Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 1639–1643

Highly efficient resolutions of 1,4-benzodioxane-2-carboxylic acid with *para* substituted 1-phenylethylamines

Cristiano Bolchi,* Marco Pallavicini, Laura Fumagalli, Nicoletta Marchini, Barbara Moroni, Chiara Rusconi and Ermanno Valoti

Istituto di Chimica Farmaceutica e Tossicologica, Università di Milano, viale Abruzzi 42, I-20131 Milano, Italy

Received 27 January 2005; accepted 31 January 2005
Available online 11 March 2005

Abstract—The salts of (*S*)- and (*R*)-1,4-benzodioxane-2-carboxylic acid with eight (*S*)-1-arylethylamines were prepared. The determination of their melting points and of their solubilities in alcohol solvents revealed large differences between the diastereomeric benzodioxanecarboxylates of (*S*)-1-(*p*-nitrophenyl)ethylamine and of (*S*)-1-(*p*-methylphenyl)ethylamine. Therefore, these latter amines were selected to resolve (±)-1,4-benzodioxane-2-carboxylic acid by diastereoselective crystallization finding that both of them display a very high resolution ability for such a substrate, which contrasts with the null efficiency of unsubstituted 1-phenylethylamine. These results are consistent with DSC evidences, which indicated that the two successfully resolved diastereomeric systems are binary mixtures exhibiting a eutectic with a high content of the more soluble diastereomeric salt. The new procedures can advantageously replace the two resolutions we had previously reported, that of the same acid with dehydroabietylamine and that of glycerol acetonide, a precursor of 1,4-benzodioxane-2-carboxylic acid, with 1-phenylethylamine.

1. Introduction

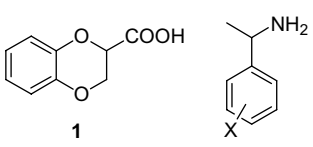
Over the course of our research concerning the synthesis of chiral benzodioxane derivatives as type-selective α-adrenoceptor ligands, we developed two different resolution approaches, which could be conveniently practised to obtain highly enantiopure 2-substituted benzodioxanes. The former method, patented in 1992, is based on the resolution of racemic glycerol acetonide through conversion into hemiphthalate and successive diastereoselective crystallization of the salt with enantiomerically pure 1-phenylethylamine.[1,2] The latter, recently reported, was a classical resolution as well, not of a relatively remote precursor, such as glycerol acetonide, but of a chiral 2-substituted benzodioxane, namely (±)-1,4-benzodioxane-2-carboxylic acid (±)-**1**, readily available by condensation of catechol with ethyl 2,3-dibromopropionate and successive saponification of the intermediate ester.[3] The new strategy involved the use of (+)-dehydroabietylamine as a resolving agent and coupled the resolution of (±)-**1** with subsequent enantiomeric enrichments by recrystallization, preferably of the conglomerate forming derivatives of the acid, such as its methyl ester and the mesylate of 2-hydroxymethyl-1,4-benzodioxane. However, we were not completely satisfied with the two resolution methods, despite their high efficiency. In fact, the necessity of derivatizing with phthalic anhydride or of resorting to an unusual resolving agent like dehydroabietylamine were penalizing limitations. Therefore, we considered the resolution of (±)-**1** with 1-phenylethylamine or, alternatively, with its ring substituted analogues. The fact that no resolutions of this acid with 1-phenylethylamine have been reported supposes that such an amine is ineffective, however this does not exclude the ability of its derivatives of resolving the same substrate. Saigo and co-workers have recently demonstrated that the almost null efficiency of the resolution of 1-phenylethylamine by enantiopure 3′,4′-methylenedioxymandelic acid is considerably improved by *para* substitution on the amine aromatic ring, becoming very high in the case of some 1-phenylethylamines bearing an electron-withdrawing substituent.[4] These results and the large availability of a number of enantiopure 1-arylethylamines, deriving from the resolutions with isopropylidene glycerol hemiphthalate or 3-carboxy-2-naphthoate we had previously developed,[5–10]

* Corresponding author. Tel.: +39 2 50317553; fax: +39 2 50317565; e-mail: cristiano.bolchi@unimi.it

0957-4166/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.01.052

prompted us to consider the possibility of resolving (±)-**1** with enantiopure 1-phenylethylamine and 1-arylethylamines **2**–**8**.

