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RESEARCH ARTICLE

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Preparation of (*R*)-3-aminopiperidine by resolution with optically active cyclic phosphoric acids

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Abstract

(*R*)-3-aminopiperidine ((*R*)-APD), a key intermediate for alogliptin, trelagliptin, and linagliptin, was successfully resolved from racemic 3-aminopiperidine with an enantiomerically pure resolving agent, namely, (*R*)-4-(2-chlohydroxy-1.3.2-dioxaphosphorinane 2-oxide ((*R*)-CPA), via diastereomeric salt formation. By this resolution approach, (*R*)-3-aminopiperidine was obtained in 99.5% yield with 99.6%*e.e.*

KEYWORDS

chiral cyclic phosphoric acids, diastereomeric salt, resolution, resolving agent, (*R*)-3-aminopiperidine

1 | INTRODUCTION

(*R*)-3-Aminopiperidine (abbreviated as (*R*)-APD, Figure 1), is a useful key chiral intermediate for the synthetic process of dipeptidyl peptidase-4 (DPP-4) inhibitors including alogliptin, trelagliptin, and linagliptin.[1–4] The existing known processes for producing (*R*)-APD mainly include (1) asymmetric synthesis starting with optical pure raw materials[5–10]; (2) resolution from diastereomeric salt formation[11–15]; and (3) resolution using enzymes.[16] With process (1), (*R*)-APD could be obtained in high optical purity. However, these processes typically suffered from the use of the expensive raw materials, tedious multi-step reactions, and lower yielding of the product. Process (3) requires the isolation of the enzymes and is confined to application at a laboratory scale. Compared to these methods, diastereomeric salt resolution of racemic mixtures remained an economical and practical procedure for chemical and pharmaceutical industries nowadays.Several approaches for resolution of *rac*-APD to achieve the optically pure (*R*)-APD have been well documented in previous patents.[11,12] In these documents, (*S*)-*N*-*p*-toluoylglutamic acid and (+)-dibenzoyl-(*D*)-tartaric acid were used as resolving agents, respectively, for the chiral resolution of *rac*-APD disclosed. However, these two chiral acids applied are quite unstable and led to only modest resolution. Hoehne and Robins disclosed the kinetic resolution of 3-aminopiperidine with ω-transaminases was facilitated by the application of a protection/deprotection group concept.[16] 1-*N*-Boc-3-aminopiperidine could be resolved with 96%*e.e.* and 55% conversion. This method suffered

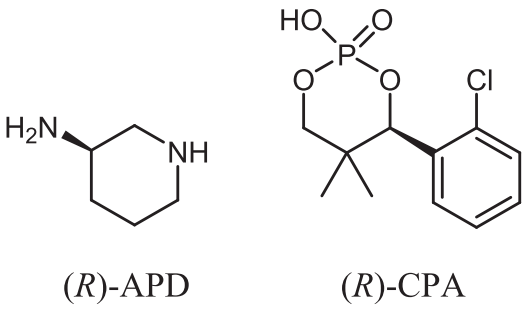

FIGURE 1 The structure of (*R*)-3-APD and (*R*)-CPA

from the tedious multi-step reactions and lower conversion of the product. In 2012, Sakurai and coworkers reported a method for resolution of *rac*-APD using *N*-tosyl-(*S*)-phenylalanine as the resolving agent,[4] and the yield of (*R*)-APD obtained is only 22%. Furthermore, (*S*)-2-(3-(4-chlorophenyl) ureido)-propionic acid has also been used as the resolving agent, affording (*R*)-APD in 78% yield and with 99.7%*e.e.*[15] With regard to the excellent *e.e.* value, this method is obviously promising for the resolution of racemic amines. However, the yield of the product in this process still needs to be further improved.In our previous work,[17] we reported that the optically active cyclic phosphoric acid, namely, (*R*)-4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-1.3.2-dioxaphosphorinane 2-oxide ((*R*)-CPA), could be used as a recyclable and cheap resolving agent (Figure 1). By using this resolving agent, we successfully completed the resolution of (*RS*)-1-(naphthyl)ethylamine by diastereomeric salt formation, affording (*R*)-1-(naphthyl) ethylamine in 95% yield and with 99.2%*e.e.* In continuation of our interests of utilizing (*R*)-CPA as resolving agent, we here report our preliminary results[18,19] on the diastereomeric resolution of *rac*-APD with this exclusive cyclic phosphoric acid.

