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Process Research for (+)-Ambrisentan, an Endothelin-A Receptor Antagonist

Wei-Dong Feng†*, Song-Ming Zhuo*‡*, Jun Yu*§*, Chuan-Meng Zhao*§*, Fu-Li Zhang*†§*

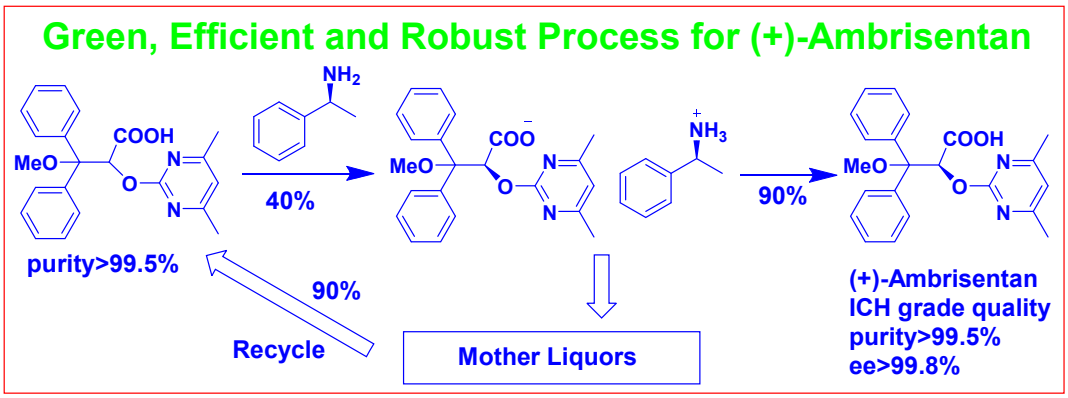
†Collaborative Innovation Center of Yangze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology, 18 Chaowang Road, Hangzhou 310014, China

‡Department of Pharmaceutial Engineering, China Pharmaceutical University, 24 Tongjiaxiang, Nanjing 210009, China

§Shanghai Institute of Pharmaceutical Industry, China State Institute of Pharmacetical Industry, 285 Gebaini Road, Pudong, Shanghai 201203, China

*E-mail: zhangfuli1@sinopharm.com

TOC graphic


Green, Efficient and Robust Process for (+)-Ambrisentan
NH2
COOH
MeO
O
N
N
40%
COO
NH3
90%
purity>99.5%
90%
Recycle
Mother Liquors
(+)-Ambrisentan
ICH grade quality
purity>99.5%
ee>99.8%

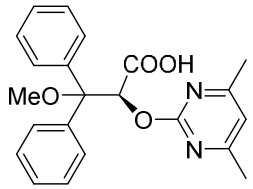
ABSTRACT

An efficient and robust synthetic route to (+)-ambrisentan ((+)-AMB) was designed by recycling the unwanted isomer from the resolution mother liquors. The racemization of AMB in the absence of either acid or base in the given solvents was reported. The recovery process was developed to produce racemates with purities over 99.5%. The mechanism of the formation of the process-related impurities of (+)-AMB is also discussed in detail. (+)-AMB was obtained in 47% overall yield with >99.5% purity and 99.8% e.e. by chiral resolution with only one recycling of the mother liquors on a 100-g scale without column purification.

KEYWORDS Process, Recovery, Ambrisentan, Pulmonary arterial hypertension

INTRODUCTION

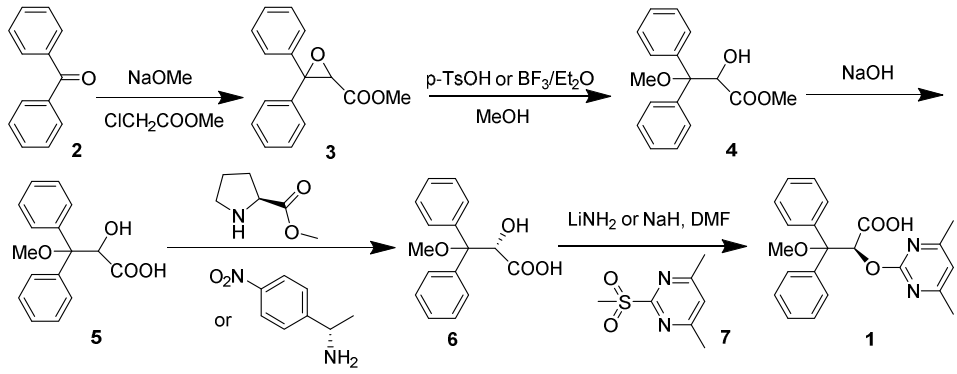
Pulmonary arterial hypertension (PAH) is a devastating chronic disease characterized by vasoconstriction, remodeling of the pulmonary arteries, progressive increases in pulmonary vascular resistance, and thrombosis.[1] The median life expectancy from the time of diagnosis in patients with PAH without targeted treatments is 2.8 years.[2] There are three targets that are used by drugs such as endothelin receptor antagonists, phosphodiesterase type-5 inhibitors, and prostacyclin derivatives to control the disease.[3]



(+)-AMB

(+)-AMB, which has the brand name Letairis®, is a selective endothelin-A (ET_A) receptor antagonist and was approved by the FDA in June 2007 for the treatment of PAH. It has far fewer side effects than bosentan, a nonselective antagonist for type A (ET_A) and type B (ET_B) receptors.[4]

