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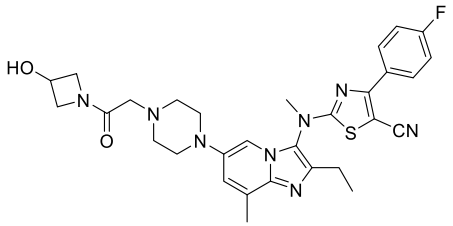
ABSTRACT

A practical and highly efficient protocol for the production of ATX inhibitor Ziritaxestat (**1**) was described. The procedure was began with a catalyst-free bicomponent cyclization for the construction of the imidazo[1,2-*a*]pyridine skeleton **16**. Subsequently, a typical Curtius rearrangement of carboxylic acid **17** followed by nucleophilic attacking of 3,5-dichlorobenzyl alcohol **18f** led to the carbamate analog **19f**. The *N*-methylated **20** was readily deprotected through HBr/HOAc treatment which further conveniently took part in an alternative K_2CO_3 induced *N*-alkylation reaction with **9** to give **10**. **10** coupled directly with piperazine to furnish **13** which ideally circumvent the removement of Boc group. As a result, the hypertoxic KCN and the hypertoxic & costly isonitrile **3** involved in the tricomponent cyclization were carefully avoided. Ultimately, the novel scalable and cost-effective route was favorably conducted to afford Ziritaxestat in 20.4 % overall yield.

KEYWORDS: ATX inhibitor, Ziritaxestat, novel synthetic strategy, bicomponent cyclization, Curtius rearrangement

INTRODUCTION

Ziritaxestat (GLPG-1690, **Figure 1**), a first-in-class small-molecule Autotaxin (ATX) inhibitor developed by Galapagos, was now undergoing phase III clinical trials to treat patients with idiopathic pulmonary fibrosis (IPF) or chronic obstructive pulmonary diseases (COPD).[1-4]



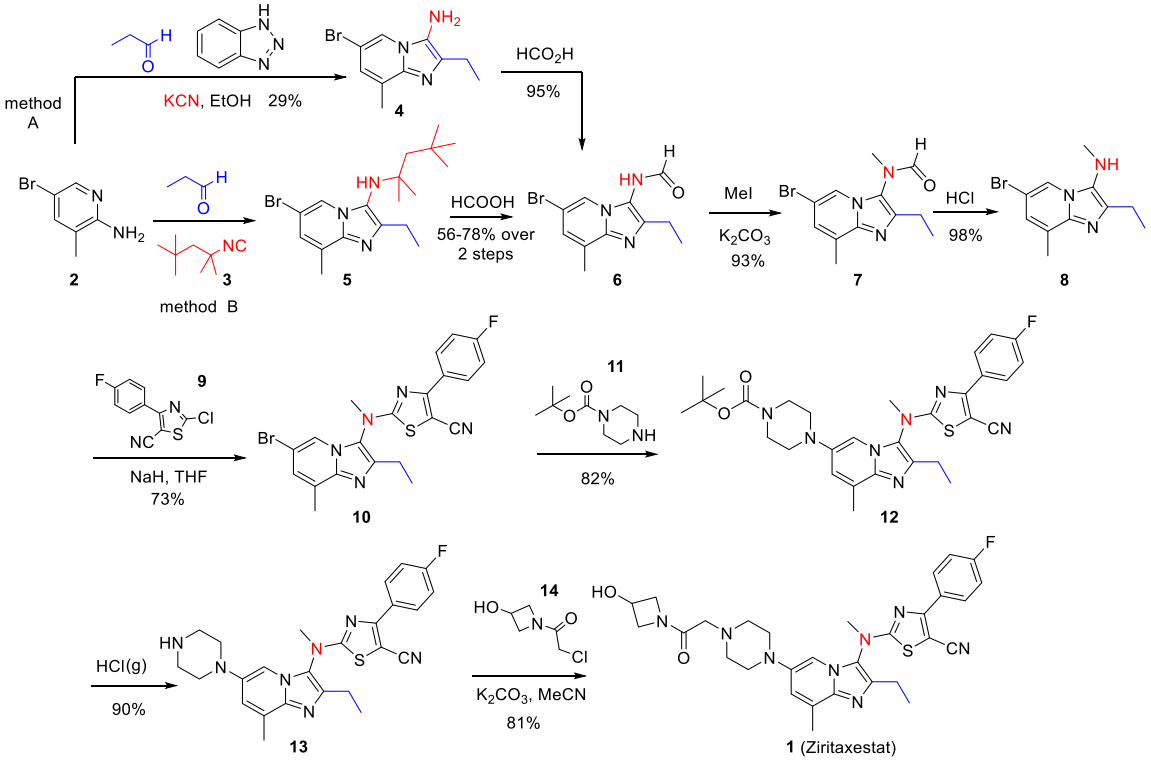
1 (Ziritaxestat)

Figure 1. Chemical structure of Ziritaxestat (GLPG-1690).

