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The effect of SDE on the separation of diastereomeric salts: a case study for the resolution of mandelic acid derivatives with Pregabalin

Zsolt Szeleczky [a], Péter Bagi [a], Emese Pálovics [b], Elemér Fogassy [a,*]

[a] *Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, 1521 Budapest, Hungary*
[b] *Research Group for Organic Chemical Technology, Hungarian Academy of Sciences, 1521 Budapest, Hungary*

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ABSTRACT

A resolution method has been elaborated for mandelic acid and 2-chloromandelic acid applying the (*R*)-(−)-3-(aminomethyl)-5-methylhexanoic acid (Pregabalin) as the resolving agent. The formation of the corresponding diastereomers was kinetically controlled. This observation was rationalized by the behavior of enantiomeric mixtures of mandelic acid, 2-chloromandelic acid, and 3-(aminomethyl)-5-methylhexanoic acid. It was found that the eutectic composition of Pregabalin influenced the diastereomeric excess of the diastereomers formed under kinetic control.

1. Introduction

The demand for enantiomerically pure compounds is increasing, hence the preparation of enantiopure chiral compounds and the fundamental understanding of chiral–chiral recognition are of interest in industrial and academic research. There are a wide variety of methods to prepare chiral compounds in optically active form including the transformation of compounds from the natural pool of chirality, asymmetric synthesis, and the resolution.[1–10]

The preparation of chiral compounds in enantiopure form via asymmetric synthesis[11,12] or fractional crystallization of diastereomers formed in the reaction of the corresponding racemic compound and a resolving agent is based on the non-linear effects of chiral–chiral recognition.[13,14] The non-linear behavior of a given enantiomeric mixture, which was named as self-disproportion of enantiomers (SDE) by Soloshonok, implies that the associates formed either from the enantiomer in excess, or from the racemic portion, may behave differently. The underlying phenomenon of SDE is the complementarity of the enantiomers, more precisely the amount and strength of the non-covalent interactions between the individual chiral molecules, which leads to the observation that the starting enantiomeric excess value may differ from the one in equilibrium if a given enantiomeric mixture is subjected to partitioning between two phases.[15–17] The self-disproportion of the enantiomers was first observed by Pasteur when he obtained pure enantiomers during the crystallization of sodium ammonium tartrate.[18] Roseboom proved that the partition equilibrium of the enantiomeric mixtures between the solid and the liquid (molten) phase is dependent on the initial composition of the enantiomeric mixture and this behavior of the enantiomeric mixtures is often not linear.[19]

Based on the binary melting point- and the ternary solubility diagrams, the enantiomeric mixtures can be divided into three groups, the conglomerate- or the racemate-forming compounds or the solid-solutions. Approximately 80% of enantiomeric mixtures are racemate-forming compounds. Often the non-linear behavior of the enantiomeric mixture can be observed when they are purified with methods based on the partitioning of the enantiomeric mixture between two phases (e.g., solid and liquid phase).[2]

The utilization of the binary melting point and the ee versus ee_0 diagrams (where ee_0 refers to the initial composition of the enantiomeric mixture and ee is the enantiomeric excess after purification) for designing the purification of a given enantiomeric mixture was the subject of our earlier study.[20] Herein we would like to emphasize on how the relative position of the initial enantiomeric composition (ee_0) compared to the eutectic composition (ee_E) influences the outcome of the enantiomeric enrichment procedure. Starting from enantiomeric mixtures that are either less pure or purer than the eutectic composition ($ee_0 < ee_E$ or $ee_0 > ee_E$), the crystalline phase obtained has a lower or higher enantiomeric purity than the initial composition, respectively, ($ee < ee_0$ or $ee > ee_0$). In these instances, it may be assumed that the equilibrium in solution is displaced toward the formation of either heterochiral or homochiral supramolecular associates, respectively.[20] These associates initiate the crystallization that is responsible for the aforementioned phenomenon. Hence the eutectic composition (ee_E) may be a characteristic value to indicate whether the

* Corresponding author. Tel.: +36 1 4631883; fax: +36 1 4633648.
E-mail address: efogassy@mail.bme.hu (E. Fogassy).

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hetero- or homochiral interaction is dominant, while the ee_E value may also show which one of the two diastereomeric associates has higher complementarity.

