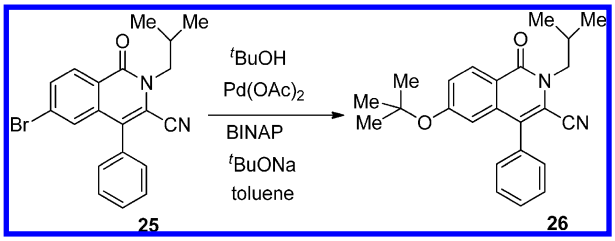


run	ligand	conversion[b] (**26**, %)
1	triphenylphosphine	0
2	tri-*tert*-butylphosphine	5
3	tri-*o*-tolylphosphine	0
4	tris(2-furyl)phosphine	0
5	tris(4-methoxyphenyl)phosphine	0
6	2-(di-*tert*-butylphosphino)biphenyl	60
7	2-(dicyclohexylphosphino)biphenyl	44
8	(*R*)-BINAP	94
9	1,2-bis(diphenylphosphino)ethane	0
10	$Pd(PPh_3)_4$	0

[a]Conditions; **25** (1.0 equiv), $Pd(OAc)_2$ (2.0 mol %), ligand (4.0 mol %), ^{t}BuOH (2.0 equiv), ^{t}BuONa (1.5 equiv), toluene (10 v/w), 100 °C, 2−4 h. [b]Determined by HPLC (condition 1)

Next, the coupling reaction conditions of $Pd(OAc)_2$ and BINAP were optimized further (Table 2). A 1:3 ratio of catalyst to ligand was the most effective (run 1), and it was found that *rac*-BINAP could be used in place of (*R*)-BINAP. We also found that the reaction rate was improved using recrystallized **25** (runs 1 vs 4). Our project schedule required a manufacturing-scale synthesis at this point, so the coupling reaction conditions of run 4 were used, as shown in the Experimental Section, but further optimization was continued as shown in runs 5−8. Generally, alcohols were used for the oxygen sources. The fact that the reaction proceeded without addition of *tert*-butanol (run 5) revealed that ^{t}BuONa worked as both a base and an oxygen source. In addition, we also evaluated this reaction using low catalyst loadings in order to improve the cost effectiveness (runs 6−8) and showed that $Pd(OAc)_2$/*rac*-BINAP = 0.5:1.5 (mol %)

Table 2. Optimization of the coupling reaction in the presence of $Pd(OAc)_2$ and BINAP[a]



run	$Pd(OAc)_2$ (mol %)	ligand (mol %)	^{t}BuOH (equiv)	time (h)	conversion[c] (**26**, %)
1	1.0	(*R*)-BINAP (3.0)	2.0	4	94
2	1.0	(*R*)-BINAP (2.0)	2.0	23	76
3	1.0	(*R*)-BINAP (1.2)	2.0	8	20
4[b]	1.0	*rac*-BINAP (3.0)	2.0	2	98
5[b]	1.0	*rac*-BINAP (3.0)	–	2	97
6[b]	0.5	*rac*-BINAP (1.5)	–	24	98
7[b]	0.4	*rac*-BINAP (1.2)	–	24	60
8[b]	0.2	*rac*-BINAP (0.6)	–	24	16

[a]Conditions; ^{t}BuONa (1.5 equiv), toluene, 100 °C. [b]Recrystallized **25** was used. [c]Determined by HPLC (condition 1)

was the most favorable reaction condition (run 6). Further lowering of catalyst loading decreased conversion (runs 7, 8), so the run 6 condition was selected as the optimum condition.

The coupling product **26** was used without purification after extraction. Deprotection of the *tert*-butyl group with trifluoroacetic acid[13] in acetonitrile afforded **27** in excellent yield over two steps. Compound **27** was then reacted with chloroacetamide in the presence of potassium carbonate as a base in *N*,*N*-dimethylformamide (DMF) to give **28** in excellent yield (Scheme 6).

