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Lewis Acid-Catalyzed Racemization and Recycling of the Undesired (*R*)-Ketamine

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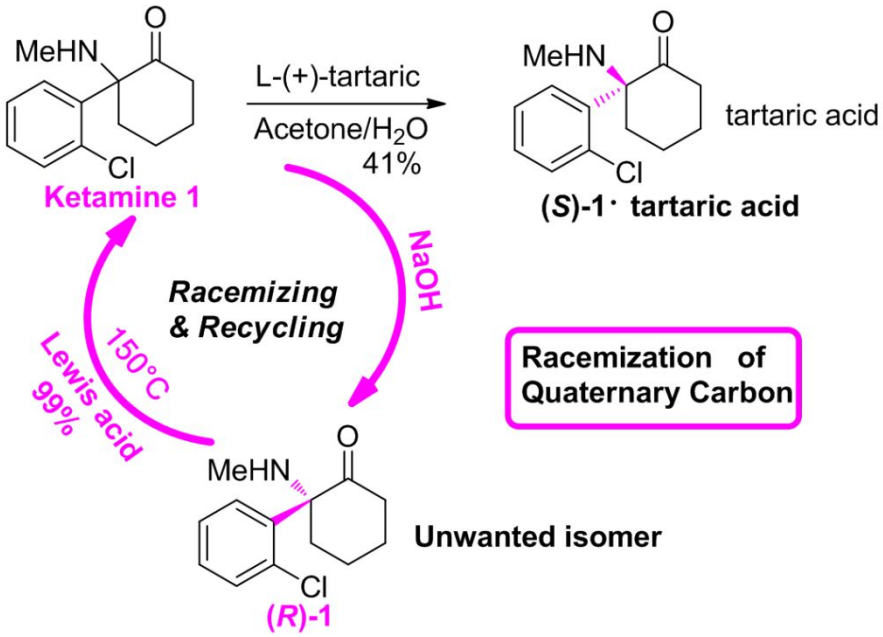
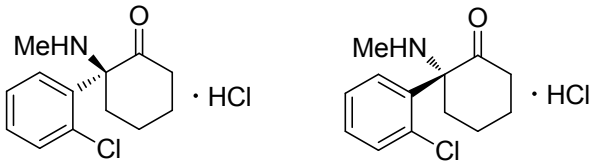


ABSTRACT: The first detailed description of the Lewis acid-catalyzed racemization of (*R*)-ketamine was reported. The process for racemization of the undesired (*R*)-ketamine enantiomer, produced from the resolution for preparing a NMDA receptor antagonist (*S*)-ketamine, was developed in quantitative yield with 99% chemical purity in the presence of Lewis acid at 150 °C. Varying degrees of racemization were observed in the presence of various frequently-used Lewis acids separately and the catalytic efficiency were arranged as follow: $MgCl_2$ ≈ $AlCl_3$ > $FeCl_3$ > $ZnCl_2$ > BF_3 > $CaCl_2$. The racemized ketamine was subsequently resolved by L-(+)-tartaric acid to obtain (*S*)-ketamine in 41% yield and with 99.5% ee. Such a concise and cost-efficient approach of the racemization can be industrially useful to recycle the waste (*R*)-ketamine enantiomer into the resolution process to obtain the (*S*)-ketamine.

KEYWORDS: Racemization, Ketamine, Lewis Acid, NMDA Receptor Antagonis.

INTRODUCTION

Ketamine ((±)-**1**) is chemically known as (±)-2-(2-Chlorophenyl)-2-(methylamino)-cyclohexanone and marketed as Ketalar, which acts on the central nervous system as an N-methyl-Daspartate (NMDA) receptor antagonist, and was primarily used for the induction and maintenance of general anesthesia.[1]



(*S*)-1 · HCl **(*R*)-1 · HCl**

Ketamine is a racemic mixture containing equal parts of (*R*)-ketamine and (*S*)-ketamine. Comparing with (*R*)-**1**, the (*S*)-**1** enantiomer shows greater anesthetic potency and approximately fourfold higher affinity for the NMDA reception which contribute to potentially allow for lower dosages.[2] The results of the clinical studies showed the rapid and efficient relief of depression symptoms in just one day of treatment.[3] The (*S*)-ketamine hydrochloride was approved by the FDA in March 2019 for the treatment of major depressive disorder.[4]

