Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 3779–3785

TETRAHEDRON: *ASYMMETRY*

A short entry to enantiopure 2-substituted 1,4-benzodioxanes by efficient resolution methods

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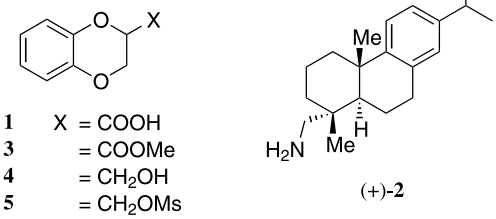
Received 4 August 2003; accepted 9 September 2003

Abstract—(*R*)-1,4-Benzodioxane-2-carboxilic acid (*R*)-**1** was obtained by resolution of the racemic acid **1** with stoichiometric or nonstoichiometric (+)-dehydroabietylamine (+)-**2** in high chemical yield and enantiomeric excess. (*S*)-**1** was isolated from the mother liquors of the crystallisation of (*R*)-**1**·(+)-**2** and its enantiomeric excess maximised by recrystallisation procedures involving a precipitation under kinetic control or, alternatively, by conversion into the methyl ester followed by a single crystallisation. The different mechanisms of the two *S* enrichments is well explained by the binary phase diagrams of the acid and of the ester, which show that the former is a racemic compound, whereas the latter a conglomerate. The DSC analyses were extended to 2-hydroxymethyl- and 2-mesyloxymethyl-1,4-benzodioxane, establishing that the alcohol forms a racemic compound, while its mesyl ester a conglomerate. On the basis of these results, different resolution strategies can be designed to obtain useful homochiral 2-substituted 1,4-benzodioxanes coupling the resolution of **1** via diastereomeric salt formation with the enantiomeric enrichments by recrystallisations, preferably of its conglomerate forming derivatives.

1. Introduction

The 2-substituted 2,3-dihydro-1,4-benzodioxin ring system has been widely used in the design of therapeutic agents, whose affinity for the respective biological targets is strongly influenced by the absolute configuration at the stereogenic C_2 of the benzodioxane unit. In the course of our research concerning the synthesis of chiral benzodioxane derivatives as type-selective α-adrenoceptor ligands,[1,2] we needed to obtain, with very high enantiomeric excess, both enantiomers of 1,4-benzodioxanes bearing in position 2 a hydroxy-, mesyloxy-, tosyloxy-, halo- or aminomethyl substituent. Their preparation typically involves the use of building blocks from the 'chiral pool', such as glycerol or glycidol derivatives,[1–4] or the resolution of the respective racemates catalysed by enzymes[5–7] or accomplished after conversion of the enantiomers into diastereoisomers.[8,9] In our case, we applied an efficient chemical resolution of the chiral precursor glycerol acetonide we had previously developed and patented.[10,11] More recently, however, our attention was drawn to the resolution of 1,4-benzodioxane-2-carboxilic acid **1** with (+)-dehydroabietylamine (+)-**2**, a method confusedly described in 1987[12] and afterwards repeatedly cited by other authors[6,7] as an interestingly straightforward, but very inefficient (2% yield) procedure to obtain homochiral 2-substituted 1,4-benzodioxanes. Herein, on the contrary, we describe highly efficient resolutions of **1** with (+)-**2** leading to both the enantiomers of the acid and, at the same time, provide a detailed analysis, based on DSC data, of the nature of its racemate as well as of the racemates of its methyl ester **3** and of 2-hydroxymethyl- and 2-mesyloxymethyl-1,4-benzodioxane, **4** and **5**, respectively (Chart 1).



1 X = COOH
3 = COOMe
4 = CH_2OH
5 = CH_2OMs

(+)-**2**

Chart 1.

