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The first asymmetric synthesis of a 4-aryl-substituted 5-carboxy-3,4-dihydropyridin-2-one derivative

Xiaojun Huang *, Jiang Zhu, Scott Broadbent

Chemical Synthesis, Roche Palo Alto LLC, 3431 Hillview Avenue, Palo Alto, CA 94304, USA

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ABSTRACT

A simple and practical route for the asymmetric synthesis of (*S*)-4-(4-fluorophenyl)-1,4,5,6-tetrahydro-6-oxo-3-pyridinecarboxylic acid (**1**) is presented. The procedure comprises catalytic desymmetrization of a *meso*-anhydride using a chiral thiourea organocatalyst, followed by selective formylation and cyclization.

1. Introduction

The synthesis of (*S*)-4-(4-fluorophenyl)-1,4,5,6-tetrahydro-6-oxo-3-pyridinecarboxylic acid (**1**, Fig. 1) attracted our attention because a number of compounds derived from this core structure showed very promising biological activities in models of rheumatoid arthritis and chronic inflammatory pain. This type of 4-aryl-substituted 5-carboxy-3,4-dihydropyridin-2-one structure has not often been described in the literature. A racemic synthesis involving selective 1,4-addition of Grignard reagents to 6-chloronicotinic acid derivatives has been disclosed.[1] The enantiomers of **1** could be separated by chiral chromatography, however this is not desirable for large-scale preparation. To the best of our knowledge, there is no literature precedent for the asymmetric synthesis of this type of dihydropyridinone structure. In order to satisfy our need for multi-kilogram amounts of acid **1**, an enantioselective synthesis was envisioned.

We disclose herein our studies on the first practical asymmetric synthesis of **1**. We focused on the set of retrosynthetic disconnections as shown in Scheme 1. The selective formylation and cyclization of the monoester of 3-arylglutaric acids should give the desired dihydropyridinone core. The chiral monoester of 3-arylglutaric acids can be synthesized by the asymmetric methanolysis of 3-arylglutaric anhydrides, the latter readily available from the corresponding benzaldehydes.

2. Results and discussion

4-(4-Fluorophenyl)-glutaric anhydride (**5**) was readily available from 4-fluorobenzaldehyde (**3**) following slightly modified literature procedures (Scheme 2). The condensation of **3** with ethyl acetoacetate, followed by decarbonylation, gave diacid **4** in 60–65% yield over three steps.[2] Preparation of **4** was also achieved by condensation of **3** with diethyl malonate, followed by decarboxylation to a give better (84%) overall yield.[3] Dehydration to the anhydride was performed equally well using any of the following conditions: (a) acetyl chloride under reflux;[2a,b] (b) trifluoroacetic anhydride, THF, 55 °C;[2c] and (c) acetic anhydride, toluene under reflux.[2d] Acetic anhydride in toluene was used for large-scale work because of its low cost.

The enantioselective synthesis of mono acid **7** from anhydride **5** was investigated extensively. Literature precedent suggested that desymmetrization of prochiral anhydride **5** to set the absolute stereo-chemistry of the stereogenic center would be best accomplished by enantioselective alcoholysis. We first investigated the enzymatic desymmetrization with methanol using Novozym® 435.[2a] About 4% conversion was observed after 5 days and the enantiomeric excess was only ~14% in favor of the undesired (*S*) enantiomer. Methanolysis of anhydride **5** was also investigated using a stoichiometric amount of quinine, in toluene.[4] Moderate ee was observed at low temperatures: 48% at −40 °C, 58% at −45 °C, 67% at −55 °C.

The most promising lead came from a reported enantioselective desymmetrization of *meso*-anhydrides by a bifunctional thiourea-based organocatalyst (**6**), whereby Connon and co-workers demon-

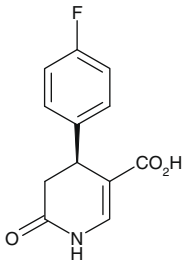

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Figure 1. Structure of compound **1**.