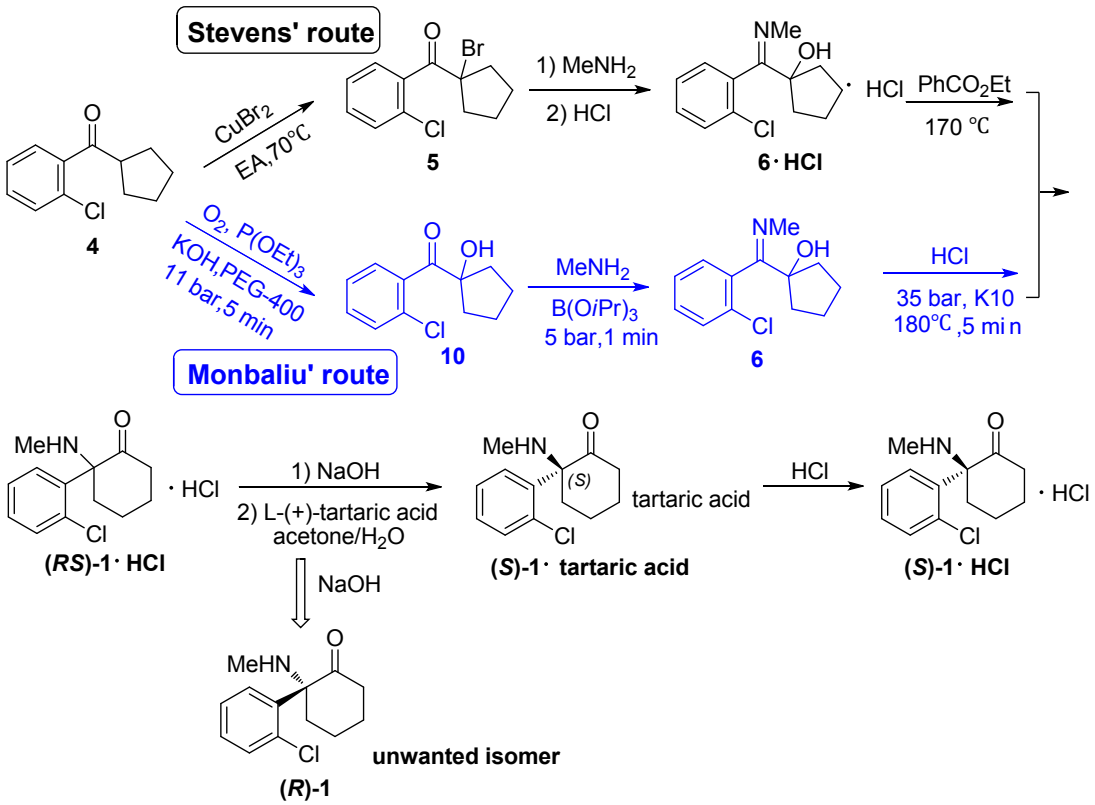
Several papers on the asymmetric synthesis of (*S*)-**1** have been reported in recent years. For instance, Kiyooka et al.[5] reported a procedure for the asymmetric synthesis of (*S*)-**1** with an overall yield of 21% in 10 steps. To achieve high enantioselectivity (97% ee), this route used excess BINAL-H (3.4 equiv) for the reduction of an enone. Another, the chiral center of (*S*)-**1** was constructed through direct asymmetric electrophilic amination with di-tert-butyl azodicarboxylates according to the literature,[6] and the approach for the preparation of (*S*)-**1** was obtained in 30% yield (99% ee) over three steps. However, the key step was carried out at 40 °C for 50-60 h and relied on the complex chiral organophosphorus ligand which has not yet been

