Diastereomeric Resolution of Racemic *o*-Chloromandelic Acid

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ABSTRACT The separation of *rac*-*o*-chloromandelic acid **1** with enantiopure aryloxypropylamine via diastereomeric salt formation was investigated. (*R*)-*o*-chloromandelic acid (*R*)-**1**, a key intermediate for the antithrombotic agent clopidogrel, was obtained in 65% yield and 98% ee by Dutch resolution of *rac*-**1** with (*S*)-2-hydroxyl-3-(*p*-chlorophenoxy) propylamine (*S*)-**5** as resolving agent and (*S*)-2-hydroxyl-3-(*o*-nitrophenoxy) propylamine (*S*)-**4** as nucleation inhibitor. *Chirality 00:000–000, 2012.* © 2012 Wiley Periodicals, Inc.

KEY WORDS: racemic *o*-chloromandelic acid; diastereomeric resolution; aryloxypropylamine

INTRODUCTION

The (*R*)-*o*-chloromandelic acid (*R*)-**1** is the key chiral intermediate for the industrial synthesis of the antiplatelets aggregation agent clopidogrel[1–4] (Fig. 1). Known processes for producing the chiral acid include (1) asymmetric synthesis via metal catalysts[5–7] or biocatalyst;[8,9] (2) racemic resolution by chromatography;[10] (3) racemic resolution from the racemic acid,[11] the corresponding nitrile/ester[12–15] or alpha-keto acids[16,17] using microbial methods; (4) alcoholysis of 1,3-dioxolane-2,4-diones with chiral auxiliary;[18] and (5) diastereomeric salt resolution.[19–22]

Processes (1)–(4) consist of using metal catalysts, chiral organic catalysts, whole living cells, and isolated enzymes. With these methods, (*R*)-**1** could be obtained in high optical purity. However, these methods are used mainly in laboratory scale because of the high price of the efficient chiral ligands and catalysts and also due to the lack of efficient, scalable processes for industrial purposes. Therefore, diastereomeric resolution of racemic mixtures remained an economical and frequently used procedure at chemical and pharmaceutical industries nowadays.

Because of the practical application, the diastereomeric resolution of *rac*-**1** has attracted scholars's interest. However, there were a limited number of reports on it. To our knowledge, there were only three kinds of resolving agents for resolution of *rac*-**1**: enantiopure *N*-benzyl-α-phenylethanamine (BPA),[19] 1-aryl-2-amino-1,3-propane-diol (SA),[21,22] and alanine[20] (Fig. 2). Using BPA, (*R*)-**1** can be obtained in high yield and high optical purity, but the price of BPA is high. Enantiopure SA is not easy to get on account of its two chiral centers, which can be obtained by optical resolution or asymmetric synthesis. With optical pure alanine, the diastereomeric salt needs to be recrystallized once or more, the yield of (*R*)-**1** is low. So, exploring new resolving agent that is cheap and easy to obtain is necessary.

Enantiopure aryloxypropylamine with a base site, an aromatic ring, a hydrogen bond donor, or acceptor, appears to be a good candidate for chiral discrimination processes. Additionally, it is easy to synthesize.[23] In our previous wok, aryloxypropylamine could be kinetic resolved by C-12 higher carbon sugar without enzymes[24] and was used for the chiral preparation of optically pure β-blockers.[25] There was no report on the enantiopure aryloxypropylamine used as resolving agent. In order to expand the scope of application of enantiopure aryloxypropylamine, we explored the resolution with it. Herein, the preliminary results were presented on the diastereomeric resolution of *rac*-**1** with enantiopure aryloxypropylamine.