2 | MATERIALS AND METHODS

Racemic 3-aminopiperidine hydrochloride (*rac*-APD·2HCl) was purchased from Sinopharm Chemical Reagent Co., Ltd (China) and was used without further purification. The resolving agents were synthesized according to the reported method.[20] ^{1}H NMR and ^{13}C NMR were recorded at 500 MHz on Brucker Avance 500 using D_2O and (Tenglong Weibo Technology Co., Ltd, Qingdao, China) as solvent, and tetramethylsilane was used as the internal reference. The solubility of diastereomeric salts were determined in accordance with literature.[17] The optical purity of resolving agent, (*R*)-APD·(*R*)-CPA and (*R*)-APD were determined by optical rotation on SGW-2 (Optical Activity Limited) or by HPLC using Chrom Tech Chiral-AGP. HPLC was carried out on Tian Mei1200 (Shang Hai) separation module with a UV detector. The output signal was monitored at 254 nm. Infrared (IR) spectra were measured on Perkinelmer Frontier spectrometer in KBr pellets.

2.1 | Preparation of (*S*)-APD·(*R*)-CPA and (*R*)-APD·(*R*)-CPA from *rac*-APD and (*R*)-CPA

To a 250 ml flask was added *rac*-APD·2HCl (10 g, 1.0 mol) and *tert*-butyl alcohol (TBA) (40 ml, 90% v:v) and stirred at 10°C under nitrogen atmosphere, then