industrialized. Gohari[7] utilized tert-butanesulfinamide to induce the chiral center following Grignard reagent as nucleophile at -78 °C, and the (*S*)-**1** was synthesized under ozonolize condition and gave the unsatisfactory 75% ee. More recently, Chen and Lu.[8] developed an efficient asymmetric synthesis of (*S*)-**1** based on catalytic enantioselective transfer hydrogenation of cyclic enone and [3,3]-sigmatropic rearrangement of allylic cyanate to isocyanate. [(*S*,*S*)-Teth-TsDPEN]RuCl (0.1 mol %)-catalyzed transfer hydrogenation of enone affords allylic alcohol in 98% ee, and subsequent [3,3]-sigmatropic rearrangement installs the desired quaternary stereocenter with integrity of chirality. Although these asymmetric synthesis of (*S*)-**1** has achieved some success, each route has limitations on its industrialization. Thus, classical resolution of the inexpensive racemate (±)-**1** with L-(+)-tartaric acid [9] remains the best choice for the industrialization of (*S*)-**1** due to its straightforward and commercial scalability (**Scheme 1**).

An approach appropriate to industrial production to synthesize racemic ketamine **1** was reported in the early 1960s by Stevens[10-14], by using (2-chlorophenyl) (cyclopentyl) methanone **4** as a starting material (**Scheme 1**). The conceptionally elegant synthesis of ketamine **1** involved a bromination-imination-thermal rearrangement sequence and was adopted for the preparation of ketamine analogs by the Janssen Pharmaceutical Company in the laboratory.[9] Another economical and environmental procedure for the preparation of racemic ketamine under sustainable continuous flow conditions was reported by Monbaliu in 2019.[4] Starting from **4**, this flow process features three steps including (a)

hydroxylation with molecular oxygen, (b) imination with methylamine relying on triisopropyl borate and (c) a thermal rearrangement using Montmorillonite K10 as catalyst. The procedure can also be used to prepare ketamine analogs such as norketamine.

As is known, the highest yield of the resolution is only 50%, and the unwanted (*R*)-**1** isomer lost in the mother liquors not only lowers the total yield of the route, but also produces a large amount of waste. However, the defects can be overcome adequately supposing that the conversion of (*R*)-**1** back to the racemic **1**. Herein, we report a Lewis acid catalyzed racemization process for the recycling of the unwanted (*R*)-**1** enantiomer.



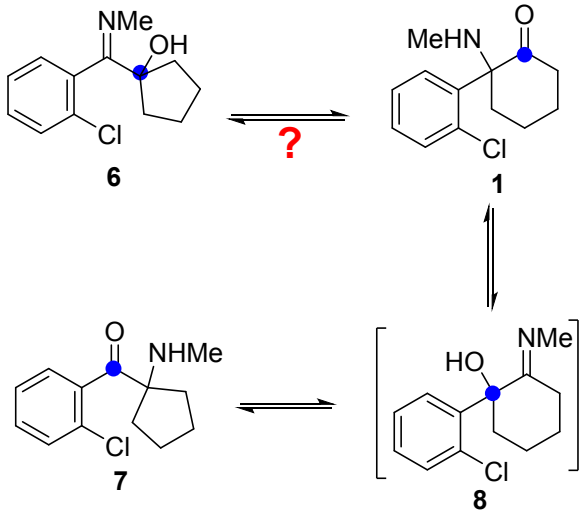
Scheme 1 Synthetic Routes to (*S*)-1 Hydrochloride

RESULTS AND DISCUSSION

The resolution of (±)-**1** by using L-(+)-tartaric acid in acetone/H_2O, was achieved in 41% yield with >99% ee. Acetone was removed from the mother liquor after the resolution step via the distillation and then **1** enriched with (*R*)-isomer was obtained after basification with aqueous NaOH. The chiral HPLC analysis revealed typically about 85-90% of the undesired (*R*)-**1** isomer along with 10-15% of the (*S*)-**1**.

We were faced with a challenge, that is, the racemization of quaternary carbon, which has no hydrogen atom in the chiral center, means that (*R*)-**1** isomer cannot be racemized through conventional approaches. At present there is no reports on racemization of (*R*)-**1** isomer based on accessing the literature extensively. Even though the (*R*)-**1** isomer is not equipped with functionality that is susceptible for racemization, we hypothesized the unwanted (*R*)-**1** isomer could be racemized through the ring-opening/closing reaction with catalysts. Unfortunately, no product (*S*)-**1** was detected in the reaction mixture as analyzed by chiral HPLC when the pure (*R*)-**1** isomer was exposed to the high temperature (180 °C) for 24 h (**Table 1**, entry 1). In addition, the treatment of (*R*)-**1** with KOH in dimethyl sulfoxide at high temperature (150 °C) for several hours also had no racemization (entry 2). Not surprisingly, the racemization catalyzed by HCl did not obtained the satisfactory results on account of the fact that (±)-**1** was obtained under the acidic and high temperature conditions, which indicated that it was stable under this condition (entry 3). The unsuccessful racemization of (*R*)-**1** isomer under the above conditions urge us to explore other possible chemistry.