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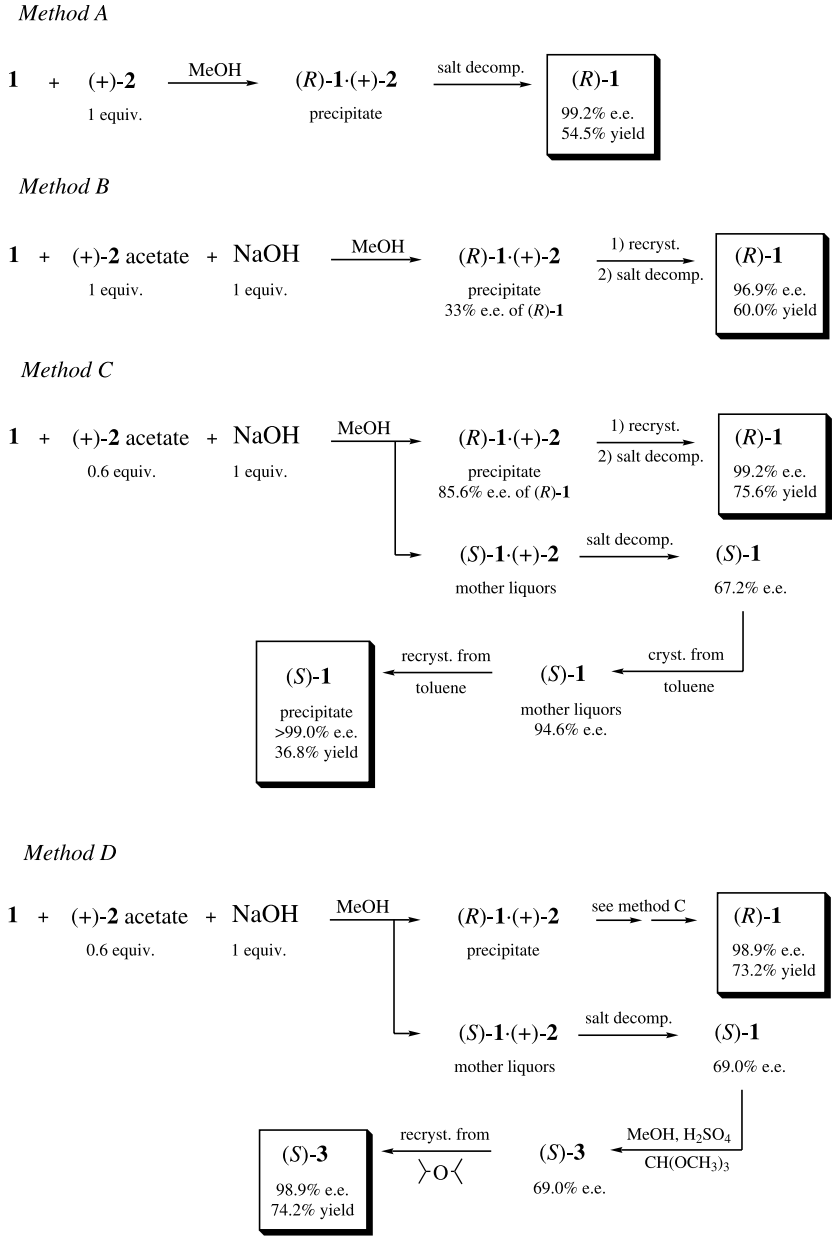
doi:10.1016/j.tetasy.2003.09.012

2. Results

Our first approach to the resolution of **1** with (+)-**2** consisted in reacting **1** with an equivalent amount of (+)-**2** in methanol. After performing several experiments, the optimal value of C_0 (initial concentration of the 1:1 diastereomeric salt mixture, i.e. before crystallisation) was found to be close to 40 mg/mL. Under these conditions, (*R*)-**1**·(+)-**2** salt precipitated in 54.9% yield (relative to the theoretical amount) and with 99.2% e.e. of (*R*)-**1** (resolution efficiency (*S*) 0.54) (Scheme 1 and Table 1, method A).

Subsequently, we tried the use of the solid (+)-**2** acetate, which is easier to handle than the semifluid free amine (+)-**2**, in drastically reduced volumes of methanol. Treatment of **1** with equivalent amounts of sodium hydroxide and (+)-**2** acetate in methanol ($C_0 = 306$ mg/mL) resulted in the precipitation of (*R*)-**1**·(+)-**2** salt in 132% yield (relative to the theoretical amount) and with 33% e.e. of (*R*)-**1**. Prolonged trituration of this precipitate with boiling methanol raised the enantiomeric excess of (*R*)-**1** to 96.9% and reduced the yield to 60.8% resulting in a 0.59 total resolution efficiency or resolvability (Scheme 1 and Table 1, method B).

