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Crystallization-based resolution of 1,4-benzodioxane-2-carboxylic acid enantiomers via diastereomeric 1-phenylethylamides

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ABSTRACT

Unlike the diastereomeric 1-phenylethylammonium salts, the diastereomeric *N*-1-phenylethylamides of (*S*)- and (*R*)-1,4-benzodioxane-2-carboxylic acid show significant differences in fusibility and solubility so as to be efficiently resolved by precipitation of the less soluble diastereomer (>98% de), while chromatographic purification of the unprecipitated fraction affords the more soluble one (>99% de). Overall, 95% of the former and 80% of the latter are recovered. The hydrolysis of the two resolved amides provides the two acid enantiomers and the resolving amine in quantitative yield and with unchanged stereoisomeric purity.

1,4-Benzodioxanes functionalized at C(2) with a suitably substituted carbon are important chiral building blocks because of the presence of the 2-benzodioxanyl residue in a number of biologically active compounds, the potency of which often greatly varies dependently on the absolute configuration of the stereogenic C(2). That's what we have observed in many unichiral benzodioxane-based compounds endowed with different pharmacological activities such as subtype selective adrenergic antagonists,[1] FtsZ inhibitors,[2] neuronal nicotinic agonists[3] and FTase inhibitors.[4] Historically, 1,4-benzodioxane-2-carboxylic acid (**1**) is one of the most readily available and synthetically versatile 2-substituted 1,4-benzodioxanes. Both the enantiomers of **1** can be synthesized from unichiral 1,2-cyclic ketals or 1-ethers of glycerol,[5] accessible from 'chiral pool',[5] from racemic solketal[6] or from prochiral 1,3-dihydroxyacetone monoethers.[7] On the other hand, *rac*-**1** can be very easily synthesized by condensation of catechol with ethyl 2-dibromoproprionate[8] and successive saponification and then it can be resolved with (+)-dehydroabietylamine[9] or with *p*-methyl or *p*-nitro substituted 1-phenylethylamine enantiomers[10] or directly by entrainment after conversion into methyl ester.[11]

Our studies on a series of pairs of diastereomeric salts of (*R*)-**1** and (*S*)-**1** with the *S* enantiomer of 1-phenylethylamine (**2**) and of differently *p*-substituted 1-phenylethylamines have shown that the capability of resolving *rac*-**1** is not shared by all the phenylethylamines: only the diastereomeric *p*-nitro- and *p*-methylphenylethylammonium benzodioxanecarboxylates have significantly different solubilities in alcoholic solvents and thus can be efficiently resolved, while (*S*)-**2**, and its *p*-halo and *p*-methoxy analogues are ineffective as resolving agents.[12] Crystallographic analyses have pointed out remarkable differences in solid state structure between the diastereomers having different solubility, namely those of the two resolvable salts of **1** with *p*-nitro- and *p*-methylphenylethylamine.[12] However, the diastereo-discrimination conferred to **2** by the *para*-substitution remains unpredictable and such a difficulty may be due to the ionic nature of the diastereomers and to the role played by the solvent. Differentiated interactions, such as for instance hydrogen bonds or π and hydrophobic interactions, between the cationic enantiomer of the resolving agent and the two anionic enantiomers of the racemate are determinants for different crystal structures of the two diastereomeric salts, but the same interactions can be negligible when these ions are surrounded by solvent molecules in solution. Different is the case of covalent diastereomers, much less exemplified than diastereomeric salts in the literature:[13] the resolving agent is covalently attached to the two enantiomers and exerts a stricter diastereo-discrimination also in solution, where non-labile differences in conformation and in solubility can thus occur between the two diastereomers. It is notable that variation of the molar ratio solvent/covalent diastereomers is reported not to greatly affect the resolution efficiency unlike what happens with diastereomeric salts.[14]

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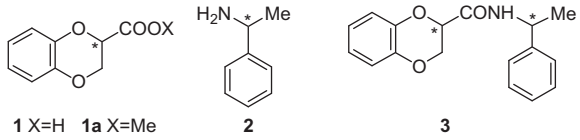


