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Reciprocal resolutions between 1-phenylethylamine and carboxyesters of isopropylidene glycerol: improvement of the method by replacing mono-phthalate with 3-carboxy-2-naphthoate

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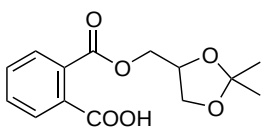
Abstract—A novel resolving agent, isopropylidene glycerol 3-carboxy-2-naphthoate **2**, was designed on the basis of the consideration that replacement of phenyl group with a naphthyl group would improve the resolving ability of isopropylidene glycerol hydrogen phthalate **1** while also conferring more suitable physicochemical properties for such a specific use. Indeed, 1-phenylethylamine **4** was resolved by **2** more efficiently than by **1** (respective resolution efficiencies, (*S*) 0.88 and 0.81), while **1** and **2** were resolved by **4** with *S* ranging between 0.54 and 0.59. Furthermore, **2** is a solid, whereas **1** is a viscous oil, and its recovery at the end of the resolution procedure is easier than that of **1**. In order to understand the chiral discrimination mechanism of the two reciprocal resolutions, the binary melting point phase diagrams of the four diastereomeric systems (*S*)-**2**·(*S*)-**4**/(*S*)-**2**·(*R*)-**4**, (*S*)-**2**·(*S*)-**4**/(*R*)-**2**·(*S*)-**4**, (*S*)-**1**·(*S*)-**4**/(*S*)-**1**·(*R*)-**4** and (*S*)-**1**·(*S*)-**4**/(*R*)-**1**·(*S*)-**4** were determined. The first two systems form ideal conglomerates, characterised by identical diagrams, in which the eutectic corresponds to a 0.10 molar ratio of (*S*)-**2**·(*S*)-**4**. The same behaviour was shown by the other two systems, whose eutectics, however, correspond to a 0.18 molar ratio of (*S*)-**1**·(*S*)-**4**. On the basis of the present results, which indicate an excellent resolution ability of **2** for **4**, the application of this new acid to the resolution of other 1-arylalkylamines seems to have very good prospects, worthy of investigation.

1. Introduction

The hydrogen phthalate of isopropylidene glycerol **1** has proven to be an efficient resolving agent of 1-phenylethylamine **4** and of many other primary amines.[1–4] On the other hand, its resolution with **4** has also been reported as a useful method to prepare both **1** and isopropylidene glycerol with very high enantiomeric purity.[1,5,6] Believing that replacement of the phenyl with a naphthyl group would improve the resolving ability of **1** and widen its range of application, as suggested by recent investigations on mandelic acid,[7] we considered the use of the carboxynaphthoates of isopropylidene glycerol as an advantageous alternative. We speculated that a rigid and large naphthyl group would produce more stable crystal structures for the less soluble salts, accentuating the solubility difference between the diastereoisomers. Last but not least, the introduction of a fused second phenyl ring would hopefully result in solid hemiester derivatives of glycerol acetonide, easier to handle, recover and purify than **1**, which is, on the contrary, a viscous oil.



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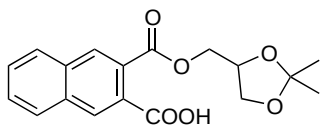

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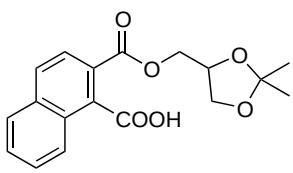

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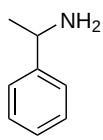

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Herein, we describe the preparation of isopropylidene glycerol 3-carboxy-2-naphthoate and 1-carboxy-2-naphthoate, **2** and **3**, respectively, and the results of the successful reciprocal resolution between **2** and **4**. These results are compared with those of the previous reciprocal resolution between **1** and **4**[1,5] and both are evaluated on the basis of the respective binary melting point phase diagrams. The latter were determined in order to identify the type of diastereomeric salt mixtures occurring in the two reciprocal resolutions and to assess the degree of optimisation of the procedures.

2. Results

The racemic acid **2** was obtained by reaction of 2,3-naphthalic anhydride with racemic isopropylidene glycerol in pyridine. The anhydride was in turn prepared by heating naphthalene–2,3-dicarboxylic acid in refluxing acetic anhydride as reported in the literature.[8] (*S*)-**2** and (*R*)-**2** were synthesised by the same method, but starting from (*R*)- and (*S*)-isopropylidene glycerol, respectively. In any case, the pure hemiesters were isolated as viscous oils in near quantitative yield by simple dilute sulphuric acid/ethyl acetate extraction, which turned into high melting solids upon standing at room temperature overnight.