On the basis of this positive result, it seemed worthwhile to test the resolution with less than 1 equiv. of the resolving agent. Treatment of **1** with 0.6 equiv. of (+)-**2** acetate and 1 equiv. of sodium hydroxide in methanol led to the crystallisation of (*R*)-**1**·(+)-**2** salt in 84.7% yield (relative to half of starting racemic acid) and with 85.6% e.e. of (*R*)-**1**. After prolonged treatment of this salt with boiling methanol, the yield and the enan-



Scheme 1.

Table 1. Resolution of acid **1** with amine (+)-**2**

Method	C_0[a]	Yield of (*R*)-**1**·(+)-**2**(%)[b]		Yield of (*S*)-**1**[c]	Ee of (*R*)-**1** (%)[d]		Ee of (*S*)-**1**[d]	S_{exp}[e]
		1st cryst.	2nd cryst.		1st cryst.	2nd cryst.		
A[f]	40	54.9	–[g]	–[h]	99.2	–	–	0.54
B[i]	306	132.0	60.8	–[h]	33.0	96.9	–	0.59
C[j]	229	84.7	75.9	36.8	85.6	99.2	>99.0	0.75
D[k]	229	86.2	73.5	74.2[l]	84.3	98.9[l]	98.9[l]	0.73

[a] Sum of the initial concentrations (mg/mL) of **1** and (+)-**2**, i.e. before precipitation.
[b] Relative to the theoretical amount, i.e. half of the starting racemic acid, and assimilable to that of (*R*)-**1**, the recovery of the acid from the salt being quantitative.
[c] Overall, i.e. at the end of the enantiomeric enrichment effected according to the respective method.
[d] Enantiomeric excess determined by chiral HPLC.
[e] Experimental resolution efficiency or experimental resolvability, calculated from the yield of the precipitated (*R*)-**1**·(+)-**2** salt and the enantiomeric excess of the acid liberated from the same.
[f] Treatment of **1** with stoichiometric (+)-**2** in methanol.
[g] The recrystallisation was not effected, because unnecessary.
[h] (*S*)-**1** was not isolated from the alcoholic solutions remaining from the original crystallisations of (*R*)-**1**·(+)-**2**.
[i] Treatment of **1** with stoichiometric NaOH and (+)-**2** acetate in methanol.
[j] Treatment of **1** with stoichiometric NaOH and 0.6 equiv. of (+)-**2** acetate in methanol; *S* enrichment of the acid from the mother liquors by two crystallisations from toluene.
[k] (*R*)-**1**·(+)-**2** separation according to method C; *S* enrichment of the acid from the mother liquors by a single crystallisation from diisopropyl ether, after conversion into methyl ester.
[l] Of the methyl ester of (*S*)-**1**, namely (*S*)-**3**.

tiomeric excess became 75.9 and 99.2%, respectively. From the mother liquors of the crystallisation of (*R*)-**1**·(+)-**2**, the *S* acid was recovered in 114% yield and with 67.2% e.e. (Scheme 1 and Table 1, method C).

The further enantiomeric enrichment of (*S*)-**1** was effected by two alternative ways: (a) by crystallisation of the same acid (method C); (b) by crystallisation of its methyl ester (method D). As recently reported in the literature[6] and well documented by our DSC and IR analyses, **1** forms a racemic compound, which melts at higher temperature than the pure enantiomers (125.4°C versus 97.5°C) and whose binary phase diagram shows two eutectics, E^+ and E^-, corresponding to 0.94 mole fraction of (*R*)-**1** and (*S*)-**1**, respectively, and melting at 94.1°C (see Fig. 1). In toluene and at 25°C, **1**, (*R*)-**1** and their eutectic mixture E^+ exhibit increasing solubility: 10.9, 51.3 and 73.0 mg/mL, respectively. Consistently with these data, the recrystallisation, from toluene, of the *S* acid with an enantiomeric excess (67.2%) lower than that of E^- (88%) produced, when equilibrium had been attained, a nearly racemic precipitate and mother liquors with composition E^-. However, in a carefully run 'kinetic' recrystallisation, it was surprisingly possible to surmount the 'thermodynamic obstacle' of the eutectic composition of the mother liquors and to recover, by concentration of these latter, (*S*)-**1** with an enantiomeric excess (94.6%) sensibly higher than that of E^- and in 48.4% yield. As expected, the final recrystallisation easily led to the precipitation of virtually enantiopure (*S*)-**1** (>99% e.e.) in 36.8% yield (relative to half of starting racemic acid) (Table 1, method C).