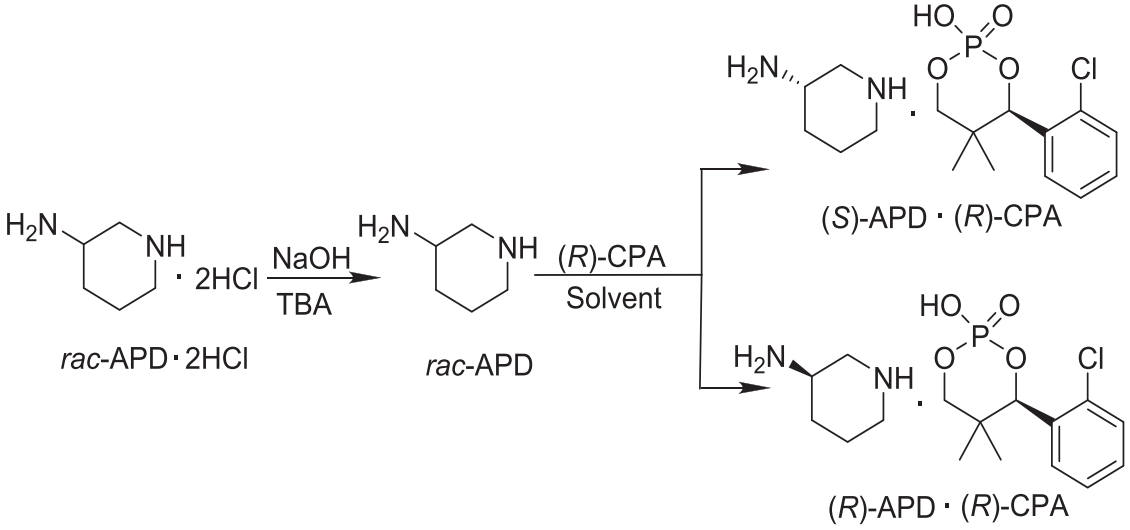

FIGURE 2 Resolution scheme of *rac*-APD with (*R*)-CPA

added NaOH (2 mol, 10% solution in *tert*-butanol). The reaction mixture was gradually warmed to room temperature and kept for 2 h, filtered and the solid was washed with 90% TBA (10 ml). Then (*R*)-CPA (31.94 g, 2.0 mol) was added to the filtrate which was subsequently heated to 50°C for 2 h. The resultant suspension was cooled to 0°C and stirred for 20 h. The solid was collected by filtration and washed with TBA (10 ml, 90% v:v) and dried in vacuum to afford (*S*)-APD·(*R*)-CPA in 83% yield. The filter was concentrated under vacuum and the residue was taken up in 90% TBA to obtain (*R*)-APD·(*R*)-CPA as a white solid (10.7 g, 98.2% yield) with 99.6%*e.e.* IR (KBr) cm^{-1}: 3396.9, 2968.7, 1631.9, 1527.7, 1473.1, 1369.9, 1235.0, 1100.6, 1062.8, 615.0, 752.1, 791.1, 720.7, 705.6; ^{1}H NMR (500 MHz, D_2O, δ): 7.61 (dd, $J = 7.8$, 1.8 Hz, 1H), 7.52–7.35 (m, 3H), 5.79 (d, $J = 2.1$ Hz, 1H), 4.27 (d, $J = 11.1$ Hz, 1H), 3.85 (dd, $J = 23.9$, 11.3 Hz, 1H), 3.01 (d, $J = 12.2$ Hz, 1H), 2.89 (d, $J = 12.6$ Hz, 1H), 2.75–2.68 (m, 1H), 2.45 (t, $J = 11.6$ Hz, 1H), 2.30–2.21 (m, 1H), 1.91 (d, $J = 12.7$ Hz, 1H), 1.74–1.67 (m, 1H), 1.46 (q, $J = 12.4$ Hz, 1H), 1.18 (q, $J = 11.9$ Hz, 1H), 1.08 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (125 MHz, D_2O, δ): 134.6, 132.6, 130.0, 129.7, 129.3, 126.7, 80.9, 77.2, 77.1, 44.8, 44.6, 43.3, 37.0, 26.2, 19.7, 17.0.

TABLE 1 Screening solvent for the resolution

Entry	Solvent	Yield (%)	*de* (%)[a]	E (%)[b]
1	CH_3OH	80.5	72.5	58.4
2	H_2O	80.2	39.8	31.9
3	2-Propanol	87.6	4.3	3.8
4	Propanol	82.4	12.5	10.3
5	CH_3CN	70.9	6.8	4.8
6	TBA	89.6	83.0	74.4
7	85% TBA	94.3	95.4	90.0
8	90% TBA	98.2	99.6	97.8
9	95% TBA	90.2	97.5	87.9

[a]*de* of the salt was based on the *e.e.* of the (*R*)-APD liberated from the salt.
[b]Resolution efficiency E(%) = yield (%) × *de* (%).

2.2 | Preparation of (*R*)-APD·2HCl

Hydrogen chloride (20 ml of a 20% solution in 2-propyl alcohol, 3 mol) was added in drops to a suspension of (*R*)-APD·(*R*)-CPA (10 g) in 2-propanol (30 ml) at 30°C. After stirring at this temperature for 2 h, the solution was cooled to 20°C. The solid was collected by filtration under vacuum and then sequentially washed with 2-propyl alcohol. The solid was dried in vacuo to give (*R*)-APD·2HCl as a white solid (2.8 g, 95.7% yield) with 97.4% *e.e.* $[\alpha]_D^{25} = -1.77$ ($c = 1$ in CH_3OH).

2.3 | Preparation of (*R*)-APD

(*R*)-APD·2HCl (10 g) was added to CH_3OH (30 ml) and the mixture was stirred under nitrogen atmosphere for 4 h. Then NaOH (47.4 g, 10% aq. solution) was added in drops within 1 h. The mixture was then filtered and the solid was washed with CH_3OH, and filtrate was concentrated to give (*R*)-APD in 99.5% yield with 99.6%*e.e.*

3 | RESULTS AND DISCUSSION

3.1 | Determination of the optimal solvent for the resolution

An appropriate solvent is of significant importance in resolution process. In this work, resolution of *rac*-APD with (*R*)-CPA was carried out as the scheme (Figure 2) in several solvents respectively, as shown in Table 1.