Before undertaking resolution of **4** with **2**, samples of diastereomeric salts (*S*)-**2**·(*S*)-**4** and (*S*)-**2**·(*R*)-**4** were prepared in order to determine the respective melting points and solubilities in alcohols. The results of these measurements are listed in Table 1, where the data obtained for the corresponding diastereomeric phthalates of 1-phenylethylamine (*S*)-**1**·(*S*)-**4** and (*S*)-**1**·(*R*)-**4**[9] are also reported. Resolution of **4** with **2** was performed in methanol, which, unique among the tested alcohols, showed largely differentiated and, at the same time, reasonable dissolving abilities for the two diastereomeric salts. The resolving agent **2** was used in the (*S*)-form and in equimolar amount to the racemic substrate. The salt of (*S*)-**4** with (*S*)-**2** precipitated in 90% yield (relative to the theoretical amount, i.e. half of the overall starting salt). (*S*)-**4** was liberated from the precipitate and isolated by distillation with e.e. 98.3%, determined by chiral HPLC, and in 74.4% yield (37.2% of the starting **4**) (Table 2, entry 1). (*S*)-**2**·(*R*)-**4** was obtained by concentration of the methanolic filtrate in 108.8% yield (54.4% of the overall starting salt) and decomposed to give crude (*R*)-**4**, which was isolated by distillation with 80.0% e.e. and in 82.0% yield (41.0% of the starting **4**). The total recovery of the resolving agent from the two separated diastereomeric salts amounted to 93.4% of the initially employed quantity.

Table 1. Melting point and solubilities of the salts of (*S*)-**2** and (*S*)-**1** with (*S*)- and (*R*)-**4**

	(*S*)-**2**·(*S*)-**4**	(*S*)-**2**·(*R*)-**4**	(*S*)-**1**·(*S*)-**4**	(*S*)-**1**·(*R*)-**4**
Mp (K)[a]	427.3	408.9	413.7	400.7
Solubility (g/100 mL solvent)[b]				
In methanol	2.1	20	4.4[c]	20[c]
In ethanol	0.3	2.7	–[d]	–[d]
In 2-propanol	0.2	1.2	–[d]	–[d]

[a] Determined by DSC analysis at a scan rate of 2.5°C min^{-1}.
[b] Determined at 20°C or, in the only case of 2-propanol, at 45°C.
[c] Previously reported in Ref. 9.
[d] Not determined.

Table 2. Resolutions, performed in methanol, of **4** with (*S*)-**2** and (*S*)-**1** and of **2** and **1** with (*R*)- and (*S*)-**4**, respectively

Entry	Racemic substrate	Resolving agent	Precipitate	Yield[a] (%)			E.e.[b] (%)		*S*[c]
				1st cryst.[d]	2nd cryst.	Recovered substrate	1st cryst.	2nd cryst.	
1	**4**	(*S*)-**2**	(*S*)-**2**·(*S*)-**4**	89.7	–	74.4	98.3	–	0.88
2	**2**	(*R*)-**4**	(*R*)-**2**·(*R*)-**4**	88.9	60.8	60.2	64.8	92.0	0.56
3	**2**	(*R*)-**4**	(*R*)-**2**·(*R*)-**4**	76.5	48.9[e]	48.0	70.7	96.1	0.54[f]
4[g]	**4**	(*S*)-**1**	(*S*)-**1**·(*S*)-**4**	82.0	–	62.8	>99	–	0.81
5[h]	**1**	(*S*)-**4**	(*S*)-**1**·(*S*)-**4**	70.8	–	–	81.0	–	0.57
6[g]	**1**	(*S*)-**4**	(*S*)-**1**·(*S*)-**4**	71.8	59.8	58.3	–[i]	>99	0.59

[a] Relative to the theoretical amount, i.e. half of starting racemate.
[b] Enantiomeric excess (determined by chiral HPLC) of the substrate liberated from the precipitate.
[c] Experimental resolution efficiency calculated from S=chemical yield of the diastereomeric salt (%)×e.e. of the liberated substrate (%)/10000.
[d] From the solution containing equivalent amounts of racemic substrate and resolving agent.
[e] Two treatments of the first precipitate were performed in refluxing ethanol instead of recrystallising from methanol.
[f] Calculated from $S=76.5\times70.7/10000$.
[g] Data previously reported in Ref. 1.
[h] Data previously reported in Ref. 5.
[i] Not determined.