How the complementarity between the racemic compound and the resolving agent affects the efficiency of those resolutions when the enantiomers of racemic amino acid derivatives were separated using resolving agents with a structure related to the corresponding racemic compound has previously been investigated. If the racemic compound and the structurally related resolving agent were reacted in a ratio of 1:1, the mixture obtained may be regarded as a quasi-enantiomeric mixture with a quasi-enantiomeric excess of 50%. It was established that the enantiomeric purity of the enantiomeric mixtures obtained from the corresponding crystalline diastereomers (ee_D) was in good agreement with the eutectic composition of the racemic amino acid derivatives ($ee_D \cong ee_E$) when structurally related resolving agents were used.[21,22] Similar trends were observed in those resolutions when the enantiomers of the racemic compound were separated using a structurally non-related resolving agent.[23]

In continuation of this, we wished to investigate in more detail those resolutions when the racemic compound was reacted with a resolving agent having a non-related structure. Hence herein, racemic mandelic acid **MA** and racemic 2-chloromandelic acid **CMA** were chosen as model compounds and were resolved using the structurally unrelated (*R*)-(−)-3-(aminomethyl)-5-methylhexanoic acid **PREG** (Pregabalin) as the resolving agent (Fig. 1). In order to elaborate upon a resolution procedure for the mandelic acid derivatives **MA** and **CMA**, our aim was to study how the eutectic composition (ee_E) of the racemic compound **MA** or **CMA** or the resolving agent **PREG** influenced the efficiency of the resolution, as well as the purity of the enantiomeric mixtures (ee_D) of the mandelic acid derivatives **MA** or **CMA** under kinetic or thermodynamic control.

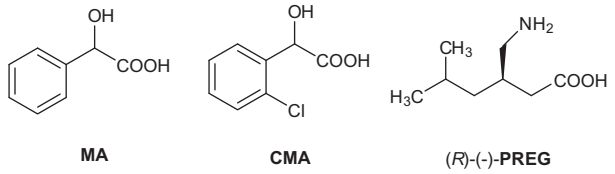


Figure 1. Mandelic acid **MA**, 2-chloromandelic acid **CMA**, and (*R*)-(−)-3-(aminomethyl)-5-methylhexanoic acid **PREG** used herein.

2. Results and discussion

2.1. The behavior of enantiomeric mixtures of mandelic acid MA, 2-chloromandelic acid CMA, and 3-(aminomethyl)-5-methylhexanoic acid PREG

In order to investigate the behavior of the enantiomeric mixtures of mandelic acid **MA**, 2-chloromandelic acid **CMA**, and 3-(aminomethyl)-5-methylhexanoic acid **PREG**, racemic and enantiopure **MA**, **CMA**, or **PREG** were mixed to obtain the corresponding enantiomeric mixtures as detailed in Table 1, and were dissolved in the corresponding hot solvent. Water was used as the solvent for mandelic acid **MA** and 2-chloromandelic acid (**CMA**), while aqueous ammonia was used as the solvent for Pregabalin (**PREG**). The crystals were obtained by gradually cooling the reaction mixture to 26 °C and then separating them from the mother liquor after 30 min of crystallization. The results are summarized in Table 1.

The correlation between the initial enantiomeric purity (ee_0) and the final enantiomeric purity (ee) in case of the **MA**, **CMA**, or **PREG** is shown in Figure 2. Mandelic acid **MA**, 2-chloromandelic acid **CMA**, and Pregabalin **PREG** are all racemate-forming compounds with eutectic compositions (ee_E) of 38%, 10%, and 80%, respectively.

2.2. The resolution of mandelic acid MA or racemic 2-chloromandelic acid CMA with (*R*)-(−)-3-(aminomethyl)-5-methylhexanoic acid (*R*)-PREG

The resolution of the racemic mandelic acid **MA** or the 2-chloromandelic acid **CMA** was carried out using (*R*)-Pregabalin **PREG** as the resolving agent. Mandelic acid **MA** or 2-chloromandelic acid **CMA** was mixed with 0.5 equiv of (*R*)-Pregabalin (**PREG**) and 0.25 equiv of sodium carbonate as the achiral auxiliary[24] and the mixture obtained was dissolved in hot water. The reaction mixture was allowed to cool to 26 °C whereupon the crystalline diastereomeric salt (*R*)-**MA**·(*R*)-**PREG** or (*R*)-**CMA**·(*R*)-**PREG** appeared and this was separated from the mother liquor appeared after 15 min or 168 h, respectively, (Scheme 1 and Table 2).