1 X=H **1a** X=Me **2** **3**

We therefore reasoned that (*S*)-**2**, though unable to resolve *rac*-**1** when used as a salifying agent,[12] could generate diastereomers separable by crystallization if covalently attached to *rac*-**1**. The larger availability of the enantiomers of **2**, compared to that of its *para*-substituted analogues, prompted us to this approach as well as some significant successful examples reported in the literature.[13,15–18]

Covalent attachment was realized through an amide bond. An equimolar mixture of the two diastereomeric amides between (*R*)-**2** and (*R*)- and (*S*)-**1**, namely (*R*,*R*)-**3** and (*S*,*R*)-**3**, was near quantitatively obtained by reaction of *rac*-**1a**,[9] the methyl ester of *rac*-**1**, with an excess of (*R*)-**2** in THF in the presence of a little more than stoichiometric amount of magnesium chloride.[19] Removal of the excess of (*R*)-**2**, then quantitatively recovered, allowed the mixture of (*R*,*R*)-**3** and (*S*,*R*)-**3** to be isolated by simple concentration and treatment with diisopropyl ether as a white solid.

Alongside this, we analogously prepared two samples of (*R*,*R*)-**3** and (*S*,*R*)-**3** from the methyl esters (*R*)-**1a**[9] and (*S*)-**1a**[9], respectively, in order to determine the physical properties of the two diastereomeric amides and to investigate the solid phase behaviour of their mixtures. We found that the melting temperature of (*S*,*R*)-**3** (102.7 °C) largely exceeded that of (*R*,*R*)-**3** (75.0 °C), while DSC analysis of a series of differently proportioned (*R*,*R*)-**3**/(*S*,*R*)-**3** mixtures revealed that the two diastereomeric amides produce a simple eutectic. The resultant experimental binary melting-point phase diagram, depicted in Figure 1, is typical of a conglomerate.

As can be seen in the same figure, the experimental values acceptably fit within the theoretical ones (solid curve) calculated on the basis of the melting points of (*S*,*R*)-**3** and (*R*,*R*)-**3** and of the respective enthalpies (27.68 and 24.88 kJ mol^{-1}) using the Schröder-van Laar equation, although some difference can be observed between the eutectic composition indicated by the intersection of the two branches of the theoretical curve (0.32 χ_{eu} of the higher melting diastereomer (*S*,*R*)-**3**) and the composition of the mixture exhibiting the lowest experimental melting point (0.20 χ_{eu} of (*S*,*R*)-**3**). The latter χ_{eu} value prospects, under the best crystallization conditions, a maximum 0.75 resolution efficiency (*S*),[20] that is the precipitation of 75% of (*R*,*S*)-**3** diastereomerically pure, whereas the former χ_{eu} value (0.32) a modest 0.53 resolution efficiency.[21]

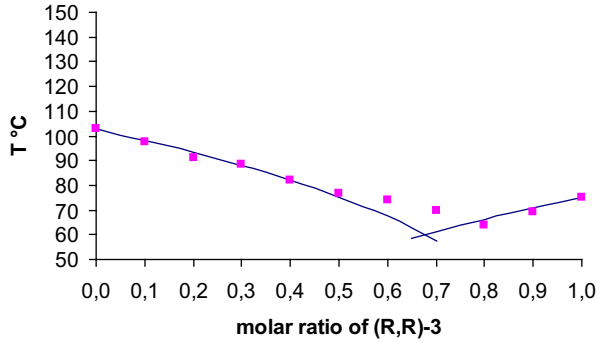


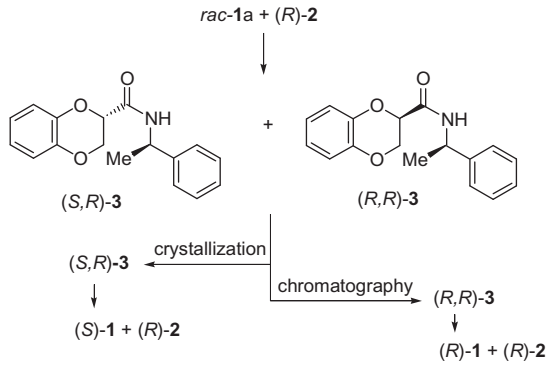
Figure 1. Binary melting-point phase diagram for the diastereomeric system (*R*,*R*)-**3**/(*S*,*R*)-**3**. The solid curve represents the values calculated on the basis of the Schröder-van Laar equation.

