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Efficient Resolution of Menthylamine with Inexpensive (*R*,*R*)-Tartaric Acid by Dielectrically Controlled Resolution (DCR)

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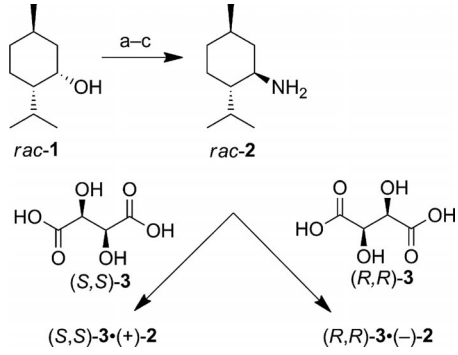
A practical procedure for the resolution of menthylamine **2** with (*R*,*R*)-tartaric acid [(*R*,*R*)-**3**] as resolving agent is presented. Variation of the solvent system allows both enantiomers of **2** to be selectively crystallized. Performing the resolution in methanol containing 6 % water leads to (–)-**2**·(*R*,*R*)-**3**·MeOH. The other, less-soluble diastereomeric salt is obtained by applying a solvent system consisting of methanol with 19 % water with a yield of 14 %. Subsequent basic workup with aqueous sodium hydroxide gave the free menthylamine compounds. Further workup of the mother liquors and an additional recrystallization step allowed the (–)-**2**·(*R*,*R*)-**3**·MeOH salt to be obtained in an overall yield of 22 %; the other salt (+)-**2**·(*R*,*R*)-**3**·MeOH·H_2O was obtained in 23 % yield. This is another important example of the dielectrically controlled resolution of an interesting amine by using inexpensive (*R*,*R*)-tartaric acid as resolving agent.

Introduction

Diastereomeric salt formation and subsequent selective crystallization represents one of the oldest and most powerful strategies for the resolution of racemates. Due to the easy experimental setup and the reversibility of the salt formation, separation of enantiomers by this method has had a high industrial impact. The importance of obtaining enantiopure compounds for the production of many pharmaceuticals makes it necessary to develop and improve protocols that are cost effective and that can be scaled up.

Menthylamines have only been utilized in a few situations, whereas menthol and the 8-substituted derivatives play a dominant role in stereoselective synthesis.[1] (–)-Menthylamine has been used for the construction of supramolecular receptors that allow enantiofacial discrimination of single substrates,[2] an efficient binding of caffeine[3] or explosives.[4] Epimeric mixtures of optically enriched menthylamine and neomenthylamine have been used in the synthesis of high-performance stationary phases for column chromatography, for example for the racemic resolution of a cerivastatin precursor.[5] However, the poor availability of menthylamines has led to them being neglected as a class of chiral amines.[6] The preparation of optically pure menthylamine on a larger scale can be performed through two major synthetic routes: Firstly, by electrochemical reduction of (–)-menthone oxime.[7] Secondly, by conversion of *rac*-neomenthol (*rac*-**1**) as starting material employing standard protocols and subsequent resolution.[8] The latter pathway is of particular interest because *rac*-**1** is produced as a by-product in a technical menthol synthesis.[9]

Unfortunately, the reported resolution protocol for racemate **2** was very sensitive to the applied conditions (Scheme 1). Additionally, both antipodes of tartaric acid were required as optically pure resolving agents, and the yields were rather low.[8]



Scheme 1. Conversion of *rac*-neomenthol into *rac*-menthylamine and subsequent resolution with tartaric acid as resolving agent.[8] *Reagents and conditions:* (a) MsCl, Et_3N, 1-methylimidazole, toluene, room temp., 2 h, quant.; (b) NaN_3, DMF, 40 °C, 2 d, 70%; (c) Ni, H_2, THF, room temp., 3 d, 98%.