Herein, we report (i) a detailed analysis of the melting points and of the solubilities of all the salts resulting from the combination of the acid enantiomers with the *S* forms of 1-phenylethylamine and 1-arylethylamines **2**–**8**; (ii) some DSC data for the diastereomeric systems submitted to resolution, namely the (*S*)-**2**·(*S*)-**1**/(*S*)-**2**·(*R*)-**1** and (*S*)-**6**·(*S*)-**1**/(*S*)-**6**·(*R*)-**1** systems and (iii) the highly efficient resolutions of (±)-**1** with (*S*)-**2** and (*S*)-**6**.



1

2 X = *p*-Me
3 = *p*-OMe
4 = *p*-Cl
5 = *p*-Br
6 = *p*-NO_2
7 = 2,3 -CH=CH-CH=CH-
8 = 3,4 -CH=CH-CH=CH-

2. Results and discussion

Among the enantiopure amines obtained by resolution with carboxyesters of isopropylidene glycerol, we selected the following candidates for the resolution of (±)-**1**: (*S*)-1-phenylethylamine, (*S*)-1-naphthylethylamine (*S*)-**7**, (*S*)-2-naphthylethylamine (*S*)-**8** and the five ring substituted analogues of (*S*)-1-phenylethylamine (*S*)-**2**–(*S*)-**6**, bearing a methyl, a methoxyl, a chlorine, a bromine and a nitro group at the *para* position, respectively. In order to characterize the resultant eight pairs of diastereomeric salts with (*S*)- and (*R*)-**1**, all the 16 compounds were individually obtained by concentration of methanolic solutions containing equivalent amounts of (*S*)-amine and (*S*)- or (*R*)-acid and successive crystallization of the solid residue from 2-propanol.

First, the melting point of each of these salts was determined. It is known that the melting points of a diastereomeric salt pair can give some reliable predictions of its resolution process without preparative experiments, when the laborious determination of the binary phase diagram is to be spared or cannot be accomplished due to thermal decomposition.[11] In fact, providing that both diastereomeric salts crystallize separately, efficient resolution can be expected by preferential crystallization when they are substantially different in physico-chemical properties, as simply revealed by a large difference, at least 20 °C, between their respective melting points. As shown in Table 1, such a condition was fulfilled by the diastereomeric salts of (*S*)-**2** and (*S*)-**6**, whose fusions are separated by 29 and 32 °C, respectively. For the other diastereomeric pairs, we observed significantly lower or null differences in melting point. These results promoted (*S*)-**2** and (*S*)-**6** as the best candidates for the resolution, while rejecting (*S*)-**3** and the two naphthylethylamines. In the case of the parent unsubstituted 1-phenylethylamine and of its two *p*-halo analogues, the melting point differences were considerable, but not so promising as those of the *p*-methyl and *p*-nitro derivatives.

After determining the melting points, we measured the solubility of each salt in alcohols at room temperature (see Table 1). Methanol, ethanol and 2-propanol, the most frequently used alcohols as solvents in the resolutions of diastereomeric salts, were selected for the experiments. The results listed in Table 1 show that the solubility (k_n) of the *n* salts, those formed by (*R*)-**1** with the (*S*) form of these 1-arylethylamines, is always higher than the solubility (k_p) of the *p* salts, that is, the salts between the same (*S*)-amines and (*S*)-**1**. The only exceptions are represented by (*S*)-**3**·(*R*)-**1**, less soluble than (*S*)-**3**·(*S*)-**1** in methanol, and by (*S*)-**8**·(*R*)-**1**, less soluble than (*S*)-**8**·(*S*)-**1** in 2-propanol. As expected, dissolving ability increases from 2-propanol to methanol. In particular, this latter alcohol is capable of dissolving the more soluble salt of each diastereomeric pair enough (5–16 g/dL) to design resolution procedures with acceptable

Table 1. Melting point (°C) and solubility (g/dL) of the salts of (*S*)-1-phenylethylamine and the amines (*S*)-**2**–(*S*)-**8** with (*S*)-**1** and (*R*)-**1** in alcohols at 25 °C