The information provided by the binary phase diagram is very useful, but the composition of the eutectic of this diagram is not always independent of the nature of the crystallization solvent and it has to be compared with solubility measurements. These indicated that (*R*,*R*)-**3**, the lower melting diastereomer, has a 17.2 g/100 mL solubility in toluene at 25 °C, while (*R*,*S*)-**3**, the higher melting diastereomer, has a 5.2 g/100 mL solubility under the same conditions. Such a considerable solubility difference prospected a maximum 0.70 resolution efficiency,[22] a value close to 0.75 indicated by the experimental 0.20 χ_{eu}.

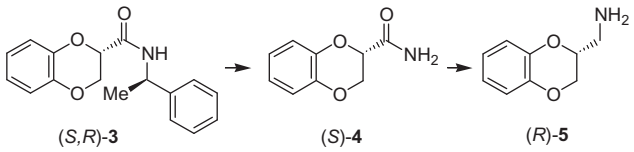
The whole resolution procedure is shown in Scheme 1.

Crystallization of 5 g of equimolar mixture of (*R*,*R*)-**3** and (*S*,*R*)-**3** from a toluene volume (14.5 mL) sufficient to keep 2.5 g of (*R*,*R*)-**3** dissolved at 25 °C gave results in line with the foreseen 0.70–0.75 resolution efficiency: a precipitate of (*S*,*R*)-**3** was isolated in 70.4% yield (1.76 g) and with >98% diastereomeric excess.[23] Moreover, the mother liquors were concentrated and chromatographed on silica gel to yield 2.0 g of (*R*,*R*)-**3** and additional 0.61 g of (*R*,*S*)-**3**, both with >99% de. Overall, at the end of the procedure, 94.8% of (*S*,*R*)-**3** and 80% of (*R*,*R*)-**3** were, respectively, recovered.[23] Successive hydrolyses, accomplished in dioxane and 6 N HCl, provided (*S*)-**1** and (*R*)-**1** in quantitative yield and with no less enantiomeric excess than the diastereomeric excess of the respective parent amides, as demonstrated by chiral HPLC analysis according to a previously reported method. Also the recovery of (*R*)-**2** was near quantitative.[24]

We have recently reported that mandelic acid efficiently resolves 2-aminomethyl-1,4-benzodioxane (**5**)[25] and we have successively demonstrated that (*S*)-**5** and (*R*)-**5** are valuable intermediates which give access, among others, to the enantiomers of 1,4-benzodioxane-2-carboxamide (**4**).[26] Indeed, the conversion of (*R*,*R*)-**3** and (*S*,*R*)-**3** into the enantiomers of **4** and subsequently of **5** has poor atom economy and implies deletion of the valuable chiral auxiliary (Scheme 2). Nevertheless, we wished to verify on (*S*,*R*)-**3** whether this route is practicable in terms of yield and of stereoisomeric purity preservation. In order to remove ethylbenzene and to obtain (*S*)-**4**, the resolved diastereomer (*S*,*R*)-**3** was initially submitted to hydrogenolysis under different conditions but



Scheme 1. Resolution of **1** via diastereomeric phenethylamides.