* Corresponding author. Tel.: +1 650 704 6432.
E-mail address: xiaojun.huang5@gmail.com (X. Huang).

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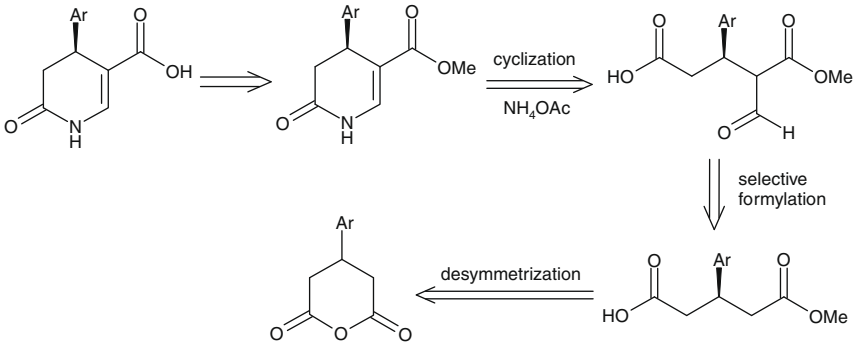
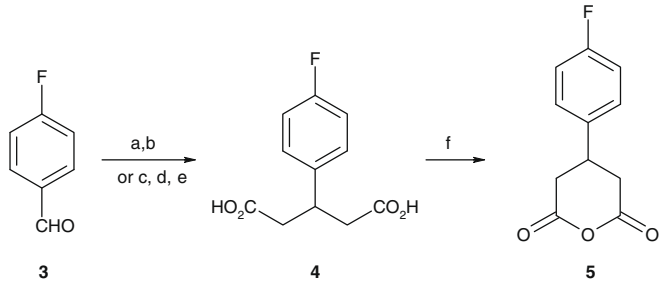


Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: (a) ethyl acetoacetate, piperidine, rt, 3 d; (b) 25% sodium methoxide in methanol, water, ethanol, 80–90 °C, 3 h, 60–65% yield from **3**; (c) diethyl malonate, piperidine, toluene, reflux, 2.5 h; (d) diethyl malonate, sodium ethoxide, ethanol, 0 °C, 15 min; (e) concd hydrochloric acid under reflux, 8 h, 84% from **3**; and (f) acetic anhydride, toluene under reflux, 80–90% yield.

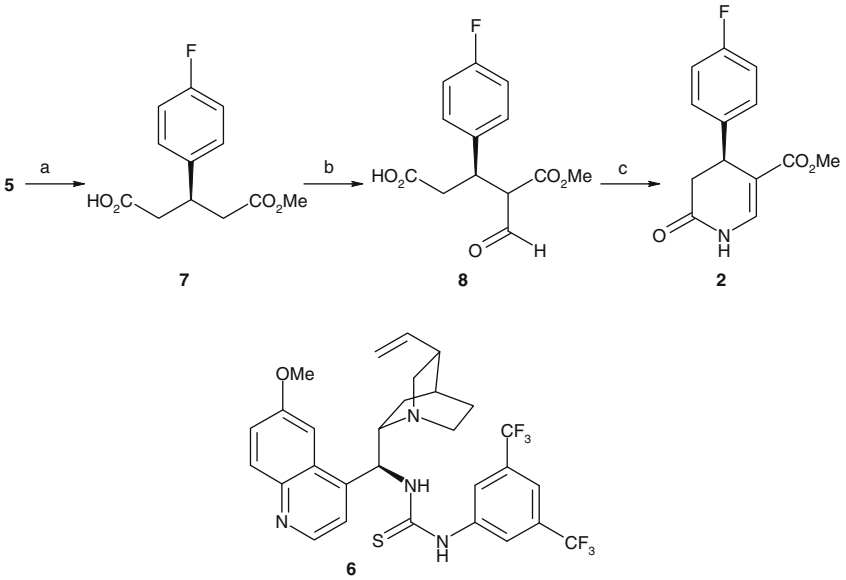
strated the successful asymmetric methanolysis of succinic anhydride derivatives and glutaric anhydrides.[5] The results of our preliminary investigations to test this method are outlined in Table 1. As a starting point, the methanolysis of the *meso*-anhydride **5** was carried out using 10 equiv of methanol, 2 mol % of **6**, in 40 volumes of methyl *t*-butyl ether (MTBE) at ambient temperature (entry 1). Full conversion was achieved after 24 h, and 73% ee was observed for the crude product. We then studied this reaction with a wide range of solvents of differing polarity (entries 1–14). The reactions were usually very clean and no byproducts were observed using organocatalyst **6**. Level of polarity was very important to achieving good conversion and enantioselectivity. Low conversion was observed if the solvent was too polar (entries 2–5), presumably because of catalyst solvation. Less polar solvents usually gave full conversion (entries 6–14), but the enantioselectivity was poor when the polarity of the solvents was too low (entries 6 and 7). Ethers proved to be the best solvents. Both THF (entry 11) and 2-methyl-THF (entry 14) gave 100% conversion and the best observed ee (80%). 2-Methyl-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 period. The product enantioselectivity was slightly increased at lower reaction concentrations (entries 14–17). For practical reasons, forty volumes of 2-methyl-THF were chosen for large-scale studies. The use of 5, 10, or 20 equiv of methanol led to the same enantioselectivity (entries 14, 18, and 19), but the reaction rate was slower when less methanol was used. Catalyst loading was also screened (entries 20–22). Lower catalyst loading resulted in lower ee and slower reaction. The enantioselectivity reached the maximum observed value when 2 mol % of **6** was used.