Salt	Mp[a]	Solubility in MeOH	Solubility ratio *SR*/*SS* in MeOH	Solubility in EtOH	Solubility ratio *SR*/*SS* in EtOH	Solubility in 2-PrOH	Solubility ratio *SR*/*SS* in 2-PrOH
(*S*)-1-Phenylethylamine·(*R*)-**1**	179	15.80	1.3	3.27	1.4	0.25	1.2
(*S*)-1-Phenylethylamine·(*S*)-**1**	194	12.13		2.34		0.20	
(*S*)-**2**·(*R*)-**1**	190[b]	16.45	5.4	3.47	7.9	0.58	11
(*S*)-**2**·(*S*)-**1**	219[b]	3.07		0.44		0.05	
(*S*)-**3**·(*R*)-**1**	185[b]	10.50	0.7	2.33	1.1	0.35	1.1
(*S*)-**3**·(*S*)-**1**	178	14.33		2.05		0.33	
(*S*)-**4**·(*R*)-**1**	182	10.16	1.6	2.11	1.8	0.42	3.2
(*S*)-**4**·(*S*)-**1**	199[b]	6.32		1.15		0.13	
(*S*)-**5**·(*R*)-**1**	191[b]	9.14	1.8	1.67	1.6	0.21	2.6
(*S*)-**5**·(*S*)-**1**	204[b]	5.13		1.02		0.08	
(*S*)-**6**·(*R*)-**1**	182[b]	5.73	6.3	1.51	10.8	0.17	14.2
(*S*)-**6**·(*S*)-**1**	214[b]	0.91		0.14		0.012	
(*S*)-**7**·(*R*)-**1**	202[b]	6.47	1.1	1.34	1.1	0.21	1.4
(*S*)-**7**·(*S*)-**1**	202[b]	5.89		1.18		0.15	
(*S*)-**8**·(*R*)-**1**	200[b]	8.16	1.6	1.35	1.5	0.14	0.6
(*S*)-**8**·(*S*)-**1**	201[b]	5.09		0.9		0.24	

[a] Determined by a capillary melting point apparatus.
[b] With decomposition.

volumetric productivity. The most interesting indication of these solubility tests was that the trend of the solubility difference between diastereomeric salts parallels that of the differences in melting point. The *p* salts (*S*)-**2**·(*S*)-**1** and (*S*)-**6**·(*S*)-**1**, whose melting point exceed that of the corresponding *n* salts of the greatest extent (~30 °C), are about sixfold less soluble than those latter in methanol while the solubility ratio (k_n/k_p) is even higher in ethanol and in 2-propanol. Conversely, solubility differences are insignificant for the pairs of diastereomeric salts formed by the two naphthylethylamines, (*S*)-**7** and (*S*)-**8**, having identical melting points. On this scale, a middle position is occupied by the four pairs of salts of (*S*)-**3**, (*S*)-**4**, (*S*)-**5** and (*S*)-1-phenylethylamine, which associate moderate melting point differences with appreciable differences in solubility.

A detailed DSC analysis, aimed at the construction of the binary phase diagrams, was hampered by the thermal decomposition of one or both salts of each pair, which started before the fusion was complete. This hindered the determination of the heats of fusion, allowing approximate melting points, corresponding to the DSC melting curve maxima, to be only recorded. This notwithstanding, we collected the DSC data for a number of different mixtures of the diastereomeric salts formed by (*S*)-**2** and (*S*)-**6**, hoping that the two diastereomeric systems (*S*)-**2**·(*S*)-**1**/(*S*)-**2**·(*R*)-**1** and (*S*)-**6**·(*S*)-**1**/(*S*)-**6**·(*R*)-**1** would produce DSC curves typical of conglomerates with two clearly detectable fusions, the former of the eutectic and the latter of the exceeding pure diastereomer. Indeed, the DSC data indicated that both the systems are binary mixtures exhibiting an eutectic and thus susceptible of resolution by crystallization. In the case of the (*S*)-**2**·(*S*)-**1**/(*S*)-**2**·(*R*)-**1** system, we analyzed nine mixtures with constantly increasing mole fraction of (*S*)-**2**·(*S*)-**1** (from 0.1 to 0.9) finding that the fusion of the eutectic ranges between 175.2 and 177.8 °C and its composition should be higher than 0.2, but lower than the 0.3 mole fraction of (*S*)-**2**·(*S*)-**1**. For the (*S*)-**6**·(*S*)-**1**/(*S*)-**6**·(*R*)-**1** system, the same investigation showed that the eutectic melts between 176 and 177 °C, but an even approximate determination of its composition was impossible due to the decompositions subsequent to its fusion and to that of the major diastereomer. However, we could establish that this eutectic was significantly richer in the more soluble diastereomeric salt than that of the (*S*)-**2**·(*S*)-**1**/(*S*)-**2**·(*R*)-**1** system. In fact, the presence of the eutectic became appreciable in the DSC traces of the (*S*)-**6**·(*S*)-**1**/(*S*)-**6**·(*R*)-**1** mixtures for relatively high mole fractions (>0.2) of the more soluble salt, while small amounts of this latter (mole fraction <0.05) were enough to produce an evident fusion peak of the eutectic in the DSC curves of the (*S*)-**2**·(*S*)-**1**/(*S*)-**2**·(*R*)-**1** mixtures, as exemplified by the traces depicted in Figure 1.