Scheme 2. Unichiral 1,4-benzodioxane-2-carboxamide and 2-aminomethyl-1,4-benzodioxane from the resolved phenethylamide of 1,4-benzodioxane-2-carboxylic acid.

with no success. The conversion was instead accomplished by treatment of (*S*,*R*)-**3** with *p*-toluenesulfonic acid in refluxing toluene;[27] (*S*)-**4** was isolated in a very good 80% yield and with 98.4% enantiomeric excess.[28] The successive reduction of (*S*)-**4** with $LiAlH_4$ in THF afforded (*R*)-**5** in an excellent 90% yield and with 97.5% enantiomeric excess.[29]

In summary, we have developed an alternative method for the resolution of 1,4-benzodioxane-2-carboxylic acid through the preparation and facile separation of the corresponding diastereomeric mixture of amides with (*R*)-1-phenylethylamine. It should be emphasized that one enantiomer of the resolving 1-phenylethylamine afforded both the enantiomers of 1,4-benzodioxane-2-carboxylic acid and was able, covalently linked to the racemic substrate, to produce that significant diastereo-discrimination which had failed to effect when used as a salifying agent. Though less advantageously, the two diastereomeric amides also allow to access to the enantiomers of 1,4-benzodioxane-2-carboxamide and 2-aminomethyl-1,4-benzodioxane.