Diastereomeric salts (*R*)-APD·(*R*)-CPA were obtained in all the cases. However, the resolution efficiency varied

TABLE 2 Resolution results in various conditions

Entry	Solid/solvent (g/ml)	Temperature (°C)	Yield (%)	*de* (%)[a]	E (%)[b]
1	1:4	50	78.9	80.3	63.4
2	1:6	50	84.8	86.5	73.4
3	1:8	50	98.2	99.6	97.8
4	1:10	50	94.5	93.4	88.1
5	1:8	60	87.4	89.3	78.0
6	1:8	40	95.3	98.4	93.8

[a]*de* of the salt was based on the *e.e.* of the *(R)*-APD liberated from the salt.
[b]Resolution efficiency E(%) = yield (%) × *de* (%).

significantly in different solvents. The resolution results were evaluated by the yield of product and diastereomeric purity of (*R*)-APD·(*R*)-CPA. The results indicated that purity of salts was pretty high in several alcoholic solvents including methanol, TBA and TBA/water. Among them, TBA (90% v:v) was found to be the optimal solvent system.

3.2 | Determination of the solid/solvent ratio and the reaction temperature

With the optimal solvent in hand, the other factors affecting the preparation of (*R*)-APD·(*R*)-CPA, including solid/solvent ratio and the reaction temperature were further investigated, with the results summarized in Table 2. Experimental results indicated that the solid/solvent ratio had a great effect on the purity and yield of the product. With the solid/solvent ratio increased from 1:4 to 1:8, the purity and yield of (*R*)-APD·(*R*)-CPA reached a high level of 99.6% *de* with 98.2% yield and then was slightly decreased when the solvent amount was further increased. The reaction temperature also had a big influence on the outcome of (*R*)-APD·(*R*)-CPA. The results showed that when the reaction temperature was 50°C, the yield and purity of the product were the highest. Therefore, the optimal resolution conditions were determined as follows: the solid/solvent ratio was 1:8; the reaction temperature was 50°C. Furthermore, the resolution was performed three times under the optimal conditions, the experimental purity and yield of (*R*)-APD·(*R*)-CPA were 99.6 ± 0.08% and 98.2 ± 0.14%.

TABLE 3 Thermal properties of diastereomeric salts of (*R*)-APD·(*R*)-CPA and (*S*)-APD·(*R*)-CPA

Diastereomeric salts	Melting point (°C)	Solubility (g)[a]
(*R*)-APD·(*R*)-CPA	325.47	1.31
(*S*)-APD·(*R*)-CPA	283.15	0.2554

[a]Weight (g) of the solute dissolved in 90% TBA (100 g, 90% v:v) at 0°C.

3.3 | Physical properties of the pair of diastereomeric salts (*R*)-APD·(*R*)-CPA and (*S*)-APD·(*R*)-CPA

To study the enhanced chiral recognition ability of (*R*)-CPA, the corresponding diastereomeric salts were synthesized and the physical properties of (*R*)-APD·(*R*)-CPA and (*S*)-APD·(*R*)-CPA were determined and listed in Table 3. The differential scanning calorimeter curves of more and less soluble salts are shown in Figure 3. As shown in Table 3, the melting point of less soluble salt and more soluble salt is 283.15°C and 325.47°C, respectively. The difference between the two values reaches 42.32°C. The comparison of the thermal properties suggests that the more soluble salt is much more stable than the less soluble salt. The solubility ratio of more soluble