In order to obtain the enantiomeric mixtures of **MA** and **CMA**, the corresponding diastereomer (*R*)-**MA**·(*R*)-**PREG** or (*R*)-**CMA**·(*R*)-**PREG**, respectively, was treated with aqueous ammonia, whereupon the (*R*)-Pregabalin **PREG** precipitated. Next, hydrochloric acid was added to the mother liquor and the crystals of **MA** or **CMA** were collected after 2 h of crystallization. The results are summarized in Table 2.

In the resolution experiments of mandelic acid **MA** or 2-chloromandelic acid **CMA** with (*R*)-Pregabalin **PREG**, the enantiomeric excess (ee_D) and the resolving capability values (F) were ee_D = 80% and F = 0.45 in the case of **MA**, or ee_D = 92% and F = 0.49 for **CMA** after 15 min (Table 2, entries 1 and 3). These values decreased to ee_D = 62% and F = 0.43 for **MA** or ee_D = 29% and F = 0.36 for **CMA** when the crystallization time was 168 h (compare Table 2, entries 1 and 2 or 3 and 4).

Based on the data shown in Table 2, it can be concluded that kinetic control governed the initial formation of the (*R*)-**MA**·(*R*)-**PREG** and (*R*)-**CMA**·(*R*)-**PREG** diastereomers leading to good enantiomeric separation of **MA** or **CMA** after 15 min of crystallization. The decrease in the enantiomeric excess (ee_D) and in the resolving capability values (F) over time may be explained by the effect of thermodynamic control, i.e., the formation of (*S*)-**MA**·(*R*)-**PREG** or (*S*)-**CMA**·(*R*)-**PREG** diastereomers became more favorable after 168 h of crystallization than at the initial stages of the crystallization.

The behavior of the enantiomeric mixtures of the corresponding racemic compound **MA** or **CMA** and the resolving agent **PREG** may be the underlying phenomenon of these kinetic effects observed during the resolution of **MA** or **CMA** with (*R*)-**PREG**. As it was shown in Section 2.1, mandelic acid **MA**, 2-chloromandelic acid **CMA**, and Pregabalin **PREG** are all racemate-forming compounds (Table 1 and Fig. 2). This behavior indicates that in the case of enantiomeric mixtures with an enantiomeric purity above the eutectic composition, the equilibrium in the solution is displaced toward the formation of the corresponding homochiral supramolecular associates, which may help the initial crystallization of the corresponding diastereomeric salts during the resolution of **MA** or **CMA** with (*R*)-**PREG** leading to high enantiomeric excess and resolving capability values after 15 min of crystallization (Table 2, entries 1 and 3). This hypothesis can also be verified by the fact that the difference between the corresponding eutectic composition values (ee_E) is greater in the case of 2-chloromandelic acid **CMA** and Pregabalin **PREG** [ee_E(**CMA**) = 10% vs ee_E(**PREG**) = 80%] than the ee_E difference of mandelic acid **MA** and Pregabalin **PREG** [ee_E(**MA**) = 38% vs ee_E(**PREG**) = 80%] which led to more efficient separation of the 2-chloromandelic acid enantiomers **CMA**.

It was shown in our previous study that the eutectic composition (ee_E) of the racemic compounds is in good agreement with

Table 1
Recrystallization of the enantiomeric mixtures of mandelic acid **MA**, 2-chloromandelic acid **CMA**, and 3-(aminomethyl)-5-methylhexanoic acid **PREG**

Starting enantiomeric mixtures of **MA**, **CMA**, or **PREG** (ee_0)	The yield and the enantiomeric purity of the recrystallized product					
	MA		**CMA**		**PREG**	
	Yield (%)	ee[a] (%)	Yield (%)	ee[a] (%)	Yield (%)	ee[a] (%)
0	—	0	—	0	—	0
5	—	n.d.	72[b]	4	—	n.d.
10	60	2	73[b]	11	82	1
20	54	11	25	47	74	2
30	57	27	25	65	80	2
40	52	42	33	72	51	5
50	51	55	37	84	43	5
60	51	69	49	95	31	14
70	51	88	39	92	25	34
80	53	97	59	95	63	73
90	68	99	58	98	60	94
100	—	100	—	100	—	100

[a] Enantiomeric purity based on the specific rotation.
[b] 4.4 mmol of **CMA** was recrystallized, while in all other instances, 1.1 mmol of **CMA** was used.