EXPERIMENTAL

General

Racemic *o*-chloromandelic acid *rac*-**1** was purchased from Sinopharm Chemical Reagent Co., Ltd (China) and was used without further purification. The resolving agents (*S*)-**2**, (*S*)-**3**, (*S*)-**4**, (*S*)-**5**, (*S*)-**6**, and (*S*)-**7** were synthesized according to the reported method[25] and determined by NMR, high-performance liquid chromatography (HPLC), or optical rotation. Results implied that they were all enantiopure. ^{1}H NMR and ^{13}C NMR were recorded at 400 MHz on Bruke Avance II using D_2O and $CDCl_3$ (Tenglong Weibo Technology Co., Ltd, Qingdao, China) as solvent, and tetramethylsilane was used as the internal reference. The optical purity of resolving agents were determined by optical rotation on PolAAr 3001 (Optical Activity Limited) or by HPLC using chiral column Lux Cellulose-1 (4.6 × 250 mm I.D., 3 μm, Phenomenex). The optical purity of the acid **1** liberated from salt was determined by HPLC using chiral column Lux Cellulose-2 (4.6 × 250 mm I.D., 3 μm, Phenomenex). Infrared (IR) spectra were measured on a JASCO FT/IR-230 spectrometer in KBr pellets. Melting points were obtained on Shimadzu DSC-60A.

Preparation of resolving agents (*S*)-2, (*S*)-3, (*S*)-4, (*S*)-5, (*S*)-6, and (*S*)-7. Resolving agents were synthesized according to reported method.[25] Preparation of (*S*)-**2**: 2-chlorophenol was added to (*S*)-epichlorohydrin in the presence of K_2CO_3 with stirring. The mixture was heated and kept at 110 °C for 2–3 h followed by filtration and concentrated under vacuum pressure to recover the (*S*)-epichlorohydrin. The residue was added dropwise into excess ammonia water for 24 h at room temperature. Filtrated the deposition, filter liquor was vaporated under vacuum to remove the water and excess NH_3, then dissolved the residue with hot ethyl acetate and white deposition appeared. The precipitate (*S*)-**2** was filtrated. If the optical purity of (*S*)-**2** was not high, (*S*)-**2** could be recrystallized in ethyl acetate.

Additional Supporting Information may be found in the online version of this article.

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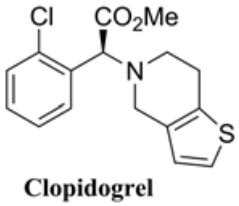

Clopidogrel

Fig. 1. The structure of Clopidogrel.

Preparation of (*S*)-**3**, (*S*)-**4**, (*S*)-**5**, (*S*)-**6**, and (*S*)-**7** was the same as that of (*S*)-**2**, just replacing the 2-chlorophenol with 2-methoxylphenol, 2-nitrophenol, 4-choloro phenol, 3-nitrophenol, and 4-nitrophenol, respectively.

(*S*)-**2**. Yield: 82%; mp: 102–106 °C; IR (KBr): 3381, 3140, 3069, 2935, 2869, 1589, 1577, 1487, 1455, 1298, 1283, 1252, 1102, 1073,1062, 1002, 958, 749, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.23 (td, *J* = 8.3, 1.6 Hz, 1H), 6.94 (ddd, *J* = 15.1, 7.8, 1.3 Hz, 2H), 4.13–3.97 (m, 3H), 3.02 (dd, *J* = 12.9, 4.1 Hz, 1H), 2.98–2.89 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1, 130.2, 127.8, 122.9, 121.8, 113.6, 71.5, 70.0, 44.0. High-resolution mass spectrometry (HRMS) (electrospray ionization, ESI) calcd. for $C_9H_{12}ClNO_2$ $[M+H]^+$: 202.0557, found 202.0634. The optical purity of (*S*)-**2** was determined by HPLC with Lux Cellulose-1 column (4.6 × 250 mm I.D., 3 μm, Phenomenex). The mobile phase was hexane/isopropanol (50/50) with 0.2% diethylamine and flow rate was 0.8 ml/min under detection wavelength of 224 nm. Retention time: (*S*)-**2** 5.82 min, (*R*)-**2** 6.95 min. $[\alpha]_D^{19}$ = +9.5 (*c* 1.0, Methanol).