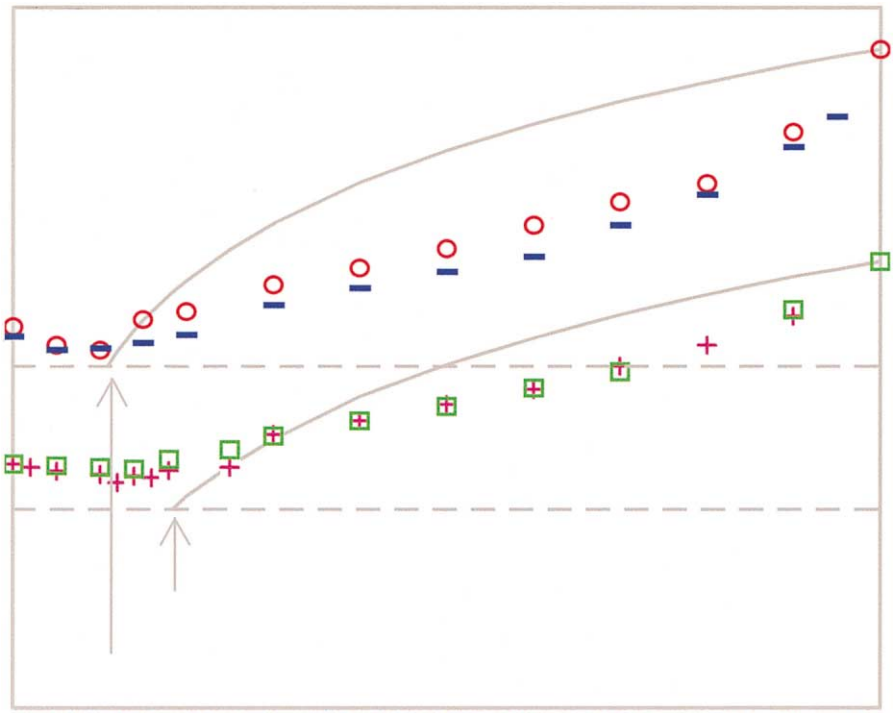

Figure 1. Binary melting-point phase diagrams for the diastereomeric systems (*S*)-**1**·(*S*)-**4**/(*S*)-**1**-(*R*)-**4** (crosses), (*S*)-**1**·(*S*)-**4**/(*R*)-**1**-(*S*)-**4** (squares), (*S*)-**2**·(*S*)-**4**/(*S*)-**2**-(*R*)-**4** (dashes) and (*S*)-**2**·(*S*)-**4**/(*R*)-**2**-(*S*)-**4** (circles). The upper solid curve represents the values calculated on the basis of the Schröder–van Laar equation for the mixtures containing (*S*)-**2**·(*S*)-**4**, while the lower one those analogously calculated for the mixtures containing (*S*)-**1**·(*S*)-**4**.

Contrary to the preparation of **2**, that of the acid **3** immediately appeared quite laborious due to the poor availability of 1,2-naphthalic anhydride and also to the expected formation of the positional isomer of **3**, isopropylidene glycerol 2-carboxy-1-naphthoate, from the reaction of the same anhydride with glycerol acetonide. Nevertheless, the synthesis was undertaken. A few grams of 1,2-naphthalic anhydride were prepared from α-bromostyrene and maleic anhydride according to the procedure reported in the literature.[10] In order to assess the resolving properties of **3** immediately, the preparation of its racemate was omitted and the trial reactions of 1,2-naphthalic anhydride with isopropylidene glycerol directly performed using the optically active alcohol. Independently on the temperature, treatment of 1,2-naphthalic anhydride with (*R*)-isopropylidene glycerol in pyridine afforded an approximately 2:1 mixture of (*S*)-**3** and (*S*)-isopropylidene glycerol 2-carboxy-1-naphthoate. The latter could be completely removed by one crystallisation of the mixture from toluene. Isolated (*S*)-**3**, which is a high melting point white solid, was then mixed with pure samples of (*S*)-**4** and (*R*)-**4**. The two diastereomeric salts, in contrast to those of (*S*)-**2** with (*S*)-**4** and (*R*)-**4**, were unfortunately amorphous and precipitation of solids did not occur from their alcoholic solutions.

Finally, prompted by the ready availability and cheapness of 1,8-naphthalic anhydride, we contemplated the preparation of isopropylidene glycerol 8-carboxy-1-naphthoate. However, such a project was promptly dropped considering the intrinsic instability of the hemiesters of 1,8-naphthalic acid.

The reciprocal resolution, i.e. that of **2** with **4**, was performed in methanol using the (*R*)-amine as a resolving agent. The salt (*R*)-**2**·(*R*)-**4** precipitated in 88.9% yield. The enantiomeric excess of (*R*)-**2**, determined by chiral HPLC after liberation from a sample of the precipitate and methylation with diazomethane, was 64.8%. Recrystallisation of the salt from methanol raised the enantiomeric excess of (*R*)-**2** to 92.0% lowering the overall yield to 60.8%. Finally, (*R*)-**2** was liberated and isolated in 60.2% yield (30.1% of the starting **2**) (Table 2, entry 2).

A second attempt at resolving **2** with **4** was made increasing the methanol volume and replacing the recrystallisation of the first precipitate from this solvent with two successive treatments in refluxing ethanol (Table 2, entry 3). Furthermore, in order to obtain both (*R*)-**2** and (*S*)-**2**, (*R*)- and (*S*)-**4** were used in sequence. At the end of the procedure, (*R*)-**2** and (*S*)-**2** were recovered with 96.1 and 98.8% e.e. and in 48.0 and 48.4% yield, respectively. Successive saponification allowed the recovery, in near quantitative yield, of naphthalene 2,3-dicarboxylic acid and the enantiomers of isopropylidene glycerol with enantiomeric purities consistent with the enantiomeric excesses of the respective parent hemiesters.