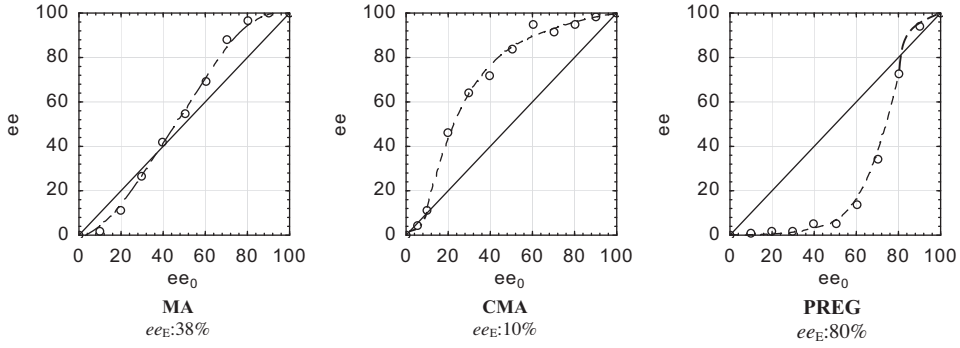
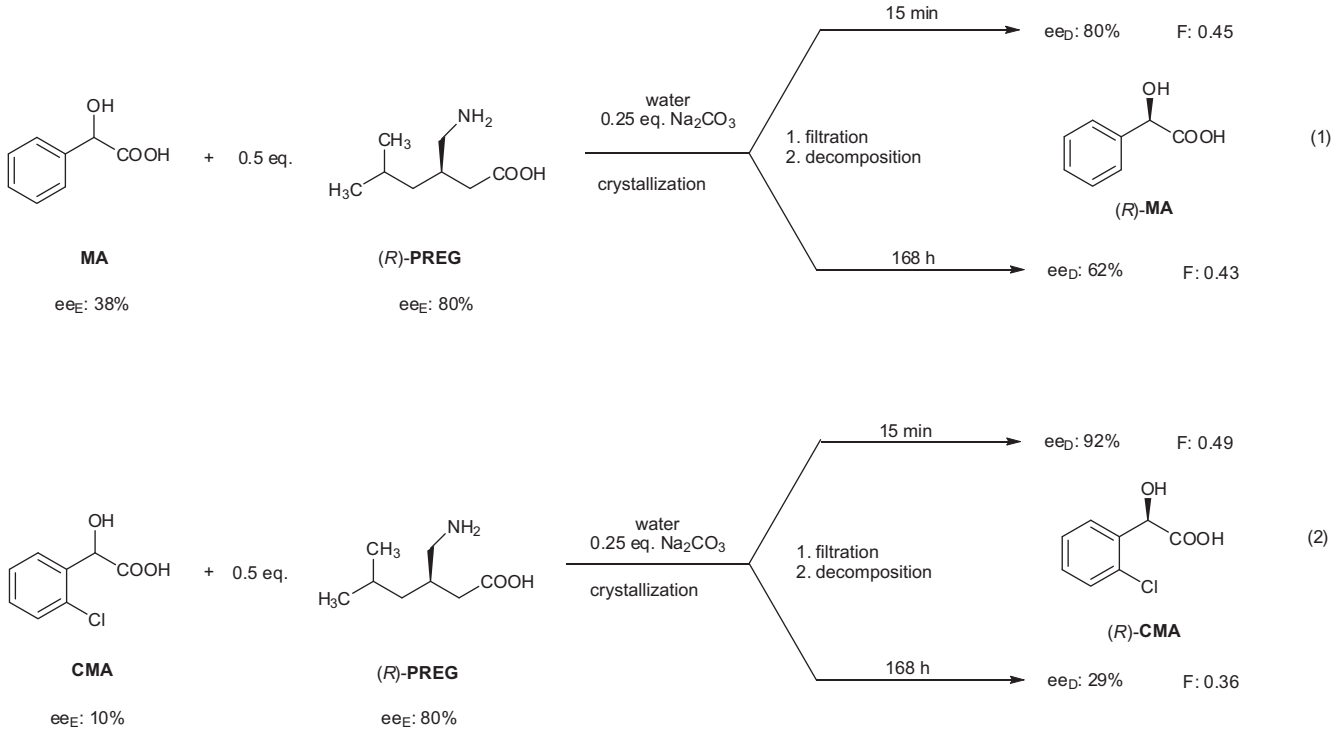


Figure 2. The correlation between the initial and final enantiomeric purity (ee_0 and ee) obtained by fractional crystallization of enantiomeric mixtures of **MA**, **CMA**, or **PREG**.