Hirayama et al.[10] found that a chiral resolution yielding both enantiomers is possible by using a single antipode of the resolving agent. Because the dielectric constant (ε) of the solvent system plays the key role in controlling the outcome of the crystallization, this phenomenon was termed "dielectrically controlled resolution" (DCR). The first example described the resolution of *rac*-α-amino-ε-caprolactam with *N*-tosyl-(*S*)-phenylalanine as resolving agent.[10] The first resolution of a substrate without aromatic moie-

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ties was *rac*-2-methylpyrrolidine, which was achieved with (*R*,*R*)-tartaric acid as resolving agent.[11] Separation of the enantiomers was accomplished by adjusting the concentration of water in ethanol. It was shown by crystallographic analysis that the hydrophilic layers grow as a concomitant effect of increased water concentration. Therefore, the (*S*)-enantiomer is built into the structure. It is believed that the size of the hydrophilic layer depends on the dielectric constant (ε) of the solvent system. Three further examples of this strategy have so far been described by Sakai et al., focusing on the resolution of amines.[12]

Here, in another example of DCR, we report an efficient resolution of racemic menthylamine by the use of (*R*,*R*)-tartaric acid as sole resolving agent (Scheme 1). By adjusting the concentration of water in the system, either of the enantiomers can be selectively crystallized by forming the corresponding diastereomeric salt. It should be noted that (*R*,*R*)-tartaric acid is one of the most inexpensive exchiral pool materials and is therefore widely used in organic chemistry.[14]

Results and Discussion

Our previous work described the resolution of menthylamine by applying both optically pure antipodes of tartaric acid as resolving agents.[13] The acid determines which diastereomeric salt crystallizes (Scheme 1). In the described protocol, equimolar amounts of acid and amine were added to perform the resolution. However, although the approach provides good enantiomeric purities (up to >95%*ee*), the procedure was unreliable and delivered yields of less than 13%.[8] The water concentration (in methanol) in these initial studies ranged between 5 to 7.5%.[8]

To investigate the optimal amount of tartaric acid in the resolution we altered the ratio *rac*-**2**/(*R*,*R*)-**3** systematically from 2:1 to 1:1 (Table 1). The isolated yield of the free amine obtained from the precipitate and its enantiomeric excess are displayed. The applied amount of (*R*,*R*)-**3** was found to have a significant influence on the crystallization process as well as on the efficiency. The use of one amine per carboxylic moiety resulted in no salt formation. Interestingly, the highest enantiomeric excess (but moderate amount of the resulting menthylamine) was obtained when applying a *rac*-**2**/(*R*,*R*)-**3** ratio of 2:1.2. Upon basic workup, an *ee* of 68% was achieved with a yield of 16%.

Table 1. Influence of stoichiometric ratio *rac*-**2**/(*R*,*R*)-**3** on the resolution (solvent: MeOH with 5% H_2O; no seed crystal).

Entry	Ratio *rac*-**2**/(*R*,*R*)-**3**	$[\alpha]_D^{20}$[a]	Yield [%][b]	*ee* [%][c]
1	2:1.0	–	–	–
2	2:1.2	–24.1	16	68
3	2:1.4	–4.9	51	14
4	2:1.6	–2.7	48	8
5	2:1.8	–2.2	49	6
6	2:2.0	–2.2	51	6

[a] Optical rotation of the liberated amine from crystallized diastereomeric salt (*c* 0.5, $CHCl_3$). [b] Yield of isolated product. [c] Determined by optical rotation of (–)-**2** (–35.7° in $CHCl_3$).

Because the amount of crystallized material was rather low, the influence of the solvent system was also systematically investigated. It was known that altering the amount of water in the media can lead to enhanced yields,[15] and positive effects on the resolution with respect to both yield and enantiomeric excess by tuning the solvent mixture have also been reported.[16]

Application of the DCR concept would allow easy access to both enantiomers of menthylamine and avoid the required use of the prohibitively more expensive (*S*,*S*)-**3**. For this reason, the concentration of water in the methanolic crystallization media was varied from 4 to 20 vol.-%. The effect of this variation in water content upon the enantiomeric excess of the liberated menthylamine is depicted in Figure 1.