In Table 2, the results of all the above resolutions, including the respective experimental efficiencies S (yield× e.e.), are compared with the data previously reported for the reciprocal resolution between **1** and **4** (entries 4–6).[1,5]

Binary melting-point phase diagrams were accurately determined for the four diastereomeric systems (*S*)-**2**·(*S*)-**4**/(*S*)-**2**·(*R*)-**4**, (*S*)-**2**·(*S*)-**4**/(*R*)-**2**·(*S*)-**4**, (*S*)-**1**·(*S*)-**4**/(*S*)-**1**·(*R*)-**4** and (*S*)-**1**·(*S*)-**4**/(*R*)-**1**·(*S*)-**4** (see Fig. 1) using the

DSC data recorded for a number of different mixtures, which were prepared from the salts obtained by combining the single enantiomers of the amine and the hemiester and recrystallising the resultant precipitates from methanol. Two clearly distinct peaks characterised the DSC melting profiles of the 1:1 diastereomeric mixtures and of those with composition near to such a ratio. Therefore, on the basis of the T value corresponding to the first peak, the melting points for the eutectics (T_{eu}) could be easily established (see Fig. 1). Using the Schröder–van Laar equation, the right branches of the diagrams, the solid curves represented in Fig. 1, were calculated from the melting points of the two less soluble salts, i.e. (*S*)-**2**·(*S*)-**4** and (*S*)-**1**·(*S*)-**4**, and from the fusion enthalpies of these latter (161.8 and 145.8 kJ mol^{-1}, respectively).[11] As can be seen, the two diastereomeric systems (*S*)-**2**·(*S*)-**4**/(*S*)-**2**·(*R*)-**4** and (*S*)-**2**·(*S*)-**4**/(*R*)-**2**·(*S*)-**4** form conglomerates, characterised by identical diagrams with 0.10 eutectical composition (χ_{eu}). The other two systems, (*S*)-**1**·(*S*)-**4**/(*S*)-**1**·(*R*)-**4** and (*S*)-**1**·(*S*)-**4**/(*R*)-**1**·(*S*)-**4**, also form conglomerates with identical diagrams, but the eutectic corresponds to a sensibly higher molar ratio of (*S*)-**1**·(*S*)-**4** (0.18 χ_{eu}).

In Table 3, the theoretical values of resolution efficiency, calculated from both the eutectic compositions and the observed solubilities of the diastereomeric salts in methanol, are compared to those experimentally obtained for the two reciprocal resolutions.

3. Discussion

Replacement of the phenyl group of **1** with a naphthyl group produced the desired effects, i.e. more suitable characteristics for the use as a resolving agent. In fact, both **2** and **3** are high melting solids, more efficiently recoverable than **1** by water/organic solvent extraction and easy to purify by crystallisation. As expected, such properties facilitated dosing and handling through the resolution procedures. However, of the two carboxynaphthoates of isopropylidene glycerol, only **2** formed crystalline salts with **4**. In the case of naphthoate **3**, the α position of the carboxyl, even when *ortho* to the ester function, was unfavourable to the achievement of crystalline structures and both the diastereomeric salts of (*S*)-**3** with (*S*)- and (*R*)-**4** proved to be amorphous.

Comparison of (*S*)-**2**·(*S*)-**4** salt with (*S*)-**1**·(*S*)-**4** shows that the former is more stable, as proved by the higher mp and heat of fusion. Furthermore, the solubility and mp differences between (*S*)-**2**·(*S*)-**4** and its (*S*)-**2**·(*R*)-**4** diastereomer are much more pronounced than between the two respective diastereomeric salts of (*S*)-**1** (Table 1). Finally, as shown by the binary melting-point phase diagrams (Fig. 1), both the diastereomeric systems (*S*)-**2**·(*S*)-**4**/(*S*)-**2**·(*R*)-**4** and (*S*)-**1**·(*S*)-**4**/(*S*)-**1**·(*R*)-**4** form conglomerates, but, in the case of the former, the eutectic composition lies sensibly closer to the end of the diagram (0.10 versus 0.18 χ_{eu}). All these data are consistent with the fact that **2** exhibited a higher resolving ability ($S=0.88$) than **1** ($S=0.81$), as shown in Table 2. Both the experimental resolution efficiencies, 0.88 and 0.81, are higher than the theoretical ones, calculated from k_n (solubility of the more soluble n-salt) and the initial concentrations of the 1:1 diastereomeric mixtures (C_0), and very close to the maximum values, 0.89 and 0.78, calculated from the eutectical composition or, alternatively, from the equation $S=(k_n-k_p)/k_n$, where k_p is the solubility of the less soluble p-salt (see Table 3). Therefore, this indicates that the two experimental values of S are meaningful and the two resolution procedures of **4** with **2** and **1** were carried out under optimal conditions. Furthermore, the perfect agreement of the maximum theoretical efficiencies calculated from the eutectical compositions with those calculated from $(k_n-k_p)/k_n$ can be assumed as an indirect mutual validation between the measurements of the solubility differences and the DSC data.

