Asymmetric Synthesis of a 5,6,7,8-Tetrahydro-1,6-naphthyridine Scaffold Leading to Potent Retinoid-Related Orphan Receptor γt Inverse Agonist TAK-828F

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ABSTRACT: An asymmetric synthesis of the tetrahydronaphthyridine scaffold of TAK-828F as a RORγt inverse agonist has been developed. The synthesis features a newly discovered atom-economical protocol for Heck-type vinylation of chloropyridine using ethylene gas, an unprecedented formation of dihydronaphthyridine directly from 2-vinyl-3-acylpyridine mediated by ammonia, and a ruthenium-catalyzed enantioselective transfer hydrogenation as key steps. This represents the first example of the enantioselective synthesis of a 5,6,7,8-tetrahydro-1,6-naphthyridine compound. The new synthesis is also free of chromatography or distillation purification processes and therefore qualifies for extension to large-scale manufacture.

INTRODUCTION

Retinoid-related orphan receptor (RORγt), which is an orphan nuclear receptor, plays an important role in the differentiation of Th17 cells and production of IL-17A/IL-17F.1 Th17 cells and inflammatory cytokines (such as IL-17A and IL-17F) result in a severe etiology accompanying the enhancement of a systemic new immune response in various autoimmune diseases, such as inflammatory bowel disease (IBD), rheumatoid arthritis, multiple sclerosis, and psoriasis.2 RORγt has been reported to be mainly expressed in Th17 cells and functions as a transcription factor of IL-17A and IL-17F and a master regulator of Th17 cell differentiation.3 Therefore, a medicament that inhibits the action of RORγt is expected to have a treatment effect on various immune diseases by suppressing the differentiation and activation of Th17 cells.

Through drug discovery, TAK-828F (1) has been identified by Takeda as a potent, selective, and orally available RORγt inverse agonist.4 TAK-828F (1) is a tetrahydronaphthyridine ring-fused chiral amino acid bearing indane and cyclobutane moieties through two peptide bonds. The original synthetic route developed by the medicinal chemistry group is shown in Scheme 1.4c Pyridinylethylamine 5 was prepared from 2-methoxy-6-methylpyridine (2) via metalation and nucleophilic addition to paraformaldehyde, amination under Mitsunobu conditions, and finally deprotection using hydrazine. The Pictet–Spengler reaction with an ethyl glyoxylate polymer gave tetrahydronaphthyridine 6 as the HCl salt. After Boc protection of the secondary amine, silver-mediated O-selective methylation and hydrolysis of the ethyl ester afforded carboxylic acid 9, which was then condensed with aminoindane 10. The resulting racemate of 11 was subjected to chiral HPLC resolution to give optically pure (R)-11. After deprotection of the Boc group, the second amide bond formation with cyclobutanecarboxylic acid 13 and deprotection of the tert-butyl ester finally produced target compound 1.

As the program advanced into the drug development stage, a synthetic process suitable for producing large quantities of the TAK-828F drug substance was needed. In this regard, the original synthesis described above had inherent issues, including (i) a poor overall yield (3.6% over 12 steps in the longest linear sequence); (ii) chromatographic purification; (iii) cryogenic reaction conditions; (iv) hazardous reagents, such as 1,1′-(azodicarbonyl)dipiperidine (ADDP) and hydrazine; (v) undesired methyl ether cleavage during the Pictet–Spengler reaction, resulting in the need for subsequent re-