To our great knowledge, there are no researches focusing on the synthetic procedure of Ziritaxestat other than the developer Galapagos[2,4]. The reported synthetic routes from Galapagos were present in **Scheme 1**. In the course of preparing **6**, similar tricomponent cyclization protocols (method A & B) were utilized to construct the imidazo[1,2-*a*] pyridine core. According to the original method A (**1**-**4**-**6**), two obvious disadvantages were uncovered[2]. Firstly, the involvement of the hypertoxic KCN was an inevitable challenge to industrial manufacturing; more importantly, the cyclization reaction suffered from low yield (29%). Alternatively, although the **1**-**5**-**6** protocol (method B) gave an acceptable yield (56-78% in two steps), the involvement of 1,1,3,3-tetramethylbutyl isonitrile (**3**, CAS No.: 14542-93-9) was an indeed troublesome matter. It should also be stated that he isonitrile species is hypertoxic with a disgusting odour. Most of all, **3** is prohibitively expensive (5 g: $ ~170; 500 g: $ ~4,096) which could even determine the total cost of the entire synthetic route[1]. Generally, both

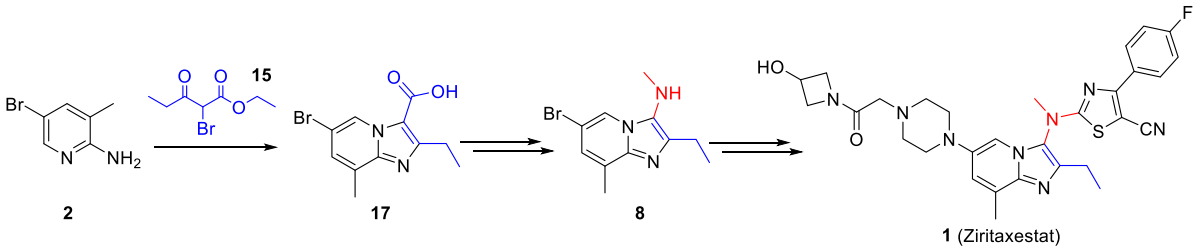
synthetic strategies mentioned above bore three independent introduction & removement of protecting groups which accounted for the frustratingly poor efficiency.

Scheme 1. Reported Synthetic Route of Ziritaxestat[1,2]



Given the conditions above, an alternative strategy should be proposed to construct the imidazo[1,2-*a*] pyridine core. Typically, the 2-aminopyridine analogs and 2-haloketone esters were often combined to furnish an alkylation/condensation bicomponent cyclization[5-9]. Also, 2-halo-1-phenacyl/alkyl pyridinium salts, pyridinium azomethine ylides, and other derivatives have been explored as precursors for construction of the scaffold[10]. The imidazopyridine nucleus have reportedly been synthesized from substituted imidazoles[11], too. The alkylation/condensation strategy turned out to feature ease of operation, low cost and high yields. As a consequence, the bifunctional 5-bromo-3-methylpyridin-2-amine (**2**) and ethyl 2-bromo-3-oxopentanoate (**15**) were utilized which efficiently brought the imidazo[1,2-a] pyridine skeleton **16**. Both materials (**2** & **15**) are highly available chemical intermediates with extremely low cost (500 g: $ <43).

Scheme 2. Schematic presentation of the preliminary synthetic route of Ziritaxestat (1)

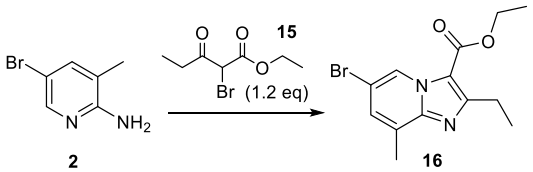


With the aid of the catalyst-free alkylation/condensation cyclization strategy, a novel synthetic protocol was forwarded that featured a typical functional group transformation (**Scheme 2**). After a routine saponification, the carboxylic acid derivative **17** was undergoing a certain rearrangement to afford the methyl amine derivative **8**. Following the literature method, **8** was supposed to smoothly bring the final product **1** as reported. Herein, the development of a practical manufacturing process for Ziritaxestat was discussed.

RESULTS AND DISCUSSION

Preparation of Key Intermediate 16 containing imidazo[1,2-*a*] pyridine skeleton. To construct the imidazo[1,2-*a*] pyridine core, the bifunctional 5-bromo-3-methylpyridin-2-amine (**2**) and ethyl 2-bromo-3-oxopentanoate (**15**) were combined to accomplish the alkylation/condensation bicomponent cyclization reaction. Firstly, EtOH was chosen as the solvent and no further additives was added to the system[12, 13] (**Table 1**, entry 1). This condition led to 87% conversion ratio of **2** and an acceptable 69.1% yield. Although the unreacted **2** could be easily recovered by treating with MeCN (**2** is insoluble in MeCN), the relatively low conversion ratio was quite unsatisfying. It was suggested in some papers that the involvement of base could drive the cyclization[14, 15], and to this end, several solvents were screened in the presence of $NaHCO_3$ or TEA (entries 4-8). To our disappointment, obviously decreased conversion ratios and yields were detected. When TEA was involved in EtOH, the reaction efficiency also descended (entry 2).