Having identified a readily available organocatalyst and reaction conditions (10 equiv methanol, 2 mol % **6**, 40 vol 2-Me-THF)

Table 1
Initial catalyst screening and optimization of the asymmetric methanolysis of anhydride **5**[a]

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_2Cl_2	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_2O	40	10	24	100	70
11	2	THF	40	10	24	100	80
12	2	Dioxane	40	10	24	100	77
13	2	*i*-Pr_2O	40	10	24	100	62
14[b]	2	2-Me-THF	40	10	24 (4.5)	100	80
15	2	2-Me-THF	20	10	24	100	75
16	2	2-Me-THF	80	10	24	100	82
17	2	2-Me-THF	800	10	24	100	88
18	2	2-Me-THF	40	5	4.5	98	80
19	2	2-Me-THF	40	20	4.5	100	80
20	4	2-Me-THF	40	10	4.5	100	80
21	1	2-Me-THF	40	10	4.5	86	79
22	0.5	2-Me-THF	40	10	4.5	83	77

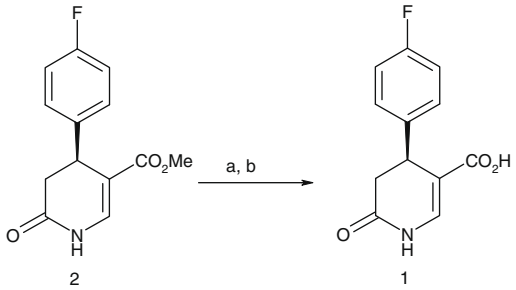
[a] **6**, methanol (*x* equiv), solvent, rt.
[b] Achieved full conversion after 4.5 h.



Scheme 3. Reagents and conditions: (a) 10 equiv methanol, 2 mol % **6**, 2-Me-THF, rt, overnight, 80% ee; then treatment with toluene/hexane, 96% ee; (b) LDA, methyl formate, THF, −45 °C; and (c) ammonium acetate, acetic acid, 80 °C, overnight, 48% overall yield (three steps).

conducive to clean asymmetric anhydride desymmetrization at room temperature, attention now turned to enhancement of the enantiomeric purity of monoacid **7**. The goal was to improve the ee from 80% to >95%. Attempts to make solid amine salts of **7** using triethylamine, Hünig's base, *t*-butyldimethylamine, tributylamine, and pyridine were unsuccessful, as were attempts to make sodium or lithium salts using sodium methoxide or *n*-butyllithium. Some solids were collected but there were some byproducts, including diacid **4** as the major one. It was finally found that treatment of crude **7** with a toluene/hexane mixture (8 vol/4 vol) caused solid **7** to precipitate in near-racemic form (<10% ee). The enantiomeric excess of monoacid **7** in the mother liquor was enriched to >95%. The ee in the mother liquor could be further increased to >98% by running at lower temperatures, but the ee of the solid also increased. It is noteworthy that both the 2-Me-THF solvent and catalyst **6** can be recovered and re-used to effect this transformation with the same outcome.

