

# Pilot-Plant Preparation of 3,4-Dihydropyridin-2-one Derivatives, the Core Structures of P2X<sub>7</sub> Receptor Antagonists

Xiaojun Huang,<sup>\*,†</sup> Scott Broadbent,<sup>†</sup> Charles Dvorak,<sup>†</sup> and Shu-Hai Zhao<sup>‡</sup>

Chemical Synthesis and Medicinal Chemistry, Roche Palo Alto, 3431 Hillview Avenue, Palo Alto, California 94304, U.S.A.

## Abstract:

The pilot-plant syntheses of **3** and **4**, the core structures of a series of P2X<sub>7</sub> antagonists are described. The sole stereogenic center in the dihydropyridinone ring was generated by catalytic desymmetrization. Selective formylation, followed by a tandem imination/lactamization sequence, produced the 3,4-dihydropyridin-2-one ring. The compounds **3** and **4** were produced at multikilogram scale in good overall yield (~22% over six steps) and excellent stereochemical purity (97% ee for **3**, 100% ee for **4**).

## 1. Introduction

P2X<sub>7</sub> receptors belong to the family of ATP-sensitive ionotropic P2X receptors that are composed of seven homomeric receptor subtypes (P2X<sub>1</sub>–P2X<sub>7</sub>). P2X<sub>7</sub> receptors are selectively expressed on cells of hematopoietic lineage including mast cells, lymphocytes, erythrocytes, fibroblasts, and peripheral macrophages. Due to the presence of the P2X<sub>7</sub> receptor on cells of the immune system (macrophages, microglia, etc.) and the relationship between P2X<sub>7</sub> activation and cytokine or glutamate release, this receptor may play an important role in the development and progression of various disease states or conditions such as chronic inflammation,<sup>1</sup> neurodegeneration,<sup>2</sup> and chronic pain.<sup>3</sup> The landscape of P2X<sub>7</sub> medicinal chemistry has evolved considerably over the last 5–6 years.<sup>4</sup> Efforts at Roche have led to the discovery of two series of potent P2X<sub>7</sub> receptor antagonists, represented by structures **1** and **2** (Figure 1), featuring a *N*-substituted 4-(4-fluorophenyl)-5-carboxy-3,4-dihydropyridin-2-one template. These compounds belong to a very rare structure type and there were only limited literature precedents for their racemic synthesis.<sup>5</sup> Asymmetric synthetic routes to the heterocyclic systems represented by **3** and **4**, the

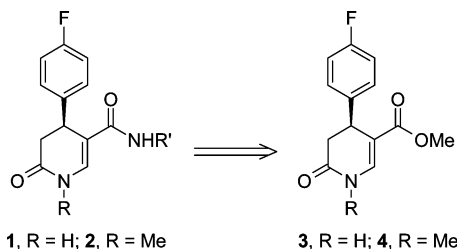


Figure 1. Structures of **1**, **2**, **3**, and **4**

core structures of **1** and **2**, had not been reported before our own work.<sup>6</sup>

We disclose here the full details of the pilot-scale enantioselective synthesis of **3**, as well as the kilogram-scale production of *N*-methyl derivative **4**.