It was reported by Stevens[13] in 1966 that the amino ketone **7** and (±)-**1** can be converted to each other through the transition state of imine **8** at high temperature in 20% yield (**Scheme 2**). Nevertheless, we did not detect **7** in reverse-phase HPLC when the (*R*)-**1** isomer was exposed to decalin at 180 °C for 24 h. The HPLC and NMR spectra of **7** were shown in the supporting information. However, Stevens' report aroused our thinking that whether the (±)-**1** could back to the α-hydroxyimine **6** under the action of catalysts? According to the literature[11], the thermal rearrangement of α-hydroxyimine **6** to (±)-**1** was an acid catalytic process. Therefore, our first thought were the frequently-used acid catalysts, Lewis acid, which were used to catalyze the rearrangement of (±)-**1** back to **6**.



Scheme 2 the Rearrangement of 6 or 7 to (±)-1

Afterwards, (*R*)-**1** (99.0% ee) was exposed to ethyl benzoate in the presence of 0.5 equivalent of $AlCl_3$ at 150 °C for 5 h. To our delight, the reaction mixtures were detected by HPLC, which indicated that (*R*)-**1**-enriched (~69%, reversed-phase HPLC area %) mixture with the formation of **6** (~30%) (entry 4 of **Table 1**). Based on this experimental data, we believe the racemization will be successful in this premise of (*R*)-**1** could convert to **6** completely. However, the α-hydroxyimine **6** almost disappeared with the prolongation of time (entry 5). To our surprise, the chiral HPLC examination of the above reaction mixture indicated that the (*R*)-**1** had already been converted to a near racemic mixture (entry 5), which meant ring-reducing rearrangement of (*R*)-**1** to the desired **6** was accompanied by the racemization of (*R*)-**1**. Obviously, the endpoint was determined by degree of racemization of (*R*)-**1** rather than achieving complete conversion to **6**. According to the report [11], the irreversible rearrangement of **6** was 24% complete in 35 min at 176 °C while its hydrochloride salt was completely converted to **1** in 30 min at this same temperature. Hence, (*R*)-**1** was replaced with its hydrochloride

salt, and the result was as expected to shorten the reaction time from 10 h to 2 h (entry 6). Subsequently, a number of frequently-used Lewis acids such as $MgCl_2$, $ZnCl_2$, $FeCl_3$, BF_3, and $CaCl_2$, were screened to check the feasibility of the racemization, and the results were summarized in the **Table 1**. Varying degrees of racemization were observed under the investigated conditions (entries 7-11). The catalytic efficiency are arranged as follow: $MgCl_2 \approx AlCl_3 > FeCl_3 > ZnCl_2 > BF_3 > CaCl_2$.

Table 1. Racemization of (*R*)-1 and its hydrochloride [a]

Entry	Catalysts	*T* (°C)	*t*(h)	**1**[b] ((*R*)-**1**/(*S*)-**1**) [c] (%)	**6** (%)[b]	Impurities (%)[b]
1	-	180	24	99.5 (99.5/0.5)	ND [d]	0.5
2	KOH	150	24	99.2 (99.5/0.5)	ND	0.8
3	HCl	150	24	99.5 (99.4/0.6)	ND	0.5
4	$AlCl_3$	150	5	69.0 (49.8/50.2)	30.5	0.5

5 [e]	$AlCl_3$	150	10	98.1 (50.8/49.2)	1.0	0.9
6 [f]	$AlCl_3$	150	2	99.2 (50.5/49.5)	0.6	0.2
7 [f]	$MgCl_2$	150	2	98.5 (49.6/50.4)	1.2	0.3
8 [f]	$FeCl_3$	150	10	42.5 (55.0/45.0)	10.3	47.2
9 [f]	$ZnCl_2$	150	10	83.3 (72.7/27.3)	1.3	15.4
10 [f]	BF_3	150	10	69.2 (77.7/22.3)	30.0	0.6
11 [f]	$CaCl_2$	150	10	98.6 (96.9/3.1)	0.9	0.5

[a] Reaction conditions: 0.1 g/mL (*R*)-**1** (99.0%ee) in ethyl benzoate with 50 mol% catalysts. [b] Measured by HPLC on a Waters X-Bridge C18 column. [c] Measured by HPLC on a Chiralpak OD-3 column. [d] ND = not detected. [e] The time expand of entry 4. [f] The (*R*)-**1** hydrochloride (99.0% ee) was used.