Preparation of 1 through Reduction of Nitrile. The reduction of a cyano group to an aminomethyl group was also an important point for this strategy. Hydrogenation in the presence of Raney nickel[14] is a practical method for nitrile hydrogenation. It was found to be a valuable method for this compound (Table 3). Comparison of solvents tetrahydrofuran (THF) and *N*,*N*-dimethylacetamide (DMAC), showed that **28** dissolved easily in DMAC, and the reduction worked well under 0.6−0.8 MPa hydrogen atmosphere at 50 °C (run 4). The reduction under low hydrogen pressure (0.2 MPa) proceeded within 24 h (run 5). In general, it is well-known that dimer products are produced in the reduction of nitriles,[14b] and ammonia solution is often used to prevent the production of dimers. Therefore, we added ammonia solution to the reaction mixture (runs 1−5). Our project schedule required a manufacturing-scale synthesis at this point so that the reaction conditions of run 4 were used, as shown in the Experimental Section. However, it was found that the addition of ammonia was not necessary for the reduction of this compound (run 6), presumably due to the bulky group (isobutyl and phenyl) adjacent to the nitrile, inhibiting the dimerization by steric hindrance. After the reaction was completed, the amine was extracted to the aqueous layer with hydrogen chloride, and then

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Scheme 6. Process route of 1

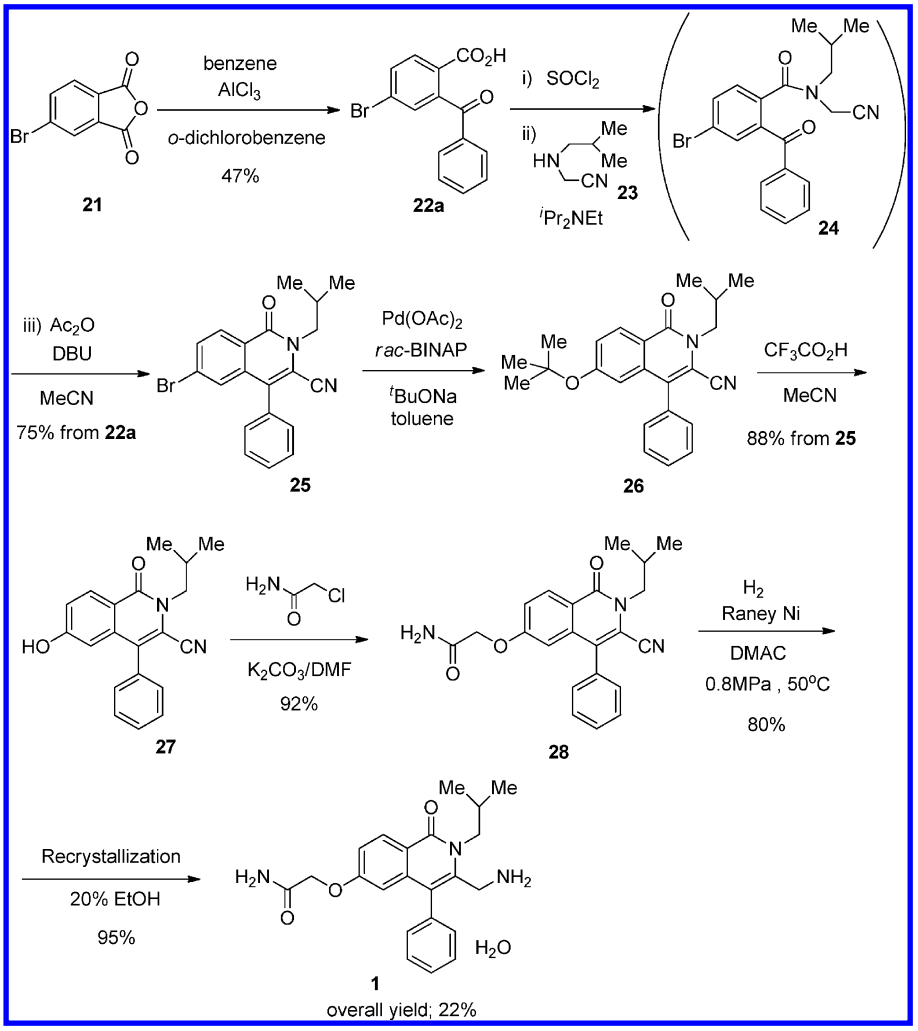
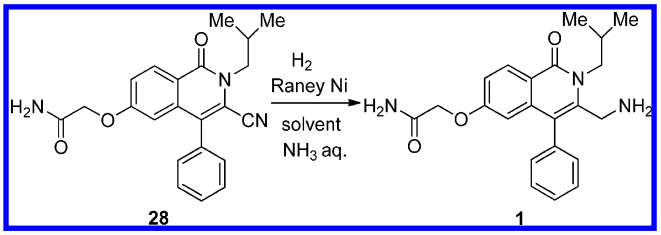


Table 3. Reduction of nitrile to aminomethyl



run	solvent (v/w)	aq NH_3 (v/w)	temperature (°C)	time (h)	H_2 pressure (Mpa)	conversion[a] (**1**, %)
1	THF (15)	0.15	70	4	1	96.4
2	DMAC (5)	0.15	70	4	1	96.7
3	DMAC (4.5)	0.15	70	5	0.6–0.8	97.3
4	DMAC (4.5)	0.15	50	7	0.6–0.8	97.8
5	DMAC (4.5)	0.15	70	24	0.2	95.3
6	DMAC (4)	–	70	4	1	96.9

[a]Determined by HPLC (condition 2).

neutralization of the aqueous layer gave the free base **1** as crystals in high yield and high quality (80% yield, 99% HPLC area%).

