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Practical Asymmetric Hydrogenation-Based Synthesis of a Class-Selective Histone Deacetylase Inhibitor

Junli Chen,[†,‡] Tianqi Chen,[⊥] Qiupeng Hu,[⊥] Kurt Püntener,[§] Yi Ren,[‡] Jin She,[‡] Zhengming Du,*[,‡] and Michelangelo Scalone*[,§,∥]

[†]Institute of Drug Discovery and Development, East China Normal University, 3663 North Zhongshan Road, Shanghai 200062, China

[‡]Roche Innovation Center Shanghai, Process Research & Synthesis, 720 Cailun Road, Building 5, Pudong, Shanghai, 201203, China

[§]Roche Innovation Center Basel, Process Research & Synthesis, Grenzacherstrasse 124, CH-4070 Basel, Switzerland

[∥]F. Hoffmann-La Roche Ltd., Pharma Technical Development, Process Research & Development, Grenzacherstrasse 124, CH-4070 Basel, Switzerland

[⊥]School of Pharmacy, East China University of Science and Technology, Shanghai 200237, China

Supporting Information

ABSTRACT: Two syntheses of the class-selective histone deacetylase inhibitor **1** are reported. In the first, eight-step entailing synthesis, the key transformations were a highly efficient [3 + 2] dipolar cycloaddition affording *trans-rac*-**5** and its resolution. In the second, asymmetric approach, the key steps were a highly selective asymmetric hydrogenation to produce the *cis*-(*S*,*S*)-3,4-disubstituted pyrrolidine **18** followed by an amide formation with simultaneous chiral inversion of the carboxy stereocenter to generate the key intermediate *trans*-(*R*,*S*)-3,4-disubstituted pyrrolidine **19**. The overall yield increased from ∼6% for the resolution approach to ∼26% for the enantioselective approach.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a leading cause of cancer deaths worldwide. The incidence of hepatocellular carcinoma is highest in Asia and Africa, where the endemic high prevalence of hepatitis B and hepatitis C strongly predisposes to the development of chronic liver disease and subsequent development of hepatocellular carcinoma.[1] Histone deacetylase (HDAC) is recognized as one of the promising targets for cancer treatment as many HDAC inhibitors have entered clinical trials for both solid and liquid tumors.[2] With respect to HDACs as potential targets for HCC treatment, HDAC1 in particular has been found to be significantly overexpressed in HCC patient tumor samples, and its expression in this context is negatively correlated to overall survival.[3] Our medicinal chemists had discovered the class-selective histone deacetylase (HDAC) inhibitor **1**, which has excellent drug-like properties while maintaining selectivity toward the class I HDAC family with particular potency against HDAC1.[4] The process development described in this paper was conducted to provide API in a quality which would allow to define safety and pharmacological properties in the preclinical studies.

The original synthesis of **1** proceeded through the racemic pyrrolidine **5** which was resolved by chiral chromatography (Figure 1, upper route).[4] A SFC chiral separation provided indeed enough material for preliminary investigations but was clearly unsuitable for larger scale production. Notably, the synthesis suffered from low yield and safety issues in the [3 + 2] dipolar cycloaddition. As a result, the initial process trouble shooting work focused both on the optimization of the [3 + 2] dipolar cycloaddition step and on finding a suitable resolving agent to obtain enantiomerically pure (*R*,*S*)-**5** without need for chromatography. In spite of the improvements, however, the loss of ca. 60% of the material during the resolution step and the very low overall yield (6.3%) rendered this synthesis not acceptable.

Therefore, a new, more efficient enantioselective sequence was developed (Figure 1, lower route) which contained the formation of the dihydropyrrole **17**, its asymmetric hydrogenation, and the subsequent coupling reaction with simultaneous inversion of the configuration of the adjacent center on the pyrrolidine ring. Gratifyingly, the overall yield of this new synthesis increased to 25.6%. Herein we report both routes to **1** and address the key process issues.

RESULTS AND DISCUSSION

Classical Resolution Approach to HDAC Inhibitor 1. (*E*)-3-(4-Bromophenyl) acrylic acid ethyl ester **4**, the first intermediate of the classical resolution synthesis (Scheme 1), is not commercially available in bulk amounts. For its synthesis the use of various bases (e.g., KO*t*Bu or NaH,[5] DBU, or Verkade's bicyclic triaminophosphine[6]) as well as various methods such as solvent-free reaction using high-speed ball milling[7] or solid−liquid phase transfer with sodium hydroxide[8] have been reported.

We have conducted the reaction using aqueous sodium hydroxide in a THF/water mixture at 2−15 °C. The phosphate byproduct was easily removed by a water extraction. On a 50 kg scale, the crude product **4** was used directly in next step as an

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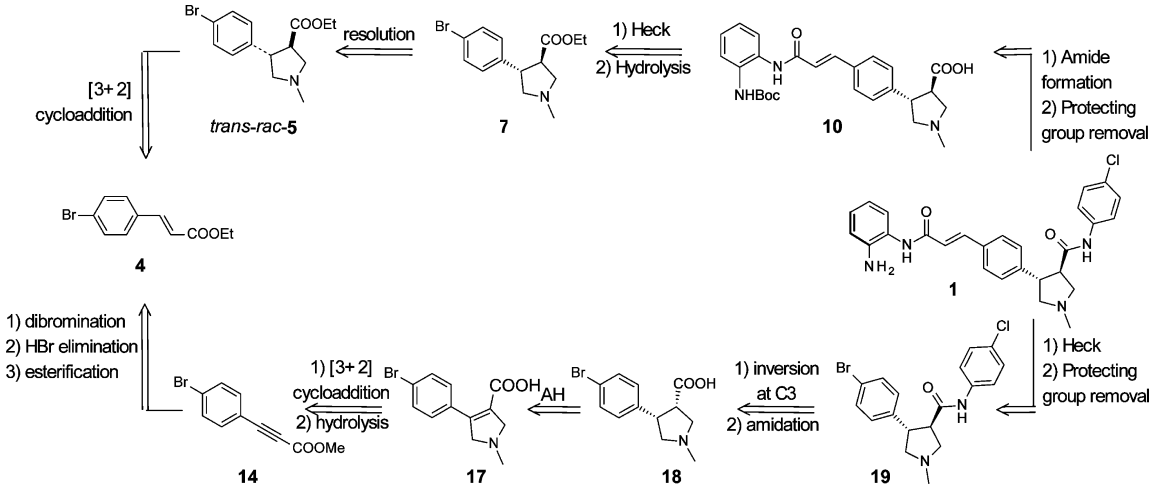

Figure 1. Classical resolution vs asymmetric hydrogenation route.

Scheme 1. Classical resolution-based synthesis of 1

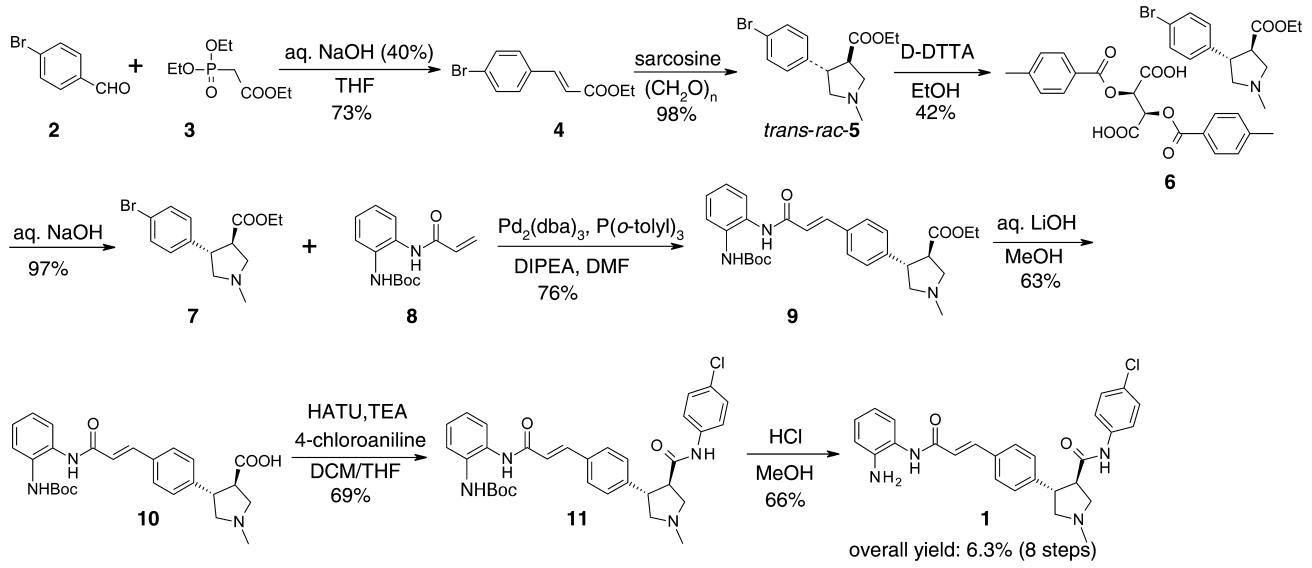

Table 1. Effect of solvents and additives in the [3 + 2] dipolar cycloaddition[a]

entry	sarcosine (equiv)	$(CH_2O)_n$ (equiv)	solvent[b]	additive[c] (amount)	T (°C)	ratio **5**/**4**[d]	isolated yield of *rac*-**5** [%]	scale-up issues[e]
1	4.5	20	toluene		110	40/60	43	Y
2	6.8	30	cyclohexane		80	n.a.	35	Y
3[f]	4.8	16	xylenes		130	57/43		Y
4	4.8	16	chlorobenzene		130	54/45		Y
5	4.8	16	THF		66	38/62		Y
6	4.8	16	2-Me-THF		80	79/21		Y
7	4.8	16	1,4-dioxane		100	59/41		Y
8	4.8	16	isopropanol		80	11/89		Y
9	4.8	16	DMPU		108	31/69		N
10	4.8	16	DMEU		108	61/39		N
11	4.8	16	DMF		85	56/44		N
12	4.8	16	NMP		85	75/25		N
13	4.5	20	toluene	TsOH	110	38/62	70%	Y
14	4.8	16	DMF	AcOH	85	47/53	42%	N
15	4.8	16	NMP	TsOH	85	43/57	43%	N
16	2.3	2.0	NMP		110	>99/1	98%	N

[a]Conditions: 5−10 g scale; molar equivalents relative to **4**; sarcosine and paraformaldehyde were added in 2−4 portions for entry **1**−**14** and all at once for entry **15**. [b]DMPU: 1,3-dimethyl-propyleneurea; DMEU: 1,3-dimethyl-ethyleneurea. [c]5 wt %. [d]Ratio of HPLC A% normalized to **4** and **5**. [e]The scale-up issues include stirring and clogging of the condenser. [f]Water was removed azeotropically.