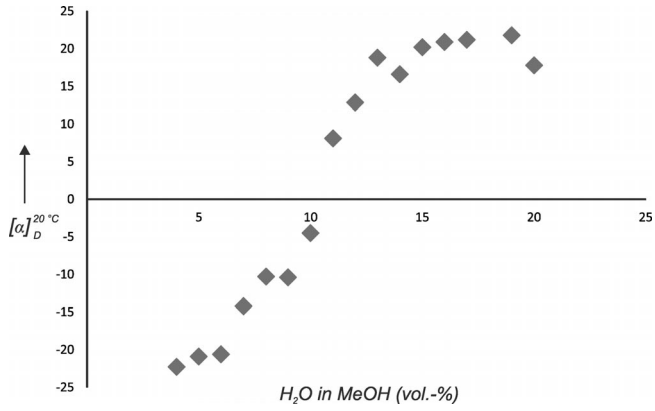

Figure 1. Resolution of menthylamine with (*R*,*R*)-tartaric acid as a function of the amount of water in methanol in the crystallization step. Optical rotation of the liberated menthylamine is given. Pure (–)-**2** exhibits an optical rotation of –35.7° (see the Supporting Information, Table S3).

A concentration of significantly less than 10% water in the media promotes the formation of diastereomeric salt containing (–)-**2**. The highest enantiomeric purity for (–)-**2** was achieved by applying a water concentration of approximately 4%. When 10% water was included in the mixture, the optical rotation changes sign. Interestingly, previous resolution experiments were close to this composition and turned out to be less reliable.[8] Further increases in the amount of water concentration in the solvent led to favored crystallization of the (+)-**2**·(*R*,*R*)-**3** diastereomeric salt combination. The best enantiomeric excess regarding (+)-**2** was found with a water content of 19%. Beneficially, these conditions also allow the highest yields (see the Supporting Information).

The findings are supported by X-ray crystal structure analysis of suitable crystals grown from the respective media. In both structures a complex network of hydrogen bonds was observed, with the corresponding crystal structures showing different molecular interactions. In (–)-**2**·(*R*,*R*)-**3**·MeOH all molecules are connected with tartrate anions by hydrogen bonds (Figure 2, a). Methanol molecules act in the structure as bridges between the tartrate molecules, which leads to the formation of strings consisting of tartrate anions and methanol. Along these strings

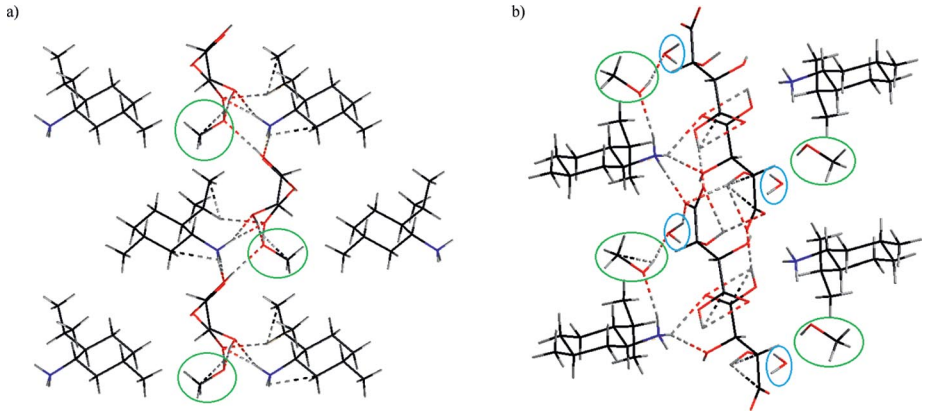

Figure 2. Illustration of the network of the hydrogen bonds of the diastereomeric salt pairs; (a) (–)-**2**·(*R*,*R*)-**3**·MeOH; (b) (+)-**2**·(*R*,*R*)-**3**·MeOH·H_2O.

the menthylammoniumhydrogen cations are arranged and form hydrogen bonds directed to the tartaric anions (see the Supporting Information, Table S1). This leads to the formation of monomeric layers consisting of the anionic strings and the menthylammoniumhydrogen cations. These layers are interconnected by weak van der Waals interactions between the hydrophobic regions of the menthylammoniumhydrogen cations.