## 2. Results and Discussion

Medicinal chemists at Roche synthesized racemic **3** by the treatment of 6-chloronicotinic acid (**5**) with 4-fluorobenzylmagnesium bromide (**6**) in ethyl ether (Scheme 1).<sup>5</sup> The two enantiomers of **7** were separated by chiral chromatography to give the enantiomerically enriched material. Initial efforts were focused on the modification of the Medicinal Chemistry racemic synthesis route, followed by resolution. Ethyl ether delivered the best yield of the solvents investigated. The reaction in THF usually gave less than 10% yield, and the major byproduct was the diaryl ketone **8**. MTBE and dibutyl ether also gave results that were inferior to ethyl ether (<40% yield). A toluene and THF mixed solvent gave 40–50% yield of *rac*-**7**. The resolution of *rac*-**7** was investigated using a number of chiral bases, including *R*-(+)- $\alpha$ -methylbenzylamine, (1*R*,2*S*)-(-)-ephedrine, (1*R*,2*R*)-(-)-pseudoephedrine, *S*-(-)-1-(1-naphthyl)ethylamine, (1*S*,2*R*)-(-)-*cis*-1-aminoindanol, *N*-octylglucosamine and cinchonidine. Only (+)-ephedrine gave the desired enantiomer of **7**, but with very irreproducible results (ee ranged from 0% to ~80% after a single resolution). A second resolution with (+)-ephedrine was necessary to achieve ~95% ee. The procedure was further complicated by the generation of several crops of materials in order to achieve a reasonable yield (usually at 20–30% yield). These studies and results underlined the urgent need for an enantioselective synthesis of **3** and **4**.

The enantioselective synthesis of **3** was investigated, and we focused on the process outlined in Scheme 2. The condensation of 4-fluorobenzaldehyde (**9**) with ethyl acetoacetate, followed by decarbonylation, gave diacid **11** via adduct **10**.<sup>7</sup> The bisacetyl bisester compound **10** was not isolated as pure form,

\* Author for correspondence. E-mail: xiaojun.huang5@gmail.com.

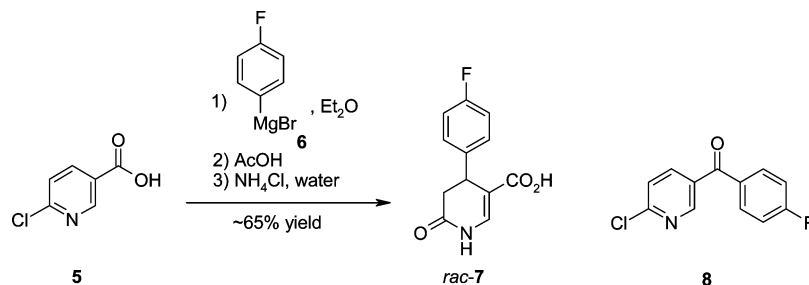
<sup>†</sup> Chemical Synthesis

<sup>‡</sup> Medicinal Chemistry

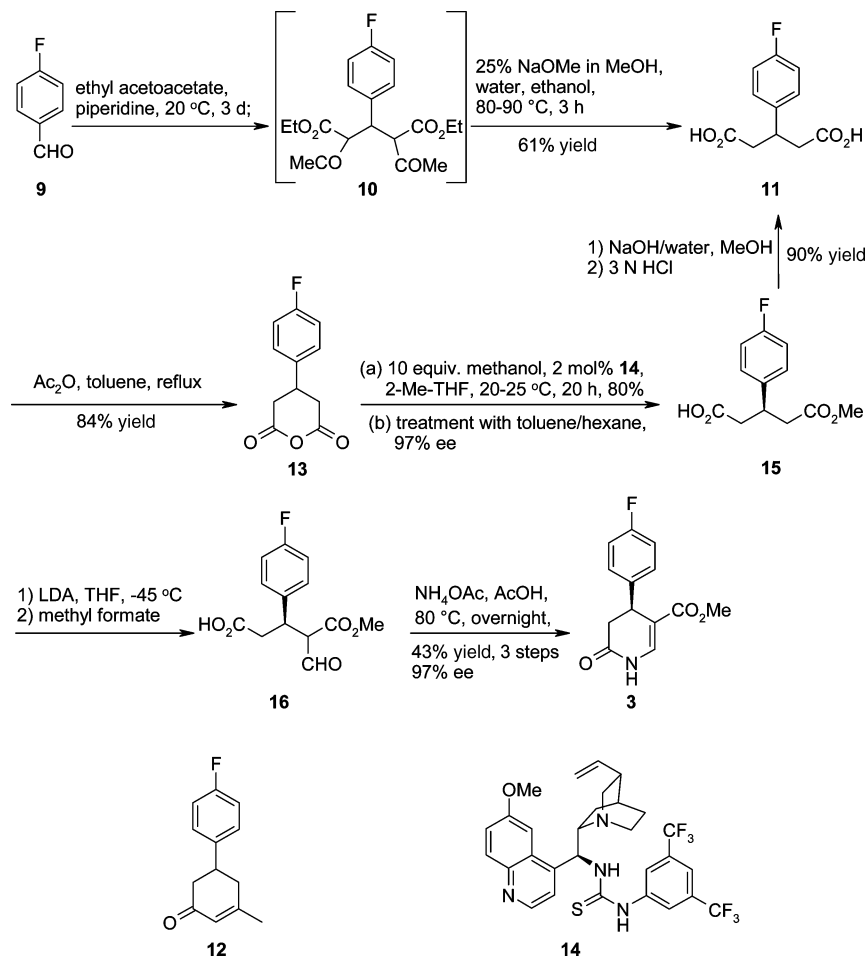
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## Scheme 1. Racemic synthesis