(*S*)-**3**. Yield: 87%; mp: 97–101 °C; IR (KBr): 3417, 3007, 2935, 2841, 1594, 1509, 1465, 1450, 1258, 1230, 1125, 1025, 913, 860, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.03–6.85(m, 4H), 4.12–4.03 (m, 1H), 3.99 (dq, *J* = 12.6, 6.3 Hz, 2H), 3.90–3.83 (m, 3H), 2.96 (d, *J* = 12.7 Hz, 1H), 2.88 (t, *J* = 8.7 Hz, 1H), 2.48–1.76 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.8, 148.1, 122.0, 121.0, 114.8, 111.8, 72.4, 70.3, 55.8, 44.0. HRMS (ESI) calcd. for $C_{10}H_{15}NO_3$ $[M+H]^+$: 198.1127, found 198.1127. The optical purity of (*S*)-**3** was determined as the same as (*S*)-**2**. Retention time: (*S*)-**3** 7.75 min, (*R*)-**3** 22.98 min. $[\alpha]_D^{20}$ = +5.5 (*c* 1.0, Methanol).

(*S*)-**4**. Yield: 83%; mp: 91–95 °C; IR (KBr): 3378, 3301, 3190, 2921, 2881, 1610, 1583, 1524, 1347, 1278, 1169, 1151, 1089, 1201, 860, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.1 Hz, 1H), 7.55 (t, *J* = 7.9 Hz, 1H), 7.24–6.91 (m, 2H), 4.63–4.08 (m, 2H), 4.01 (dt, *J* = 10.1, 5.0 Hz, 1H), 2.96 (ddd, *J* = 19.3, 12.8, 5.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.7, 138.6, 135.5, 125.9, 121.1, 115.0, 71.2, 67.9, 42.3. HRMS (ESI) calcd. for $C_9H_{12}N_2O_4$ $[M+H]^+$: 213.0797, found 213.0878. $[\alpha]_D^{20}$ = +7.0 (*c* 1.0, Methanol).

(*S*)-**5**. Yield: 91%; mp: 115–119 °C; IR (KBr): 3345, 3276, 3066, 2962, 2923, 2870, 2750, 1596, 1581, 1492, 1466, 1317, 1289, 1248, 1219, 1170, 1118, 1102, 1028, 999, 823, 673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.21 (m, 2H), 6.91–6.81 (m, 2H), 4.01–3.91 (m, 3H), 3.03–2.94 (m, 1H), 2.86 (ddd, *J* = 12.7, 7.3, 3.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 129.3, 125.9, 115.7, 70.4, 70.2, 43.9. HRMS (ESI) calcd. for $C_9H_{12}ClNO_2$ $[M+H]^+$: 202.0557, found 202.0633. The optical purity of (*S*)-**5** was determined as the same as (*S*)-**2**. Retention time: (*S*)-**5** 5.53 min, (*R*)-**5** 6.35 min. $[\alpha]_D^{19}$ = +4.5 (*c* 1.0, Methanol).

(*S*)-**6**. Yield: 83%; mp: 105–109 °C; IR (KBr): 3336, 3290, 3100, 2950, 2927, 2862, 2789, 1615, 1581, 1514,1481, 1461,1355, 1321,1253, 1139, 1003, 990, 906, 863, 815, 791, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90–7.81 (m, 1H), 7.77 (t, *J* = 2.1 Hz, 1H), 7.45 (t, *J* = 8.2 Hz, 1H), 7.27 (dd, *J* = 8.6, 2.7 Hz, 1H), 4.12–4.05 (m, 2H), 4.01 (ddd, *J* = 11.9, 9.1, 4.4 Hz, 1H), 3.02 (dd, *J* = 12.8, 3.9 Hz, 1H), 2.88 (dd, *J* = 12.8, 7.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 149.1, 130.0, 121.6, 116.1, 108.9, 70.8, 70.0, 43.7. HRMS (ESI) calcd. for $C_9H_{12}N_2O_4$ $[M+H]^+$: 213.0797, found 213.0870. $[\alpha]_D^{20}$ = +2.5 (*c* 1.0, Methanol).