In the crystal structure of (+)-**2**·(*R*,*R*)-**3**·MeOH·H_2O, strings of tartrate and solvent molecules are also found, but the bridges between the tartrate anions are longer and are formed by water molecules among others (Figure 2, b). The methanol molecules show no hydrogen bonding to the tartrate anion, but build hydrogen bonds to the water molecules and ammonium cations. Thus, direct hydrogen bonds between the ammonium cation and the tartaric anion and further methanol and water molecules build bridges between the cations and the anions. This network of hydrogen bonds is more complex and the number is higher than in the crystal structure of (–)-**2**·(*R*,*R*)-**3**·MeOH.

When the crystallization was performed in the presence of sufficient water, this solvent was incorporated into the lattice, creating a different chiral environment and the other antipode of menthylammonium is accommodated. At a low concentration of water this solvent is not incorporated into the lattice and the ammonium cation of (–)-**2** is built in the solid state (Figure 2). This is consistent with the DCR concept.

With these results in mind, because the individual crystallization procedures provide only a moderate amount of material, we applied this concept to a stepwise resolution of the racemate. Thus, by alternation of the solvent mixtures, both diastereomeric salt pairs were obtained separately in high *ee* (Figure 3).

In a first step, *rac*-**2** was crystallized in MeOH with 19% H_2O and a ratio of 2:1.2 *rac*-**2**/(*R*,*R*)-**3**. The obtained (+)-**2**·(*R*,*R*)-**3**·MeOH·H_2O was filtered off, followed by a basic workup. The filtrate of this resolution was evaporated to dryness providing a residue enriched in (–)-menthylamine with tartaric acid. To guarantee a constant ratio of (*R*,*R*)-**3** in the media, optically pure tartaric acid was added (as a rule of thumb, 200 mg (*R*,*R*)-**3** was added per gram diastereomeric salt filtered off). The next mixture was dissolved in MeOH with 6% H_2O and crystallized for 3 d at 8 °C. The obtained crystals were filtered off and subsequent resolution steps were followed (Figure 3).

The results of a resolution sequence are listed in Table 2. The initial resolution steps result in a good yield and acceptable enantiomeric excess. Later in the sequence a lower enantiomeric excess with higher yield was found (steps 5–7). The fractions of the corresponding enantiomers were combined and transferred again with two equivalents of (*R*,*R*)-**3** into the diastereomeric salt pairs.

Table 2. Yields and enantiomeric excess for resolution steps (94 mmol scale) of *rac*-**2**.

Step	H_2O/MeOH [%]	$[\alpha]_D^{20}$[a]	Yield [%][b]	*ee* [%][c]
1	19	+27.7	13	76
2	6	–30.7	7	86
3	19	+30.3	9	85
4	6	–23.8	19	67
5	19	+20.0	10	56
6	6	–15.3	16	43
7	19	+12.6	9	35

[a] Optical rotation of the liberated amine from crystallized diastereomeric salt (*c* 0.5, $CHCl_3$). The ratio of 2:1.2 *rac*-**2**/(*R*,*R*)-**3** was kept constant by addition of ca. 200 mg (*R*,*R*)-**3** per gram of removed salt. [b] Yield of isolated product. [c] Determined on the basis of the optical rotation of (–)-**2** (–35.7° in $CHCl_3$).

The salts were then recrystallized separately, leading to high yields of 22% and an *ee* of >95% for (–)-**2** and a yield of 23% and an *ee* of 93% for (+)-**2** (Table 3 and the Supporting Information). The given yields refer to *rac*-**2** as starting material.