## Scheme 2. Pilot-plant synthesis of 3



but it was confirmed by LC/MS at  $m/z$  367.0  $[M + H]^+$ . A mass peak at  $m/z$  237.0  $[M + H]^+$ , representing the dehydrated mono-adduct of aldehyde **9** with one molecule of ethyl acetoacetate, was also observed in the process to prepare **10**. It may seem unusual to observe loss of the acetyl groups (**10**→**11**) instead of decarboxylation; however, this is well preceded for a number of glutamic acid precursors.<sup>8</sup> It is well-known that the decarboxylation of a  $\beta$ -ketoester/ketoacid proceeds through a cyclic six-membered transition state, which is facilitated by acidic conditions.<sup>9</sup> However, the decarbonylation proceeded preferably over the decarboxylation under basic

conditions. Compound **12**, which came from decarboxylation of **10** followed by aldol condensation of the resulting diketone, was observed as a major byproduct by LC/MS at  $m/z$  205.0  $[M + H]^+$ . Dehydration of **11** to anhydride **13** was performed equally well (100% conversion, >90% yield) using acetyl chloride,<sup>7a,b</sup> trifluoroacetic anhydride,<sup>7c</sup> or acetic anhydride/toluene.<sup>7d</sup> Acetic anhydride in refluxing toluene was chosen for large-scale production because of its low cost.

The enantioselective synthesis of mono acid **15** from anhydride **13** was investigated extensively. An enzymatic desymmetrization with methanol using Novozym 435 was first investigated, but only about 4% conversion was observed after

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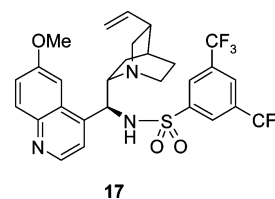
**Table 1.** Asymmetric methanolysis of anhydride **13** to **15** by catalyst **14**<sup>a</sup>

entry	cat. (mol %)	solvent	solvent vol	x (equiv)	t (h)	conv. (%)	ee (%)
1	2	MTBE	40	10	24	100	73
2	2	DMSO	40	10	24	24	6
3	2	NMP	40	10	24	17	36
4	2	DMF	40	10	24	30	29
5	2	MeCN	40	10	24	78	51
6	2	PhMe	40	10	24	100	47
7	2	CH <sub>2</sub> Cl <sub>2</sub>	40	10	24	100	49
8	2	EtOAc	40	10	24	100	70
9	2	diethyl carbonate	40	10	24	100	61
10	2	Et <sub>2</sub> O	40	10	24	100	70
11	2	THF	40	10	24	100	80
12	2	dioxane	40	10	24	100	77
13	2	<i>i</i> -Pr <sub>2</sub> O	40	10	24	100	62
14 <sup>b</sup>	2	Me-THF	40	10	24 (4.5)	100	80
15	2	Me-THF	20	10	24	100	75
16	2	Me-THF	80	10	24	100	82
17	2	Me-THF	800	10	24	100	88
18	2	Me-THF	40	5	4.5	98	80
19	2	Me-THF	40	20	4.5	100	80
20	4	Me-THF	40	10	4.5	100	80
21	1	Me-THF	40	10	4.5	86	79
22	0.5	Me-THF	40	10	4.5	83	77

<sup>a</sup> **14**, MeOH (x equiv), solvent, rt. <sup>b</sup> Achieved full conversion after 4.5 h.