Scheme 1. General synthetic route to (+)-AMB



The general route[5] for the synthesis of (+)-AMB, as shown in **Scheme 1**, involves the formation of epoxide **3** via the Darzens reaction with benzophenone and methyl chloroacetate in the presence of NaOMe in THF and subsequent acid-catalyzed ring-opening with MeOH to produce ester **4**. The hydrolysis of ester **4** to carboxylic acid **5** followed by chiral resolution with various amines yields optically active carboxylic acid **6**, which undergoes nucleophilic substitution with pyrimidine **7** to give final

product **1**. The selection of the optical resolution agent has been studied a number of times in the past few years. The use of methyl *L*-prolinate and (*S*)-1-(4-nitrophenyl)ethan-1-amine as optical resolution agents on a laboratory scale has been reported, and a yield of 35% based on the racemates and an optical purity of 99.8% were achieved.[6] However, when the described reaction step is scaled up (several kg to 100 kg), additional work-up procedures become necessary to ensure a high optical purity. The diastereomeric salt of (*S*)-2-hydroxypropionic acid **6** and (*S*)-1-(4-nitrophenyl)ethan-1-amine is difficult to crystallize in the scale-up process, and it cannot been smoothly removed by filtration. As a result, some of the mother liquor containing the undesired enantiomer remains in the crystals. Only when the crystals are subsequently stirred in a tank together with fresh solvent and are filtered to give a fresh solid, which is then rewashed several times with solvent, is the required optical purity obtained. The chiral separation of **5** using (*S*)-1-(4-chlorophenyl)ethan-1-amine as the optically active base successfully avoids the above problem;[7] however, the amine is a chemical by-product and has not been widely commercialized. Furthermore, the maximum yield can only be 50% from **5** to **6** via chiral resolution, and discarding the isomer of **6** as waste is not environmentally friendly.

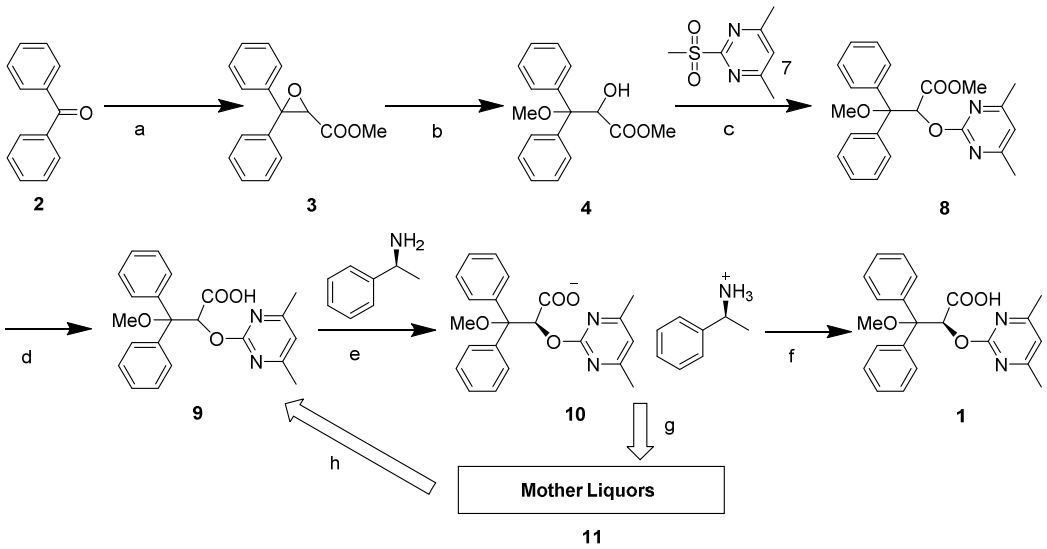
Methodologies for the preparation (+)-AMB via asymmetric techniques, such as asymmetric epoxidation,[8] asymmetric Darzens

reaction,[9] and asymmetric reduction,[10] have been reported. However, these asymmetric methods have many drawbacks, such as (a) the starting material or the chiral catalyst not being available commercially, (b) the synthetic route being too long, and (c) the enantioselectivity not being sufficiently high. Moreover, even though it only accounts for 1% of the final product, (-)-AMB is not easily purged by recrystallization because the solubility of (±)-AMB is very poor in alcoholic solvents. Thus, none of the above approaches are suitable for manufacturing scale-up. Developing an economical, efficient, practical and robust process route for commercialization is highly desirable.

RESULT AND DISCUSSION

We herein report an improved synthetic route for the preparation of (+)-AMB (**1**), as shown in **Scheme 2**.

Scheme 2. Improved synthetic route to (+)-AMB[a]

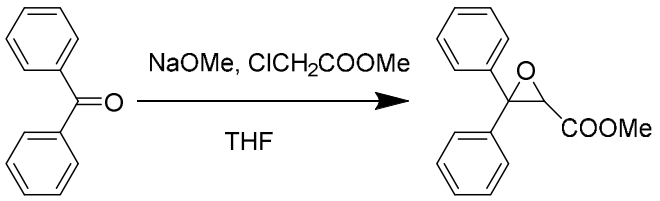


[a]Reagents and conditions: (a) NaOMe, $ClCH_2COOMe$, THF, -10~-5 °C, 3 h, 95%; (b) conc. HCl, MeOH, 25~30 °C, 3 h, 90%; (c) K_2CO_3, DMF, 85 °C, 8 h, 94%; (d) KOH, H_2O, dioxane, 80 °C, 4 h, 96%; (e) S-α-phenylethylamine, recrystallized with IPA and MTBE, 40%; (f) (1) HCl, H_2O, IPA; (2) crystallized with IPA and H_2O, 90%; (g) HCl, H_2O, IPA; (h) MeCN, reflux, 3 h, 90%.

Preparation of methyl 3,3-diphenyloxirane-2-carboxylate (3). The Darzens condensation was carried out with excess $ClCH_2COOMe$ and NaOMe at 0~5 °C.[5b] Under the above conditions, approximately 14.9% benzophenone remained by HPLC because the competing Williamson reaction preferentially occurred between $ClCH_2COOMe$ and NaOMe at 0~5 °C, as shown in **Table 1** (entry 3). The temperature had to be appropriately controlled to avoid the Williamson reaction as much as possible. The temperature screening experiments indicated that the reaction proceeded much faster at -10~-5 °C, as shown in **Table 1** (entry 2). However, when the reaction was run at lower temperatures even with an extended reaction time, the conversion rate did not increase significantly, as shown in **Table 1** (entry 1). Since the reaction requires excess $ClCH_2COOMe$ and NaOMe, the stoichiometry of the reagents was also investigated, and the results are summarized in **Table 2**. The best result was obtained with 1.7 eq of both $ClCH_2COOMe$ and NaOMe (**Table 2**, entry 3). If the amounts of $ClCH_2COOMe$ and NaOMe were

further increased, the reaction did not reach completion, and 3.2% of the starting material remained, as shown in **Table 2** (entry 4).