Table 3. Recrystallization of both diastereomeric salt pairs, followed by basic workup.

	H_2O/MeOH [%]	$[\alpha]_D^{20}$[a]	Yield [%][b]	*ee* [%][c]
(–)-**2**	19	–34.7	22	>95
(+)-**2**	6	+32.6	23	93

[a] Optical rotation of the liberated amine from crystallized diastereomeric salt (*c* 0.5, $CHCl_3$). [b] Yield of isolated product. [c] Determined by optical rotation of (–)-**2** (–35.7° in $CHCl_3$).

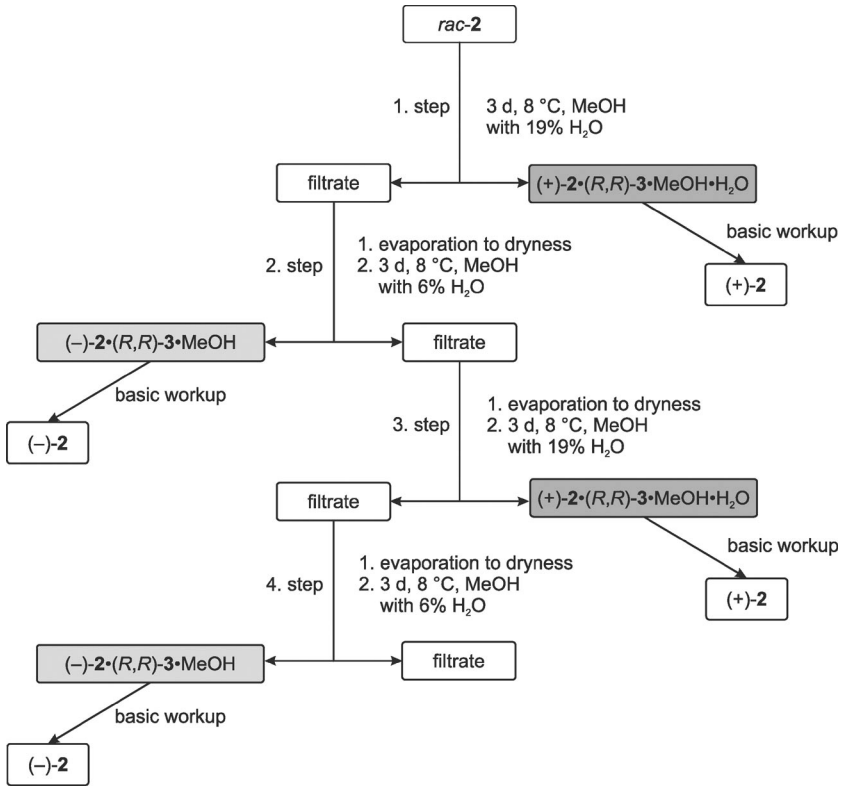

Figure 3. Pathway for effective resolution of menthylamine.

Table 4. Recrystallization of the collected diastereomeric salt pairs, followed by basic workup.

Diastereomeric salt pair	Combined amount [%]	Liberated amine	$[a]_D^{20}$[a]	Yield [%][b]	*ee* [%][c]
(–)-**2**•(*R*,*R*)-**3**•MeOH	39	(–)-**2**	–34.1	27	>95
(+)-**2**•(*R*,*R*)-**3**•MeOH•H_2O	37	(+)-**2**	+31.1	20	87

[a] Optical rotation of the liberated amine from crystallized diastereomeric salt (*c* 0.5, $CHCl_3$). [b] Yield of isolated product. [c] Determined by optical rotation of (–)-**2** (–35.7° in $CHCl_3$).

Finally, it was important to simplify the protocol with respect to the basic workup of the diastereomeric salt pairs, which required the most manual effort. Thus, fractions of the corresponding diastereomerically enriched salt pairs were pooled and a simple recrystallization step in the matching solvent system was applied. Upon basic workup, good yields and high enantiomeric excess of (–)-**2** and (+)-**2** were obtained (Table 4 and Figure 4).