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easy-to-handle NMP solution (118 kg with 17.7 wt % concentration) without further purification.

The [3 + 2] dipolar cycloaddition reaction of *N*-methyl glycine and paraformaldehyde (via in situ azomethine-ylide formation) with alkenes to form *N*-methyl pyrrolidines had been reported to proceed with 46% yield.[9] The reaction had originally been carried out in refluxing toluene. However, this procedure gave a biphasic mixture containing a large amount of sticky material which adhered to the reactor wall and the agitator (Table 1, entry 1). Moreover, formaldehyde sublimed and accumulated as a solid on the condenser walls. As a consequence, a large excess of paraformaldehyde was needed to drive the reaction to completion. Unfortunately, on scale-up the condenser was clogged and had to be replaced. To solve this safety issue, alternative solvents such as cyclohexane, xylene, chlorobenzene, 2-Me-THF, THF, dioxane, and IPA were tested but did not improve this aspect (Table 1, entries 2−8). Fortunately, no blocking issues were observed in DMPU, DMF, and NMP as solvents (Table 1, entries 9−12). Moreover, attempts to lower the reaction temperature by using an acid as an additive failed (Table 1, entries 13−15).[10] Finally, running the reaction in NMP at 110 °C without an additive led to high conversion in the presence of only a small excess of paraformaldehyde and sarcosine (Table 1, entry 16). With the safety issue solved, the reaction was run in a 1000 L reactor with excellent results (98% yield) which compare very favorably with those reported previously for the same step.[4] As already in the previous step, *trans-rac*-**5** was not isolated but telescoped as an ethanolic solution directly into the next step.

The enantioselective enzymatic hydrolysis of esters using the food-grade subtilisin Carlsberg (alcalase) has been reported.[11] We investigated its use in the selective hydrolysis of racemic **5**. Stirring the reaction mixture in a K_2HPO_4/KH_2PO_4 buffer (pH = 7.8−8.2) at 35−40 °C for ca. 20 h led to complete hydrolysis of the undesired (*S*,*R*) enantiomer. After workup, the ee value of (*R*,*S*)-**7** was up to 98.5%, but the isolated yield (30%) and the purity of crude **7** (79% as sticky oil) were unsatisfactory.[12] The purification could be achieved only by column chromatography which again is not a preferred method on the production scale.

Finally, the classical chemical resolution offered a viable alternative. After optimization of the crystallization conditions, the salt of **5** with D-DTTA afforded pure ester **7** in 99.6% ee.

For the subsequent Heck coupling of (*R*,*S*)-**7** with acrylamide **8**, various palladium catalysts and bases were tested (Table 2). As a result, the combination of $Pd_2(dba)_3$ and P(*o*-tolyl)$_3$ gave the most effective catalyst (Table 2, entry 7). The best base was DIPEA (Table 2, entry 8). Sodium ethoxide and DBU (Table 2, entries 9 and 10) brought about the decomposition of both **7** and **9** (Table 2, entries 9 and 10). Inorganic bases such as Cs_2CO_3 or $NaHCO_3$ (Table 2, entries 11 and 12) led to low conversion. The production of **9** in the pilot plant scale was carried out under the condition of entry 8. The crude product **9** (3.43 kg, 65.2 wt %) was not isolated but telescoped directly to the subsequent hydrolysis.

The hydrolysis of ester **9** proceeded uneventfully with aqueous LiOH in methanol at room temperature. However, after removing the solvent and adjusting the pH to 6.5−7.0 with 2 N HCl, the acid separated as a sticky solid. Prolonged stirring did not help form a crystalline solid. A solvent screening showed that acid **10** is poorly soluble in most organic solvents. Finally, *n*-butanol was identified to be a good cosolvent to be added before the neutralization of the reaction mixture. Thus, the acid **10** was extracted into the *n*-butanol layer when the pH reached 6.5−7.0. After removal of *n*-butanol as an azeotrope with toluene, the addition of MTBE led to the precipitation of **10** which was isolated easily by filtration. The crude was further purified by a reslurry in methanol.

Table 2. Optimization of the Heck coupling of 7 and 8[a]

entry	catalyst	base	time (h)	ratio **9**/**7** [%][d]
1	$Pd(PPh_3)_2Cl_2$	TEA	18	43/10
2	$Pd(OAc)_2/PPh_3$ (1:3)	TEA	18	19/23
3	$Pd(PPh_3)_4$	TEA	18	35/14
4	$Pd_2(dba)_3/PPh_3$ (1:5)	TEA	18	33/10
5	$Pd_2(dba)_3$/P(*t*-Bu)$_3$ (1:5)	TEA	18	60/10
6[b]	$Pd_2(dba)_3$/P(*n*-Bu)$_3$ (1:5)	TEA	18	no product
7	$Pd_2(dba)_3$/P(*o*-tolyl)$_3$ (1:2)	TEA	5	85/2
8	$Pd_2(dba)_3$/P(*o*-tolyl)$_3$ (1:2)	DIPEA	5	91/0
9[c]	$Pd_2(dba)_3$/P(*o*-tolyl)$_3$ (1:2)	EtONa	2	dec.
10[c]	$Pd_2(dba)_3$/P(*o*-tolyl)$_3$ (1:2)	DBU	2	dec.
11[b]	$Pd_2(dba)_3$/P(*o*-tolyl)$_3$ (1:2)	Cs_2CO_3	5	no product
12	$Pd_2(dba)_3$/P(*o*-tolyl)$_3$ (1:2)	$NaHCO_3$	5	59/5

[a]Conditions: 1 g scale; DMF as solvent; 0.02 equiv of palladium precursor, 2.5 equiv of base, 1.05 equiv of **8**, 110 °C. [b]For entries 6 and 11, a part of **7** decomposed, but **9** was not found. [c]Decomposition of **7** and **9** was observed. [d]Determined by HPLC (A%).

For the amide formation reaction, coupling reagents HATU, T3P, EDC/HOBt, diethyl chlorophosphate, DIC/HOBT, and isobutyl chloroformate were tested. HATU gave the best result when the amide formation was run in a mixture of DCM/THF (14.4/1 wt/wt).[13] Crystallization from acetonitrile afforded amide **11** in 69% yield with 96.6% purity.

The last step of the sequence, the removal of the Boc protecting group, was performed in a solution of HCl in methanol (10 mol/L) at 0−5 °C for 1 h. The concentration of the methanolic solution and addition of aqueous sodium bicarbonate led to the precipitation of **1** which could be easily isolated by filtration. After drying, the solid was suspended in a methanol/water mixture to give the desired polymorph B. With this synthesis, 913 g of API **1** was prepared.

Asymmetric Hydrogenation-Based Synthesis of 1. In order to improve the supply efficiency, alternative asymmetric syntheses were considered. Various enantioselective entries into *trans*-3,4-disubstituted pyrrolidines had been reported. The [3 + 2] dipolar cycloaddition using chiral auxiliaries proceeded usually with moderate diastereoselectivity.[14] The rhodium-catalyzed asymmetric 1,4-arylation of pyrrolines with arylboronic acids provided *trans*-3,4-disubstituted pyrrolidines in good enantioselectivity but modest yields.[15] The enantioselective nitrile anion cyclization had been reported to form 3,4-disubstituted pyrrolidines efficiently.[16] In our hands, however, this method failed to form the desired product. Finally, we decided to use an approach which had been used previously at Roche to prepare similarly substituted pyrrolidines in a highly enantioselective manner.[17] Accordingly, an asymmetric hydrogenation-based synthesis of **1** was conceived (Scheme 2).

For the synthesis of the asymmetric hydrogenation substrate **17**, the cynnamic ester **4** was chosen as starting material.[18] Dibromination of **4** using bromine in tetrachloromethane or organocatalysis have been reported.[19] We have run this reaction simply in DCM at room temperature and obtained the 2,3-dibromoester **12** as a solid in 96% yield. In the subsequent steps, the double HBr elimination followed by the esterification

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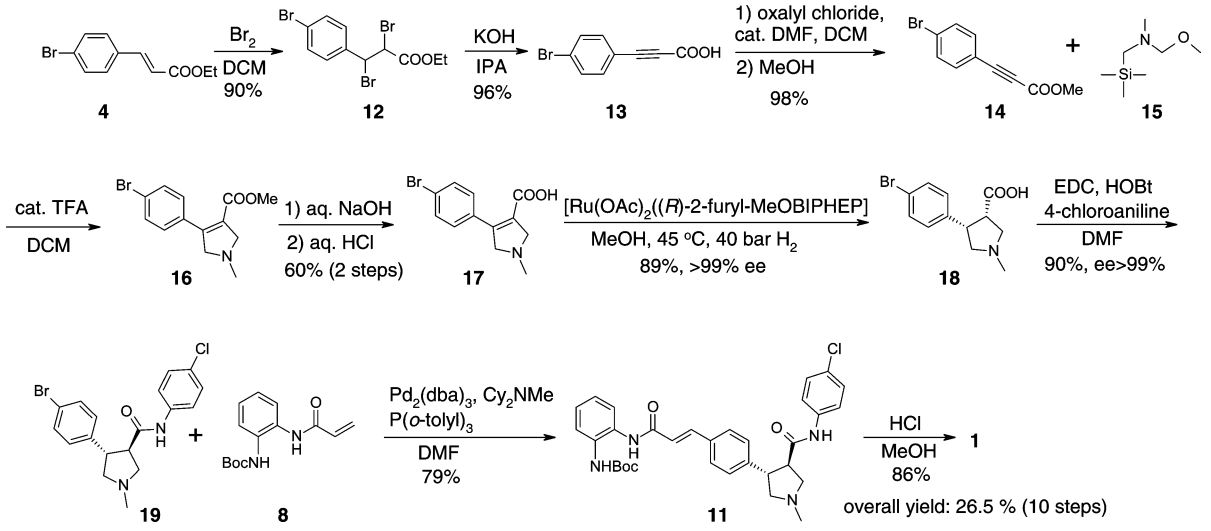
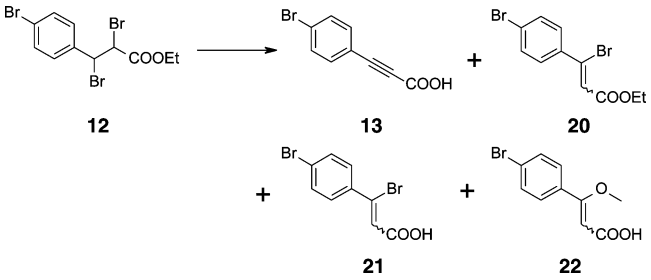
Scheme 2. Asymmetric hydrogenation-based synthesis of 1



of the intermediate acid **13** provided the acetylenic ester **14**. The double HBr elimination reaction was quite challenging due to the formation of various impurities (Scheme 3). The product