Design of Quality Control for API. The quality of final product **1** using the improved manufacturing process was evaluated. The residual metals such as palladium and nickel were extremely low, less than 0.1 ppm in the API. The final compound had four polymorphs, which were two hydrates and two free bases. The free bases were hygroscopic, and the monohydrate form A was dehydrated above 50 °C in vacuo. The monohydrate form B was selected as the development form because of its stability. As a result of our detailed study, it was found that the different monohydrate forms A and B could be selectively produced, depending on the temperature at crystallization. The pure monohydrate form B was constantly obtained by the recrystallization from aqueous ethanol above 50 °C.

■ CONCLUSIONS

In summary, we have developed an efficient and convenient manufacturing process for the DPP-4 inhibitor **1**, giving a large-scale preparation in short steps using a palladium-catalyzed cross-coupling reaction of bromoisoquinolone **25** with ^{t}BuONa as a key reaction and avoiding column chromatography. In addition, the reduction of a cyano group to an aminomethyl group by hydrogenation in the presence of Raney nickel as the catalyst gave **1** in good yield and high quality. We have also achieved good

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quality control of the API. Our improved method enabled the synthesis of **1** in only seven steps and 22% overall yield (Scheme 6), and we have successfully applied the established manufacturing method to multikilogram-scale preparations.

EXPERIMENTAL SECTION

General. Melting points were determined by using the capillary method on a Büchi 535 apparatus and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were determined in $CDCl_3$ or DMSO-d_6 on a Bruker DPX-300 or Bruker Avance 500 and reported in δ ppm using tetramethylsilanes as the internal standard. The following abbreviations were used: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublets of doublet, br = broad. Elemental analyses were carried out by Takeda Analytical Laboratories Ltd. The purities of the products were assessed by HPLC analyses using a YMC column ODS-A A-302 (4.6 mm × 150 mm) at 25 °C with UV detection at 254 nm. Elution was conducted at 1.0 mL/min using condition 1: 0.05 mol/L KH_2PO_4/CH_3CN = 3:7, and condition 2; 0.05 mol/L KH_2PO_4/CH_3CN = 6:4.

4-Bromo-2-(phenylcarbonyl)benzoic Acid (22a). A suspension of benzene (5.16 kg, 66.06 mol) and anhydrous aluminum chloride (11.8 kg, 88.50 mol) in *o*-dichlorobenzene (40 L) was cooled to 0 °C. 5-Bromo-2-benzofuran-1,3-dione **21** (10.0 kg, 44.05 mol) was added to the mixture portionwise under 10 °C. After addition, the mixture was stirred at room temperature for 1 h and 80 °C for 1 h. After cooling to 5 °C, ethyl acetate (80 L) was added to the mixture. Water (40 L) was then added carefully, keeping the temperature under 40 °C. The organic layer was separated and washed with 4 mol/L aq HCl (40 L) and water (40 L) successively. The organic layer was concentrated in vacuo. Toluene (50 L) was added to the residue, and the organic layer was concentrated in vacuo again. Toluene (60 L) and ethyl acetate (6 L) were added to the residue, and the solids were dissolved at 80 °C. The mixture was cooled to room temperature and stirred at room temperature for 1 h. The resulting precipitate was collected by filtration and washed with toluene (12 L). The crude crystals were dissolved in toluene (60 L) and ethyl acetate (3 L) at 95 °C. The mixture was cooled to 5 °C and stirred at 5 °C for 1 h. The resulting precipitate was collected by filtration, washed with toluene (12 L), and dried in vacuo at 50 °C to give the title compound (6.34 kg, 47.2% yield) as white crystals. (HPLC area % 99%, condition 2); mp 195−198 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 (t, J = 7.8 Hz, 2H), 7.53−7.60 (m, 2H), 7.71 (m, 4H), 7.94 (d, J = 8.3 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 126.88, 129.17, 129.43, 129.64, 130.52, 132.39, 133.19, 133.75, 136.99, 143.83, 166.62, 195.11. Anal. Calcd for $C_{14}H_9O_3Br$: C, 55.11; H, 2.97; Br, 26.19. Found: C, 55.01; H, 2.98; Br, 26.13.