Table 1. Effects of Solvents and bases on the Bicomponent Cyclization Reaction



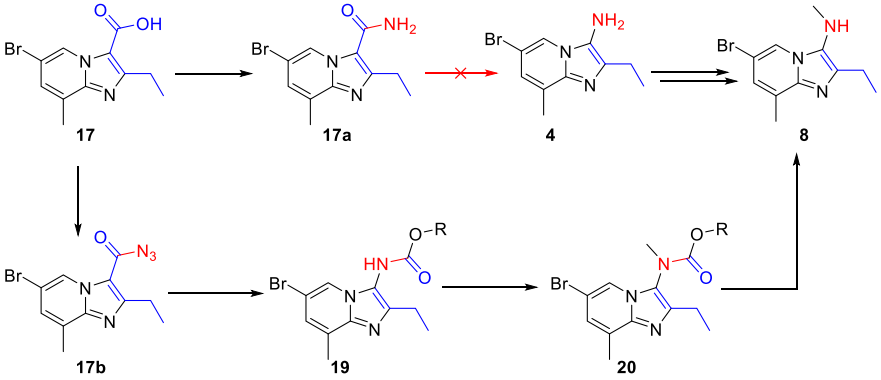
entry[a]	solvent	bases (equiv)	T (°C)	time(h)	conversion ratio (%)	yield (%)[b]
1	EtOH	-	80	5	87	69.1
2	EtOH	TEA (2)	80	10	69	58.3
3	H_2O	-	100	5	47	31.1
4	H_2O	$NaHCO_3$ (2)	100	5	53	33.1
5	DMF	$NaHCO_3$ (2)	100	5	43	25.7
6	DMF	TEA (2)	100	5	37	21.9
7	THF	$NaHCO_3$ (2)	70	5	39	25.3
8	1,4-dioxane	$NaHCO_3$ (2)	100	5	55	38.7
9	HOAc	-	100	5	73	57.7
10	*n*-BuOH	-	100	3	>99	78.5
11	*n*-BuOH	TEA (2)	100	3	91	75.3

[a]Standard conditions: **2** (0.02 mol), **15** (0.024 mol), solvent (50 mL). [b]Isolated yield after workup.

Afterwards, HOAc, *n*-BuOH and H_2O were tested successively as alternative solvents, and *n*-BuOH resulted to be the preferred one which could realize >99% conversion ratio and 78.5% yield. It should be noted that the utilization of TEA in *n*-BuOH also lowered down the reaction rate and decreased the conversion ratio to some degree (91%). Economically, most *n*-BuOH involved in the reaction was proved to be recycled conveniently through distillation.

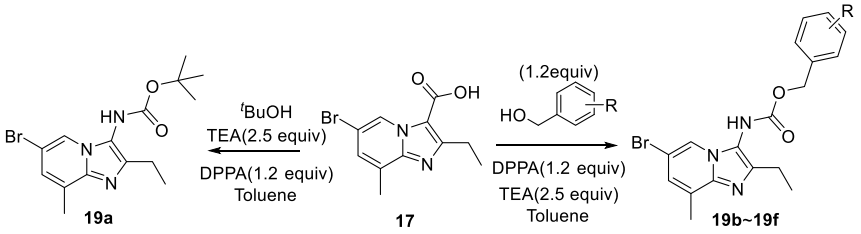
Taking *n*-BuOH as the optimal solvent (without bases), **16** could be acquired in a kilogram level (yield 77.6%). Subsequently, **16** was smoothly hydrolyzed with 4 M NaOH to result in the carboxylic acid intermediate **17** in 72.1% yield.

Scheme 3 Possible approaches for acquiring 8



Preparation of the carbamate derivative 19 through a Curtius rearrangement reaction. With the carboxylic acid **17** in hand, the following crux was the transformation of functional group from -COOH to amine (**Scheme 3**). Firstly, the amide intermediate **17a** was prepared using NH_4Cl as a synthon, however, the following Hofmann rearrangement strategy ($NaOH/Br_2$ or NaClO) was failed to bring **4**. Alternatively, the Curtius rearrangement reaction was thereby taken into consideration. Given the fact that NaN_3 was highly explosive and hard for available, the liquid material DPPA was selected for the generation of acyl azide intermediate. Various alcohols were utilized in pursuit of acquiring stable carbamate intermediates[16]. The screening details were present in **Table 2** and 3,5-dichlorobenzyl alcohol **18f** (entry 6) turned out to be the best choice with a relatively high yield (79.3%) and purity (95.4%). It should be noted that the potential risk of DPPA may be reduced by slow addition (<500 mL/h) which could allow the slow release of the N_2. In the meantime, as an organophosphate ester, the toxicity of DPPA should be carefully treated with.

Table 2. Screening of the alcohol reactant



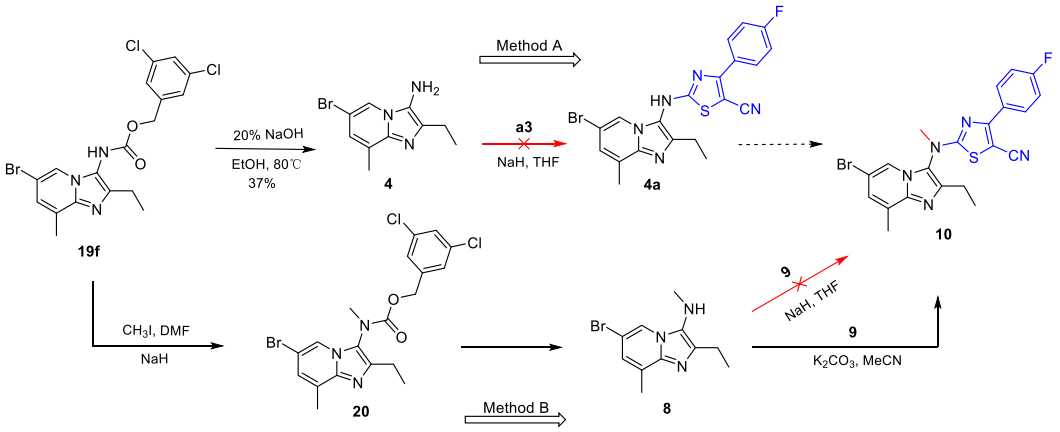
entry[a]	Ar	time(h)	desired product	yield[b]	HPLC (%)
1	-	2.5	**19a**	57.2	81.3
2	Ph-	2	**19b**	59.5	79.2
3		3	**19c**	45.7	71.8
4		2	**19d**	61.1	84.7

5		2	**19e**	67.3	87.1
6		2	**19f**	79.3	95.4

[a]Standard conditions: **17** (0.03 mol), DPPA (0.036 mol), TEA (0.075 mol), alcohols (0.036 mol), Toluene (50 mL), 110°C. [b]Isolated yield after workup.