Table 1. Screening of the reaction temperature for the Darzens reaction

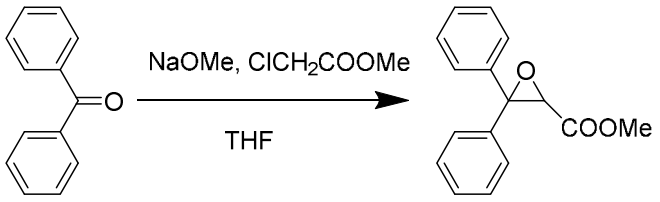


2 **3**

			HPLC (%)[b]	
entry[a]	T (°C)	T (h)	**2**	**3**
1	-20~-15	6	7.2	92.8
2	-10~-5	3	3.2	96.8
3	0~5	3	14.9	85.1

[a]Reaction conditions: $ClCH_2COOMe$ (2.0 eq), NaOMe (2.0 eq). [b]Only peak areas (%) of **2** and **3** were integrated on HPLC.

Table 2. Screening of reaction stoichiometry for the Darzens reaction



2 **3**

			HPLC (%)[b]	
entry[a]	eq	t (h)	**2**	**3**
1	1.3	6	25.2	74.8
2	1.5	3	15.9	84.1
3	1.7	3	3.5	96.5

4	2	3	3.2	96.8

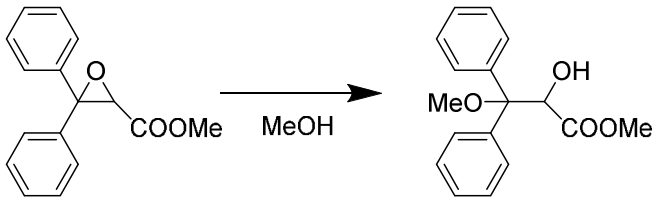
[a]Reaction temperature: -10 °C~-5 °C. [b]Only peak areas (%) of **2** and **3** were integrated on HPLC.

The work-up procedure involved dilution of the reaction mixture with MTBE followed by cold water washes to neutralize the pH to minimize the hydrolysis of epoxide **3**, and this was followed by concentration of the mixture and a solvent swap with methanol. The minor quantities of 2 and the methoxymethylacetate impurity were removed in the next step. The hydrolytic impurity of **3** was detected by LC-MS to be less than 1.0%, and it can be removed by washing with water. The organic phase was concentrated and exchanged with MeOH under reduced pressure. The weight content of **3** in MeOH was determined by HPLC analysis using the external standard method to obtain an accurate yield.

Preparation of methyl 2-hydroxy-3-methoxy-3,3-diphenylpropanoate (4). The ring opening of epoxides using nucleophiles under acid catalysis is well known. Intermediate **4** was obtained from epoxide **3** in the presence of an acid catalyst and MeOH due to the formation of a stable diphenylmethylium species, and MeOH not only served as the solvent but also as the nucleophilic reagent. The ring-opening of epoxide **3** was catalyzed with either a Lewis or Brønsted acid, as described in the literature.[8,11] Catalysts such as BF_3, conc. HCl, and H_2SO_4 were screened in our study, and the results shown in **Table 3** indicated that the reaction

proceeded with high conversion in all cases. Since the quenching of BF_3 required the addition of water, which produced highly toxic HF smog, it was unsuitable for scale-up at a plant. Reactions of p-TsOH or $MeSO_2OH$ with methanol would generate p-TsOMe or $MeSO_2OMe$, which are genotoxic to humans.[12] Similarly, the potential esterification of MeOH with H_2SO_4 produces Me_2SO_4, a highly toxic carcinogen.[13] HCl was chosen as the safe acid catalyst for large-scale commercial processes because unlike H_2SO_4 and HNO_3, it is not an oxidant.

Table 3. Preparation of 4 with various acid catalysts



3 **4**

entry	acid	T/t (°C/h)	Yield (%)[a]
1	BF_3	50/4	86
2	TsOH	35/3	88
3	$MeSO_2OH$	30/2	91
4	conc. HCl	30/3	90
5	HNO_3	25/3	86
6	H_2SO_4	25/2	89

[a]Isolated yield of 4.

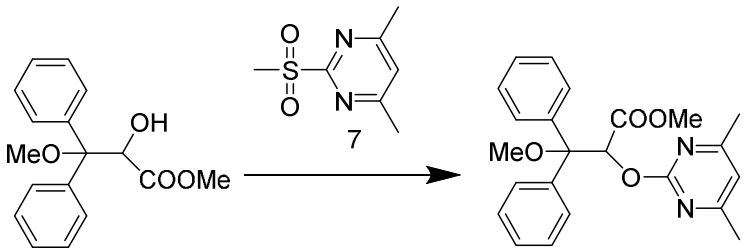
The hydrolytic impurity of **4** was detected on LC-MS and HPLC and accounted for approximately 2.0% of the material. The ring-opening impurities resulting from Cl^- and H_2O as nucleophilic reagents were also detected by LC-MS to be less than 1.0%. These impurities were

successfully removed along with those carried over from the previous step by recrystallization in MeOH.

Preparation of methyl 2-((4,6-dimethylpyrimidin-2-yl)oxy)-3-methoxy-3,3-diphenylpropanoate (8). The coupling reaction of **4** and **7** in the presence of a base at appropriate temperatures afforded ether **8**. Initially, we followed the reaction conditions for the preparation of **1** as shown in **Scheme 1,** and a strong base, such as NaH or $NaNH_2$, was used in the literature.[14] The hydrolytic byproducts of **4** and **8** were detected at approximately 2.3% and 1.2% on HPLC, respectively, because of the presence of a small amount of water from the solvent and atmosphere in the reaction mixture. The byproducts from the elimination of MeOH and the C-O cleavage of the pyrimidyl ether moiety of **8** were detected by LC-MS. Furthermore, the reaction mixtures of NaH or $NaNH_2$ and DMF have potential risks of explosion in pilot plants,[15] and therefore, various alternative bases and solvents were screened for this reaction. If an inorganic base is used as the deprotonation reagent, aprotic solvents are preferable over protic solvents. We have attempted this coupling reaction using solvents such as MeCN, THF, and DMF, as summarized in **Table 4**. When THF or toluene was used, the formation of a highly viscous mass hampered the reaction and caused incomplete conversion of the starting material (entries 2 and 3). The coupling reaction performed well using MeCN as the solvent but