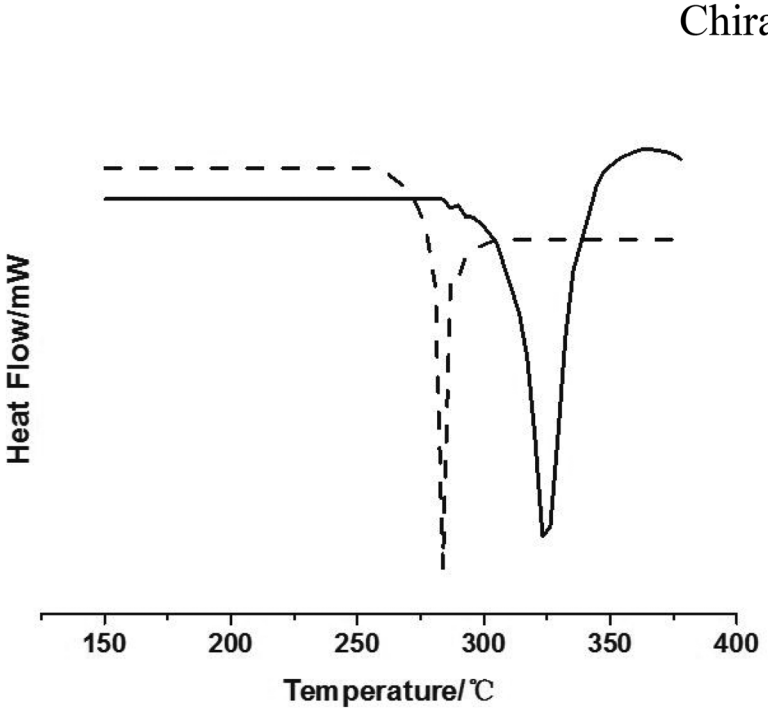

FIGURE 3 The DSC spectrum of (*R*)-APD·(*R*)-CPA (solid line) and (*S*)-APD·(*R*)-CPA (dotted line)

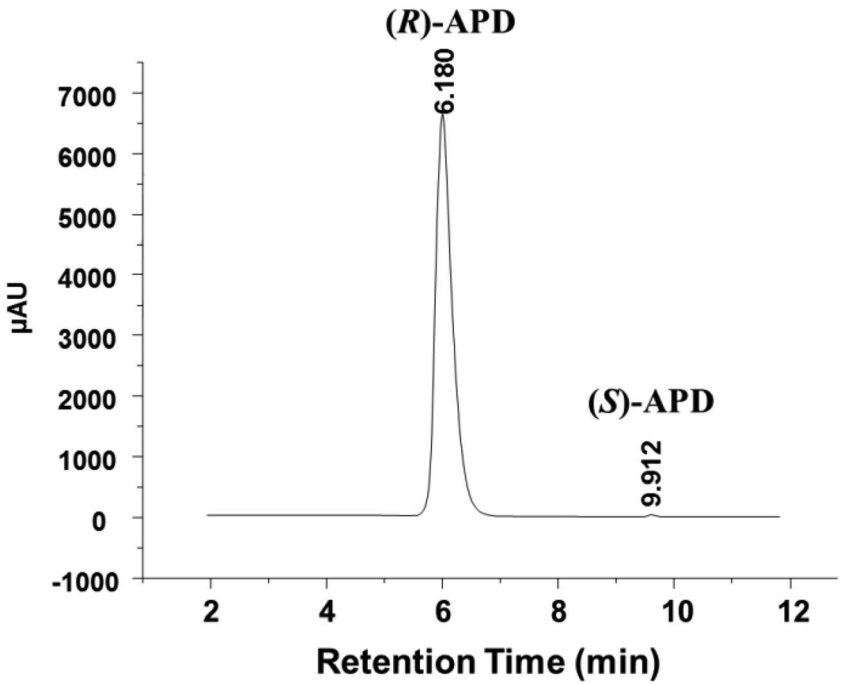

FIGURE 4 The chromatogram of HPLC analysis of the (*R*)-APD

salt to less soluble salt in 90% TBA is 5.25:1, which is very large. We propose that the large difference in physical properties of the pair of diastereomeric salts is the crucial factor that leads to an efficient resolution.

3.4 | Determination of enantiomeric excess of (*R*)-APD

The (*R*)-APD was liberated from the diastereomeric salt with optical purity of 99.6%*e.e.* and in a yield of 99.5%. (*R*)–APD was determined by HPLC analysis on chiral column AGP. The mobile phase was 1% 2-propanol/99% NaH_2PO_4 aqueous solution (pH = 5.5) by flow rate of 1 ml/min. The column temperature was 30°C and the wavelength was 254 nm. Retention time of (*R*)-APD was 6.180 min. The typical chromatogram of enantiomeric excess measured of (*R*)-APD by HPLC analysis was shown in Figure 4.

4 | CONCLUSION

By using (*R*)-CPA as resolving agent, racemic APD was successfully resolved by diastereomeric salt formation. The optimal resolution conditions were systematically optimized, and (*R*)-APD could be obtained in 99.5% yield with 99.6%*e.e.*, the outcomes of which are comparable with any previous methods. The experimental results further demonstrated that the successful resolution of *rac*-APD might be attributed to the significant difference of physical properties between the less and more soluble salts.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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