5 days, and the enantiomeric excess was only ~14% in favor of the undesired (*S*)-enantiomer.<sup>7a</sup> The asymmetric methanolysis of anhydride **13** was also investigated using a stoichiometric amount of quinine in toluene,<sup>10</sup> but only moderate enantiomeric purity was observed at low temperatures: 48% at -40 °C, 58% at -45 °C, 67% at -55 °C. A bifunctional thiourea-based organocatalyst (**14**) stood out for the asymmetric methanolysis of **13** (Table 1).<sup>11</sup> THF and Me-THF gave full conversion and the highest enantioselectivity (80% ee) among 14 solvents screened (entries 1–14). Me-THF was chosen for further studies since it gave a faster reaction rate—full conversion was achieved in 4.5 h compared to 89% conversion in THF over the same time period. The reaction was screened over solvent volume (entries 14–17), methanol equivalents (entries 14, 18, 19), and catalyst loading (entries 20–22). Ten equivalents of methanol, 2 mol % **14**, and 40 vol Me-THF were the optimal conditions and were used in the pilot-plant production. The desired enantiomer of **15** was produced in the same 80% ee in the pilot plant as in the lab.

The next process was to improve the enantiomeric purity of **15** from 80% ee to greater than 95% ee. Attempts to make solid amine salts of **15** using triethylamine, Hünig's base, *tert*-butyldimethylamine, tributylamine, and pyridine were unsuccessful, as were attempts to make sodium or lithium salts using sodium methoxide or *n*-butyllithium. The enantiomeric improvement of **15** eventually succeeded by the trituration of a toluene (8 vol)/hexane (4 vol) mixture. The enantiomeric purity

**Figure 2.** Structures of **17**

of **15** in the mother liquor was enriched to 96–97% ee, while the solid was nearly racemic (around 7% ee). The solids could be recycled by hydrolysis to diacid **11**.

The only procedure for the selective alkylation or acetylation of glutaric acid monoester derivatives found in the literature used 2.2 equiv of LDA in HMPA/THF at -78 °C for the *C*-methylation of glutaric acid monoester derivatives.<sup>12</sup> When methyl iodide was used as the alkylating agent, the product was isolated in 60–93% yield. When the same conditions were used for the selective formylation of monoacid **15** with methyl formate, the desired product was formed in about 70% conversion. The reaction achieved the best conversion at 85–90% with 2.5 equiv of LDA (2.2, 2.5, 3, and 4 equiv were tested). Moreover, the formylation worked at -45 °C, a temperature that can be easily achieved in our pilot plant. This low-temperature reaction performed really well in the pilot plant and gave the same consistent results as in the lab, except that longer addition times (3–4 h) were needed to make the enolate of **15** using LDA. The unreacted starting material (**15**) was easily removed by an aqueous base wash after the next cyclization step.

Dihydropyridinone **3** was obtained by the treatment of **16** with ammonium acetate in acetic acid at 80 °C through a tandem imination/lactamization sequence. The initial aqueous workup (saturated aqueous sodium carbonate), followed by extraction with EtOAc, and then recrystallization from toluene gave product **3** in good yield (45% yield over three steps) and purity (100% HPLC purity, >99% ee). The workup/isolation procedure was simplified by adding water to the crude mixture followed by a filtration and toluene wash. Dihydropyridinone **3** was isolated in 97% ee and 43% yield over three steps (~53% yield based on recovered **15**) as an off-white solid for a pilot-plant run.