The availability of (*S*)-**1** allowed us to prepare the respective salt with (+)-**2** and to compare its solubility with that of (*R*)-**1**·(+)-**2**. On the basis of measured k_n (19.3 mg/mL) and k_p (7.4 mg/mL) (solubilities in methanol, at 25°C, of (*S*)-**1**·(+)-**2** (*n* salt) and (*R*)-**1**·(+)-**2** (*p* salt), respectively), a value of 0.62 was calculated for the maximum theoretical resolvability of **1** with stoichiometric (+)-**2** by using the equation $S=(k_n-k_p)/k_n$.[13]

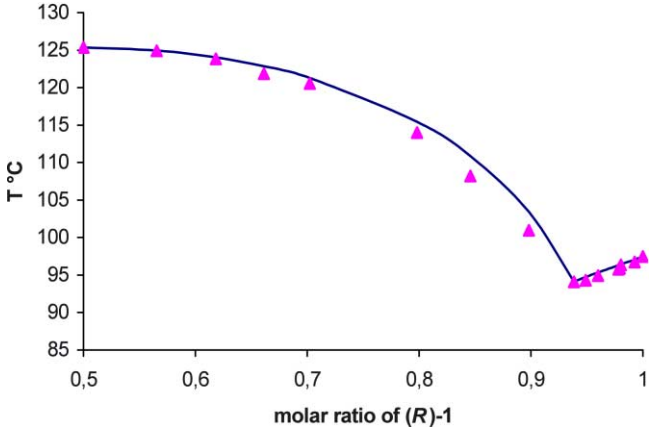


Figure 1. Binary melting-point phase diagram for the enantiomeric system (*R*)-**1**/(*S*)-**1**. The solid curve represents the values calculated on the basis of the Prigogine–Defay and the Schröder–van Laar equations.

The alternative approach for the enantiomeric enrichment of (*S*)-**1** implied its conversion into methyl ester and the recrystallisation of this latter (Scheme 1, method D). Samples of racemic methyl ester **3** and of its *R* enantiomer had been previously prepared from **1** and (*R*)-**1**, respectively, by treatment with methanol, concentrated sulphuric acid and trimethyl orthoformate. The reaction had provided the ester in quantitative yield and, in the case of (*R*)-**3**, with unchanged enantiomeric excess with respect to that of the parent

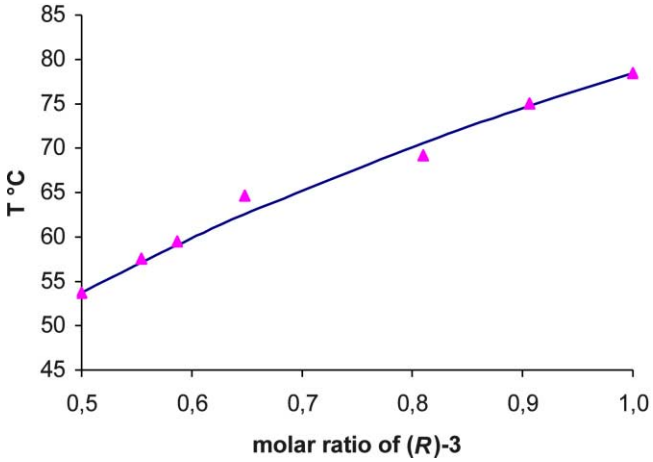


Figure 2. Binary melting-point phase diagram for the enantiomeric system (*R*)-**3**/(*S*)-**3**. The solid curve represents the values calculated on the basis of the Schröder–van Laar equation.