The Exploration on the Process of Preparing 10 from 19f. After the successfully preparation of carbamate **19f**, the removement of the 3,5-diCl CBZ group was put on the agenda. In the process of preparing **10** from **19f**, there are two possible ways to get the desired product (**Scheme 4**). As an attempt, method A (**19f-4-4a-10**) was first explored. **19f** was deprotected by treating with 20% NaOH[17] to give **4** in 37% yield. But the following *N*-alkylation reaction with **9** made a complex mixture and no target product was obtained which left this method to be abandoned.

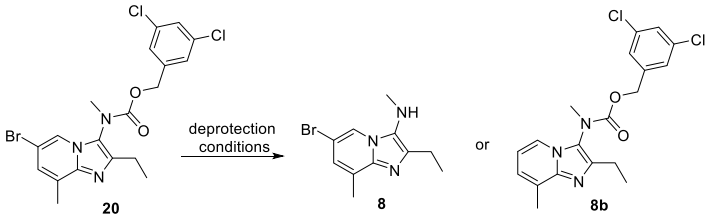
Scheme 4. Possible Preparation Sequences of 10 from 19f



Alternatively, we put our attention on the **19f-20-8-10** procedure (method B) with the aim of acquiring **10** in an efficient manner. Generally, the 3,5-diCl CBZ-protected intermediate **19f** brought great convenience for the subsequent methylation (91.1% yield) without introduction & removement of alternative protecting groups. Subsequently, we focused our attention on the deprotection of the methylated intermediate **20**.

To begin with, 20% NaOH was applied but unsatisfying conversion ratio and yield were observed (**Table 3**, entry 6). Alternatively, other general de-protection conditions were screened as depicted in **Table 3**. Firstly, the H_2 and $NiCl_2$+$NaBH_4$ protocol surprisingly led to 100% conversion[18,19]. However, to our great disappointment, the products in entries 1 and 2 resulted to be the 6-des-bromo **8b**. This was also the case when **19f** was used in a deprotection step (MW: 377.07). Next, the dioxane solution of HCl (g) and TMSI[20] (entries 3 and 4) turned out to be ineffective with no raw materials consumed. Then, Bu_4NF was utilized with 53% conversion ratio but only trace product was detected[21].

Table 3. Condition Screening of the Deprotection Reaction to Afford 8



entry [a]	deprotecting agents	solvent	temp. (°C)	conversion ratio (%)	yield (%) [b]

1	Pd/C (0.1 equiv), H_2	MeOH	60	100	0 (6-des-Br)
2	$NiCl_2$+$NaBH_4$	MeOH	25	100	0 (6-des-Br)
3	HCl(g)	1,4-dioxane	25	0	0
4	TMSI	CH_3CN	25	0	0
5	Bu_4NF	THF	66	53	<1
6	20% NaOH	EtOH	100	47	26.7
7	HBr (8 equiv)	H_2O	25	10	5.1
8	HBr (4 equiv)	HOAc	25	97	86.3
9	HBr (6 equiv)	HOAc	25	100	89.1
10	HBr (8 equiv)	HOAc	25	100	88.7

[a]Standard conditions: **20** (0.02 mol); [b]Isolated yield after workup.

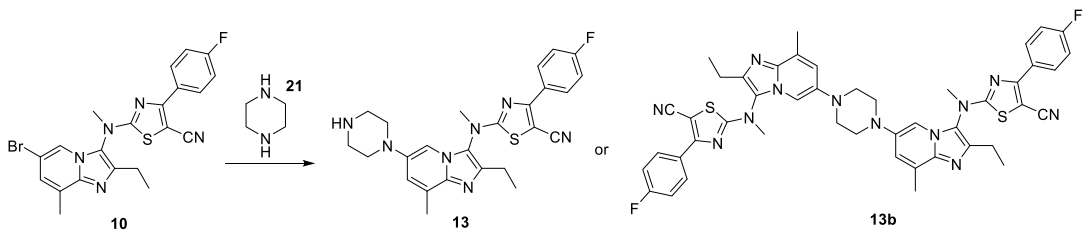
Finally, 40% HBr aqueous solution was tested with only 10% conversion ratio and 5.1% isolated yield. This methodology did provide a promising way to generate **8**. As an attempt, we altered the solution from H_2O to HOAc (33% HBr) [22a, 22b]. 4 equiv. of HBr in HOAc was firstly applied and a surprisingly 97% conversion ratio was achieved which shed a light on the finally victory in obtaining **8** efficiently. As expected, when the HBr amount was raised to 6 equiv., the raw material was completed consumed and 89.1% yield was achieved. While 8 equiv. HBr was used, the yield decreased slightly to 88.7%. Given the conditions mentioned above, 6 equiv. HBr was finally utilized for a scalable production and the yield would not decrease.