(*S*)-**7**. Yield: 86%; mp: 125–129 °C; IR (KBr): 3354, 3298, 3076, 2933, 2883, 2831, 2717, 1622, 1606, 1593, 1498, 1451, 1344, 1270, 1179, 1112, 1090, 982, 939, 861, 824, 752, 683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32–8.17 (m, 2H), 7.08–6.93 (m, 2H), 4.14–4.05 (m, 2H), 4.01 (ddd, *J* = 9.3, 7.2, 5.1 Hz, 1H), 3.03 (dd, *J* = 12.8, 4.0 Hz, 1H), 2.87 (dd, *J* = 12.8, 7.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.6, 141.7, 125.9, 114.5, 70.7, 69.8, 43.7. HRMS (ESI) calcd. for $C_9H_{12}N_2O_4$ $[M+H]^+$: 213.0797, found 213.0872. $[\alpha]_D^{19}$ = +3.0 (*c* 1.0, Methanol).

Determination of diastereomeric excess of 1 in the salt. The diastereomeric excess (% de) of the salt (=enantiomeric excess (% ee) of **1**) was determined by HPLC with Lux Cellulose-2 column (4.6 × 250 mm I.D., 3 μm, Phenomenex). The salt was treated with HCl aq. The liberated acid was extracted by ethyl acetate and dried with anhydrous Na_2SO_4. After removal of solvent under reduced pressure, the enantiopurity of the liberated **1** was determined by HPLC analysis on chiral column Lux Cellulose-2. The mobile phase was hexane/ethanol (93/7) with 0.15% trifluoroacetic acid (TFA), and flow rate was 1.0 ml/min under detection wavelength of 210 nm. Retention time: (*S*)-**1** 15.47 min, (*R*)-**1** 18.16 min.

Resolution of *rac*-1. Traditional resolution procedure is as follows. To a 5 ml flask were added 186 mg of *rac*-**1** (1 mmol), 1 mmol of resolving agent, and 1 ml of resolving solvent followed by heating under stirring to obtain a clear solution at 70 °C. The solution was gradually cooled to 25 °C and kept for about 7 days,[1] and the precipitated diastereomeric salt was filtered off and washed with cooled resolving solvent to yield salt crystals, followed by drying at 45 °C under vacuum.

Dutch resolution procedure was the same as traditional resolution procedure, just replacing 0.1 mmol of resolving agent with additive. In other words, 0.9 mmol resolving agent and 0.1 mmol additive were added to the resolution system.

Analytical data of the less soluble salt (*R*)-**1**·(*S*)-**5** by the Dutch resolution are shown as follows. (*R*)-**1**·(*S*)-**5**: $[\alpha]_D^{21}$ = −78 (*c* 1.0, Ethanol); mp: 126–130 °C; IR (KBr) cm^{-1} : 3394, 3101, 2921, 1583, 1492, 1473, 1438, 1367, 1285, 1245, 1088, 821, 749; ^1H NMR (400 MHz, D_2O) δ 7.33–7.27 (m, 1H), 7.27–7.21 (m, 1H), 7.18 (dd, *J* = 9.1, 3.3 Hz, 4H), 6.81 (d, *J* = 8.9 Hz, 2H), 5.17 (s, 1H), 4.09 (dt, *J* = 8.4, 4.1 Hz, 1H), 3.92 (qd, *J* = 10.3, 4.6 Hz, 2H), 3.11 (dd, *J* = 13.2, 3.3 Hz, 1H), 3.00 (dd, *J* = 13.2, 9.1 Hz, 1H).; ^{13}C NMR (101 MHz, D_2O): 178.6, 156.5, 137.6, 133.2, 129.7, 129.6, 129.4, 129.3, 127.3, 125.7, 125.7, 116.0, 72.0, 69.6, 65.9, 41.6.

RESULTS AND DISCUSSION

Traditional Resolution of Rac-1 with Resolving Agents

Optical active (*R*)-phenylethylamine (PEA) is well known to be a good resolving agent for mandelic acid derivatives.[26–28] The *m*-chloromandelic acid and *p*-chloro mandelic acid can be resolved by enantiopure PEA, but *rac*-**1** could not.[29] Maybe, the *o*-chlorine disturbs the aromatic interactions of PEA and *o*-chloromandelic acid. In order to find the suitable resolving agent for *rac*-**1**, enantiopure aryloxypropylamines with heteroatom Cl or hetero groups OCH_3 and NO_2 on benzene ring were chosen as resolving agents.[30,31] Halogen bonding interactions may occur between chlorine of *rac*-**1** and heteroatoms (Fig. 3). A series of aryloxypropylamines were synthesized according to the reported method.[25]