[(2-Methylpropyl)amino]acetonitrile (23). A mixture of isobutylamine (6.75 kg, 92.29 mol) and triethylamine (10.30 kg, 101.79 mol) in ethyl acetate (33.8 L) was cooled to 5 °C. Bromoacetonitrile (11.10 kg, 92.54 mol) was added dropwise under 30 °C over 2 h. After addition, the mixture was stirred at 25 °C for 3 h, and then water (33.8 L) was added. The organic layer was separated and washed with 10% aq NaCl (33.8 L). The organic layer was concentrated in vacuo, and purified by distillation under 10 mmHg/82 °C to give the title compound (5.99 kg, 57.9% yield) as a yellow oil.; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (d, J = 6.6 Hz, 6H), 1.17 (br, 1H), 1.74 (m, 1H), 2.54 (d, J = 6.6 Hz, 2H), 3.59 (s, 2H).

6-Bromo-2-(2-methylpropyl)-1-oxo-4-phenyl-1,2-dihydroisoquinoline-3-carbonitrile (25). Thionyl chloride (2.92 kg, 24.54 mol) was added to a mixture of **22a** (6.24 kg, 20.45 mol), *N*,*N*-dimethylformamide (125 mL, 1.62 mol), and toluene (81.1 L) under nitrogen atmosphere. The mixture was stirred at 50 °C for 1.5 h. The mixture was concentrated in vacuo. Toluene (32.1 L) was added to the residue and concentrated in vacuo again. The residue was dissolved at 90 °C in toluene (12.5 L) under nitrogen atmosphere. *N*-Ethyldiisopropylamine (3.96 kg, 30.64 mol) was added to the mixture and stirred at 90 °C for 5 min. Then **23** (3.81 kg, 33.97 mol) was added to the mixture and stirred at 90 °C for 3 h. After cooling to room temperature, 1 mol/L aq HCl (62.4 L) was added, and the organic layer was separated. The organic layer was washed with 10% aq NaCl (62.4 L) and concentrated in vacuo. Acetonitrile (31.2 L) was added to the residue and concentrated in vacuo again. Ethanol (18.7 L) was added to the mixture. After heating to 40 °C, acetic anhydride (2.51 kg, 24.59 mol) and 1,8-diazabicyclo[5.4.0]-undec-7-ene (6.23 kg, 40.92 mol) were added successively. The mixture was stirred at 50 °C for 1 h. After cooling to room temperature, water (15.6 L) was added, and the mixture was stirred at room temperature for a further 1 h. The resulting precipitate was collected by filtration, washed with 70% aq ethanol (25 L) and dried in vacuo at 50 °C to give the title compound (5.97 kg). A suspension of crude **25** in THF (59.7 L) was heated to 55 °C. Activated carbon (Shirasagi A) (0.3 kg) was added to the solution and stirred at 55 °C for 10 min. Activated carbon was filtered off and washed with THF (17.9 L). The filtrate was concentrated in vacuo until the weight of the mixture reached 17.2 kg. The mixture was stirred at 45 °C, and heptane (59.7 L) was added to the mixture. The whole mixture was stirred at 40−45 °C for 30 min and then at 0−10 °C for 1 h. The precipitate was collected by filtration, washed with cooled THF/heptane (1:5, 6.0 L), and dried in vacuo at 50 °C to give the title compound (5.88 kg, 75.4% yield) as white crystals. (HPLC area % 99.9%, condition 2); mp 206.5−208.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (d, J = 6.7 Hz, 6H), 2.30−2.39 (m, 1H), 4.15 (d, J = 7.5 Hz, 2H), 7.39−7.44 (m, 3H), 7.55−7.60 (m, 3H), 7.76 (dd, J = 8.6, 1.9 Hz, 1H), 8.39 (d, J = 8.6 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 19.93, 28.41, 54.55, 113.01, 116.70, 126.11, 128.28, 129.03, 129.21, 129.33, 129.51, 129.65, 130.27, 130.28, 133.10, 136.35, 160.28. Anal. Calcd for $C_{20}H_{17}N_2OBr$: C, 63.00; H, 4.49; N, 7.35; Br, 20.96. Found: C, 62.96; H, 4.41; N, 7.36; Br, 20.86.