With the chiral monoacid (*R*)-**7** of desired enantiomeric excess available, the next step was the selective formylation to make intermediate **8**. Very few examples have been reported for the selective alkylation or acetylation of glutaric acid monoester derivatives. In fact, the only procedure 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.[6] When methyl iodide was used as the alkylating agent, the product was isolated in 60–93% yield. The formylation of esters is well known in the literature.[7] However, no examples utilizing an ester/acid longer than four carbons similar to **7** are known. When the same conditions used in the methylation were used for the selective formylation of monoacid **7** with methyl formate, we were delighted to find that the desired product was formed in about 70% conversion. Since we targeted multi-kilogram preparations of acid **1** in our pilot plant, the elimination of HMPA was necessary. It was found that the reaction did not require the presence of HMPA. The reaction achieved best conversion (85–90%) with 2.5 equiv of LDA (2.2, 2.5, 3, and 4 equiv were tested). Moreover, it worked at −45 °C, a temperature that can easily be achieved in our pilot plant. It is noteworthy that the addition of **7** to LDA was preferred for the deprotonation step, because the reaction mixture is physically easier to agitate, and better conversion was achieved. The cyclization of **8** with ammonium acetate in the presence of acetic acid smoothly gave product **2** in good overall yield (48%, three steps) and >95% ee (Scheme 3).[8]



Scheme 4. Reagents and conditions: (a) 1.5 N aqueous lithium hydroxide, methanol, rt, overnight; and (b) 1 N hydrochloric acid, 86% yield.

The hydrolysis of **2** by the action of lithium hydroxide in water/methanol afforded acid **1** in 86% isolated yield after acidification (Scheme 4).[9] Sodium hydroxide was also tried for this transformation but it led to some ring-opening byproducts.

In conclusion, we have demonstrated the first asymmetric synthesis of **1**, which represents a novel class of 5-carboxy-3,4-dihydropyridin-2-one structures. The chiral center was set by the desymmetrization of anhydride **5** with thiourea-based chiral catalyst **6**, and the enantiomeric excess of **7** was improved from 80% to >95% by treatment with toluene/hexane. Selective formylation and cyclization were key reactions to achieving the dihydropyridinone core. The whole process is amenable to a large-scale synthesis.