The asymmetric methanolysis of anhydride **13** was further investigated. The goal was to improve the initial enantioselectivity (80% ee) and/or lower the solvent volume (40 vol of Me-THF). Sulfonamide-based bifunctional organocatalyst **17** (Figure 2) showed good catalytic activity and enantioselectivity in the methanolytic desymmetrization of a variety of *meso* cyclic anhydrides, even at relatively high concentrations.<sup>13</sup> Catalyst **17** was applied to the desymmetrization of anhydride **13** (Table 2). Me-THF gave the best enantiomeric purity at 86% ee among the solvents tested, (entries 1–5). Lower volumes of solvent gave lower ee (entries 5, 6, 9), while higher catalyst loading gave higher values (entries 6–8). Enantiomeric purity of **15** was achieved at 82% ee using 20 vol of Me-THF (entry 6), a considerable improvement in *V*<sub>max</sub> compared to that with the thiourea catalyst **14** (80% ee using 40 vol of Me-THF).

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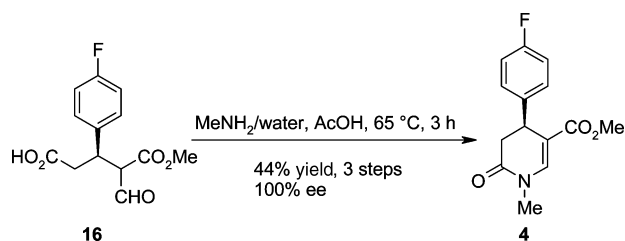
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**Table 2.** Asymmetric methanolysis of anhydride **13** to **15** by catalyst **17**<sup>a</sup>

entry	cat. (mol %)	solvent	solvent vol	t (h)	conv. (%)	ee (%)
1	2	MTBE	40	4.5	100	84
2	2	Et <sub>2</sub> O	40	4.5	100	79
3	2	<i>i</i> -Pr <sub>2</sub> O	40	4.5	100	76
4	2	THF	40	24	100	82
5	2	Me-THF	40	24	100	86
6	2	Me-THF	20	24	100	82
7	4	Me-THF	20	24	100	85
8	1	Me-THF	20	24	100	79
9	1	Me-THF	10	24	100	67

<sup>a</sup> **17**, MeOH (10 equiv.), solvent, rt.

### Scheme 3. Pilot-plant synthesis of **4**



The same intermediate **16** was used for the synthesis of *N*-methyl-3,4-dihydropyridinone derivative **4** (Scheme 3). Crude **16** was reacted with aqueous methylamine in the presence of acetic acid at 65 °C. After aqueous workup and recrystallization from MTBE, dihydropyridinone **4** was isolated in 44% yield and 100% ee over three steps (from **13**) as a white solid.

### 3. Conclusion

In summary, dihydropyridinone **3** and **4** were prepared at multikilogram scale in high yield (~22%) and enantioselectivity (>96% ee) via a six-step process from readily available 4-fluorobenzaldehyde (**9**). The key processes included catalytic desymmetrization, selective formylation, and a tandem imination/lactamization. Thiourea catalyst **14** was used for the desymmetrization reaction to give the monoacid **15** in 80% ee, and it was used in the pilot-plant synthesis. This desymmetrization reaction was also investigated using a more efficient sulfonamide catalyst **17**, which produced **15** in higher ee (82%) at half the solvent volume (20 vol). This process also provided a general method for the synthesis of *N*-alkyl 5-carboxy-3,4-dihydropyridin-2-one derivatives.