Scheme 3. Alkyne acid 13 formation by double hydrogen bromide elimination/hydrolysis

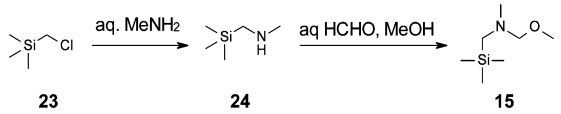


was a mixture of *Z*- and *E*-3-bromo intermediates (**20**) when TEA was used as a base. The reactions using NaH in toluene and NaO*t*Bu in 2-Me-THF gave a mixture of **13** and **21**. In methanol, ethanol, or mixed solvents such as ethanol/water and IPA/water, the desired acid **13** was formed together with the two major impurities **21** and **22**.[20] Finally, a clean reaction was obtained in refluxing isopropanol as a solvent and KOH as a base. After 3 h the solvent was partially removed and replaced with water. A solid precipitated when the pH was adjusted to 2 by addition of conc. HCl. The alkyne acid **13** was isolated by filtration in 96% yield with >98% purity.

The preparation of ester **14** by treatment of acid **13** with diazomethane has been reported.[19a] We tried to run this reaction under classical conditions (MeOH/cat. H_2SO_4) but obtained no methyl ester **14**. Finally, acid **13** could be converted to the acyl chloride by treatment with $(COCl)_2$/cat. DMF and then quenched with excess MeOH to produce ester **14** as a light yellow solid in 98% yield. As a potentially shorter alternative, the alkyne **14** formation was also attempted by Pd-catalyzed cross coupling of propynoic acid methyl ester (via its in situ conversion into alkynylzinc derivative) and aryl iodide.[21] However, the conversion was only ca. 60%, and the side products could be removed only by chromatographic purification. Therefore, the four steps synthesis of the alkyne **14** was used for further scale-up.

With the alkyne **14** available, the [3 + 2] cycloaddition was investigated to evaluate its scalability. Sarcosine and paraformaldehyde had been used in the first protocol of the [3 + 2] reaction. However, this protocol led to low conversion and poor selectivity. The use of *N*-methoxymethyl-*N*-methyl-1-(trimethylsilyl)-methylamine **15** resulted to be much more convenient. This reagent was not commercially available but could be easily prepared from chloromethyl(trimethyl)silane **23** in two steps using modified literature conditions (Scheme 4).[22]

Scheme 4. Formation of 15



A mixture of neat chloromethyl(trimethyl)silane and a large excess of aqueous methylamine was stirred at 90 °C in a sealed stainless steel reactor. The crude intermediate **24** was isolated by phase separation and could be used directly in the subsequent reaction. Typically the crude aminal **15** was used immediately. If required, it could be stored at −20 °C for months without substantial degradation.

The [3 + 2] cycloaddition between the alkyne ester **14** and the crude amine **15** was then accrued. An excess amount of **15** was required to increase the conversion in the presence of TFA as a catalyst. This caused the formation of 5−11% of the bicyclic ester **25** as well as 2−8% of the pyrrole **26** (Figure 2). However, the impurity levels could be kept within an acceptable range by controlling the amount of **15**. Subsequently, the hydrolysis of **16** proceeded smoothly with aq 2N NaOH in methanol. Under these conditions, the side products **25** and **26** were not hydrolyzed and could be easily removed by

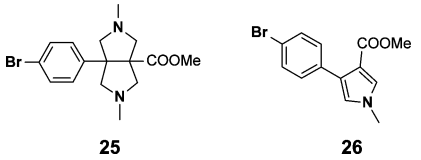


Figure 2. Side products of the [3 + 2] cycloaddition.

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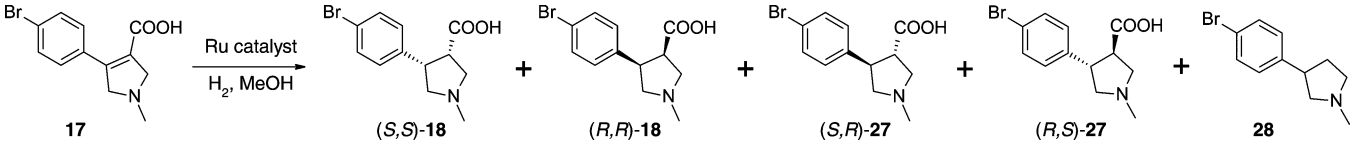
Scheme 5. Asymmetric hydrogenation of 17



extraction with MTBE. The targeted unsaturated acid **17** was then crystallized from water at 0 °C upon adjusting the pH to 6.8 by conc. HCl. An easy filtration afforded **17** as a white solid in 60% yield from alkyne ester **14**.

Asymmetric Hydrogenation. The asymmetric hydrogenation of **17** was the key transformation for the second-generation synthesis (Scheme 5). A variety of chiral ruthenium catalysts were evaluated (Table 3). Only the ruthenium catalysts containing (*R*)-MeOBIPHEP ($\mathbf{L_1}$) and (*R*)-2-furyl-MeOBIPHEP ($\mathbf{L_2}$) (Figure 3) afforded the desired (3*S*,4*S*)-4-(4-bromo-phenyl)-1-methyl-pyrrolidine-3-carboxylic acid (**18**) with high chemo- (100% in both entries 1 and 2, no decarboxylated side product **28** formed), enantio- (96.0% and 100% ee, respectively), and diastereoselectivity (0.7% and no **27** formed, respectively).[23] With all other catalytic systems both the ee and the de values were unsatisfactory with variable amounts of **28** being formed. From the hydrogenation with the lowest chemoselectivity (entry 6), **28** was isolated as a reference for analytical purposes. The rate of the hydrogenation in the presence of [$Ru(OAc)_2$(*R*)-$\mathbf{L_2}$)] (**29**) was strongly dependent on the pH. In acidic medium the reaction was almost suppressed, whereas it proceeded with highest rate in neutral to slightly basic medium (Table 4). These findings strongly suggest that the coordination of the carboxylate group to the metal is a condition for the fast hydrogenation of the double bond. An analogous behavior has been observed in the asymmetric hydrogenation of an acrylic acid containing a tetra-substituted double bond.[24] The hydrogenation under the conditions of entry 2 of Table 3 could be easily scaled up. On a 20 g scale the hydrogenation was complete after 3 h at S/C 500 to afford (*S*,*S*)-**18** with >99.9% ee and in 89.4% isolated yield after crystallization.

Table 3. Ru-catalyzed hydrogenation of 17[a]

entry	catalyst	(*S*,*S*)/(*R*,*R*)-**18**[b] (%)	(*S*,*R*)/(*R*,*S*)-**27**[b] (%)	**28**[b] [%]
1	$Ru(OAc)_2$((*R*)-$\mathbf{L_1}$)	97.2/2.0	0.7/–	
2	$Ru(OAc)_2$((*R*)-$\mathbf{L_2}$)	100/–	–/–	
3	$Ru(OAc)_2$((*R*)-$\mathbf{L_3}$)	95.0/2.7	–/–	2.2
4	$Ru(OAc)_2$((*R*)-$\mathbf{L_4}$)	39.9/18.5	–/–	26.3
5	$Ru(OAc)_2$((*R*)-$\mathbf{L_5}$)	85.5/5.1	–/–	9.1
6	$Ru(OAc)_2$((*R*)-$\mathbf{L_6}$)	41.5/13.8	–/–	44.3*S*)
7	$Ru(OAc)_2$((*R*)-$\mathbf{L_7}$)	68.6/3.2	2.0/–	25.6
8	$Ru(OAc)_2$((*R*)-$\mathbf{L_8}$)	73.5/2.8	1.8/0.6	14.6
9	$Ru(OAc)_2$((*S*)-$\mathbf{L_9}$)	0.5/85.6	1.0/1.0	4.3
10	$Ru(OAc)_2$((*R*)-$\mathbf{L_{10}}$)	56.9/3.8	1.7/-	36.2
11	$Ru(OAc)_2$((*R*)-$\mathbf{L_{11}}$)	1.8/92.1	0.5/0.4	1.6
12	$Ru(OAc)_2$((*S*,*S*)-$\mathbf{L_{12}}$)	5.3/65.5	1.6/0	22.8

[a]Conditions: 100 mg of **17**, S/C 50, MeOH (2 mL), 45 °C, 40 bar H_2, 18 h. Conversion was ≥98% in all cases except in entry 4 with 95%. [b]Determined by HPLC on chiral column (A%).

Table 4. Influence of pH on the hydrogenability of 17[a]

pH	3.67	4.05	6.35	6.53	6.7	7.81	8.45
conv. %	2	10	20	45	100	91	56

[a]The pH was measured in methanol; it was adjusted to 3.67–6.70 by HCl (conc. in water) or to 7.81–8.45 by sodium methoxide. The conversion was determined by HPLC (A%).