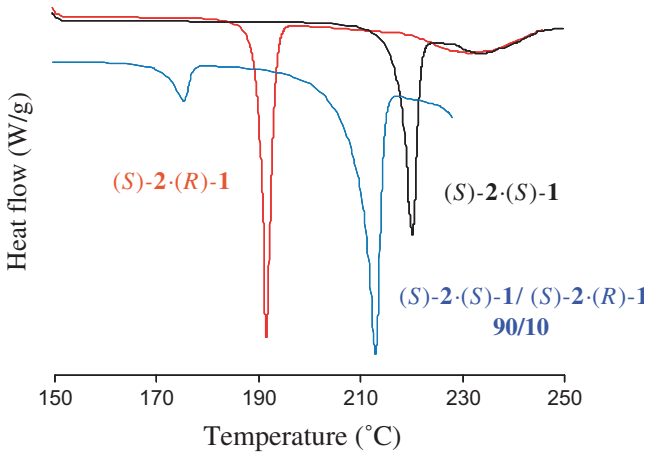


Figure 1. DSC traces of the pure salts (*S*)-**2**·(*S*)-**1** and (*S*)-**2**·(*R*)-**1** (upper curves) and of their 9:1 mixture (lower curve).

On the basis of all these preliminary results, we were confident that (±)-**1** could be successfully resolved by (*S*)-**2** and, even more efficiently, by (*S*)-**6**. This amine was tried first. Equivalent amounts of the racemic acid and (*S*)-**6** were combined in a volume of methanol slightly larger than the minimum required to dissolve the more soluble diastereomer at room temperature. After stirring for 5 h at boiling temperature and then overnight at room temperature, a precipitate of (*S*)-**6**·(*S*)-**1** was collected in 93.3% yield [46.6% of the starting (±)-**1**] and with 99.0% ee of (*S*)-**1** (Table 2, entry 1). Such a high resolution efficiency indicated that the procedure had been carried out under optimal conditions and was not susceptible to further significant improvements. In spite of the more favourable solubility ratios between (*S*)-**6**·(*S*)-**1** and (*S*)-**6**·(*R*)-**1** in ethanol and in 2-propanol, the use of these two alcohols was not tried due to their very low dissolving ability of the more soluble (*S*)-**6**·(*R*)-**1** salt. Otherwise, in the successive experiments of resolution with (*S*)-**2**, methanol and ethanol were both tested only rejecting 2-propanol. Again, equivalent

Table 2. Resolution of acid (±)-**1** with amines (*S*)-**2** and (*S*)-**6**

Entry	Resolving agent	Solvent	Precipitate	Yield[a] (%)		Ee[b] (%)	S_{exp}[c]	S_{calcd}[d]
				Precipitate	Recovered acid			
1	(*S*)-**6**	Methanol	(*S*)-**6**·(*S*)-**1**	93.3	93.2	99.0	0.92	0.84
2	(*S*)-**2**	Ethanol	(*S*)-**2**·(*S*)-**1**	82.7	82.6	99.8	0.82	0.87
3	(*S*)-**2**	Methanol	(*S*)-**2**·(*S*)-**1**	80.1	80.0	98.6	0.79	0.81

[a] Relative to the theoretical amount, that is, half of the starting racemic acid.
[b] Enantiomeric excess (determined by chiral HPLC) of the acid liberated from the precipitated salt.
[c] Experimental resolution efficiency or experimental resolvability calculated from S = chemical yield of the precipitate (%) × ee of the liberated acid (%)/10,000.
[d] Maximum theoretical resolvability, calculated from $S = (k_n - k_p)/k_n$, where k_n is the solubility of the more soluble (*S*)-**2**·(*R*)-**1** or (*S*)-**6**·(*R*)-**1** salt and k_p the solubility of the less soluble (*S*)-**2**·(*S*)-**1** or (*S*)-**6**·(*S*)-**1** salt.