### 4. Experimental Section

**General.** HPLC analysis was performed using the following system: Waters 2690 HPLC with Zorbax SB-C8 column 4.6 mm × 75 mm, 3.5 μm particles; mobile phase consisting of solvent A, 0.1% trifluoroacetic acid in water, solvent B, 0.1% trifluoroacetic acid in MeCN. Gradient from 10–90% mobile phase B in 10 min; λ = 210, 260 nm. Chiral purity was monitored by SFC as the trifluoroacetamide using the following system: Mettler-Toledo/Berger Analytical SFC with (*R,R*)-Whelk-O1 column, 4.6 mm × 250 mm, 5 μm particles. Mobile phase consisted of 95% carbon dioxide and 5% ethanol containing 0.4% (v/v) isopropylamine at a flow rate of 2.5 mL/

min and 125 bar backpressure. Column temperature was 40 °C, detection was UV at 262 nm. Run time was 6 min.

**3-(4-Fluorophenyl)pentanedioic Acid (**11**).**<sup>7b</sup> Ethanol (8.3 L) and ethyl acetoacetate (6.73 kg, 51.7 mol) were added to 4-fluorobenzaldehyde (**9**, 3.2 kg, 25.8 mol) under nitrogen at 20 °C. To the briskly stirred mixture, piperidine (308 g, 3.6 mol) was added over 10 min. The reaction mixture was stirred for 64 h at room temperature. Starting material (**9**) was shown to be <0.5% by GC/LC analysis. The thick, yellow slurry was filtered, and the cake was washed with cold ethanol (16.5 L). The resulting white cake was partially dried under vacuum in the filter at 20 °C using a nitrogen bleed for 12 h, which was used directly in the next step. MS *m/z* 367.0 [M + H]<sup>+</sup>.

The partially dried intermediate (~7.0 kg) was returned to the previously used reactor under nitrogen, followed by the addition of ethanol (5.5 L). Sodium methoxide/methanol (25% in MeOH, 22.7 kg, 105 mol) was added to a second reactor, and the solution was cooled to 10 °C. Water (2.0 kg, 111 mol) was added to the chilled sodium methoxide solution, and the resulting solution was then transferred to the ethanol slurry in the previous reactor and briskly stirred while heating under reflux for 6 h. The resulting homogeneous reaction mixture was concentrated using vacuum distillation to a minimum stir volume (~10 L) and then cooled to 20 °C. Water (20 kg) was added to completely dissolve all solids. The solution was extracted with MTBE (10.9 kg) to remove neutral impurities. The aqueous phase was cooled to 5–10 °C, and then acidified to pH < 2 via the slow addition of conc. HCl (9.5 kg), to precipitate diacid **11**. The slurry was then filtered, and the cake washed with cold water (5 kg, 5–10 °C). The cake was thoroughly dried under reduced pressure (30–50 Torr) at 65 °C in a vacuum oven for 60 h to give **11** (3.56 kg, 61%) as a white solid. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 2.50 (dd, *J* = 16.00, 8.70 Hz, 2 H), 2.65 (dd, *J* = 16.00, 6.00 Hz, 2 H), 3.30–3.51 (m, 1 H), 7.09 (t, *J* = 8.67 Hz, 2 H), 7.24–7.37 (m, 2 H), 12.10 (s, 2 H).

**4-(4-Fluorophenyl)-dihydropyran-2,6-dione (**13**).**<sup>7a</sup> Acetic anhydride (2.52 kg, 24.7 mol) was added to diacid **11** (3.56 kg, 15.7 mol) in toluene (18.0 kg) under nitrogen. The solution was atmospherically distilled to remove acetic acid azeotropically at 108 °C. The mixture was then slowly cooled to 20 °C over 10 h while adding heptane (7.3 kg) to induce crystallization. The mixture was aged at 20 °C for 15 h with slow agitation. The slurry was then filtered, and the cake was washed with toluene/heptane (1.0 kg/7.3 kg) followed by heptane (7.3 kg). The white cake was dried in the filter at 20 °C under vacuum with a nitrogen bleed for 5 h and then transferred to a vacuum oven and dried at 60 °C for 24 h under reduced pressure (30–50 Torr) with nitrogen bleed to give **13** (2.76 kg, 84.4%) with 99.7% HPLC purity. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 2.89–3.15 (m, 4 H), 3.60 (tt, *J* = 11.02, 5.37 Hz, 1 H), 7.15–7.26 (m, 2 H), 7.28–7.44 (m, 2 H).