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methylation using a stoichiometric amount of silver carbonate; and (vi) racemic synthesis with chiral HPLC resolution at a late stage of the synthesis. Based on these issues, an alternative synthetic route clearly needed to be pursued to develop a scalable synthetic process. However, after an extensive literature search, the synthesis of tetrahydro-1,6-naphthyridines was found to still be underdeveloped despite their significant value as a scaffold of biologically active molecules. Furthermore, to the best of our knowledge, no enantioselective synthesis of this particular ring system had been reported at that time, with only two other reports found on non-enantioselective methods. In the original medicinal chemistry synthesis (Scheme 1), the chiral center of target molecule 1 was generated by a Pictet−Spengler-type cyclization. However, enantioselective Pictet−Spengler reactions have been reported only for highly activated (hetero)aromatic substrates, such as pyrroles or indoles, with no successful examples reported for inactivated aromatic rings, such as...
pyridines. Therefore, we aimed to evaluate a different chemical transformation to establish the chiral stereogenic center in an enantioselective fashion. Scheme 2 outlines the retrosynthetic analysis of the projected synthesis. We envisaged that the chiral stereogenic center in the naphthyridine core could be established by asymmetric reduction of dihydronaphthyridine 17. The resulting chiral tetrahydronaphthyridine 16 could then be coupled with 15 to give 12, which is the same precursor in the existing route to target compound 1 (Scheme 1). We expected that the synthesis of 17 would be achieved by the amination of 2-vinyl-3-acylpyridine 19 followed by intramolecular condensation, inspired by few literature precedents.\(^9\)\(^{-11}\) For an even more streamlined synthesis, we decided to pursue a tandem reaction to achieve these two transformations in one pot.

## RESULTS AND DISCUSSION

Pyridinyl-2-oxoacetamide 23, a precursor to vinylpyridine key intermediate 19, was prepared via two different synthetic routes (Scheme 3). In route A, the cyanation\(^12\) of nicotinic acid chloride 21, followed by bromide-mediated hydration\(^13\) afforded 23 in good yield. In route B, an ethyl oxalyl group was introduced by metalation of 24 with a Grignard reagent, followed by mild-temperature treatment with diethyl oxalate. The resulting 25 was then treated with ammonia in ethanol to give 23 in high yield. As compounds 21 and 22 were susceptible to hydrolysis, route B was eventually selected for scale-up synthesis.

The vinylation of chloropyridine 23 was initially conducted using potassium vinyltrifluoroborate (Scheme 4, method A)\(^10\) to give 19 in good yield. As the trifluoroborate was glass-corrosive, not atom-economical, and an expensive vinyl source, its replacement with ethylene gas was attempted. Although the Heck reactions using ethylene gas had been reported for an aryl chloride\(^14\) and aryl bromides,\(^15\) no example was available for the conversion of chloropyridines. Nonetheless, we launched high-throughput screening (Table 1)\(^16\) and successfully identified a new and effective set of conditions for the vinylation of 23 using DPEphos as the ligand (Scheme 4, method B).

![Scheme 4. Vinylation of Chloropyridine 23](image)

**Table 1. Summary of High-Throughput Ligand Screening for the Vinylation of 23 with Ethylene Gas**

| entry | cat (mol %) | HPLC (area %) |
|-------|-------------|---------------|
|       | 23          | 19            |
| 1     | PdCl\(_2\) (20), (p-Tol)_3P(40) | 20.2 | 53.6 |
| 2     | PdCl\(_2\) (20), (o-MeOC\(_6\)H\(_4\))_3P(40) | 43.6 | 9.2 |
| 3     | Pd(OAc)\(_2\) (20), Xantphos (20) | 12.3 | 70.7 |
| 4     | Pd(dppf)Cl\(_2\)·CH\(_2\)Cl (10) | 69.6 | 13.8 |
| 5     | PdCl\(_2\) (20), DPEphos (20) | 9.9 | 61.1 |
| 6     | Scheme 4, method B | ND b | 94.5 |

\(^{a}\)The reaction was conducted in DMF (50 v/v) in the absence of PTZ. \(^{b}\)ND = not detected.

With 2-vinyl-3-acylpyridine 19 in hand, the next target was to develop a one-pot hydroamination/cyclization reaction to construct the dihydronaphthyridine ring (Scheme 5). As projected in the retrosynthesis, dihydronaphthyridine 17 was obtained in good yield by heating 19 in NH\(_3\) solution in MeOH. A small amount of aromatized byproduct 26 was also observed, which was presumably generated from the oxidation of 17 by residual oxygen in the reaction mixture. Indeed, when previously isolated 17 was treated with aq. NaOH in MeOH under air, it was immediately oxidized and converted to 26. Owing to the air sensitivity of the product in solution, the formation of 26 in this step was difficult to completely prevent on a lab scale. However, the oxidized impurity was easily removed by an aqueous workup in the next step and caused no significant issue for the overall synthesis.