amounts of resolving agent and racemic substrate were combined to give almost saturated solutions of the more soluble salt, (*S*)-**2**·(*R*)-**1**, at room temperature. From ethanol, (*S*)-**2**·(*S*)-**1** precipitated in 82.7% yield [41.3% of the starting (±)-**1**] and with 99.8% ee of (*S*)-**1** after stirring at boiling temperature for 20 min, then at 50 °C for further 5 h and, finally, overnight at room temperature (Table 2, entry 2). Analogous results were obtained by a simple precipitation using methanol under conditions of quasi-saturation for (*S*)-**2**·(*R*)-**1**: 80.1% yield of (*S*)-**2**·(*S*)-**1** and 98.6% ee of (*S*)-**1** (Table 2, entry 3). The recovery of the *S* acid from (*S*)-**6**·(*S*)-**1** and (*S*)-**2**·(*S*)-**1** precipitates was always quantitative. Finally, the foreseen inability of unsubstituted 1-phenylethylamine to resolve (±)-**1** was verified determining negligible enantiomeric excesses for the acid resultant from precipitated (*S*)-1-phenethylammonium salts.

At the end of the trial resolutions, we were able to compare their experimental efficiencies (*SS* salt yield × *S* acid ee) with the maximum theoretical resolvabilities resulting from the relative solubility differences between the diastereomeric salts, that is, $(k_n - k_p)/k_n$. As shown in Table 2 (entries 2 and 3), the experimental efficiencies (S_{exp}) are very close to the maximum theoretical resolvabilities (S_{calcd}) for the resolutions with (*S*)-**2** both in methanol (0.79 vs 0.81) and in ethanol (0.82 vs 0.87), while, in the case of (*S*)-**6** (Table 2, entry 1), the experimental data (0.92) is even better than the theoretical one (0.84). The higher resolving ability of (*S*)-**6** with respect to (*S*)-**2** was consistent with the DSC results, which indicated an eutectic composition closer to the pure more soluble salt for the (*S*)-**6**·(*S*)-**1**/(*S*)-**6**·(*R*)-**1** system. In particular, a 0.17 value of χ_{eu} is obtained equating the maximum theoretical resolvability expression $(1 - 2\chi_{eu})/(1 - \chi_{eu})$ to 0.8, the mean experimental efficiency of the resolutions with (*S*)-**2**. Such an eutectic composition is not far from the 0.2 to 0.3 range previously suggested by the inspection of the DSC traces. In the case of (*S*)-**6**, the corresponding equation, that is, $(1 - 2\chi_{eu})/(1 - \chi_{eu}) = 0.92$, is satisfied by $\chi_{eu} = 0.07$. This value cannot be demonstrated by DSC evidence. It is significantly lower than the eutectic composition inferred for the (*S*)-**2**·(*S*)-**1**/(*S*)-**2**·(*R*)-**1** system, thus confirming what the comparison of the DSC traces of the two conglomerates had suggested before the resolution experiments.

3. Conclusion

In summary, we have demonstrated that (±)-**1** can be efficiently resolved by two readily available *p*-substituted 1-phenylethylamines, (*S*)-**2** and (*S*)-**6**, via simple procedures. Preliminary investigations on the physical properties of the salts formed by the 1-arylethylamines (*S*)-**2**–(*S*)-**8** with the enantiomers of **1** allowed (*S*)-**2** and (*S*)-**6** to be rapidly identified as the best candidates for the resolution of (±)-**1** and their efficiency to be correctly predicted. Interestingly, two very different substituents, NO_2 and CH_3, at the *para* position of 1-phenylethylamine are both able to make this latter amine an excellent resolving agent of (±)-**1**. In particular, the high resolving ability of (*S*)-**2**, opposite to the null efficiency of unsubstituted (*S*)-1-phenylethylamine, surprised us due to the relatively insignificant effects of methyl substituent. It is evident that the ability of (*S*)-**2** and (*S*)-**6** to resolve (±)-**1** cannot be associated with a common effect of the ring substituent, as in the case of the above cited resolutions with 3′,4′-methylenedioxymandelic acid,[4] or, generically, with the occupation of the *para* position of 1-phenylethylamine. If the rationalization of such results seems impossible at the moment, this is due to the fact that the resolvability of diastereomers arises from unpredictable differences between their crystal structures. We think that the X-ray determination of these latter, which is in progress for some of the present diastereomeric pairs, will be explicative.