required a large quantity of MeCN. The stirring efficiency of the reaction mixture was improved, and the yield sharply increased when DMF was used as the solvent (entry 5). Experimental results suggested that the reaction conversion was considerably higher with solvents of high polarity; therefore, DMF was selected for this reaction. Not surprisingly, no desired product was found in the absence of base even if the solvent was DMF (entry 9). Different bases, such as $NaHCO_3$, Na_2CO_3 and Cs_2CO_3, were investigated during optimization studies. Generally, higher conversions were observed with stronger bases, as shown in **Table 4** (entries 5, 6, 7 and 8). As expected, potassium and cesium were both better counterions than sodium, as they provided higher conversions in the substitution reaction. With the additional consideration of the high cost and hygroscopicity of Cs_2CO_3, K_2CO_3 was selected as the preferred base. When the temperature was lowered, a longer reaction time was required (entry 10). To summarize the above results, the optimized reaction conditions for the coupling of **4** and **7** were K_2CO_3 as the base in DMF at 90 °C for 8 h.

Table 4. Coupling of 4 and 7 under various conditions



4 8

entry	solvent	base (1.0 eq)	T/t (°C/h)	HPLC[a]
1	MeCN	K_2CO_3	80/16	95.5
2	THF	K_2CO_3	65/16	79.7
3	toluene	K_2CO_3	90/16	73.8
4	dioxane	K_2CO_3	90/16	94.7
5	DMF	K_2CO_3	90/8	97.3
6	DMF	$NaHCO_3$	90/16	82.4
7	DMF	Na_2CO_3	90/16	88.9
8	DMF	Cs_2CO_3	90/8	96.5
9	DMF	none	90/16	ND
10	DMF	K_2CO_3	70/16	95.3

[a]HPLC purity of the reaction mixture.

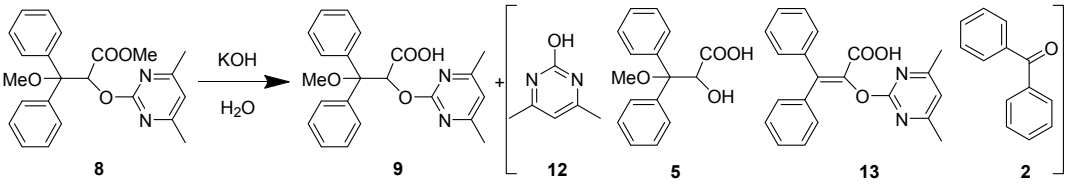
The previously mentioned methanol elimination and C-O cleavage byproducts were not detected by LC-MS under the present reaction conditions. The hydrolytic impurities of **4** and **8** were both less than 1.0% by HPLC analysis, and the hydrolytic byproduct of **8** was racemic **9**, which was the product of the next step. The hydroxy-substituted impurity of **7** was also detected by LC-MS (<1.0% on HPLC). Intermediate **8** was a hydrophobic organic compound so it could be precipitated from the mixture of DMF and H_2O. However, despite the water being added to the reaction mixture very slowly, a sticky bulk solid appeared, which would cause difficulties during scaling up in the pilot plant. In view of this, it was not practical to directly add water to the reaction mixture. The addition of a third solvent that was not only miscible with DMF and H_2O but also partially dissolved intermediate **8** was considered. Ultimately,

MeOH was selected through solvent screening. In the end, the most practical work-up procedure was dilution of the reaction mixture with MeOH followed by slow addition of water to generate the precipitate, and desired intermediate **8** was easily filtered from the mixture. No remaining desired product was detected in the filtration mother liquors by HPLC. The crude product was further purified by recrystallization in methanol and water to give intermediate **8** with over 99.5% purity on HPLC.

Preparation of racemic (±)-AMB (9). The steric hindrance from the ester moiety of **8** was larger than that of **4** and disfavored the hydrolysis. Therefore, harsh ester hydrolysis conditions were applied in the step. A large amount of **8** was unreacted even when refluxing in a mixture of aqueous KOH and THF for 16 hours, as shown in **Table 5** (entry 1), because the solubility of **8** was poor in aqueous THF. The hydrolysis of **8** was very rapid in NMP (entry 3), but byproduct **13** from MeOH elimination was detected by HPLC (approximately 31%). The data in the table showed that the content of impurity **13** increased with increasing solvent polarity. Impurity **13** was likely formed via the elimination of MeOH from **8** followed by ester hydrolysis in aqueous potassium hydroxide because the carbonyl α-H of **8** was more susceptible to deprotonation than its counterpart in acid **9**. Similarly, impurity **13** was also detected (approximately 14% on HPLC) when using MeOH as the reaction solvent (entry 2). When dioxane was eventually chosen as the

reaction solvent, the level of impurity **13** decreased substantially (only approximately 7% on HPLC). In all cases, hydroxyl-containing impurity **5** was detected (<5%) and was presumably formed by the nucleophilic displacement of the pyrimidinoloxy moiety by a hydroxide anion, simultaneously generating impurity **12**. The formation mechanism of impurity **2** along with **12** was proposed as in **Scheme 3**. The deprotonation of the methine group adjacent to the carboxylic ester in the basic environment could lead to the elimination of the methoxy group to afford α,β-unsaturated ester **8a**, which upon Michael addition with hydroxide would lead to **8b**. This intermediate finally fragmented into impurities **2** and **12** under the strong basic conditions as indicated. Interestingly, experiments showed that desired product **9** was not degraded in the strong basic conditions since the elimination of the methoxy group in **9** was unlikely due to the reduced acidity of the carbonyl α-H of **9.**