6-*tert*-Butoxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinecarbonitrile (26).[15] A suspension of $Pd(OAc)_2$ (34.7 g, 0.15 mol) and *rac*-BINAP (288.7 g, 0.46 mol) in toluene (56.1 L) was stirred at 40 °C for 30 min under nitrogen atmosphere. The mixture was cooled to 25 °C, and **25** (5.90 kg, 15.47 mol), *tert*-butanol (2.92 L, 30.94 mol), ^{t}BuONa (2.23 kg, 23.2 mol), and toluene (2.95 L) were added. After stirring at 25 °C for 20 min, the solution was heated at 95−100 °C for 2.5 h. Then the mixture was cooled to 15 °C, diluted with 0.5 mol/L aq HCl (29.5 L), and stirred at 25 °C for 30 min. After dissolution with toluene (17.7 L), the organic layer was separated and washed with water (29.5 L) twice. The organic layer was concentrated in vacuo, and acetonitrile (29.5 L) was added to the residue. The mixture was concentrated in vacuo again. Acetonitrile (29.5 L) was added to the residue and concentrated in vacuo until the weight of the mixture reached 14.8 kg. The residual solution was used in the next reaction without further purification. (HPLC area % 95.9%, condition 1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.03 (s, 3H), 1.05 (s, 3H), 1.33 (s, 9H), 2.30−2.39 (m, 1H), 4.14 (d, J = 7.5 Hz, 2H), 6.78−6.79 (m, 1H),

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7.23−7.24 (m, 1H), 7.39−7.43 (m, 2H), 7.52−7.57 (m, 3H), 8.42 (d, J = 8.8 Hz, 1H).

6-Hydroxy-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-3-isoquinolinecarbonitrile (27). Trifluoroacetic acid (2.30 L, 30.96 mol) was added to the solution of **26** described above, and the mixture was stirred at 55−65 °C for 5 h. After cooling to 20 °C, the reaction mixture was diluted with water (29.5 L) and ethyl acetate (70.8 L). The organic layer was separated, washed with water (29.5 L), and concentrated in vacuo until the weight of the mixture reached 18.9 kg. Heptane (35.4 L) was added to the residue at 20−30 °C, and the mixture was stirred at 0−5 °C for 1 h. The resulting precipitate was collected by filtration, washed with cooled ethyl acetate/heptane (1:3, 8.9 L), and dried in vacuo at 50 °C to give the title compound (4.34 kg, 88.1% yield for two steps) as yellow crystals. (HPLC area % 99.2%, condition 1); mp 258−262 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (s, 3H), 1.01 (s, 3H), 2.26−2.35 (m, 1H), 4.11 (d, J = 7.4 Hz, 2H), 6.72−6.73 (m, 1H), 7.16−7.23 (m, 1H), 7.37−7.40 (m, 2H), 7.48−7.51 (m, 3H), 8.35 (d, J = 8.8 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 20.28, 28.54, 53.91, 110.67, 114.05, 115.88, 119.70, 119.99, 129.37, 129.51, 129.62, 130.75, 130.83, 134.10, 137.10, 160.11, 162.06. Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.38; H, 5.87; N, 8.75.

2-[(3-Cyano-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl)oxo]acetamide (28). A suspension of **27** (4.30 kg, 13.51 mol), 2-chloroacetamide (1.52 kg, 16.25 mol) and potassium carbonate (2.24 kg, 16.21 mol) in *N*,*N*-dimethylformamide (21.5 L) was stirred at 75−85 °C for 3 h. After cooling to 25 °C, acetonitrile (21.5 L) was added to the mixture. The pH of whole mixture was adjusted to 5−6 at 15−25 °C with 1 mol/L aq HCl, and water (28.0 L) was added. Then the mixture was stirred at 20−30 °C for 1 h. The precipitate was collected by filtration, washed with acetonitrile/water (1:3, 8.6 L) twice, and dried in vacuo at 50 °C to give the title compound (4.64 kg, 91.5% yield) as yellow crystals. (HPLC area % 99.2%, condition 1); mp 198−200 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 (s, 3H), 1.05 (s, 3H), 2.30−2.39 (m, 1H), 4.14 (d, J = 7.5 Hz, 2H), 4.41 (s, 2H), 5.78 (br s, 1H), 6.46 (br s, 1H), 6.67−6.68 (m, 1H), 7.22−7.25 (m, 1H), 7.38−7.42 (m, 2H), 7.54−7.58 (m, 3H), 8.51 (d, J = 8.9 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6): δ 20.26, 28.53, 54.05, 67.07, 110.53, 113.99, 116.27, 118.69, 121.26, 129.43, 129.46, 129.77, 130.65, 130.84, 133.64, 136.67, 159.99, 161.66, 169.36. Anal. Calcd for $C_{22}H_{21}N_3O_3$: C, 70.38; H, 5.64; N, 11.19. Found: C, 70.35; H, 5.80; N, 11.08.