The ruthenium complex **29** is so far unreported in the open literature. In was prepared according to a reported procedure.[25] Treatment of [$Ru(OAc)_2$(*p*-cymene)] with (*R*)-2-furyl-MeO-BIPHEP in toluene afforded **29** as a yellow solid in 93% yield after crystallization. Its solid state structure has been determined by X-ray diffraction (Figure 4). The structure is very similar to that of [$Ru(OAc)_2(\mathbf{L_1})$] both as to the geometry around the ruthenium atom (a distorted octahedron) and as the most significative bond lengths and angles.[26]

Synthesis of the Amide 19 and API 1. With the *cis*-(3*S*,4*S*)-4-(4-bromophenyl)-1-methyl-pyrrolidine-3-carboxylic acid (**18**) in hand, the *trans*-(3*R*,4*S*)-amide **19** formation was originally conducted in three steps, which included the formation of the acyl chloride, the coupling with 4-chloroaniline in DCM to give *cis*-(3*S*,4*S*)-amide **30** and epimerization under basic conditions (Scheme 6). Various bases and solvents

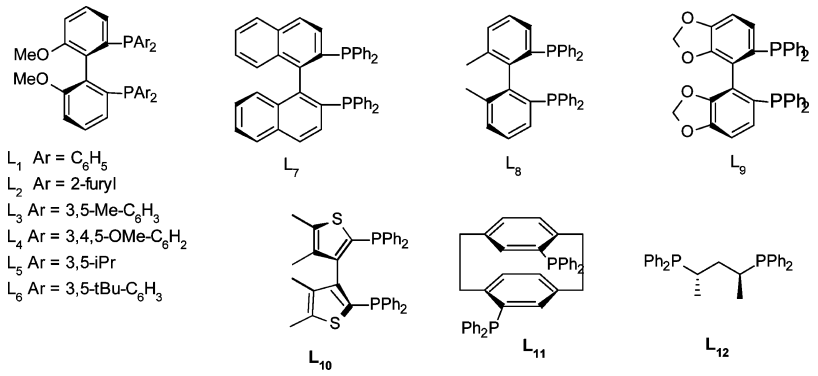


Figure 3. Ligands used in the asymmetric hydrogenation of **17**.

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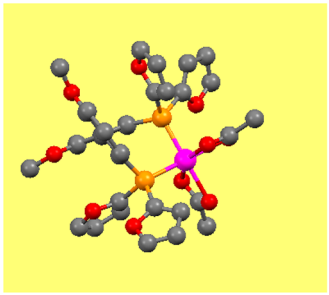


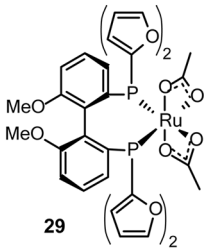


Figure 4. X-ray structure of **29**; a DCM molecule has been removed for clarity.

were evaluated in the chiral inversion step. Organic bases (DIPEA, *N*-methyl-bicyclohexylamine) did not epimerize the chiral center. In contrast, K_2CO_3 promoted the epimerization reaction in DMF or in ethylene gylcol/water (5/1). The best condition was identified as using 0.2 equiv of DBU in DMF/ethylene glycol (10/1) at 120 °C for 7 h to achieve 94% of conversion to **19**. However, the overall yield over these three steps was only 56%.

Surprisingly, the amide formation with EDC/HOBt as coupling reagent gave both compounds **30** and **19**. This result enabled the alternative one-step entry into **19** from **18** directly. At first, acid **18**, EDC (1.5 equiv), and HOBt (0.2 equiv) were combined to form the active intermediate which was aged for some time before adding 4-chloroaniline. It is not surprising that the **19**/**30** ratio became higher with a longer holding time and reached 98/2 after 4 h (Table 6). However, a significant amount of *N*-acylurea side products was detected (Figure 5). Increasing the amount of HOBt was expected to minimize the *N*-acylurea formation but could also have reduced the racemization during the amide bond formation.[27] Fortunately, in our case favorable effects were observed. When 1.0 equiv or more of HOBt was added, the competing *N*-acylurea formation was completely suppressed, while the chiral inversion still did proceed such that only **19** was obtained after addition of 4-chloroaniline. From a mechanistic point of view two pathways are likely (Figure 6). The initially formed *O*-acylisourea intermediate (**A**) can epimerize to the thermodynamically more stable *trans*-HOBt activated intermediate (**D**) via Pathway 2 or via the *cis*-HOBt activated intermediate (**C′**) in Pathway 1.

In the next step, the Heck coupling between acrylamide **8** and aryl bromide **19** reached quantitative conversion with 1 mol % of $Pd_2(dba)_3$, 2 mol % of P(*o*-tolyl)$_3$, and 1.3 equiv of *N*-methyl dicyclohexyl amine. The final deprotection reaction was performed according to the first generation process to give compound **1** in 86% yield with ≥98% purity.

In summary, we have demonstrated the viability of two processes for production of the HDAC inhibitor **1**. The first comprised a [3 + 2] dipolar cycloaddition followed by the resolution of the resulting *rac*-**5** to give the pure chiral compound **7**. With this route 913 g of **1** were prepared to supply the first series of preclinical tox studies. In view of the successive campaign, a very efficient enantioselective synthesis was demonstrated which entailed three well scaleable and high yielding steps: a [3 + 2] dipolar cycloaddition, a ruthenium catalyzed asymmetric hydrogenation, and a subsequent simultaneous coupling/epimerization to generate the chiral amide **19**, which was easily converted into the final product **1**. Accordingly, the overall yield was improved from 6.3% to 26.5%.

Table 6. Relation between chiral conversion and aging time

time (h)	0.5	1	2	4	12
19/**30**[a]	85/15	90/10	94/6	98/2	>99/1

[a]A%: determined by HPLC (A%).

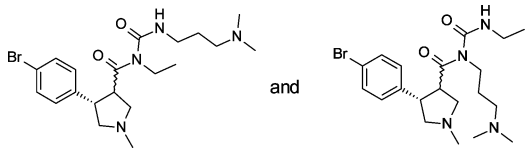


Figure 5. *N*-acylurea side products.

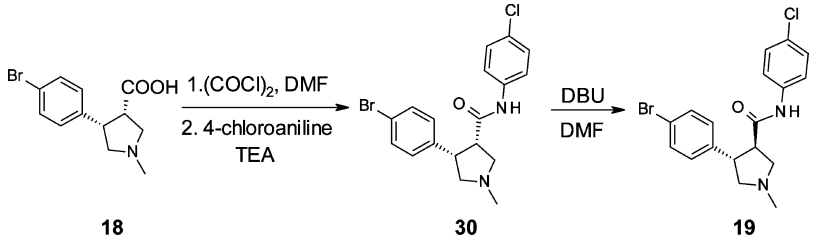
EXPERIMENTAL SECTION

General. All commercially available reagents and solvents were used without further purification unless otherwise noted. The solvents for hydrogenation reactions were distilled under argon prior to use. All complexes, solvents, and additives used for the hydrogenation reactions were stored and used in a glovebox under an argon atmosphere (<2 ppm of O_2).

^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker 400 MHz NMR spectrometer at 400 and 100 MHz, respectively, or on a Bruker 600 MHz spectrometer at 600 and 150 MHz with TMS as an internal reference. IR spectra (cm^{-1}) were recorded neat on Thermo NICOLET AVATAR 370 spectrometer. Melting points were performed on TA Instruments DSC Q 2000. HRMS mass spectra were acquired on Agilent QTOF 6350 spectrometer. Optical rotation data were obtained on RUDOLPH AUTOPOL V autometric polarimeter. HPLC and chiral LC were measured on an Agilent 1200 and Shimadzu LC-20A spectrometer. Details on HPLC analyses are reported in the Supporting Information.

(*E*)-3-(4-Bromophenyl)-acrylic Acid Ethyl Ester (4). To a 500 L reactor equipped with a condenser, mechanical stirrer, temperature probe, and nitrogen inlet, 4-bromobenzaldehyde (**2**, 20.7 kg, 111.9 mol), triethyl phosphonoacetate (**3**, 30.0 kg, 133.8 mol), and THF (100 kg) were charged. The mixture was stirred at 0−5 °C. A solution of NaOH (5.80 kg, 145 mol) in water (8.9 kg) was charged to the mixture over 1.4 h to

Scheme 6. Amide 19 formation by acyl chloride coupling and chiral inversion



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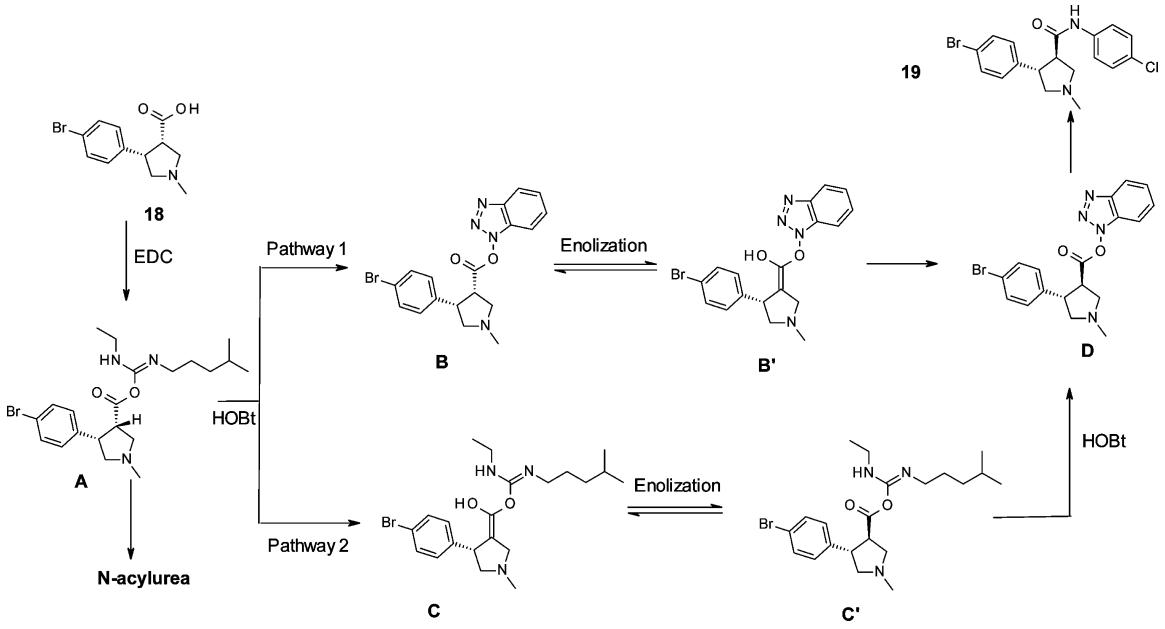