Table 5. Hydrolysis of 8 using various solvents

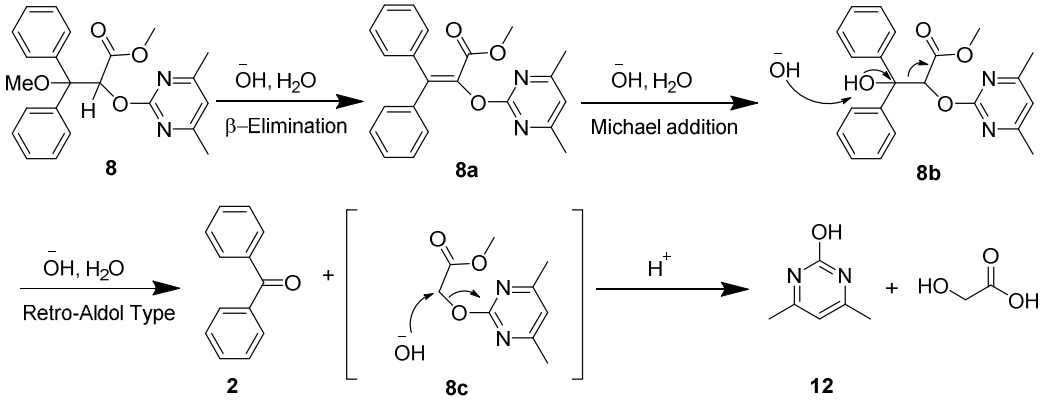


			HPLC[b]					
entry[a]	solvent	T/t(°C/h)	**8**	**9**	**12**	**5**	**13**	**2**
1	THF	65/16	82.56	16.08	0.21	0.41	0.17	0.60
2	MeOH	65/16	0.74	82.53	0.13	1.47	14.41	0.70

3	NMP	80/1	0.27	61.16	2.36	4.43	30.84	0.95
4	dioxane	80/5	0.28	91.61	0.47	0.70	6.89	0.04

[a]KOH (2 equiv), 15% NaOH aqueous solution. [b]HPLC purity of the reaction mixture.

Scheme 3. Proposed formation mechanism of impurities 2 and 12



After the reaction was completed, the reaction mixture was diluted with water and extracted with DCM to remove nonpolar impurities. If dilute hydrochloric acid was directly added to the separated water layer, a substantial amount of viscous matter precipitated, which hampered stirring during scale-up. The improved work-up procedure was as follows: the reaction mixture was first diluted with IPA, and the acid was then slowly added to precipitate the product without the formation of the viscous matter.

Preparation of (+)-AMB (1). Commercially available and inexpensive *S*-α-phenylethylamine was first chosen as the chiral resolution agent. To our delight, the optical purity of the diastereomeric salt **10** was up to 98.5% in MeOH, but the best yield was only 20%. When it was replaced by EtOH and IPA, the yield increased to 24% and 30%, respectively. The

yield was further improved by adding an antisolvent such as n-heptane, IPE or MTBE. The experiments indicated that the chiral purity of diastereomeric salt **10** was highest when the chiral resolution was performed in a mixture of IPA and MTBE. The other isomer was undetectable by chiral HPLC following a simple recrystallization of the crude salt in the same solvent, and the yield of the chiral resolution was up to 40%.

Generally, diastereomeric salt **10** was dissociated with dilute hydrochloric acid, and the free (+)-AMB was extracted with solvents such as EA, toluene or DCM, but its solubility was very poor in most of these solvents. Although it was highly soluble in DCM, partial racemization of (+)-AMB was observed on chiral HPLC. In addition, a large amount of solvent would need to be distilled, which is not convenient for scale-up production. The improved procedure was as follows: diastereomeric salt **10** was dissolved in IPA at 50 °C, and then dilute hydrochloric acid was slowly added to the resulting clear solution to precipitate desired free acid **1** without using extraction or distillation operations.

Purification of crude **1** to obtain highly pure (+)-AMB was a challenging task. Our primary goal was to reduce the production cost by minimizing the loss of the product during the purification process. Therefore, we tested a variety of recrystallization conditions using

solvents such as MeOH, IPA, and H_2O and mixtures of these solvents. Finally, IPA and H_2O in a 1:1 ratio provided good yield (~90%) of highly pure (+)-AMB of ICH-grade quality. The polymorphic stability of (+)-AMB was examined under different temperatures and humidity levels by powder X-ray diffraction (PXRD) studies and thermogravimetric analysis (TGA). PXRD analysis demonstrated that the product had the same crystal form as that reported for (+)-AMB in the literature.[5d] In the TGA experiments, the material lost less than 0.03% of its weight, which indicated that the residual solvent and water content were low.

Recovery of (±)-AMB (9). Chiral resolution is not cost-effective as the maximum possible yield is 50%. The recovery of the unwanted isomer from the chiral resolution mother liquors was studied herein. Partial racemization of **1** was observed during the conversion of diastereoisomer salt **10** to free acid **1** in DCM. Although the spontaneous racemization of some chiral compounds in polar aprotic solvents has been previously reported,[16] there has been no precedent for such racemization of (+)-AMB in the absence of an acid. Different solvents were screened for the racemization of **1**, as shown in **Table 6**. Complete racemization of **1** was observed in EA, MeCN, toluene and pyridine at elevated temperature, but the HPLC purity was lower when the reaction was conducted in toluene or pyridine due to partial thermal degradation. MeCN was finally chosen as the solvent because the racemization time was the shortest

compared with the above solvents (entry 18). Generally, the racemization of **1** occurred easily in polar aprotic solvents at elevated temperature, as shown in **Table 6**. It was unclear whether the racemization could be catalyzed by a small amount of residual hydrochloric acid from the preceding steps. This hypothesis was ruled out by the following experiments. Solid (+)-AMB with high optical purity was dissolved in EA and washed with an aqueous solution of 5% $NaHCO_3$ and water three times. Racemic AMB was again obtained when the solution was dried over Na_2SO_4 and refluxed for 16 h.