[1]In the resolution of *rac*-**1** with (*S*)-**5** and (*S*)-**4**, in order to obtain the less soluble salt in a short time, three types of experiments were performed: (a) stay the solution containing the less soluble salt at 0 °C, (b) stir the solution containing the less soluble salt at room temperature, (c) stir the solution containing the less soluble salt at 0 °C. As a result, the salt precipitated at moment with the conditions (a) and (c). However, the salt turned sticky immediately once it was put at room temperature. So, it is too difficult to filter the salt. With condition (b), the salt precipitated in half to 1 h and the salt was powdered; the yield of the salt was 82%. However, the enantiopurity of the salt was poor, and the *de* value was 23%. When the solution was stayed at room temperature for 7 days, the precipitation was spherical, which was easy to filter, and the enantiopurity of the salt was high, the ee value was 98%. So, it was the best choice for obtaining the best salt when staying the solution for 7 days at room temperature.

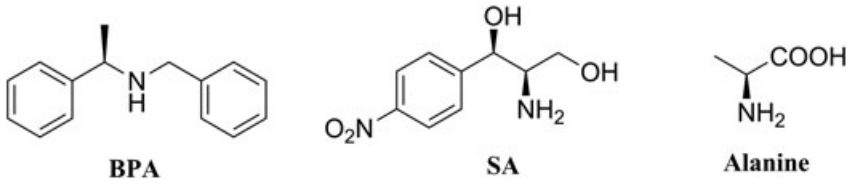

Fig. 2. Structures of enantiopure *N*-benzyl-α-phenylethanamine (BPA), 1-aryl-2-amino-1,3-propane-diol (SA), and Alanine.

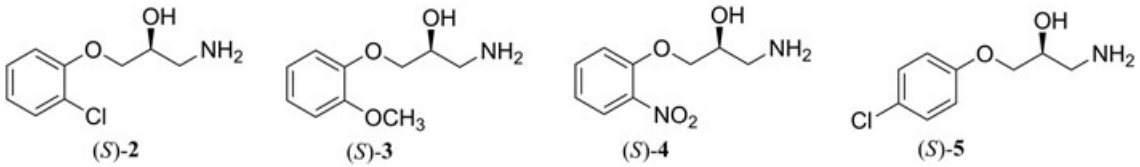

Fig. 3. Resolving agents (*S*)-**2**, (*S*)-**3**, (*S*)-**4**, and (*S*)-**5**.

An equimolar resolving agent was used with *rac*-**1** (186 mg, 1 mmol), the resolving solvent was chosen from ethanol and isopropanol, and the volume was 1 ml. Experimental results are summarized in Table 1.

To our excitement, three aryloxypropylamines gave good to excellent yield of salt although the chiral purity was poor (0–26% de, $E = 0$–35%) (Table 1, entries 2–4 and 7–8). (*S*)-**2**, (*S*)-**3**, and (*S*)-**5** were benefits to the precipitation of salt except (*S*)-**4**. From comparison, para-chloro aryloxypropylamine (*S*)-**5** was better in chiral recognition. Maybe, para-substituted group affected the CH/π interaction slightly while ortho-substituted group seriously.[32] To clarify the resolving agents with different substituted groups on phenyl ring showing different chiral recognition abilities, a more in-depth analysis is necessary. Weak molecular forces, the crystal packing, the state of hydration, and the ion-pair interactions in the solvent may give rise to differences in solubility and resolution.

The salt of (*S*)-**4** and *rac*-**1** had difficulty in precipitation; therefore, to improve the optical purity of the diastereomeric salt, Dutch resolution was carried out with enantiopure **4**.