The workup procedure of the racemization was just the simple filtration, consequently, the added Lewis acid would also be filtered out along with the racemate **1**

hydrochloride. The free base **1** was precipitated from aqueous phase by the treatment with the mixture of 2 N sodium hydroxide aqueous solution. In the process of alkalization, $AlCl_3$ was converted into water-soluble $NaAlO_2$ and stayed in aqueous phase, while $Mg(OH)_2$ was remained in free base **1** due to its insoluble in water. In consideration of $AlCl_3$ being a preferred commercial Lewis acid and can be easily removed thought $NaAlO_2$ by excessive alkali, $AlCl_3$ was chosen as the optimal Lewis acid to catalyze the racemization.

The lager dosage of $AlCl_3$ will put great pressure on the environment. Therefore, further racemization of the $AlCl_3$ quantity was tried and the results were summarized in **Table 2**. To our delight, 20 mol % of $AlCl_3$ was found to be adequate although the reaction time was extended to 10 h (entry 2). The possibility of further racemization of the $AlCl_3$ was attempted, and it was observed that 10 mol % of $AlCl_3$ was adequate to afford a near racemic mixture of (*R*)-**1**/(*S*)-**1** (65.2%/34.8%) in 10 h (entry 3). On the other hand, when the reaction temperature was dropped to 130 °C with 20 mol % of $AlCl_3$, the racemization rate was much slower compared to that at 150 °C (entry 4). The

racemization procedure was as follows: (*R*)-**1** hydrochloride was heated in the presence of 20 mol % $AlCl_3$ in ethyl benzoate at 150 °C for 10 h.

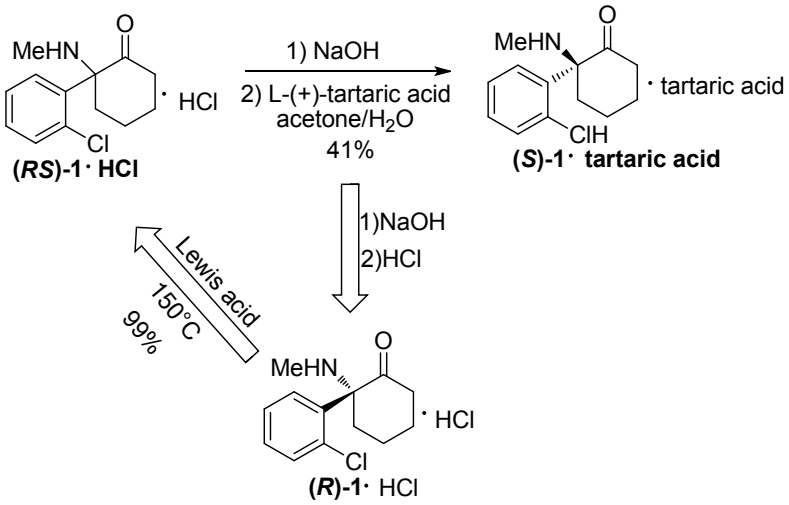
Table 2. Optimization of $AlCl_3$ and temperature for the (*R*)-1 racemization [a]

Entry	$AlCl_3$ (eq)	*T* (°C)	*t*(h)	(*R*)-**1**/(*S*)-**1** (%)[b]	**6** (%)[c]
1	0.5	150	2	50.5/49.5	0.6
2	0.2	150	10	49.8/50.2	0.4
3	0.1	150	10	65.2/34.8	10.9
4	0.2	130	10	81.2/18.8	30.5

[a] Reaction conditions: 0.1 g/mL (*R*)-**1** hydrochloride (98.5%ee) in ethyl benzoate. [b] Measured by HPLC on a Chiralpak OD-3 column. [c] Measured by HPLC on a Waters X-Bridge C18 column.