Table 6. Racemization of (+)-AMB in various solvents and at various temperatures

entry[a]	solvent	T/t (°C/h)	HPLC[b]
1	MeOH	65/16	99.9
2	EtOH	78/16	99.9
3	IPA	82/16	99.9
4	IPE	68/16	99.9
5	MTBE	55/16	99.8
6	heptane	98/16	99.9
7	THF	66/16	99.4
8	2-Me-THF	80/6	99.1
9	acetone	56/16	98.4
10	Et_3N	90/16	95.9
11	dioxane	100/16	96.3
12	HOAc	90/16	96.1
13	CH_2Cl_2	39/16	83.3
14	NMP	100/16	83.1
15	DMSO	100/16	86.6
16	DMF	100/8	58.6

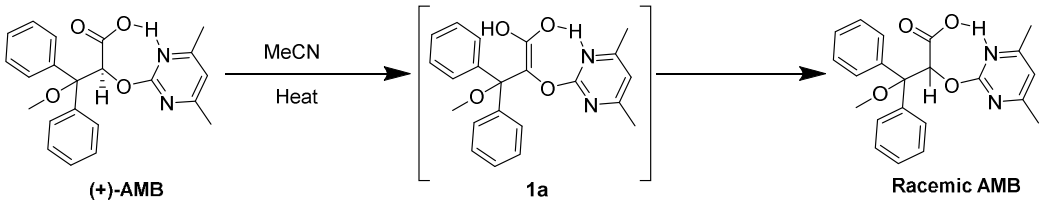
17	EA	77/16	50.2[c]
18	MeCN	81/3	50.1[d]
19	pyridine	90/16	49.4[e]
20	toluene	100/16	51.1[f]
21	MeOH/HCl	60/16	99.9
22	MeOH/MeONa	60/16	99.8

[a]Optical purity is over 99.9% and HPLC purity is over 99.9% for (+)-AMB. [b]Optical purity. [c,d]HPLC purity is 99.9%. [e]HPLC purity is 95.6%. [f]HPLC purity is 97.1%.

The possible racemization mechanism of (+)-AMB is depicted in **Scheme 4**. Although the pyrimidine moiety and the carboxy group could not form a stable salt, the possible intramolecular hydrogen bonds would result in a relatively stable bicyclic structure in polar aprotic solvents such as EA and MeCN. This could in turn enhance the carbonyl's tendency to undergo thermal or acid-catalyzed enolization with the formation of unstable intermediate **1a**. Upon tautomerization of the enol to the carbonyl compound, racemic AMB would be generated. The racemic mixture was eventually obtained in equilibrium since it was thermodynamically more stable than the corresponding enantiomers. This process was further facilitated by the fact that the racemate precipitated from the solution due to its lower solubility than the enantiomers. Racemization did not occur in protic solvents such as MeOH (entries 1, 2, 3, 21, and 22) probably because these solvents prevented the formation of the intramolecular hydrogen bond. The more difficult racemization in very polar aprotic solvents such as DMSO might be explained by the fact

that the racemate could not precipitate under these conditions (entries 13, 14, 15, and 16). The extremely low solubility of (+)-AMB in nonpolar solvents such as heptane could be the reason that it did not racemize by simple heating.

Scheme 4. Proposed racemization mechanism of (+)-AMB



The chemical purity of the resolution mother liquors was only approximately 95%, excluding *S*-α-phenylethylamine on HPLC, and it was enriched in (-)-AMB. The free acid was precipitated from the resolution mother liquors by the treatment with the mixture of dilute hydrochloric acid and IPA, and the purity of the solid was over 99.5% after a simple filtration work-up procedure. The free acid was refluxed in MeCN for 3 h and filtered to give racemic **9**, which was subjected to the same resolution process with S-α-phenylethylamine to give (+)-AMB in high purity.

CONCLUSION

In conclusion, we have developed a recoverable, cost-effective, industrially scalable synthetic route to (+)-AMB, an endothelin-A receptor antagonist. Throughout the synthetic route, common and inexpensive regents, such as the resolving agent *S*-α-phenylethylamine,

were used. Every process step was optimized, and all process-related impurities were successfully removed to give the drug substance in high chemical and chiral purities. The practicable method involved a thermal racemization of chiral AMB, which was disclosed in the selected polar aprotic solvents without the aid of an external acid or base. Accordingly, an efficient recycling resolution process was developed to improve the overall yield. Furthermore, the process of converting the salt to the free acid served the dual purpose of dissociating diastereomerically pure salt **10** and recovering free acid **11** from the resolution mother liquors. When the unwanted isomer from the resolution mother liquors was recycled only once, the overall process yield was up to 47% in contrast to 18% for the usual route, as depicted in **Scheme 1**.[5d.]

EXPERIMENTAL SECTION

All solvents and reagents were purchased from suppliers and were used without further purification. NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer in DMSO-d_6 with Me_4Si (TMS) as an internal standard. Mass spectra (MS) were recorded on an Agilent 6210 series single quadrupole LC/MS. High-resolution mass spectrometry (HRMS) measurements were recorded on a Bruker Daltonics Solarix 7.0T. Melting points (MP values) were measured on a WRS-1B apparatus. Thermogravimetric analysis (TGA) was performed on a TA TGA Q500 analyzer with a heating rate of 10 °C/min under a nitrogen atmosphere.

Elemental analysis (EA) was performed on a Thermo Flash 2000 instrument. Specific rotation data were measured on an Anton Paar MCP 500. Powder X-ray diffraction (PXRD) data were recorded on a Bruker D8 Advance. The reactions were monitored by HPLC, and the purities were calculated from the HPLC peak areas. The HPLC analyses were recorded using a standard method on a Dionex UltiMate 3000 HPLC instrument using a Fortis C18 column (250 mm × 4.6 mm, 5 μm), 30 °C, 1 mL/min, 220 nm, 45 min. The mobile phase involved the mixture of 32% MeCN and 68% aqueous KH_2PO_4 (0.02 mol/L, pH adjusted to 3.0 by using phosphoric acid) as phase A and MeCN as phase B. The HPLC analyses were accomplished with a gradient elution program (time (min)/% B: 0/0, 10/0, 20/50, 35/50, and 45/0). The chiral HPLC separations were performed using a CHIRALPAK AD-H (250 mm × 4.6 mm, 5 μm, DAICEL, Shanghai) column with a mobile phase of 95% hexane and 5% EtOH (0.1% TFA), 30 °C, 0.5 mL/min, 263 nm, and 35 min.