Figure 6. Possible pathways for the selective formation of amide **19**.

maintain the reaction temperature at 2−15 °C. After addition, the mixture was stirred for an additional 30 min at 10−15 °C. HPLC analysis (Method A: **2** RT 7.2 min, RRT 0.48; **4** RT 15.2 min, RRT 1.0) showed that **2** was not detected. MTBE (34.0 kg) and water (45.0 kg) were charged, while the batch temperature was maintained at 10−15 °C. The organic layer was separated, and the aqueous layer was extracted with MTBE (2 × 22 kg). The combined organic layers were washed with water (32 kg) and aqueous NaCl (2 × 21 kg, 15%) and then dried over Na_2SO_4 (3.2 kg). The suspension was filtered, and the cake was washed with MTBE (15 kg). The filtrate was concentrated at <40 °C under reduced pressure (60−80 mbar). To the residue, NMP (81 kg) was added. The mixture was concentrated at <40 °C under reduced pressure (40−60 mbar) to further remove MTBE and THF. The product solution was transferred to a plastic drum, the reactor was rinsed with NMP (15.2 kg), and the washings transferred to the same drum to give a solution of **4** in NMP (118.4 kg, 98.7A% (HPLC method A), 17.7 wt %, 73% yield), which was used directly in the next step.

***trans-rac*-4-(4-Bromophenyl)-1-methyl-pyrrolidine-3-carboxylic Acid Ethyl Ester (5).** To a 1000 L reactor equipped with a condenser, mechanical stirrer, temperature probe, and nitrogen inlet, *N*-methyl glycine (14.7 kg, 165 mol), paraformaldehyde (4.80 kg, 159.8 mol), and NMP (72 kg) were charged, and the mixture was stirred at 20−25 °C. A solution of **4** in NMP (118.4 kg, 17.7 wt %, 82.3 mol) was charged. The mixture was stirred at 100−110 °C for 1.0 h and then slowly cooled to ca. 40 °C. IPC by HPLC analysis (method A: **4** RT 15.2 min, RRT 1.14; **5** RT 13.3 min, RRT 1.0)) showed that **4** was not detected. The mixture was diluted with EtOAc (152 kg) and water (335 kg) and the aqueous layer was separated. The aqueous layer was then extracted with EtOAc (3 × 153 kg). Combined organic layers were washed with water (3 × 70 kg), aqueous NaCl (25 wt %, 42 kg), and dried over Na_2SO_4 (7.5 kg). The suspension was filtered, and the cake was washed with EtOAc (22 kg). The filtrate was concentrated to ca. 40 L at <45 °C under reduced pressure (35−55 mbar). Ethanol (106 kg) was charged, and the mixture was concentrated again to ca. 40 L at <45 °C under reduced pressure (30−50 mbar) to further remove EtOAc. The resulting solution was transferred to a plastic drum. The reactor was washed with ethanol (11 kg), and the washings were transferred to the same drum to give a solution of **5** in ethanol (49.2 kg, 98.A% (HPLC method A), 51.1 wt %, 98% yield). Analytically pure **5** (oil) was obtained by preparative HPLC. IR (neat) 1731, 1488, 1372, 1246, 1179, 1157, 1126, 822 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.3 Hz, 2H), 4.21−4.07 (m, 2H), 3.69−3.56 (m, 1H), 3.06−2.95 (m, 3H), 2.92−2.82 (m, 1H), 2.67 (dd, J = 6.5, 9.3 Hz, 1H), 2.40 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 142.7, 131.2, 128.9, 120.0, 63.5, 60.5, 59.2, 52.0, 46.6, 41.6, 13.9 HRMS m/z $[M + H]^+$ calcd for $C_{15}H_{23}N_2O$, 311.0521; found, 311.0524.

(3*R*,4*S*)-4-(4-Bromophenyl)-1-methyl-pyrrolidine-3-carboxylic Acid Ethyl Ester (7). To a 500 L reactor equipped with a condenser, mechanical stirrer, temperature probe, and nitrogen inlet, ditoluoyl-D-tartaric acid (31 kg, 80.2 mol), a solution of **5** in ethanol (49.2 kg, 51.1 wt %, 80 mol), and ethanol (165.0 kg) were charged. Under agitation, the reaction mixture was heated to 76 °C over 1 h and maintained at that temperature for 10 min. The mixture was cooled to 15 °C over 2 h and maintained for 1 h at 10−15 °C. The crude chiral salt **6** was centrifuged, and the cake was washed with ethanol (26.0 kg). The cake and fresh ethanol (188 kg) were charged back into the reaction vessel and stirred for 10 min at 75 °C. The suspension was cooled to 10−15 °C and maintained for 1 h at this temperature. The solid was centrifuged, and the cake was washed with ethanol (14 kg) to give 24.8 kg of chiral salt **6**. The wet cake was dried for ca. 12 h at 40−45 °C under reduced pressure (25−40 mbar) to give **6** (23.4 kg, 99.7A% (HPLC method A), 42.0% yield). The chiral assay (method B: **7** (free from salt **6**) RT 11.2 min, RRT 1.0; isomer (3*S*, 4*R*)-**5** RT 9.1 min, RRT 0.82) gave 99.6% ee for isolated **6**; mp (DSC): peak 154.38 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 7.88 (d, J = 8.3 Hz, 4H), 7.47 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.0 Hz, 4H), 7.28 (d, J = 8.5 Hz, 2H), 5.73 (s, 2H), 4.08−3.93 (m, 2H), 3.62 (q, J = 8.8 Hz, 1H), 3.46−3.23 (m, 4H), 3.08 (t, J = 10.0 Hz,

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1H), 2.64 (s, 3H), 2.38 (s, 6H), 1.08 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.6, 168.7, 165.3, 144.5, 139.9, 131.8, 130.4, 129.9, 127.0, 120.7, 72.6, 61.2, 61.1, 57.1, 50.1, 46.3, 21.7, 14.4.

To a 30 L reactor equipped with a condenser, mechanical stirrer, temperature probe, and nitrogen inlet, chiral salt **6** (8.00 kg, 11.5 mol) and water (10 kg) were charged. The agitation was started, and aqueous NaOH (10 wt %, 9 kg) was added slowly to adjust pH (aqueous layer) to 7.5−8.0 while maintaining the batch temperature at 10−25 °C. After addition, the mixture was stirred at 20−25 °C for additional 40 min. The resulting white suspension was filtered, and the filtrate was extracted with EtOAc (3 × 6 L). The combined organic layers were dried over Na_2SO_4. After filtration, the filtrate was concentrated to give **7** (3.71 kg, 99.9 A% (HPLC method A), assay 93.8 wt %, 97.2% yield) as light yellow oil. IR (neat) 1731, 1488, 1372, 1245, 1179, 1158, 1010, 823 cm^{-1}; ^{1}H NMR (400 MHz, CDCl3) δ 7.42 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 4.22−4.06 (m, 2H), 3.67−3.57 (m, 1H), 3.07−2.92 (m, 3H), 2.91−2.81 (m, 1H), 2.67 (dd, J = 6.5, 9.3 Hz, 1H), 2.39 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 143.4, 131.9, 129.5, 121.7−117.7 (m), 64.2, 61.1, 59.9, 52.6, 47.3, 42.2, 14.5; HRMS m/z [M + H]$^+$ calcd for $C_{15}H_{23}N_2O$, 311.0521; found, 311.0524. $[\alpha]_D^{20}$ = +65.49° (0.488, MeOH).

(3*R*,4*S*)-4-{4-[(*E*)-2-(2-*tert*-Butoxycarbonylamino-phenylcarbamoyl)-vinyl]-phenyl}-1-ethyl-pyrrolidine-3-carboxylic Acid Ethyl Ester (9). To a 20 L reactor equipped with a condenser, mechanical stirrer, temperature probe, and nitrogen inlet, **7** (1.96 kg, 92.8 wt %, 5.93 mol), (2-acryloylamino-phenyl)-carbamic acid *tert*-butyl ester (**8**, 1.56 kg, 5.95 mol), $Pd_2(dba)_3$ (54.8 g, 59.8 mmol), tri(*o*-tolyl)-phosphine (36.4 g, 0.119 mol), DMF (8.0 L), and DIPEA (1.93 kg, 14.9 mol) were charged. The mixture was stirred at 105−110 °C for 5 h and cooled to 50 °C. HPLC analysis (method C: **7** RT 3.7 min, RRT 0.27; **8** RT 11.8 min, RRT 0.87; **9** RT 13.6 min, RRT 1.0) showed that 1.9% of **7** was unreacted. The resulting mixture was concentrated at 80 °C under reduced pressure (20−30 mbar) to remove DMF. The residue was diluted in EtOAc (8.0 L) and then filtered through Celite. The filtrate was washed with water (2 × 5.0 L) and aqueous NaCl (15%, 2 × 4.0 L). The combined aqueous layers were filtrated through Celite and then extracted with EtOAc (4 × 3.0 L). The combined organic layers were concentrated under reduced pressure (30−50 mbar). The resulting brown gummy residue **9** (3.43 kg, 79.0 A% (HPLC method C), 65.2 wt %, 76% yield) was used directly in the next step. Analytically pure **9** (sticky oil) was obtained by preparative HPLC. IR (neat) 1730, 1516, 1455, 1367, 1244, 1158, 1023, 825 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.70 (s, 1H), 8.48 (s, 1H), 7.65−7.50 (m, 5H), 7.39 (d, J = 8.0 Hz, 2H), 7.19−7.07 (m, 2H), 6.89 (d, J = 15.6 Hz, 1H), 4.07 (quin, J = 6.8 Hz, 2H), 3.61−3.51 (m, 1H), 3.12−3.02 (m, 1H), 2.91 (td, J = 8.7, 13.2 Hz, 2H), 2.84−2.77 (m, 1H), 2.59−2.52 (m, 1H), 2.29 (s, 3H), 1.46 (s, 9H), 1.16 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.4, 164.1, 153.1, 145.8, 140.2, 132.9, 131.0, 129.8, 128.0, 127.9, 125.1, 124.5 (br), 123.9, 123.8−123.7 (m), 121.4, 79.4, 63.6, 60.3, 58.8, 51.1, 47.1, 41.5, 28.0, 14.0; HRMS m/z [M + H]$^+$ calcd for $C_{28}H_{35}N_3O_5$, 493.2577; found, 493.2575; $[\alpha]_D^{20}$ = +67.13° (0.301, MeOH).