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19. Magnesium chloride (534.2 mg, 5.61 mmol) was added to a solution of *rac*-**1a** (1 g, 5.15 mmol) in THF (10 mL). After stirring at room temperature for 1 h, (*R*)-**2** (2.66 mL, 20.6 mmol) was added dropwise. The mixture was stirred overnight at room temperature and then concentrated. The residue was treated with dichloromethane (50 mL) and 10% HCl (25 mL). The organic phase was separated and washed with 10% HCl (25 mL) again. The aqueous phases were combined, made alkaline, and extracted with ethyl acetate (2 × 40 mL) to recover the excess of (*R*)-**2**. Evaporation of ethyl acetate gave 1.79 of (*R*)-**2**, while the concentration of the dichloromethane solution yielded a residue which became a white solid upon stirring in diisopropyl ether (5.5 mL). Such a solid (1.39 g, 95.2%) was isolated by filtration. Its HPLC analysis showed the presence of two peaks of equal area corresponding to (*S*,*R*)-**3** and (*R*,*R*)-**3** (see conditions and t_R reported in note 23 for the two separated diastereomers). ^{1}H NMR spectrum consisted of the signals of the two diastereomeric amides given below (cf. with the spectra reported in note 23).
20. Calculated from $S = (1 - 2\chi_{eu})/(1 - \chi_{eu}) = (1 - 2{\cdot}0.20)/(1 - 0.20) = 0.75$.
21. Calculated from $S = (1 - 2\chi_{eu})/(1 - \chi_{eu}) = (1 - 2{\cdot}0.32)/(1 - 0.32) = 0.53$.
22. Calculated from $S = (17.2 - 5.2)/17.2 = 0.70$.
23. An equimolar mixture of (*S*,*R*)-**3** and (*R*,*R*)-**3** (5 g, 17.65 mmol) obtained from *rac*-**1a** and (*R*)-**2** was dissolved in boiling toluene (14.5 mL). After stirring at room temperature overnight, a white precipitate was recovered by filtration and dried to give (2*S*,1′*R*)-*N*-(1′-phenylethyl)-1,4-benzodioxane-2-carboxamide [(*S*,*R*)-**3**] (1.76 g, 70.4%) as a white solid: mp 102.7 °C; 98.02% de (by HPLC on a RP-18 Lichrospher®-100 column; water/acetonitrile 50/50; 0.5 mL/min; λ = 276 nm; t_R 18.5 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.31–7.15 (m, 5H), 6.98–6.91 (m, 4H), 6.89 (d, 1H, *J* = 6.9 Hz) 5.18 (quintet, 1H, *J* = 6.9 Hz), 4.71 (dd, 1H, *J* = 7.2, 2.8 Hz), 4.52 (dd, 1H, *J* = 11.3, 2.8 Hz), 4.15 (dd, 1H, *J* = 11.3, 7.2 Hz), 1.55 (d, 3H, *J* = 6.9 Hz). The mother liquor was concentrated and the residue was chromatographed on silica gel (cyclohexane/ethylacetate; 80/20) to yield (2*R*,1′*R*)-*N*-(1′-phenylethyl)-1,4-benzodioxane-2-carboxamide [(*R*,*R*)-**3**] (2.0 g, 80%) as a white solid: mp 75.0 °C; 99.2% de (by HPLC on a RP-18 Lichrospher®-100 column; water/acetonitrile 50/50; 0.5 mL/min; λ = 276 nm; t_R 20.0 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.41–7.25 (m, 5H), 6.98–6.90 (m, 4H), 6.85 (d, 1H, *J* = 6.9 Hz) 5.18 (quintet, 1H, *J* = 6.9 Hz), 4.61 (dd, 1H, *J* = 7.2, 2.8 Hz), 4.57 (dd, 1H, *J* = 11.3, 2.8 Hz), 4.19 (dd, 1H, *J* = 11.3, 7.2 Hz), 1.49 (d, 3H, *J* = 6.9 Hz). The chromatography of the residue resultant from the mother liquor afforded also additional 0.61 g of (*S*,*R*)-**3**, whose total recovery thus raised to 2.37 g (94.8%).
24. (2*S*,1′*R*)-*N*-(1′-Phenylethyl)-1,4-benzodioxane-2-carboxamide [(*S*,*R*)-**3**] (1 g, 3.53 mmol) was suspended in 6 N HCl (100 mL) and dioxane 10 mL. The suspension was heated at 90 °C overnight and, after cooling, ethyl acetate was added (50 mL). The aqueous phase was separated, made alkaline, and treated with ethyl acetate to extract (*R*)-**2**, which was near quantitatively recovered (400 mg) by evaporation of ethyl acetate. On the other hand, the organic layer resulting from the addition of ethyl acetate to the reaction mixture was separated and extracted with 10% $NaHCO_3$. The alkaline aqueous extract was washed with ethyl acetate, acidified and extracted with ethyl acetate. The ethyl acetate extract was dried and concentrated under vacuum to give (*S*)-1,4-benzodioxane-2-carboxylic acid [(*S*)-**1**] (636 mg, ∼100%) as a white solid: mp 97.3 °C; $[\alpha]_D^{25}$ −61.7 (*c* 1, $CHCl_3$); 98.5% ee (determined as reported in Ref. 9); ^{1}H NMR identical to that previously reported.[9] (2*R*,1′*R*)-*N*-(1′-Phenylethyl)-1,4-benzodioxane-2-carboxamide [(*R*,*R*)-**3**] (1 g, 3.53 mmol) was hydrolysed by the same procedure to give (*R*)-**2** and (*R*)-1,4-benzodioxane-2-carboxylic acid [(*R*)-**1**] in quantitative yield. (*R*)-**1**: mp 97.5 °C; $[\alpha]_D^{25}$ +62.0 (*c* 1, $CHCl_3$); 99.0% ee (determined as reported in Ref. 9); ^{1}H NMR identical to that previously reported.[9]
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28. A mixture of (*S*,*R*)-**3** (800 mg, 2.82 mmol) and *p*-toluenesulfonic acid (2.15 g, 11.28 mmol) in toluene (10 mL) was refluxed for 2 h. After cooling to room temperature, dichloromethane (20 mL) and 10% $NaHCO_3$ (20 mL) were added. The aqueous phase was removed and the organic phase was washed with water (10 mL), dried and concentrated to give (*S*)-1,4-benzodioxane-2-carboxamide [(*S*)-**4**] (404 mg, 80.0%) as a white solid: mp 139.2 °C; $[\alpha]_D^{25}$ −103.7 (*c* 1, MeOH); 98.4% ee (determined as reported in Ref. 26).
29. A solution of (*S*)-**4** (200 mg, 1.12 mmol) in THF (8 mL) was added dropwise to a suspension of $LiAlH_4$ (127.5 mg, 3.36 mmol) in THF (2 mL) cooled at 0 °C. The mixture was refluxed for 2 h and then quenched with water and diluted with dichloromethane. The organic phase was separated, washed with brine, dried and concentrated to give (*R*)-2-aminomethyl-1,4-benzodioxane [(*R*)-**5**] (167 mg; 90.0%) as a colourless oil: $[\alpha]_D^{25}$ +56.8 (*c* 1 $CHCl_3$), 97.5% ee determined as reported in Ref. 25).