In the case of the two reciprocal resolutions, i.e. those of **2** and **1** with **4**, experimental S ranged from 0.54 to 0.59 (see Table 2), i.e. very far from the calculated theoretical values (see Table 3). These results were not expected, since the eutectic compositions (see Fig. 1)

Table 3. Theoretical and experimental values of S (resolution efficiency) for the reciprocal resolutions between **2** and **4** and between **1** and **4** in methanol

Substrate	Resolving agent	S^a	S^b	S^c	S^d
4	(*S*)-**2**	0.89	0.89	0.73	0.88[e]
2	(*R*)-**4**	0.89	0.89	0.86, 0.75	0.58[f], 0.54[g]
4	(*S*)-**1**	0.78	0.78	0.66	0.81[h]
1	(*S*)-**4**	0.78	0.78	0.71	0.57[i]

[a] Calculated from $S=(1-2\chi_{eu})/(1-\chi_{eu})$.
[b] Calculated from $S=(k_n-k_p)/k_n$, where k_n and k_p are the solubilities in methanol of the more soluble n-salt and the less soluble p-salt, respectively.
[c] Calculated from $S=(0.5C_0-k_p)/0.5C_0$, when $0.5C_0<k_n$, or from $S=(k_n-k_p)/0.5C_0$, when $0.5C_0>k_n$. C_0 is the initial concentration (of the 1:1 diastereomeric mixture) adopted in the experiment in question.
[d] Experimental, i.e. calculated from yields and enantiomeric excesses.
[e] See Table 2, entry 1.
[f] Calculated from $S=88.9\times64.8/10000$ (see Table 2, entry 2). The corresponding theoretical value in the adjacent column is 0.86.
[g] See Table 2, entry 3. The corresponding theoretical value in the adjacent column is 0.75.
[h] See Table 2, entry 4.
[i] See Table 2, entry 5.

and, obviously, the solubility differences coincided with those previously determined for the diastereomeric salts involved in the resolutions of **4** with **2** and **1**. In order to verify that such behaviour was not attributable to the use of crude racemic acids as substrates, trial resolutions were carried out using previously recrystallised **2** or, in the case of **1**, dissolving in methanol equimolar amounts of crystallised (*S*)-**1**·(*S*)-**4** and (*R*)-**1**·(*S*)-**4**. This notwithstanding, the experimental efficiencies did not improve, thus showing the existence of markedly unbalanced reciprocities between the two pairs of procedures, invariably in favour of the resolutions of **4** over those of **2** and **1**. Such results would be better evaluated knowing the ternary phase diagrams of the four diastereomeric systems. Actually, we can underline that the reciprocity of the present resolutions, though largely imperfect, is proved and well supported by the identity of the binary diagrams, showing that reciprocity does not necessarily imply identical or similar efficiencies, since reciprocal resolutions are not mirror-image related and thus not subjected to the Marckwald principle.

4. Conclusions

By replacing the phenyl of isopropylidene glycerol hydrogen phthalate **1** with a naphthyl group, we have obtained a novel resolving agent, the 3-carboxy-2-naphthoate **2**, which resolves 1-phenylethylamine **4** even more efficiently than **1**. The new hemiester has solid consistency and more suitable properties for such a specific use. Its resolution with **4** takes place with moderate efficiency, similar to that exhibited by the same amine in resolving **1**.

Apart from theoretical considerations on the reciprocity of these resolutions, we finally wish to point out the uncommon resolving ability of **2**, which is worthy to be further explored testing other amines. On the other hand, our previously described resolution of **1** with **4**,[1,5] though not more efficient than the present resolution of **2** with **4**, remains preferable to the latter in order to obtain, after saponification, (*R*)- and (*S*)-isopropylidene glycerol, considering that phthalic anhydride is much more available than 2,3-naphthalic anhydride.

5. Experimental

^{1}H NMR spectra were recorded on a Varian Gemini 300 (300 MHz) instrument. Melting points were recorded on a Büchi Melting Point B-450 apparatus and are uncorrected. DSC curves were recorded with a Mettler DSC 20 instrument and processed with a Mettler TC 10 A processor. Optical rotations were measured in a 1 dm cell of 1 mL capacity using a Perkin–Elmer 241 polarimeter. HPLC analyses were performed on Chiralcel and Crownpack columns from Daicel using a Waters 510 pump, a Hitachi L-7400 UV detector and a Hitachi D-7000 HPLC System Manager software.