(3*R*,4*S*)-4-{4-[(*E*)-2-(2-*tert*-Butoxycarbonylamino-phenylcarbamoyl)-vinyl]-phenyl}-1-methyl-pyrrolidine-3-carboxylic Acid (10). To a 30 L reactor equipped with a condenser, mechanical stirrer, temperature probe, and nitrogen inlet, a solution of **9** (2.99 kg, 65.2 wt %, 3.95 mol) in methanol (7.18 kg) was charged. With agitation, a solution of LiOH·H_2O (332 g, 7.91 mol) in H_2O (4.2 kg) was added while maintaining the batch temperature at 10−30 °C. The resulting mixture was stirred at 18−23 °C for 2 h. HPLC (method C: **9** RT 13.6 min, RRT 1.31; **10** RT 10.4 min, RRT 1.0) showed complete consumption of **9**. MeOH was removed at 30−35 °C under reduced pressure (30−50 mbar). The residue was diluted with water (30 kg), and the solution was extracted with EtOAc (2 × 2.4 kg). The aqueous layer was diluted with *n*-butanol (10.5 kg), then the pH was adjusted to 6.5 by slow addition of aqueous HCl (2N) at 10−20 °C. The aqueous layer was separated and further extracted with *n*-BuOH (2 × 5.4 kg). The combined organic layers were washed with water (2 × 3 kg) and concentrated at 45−50 °C under reduced pressure (20−40 mbar). Toluene (10.5 kg) was added to the resulting suspension and concentrated in vacuo to further remove the *n*-butanol. After addition of MTBE (12.5 kg), the solid was isolated by filtration and dried in a vacuum oven at 40−50 °C/20−30 mbar for 8 h. The solid was reslurried in methanol (12 kg) and filtered. After drying in vacuo at 40−50 °C/20−30 mbar for 48 h, **10** (1.64 kg, 92.1 A% (HPLC method C), 88.9 wt %, 63% yield) was obtained as an off-white solid. Analytically pure **10** (solid) was obtained by preparative HPLC. IR (neat) 1711, 1626, 1512, 1437, 1159, 1022, 826 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.84 (br. s., 1H), 8.56 (br. s., 1H), 7.70−7.51 (m, 5H), 7.41 (d, J = 8.0 Hz, 2H), 7.24−7.06 (m, 2H), 6.93 (d, J = 15.8 Hz, 1H), 3.63 (q, J = 7.0 Hz, 2H), 3.08−2.92 (m, 3H), 2.89−2.79 (m, 1H), 2.65−2.55 (m, 1H), 2.33 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.6, 164.6, 153.6, 146.7, 140.6, 133.2, 131.4, 130.3, 128.5, 128.4, 125.48 (br), 125.0, 124.4, 124.3, 121.8, 79.8, 64.0, 59.7, 52.1, 47.4, 42.0, 28.5; HRMS m/z [M + H]$^+$ calcd for $C_{26}H_{31}N_3O_5$, 465.2264; found, 465.2258; $[\alpha]_D^{20}$ = +56.07° (0.283, MeOH).

[2-((*E*)-3-{4-[(3*S*,4*R*)-4-(4-Chlorophenylcarbamoyl)-1-methyl-pyrrolidin-3-yl]-phenyl}-acryloylamino)-phenyl]-carbamic Acid *tert*-Butyl Ester (11). To a 30 L reactor equipped with condenser, mechanical stirrer, temperature probe and nitrogen inlet, **10** (800 g, assay 88.9%, 1.53 mol), DCM (20.8 kg,) and THF (1.44 kg) were charged. To the stirred suspension was added HATU (784 g, 2.06 mol) followed by triethylamine (435 g, 4.30 mol), and the mixture was stirred at 20−23 °C for 20 min. Then 4-chloroaniline (230 g, 1.80 mol) was added, and the mixture was stirred at same temperature for additional 3 h. HPLC analysis (method C) showed that more than 10% of **10** was still unreacted. Additional HATU (2 × 196 g, 0.515 mol) was added and the mixture stirred overnight. The second IPC (method C: **10** RT 10.4 min, RRT 0.75; **11** RT 13.9 min, RRT 1.0) showed that the amount of residual **10** had decreased to 3.3%. Aqueous Na_2CO_3 (10 wt %, 5 L) was added to quench the reaction. The phases were separated. The organic layer was washed with aq. Na_2CO_3 (10 wt %, 5 L) and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure (40−60 mbar) to give the crude **11** (2.70 kg). The residue was slurried in CH_3CN (2.5 kg) at 20 °C for 1 h; the solid was collected by filtration to give **11** (627 g, 89.5 A% (HPLC method C), 96.6 wt %, yield 69%) as an off-white solid. Analytically pure **11** (solid) was obtained by preparative HPLC. IR (neat) 1737, 1654, 1525, 1453, 1242, 1160, 826 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.04 (s, 1H), 9.69 (s, 1H), 8.48 (s, 1H), 7.68−7.52 (m, 7H), 7.41−7.28 (m, 4H), 7.22−7.04 (m, 2H), 6.88 (d,

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J = 15.8 Hz, 1H), 3.83−3.62 (m, 1H), 3.19−3.02 (m, 2H), 2.88 (t, J = 8.7 Hz, 1H), 2.75 (dd, J = 5.8, 9.0 Hz, 1H), 2.65−2.57 (m, 1H), 2.32 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.6, 164.1, 153.0, 146.5, 140.2, 138.0, 132.8, 130.9, 129.8 (br), 128.6, 128.0, 127.9, 126.8, 125.0 (br), 124.5 (br), 123.9, 123.9−123.7 (m), 121.3, 120.7, 79.4, 63.3, 60.5, 53.8, 46.7, 41.6, 28.0; HRMS m/z [M + H]$^+$ calcd for $C_{32}H_{35}ClN_4O_4$, 574.2347; found, 574.2352; $[\alpha]_D^{20}$ = +200.45° (0.313, MeOH).

(3*R*,4*S*)-4-{4-[(*E*)-2-(2-Aminophenylcarbamoyl)-vinyl]-phenyl}-1-methyl-pyrrolidine-3-carboxylic Acid (4-Chlorophenyl)-amide (1). To a 30 L reactor equipped with a condenser, mechanical stirrer, temperature probe, and nitrogen inlet, **11** (1.69 kg, 2.94 mol) and MeOH (2.70 kg) were charged. The internal temperature was adjusted at 0−5 °C. To the suspension was added a solution of HCl in methanol (10 mol/L, 6.25 kg) at 0−5 °C under stirring over 1 h. After the addition, the reaction mixture was stirred at 0−5 °C for 3 h. IPC by HPLC analysis (method C: **11** RT 13.9 min, RRT 1.13; **1** RT 12.3 min, RRT 1.0) to show that 1.2% of **11** was unreacted. Most of the MeOH and excess HCl was removed at 15−20 °C under reduced pressure (30−50 mbar). The oily residue was dissolved in MeOH (5.10 kg) and concentrated again at 15−20 °C bath temperature; then it was dissolved in MeOH (40.56 kg). Saturated aqueous Na_2CO_3 was added to the solution at 10−20 °C with stirring until the pH of the reaction mixture was 8.0. Saturated aqueous $NaHCO_3$ (25.4 kg) was added, and the suspension was stirred for 30 min. After filtration, the filter cake was slurried in water (5.07 kg) for 1 h. After filtration, the filter cake was dried in a vacuum oven at 45−50 °C for 2 days. Thereafter, the dried solid was reslurried in methanol (7.6 kg) and stirred at 60−65 °C for 20 min; the slurry was cooled to 5−10 °C and filtered. The filter cake was dried in a vacuum oven at 45−50 °C/25 mbar for 24 h. The dried solid was reslurried in MeOH (11.8 kg) and stirred at 50−55 °C for 3 h; then water (16.9 kg) was added to the suspension at 40−55 °C slowly. The slurry was cooled to 5−10 °C and filtered. The filter cake was dried in a vacuum oven at 45−50 °C/30 mbar for 2 days to give **1** (913 g, 98.2 A% (HPLC method C), yield 65.5%, >99% ee (HPLC method D: **1** RT 13.5 min, RRT 1.0; isomer (3*S*,4*R*)-**1** RT 19.8 min, RRT 1.47) as an off-white solid with the desired polymorph B. Mp (DSC): peak 233.32 °C. IR (neat) 1655, 1529, 1494, 1226, 973, 827 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H) 9.38 (s, 1H), 7.62−7.51 (m, 5H), 7.38−7.33 (m, 5H), 7.94−6.85 (m, 2H), 6.76 (d, J = 8.0, 1H), 6.58 (t, J = 8.0, 1H), 4.95 (s, 2H), 3.76−3.71 (m, 1H), 3.13−3.08 (m, 2H), 2.90−2.86 (m, 1H), 2.77−2.74 (m, 1H), 2.65−2.60 (m, 1H), 2.33 (s, 3H); HRMS m/z [M + H]$^+$ calcd for $C_{27}H_{27}ClN_4O_2$, 474.1823; found, 474.1817; $[\alpha]_D^{20}$ = +244.24° (0.264, MeOH).