With the successful development of the ring-closure reaction, our attention was turned to enantioselective reduction of the resulting carbon–nitrogen double bond. High-throughput screening was conducted under more than...
100 sets of conditions, including Ru-catalyzed transfer hydrogenation reactions and Ru, Rh, and Ir-catalyzed hydrogenation reactions (Table 2),\textsuperscript{16} based on previous reports on the asymmetric reduction of dihydroisoquinolines.\textsuperscript{17,18} As a result, transfer hydrogenation using catalyst \textsuperscript{30} was found to be optimal (entry 4, Table 2). The reaction was further optimized to a \textsuperscript{19} with excellent conversion and high enantioselectivity (Scheme 6). Compound \textsuperscript{16} was then Boc-protected and isolated as compound \textsuperscript{31} by crystallization with effective upgrade of the enantiomeric purity.

The coupling reaction of \textsuperscript{16} or \textsuperscript{31} with haloindane \textsuperscript{15} was then examined to obtain the corresponding amide \textsuperscript{12} or \textsuperscript{11} (Scheme 7) as the precursor to target compound TAK-828F (1). Initially, common Pd-catalyzed conditions\textsuperscript{20} and copper-mediated methods\textsuperscript{21} for amidation were examined using substrate \textsuperscript{16}. Although the Pd-catalyzed conditions were not effective, the copper-mediated conditions afforded the desired coupling product \textsuperscript{12}, albeit in a low yield with oxidized byproducts \textsuperscript{32} and \textsuperscript{33} (Scheme 7). However, for the copper-mediated reactions, significant erosion of the optical purity was observed, even under mildly basic conditions. This was an unexpected result because the stereogenic center had proven to be stable under strongly basic conditions, as shown in Table 2 (entry 1). Therefore, the undesired racemization was hypothesized to occur mainly through a redox-based pathway between \textsuperscript{12} and \textsuperscript{32}, which might be promoted in the presence of copper. To prevent the undesired redox-based side reactions, N-Boc-protected dihydronaphthyridine \textsuperscript{31} was employed as the substrate for the reaction with aryl iodide \textsuperscript{15a} or bromide \textsuperscript{15b} as coupling partners (Table 3). Although the use of a substoichiometric amount of copper iodide afforded good conversion with a slight loss in enantioselectivity, the reactivity was only moderate (entry 1). In contrast, the reaction using a stoichiometric amount of copper iodide gave a much better yield with reasonable retention of the stereochemical integrity (entry 2). However, further racemization was observed after a prolonged reaction (entry 3). To our delight, deterioration of the enantiomeric purity was effectively suppressed by lowering the reaction temperature and using a slight excess of aryl iodide \textsuperscript{15a} (entry 4). The reaction with aryl bromide \textsuperscript{15b} gave a lower conversion, even at higher temperatures, with significant racemization observed (entry 5) (Table 3).

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Finally, the validity of the new synthetic route was confirmed by converting the resulting compound \textsuperscript{(R)-11} into the target molecule \textsuperscript{1} according to the original route (Scheme 1). Compared with the original synthesis of \textsuperscript{(R)-11}, the new
and eliminated the need for hazardous or expensive reagents employed in the original synthesis (Scheme 1). Furthermore, the new intermediate, 15a, was readily prepared from the indane fragment 15b through single-step iodination, while the original route required three steps for the conversion of fragment 15b to aminoidane 10 (Scheme 8).22

Conclusions
A highly efficient asymmetric synthesis of ROR\(\alpha\) inverse agonist TAK-828F (1) has been achieved by developing a new synthetic route to the chiral tetrahydronaphthyridine core scaffold. The new synthesis features several key transformations, namely, the Heck reaction of 2-chloropyridine 23 with ethylene gas, the unprecedented one-pot cyclization and amination of 3-acetyl-2-vinylpyridine 19, and the enantioselective transfer hydrogenation of dihydronaphthyridine 17. The new synthetic route is also free of chromatographic purification, making it suitable for scale-up.23 We expect this method to be extendable for the synthesis of various other chiral tetrahydronaphthyridine compounds.