The elaborated protocol is easily scaled up to 100 g (0.65 mol) in *rac*-**2**. However, upon up-scaling, the evaporation of the solvent mixture needs more attention. Usually, the residue forms while being concentrated on the rotivap device as a foamy glass. Complete removal of the solvents this way is tedious on larger scale. Nevertheless, control of the water content in the crystallization mixture is crucial for resolution of *rac*-**2**. Therefore, we recommend the use of lyophilization. Application of this technique led to reliable results that were comparable those achieved on a smaller scale.

Conclusions

We have developed an efficient and very practical method for the resolution of menthylamine that can be performed with inexpensive, optically pure (*R*,*R*)-tartaric acid. The amount of water present in the crystallization media determines which antipode is incorporated into the diastereomeric salt. The effect of water is clearly understood on the basis of the corresponding crystal structures, which promote the incorporation of individual enantiomers of menthylamine. The findings provide a consistent picture that fits perfectly into the DCR concept. Because the optical purity or the yield of an individual crystallization step is not sufficient, a sequence of resolutions can be applied wherein only the amount of water is altered, providing good access to (–)- and (+)-menthylamine with good optical enrichment. The process is scalable and provides reliable, inexpensive, and straightforward access to enantiomerically pure menthylamines.

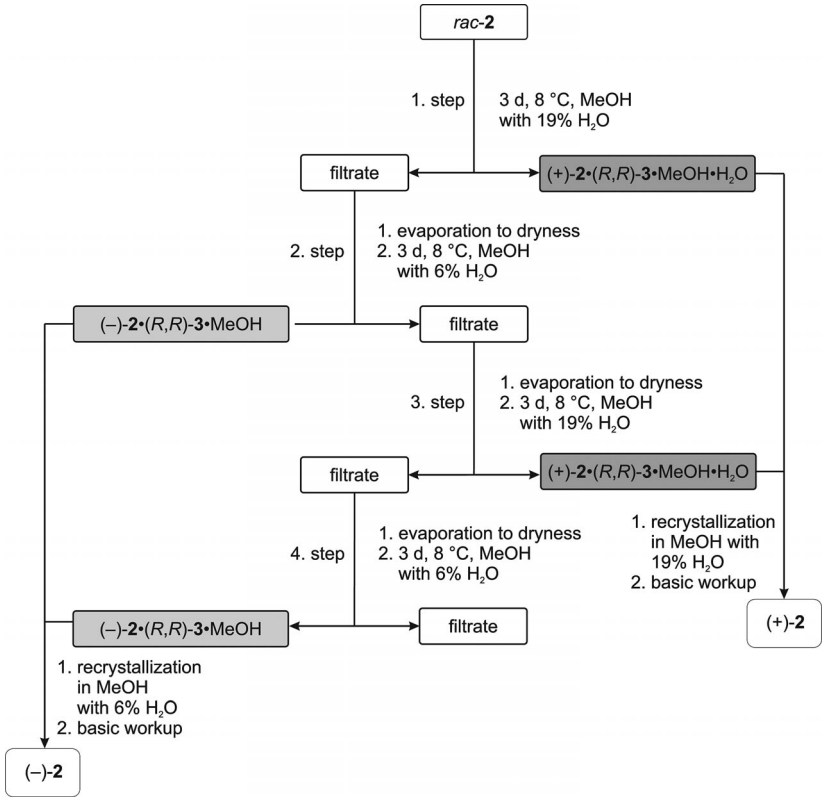

Figure 4. The diastereomeric salt pairs were collected and recrystallized in the appropriate solvent system, followed by basic workup.

Experimental Section

The complete pathway followed in the resolution is provided in the Supporting Information.

CCDC-966732 [for (–)-**2**·(*R*,*R*)-3·MeOH] and -966733 [for (+)-**2**·(*R*,*R*)-3·MeOH·H_2O] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Detailed protocols and analytical data are given.

Acknowledgments

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