Unexpectedly, the *N*-alkylation reaction between **8** and **9** in the catalysis of NaH was proved to be unstable. With our observation, in most cases, the hydrolysis product of **9** (from -Cl to -OH, **9'**) turned out to be the main product with the effect of the strong base NaH. We alternatively utilized the K_2CO_3/MeCN system which finally achieved a robust synthetic process and the *N*-alkylation between **8** and **9** to give **10** went thoroughly with 83.1% yield in a scale-up batch.

The Preparation of 13 through Buchwald Coupling Reaction. The Buchwald coupling reaction between **10** and *N*-Boc piperazine to give **12** and the following Boc-removement with HCl (g, dioxane) went thoroughly with 78.6% overall yield in two steps[2]. But there is interest in getting rid of the Boc-removement step which could obviously relieve the laborious works. Consequently, the free piperazine was utilized directly to experience the C-N coupling with **10**. Taking the conditions used in the C-N coupling reaction between **10** and *N*-Boc piperazine as a reference, the same ingredients were applied and this system finally resulted in 83.0 % yield and only trace (<0.3%) bidentate product **13b** was detected which could be easily removed by a principle acid-base extraction.

Given the fact that the existing condition gave a relatively satisfying result, we subsequently examine the potential effects in the use of each agent point by point. Alternative P-ligands, bases and the solvents were screened separately using a variable-controlling approach. According to the results in **Table 4**, generally, the P-ligand made a great influence in the yield of **13**. According to the structure of the organophosphorus fragment in P-ligand, the ratio of aliphatic alkyl group (e.g.: the *t*-Bu in JohnPhos) may account for the discrimination in different reaction outcomes. When the three substituents on the P atom were all aromatic rings, the reaction systems generally brought unsatisfying results (entries 2, 3). In terms of the base, Cs_2CO_3 performed worse than ^{t}BuONa and ^{t}BuOK (entries 1, 4 and 5). Alternatively, the influence of solvents was slightly smaller (entries 1, 4, 5, 6 and 7).

Table 4. Condition Checking of the Buchwald Coupling Reaction



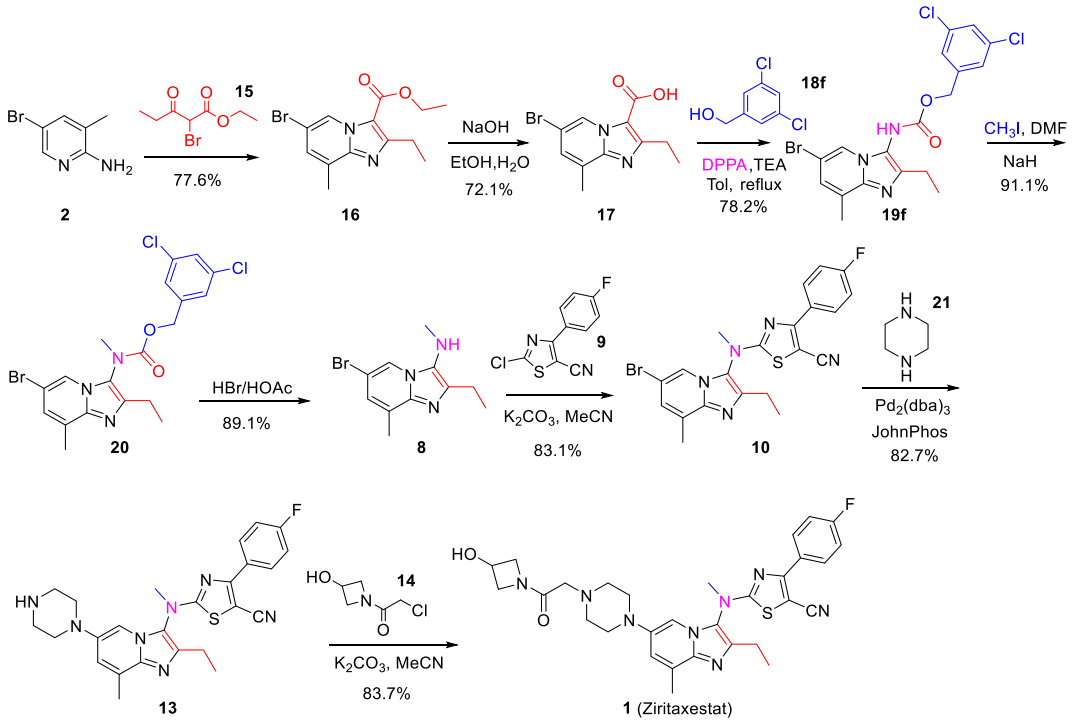
entry[a]	catalysts	P-ligand	base	solvent	temp. (℃)	**13b** (%)	yield (%) [b]
1	$Pd_2(dba)_3$	JohnPhos	^tBuONa	toluene	110	<0.3	83.0
2	$Pd_2(dba)_3$	XantPhos	^tBuONa	toluene	110	<0.1	31.7
3	$Pd_2(dba)_3$	BINAP	^tBuONa	toluene	110	<0.1	22.3
4	$Pd_2(dba)_3$	JohnPhos	^tBuOK	toluene	110	<0.3	79.5
5	$Pd_2(dba)_3$	JohnPhos	Cs_2CO_3	toluene	110	<0.3	69.3
6	$Pd_2(dba)_3$	JohnPhos	^tBuONa	1,4-dioxane	102	<0.3	63.2
7	$Pd_2(dba)_3$	JohnPhos	^tBuONa	DME	85	<0.3	67.1

[a]Standard conditions: **10** (0.03 mol), **21** (0.06 mol), catalysts (0.0015 mol), P-ligand (0.003 mol), base (0.06 mol), solvent (40 mL). [b]Isolated yield after workup.