2-{[3-(Aminomethyl)-2-isobutyl-1-oxo-4-phenyl-1,2-dihydro-6-isoquinolinyl]oxy}acetamide Hydrate (1).[16] A suspension of **28** (1.05 kg, 2.80 mol) and 25% ammonium hydroxide (158 mL) in *N*,*N*-dimethylacetamide (4.73 L) was hydrogenated in the presence of Raney nickel (NDHT-90, 265 mL) under 0.6−0.8 MPa hydrogen atmosphere at 50 °C for 5.5 h. After cooling to 25 °C, Raney nickel was filtered off and washed with *N*,*N*-dimethylacetamide (1.58 L). The combined filtrate was diluted with ethyl acetate (5.25 L) and 1 mol/L aq HCl (6.3 L). The organic layer was separated and extracted with 0.2 mol/L aq HCl (2.1 L). The aqueous layer was combined and washed with ethyl acetate (3.15 L). Activated carbon (Shirasagi A) (52.5 g) was added to the aqueous layer, and the mixture was stirred at room temperature for 15 min. Activated carbon was filtered off and washed with 0.1 mol/L aq HCl (2.1 L). The pH of the combined aqueous layer was adjusted to 8.3−8.7 at 30 °C with 5% ammonium hydroxide (2.75 L), and diluted with water (2.5 L). The whole mixture was stirred at 20−30 °C for 30 min and at 0−10 °C for 1 h. The precipitate was collected by filtration, washed with 10% aq ethanol (1.58 L) and ethyl acetate (1.05 L) and dried in vacuo at 60 °C to give the title compound (856.9 g, 80.7% yield) as white crystals. (HPLC area % 99.4%, condition 2.) A suspension of crude **1** (1.12 kg) in 90% aq ethanol (3.36 L) was heated at 60−65 °C. The resulting solution was filtered through DISPOSABLE FILTER ASSEMBLY HDCII (1.2 μm, DFA3201 J012P) and washed with warmed 90% aq ethanol (1.12 L). The solution was heated at 60−65 °C, water (6.72 L) was added while keeping at 60−65 °C, and monohydrate form B (1.12 g) was added as the crystal seed. Then water (8.96 L) was added to the mixture while keeping at 60−65 °C, and the whole mixture was stirred at 60−65 °C for 1 h and then at 20−30 °C for 1 h. The precipitate was collected by filtration, washed with 20% aq ethanol (1.68 L), and dried in vacuo at 60 °C to give the title compound (1.12 kg, 95.1% yield) as white crystals. (HPLC area % 99.7%, condition 2); mp 172−175 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (s, 3H), 1.01 (s, 3H), 1.26 (br s, 2H), 2.21−2.30 (m, 1H), 3.66 (s, 2H), 4.18−4.21 (m, 2H), 4.32 (s, 2H), 6.04 (br s, 1H), 6.31−6.32 (m, 1H), 6.54 (br s, 1H), 7.01−7.05 (m, 1H), 7.26−7.28 (m, 2H), 7.45−7.54 (m, 3H), 8.43 (d, J = 8.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 20.25, 28.86, 40.91, 50.52, 66.70, 108.03, 115.40, 118.50, 119.93, 128.15, 129.11, 130.52, 130.64, 136.65, 139.39, 141.69, 159.85, 162.51, 170.44. Anal. Calcd for $C_{22}H_{26}N_3O_5$: C, 66.48; H, 6.85; N, 10.57. Found: C, 66.46; H, 7.02; N, 10.45.

AUTHOR INFORMATION

Corresponding Author

*Telephone: +81-6-6300-6552. FAX:+ 81-6-6300-6251. E-mail: misayo.sera@takeda.com.

Notes

The authors declare no competing financial interest.

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(15) Subsequent optimization of the manufacturing process showed that ^{t}BuOH was not necessary and a lower catalyst loading of $Pd(OAc)_2$ 0.5 mol% and *rac*-BINAP 1.5 mol% could be used.
(16) Subsequent optimization of the manufacturing process showed that the ammonia solution could be omitted.