After the racemization completed, the racemate **1** hydrochloride was obtained through a simple filtration process from the reaction mixture. Subsequently, the free

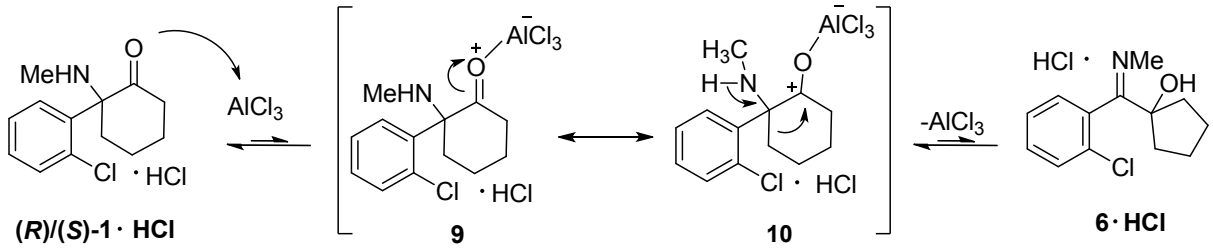
base **1** was precipitated from aqueous phase by the treatment with the mixture of 2 N sodium hydroxide aqueous solution in almost quantitative yield with the purity of over 99.0%, which was subjected to the next cycle of the resolution to give (*S*)-**1** in high purity (**Scheme 3**).



Scheme 3 the Recycling Process of (*R*)-1 Hydrochloride

A plausible mechanism for the $AlCl_3$-catalyzed rearrangement of (*R*)-**1** concomitant with racemization was depicted in **Scheme 4**. In the presence of $AlCl_3$, the carbonyl group of (*R*)-**1** coordinated with $AlCl_3$, and the α-hydroxyimine **6** was obtained through the intramolecular hydrogen transfer along with ring-opening and ring-closing process when energy was provided by the heat. Because of the higher thermal stability of **1**, the

newly generated **6** went back to **1** under that temperature, and the racemization was constantly achieved during this reversible process. In order to avoid the lone pair electrons of the amino group coordinated with $AlCl_3$, the (*R*)-**1** hydrochloride was used to replace the free base to reduce the electronegativity, thereby reducing the consumption of $AlCl_3$. This was also the explanation for the faster racemization of hydrochloride than free base with the same amount of $AlCl_3$.



Scheme 4. A Possible Mechanism for the Racemization of (*R*)-1 Hydrochloride

CONCLUSION

In conclusion, a process of racemizing the unwanted (*R*)-**1** isomer from the resolution mother liquors after treatment with 20 mol % $AlCl_3$ at 150 °C for 10 h have been developed in quantitative yield with 99% chemical purity. Varying degrees of racemization were observed in the presence of various frequently-used Lewis acids separately and $AlCl_3$ was the best catalyst due to its high catalytic efficiency and removability. The racemized ketamine was subsequently

resolved by L-(+)-tartaric acid to obtain (*S*)-**1** in 41% yield and with 99.5% ee. The concise and economical procedure, developed for the reproducible recycling of the undesired (*R*)-**1** isomer on a large scale, not only minimizes the waste generated during the resolution process, but also greatly reduces the production costs of (*S*)-**1**.

EXPERIMENTAL SECTION

General. Solvents and reagents were obtained from commercial sources and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on an Avance III 400 MHz spectrometer (Bruker, Karlsruhe, Germany). The solvents used for NMR spectroscopy were $CDCl_3$, using TMS as the internal reference. HRMS-spectra were obtained on Bruker maXis 4G Q-TOF instrument. The melting points were determined by DSC analysis and correspond to the peak maximum. The DSC curves were recorded and integrated with the aid of a TA Instruments DSC Q2000 apparatus. Optical rotations values were measured with an Anton Paar MCP 500 polarimeter at 20 °C, 589 nm (sodium ray). Thermogravimetric analysis (TGA) was performed on a TA Instruments 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. Chemical