Scheme 1. The resolution of racemic **MA** or **CMA** with (*R*)-**PREG** by fractional crystallization for 15 min or 168 h.

Table 2
The resolution of racemic **MA** or **CMA** using (*R*)-**PREG** as the resolving agent

Entry	Racemic compound	Crystallization time (h)	Yield[a] (%)	ee_D[b] (%)	*F*(−)[c]
1	**MA**	0.25	56	80	0.45
2	**MA**	168	70	62	0.43
3	**CMA**	0.25	53	92	0.49
4	**CMA**	168	124	29	0.36

[a] Based on the half of the racemic **MA** or **CMA** that was regarded to be 100% for each antipode.
[b] Enantiomeric excess based on the specific rotation.
[c] Resolving capability, also known as the Fogassy parameter [$F = (Y/100) \times (ee/100)$].[3]

the purity of the enantiomeric mixtures obtained at the end of the resolution process if a resolving agent with a related structure to the racemic compound is used.[25] Herein, the resolving agent **PREG** and the racemic compounds **MA** and **CMA** are structurally unrelated and in this case, the purity of the enantiomeric mixtures of the mandelic acid derivatives **MA** and **CMA** obtained after decomposition of the corresponding diastereomeric salts **MA**·(*R*)-**PREG** or **CMA**·(*R*)-**PREG** formed under kinetic control was similar to the eutectic composition value (ee_E) of the resolving agent **PREG**.

Based on our previous and recent results, it can also be concluded that the purity of a given enantiomeric mixture (ee_D) obtained in a kinetically controlled resolution may be determined by the eutectic composition (ee_E) of either the racemic compound or the resolving agent, whichever value is higher. The purity of the enantiomeric mixture (ee_D) obtained after decomposition of the corresponding diastereomer is similar to or even higher than the eutectic composition (ee_E) of the racemic compound or the resolving agent used in that particular resolution process.

With regard to the resolution of mandelic acid **MA** or 2-chloromandelic acid **CMA** with Pregabalin **PREG**, the presence of either the racemic compound **MA** or **CMA** or the resolving agent **PREG** with a higher eutectic composition (ee_E) may initiate the rapid nucleation required for the crystallization to afford the diastereomers (*R*)-**MA**·(*R*)-**PREG** or (*R*)-**CMA**·(*R*)-**PREG** with a diastereomeric excess of 80% or 92%, respectively. However the supramolecular structure formed has a lower thermodynamic stability, meaning that reaching the solubility equilibria of the diastereomers and the formation of a more stable crystal structure may require more time involving a decrease in the enantiomeric excess of (*R*)-**MA** or (*R*)-**CMA** (ee: 62% or 29%, respectively).

3. Conclusions

The resolution of mandelic acid **MA** or the 2-chloromandelic acid **CMA** was studied using (*R*)-Pregabalin (*R*)-**PREG** as the resolving agent. The highest enantiomeric excess obtained was 80% for **MA** and 92% for **CMA**. The separation of the enantiomers of mandelic acid **MA** or the 2-chloromandelic acid **CMA** with (*R*)-Pregabalin (*R*)-**PREG** was influenced by kinetic control. This observation was rationalized by the behavior of the enantiomeric mixtures of racemic compound **MA** and **CMA** or the resolving agent **PREG**. We found that the eutectic composition (ee_E) of the compounds involved in the kinetically controlled resolution procedure may influence the efficiency of the enantiomeric separations.

In our previous papers, we emphasized the importance of the structural similarities of the racemic compound, the resolving agent or—in some instances—the achiral additive in the process of finding the most appropriate resolution process for a given racemic compound.[26,27] Herein it seems that in addition to the structural similarities, the eutectic composition (ee_E) of the racemic compound or the resolving agent should also be taken into consideration when selecting the most appropriate resolving agent, as it seems that the eutectic compositions of the compounds involved in the resolution may play a decisive role in the overall efficiency of the resolution process. The eutectic composition (ee_E) of a given racemate-forming compound can be easily determined by a series of crystallization experiments.[20,26]

4. Experimental

4.1. General

Enantiomeric excess values (ee) were calculated by comparing the specific rotation of the enantiomeric mixture with the corresponding pure enantiomer. Optical rotations were determined on a Perkin–Elmer 241 polarimeter. (*R*)-(−)-3-(Aminomethyl)-5-methylhexanoic acid **PREG** was synthesized as described earlier.[28,29] The racemic and enantiopure mandelic acid **MA** and (*R*)-**MA** and 2-chloromandelic acid **CMA** and (*R*)-**CMA** were purchased from Aldrich Chemical Co.