**(*R*)-3-(4-Fluorophenyl)pentanedioic Acid Monomethyl Ester (**15**).**<sup>7a</sup> Methanol (23.2 kg, 724 mol) was added to a mixture of anhydride **13** (14.93 kg, 71.7 mol) and catalyst **14** (0.85 kg, 1.43 mol) in Me-THF (516 kg) at ambient temperature. The reaction achieved full conversion (80% ee) for the crude product after 20 h. The mixture was concentrated under reduced



pressure (20–40 °C) to remove the solvents (Me-THF and methanol). Toluene (104.1 kg) was added, followed by hexane (49.3 kg). The mixture was stirred overnight at 15 °C and then at 11 °C for 2 h. The mixture was filtered through a Nutsche filter, and the solid was washed with a mixture of toluene (6.6 kg) and hexane (4.9 kg). The white solid was dried at 60 °C overnight under reduced pressure to give the near racemic **15** (3.22 kg, 7% ee, 100% HPLC purity). The filtrate (97% ee) was extracted with two portions of saturated aqueous NaHCO<sub>3</sub> (160.7 kg then 81.3 kg). The combined aqueous layer was acidified with conc. HCl (32.0 kg, pH = 0.7), and the mixture was extracted with toluene (245.7 kg). The organic extract was washed with brine (180 kg) and concentrated under reduced pressure (35–65 °C, jacket temperature). THF (59.3 kg) was added to the residue (**15**, 97% ee, 100% HPLC purity), and the solution (75 kg) was used to the next step without further purification. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.53–2.87 (m, 4 H), 3.54–3.71 (m, 1 H), 3.59 (s, 3 H), 6.91–7.07 (m, 2 H), 7.12–7.25 (m, 2 H).

**(R)-3-(4-Fluorophenyl)-2-formylpentanedioic Acid 1-Methyl Ester (16).** To a solution of diisopropylamine (12.1 kg, 120 mol) in THF (62.3 kg) at –10 to 8 °C was added *n*-BuLi (33.7 kg, 2.5 M in hexane, 122 mol) over 45 min. The resulting LDA solution was kept at 0 °C overnight, and then cooled to –55 °C. To this LDA solution was added cooled (~ 0 °C) crude **15** in THF (~75 kg) over 3.5 h at < –45 °C. After 60 min at –45 to –55 °C, methyl formate (7.91 kg, 132 mol) was added over 5 min at < –35 °C. The mixture was warmed to –20 °C over 1 h and then stirred at –20 °C for 1 h. The mixture was quenched with 3 N HCl (107.9 kg) at ≤ 20 °C. The mixture was extracted with EtOAc (91.7 kg). The organic layer was separated and washed with brine (128 kg). The solution was concentrated to 97 kg under reduced pressure to give **16** as an ethyl acetate solution.

**(S)-4-(4-Fluorophenyl)-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylic Acid Methyl Ester (3).** The solvents from a solution of **16** (73.2 kg from the 97 kg batch, ~43.3 mol) were removed under reduced pressure. Acetic acid (32.3 kg, 716 mol) and ammonium acetate (8.3 g, 143 mol) were added to the residue, and the mixture was warmed to 80 °C. After being left overnight at 80 °C, the mixture was cooled to 25 °C, and water (92.0 kg) was added over 3 h. The mixture was agitated over 3 days at 25 °C, then cooled to 0 °C over 10 h, and stirred for another 10 h. The cooled mixture was filtered and washed with water (16 kg) and cold toluene (29.6 kg, 0 °C). The solid was dried at 70 °C under reduced pressure (30–50 Torr) for 20 h to give product **3** (5.75 kg, 43% yield from **13**, 97% ee) as a white solid: mp 176–178 °C; [α]<sub>D</sub><sup>20</sup> = 182.6 (MeOH); HPLC assay >99%; IR (KBr): ν 3274, 2954, 1688, 1648, 1602,