4. Experimental

^{1}H NMR spectra were recorded on a Varian Gemini 300 (300 MHz) instrument. Optical rotations were measured in a 1 dm cell of 1 mL capacity using a Perkin–Elmer 241 polarimeter. HPLC analyses were performed on a Chiralcel OD column (250 × 4.6 mm i.d.) from *Daicel* using a Hitachi 7100 pump, a Hitachi L-7400 UV detector and a Hitachi D-7000 HPLC System Manager software. Melting points were determined by a Büchi Melting Point B-540 apparatus and by DSC analysis, taking the temperature of the maximum of the peak. The DSC curves were recorded and integrated with the aid of a TA Instruments DSC 2010 apparatus.

Amines (*S*)-**2**–(*S*)-**8** were prepared by resolution of the corresponding racemates as previously reported.[5,6,8,10] The racemic acid (±)-**1** was synthesized by condensation of catechol with ethyl 2,3-dibromopropionate and successive saponification of the intermediate ester according to a literature method.[12] (*S*)-**1** and (*R*)-**1** were available from the previous resolutions of the racemate with (+)-dehydroabietylamine.[3]

4.1. Resolution of (±)-1 with (*S*)-2 in ethanol

A stirred solution of (±)-**1** (2.67 g, 14.8 mmol) in ethanol (75 mL) was added with (*S*)-**2** (2 g, 14.8 mmol), refluxed for 20 min and then slowly cooled to 50 °C initiating the crystallization of a white solid. The suspension was stirred at this temperature for 5 h and at rt overnight and finally filtered yielding (*S*)-**2**·(*S*)-**1** (1.93 g, 82.7% of the theoretical amount) as a white crystalline solid: mp 219 °C; ee of (*S*)-**1** 99.8% (determined by HPLC of the acid liberated from a sample of the salt on a Chiralcel OD column; hexane/2-propanol/formic acid 85/13.5/1.5; 0.4 mL/min; (*R*)-**1**: $k' = 3.15$; (*S*)-**1**: $k' = 2.49$); ^{1}H NMR (DMSO-d_6): δ 1.41 (d, 3H, $J = 8.8$ Hz), 2.28 (s, 3H), 4.12 (dd, 1H, $J = 11.0$, 5.9 Hz), 4.22–4.29 (m, 2H), 4.38 (dd, 1H, $J = 2.9$, 5.9 Hz), 6.69–6.84 (m, 4H), 7.17 (d, 2H, $J = 8.0$ Hz), 7.31 (d, 2H, $J = 8.0$ Hz). The salt was decomposed by treatment with 1 M NaOH and dichloromethane. The aqueous phase was separated, acidified (pH 1) and extracted with ethyl acetate four times. The organic extracts were dried with Na_2SO_4 and concentrated to give (*S*)-**1** (1.1 g, 82.6%) as a white

solid: mp 97 °C; $[\alpha]_D^{25} = -63.9$ (*c* 1, $CHCl_3$); ee identical to that previously determined for the acid liberated from a sample of the salt with (*S*)-**2**; ^{1}H NMR ($CDCl_3$): δ 4.38 (dd, 1H, $J = 2.9$, 11.4 Hz), 4.44 (dd, 1H, $J = 4.4$, 11.4 Hz), 4.90 (dd, 1H, $J = 2.9$, 4.4 Hz), 6.88–6.97 (m, 3H), 6.99–7.02 (m, 1H).

4.2. Resolution of (±)-1 with (*S*)-2 in methanol

A stirred solution of (±)-**1** (2.67 g, 14.8 mmol) in methanol (16 mL) was added with (*S*)-**2** (2 g, 14.8 mmol), refluxed for 5 h. After stirring overnight, the resultant suspension was filtered isolating (*S*)-**2**·(*S*)-**1** (1.87 g, 80.1% of the theoretical amount) as a white crystalline solid. The enantiomeric excess of the acid liberated from a sample of the salt was 98.6%. The salt was decomposed as described for the resolution in ethanol obtaining (*S*)-**1** (1.07 g, 80.0%) as a white solid: ee identical to that previously determined for the acid liberated from a sample of the precipitate.