Starting materials. Achiral and racemic reagents were obtained from commercial suppliers and used without further purification. (*R*)- and (*S*)-isopropylidene glycerol, with 99.4 and 99.6% e.e., respectively, and their immediate precursors (*S*)-**1** and (*R*)-**1** were prepared by Chemi S.p.a. according to the resolution methods previously reported.[1,5,6] (*S*)-**4** and (*R*)-**4** were purchased from Aldrich Chemical Co. 1,2-Naphthalic anhydride and 2,3-naphthalic anhydride were prepared according to literature procedures.[8,10]

5.1. Isopropylidene glycerol 3-carboxy-2-naphthoate 2

A mixture of 2,3-naphthalic anhydride (29.9 g, 151 mmol) and racemic isopropylidene glicerol (19.9 g, 151 mmol) in pyridine (20 mL) was stirred at 90°C for 1 h. After cooling, ethyl acetate and 2N H_2SO_4 were added. The organic phase was separated, washed with saturated aq. NaCl and then with water, dried and concentrated to give **2** (49.7 g, 100%) as a viscous oil, which turned into a beige solid upon standing overnight at room temperature: ^{1}H NMR (DMSO-d_6) δ 1.27 (s, 3H), 1.32 (s, 3H), 3.79 (dd, 1H, J=8.8, 5.9 Hz), 4.07 (dd, 1H, J=8.8, 6.6 Hz), 4.21–4.38 (m, 3H), 7.67–7.72 (m, 2H), 8.0.7–8.14 (m, 2H), 8.27 (s, 1H), 8.41 (s, 1H), 13.32 (br s, 1H).

5.2. 3-Carboxy-2-naphthoate of (*R*)-isopropylidene glycerol (*S*)-2

Prepared in quantitative yield from 2,3-naphthalic anhydride and (*R*)-isopropylidene glycerol as described for **2**. Crystallisation of crude (*S*)-**2** from toluene gave (*S*)-**2** as a white solid in 75.4% yield: mp 106.0–107.4°C; $[\alpha]_D^{25}$ =−12.9 (*c* 1, ethanol). ^{1}H NMR identical to **2**.

5.3. 3-Carboxy-2-naphthoate of (*S*)-isopropylidene glycerol (*R*)-2

Prepared in quantitative yield from 2,3-naphthalic anhydride and (*S*)-isopropylidene glycerol as described for **2**. Crystallisation of crude (*R*)-**2** from toluene gave (*R*)-**2** as a white solid in 58.2% yield: mp 105.3–106.2°C; $[\alpha]_D^{25}$=+ 13.3 (*c* 1, ethanol). ^{1}H NMR identical to **2**.

5.4. 1-Carboxy-2-naphthoate of (*R*)-isopropylidene glycerol (*S*)-3

A mixture of 1,2-naphthalic anhydride (2.7 g, 13.6 mmol) and (*R*)-isopropylidene glycerol (1.8 g, 13.6 mmol) in pyridine (5 mL) was stirred at 90°C for 1 h. After working up as described for **2**, an approximately 2:1 solid mixture (3.9 g) of (*S*)-**3** and 2-carboxy-1-naphthoate of (*R*)-isopropylidene glycerol was obtained.[12] Crystallisation from toluene allowed the minor component to be completely removed from the mixture and 2 g of the prevalent isomer (*S*)-**3** to be isolated as a white solid: mp 142.3–143.4°C; ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 3H), 1.45 (s, 3H), 3.90 (dd, 1H), 4.17 (dd, 1H), 4.50–4.60 (m, 3H), 7.57–7.69 (m, 2H), 7.88–8.00 (m, 3H), 8.09 (d, 1H).

5.5. Resolution of 1-phenylethylamine 4 with 3-carboxy-2-naphthoate of (*R*)-isopropylidene glycerol (*S*)-2

Compound **4** (10.48 g, 86.5 mmol) was added to a stirred solution of (*S*)-**2**[13] (28.57 g, 86.5 mmol) in methanol (80 mL). A white precipitate formed in a few minutes. The mixture was boiled for 5 min and then allowed to cool to 20°C. After 90 min, the precipitate was collected by filtration, rinsed with cold methanol and dried yielding (*S*)-**2**·(*S*)-**4** salt as a white crystalline solid (17.52 g, 90% of the theoretical amount): mp 154.4–155.6°C; ^{1}H NMR (DMSO-d_6) δ 1.25 (s, 3H), 1.31 (s, 3H), 1.49 (d, 3H, $J=7.1$ Hz), 3.82 (dd, 1H, $J=8.4$, 6.2 Hz), 4.03 (pseudo t, 1H, $J=8.4$ Hz), 4.20 (d, 2H, $J=5.5$ Hz), 4.32–4.37 (m, 2H), 7.29–7.39 (m, 3H), 7.49–7.58 (m, 4H), 7.95–7.99 (m, 3H), 8.25 (s, 1H), 8.81 (br s, 3H). The salt was decomposed by treatment with 2N H_2SO_4 and ethyl acetate. The aqueous phase was separated, made alkaline by addition of sodium hydroxide and extracted with ethyl acetate. Removal of the solvent from the extract, previously dried over Na_2SO_4, gave an oily residue, which was distilled under vacuum yielding (*S*)-**4** (3.9 g, 74.4% of the theoretical amount): $[\alpha]_D^{20}=-39.7$ (neat); e.e. 98.3% (by HPLC on a Crownpack CR (+) column; pH 1.5 $HClO_4$ aq., 0.8 mL/min at 200 nm); ^{1}H NMR identical to that reported in the literature.[14]