purity was determined by HPLC analysis on a Dionex UltiMate 3000 chromatograph system with UV detector. Diluents: acetonitrile and 10 mM potassium dihydrogen phosphate aqueous solution. Column: Waters X-Bridge (C18, 4.6 mm × 150 mm, 3.5 μm). Conditions: 35 °C, flow rate 1.0 mL/min, 210 nm, retention times of **1** is 12.7 min and **6** is 18.5 min. Chiral HPLC analysis was done on a Dionex UltiMate 3000 chromatograph at 210 nm, using a Chiralpak OD-3 column (4.6 mm × 250 mm, 3.0 μm) at 30 °C with flow rate of 0.8 mL/min in 20.0 min with *n*-hexane / 2-propanol (95:5) as eluent. The retention time of (*R*)-**1** is 8.9 min and (*S*)-**1** is 9.9 min.

Preparation of (*R*)-1 hydrochloride.

Rac-**1** (200.0 g, 0.841 mol) and L-tartaric acid (69.4 g, 0.463 mol) were dissolved in a mixture of acetone (1875 mL) and water (125 mL) by heating at reflux for 30 min. The solution was slowly cooled to 55 °C and stirred at this temperature for 2 h. And then the suspension was cooled to room temperature at approximately 5 °C/h. The resulting slurry was stirred overnight. The white solid was filtered, washed with cold acetone (2 × 300 mL)，and dried at 50 °C under vacuum overnight to yield 146.0 g (99.5% ee, Yield

41%), [α]20 D +65.8 (*c* 1.0, H_2O). (lit., [9] [α]25 D +68.8 (*c* 2.0, H_2O)). The mother liquor enriched (*R*)-**1** was distillated under reduced pressure to remove acetone and then alkalized with 2 N sodium hydroxide solution. A large amount of white solid was precipitated in this process. The resulting slurry was cooled to 0 °C, stirred for 1 h, filtered to obtain the white solid enriched (*R*)-**1** in quantitative yield. After drying at 60 °C under vacuum overnight, the white solid salted with EA-HCl in ethyl acetate to get the enriched (*R*)-**1** hydrochloride salt with 99.5% chemical purity and 85.1% chiral purity.

Racemization of (*R*)-1 hydrochloride.

A solution of the enriched (*R*)-**1** hydrochloride (120.0 g, 0.437 mol) in ethyl benzoate (1.2 L) was stirred with $AlCl_3$ (11.6 g, 20% mol) at 150 °C. The racemization process was monitored by chiral HPLC analysis. After (*R*)-**1** was found to be fully racemized, the reaction mixture was cooled to room temperature and then n-hexane (600 mL) was added to make the precipitation completely. The racemic mixture of (*R*)-**1**/(*S*)-**1** (49.7%/50.3%) as an off-white solid (123.5 g) in quantitative yield with 99.5% chemical purity. Anal. Calcd for $C_{13}H_{17}Cl_2NO$: C, 56.95; H, 6.25; N, 5.11; Found: C,

56.79; H, 6.25; N, 5.28. Mp 263.61 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.29 (s, 1H), 9.23 (s, 1H), 7.96 (dd, J = 7.0, 2.4 Hz, 1H), 7.66-7.56 (m, 3H), 3.34 (d, J = 2.4 Hz, 1H), 2.48 (dd, J = 8.6, 4.3 Hz, 1H), 2.46-2.38 (m, 1H), 2.21 (s, 3H), 2.06-1.91 (m, 2H), 1.78 (d, J = 13.9 Hz, 1H), 1.71-1.57 (m, 1H), 1.47 (dt, J = 16.4, 8.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO) δ 206.78, 134.07, 132.36, 131.67, 128.38, 128.33, 71.64, 40.15, 36.52, 29.42, 27.51, 21.12. HRMS (ESI) m/z calcd for $C_{13}H_{17}ClNO$: 238.0996, found 238.0993 ($[M+H]^+$).

ASSOCIATED CONTENT

Supporting Information

HPLC data, 1D NMR, 2D NMR, and HRMS of α-hydroxyimine **6** and **7**; Chiral HPLC data and Optical rotation for (*S*)-**1** and (*R*)-**1**; HPLC data, ^{1}H NMR, ^{13}C NMR, HRMS, DSC, TGA and Elemental analysis information for rac-**1**.

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Notes: The authors declare no conflict of interest.

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