Dutch Resolution of Rac-1 with Resolving Agents

Dutch resolution is the use of structurally related resolving agents. A mixture of these resolving agents could result in high diastereomeric excesses of the less soluble salt.[33–35] Further investigations revealed that certain family members of resolving agents were efficient nucleation inhibitors, which did not incorporate into the less soluble salt. Inhibitor acts by widening the width of the metastable zone of supersaturation (the temperature of the zone between dissolution and the lower temperature at which precipitation begins) to a greater extent for the more soluble salt than the less soluble salt.[36,37] Therefore, to increase the optical purity of the less soluble salt, Dutch resolution of *rac*-**1** was carried out with (*R*)-**4** or (*S*)-**4** as additive. 0.9 equimolar resolving agent and 0.1 equimolar (*R*)-**4** or (*S*)-**4** were used with *rac*-**1** (186 mg, 1 mmol), the resolution solvent was isopropanol, and the volume was 1 ml. Experimental results are summarized in Table 2.

TABLE 2. Dutch resolution of *rac*-1 with resolving agents in the presence of enantiopure 4

Entry	Resolving agent[a]	Additive[b]	Yield(%)[c]	de(%)[d]	*E*(%)[e]
1	(*S*)-**2**	(*R*)-**4**	18	3	1
2		(*S*)-**4**	36	5	2
3	(*S*)-**3**	(*R*)-**4**	60	8	5
4		(*S*)-**4**	100	10	10
5	(*S*)-**5**	(*R*)-**4**	16	80	13
6		(*S*)-**4**	65	98	64

[a]Molar ratio of resolving agent to *rac*-**1** was 0.9/1.0, concentration of *rac*-**1** was 186 mg/ml.
[b]Molar ratio of additive to *rac*-**1** was 0.1/1.0.
[c]Based on a half amount of the *rac*-**1** used.
[d]de of the salt was based on the ee of the acid **1** liberated from the salt.
[e]Resolution efficiency $E(\%) = \text{Yield}(\%) \times \text{de}(\%)$.

TABLE 1. Traditional resolution of *rac*-1 with resolving agents in ethanol and isopropanol

Entry	Resolving agent[a]	Solvent	Absolute configuration	Yield(%)[b]	de(%)[c]	*E*(%)[d]
1	(*S*)-**2**	Ethanol	*R*	26	0	0
2		Isoprapanol	*R*	93	3	3
3	(*S*)-**3**	Ethanol	*R*	110	5	6
4		Isoprapanol	*R*	157	6	9
5	(*S*)-**4**	Ethanol	*R*		No salts precipitate	
6		Isoprapanol	*R*		No salts precipitate	
7	(*S*)-**5**	Ethanol	*R*	98	16	16
8		Isoprapanol	*R*	134	26	35

[a]Molar ratio of resolving agent to *rac*-**1** was 1.0/1.0, concentration of *rac*-**1** was 186 mg/ml.
[b]Based on a half amount of the *rac*-**1** used.
[c]de of the salt was based on the ee of the acid **1** liberated from the salt.
[d]Resolution efficiency $E(\%) = \text{Yield}(\%) \times \text{de}(\%)$.

The addition of (*R*)-**4** or (*S*)-**4** indeed lead to a decrease in the yield of salt (Table 2 entries 2 and 3 vs Table 1 entry 2; Table 2 entries 4 and 5 vs Table 1 entry 4; Table 2 entries 5 and 6 vs Table 1 entry 8). In the case of (*S*)-**2** and (*S*)-**3** as resolving agents, (*R*)-**4** or (*S*)-**4** did not improve the optical purity of the less soluble salt. However, it was found that the use of (*R*)-**4** or (*S*)-**4** as additive cooperated with (*S*)-**5** could improve the purity of salt significantly (Table 2 entries 5 and 6 vs entries 1–4). The best salt was obtained in 65% yield with 98% de (Table 2 entry 6). The composition of the salt precipitated from the solution of *rac*-**1**, (*S*)-**5**, and (*S*)-**4** was checked by NMR. From the NMR data, it was found that the salt contained only (*S*)-**5** and *o*-chloromandelic acid; there was no detectable amount of (*S*)-**4** or (*R*)-**4**.