The methanolic filtrate resulting from the isolation of (*S*)-**2**·(*S*)-**4** was concentrated to give (*S*)-**2**·(*R*)-**4** salt (21.24 g, 108.8% of the theoretical amount). Decomposition of the latter by the procedure described for the (*S*)(*S*)-salt and successive distillation of the recovered crude amine afforded 4.3 g (82.0% of the theoretical amount) of (*R*)-**4**: $[\alpha]_D^{20}=+33.4$ (neat); e.e. 80.0% (by HPLC under the conditions reported for the (*S*)-isomer).

The two organic phases remaining after extraction of (*S*)-**4** and (*R*)-**4** with 2N H_2SO_4 were combined, washed with water several times, dried over Na_2SO_4 and concentrated recovering 26.68 g (93.4% of the starting amount) of (*S*)-**2** as a viscous oil, which solidified upon standing. NMR spectrum of such a solid confirmed the identity with the starting acid revealing only traces of the deketalised derivative, which could be easily removed by recrystallisation from toluene.

5.6. Resolution of isopropylidene glycerol 3-carboxy-2-naphthoate 2 with (*R*)-1-phenylethylamine (*R*)-4

Method A: by crystallisations from methanol. (*R*)-**4** (18.3 g, 151 mmol) was added to a stirred solution of **2** (50 g, 151 mmol) in methanol (220 mL). A white precipitate was formed in a few minutes. The mixture was boiled for 10 min and then allowed to cool to 20°C. After 90 min, the precipitate was collected by filtration, rinsed with cold methanol, and dried yielding a white solid (30.37 g), which was suspended in methanol (200 mL). The mixture was stirred under reflux for 30 min, cooled to 20°C, and filtered to give (*R*)-**2**·(*R*)-**4** salt (20.75 g, 60.8% of the theoretical amount) as a white crystalline solid: mp 149.6–150.2°C; e.e. of (*R*)-**2** 92.0% (64.8%, before recrystallisation) [determined on the corresponding methyl ester, prepared by treatment of a liberated sample of (*R*)-**2** with diazomethane, by HPLC on a Chiralcel OD column, using a mixture of *n*-hexane and propan-2-ol (96:4) as a mobile phase (flow-rate 1.5 mL/min)]; ^{1}H NMR identical to (*S*)-**2**·(*S*)-**4**. The salt was suspended in ethyl acetate and 2N H_2SO_4. The organic phase was separated, washed with water, dried over Na_2SO_4, and concentrated to give (*R*)-**2** (15.05 g, 60.2% of the theoretical amount) as a white solid: e.e. 92.0% (by chiral HPLC of the methyl ester under the above conditions); ^{1}H NMR identical to **2**.

(*R*)-**2** was saponified by treatment with 2.5N NaOH (60 mL) at 90°C for 1 h. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate. Removal of the solvent from the extract, previously dried over Na_2SO_4, gave an oily residue, which was distilled under vacuum yielding (*S*)-isopropylidene glycerol (5.44 g, 54.5% of the theoretical amount): $\alpha_D^{20}=+13.47$ (neat); ^{1}H NMR identical to that reported in the literature.[14] Addition of 2N H_2SO_4 to the aqueous phase resulted in the immediate precipitation of a white solid, which was isolated and dried to give pure naphthalene 2,3-dicarboxylic acid (8.91 g, 89.6% on the basis of the amount of (*R*)-**2**·(*R*)-**4** salt submitted to decomposition).

Method B: by crystallisations from methanol and from ethanol. (*R*)-**4** (17.36 g, 143.3 mmol) was added to a stirred solution of **2** (47.34 g, 143.3 mmol) in methanol (380 mL). Precipitation occurred after about 30 min. The mixture was stirred at room temperature overnight and then cooled to 5°C. The precipitate was collected by filtration, rinsed with cold methanol, and dried yielding a white solid (24.76 g), which was suspended in ethanol (200 mL). The suspension was boiled with stirring for 90 min, cooled to 20°C, and filtered. The isolated solid (18 g) was submitted to the same treatment again, but using 140 mL of ethanol. Filtration allowed isolation of (*R*)-**2**·(*R*)-**4** salt (15.81 g, 48.9% of the theoretical amount) as a white crystalline solid: 154.7–155.4°C; e.e. of (*R*)-**2** 96.1% (70.7%, after the crystallisation from methanol, and 90.4% after the first treatment in refluxing ethanol) (determined as described in method A); ^{1}H NMR identical to (*S*)-**2**·(*S*)-**4**.