To the end, this screening verified that the original condition turned out to be optimal and 82.7% yield could be achieved in a 300-400 g scale.

Preparation of Desired Product 1. With the efficient preparation of the piperazine derivative **13**, the final *N*-alkylation reaction with **14** implemented smoothly in MeCN under the catalysis of K_2CO_3. After a principle acid-base extraction, the final product Ziritaxestat was obtained in 83.7% yield with 99.60% purity without further complex purification.

Scheme 5. Novel Synthetic Route to Ziritaxestat



In this end, a novel 8-step synthetic protocol was established that featured a typical catalyst-free alkylation/condensation strategy and an efficient functional group transformation (**Scheme 5**). The carboxylic acid derivative **17** was undergoing a Curtius rearrangement followed by condensation with 3,5-dichlorobenzyl alcohol **18f** to afford the carbamate **19f**. The carbamate intermediate **19f** offered a great convenience for the subsequent methylation with ease of operation. After a dedicated condition screening campaign, the methylated carbamate **20** was readily deprotected by treatment with HBr/HOAc to give **8** as the substrate in a K_2CO_3 catalyzed *N*-alkylation. The *N*-alkylation product **10** was ready for a Buchwald coupling reaction directly with piperazine to furnish **13** without the involvement of Boc-fragment. Finally, the desired product **1** was obtained through a *N*-alkylation reaction between **13** and **14**.

CONCLUSION

A novel synthetic strategy was exploited to resolve plenty of challenges to the preparation of Ziritaxestat (**1**) and 20.4% overall yield was ultimately achieved. The new route was characterized by a catalyst-free bicomponent cyclization which creatively avoided the utilization of the hypertoxic KCN or the hypertoxic & costly isonitrile **3**. Surprisingly, the implementation of Curtius rearrangement perfectly realized the functionality transformation from -COOH to amine and offered a great convenience for the following methylation. Subsequently, the base alteration from NaH to K_2CO_3 in the preparing of **10** generally furnished a safer and more stable process. More importantly, laborious protecting group introduction & deblocking procedures were obviously relieved. From a commercial perspective, with the advantages of mild experimental conditions, ease of operation, and cost-effective features, the present work was proved to be quite suitable for large-scale preparation.

EXPERIMENTAL SECTION

General Information. All commercially available materials and solvents were used directly without further purification unless otherwise noted. All melting points were obtained on a Büchi Melting Point B-540 apparatus and were uncorrected. TLC analyses were performed on silica gel (200–300 mesh) from Qingdao Ocean Chemicals (Qingdao, Shandong, China). Mass spectra (MS) were taken in Electrospray ionization (ESI) mode on Agilent 1100 LC–MS (Agilent, Palo Alto, CA, USA) and a mixture of MeCN/H_2O (6:4) was utilized as the eluting system.

^{1}H and ^{13}C NMR spectra were recorded with a Bruker ARX-400 spectrometer (Bruker Bioscience, Billerica, MA, USA) using TMS as an internal standard. The reaction process, purity of Ziritaxestat and its intermediates was determined by HPLC using a Schimadzu LC-10ATVP series instrument. The HPLC analysis data was reported in relative area % and was not adjusted to weight %. The ingredients **9** and **14** were prepared according to the original procedures and therefore were not discussed in the text.

Ethyl 6-bromo-2-ethyl-8-methylimidazo[1,2-*a*] pyridine-3-carboxylate (16). To a 50 L reactor was added *n*-butanol (12 L), **15** (2.66 kg, 12 mol, 1.2 eq) and **2** (1.86 kg, 10 mol, 1.0 eq). The reaction mixture was carefully warmed to 100 ℃ and kept for 3 h until <1% **2** remained by HPLC. The system was cooled to 25 ℃, the solvent *n*-butanol was recycled by distillation. The residue was charged MeCN (2 L) after which the trace quantity of **2** was collected by filtration. Finally, the solvent was removed under a vacuum (maximum temperature 50 ℃) to give a white solid **16** in 77.6% yield (2.41 kg). HPLC(%): 99.16%, MS: 311.32$[M+1]^+$, 313.36$[M+3]^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (s, 1H), 7.55 (s, 1H), 4.37 (q, J = 7.1 Hz, 2H), 3.01 (q, J = 7.5 Hz, 2H), 2.52 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H), 1.26 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 160.94, 157.11, 145.49, 129.99, 128.29, 125.56, 112.44, 108.41, 60.89, 23.38, 16.71, 14.66, 13.90.

6-bromo-2-ethyl-8-methylimidazo[1,2-*a*]pyridine-3-carboxylic acid (17). To a 50 L reactor were charged **16** (1.55 kg, 5 mol) and ethanol (4.2 L). The material was agitated into a solution. To the mixture was introduced 4 N NaOH solution (6 L, 24 mol). After stirring at 60 ℃ for 2 h, the reaction was finished as determined by HPLC analysis. The solvent was removed under vacuum and the residue was charged 6 L H_2O and stirred to give a homogenous solution. The pH of the solution was adjusted to 2 with 2N HCl solution. A light yellow solid **17** was obtained through filtration in 72.1% yield (1.02 kg). HPLC(%): 99.49%, MS: 281.38$[M-1]^-$, ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.28 (s, 1H), 7.52 (s, 1H), 3.02 (dd, J = 14.7, 7.2 Hz, 2H), 2.53 (s, 3H), 1.26 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 162.48, 156.81, 145.24, 129.62, 128.06, 125.64, 112.93, 108.08, 23.03, 16.65, 13.99.