4.2. The recrystallization of the enantiomeric mixtures of mandelic acid MA, 2-chloromandelic acid CMA, and 3-(aminomethyl)-5-methylhexanoic acid PREG

Racemic and enantiopure (*R*)-(−)-mandelic acid **MA** and (*R*)-**MA** were mixed to obtain a total amount of 0.20 g (1.3 mmol) of the given enantiomeric mixture of mandelic acid with an ee_0 of 0–100% as reported in Table 1. This mixture was then dissolved in 0.20 mL of hot water. The solution was allowed to cool down to 26 °C, whereupon crystals appeared which were then separated from the mother liquor after 30 min of crystallization. The results are shown in Table 1.

The recrystallization of the enantiomeric mixtures of 2-chloromandelic acid **CMA** or 3-(aminomethyl)-5-methylhexanoic acid **PREG** was accomplished according to the procedure described for mandelic acid **MA**.

In the case of **CMA**, 0.20 g (1.1 mmol) of the given enantiomeric mixture of **CMA** obtained by mixing racemic and enantiopure (*R*)-(−)-**CMA** was recrystallized from 0.05 mL of water. The results are shown in Table 1.

In the case of **PREG**, 0.40 g (2.5 mmol) of the given enantiomeric mixture obtained by mixing racemic and enantiopure (*R*)-(−)-**PREG** was recrystallized from a mixture of 2.0 mL of water and 1.2 mL of 25% aqueous ammonia. The results are shown in Table 1.

4.3. The resolution of mandelic acid MA with (*R*)-(−)-3-(aminomethyl)-5-methylhexanoic acid (*R*)-PREG (representative procedure)

A mixture of 1.52 g (10 mmol) racemic mandelic acid **MA**, 0.27 g (2.5 mmol) of Na_2CO_3, and 0.80 g (5.0 mmol) of (*R*)-(−)-3-(aminomethyl)-5-methylhexanoic acid (*R*)-**PREG** was dissolved in 6.1 mL of hot water. The crystalline diastereomeric salt appeared by gradually cooling down the solution to 26 °C and was then separated from the mother liquor by filtration after 15 min. In order to decompose the diastereomer, a mixture of 1.9 mL of 25% aqueous

ammonia and 2.0 mL of water was added to the crystals. Next, 0.70 g (4.4 mmol) of crystalline (*R*)-(−)-3-(aminomethyl)-5-methylhexanoic acid (*R*)-**PREG** was filtered off after 3 h of crystallization time, after which 1.5 mL of 37% hydrochloric acid was added to the mother liquor to afford 0.43 g (56%) of (*R*)-(−)-mandelic acid (*R*)-**MA** with an ee_D of 80% that was separated from the mother liquor after 2 h of crystallization (Table 2, entry 1). $[\alpha]_D^{25} = -121.6$ (*c* 1, water); ee: 80%.

The resolution of mandelic acid **MA** was also accomplished with (*R*)-(−)-3-(aminomethyl)-5-methylhexanoic acid (*R*)-**PREG** in a similar manner, allowing the corresponding diastereomer (*R*)-**MA**·(*R*)-**PREG** to crystallize for 168 h to afford (*R*)-(−)-mandelic acid [(*R*)-**MA**] with an ee_D of 62% in a yield of 50% (Table 2, entry 2).

4.4. The resolution of 2-chloromandelic acid CMA with (*R*)-(−)-3-(aminomethyl)-5-methylhexanoic acid (*R*)-PREG

Racemic 2-chloro-mandelic acid **CMA** was resolved with (*R*)-(−)-3-(aminomethyl)-5-methylhexanoic acid (*R*)-**PREG** according to the representative procedure described in Section 4.3 with 15 min or 168 h of crystallization time to afford (*R*)-(−)-2-chloromandelic acid (*R*)-**CMA** with an ee_D of 92% in a yield of 53% or with an ee_D of 29% and in a yield of 124%, respectively, (Table 2, Entries 3 and 4). $[\alpha]_D^{25} = -111.3$ (*c* 1, water); ee: 92%.

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