Experimental Section

General Experimental Methods. All reactions were conducted under an inert gas atmosphere using commercially available reagents and solvents without further purification unless otherwise noted. All reactions that required heating were heated using an oil bath. NMR chemical shifts were recorded in ppm relative to tetramethylsilane (0 ppm) as s (singlet), bs (broad singlet), d (doublet), t (triplet), or m (multiplet).

Scheme 9. Summary of the New Synthetic Route to (R)-11

2-Chloro-6-methoxynicotinyl Chloride (21). A 100 mL round-bottom flask was charged with 2-chloro-6-methoxynicotinic acid 20 (6.0 g, 32.0 mmol) and SOCl\(_2\) (12 mL). The mixture was heated to 60 °C for 3 h with stirring. Volatiles were removed using a rotary evaporator to give a slightly yellowish white solid (6.6 g). The product was used in the next reaction without further purification owing to moisture sensitivity.\(^3\) H NMR (500 MHz, CDCl\(_3\)) \(\delta 8.30\) (d, \(J = 8.8\) Hz, 1H), 6.86 (d, \(J = 8.5\) Hz, 1H), 4.09 (s, 3H);\(^3\) C\(^{13}\) (H) NMR (126 MHz, CDCl\(_3\)) \(\delta 168.7, 163.7, 151.8, 144.1, 121.2, 113.0,\) 110.6, 55.5.

Ethyl 2-(2-Chloro-6-methoxypyridin-3-yl)-2-oxoacetate (25). A 1 L four-neck round-bottom flask was charged with 24 (120.0 g, 539.4 mmol) and dry THF (240 mL), and the resulting solution was cooled to 12 °C. A THF solution of isopropylmagnesium chloride (247.9 mL, 2 M, 1.2 equiv) was added dropwise over 40 min while keeping the reaction stirred at rt for 2 h. A separate 2 L round-bottom flask was charged with diethyl oxalate (87.6 mL, 1.2 equiv) and dry THF (240 mL) and cooled to \(-8\) °C. The arenemagnesium solution prepared as mentioned above was added dropwise to the diethyl oxalate solution over 75 min while keeping the reaction temperature below 1 °C. The reaction was stirred at 0–3 °C for 1 h and quenched by adding 1 M aq HCl (600 mL). After stirring at rt for 10 min, the organic layer was separated. The solvent was exchanged with EtOH through repeated concentration using a rotary evaporator and EtOH addition. The net solution volume was adjusted to 480 mL by adding 1 M aq HCl (600 mL). After stirring at rt for 10 min, the organic layer was separated. The solvent was exchanged with EtOH through repeated concentration using a rotary evaporator and EtOH addition. The net solution volume was adjusted to 480 mL by adding 1 M aq HCl (600 mL). After stirring at rt for 10 min, the organic layer was separated. The solvent was exchanged with EtOH through repeated concentration using a rotary evaporator and EtOH addition. The net solution volume was adjusted to 480 mL by adding 1 M aq HCl (600 mL). After stirring at rt for 10 min, the organic layer was separated. The solvent was exchanged with EtOH through repeated concentration using a rotary evaporator and EtOH addition.
2-(2-Chloro-6-methoxy-3-yl)-1,6-naphthyridine-6-carboxylic acid (17). A 120 mL autoclave vessel was charged with 19 (2.0 g, 9.7 mmol), BHT (80 mg), and dry MeOH (80 mL). The resulting mixture was stirred at rt under anhydrous condition (1.0 MPa) for 16 h. The reaction was allowed to cool to rt and the resulting mixture was purified by silica gel chromatography (20% EtOAc/hexane) to afford 19 (161.7 mg) as a pale yellow solid; 74% yield. The product was also isolated as crystals by silica gel chromatography (20% EtOAc/hexane) to a purity of 95% as a colorless solid (83.8 g); 76% yield for three steps from 20.