4.3. Resolution of (±)-1 with (*S*)-6 in methanol

A stirred solution of (±)-**1** (5 g, 27.7 mmol) in methanol (100 mL) was added with (*S*)-**6** (4.61 g, 27.7 mmol), refluxed for 5 h. After stirring overnight, the resultant suspension was filtered isolating (*S*)-**6**·(*S*)-**1** (4.48 g, 93.3% of the theoretical amount) as a white crystalline solid: mp 214 °C; ee of (*S*)-**1** 99.0%; ^{1}H NMR (DMSO-d_6): δ 1.45 (d, 3H, $J = 6.6$ Hz), 4.15 (dd, 1H, $J = 5.5$, 11.0 Hz), 4.25 (dd, 1H, $J = 2.9$, 11.0 Hz), 4.41–4.46 (m, 2H), 6.72–6.82 (m, 3H), 6.83–6.86 (m, 1H), 7.74 (d, 2H, $J = 8.8$ Hz), 8.21 (d, 2H, $J = 8.8$ Hz). The salt was decomposed as described for the resolution with (*S*)-**2** in ethanol obtaining (*S*)-**1** (2.33 g, 93.2%) as a white solid: ee identical to that previously determined for the acid liberated from a sample of the precipitate.

4.4. Thermal analyses

For DSC analyses, samples of 2–3 mg were run in hermetically sealed aluminium pans to retard the decomposition. The 1:1 (*S*)-**2**·(*S*)-**1**/(*S*)-**2**·(*R*)-**1** and (*S*)-**6**·(*S*)-**1**/(*S*)-**6**·(*R*)-**1** mixtures were prepared by concentration of solutions containing equivalent amounts of racemic acid and *S* amine. The DSC traces of such mixtures exhibited the melting peak of the eutectic, followed by the anticipated fusion of the exceeding *SS* diastereomer. The other diastereomeric mixtures were prepared by mixing (*S*)-**2**·(*S*)-**1** and (*S*)-**6**·(*S*)-**1** with increasing quantities of (*S*)-**2**·(*R*)-**1** and (*S*)-**6**·(*R*)-**1**, respectively. All the analyses were performed with a heating rate of 5 °C min^{-1}.

Acknowledgements

This work was supported by the Ministero dell'Istruzione, dell'Università e della Ricerca of Italy.

References

1. Piccolo, O.; Pallavicini, M.; Valoti, E.; Villa, L. It. Pat. Appl. 000232a/92, 1992.
2. Pallavicini, M.; Valoti, E.; Villa, L.; Piccolo, O. *Tetrahedron: Asymmetry* **1994**, *5*, 5.
3. Bolchi, C.; Fumagalli, L.; Moroni, B.; Pallavicini, M.; Valoti, E. *Tetrahedron: Asymmetry* **2003**, *14*, 2247.
4. Kinbara, K.; Oishi, K.; Harada, Y.; Saigo, K. *Tetrahedron* **2000**, *56*, 6651.
5. Pallavicini, M.; Valoti, E.; Villa, L.; Piccolo, O. *Tetrahedron: Asymmetry* **1996**, *7*, 1117.
6. Pallavicini, M.; Valoti, E.; Villa, L.; Piccolo, O. *Tetrahedron: Asymmetry* **1997**, *8*, 1069.
7. Pallavicini, M.; Valoti, E.; Villa, L.; Piccolo, O. *Tetrahedron: Asymmetry* **2000**, *11*, 4017.
8. Pallavicini, M.; Valoti, E.; Villa, L.; Piccolo, O. *Tetrahedron: Asymmetry* **2001**, *12*, 2489.
9. Pallavicini, M.; Valoti, E.; Villa, L.; Piccolo, O. *Tetrahedron: Asymmetry* **2001**, *12*, 1071.
10. Pallavicini, M.; Bolchi, C.; Fumagalli, L.; Valoti, E.; Villa, L. *Tetrahedron: Asymmetry* **2002**, *13*, 2277.
11. Kozma, D.; Acs, M.; Fogassy, E. *Tetrahedron* **1994**, *50*, 6907.
12. Koo, J.; Avakian, S.; Martin, G. J. *J. Am. Chem. Soc.* **1955**, *77*, 5373.