Methyl 3,3-diphenyloxirane-2-carboxylate (3). A 5-L reactor was charged with **2** (300.0 g, 1.65 mol), NaOMe (156.1 g, 2.89 mol) and THF (0.6 L) under an atmosphere of nitrogen. $ClCH_2COOMe$ (313.6 g, 2.89 mol) was added to the stirring mixture at -10~-5 °C over 3 h, and then the mixture was stirred for another 30 min at -10~-5 °C. The reaction was monitored by HPLC and deemed complete when **2** was less than 3.0%. The reaction mixture was diluted with MTBE (1.2 L) and water (0.6 L).

The aqueous layer was discarded, and the organic layer was washed twice with 10% aqueous NaCl until pH = 7~8. Then, the organic solvent was evaporated and replaced by MeOH (0.3 L) under reduced pressure at 35 °C. The residue was directly used for the next step. When the weight assay of **3** was performed on HPLC with the external standard method, the actual yield was 95% (purity > 97.0%). A small analytical sample of epoxide **3** was purified by recrystallization from EA and heptane. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35-7.40 (m, 8H), 7.29-7.31 (m, 2H), 4.33 (s, 1H), 3.48 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.54, 138.55, 135.42, 128.53, 128.51, 128.28, 128.19, 127.44, 126.83, 66.91, 60.98, 51.90. HRMS *m/z* $[M+Na]^+$ Calcd for $C_{16}H_{14}NaO_3$: 277.0841; found: 277.0835.

Methyl 2-hydroxy-3-methoxy-3,3-diphenylpropanoate (4). The solution from the previous stage was diluted with MeOH (1 L) and transferred to a 2-L reactor at room temperature. Hydrochloric acid (37%, 4 mL) was added to the above reactor until pH = 2. The exothermic reaction (35 °C) was complete (<2.0% of **2** by HPLC) after 2 h with the formation of a white precipitate. The reaction mixture was cooled to 0~5 °C. After stirring for 1 h, the solid product was isolated by filtration, washed with cold (0~5 °C) MeOH (0.5 L) and then dried in an air-drying oven at 40 °C to yield the title compound as a white solid (403 g, yield: 90%, purity > 99.0%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.26-7.33 (m,

8H), 7.21-7.24 (m, 2H), 5.79 (d, J = 3.6 Hz, 1H), 5.20 (d, J = 3.6 Hz, 1H), 3.40 (s, 3H), 3.19 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.78, 142.65.09, 141.64, 128.37, 127.90, 127.57, 127.10, 126.97, 126.74, 83.76, 74.20, 52.66, 51.07. HRMS *m/z* $[M+Na]^+$ Calcd for $C_{17}H_{18}NaO_4$: 309.1103; found: 309.1097.

Methyl-2-((4,6-dimethylpyrimidin-2-yl)oxy)-3-methoxy-3,3-diphenyl propanoate (8). A 10-L reactor was charged with **4** (400.0 g, 1.40 mol), 7 (273.2 g, 1.47 mol), K_2CO_3 (193.5 g, 1.40 mol) and DMF (480 mL) under an atmosphere of nitrogen. The stirring mixture was heated at 85 °C for 8 h. The reaction was monitored by HPLC, and **4** was less than 1.0%. The reaction mixture was cooled to 40~50 °C and diluted with MeOH (1.2 L). Water (1 L) was added slowly over 30 min. The solid precipitated after 15 min, and more water (2.6 L) was added to the reaction mixture over 30 min while maintaining the mixture at 40~50 °C. The mixture was cooled to room temperature and stirred for 1 h. The solid was isolated by filtration, washed with water (0.5 L) three times and then dried in an air-drying oven at 40 °C. The white powder was suspended in MeOH (1 L) and refluxed to yield a clear solution. Water (0.37 L) was slowly added to the solution over 40 min, and then the mixture was cooled to 0~5 °C. After stirring for 1 h, the obtained solid was isolated by filtration, washed with a mixture of MeOH and H_2O (1:1, 0.6 L) twice, and then dried in an air-drying oven at 40 °C to yield the title compound as a white solid (515

g, yield: 94%, purity > 99.5%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31-7.34 (m, 8H), 7.24-7.29 (m, 2H), 6.96 (s, 1H), 6.09 (s, 1H), 3.37 (s, 3H), 2.33 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.21, 168.33, 162.89, 142.02, 140.95, 127.93, 127.84, 127.75, 127.33, 127.30, 127.21, 114.98, 83.12, 78.07, 53.15, 51.42, 23.32.

2-((4,6-dimethylpyrimidin-2-yl)oxy)-3-methoxy-3,3-diphenylpropanoic acid (9). A 10-L reactor was charged with **8** (500.0 g, 1.27 mol) and dioxane (1.9 L) under an atmosphere of nitrogen. Aqueous potassium hydroxide (143.0 g of KOH in water of 0.81 L) was added to the stirring mixture at room temperature, and then the mixture was heated to 80 °C for 4 h. The reaction was monitored by HPLC, and **8** was less than 1.0%. The reaction mixture was cooled to room temperature and diluted with water (2 L) and DCM (1.5 L). The water layer was separated and diluted with IPA (2.5 L), and the solution was treated with hydrochloric acid (6 N, 0.25 L) until pH = 6~7. After stirring for 1 h, a large amount of white solid precipitated, and a second portion of the acid (6 N, 0.25 L) was slowly added over 1 h until pH = 1~2. The solid product was isolated by filtration, washed twice with a mixture of IPA and H_2O (1:1, 1 L), and then dried in an air-drying oven at 40 °C to give the title compound as a white solid (461 g, yield: 96%, purity > 99.5%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.55 (br, 1H), 7.27-7.35 (m, 8H), 7.21-7.25 (m, 2H), 6.95 (s, 1H), 6.14 (s, 1H), 3.38 (s, 3H), 2.34 (s, 6H); ^{13}C NMR (100 MHz,

DMSO-d_6) δ 169.07, 163.17, 142.66, 141.45, 127.83, 127.73, 127.71, 127.21, 127.00, 114.79, 83.14, 77.61, 53.07, 23.36. HRMS *m/z* $[M+Na]^+$ Calcd for $C_{22}H_{22}N_2NaO_4$: 401.1477; found: 401.1472.