(*E*)-3-(4-Bromophenyl)-acrylic Acid Ethyl Ester (4) (Improved Lab Procedure). To a 5 L flask equipped with a condenser, mechanical stirrer, temperature probe, and nitrogen inlet, 4-bromobenzaldehyde (191.9 g, 1.04 mol) triethyl phosphonoacetate (279.0 g, 1.24 mol) and THF (1.1 L) were charged. The internal temperature was controlled at 0−10 °C with an ice−water bath. A solution of NaOH (54.0 g, 1.35 mol) in water (90 g) was charged slowly to the mixture at 10−15 °C, and then the mixture was stirred under the same conditions for 2 h. After completion, MTBE (400 mL) was charged, and the reaction mixture was well-stirred. The organic layer was separated, and the aqueous layer was extracted with MTBE (2 × 400 mL). The combined organic layers were dried with Na_2SO_4. The mixture was concentrated under reduced pressure at 20−30 °C under reduced pressure (40−50 mbar) to give the crude **4** (254.6 g, 99.0 A%, yield 96%) as a light-yellow oil which was used directly in the next step. A reference sample of **4** was isolated by chromatography. Its ^{1}H NMR spectrum was in agreement with literature data.[6a] ^{1}H NMR (400 MHz, CD_3Cl) δ 1.29 (t, J = 7.2 Hz, 3H), 4.22 (q, J = 7.2 Hz, 2H), 6.37 (d, J = 16.0 Hz, 1H), 7.33(d, J = 8.4 Hz, 2H), 7.46 (m, J = 8.4 Hz, 2H), 7.56, (d, J = 16.0 Hz, 1H).

2,3-Dibromo-3-(4-bromophenyl)-propionic Acid Ethyl Ester (12). To a 2 L flask equipped with a mechanical stirrer, thermometer, and condenser, **4** (253.4 g, 0.993 mol) and DCM (800 mL) were charged. The internal temperature was controlled at to 0−5 °C with an ice−water bath. Bromine (166.6 g, 1.04 mol) was added to the mixture at 0−10 °C over 30 min, and then the batch was stirred at 25 °C for 30 min. After completion, sat. $NaHSO_3$ (200 mL) was added to quench the reaction. The mixture was washed with brine (20%, 300 mL) and then concentrated at 25−35 °C under reduced pressure (30−50 mbar) to give **12** (371.2 g, 98.8 A% diastereoisomer mixtures, yield 90%) as an oil, which became off-white solid on standing in refrigerator overnight. The crude was used directly in the next step. A reference sample of **12** was isolated by chromatography. Its ^{1}H NMR spectrum was in agreement with literature data.[19b] ^{1}H NMR (400 MHz, CD_3Cl) δ 1.10 (t, J = 8.0 Hz, 0.6H), 1.40 (t, J = 8.0 Hz, 3H), 4.06 (q, J = 8.0 Hz, 0.4H), 4.38 (q, J = 8.0 Hz, 2H), 4.74 (d, J = 8.0 Hz, 0.2H), 4.78 (d, J = 8.0 Hz, 1H), 5.25 (d, J = 8.0 Hz, 0.2H), 5.32 (d, J = 8.0 Hz, 1H), 7.15−7.32(m, 2.2H), 7.50, (d, J = 8.0 Hz, 0.4H), 7.55 (d, J = 8.0 Hz, 2H).

(4-Bromophenyl)-propynoic Acid (13). To a 5 L four-neck flask equipped with a mechanical stirrer, thermometer, and condenser, potassium hydroxide (85 wt %, 197.0 g, 2.98 mol) and 2-propanol (2.1 L) were charged. The batch was stirred under cooling in an ice−water bath to keep the internal temperature about 5−10 °C. **12** (312.5 g, 0.753 mol) was charged in portions to maintain the batch temperature below 60 °C, and then the mixture was heated at reflux for 3 h. After completion of the reaction, the resulting mixture was concentrated at 40 °C under reduced pressure (30−50 mbar) to remove 1.2 L of 2-propanol. The residue was diluted with water (1.2 L) and cooled in an ice bath; then the pH was adjusted to 2 using 35% hydrochloric acid while keeping the batch temperature below 25 °C. The resulting slurry was filtered, and the solid was washed with water (1.2 L). The wet solid was dried in vacuum oven at 40 °C/25 mbar to give **13** (162.2 g) as a white solid (99.0 A%, yield 96%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.62 (d, J = 8.6 Hz, 1H), 7.46 (d, J = 8.6 Hz, 1H).

(4-Bromophenyl)-propynoic Acid Methyl Ester (14). To a 5 L four-neck flask equipped with a mechanical stirrer, thermometer, and nitrogen inlet, **13** (161.2 g, 0.716 mol), DCM (1.6 L), and DMF (anhyd., 1.54 mL) were charged. The suspension was stirred in an ice−water bath, and oxalyl chloride (100 g, 0.787 mol) was added dropwise over 15 min at 10−15 °C. The mixture was held at this temperature for 15 min; then it was warmed to room temperature and stirred for additional 2 h. A sample was taken and quenched with methanol. HPLC analysis showed that acid **13** was consumed. The resulting solution was cooled to 0−5 °C, and methanol (160 mL) was added dropwise over 30 min. The mixture was stirred at room temperature for 1 h and then diluted with water (400 mL). The organic phase was separated, washed with sat. aq. $NaHCO_3$

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(400 mL) and brine (20%, 400 mL), and then dried over Na_2SO_4. After filtration, the filtrate was concentrated at 25−35 °C under reduced pressure (30−50 mbar) to give **14** (168.7 g, 98.4 A%, yield 98%) as a light-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.51 (m, 2H), 7.48−7.41 (m, 2H), 3.85 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2, 134.3, 132.0, 125.5, 118.4, 85.2.

Methyltrimethylsilanylmethylamine (24). A 2 L stainless steel autoclave was charged with chloromethyltrimethylsilane (**23**, 264 g, 2.15 mol) and aqueous methylamine (40%, 1.15 L). The mixture was stirred at 90 °C in an oil bath for 6 h and then cooled to room temperature. The organic phase was separated, washed with water (2 × 150 mL) and brine (150 mL), and dried over Na_2SO_4. After filtration, the crude **24** (221 g, 98 A% by GC (FID), 88%) was isolated as a yellow oil which was used directly in the next step.

***N*-Methoxymethyl-*N*-methyl-1-(trimethylsilyl)-methylamine (15).** To a 2 L three-neck flask equipped with a mechanical stirrer, thermometer, and nitrogen inlet, 37% aqueous formaldehyde (138 mL) was charged. **24** (149.8 g, 1.27 mol) was added dropwise over 45 min at 5−10 °C. Methanol (98.5 mL) was added dropwise over 10 min and followed by portion-wise addition of K_2CO_3 (67 g, 0.486 mol) such that the temperature was kept below 15 °C. The mixture was stirred in an ice−water bath for additional 2 h. *tert*-Butyl methyl ether (150 mL) was added, and the organic layer was separated and dried over K_2CO_3 (51 g). After filtration, the filtrate was concentrated at 40 °C under reduced pressure (100 mbar) to give crude **15** (177 g) as a light-yellow oil which was used directly in the next step.

4-(4-Bromophenyl)-1-methyl-2,5-dihydro-1*H*-pyrrole-3-carboxylic Acid Methyl Ester (16). To a 2 L three-neck flask equipped with a mechanical stirrer, thermometer, and nitrogen inlet, **14** (100.0 g, 0.418 mol) and *tert*-butyl methyl ether (1.0 L) were charged. To the suspension trifluoroacetic acid (7.2 g, 62.7 mmol) and **15** (202.5 g) were added dropwise in sequence over 30 min at 0−10 °C. The mixture was then stirred at room temperature for 40 min. HPLC showed 6.8% of **14** was detected. The batch was concentrated at 35−45 °C under reduced pressure (35−55 mbar) to give crude **16** (162.0 g) as a light-yellow oil (78.8 A%) which was used directly in the next step. Analytically pure **16** (oil) was obtained by flash chromatography. IR (neat) 1731, 1488, 1372, 1246, 1179, 1157, 1126, 822 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 3.91−3.83 (m, 4H), 3.67 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.11, 149.82, 132.63, 131.11, 129.74, 126.49, 122.91, 67.10, 63.36, 51.41, 42.20; HRMS m/z [M + H]$^+$ calcd for $C_{15}H_{23}N_2O$, 311.0521; found, 311.0524.

4-(4-Bromophenyl)-1-methyl-2,5-dihydro-1*H*-pyrrole-3-carboxylic Acid (17). To a 1 L three-neck flask equipped with a mechanical stirrer, crude **16** (162.0 g) and methanol (405 mL) were charged. The solution was cooled in an ice−water bath, and aq. NaOH (2 N, 418 mL, 0.836 mol) was added over 10 min while maintaining the temperature below 20 °C. The mixture was stirred at room temperature for additional 3 h until the conversion was complete. The batch was concentrated at 25−35 °C under reduced pressure (30−40 mbar) to remove the methanol. The residue was diluted with water (34 mL) and extracted with *tert*-butyl methyl ether (3 × 135 mL). The aqueous layer was separated, and its pH was adjusted to 6.8 by slow addition of conc. HCl while maintaining the batch temperature below 20 °C. The suspension was stirred in an ice−water bath for 30 min, and the solid was isolated by filtration. The cake was washed with water (14 mL) and dried in vacuum oven at 45 °C/25 mbar to give **17** (70.8 g, 99.6 A%, yield 60%) as off-white solid. IR (neat) 1630, 1487, 1372, 1327, 817 cm^{-1}; ^{1}H NMR (400 MHz, MeOD + D_2O) δ 7.57−7.50 (m, 2H), 7.47−7.41 (m, 2H), 4.54 (br. s., 2H), 4.43 (br. s., 2H), 3.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 148.5, 143.9, 140.2, 138.9, 137.3, 129.1, 75.2, 73.6, 51.6; HRMS m/z [M + H]$^+$ calcd for $C_{12}H_{12}BrNO_2$, 281.0051; found, 281.0046.