3,5-dichlorobenzyl (6-bromo-2-ethyl-8-methylimidazo[1,2-*a*]pyridin-3-yl)carbamate (19f). To a 20 L reactor purged with nitrogen was added **17** (846.2 g, 3 mol, 1 eq), toluene (5.2 L), TEA (758.3 g, 7.5 mol, 2.5 eq) and DPPA (990 g, 3.6 mol, 1.2 eq). Caution! The DPPA should be added slowly (<500 mL/h) under stirring. The resulting slurry was warmed to reflux for 30 min before cooling to 30 ℃. **18f** (638 g, 3.6 mol, 1.2 eq) was slowly added and the mixture was heated to reflux for 2 h as determined by HPLC analysis. The solvent was concentrated under vacuum followed by the introduction of water (3 L) and stirred. The crude product (cake) was collected through filtration and MeCN was added subsequently. The resulting slurry was stirred for 1 h and filtered, rinsed with MeCN (3*500 mL), dried to provide white solid **19f** in 78.2% yield (1.067 kg). HPLC(%): 95.21%, MS: 456.40 $[M+1]^+$, 458.41 $[M+3]^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.59 (s, 1H), 8.27 (s, 1H), 7.61 (s, 1H), 7.55 (s, 2H), 7.29 (s, 1H), 5.19 (s, 2H), 2.63 (q, J = 7.5 Hz, 3H), 2.48 (s, 3H), 1.20 (t, J = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 154.97, 142.02, 141.24, 140.19, 134.57(2C), 127.97(2C), 127.75, 126.68(2C), 121.53, 116.43, 106.65, 65.45, 20.22, 16.25, 13.73.

3,5-dichlorobenzyl (6-bromo-2-ethyl-8-methylimidazo[1,2-*a*]pyridin-3-yl)(methyl)carbamate (20). To a 20 L reactor purged with nitrogen was added **19f** (846.7 kg, 1.6 mol, 1 eq), DMF (5.3 L). The system was precooled to 0 ℃ and NaH (164 g, 4 mol, 2.5 eq) was added slowly. After a 1 h period of stirring, CH_3I (458 g, 3.2 mol, 2 eq) was added to the system and slowly warmed to 25 ℃ and held for 2 h. The mixture was cooled to 0 ℃ and slowly added to a saturated solution of NH_4Cl (10 L). The resulting slurry was stirred for 1 h, filtered, rinsed with water, dried in vacuum to result the light yellow solid **20** in 91.1% yield (794.5 g). HPLC(%): 98.47%, MS: 470.38 $[M+1]^+$, 472.40 $[M+3]^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 (s, 1H), 7.61 (s, 0.26H), 7.56 (s, 0.49H), 7.50 (s, 0.71H), 7.26 (s, 1H), 7.12 (s, 1.44H), 5.22 (s, 0.59H), 5.06 (s, 1.49H), 3.28 (s, 0.67H), 3.22 (s, 2.43H), 2.65 – 2.56 (m, 2H), 2.47 (s, 3H), 1.18 (t, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ 154.98, 142.27, 141.09, 140.62, 134.45, 128.05, 127.89, 126.64(2C), 126.59, 126.28, 121.46, 120.70, 106.83, 65.65, 37.33, 20.40, 16.24, 13.51.

6-bromo-2-ethyl-N,8-dimethylimidazo[1,2-*a*]pyridin-3-amine (8). To a 10 L reactor was charged **20** (0.656 kg, 1.4 mol, 1 eq) and HBr/HOAc (33%, 2.04 kg, 8.4 mol, 6 eq). The material was stirred at 20 ℃ for 3 h with HPLC indicating the finishing point. The mixture was added 5 L water and stirred for 30 min to give a homogenous solution. The resulting solution was extracted with EtOAc (2 L) and the organic layer was discarded. The aqueous layer was adjusted to pH =10 with 2 N NaOH solution. The resulting material was extracted with EtOAc (3×1500 mL) and the combined organic portions was concentrated under vacuum to give the light yellow solid **8** (332.7 g) in 89.1% yield. HPLC(%): 97.27%, MS: 268.0 $[M+1]^+$, 270.0 $[M+3]^+$, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.03 (s, 1H), 3.65 (m, 1H), 2.85 – 2.78 (q, 2H), 2.81 (s, 3H), 2.59 (s, 3H), 1.34 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.21, 129.72, 127.48, 127.38, 126.28, 120.41, 106.72, 35.69, 20.33, 16.56, 14.54.