The methanolic mother liquors were concentrated to give 38.86 g of a solid, whence 28.43 g of (*S*)-**2** (45.6% e.e.) were liberated upon ethyl acetate/2N H_2SO_4 extraction. Treatments with equimolar (*S*)-**4** in methanol (230 mL) and then with boiling ethanol twice (150 and 135 mL) under the same conditions as above led to the ultimate isolation of (*S*)-**2**·(*S*)-**4** salt (16.0 g, 49.5% of the theoretical amount) as a white crystalline solid: mp 153.5–154.6°C; e.e. of (*S*)-**2** 98.8% (93.4%, after the crystallisation from methanol, and 97.2% after the first treatment in refluxing ethanol) (determined as described in method A).

From the two resolved diastereomeric salts, (*R*)-**2** and (*S*)-**2** were liberated in 48.0 and 48.4% yield, respec-

tively. Saponification of (*R*)-2 and (*S*)-**2** gave (*S*)- and (*R*)-isopropylidene glycerol with +14.13 and −14.40 α_D^{20} (neat) and in 47.2 and 43.8% yield (relative to half of starting **2**), respectively.

From the combined mother liquors of all the crystallisations, excepting the initial one, isopropylidene glycerol was isolated in near racemic form ($\alpha_D^{20} = +0.4$) and in 22.8% yield (relative to the starting **2**). Naphthalene 2,3-dicarboxylic acid was recovered from the saponification steps in 85.0% overall yield (relative to the starting **2**).

DSC analyses. Samples of 3–5 mg were run in sealed aluminium pans with a heating rate of 2.5 K min^{-1}. The samples were drawn from diastereomeric mixtures of (*S*)-**2**·(*S*)-**4**, (*S*)-**2**·(*R*)-**4**, (*R*)-**2**·(*S*)-**4**, (*S*)-**1**·(*S*)-**4**, (*S*)-**1**·(*R*)-**4** and (*R*)-**1**·(*S*)-**4**. These salts were prepared combining, in equimolar amounts, the enantiomer of the amine with that of the hydrogen ester in ethyl ether and crystallising the resultant precipitate from methanol.

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References

1. Pallavicini, M.; Valoti, E.; Villa, L.; Piccolo, O. *Tetrahedron: Asymmetry* **1996**, *7*, 1117.
2. Pallavicini, M.; Valoti, E.; Villa, L.; Piccolo, O. *Tetrahedron: Asymmetry* **1997**, *8*, 1069.
3. Pallavicini, M.; Valoti, E.; Villa, L.; Piccolo, O. *Tetrahedron: Asymmetry* **2000**, *11*, 4017.
4. Pallavicini, M.; Valoti, E.; Villa, L.; Piccolo, O. *Tetrahedron: Asymmetry* **2001**, *12*, 1071.
5. Pallavicini, M.; Valoti, E.; Villa, L.; Piccolo, O. *Tetrahedron: Asymmetry* **1994**, *5*, 5.
6. Piccolo, O.; Pallavicini, M.; Valoti, E.; Villa, L. It. Pat. Appl. 000232a/92 1992, applicant Chemi/Italfarmaco Sud S.p.a. (Italia).
7. Kinbara, K.; Harada, Y.; Saigo, K. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1339.
8. Gandolfi, C.; Beggiolin, G.; Menta, E.; Palumbo, M.; Sissi, C. *J. Med. Chem.* **1995**, *38*, 526.
9. Pallavicini, M.; Valoti, E.; Villa, L.; Piccolo, O.; Marchetti, F. *Tetrahedron: Asymmetry* **2000**, *11*, 1957.
10. Newman, M. S.; Dhawan, B.; Hashem, M. M.; Khanna, V. K.; Springer, J. M. *J. Org. Chem.* **1976**, *41*, 3925.
11. The value of 69.4 kJ mol^{-1}, previously reported for (*S*)-**1**·(*S*)-**4** in Ref. 9, resulted from an improper integration of the melting peak in the DSC trace leading to underestimation of the area.
12. Such a ratio was established on the basis of the relative integrations of the two distinct pairs of singlets found in the ^{1}H NMR spectrum of the mixture for the geminal methyl residues. The two respective identities were assigned on the basis of the following observations: (i) the predominant isomer exhibited a higher R_f on silica gel (el. cyclohexane/ethyl acetate 4:6); (ii) in the ^{1}H NMR spectrum, the doublet of its proton in position 8 was found at a slightly lower field than the corresponding proton of the other isomer; (iii) formation of 1-carboxy-2-naphthoate was expected to be favoured over that of 2-carboxy-1-naphthoate.
13. Crude, not crystallised from toluene, i.e. resultant from working up the reaction of 2,3-naphthalic anhydride with (*R*)-isopropylidene glycerol.
14. Pouchert, C. J.; Behnke, J. *The Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra*, Edition I.