Acknowledgments

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8. *(S)-4-(4-Fluorophenyl)-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylic acid methyl ester* (**2**)*:* To a 5 L flask equipped with an overhead stirrer, anhydride **5** (100.0 g, 0.481 mol) and catalyst **6** (4.81 g, 0.00962 mol) were charged under nitrogen. 2-Me-THF (4.0 L) was added, followed by methanol (195 mL, 4.81 mol) at ambient temperature. The mixture was stirred overnight. The reaction achieved full conversion with 80% ee for the crude product. The mixture was concentrated under reduced pressure (23–45 °C). Toluene (1.0 L) was added, followed by hexane (0.5 L). The mixture was stirred overnight at ambient temperature, then 12 °C for 2 h. The mixture was filtered to give a solid (23 g, 6% ee). The filtrate (96% ee) was extracted with saturated aqueous $NaHCO_3$ (two times, 1 L then 0.5 L). The organic layer was concentrated to give the recovered catalyst **6** for re-use. The combined aqueous layer was acidified with concd HCl (180 mL, final pH = 0.36) and the mixture was extracted with toluene (2 L). The organic extract was washed with brine (1 L) and concentrated under reduced pressure. The residue (**7**, 96% ee) was used in the next step without further purification.
   To a solution of diisopropylamine (134 mL, 0.950 mol) in THF (548 mL) at −10 to 10 °C was added *n*-BuLi (380 mL, 2.5 M in hexane, 0.95 mol) over 20 min. After 15 min at 0 °C, the mixture was cooled to −55 °C. To this LDA solution, crude **7** (ca. 0.38 mol) in THF was added over 30 min (T < −45 °C). After 40 min at −45 to −55 °C, methyl formate (65.2 mL, 1.06 mol) was added. The mixture was slowly warmed to −20 °C over 1 h, and then stirred at −20 °C for 1 h. The mixture was slowly quenched with 3 N HCl (800 mL, final pH = 0.15) and EtOAc (0.8 L) was added. The organic layer was separated, washed with brine (0.8 L) and concentrated to give a thick oil (**8**).
   To this thick oil (crude **8**), AcOH (326 mL, 5.70 mol) and NH_4OAc (87.9 g, 1.14 mol) were added and the mixture was warmed to 80 °C. After overnight at 80 °C, the mixture was cooled to ambient temperature and water (0.825 L) was added very slowly over 3 h. After 2 h at ambient temperature, the mixture was slowly cooled to 0 °C and stirred for another 3 h. The cooled mixture was filtered and washed with water (70 mL) and cold toluene (70 mL, 0 °C). The solid was dried overnight (60 °C) under reduced pressure to give product **2** (57.7 g, 48% yield over three steps, 96% ee) as an off-white solid: mp 176–178 °C; $[\alpha]_D^{20}$ 182.6; HPLC assay >99%; IR (KBr): ν 3274, 2954, 1688, 1648, 1602, 1508, 1473, 1440, 1351, 1304, 1222, 1204, 1176, 1099, 839 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.71 (d, J = 16.58 Hz, 1H) 3.00 (dd, J = 16.58, 8.29 Hz, 1H) 3.71 (s, 3H) 4.18 (d, J = 7.16 Hz, 1H) 6.90–7.05 (m, 2H) 7.13–7.24 (m, 2H) 7.48 (d, J = 5.65 Hz, 1H) 7.93 (br s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) 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 $C_{13}H_{12}FNO_3$: C, 62.65; H, 4.85; N, 5.62. Found: C, 62.78; H, 4.77; N, 5.64.
9. *(S)-4-(4-Fluorophenyl)-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylic acid* (**1**)*:* Aqueous lithium hydroxide solution (803 mL, 1.5 M, 1.2 mol) was added to methyl ester **2** (100.0 g, 0.402 mol) in MeOH (500 mL) at ambient temperature. The reaction achieved full conversion overnight. The mixture was slowly acidified with 2 L of 1 N aqueous HCl solution (24–33 °C). The mixture was slowly cooled to 0 °C and stirred for 2 h. The cooled mixture was filtered. The solid was washed with water and dried at 70 °C under reduced pressure to give acid **1** (81.2 g, 86% yield, 96% ee) as a white solid: mp 209–212 °C; $[\alpha]_D^{20}$ 278.3; HPLC assay 100%; IR (KBr): ν 3254, 2944, 1690, 1647, 1559, 1509, 1482, 1373, 1283, 1214, 1194, 1170, 1101, 831 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.39 (d, J = 16.58 Hz, 1H) 3.00 (dd, J = 16.58, 8.29 Hz, 1H) 4.03 (d, J = 7.16 Hz, 1H) 7.01–7.27 (m, 4H) 7.36 (d, J = 5.27 Hz, 1H) 9.88 (d, J = 5.65 Hz, 1H) 12.07 (br s, 1H); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ 35.3, 38.4, 109.4, 115.3, 115.5, 128.4, 128.5, 136.8, 138.6, 159.5, 162.7, 167.2, 169.4; Anal. Calcd for $C_{12}H_{10}FNO_3$: C, 61.28; H, 4.29; N, 5.95. Found: C, 61.05; H, 4.21; N, 6.03.