2-((6-bromo-2-ethyl-8-methylimidazo[1,2-*a*]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)-thiazole-5-carbonitrile (10). To a 5 L reactor was added **8** (267.3 g, 1.0 mol, 1 eq), **9** (100.1 g, 1.2 mol, 1.2 eq), K_2CO_3 (346.7 g, 2.5 mol, 2.5 eq) and anhydrous MeCN (1.6 L). The mixture was refluxed for 3 h with the indicating of HPLC analysis. The mixture was cooled to 20 ℃ and the solvent were concentrated in vacuum. The crude product was charged with 1.2 L methanol and the yellow product **10** was obtained through filtration in 83.1% yield (389.8 g). HPLC(%): 97.48%, MS: 470.69 $[M+1]^+$, 472.71 $[M+3]^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.07 (dd, *J* = 8.1, 5.6 Hz, 2H), 7.42 (t, *J* = 8.9 Hz, 2H), 7.38 (s, 1H), 3.59 (s, 3H), 2.66 (q, *J* = 7.6 Hz, 2H), 2.52 (s, 3H), 1.25 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.63, 164.76, 162.29, 160.70, 144.09, 141.74, 130.53, 130.45, 129.31, 128.57, 127.96, 122.42, 121.78, 116.69, 116.47, 114.75, 107.51, 87.99, 20.63, 16.28, 13.37.

2-((2-ethyl-8-methyl-6-(piperazin-1-yl)imidazo[1,2-*a*]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazole-5-carbonitrile (13). To a 5 L reactor purged with nitrogen was added **10** (375.2 g, 0.8 mol), dry toluene (3 L), piperazine (104.2 g, 1.2 mol), *t*-BuONa (154.3 g, 1.6 mol), JohnPhos (24.2 g, 0.08 mol) and $Pd_2(dba)_3$ (22.1 g, 0.024 mol). The mixture was stirred to form a homogenous slurry and heated at 110℃ for 2 h. When the end point comes, the mixture was filtered through a plug of silica gel, washed with EtOAc (500 mL). The filtrate was concentrated and the resulting crude product was charged with *n*-hexane (2 L), stirred for 2 h, filtered, and the filtrate was concentrated in vacuum to afford the faint yellow solid **13** in 82.7% yield (314.3 g). HPLC(%): 99.70%, MS:476.62 $[M+1]^+$, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 2H), 7.28 (s, 1H), 7.11 (s,2H), 7.05 – 6.90 (m, 1H), 4.70 (s, 1H), 3.59 (s, 3H), 3.31 (m, 8H), 2.75 (s, 2H), 2.59 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 173.07, 162.25, 160.58, 142.71, 141.25, 140.01, 130.51, 130.42, 130.04, 129.36, 126.74, 122.45, 120.84, 116.63, 116.42, 114.85, 105.35, 87.75, 50.88(2C), 45.80(2C), 20.70, 16.67, 13.57.

Ziritaxestat; 2-((2-ethyl-6-(4-(2-(3-hydroxyazetidin-1-yl)-2-oxoethyl)piperazin-1-yl)-8-methylimidazo[1,2-*a*]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazole-5-carbonitrile (1). To a 5 L reactor was added **13** (237.8 g, 0.5 mol), MeCN (1.5 L), K_2CO_3 (172.5 g, 1.25 mol). The mixture was heated to reflux and held for 3 h. When the reaction finished as indicated by HPLC, K_2CO_3 was removed through filtration after cooling and the filtrate was concentrated in vacuum. Subsequently, the residue was dissolved with EtOAc (2L) and extracted with 4M HCl (2×1.5 L). The aqueous phase was combined and the pH was adjusted to 10 with 6 N NaOH. The resulting turbid solution was extracted with EtOAc (2×1.5L) and the organic phase was washed with brine, dried over Na_2SO_4, concentrated in vacuum to give the final product Ziritaxestat as a faint yellow solid in 83.7% yield (246.2 g). HPLC(%): 99.60%, MS: 589.92 $[M+1]^+$, 611.94 $[M+23]^+$, 587.93 $[M-1]^-$, ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.11 (dd, *J* = 8.5, 5.6 Hz, 2H), 7.43 (t, *J* = 8.8 Hz, 2H), 7.24 (s, 1H), 5.73 (s, 1H), 4.44 (s, 1H), 4.38 – 4.31 (m, 1H), 4.11 – 4.01 (m, 1H), 3.91 (dd, *J* = 9.2, 4.2 Hz, 1H), 3.65 – 3.59 (m, 1H), 3.58 (s, 3H), 3.52 (d, *J* = 8.3 Hz, 1H), 3.13 (s, 4H), 2.73 (s, 4H), 2.62 (dd, *J* = 15.1, 7.5 Hz, 2H), 2.48 (s, 3H), 1.23 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 173.05, 164.73, 162.25, 160.58, 142.74, 139.95, 130.50, 130.42, 130.04, 129.35, 129.33, 126.82, 122.53, 120.89, 116.65, 116.43, 114.86, 105.94, 87.75, 60.73 (2C), 60.55, 58.15(2C), 52.61(2C), 49.15, 20.66, 16.66, 13.53.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

Structural characterization Spectra (^{1}H and ^{13}C NMR spectra, MS spectra), HPLC purity spectra of **1** and involving intermediates or impurities.

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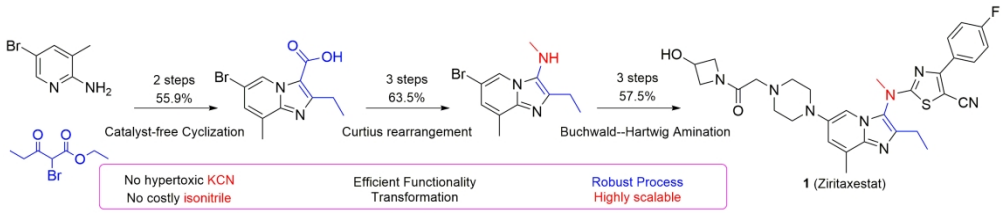

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