(3*S*,4*S*)-4-(4-Bromophenyl)-1-methyl-pyrrolidine-3-carboxylic Acid (18). A 380 mL stainless steel autoclave was charged with **17** (15.20 g, 53.9 mmol), [Ru(OAc)$_2$((*R*)-2-furyl-MeOBIPHEP)] (82.1 mg, 0.108 mmol) and methanol (150 mL) in a glovebox (O_2 content <2 ppm) under argon. The autoclave was removed from the glovebox and attached to a hydrogen line. The argon in the system was replaced with hydrogen, and then the reaction mixture was stirred under constant hydrogen pressure (40 bar) at 45 °C. After 3 h, the autoclave was cooled to room temperature, the pressure was released, and the reaction mixture (a yellow suspension) was sampled under vigorous stirring. HPLC analysis showed 99% conversion, 100% selectivity, and 100% ee for **18** as well as no presence of *trans* byproduct **27** or decarboxylated byproduct **28**. The yellow suspension was removed from the autoclave with aid of methanol (50 mL) and rotary concentrated at 35−45 °C under reduced pressure (40−60 mbar) to a total weight of ca. 60 g. The precipitated product was isolated by filtration. The filter cake was washed with methanol (15 mL) and dried at the rotavap at 50 °C/10 mbar to constant weight to give **18** (13.69 g, 98.0 A%, 100% ee (method E: (*S*,*S*)-**18** RT 2.95 min, RRT 1.0; (*R*,*R*)-**18** RT 3.61 min, RRT 1.22), yield 89.4%) as a white solid. IR (neat) 1630, 1161, 1109, 964, 836 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d^6) δ 11.9 (bs, 1H), 7.42 (m, 2H), 7.25 (m, 2H), 3.63 (m, 1H), 3.34 (m, 1H), 2.92 (m, 2H), 2.77 (dd, ^3J = 9.0 Hz, 1H), 2.63 (dd, ^3J = 9.0, 6.5 Hz, 1H), 3.34 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.8, 141.4, 131.3, 131.1, 120.0, 62.6, 57.9, 48.9, 46.3, 42.2, 40.6; HRMS m/z [M + H]$^+$ calcd for $C_{12}H_{14}BrNO_2$, 283.0208; found, 283.0212; $[\alpha]_D^{20}$ = −63.80° (0.326, MeOH).

(3*S*,4*S*)-4-(4-Bromophenyl)-1-methyl-pyrrolidine-3-carboxylic Acid (4-Chlorophenyl)-amide ((3*S*,4*S*)-19). To the suspension of **18** (2.48 g, 8.73 mmol) in DCM (18 mL) and DMF (18 uL), cooled in an ice−water bath, oxalyl chloride (1.34 g, 10.5 mol) was added in portions while maintaining the temperature below 10 °C. After stirring at room temp for 30 min, the reaction mixture was concentrated under reduced pressure at 20 °C/30−40 mbar. The residue was redissolved in DCM (15 mL) and cooled in an ice−water bath. 4-Chlorophenylamine (1.18 g, 9.00 mmol) was added and followed by addition of triethylamine (1.83 g, 18.1 mol) in portions. The mixture was stirred at room temperature for 30 min to complete the reaction. After dilution with DCM (30 mL), the resulted mixture was washed with water (20 mL) and brine (20 mL) and then dried over Na_2SO_4. After filtration, DCM was removed by vacuum distillation, and the crude product was recrystallized from ethyl acetate and heptane (v/v, 1/2). The product was collected by filtration, and the filter cake was dried in vacuum oven at 40 °C/25 mbar to give **19** (2.2 g, 95.0 A%, yield 62.1%) as an off-white solid. Analytically pure **19** (solid) was obtained by preparative HPLC. Mp (DSC): onset 180.46 °C, peak 181.13 °C. IR (neat) 1667, 1525, 1492, 1010, 821 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (s, 1H),

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7.36−7.29 (m, 2H), 7.26−7.13 (m, 6H), 3.75−3.64 (m, 1H), 3.69−3.67 (m, 1H), 3.49−3.37 (m, 1H), 3.01−2.91 (m, 2H), 2.89−2.80 (m, 1H), 2.67 (t, J = 8.3 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.1, 139.8, 137.5, 130.7, 130.3, 128.2, 126.5, 120.8, 119.3, 61.7, 57.1, 49.5, 46.7, 41.8; HRMS m/z $[M + H]^+$ calcd for $C_{18}H_{18}BrClN_2O$, 392.0291; found, 392.0293; $[\alpha]_D^{20}$ = −135.13° (0.335, MeOH).

(3*R*,4*S*)-4-(4-Bromophenyl)-1-methyl-pyrrolidine-3-carboxylic Acid (4-Chlorophenyl)-amide (19). To a 1 L three-neck flask equipped with a mechanical stirrer, temperature probe, and nitrogen inlet, **18** (98%, 85.4 g, 0.300 mol), HOBt (40.5 g, 0.300 mol), and DMF (430 mL) were charged. The suspension was stirred at room temperature, and EDC (90.8 g, 0.45 mol) was charged in four portions while maintaining the batch temperature below 26 °C. The mixture was then stirred at room temperature, and after 4 h 4-chlorophenylamine (42.1 g, 0.330 mol) was added. The batch was heated at 50 °C; after 2 h HPLC analysis showed **18** was consumed. The resulting solution was concentrated at 50 °C under reduced pressure (10−20 mbar) to remove 254 mL of DMF. The residue was diluted by the addition of water (680 mL) and stirred at room temperature for 10 min. NaOH (20 wt %, 60 g) was added dropwise over 10 min, and the batch was stirred at room temperature for additional 2 h. The solid was collected by filtration and reslurried in acetonitrile/water (v/v = 1/2, 680 mL) for 1 h. Finally, the product was collected by filtration and dried in vacuum oven at 45 °C/25 mbar for 2 days to give **19** (106 g, 99.6 A%, >99% ee method F: (*S*,*R*)-**19** RT 4.37 min, RRT 1.0; (*R*,*S*)-**19** RT 6.39 min, RRT 1.46, yield 90%) as an off-white solid. Mp (DSC): onset 199.25 °C, peak 199.79 °C. IR (neat) 1660, 1528, 1399, 1092, 1012, 825 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (s, 1H), 7.60 (d, J = 9.0 Hz, 2H), 7.49 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H), 3.73−3.61 (m, 1H), 3.14−2.99 (m, 2H), 2.84 (t, J = 8.5 Hz, 1H), 2.70 (dd, J = 5.5, 9.0 Hz, 1H), 2.62−2.52 (m, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d^6) δ 171.51, 143.93, 137.93, 131.28, 129.48, 128.53, 126.76, 120.71, 119.29, 63.25, 60.38, 53.90, 46.28, 41.55; HRMS m/z $[M + H]^+$ calcd for $C_{18}H_{18}BrClN_2O$, 392.0291; found, 392.0288; $[\alpha]_D^{20}$ = +186.14° (0.280, MeOH).

[2-((*E*)-3-{4-[(3*S*,4*R*)-4-(4-Chlorophenylcarbamoyl)-1-methyl-pyrrolidin-3-yl]-phenyl}-acryloylamino)-phenyl]-carbamic Acid *tert*-Butyl Ester (11). To a 1 L three-neck flask equipped with a mechanical stirrer, temperature probe, and argon inlet, **19** (80 g, 0.203 mol), (2-acryloylamino-phenyl)-carbamic acid *tert*-butyl ester (58.2 g, 0.224 mol), and DMF (400 mL) were charged. The solution was sparged with argon for 20 min. *N*-Methyl-dicyclohexylamine (51.6 g, 0.264 mol), $Pd_2(dba)_3$ (1.86 g, 20.3 mmol), and tri(*o*-tolyl)phosphine (1.24 g, 40.6 mmol) were added in sequence. The mixture was stirred at 80 °C for 1.5 h until the reaction was complete and then concentrated at 50−60 °C under reduced pressure (20 mbar) to remove DMF (300 mL). The residue was diluted with EtOAc (1.6 L) and filtered through Celite. The filtrate was washed with water (800 mL) and brine (20 wt %, 400 mL) and then concentrated under reduced pressure to remove the EtOAc. The residue was reslurried in MTBE (800 mL) at room temperature overnight. The solid product was collected by filtration and dried in vacuum overn at 40 °C/25 mbar for 30 h to give **11** (92.1 g, 98.9 A%, yield 79%) as an off-white solid.

(3*R*,4*S*)-4-{4-[(*E*)-2-(2-Aminophenylcarbamoyl)-vinyl]-phenyl}-1-methyl-pyrrolidine-3-carboxylic Acid (4-Chlorophenyl)-amide (1). To a 50 mL flask **11** (2.60 g, 4.33 mmol) and MeOH (26 mL) were charged under nitrogen. The suspension was stirred at 0−5 °C in an ice−water bath. A solution of HCl in ethyl acetate (3 mol/L, 30 mL) was added at 0−5 °C over 10 min. The batch was stirred at 0−5 °C for 3 h until the reaction was complete. Solvents and excess HCl was removed at 20 °C under reduced pressure (35−45 mbar). The residual oil was diluted in MeOH (20 mL) and concentrated again. The crude was redissolved in MeOH (40 mL). Aqueous Na_2CO_3 (10%) was added to the solution at 10−20 °C with stirring until the pH of the reaction mixture was 8.0. Water (25 mL) was added to the suspension and stirred for 30 min. The solid product was collected by filtration, washed with water, and then dried in a vacuum oven at 45−50 °C/30 mbar to give crude **1** (2.50 g). The solid was reslurried in reflux ethanol (16 mL) for 1 h. The suspension was cooled to 5−10 °C and filtered. The filter cake was dried in a vacuum oven at 45−50 °C for 1 day. The solid was reslurried in MeOH (12.5 mL) at 50−55 °C for 3 h, and water (35 mL) was added. The suspension was cooled to 5−10 °C and filtered. The filter cake was dried in a vacuum oven at 45−50 °C/30 mbar to give **1** (1.80 g, 98.5 A%, yield 86.5%) as a light yellow solid with the desired polymorphic form B.

■ ASSOCIATED CONTENT

Supporting Information

General analytical methods and copies of ^{1}H and ^{13}C NMR for compounds **1**, **5**, **6**, **7**, **9**, **10**, **11**, **13**, **14**, **16**, **17**, **18**, **19**, and **29**; synthesis of [Ru(OAc)$_2$((*R*)-furyl-MeOBIPHEP)] (**29**), crystallographic data (tables of bond lengths and angles, complete atomic coordinates, anisotropic displacement coefficients, and isotropic displacement coefficients for hydrogen atoms) and analytical data (HRMS, ^{1}H NMR, ^{31}P NMR, IR, and Raman). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: michelangelo.scalone@roche.com.

*E-mail: zhengming.du@roche.com.

Notes

The authors declare no competing financial interest.

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