1508, 1473, 1440, 1351, 1304, 1222, 1204, 1176, 1099, 839 cm<sup>–1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.71 (d, *J* = 16.58 Hz, 1 H) 3.00 (dd, *J* = 16.58, 8.29 Hz, 1 H) 3.71 (s, 3 H) 4.18 (d, *J* = 7.16 Hz, 1 H) 6.90–7.05 (m, 2 H) 7.13–7.24 (m, 2 H) 7.48 (d, *J* = 5.65 Hz, 1 H) 7.93 (br s, 1 H); <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>) δ 35.8, 38.1, 51.8, 111.0, 115.6, 115.9, 128.2, 128.3, 135.4, 137.1, 137.2, 160.3, 163.6, 166.3, 170.5; Anal. Calcd for C<sub>13</sub>H<sub>12</sub>FNO<sub>3</sub>: C, 62.65; H, 4.85; N, 5.62. Found: C, 62.78; H, 4.77; N, 5.64.

**(S)-4-(4-Fluorophenyl)-1-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-Carboxylic Acid Methyl Ester (4).** The solvents in a solution of **16** (23.3 kg from the 97 kg batch described above, ~13.8 mol) were removed under reduced pressure. Acetic acid (8.58 kg, 143 mol) and methylamine in water (3.21 kg, 40 wt %, 41.3 mol) were added successively to the residue with cooling (0–30 °C) over 15 min, and the mixture was warmed to 65 °C over 1 h. After 3 h at 65 °C, the mixture was cooled to 20 °C. Ethyl acetate (32.4 kg) and MTBE (26.2 kg) were added, and the mixture was washed with water (50 kg), saturated aqueous sodium carbonate (two times, 61 kg, then 55 kg), water (50 kg), and brine (40 kg). Solvent was removed under reduced pressure (30–125 Torr) at 40 °C. MTBE (4.4 kg) was added to the residue, and the mixture was heated to reflux (65 °C jacket temperature) until homogeneous. The mixture was slowly cooled to 0 °C over 4 h and aged at 0 °C for 1 h. The mixture was then filtered and washed with cooled MTBE (1.0 kg, 0 °C) to give a white solid, which was dried under reduced pressure (30–50 Torr) at 50 °C to give **4** (2.0 kg, 44% yield from **13**, 100% ee): mp 100–102 °C; [α]<sub>D</sub><sup>20</sup> = 108.0 (MeOH); HPLC assay >99%; IR (KBr): ν 3410, 3064, 2952, 1712, 1684, 1640, 1603, 1507, 1434, 1361, 1300, 1249, 1223, 1199, 1161, 1115, 1028, 960, 844, 806, 673 cm<sup>–1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 2.74 (dd, *J* = 16.58, 1.88 Hz, 1 H), 2.96 (dd, *J* = 16.58, 8.29 Hz, 1 H), 3.19 (s, 3 H), 3.68 (s, 3 H), 4.12 (dd, *J* = 8.29, 1.51 Hz, 1 H), 6.86–7.01 (m, 2 H), 7.06–7.19 (m, 2 H), 7.45 (s, 1 H); <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>) δ 34.6, 35.8, 38.4, 51.6, 110.8, 115.4, 115.7, 128.0, 128.1, 137.04, 137.1, 140.9, 160.1, 163.4, 166.2, 168.7; Anal. Calcd for C<sub>13</sub>H<sub>12</sub>FNO<sub>3</sub>: C, 63.87; H, 5.36; N, 5.32. Found: C, 63.50; H, 5.29; N, 5.25.

## Acknowledgment

We thank Drs. Pankaj Rege and Hanbiao Yang for helpful suggestions, and Frida Dobrouskin and Tim Lane for analytical support.

Received for review February 10, 2010.

OP1000447