(From 25) A 0.2 L four-neck round-bottom flask equipped with a mechanical stirrer was charged with 25 (100.0 g, 94.0 wt %, 385.8 mmol) and 2 M NH₃ in EtOH (600 mL). The reaction initially became a homogeneous solution and then turned into a thick slurry after stirring at rt for 5 min. The resulting slurry was stirred at rt for a total of 24 h. The solids were collected by filtration, washed with EtOH (200 mL), and dried in a vacuum oven at 40 °C for 2 h to give 23 as a colorless solid (77.6 g); 94% yield. 

2-(2-Methoxy-5,6,7,8-tetrahydro-1,6-naphthyridine-5-carboxamide (18). The preparation of 18 was similar to that of 20 except that acid chloride was used instead of acid anhydride.

(R)-2-Methoxy-5,6,7,8-tetrahydro-1,6-naphthyridine-5-carboxylic acid (19). The method used was similar to that of 20 except that acid chloride was used instead of acid anhydride.
with EtOH (2 mL) through repeated concentration using a rotary evaporator and EtOH addition. AcOH (2 mL), H2O (2 mL), and a crystal seed of (R)-11 were added to form a seed bed. After slow addition of H2O (9 mL), the resulting precipitate was collected by filtration, washed with H2O (10 mL), and dried in a vacuum oven at 50 °C to give (R)-11 as a colorless crystalline solid (1.4 g), 84% yield.

1H NMR (500 MHz, CDCl3) δ 8.96 (bs, 1H), 7.52 (m, 1H), 7.08 (d, J = 11.6 Hz, 1H), 7.04 (s, 1H), 6.62 (d, J = 8.5 Hz, 1H), 5.62 (bs, 1H), 3.95–4.10 (m, 1H), 3.91 (s, 3H), 3.55 (bs, 1H), 2.87–2.99 (m, 2H), 2.85 (t, J = 7.3 Hz, 2H), 1.89 (t, J = 7.4 Hz, 2H), 1.53 (s, 9H), 1.33 (s, 6H); 13C{1H} NMR (126 MHz, CDCl3) δ 168.9, 163.1, 160.4, 158.4, 152.2, 146.9, 146.8, 138.8, 137.8, 133.4, 118.8, 111.6, 108.8, 105.5, 105.6, 81.5, 54.4, 44.1, 41.9, 40.5, 31.5, 31.1, 28.4, 27.5; HRMS m/z [M + H]+ calcd. for C26H32FN3O4 470.2434, found 470.2434.

5-ido-7-fluoro-1,1-dimethyl-2,3-dihydro-1H-indene (15a). A 30 mL Schlenk tube was charged with CuI (95.2 mg, 0.5 mmol), NaI (2.4 g, 10.0 mmol). The mixture was stirred overnight under reflux. The reaction was cooled to rt and filtered through a Celite pad. The filter cake was washed with EtOAc (20 mL), and the combined solution was washed successively with 10%aq NH4OH (10 mL, twice), 20%aq citric acid (10 mL), and H2O (10 mL). The organic solvent was then removed using a rotary evaporator, and the solution was azotropically dried with EtOH, affording the target product as a yellow oil (2.7 g); 94% yield.

1H NMR (500 MHz, CDCl3) δ 7.29 (s, 1H), 7.16 (d, J = 9.1 Hz, 1H), 2.89 (t, J = 7.3 Hz, 2H), 1.91 (t, J = 7.4 Hz, 2H), 1.34 (s, 6H); 13C{1H} NMR (126 MHz, CDCl3) δ 160.5, 158.5, 148.5 (d, J = 7.3 Hz), 137.6 (d, J = 15.4 Hz), 129.6 (d, J = 3.6 Hz), 122.8 (d, J = 23.6 Hz), 90.6 (d, J = 7.3 Hz), 44.6 (d, J = 1.8 Hz), 41.7, 30.7, 27.3 (d, J = 1.8 Hz); Anal. calcd. for C11H12FI: C, 45.54; H, 4.17; found: C, 45.16; H, 3.96.

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