Both (*S*)-**4** and (*R*)-**4** worked as efficient nucleation inhibitors. Moreover, (*S*)-**4**, which has the same chiral sense with the resolving agent (*S*)-**5**, is better compared with (*R*)-**4** (Table 2 entry 5 vs 6). Therefore, more exploration on the inhibitors was carried out, especially the additives enantiopure aryloxypropylamines (*S*)-**6** and (*S*)-**7** with nitro group on benzene ring (Fig. 4). 0.9 equimolar resolving agent and 0.1 equimolar additive were used with *rac*-**1** (186 mg, 1 mmol), the resolving solvent was isopropanol, and the volume was 1 ml. Experimental results are summarized in Table 3.

The additions of (*S*)-**6** and (*S*)-**7** also gave decreased yields (Table 3 entries 1 and 2 vs Table 1 entry 4; Table 3 entries 3 and 4 vs Table 1 entry 2; Table 3 entries 5 and 6 vs Table 1 entry 8). In the case of (*S*)-**3** as resolving agent, additives (S)-**6** and (S)-**7** did not improve the optical purity (Table 3 entries 1 and 2). Cooperating with (*S*)-**2**, (*S*)-**6**, and (*S*)-**7** resulted in no salt (Table 3 entries 3 and 4). However, in the presence of (*S*)-**5**, good resolution was obtained with the salt in moderate yield and excellent de value (Table 3 entries 5 and 6).

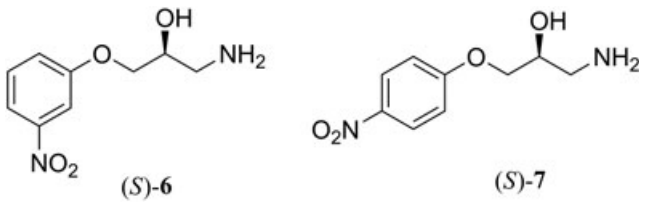

Fig. 4. Aryloxypropylamines (*S*)-**6** and (*S*)-**7**.

TABLE 3. Dutch resolution of *rac*-1 with resolving agents in the presence of (*S*)-6 and (*S*)-7

Entry	Resolving agent[a]	Additive[b]	Yield (%)[c]	de (%)[d]	*E* (%)[e]
1	(*S*)-**3**	(*S*)-**6**	100	2	2
2		(*S*)-**7**	144	1	1
3	(*S*)-**2**	(*S*)-**6**	No salts precipitate		
4		(*S*)-**7**	No salts precipitate		
5	(*S*)-**5**	(*S*)-**6**	52	98	51
6		(*S*)-**7**	50	96	48

[a]Molar ratio of resolving agent to *rac*-**1** was 0.9/1, concentration of *rac*-**1** was 186 mg/ml.
[b]Molar ratio of additive to *rac*-**1** was 0.1/1.0.
[c]Based on a half amount of the *rac*-**1** used.
[d]de of the salt was based on the ee of the acid **1** liberated from the salt.
[e]Resolution efficiency *E*(%) = Yield(%) × ee(%).

It is noteworthy that *rac*-**1** could be well resolved by using (*S*)-**5** as resolving agent in the presence of *m*- and *p*-nitrophenoxypropylamines (*S*)-**6** and (*S*)-**7**. (*S*)-**6** and (*S*)-**7** also worked as well as *o*-nitrophenoxypropylamine (*S*)-**4** in improving the resolution of *rac*-**1** (Table 3 entries 5 and 6, Table 2 entry 6). However, (*S*)-**4** was better in the salt yield and optical purity (Table 2entry 6 vs Table 3 entries 5 and 6). As a result, (*R*)-**1** could be obtained in 65% yield with 98% ee. So, the nitro-aryl aromatics may be potential nucleation inhibitors.

CONCLUSION

With this new kind of resolving agent, racemic *o*-chloromandelic acid *rac*-**1** was successfully resolved by Dutch resolution. Using (*S*)-**5** as resolving agent and (*S*)-**4** as nucleation inhibitor, (*R*)-**1** could be obtained in 65% yield with 98% ee. Structurally related resolving agents were potential nucleation inhibitors, especially the nitro-aryl aromatics. Further investigations on resolving other acids with this new agent and the synthetic applications of resolved acid are currently in progress.

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