(S)-1-phenylethan-1-aminium (S)-2-((4,6-dimethylpyrimidin-2-yl)oxy)-3-methoxy-3,3-diphenylpropanoate (10). A 5-L reactor was charged with **9** (400.0 g, 1.06 mol), *S*-α-phenylethylamine (192.1 g, 1.59 mol), IPA (0.8 L) and MTBE (3.2 L) under an atmosphere of nitrogen. The stirring mixture was heated to reflux for 30 min and became clear before being allowed to naturally cool to 35~38 °C. Crystal seeds (0.2 g) were introduced to the solution, and the mixture was stirred at 35 °C for 1 h and then at room temperature for 2 h. The solid was isolated by filtration, washed with a mixture of MTBE and n-heptane (1:1, 1.2 L) and dried in an air-drying oven at 40 °C to yield crude **10** (238 g, 45%). A 3-L reactor was charged with the crude product (238 g), IPA (0.48 L) and MTBE (1.9 L). The mixture was refluxed to form a clear solution within 30 min and then cooled naturally before the crystal seeds (0.2 g) were added to the solution. After adding the crystal seeds, the mixture was stirred at 47~50 °C for 1 h. The mixture was cooled and stirred at room temperature for 2 h. The solid was isolated by filtration and washed with a mixture of MTBE and n-heptane (1:1, 0.7 L). The combined mother liquors were concentrated under reduced pressure, and the solvents were replaced by IPA to give a solution of **11** for the recovery operation (total

volume: 0.5 L, purity: 95.0%). The diastereomerically pure salt **10** was dried in an air-drying oven at 40 °C to yield the title compound as a white solid (212 g, yield: 40%, optical purity > 99.9%, HPLC purity > 99.5% (*S*-α-phenylethylamine was not calculated)). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.12-7.39 (m, 15H), 6.84 (s, 1H), 6.15 (s, 1H), 4.09 (q, J = 4.4 Hz, 1H), 3.42 (s, 3H), 2.31 (s, 6H), 1.31 (d, J = 4.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.31, 168.49, 164.03, 144.47, 143.21, 143.04, 128.37, 127.92, 127.49, 127.39, 127.24, 127.21, 126.44, 126.39, 126.09, 113.80, 83.60, 79.05, 53.07, 49.92, 26.86, 23.41.

(S)-2-((4,6-dimethylpyrimidin-2-yl)oxy)-3-methoxy-3,3-diphenylpropanoic acid (1). A 2-L reactor was charged with **10** (200.0 g, 0.40 mol) and IPA (0.4 L) and heated to reflux for 30 min under an atmosphere of nitrogen. Dilute hydrochloric acid (1.0 N, 0.7 L) was added to the clear solution at 50 °C, and the mixture was stirred for 1 h before naturally cooling to room temperature. The precipitate was isolated by filtration and washed with deionized water (0.3 L) three times and then dried in an air-drying oven to give crude **1** (144 g). Crude **1** and IPA (0.72 L) were placed in a 2-L reactor and heated to reflux for 20 min. Deionized water (0.72 L) was added to the clear solution slowly over 30 min. The crystal seeds (0.1 g) were added to the solution, and it was stirred at 60 °C for 1 h. The mixture was allowed to cool to room temperature over 2 h. The solid was filtered and washed with a mixture of IPA and deionized water

(1:1, 0.2 L) and then deionized water (0.2 L) and dried in an air-drying oven at 40 °C to yield the title compound as a white needle-like crystalline solid (136 g, yield: 90%, optical purity > 99.9%, HPLC purity > 99.5%). Mp 185.0~185.9 °C. Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.72; H, 5.84; N, 7.60. $[\alpha]_D^{25}$ = +168.472 (*c* 1.0, MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.55 (br, 1H), 7.27-7.34 (m, 8H), 7.20-7.25 (m, 2H), 6.95 (s, 1H), 6.13 (s, 1H), 3.38 (s, 3H), 2.34 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.04, 163.16, 142.63, 141.43, 127.81, 127.71, 127.68, 127.19, 126.98, 114.75, 83.14, 77.58, 53.03, 23.33. HRMS *m/z* $[M+Na]^+$ Calcd for $C_{22}H_{22}N_2NaO_4$: 401.1477; found: 401.1472. ESI-MS m/z 377.10 $[M-H]^+$.

Recovery of 9 from the mother liquors of 11. A 5-L reactor was charged with IPA and the resolution mother liquors (total volume: 1.3 L) containing the diastereoisomeric salts (theoretical weight: 318 g) from the preparation of **10**. The stirring solution was heated at reflux to form a clear solution and then cooled to 30 °C. Then, dilute hydrochloric acid (1 N, 1.1 L) was added to the clear solution at 30 °C over 1 h. The white precipitate was isolated by filtration, washed with water three times (300 mL×3), dried in an air-drying oven at 40 °C and then transferred to a 2-L reactor. MeCN (1.2 L) was added to the reactor and heated at reflux (81 °C) for 3 h. In process control of the racemization was monitored by

chiral HPLC until the ratio of the two enantiomers reached 50:50. The whited solid was isolated by filtration, washed with MeCN (0.3 L) and dried in an air-drying oven at 40 °C to give racemate **9** (216 g, yield: 90%, HPLC purity > 99.5%).

ASSOCIATED CONTENT

Supporting Information

Analytical spectrogram and data of compound **3, 4, 8, 9, 10, 1, 12, 13, 14** and recycled racemate **9**.

AUTHOR INFORMATION

Corresponding Author

*E-mail: zhangfuli1@sinopharm.com

ORCID

Wei-Dong Feng: 0000-0002-0347-2762

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

THF, tetrahydrofuran; MTBE, methyl *tert*-butyl ether; MeCN, acetonitrile; DMF, N,N-dimethylformamide; NMP, N-methyl-2-pyrrolidone; DCM,

dichloromethane; IPA, isopropanol; EA, ethyl acetate; MeOH, methanol; EtOH, ethanol; IPE, isopropyl ether; 2-Me-THF, 2-methyltetrahydrofuran; Et_3N, triethylamine; HOAc, acetic acid; DMSO, dimethylsulfoxide; API, active pharmaceutical ingredient; IPC, in process control; (+)-AMB, (+)-ambrisentan; (-)-AMB, (-)-ambrisentan; (±)-AMB, (±)-ambrisentan, eq, equivalent.

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