acid. The melting point of (*R*)-**3** (78.5°C) exceeded that of **3** (53.7°C) by 25°C and the IR spectra of the pure enantiomer and of the racemate were identical indicating that **3** forms a conglomerate. This was confirmed by the binary phase diagram constructed using the DSC data for **3**, (*R*)-**3** and a number of their differently proportioned mixtures (see Fig. 2). On the basis of these results, we decided to repeat the resolution of **1** with 0.6 equiv. of (+)-**2**. (*S*)-**1** was isolated from the mother liquors in 110.4 yield and with 69.0% e.e., quantitatively converted into methyl ester (*S*)-**3** with unaltered enantiomeric excess and recrystallised from diisopropyl ether to give (*S*)-**3** in 74.2% yield (relative to half of starting racemic acid) and with 98.9% e.e. (Scheme 1 and Table 1, method D). Diisopropyl ether had been selected as the recrystallisation solvent considering its reasonable dissolving ability for both the racemic and the enantiomerically pure methyl ester. In fact, previous measurements had established that the solubilities of **3** and (*R*)-**3** in diisopropyl ether at 25°C are 92.9 and 39.3 mg/mL, respectively.

To complete the resolution of the acid by this procedure, (*S*)-**3** should have been converted again into (*S*)-**1**. However, our interest in the resolution of **1** was mainly due to the consequent access to the homochiral benzodioxanes derivatives **4** and **5**, which are more useful synthons than the acid. Furthermore, the identification of the nature of the racemates of these derivatives could provide relevant information and suggestions on alternative approaches for the resolution of 2-substituted 1,4-benzodioxanes. For these reasons, rather than hydrolyse (*S*)-**3**, (*R*)-**3** and **3** to the alcohols (*R*)-**4**, (*S*)-**4** and **4**, respectively, by treatment with $LiAlH_4$ in tetrahydrofuran. Afterwards, the alcohols were mesylated to give (*S*)-**5**, (*R*)-**5** and **5**.

In the case of the hydroxymethyl derivative, the melting point of the racemate (89.2°C) proved higher than that of the enantiomers (75.5°C). Moreover, the respective IR spectra turned out to be different. These data indicated that **4** forms a racemic compound analogously to the acid **1**. DSC analyses of **4**, (*S*)-**4** and a number of their mixture allowed us to construct the binary phase diagram and to locate the eutectic (E^-) at 0.9 mole fraction of (*S*)-**4** (see Fig. 3). A suitable crystallisation solvent for the racemate and the enantiomers was identified with diisopropyl ether, where (*R*)-**4** and (*S*)-**4** are nearly twice as soluble (88.5 mg/mL) as the racemate (41.3 mg/mL) at 25°C.

On the contrary, the mesyl ester **5** proved a conglomerate like the methyl ester **3**. In fact, the melting point of the enantiomers (87.6°C) exceeds that of the racemate (62.7°C) of 25°C and the respective IR spectra are identical. Such indications were further substantiated by the DSC analyses of **5**, (*R*)-**5** and a number of their mixture which led to the construction of the typical binary phase diagram of a conglomerate (see Fig. 4). As

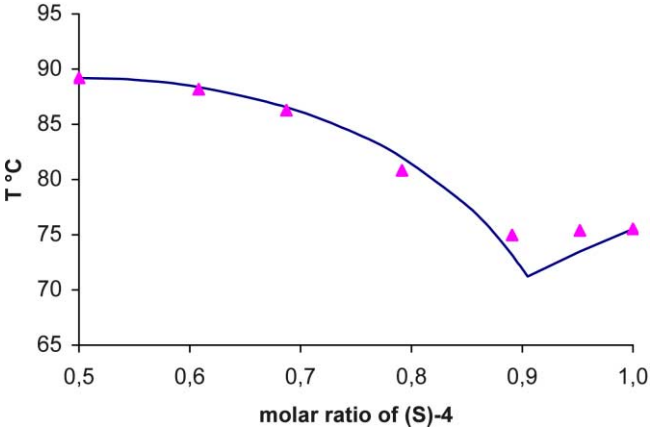


Figure 3. Binary melting-point phase diagram for the enantiomeric system (*R*)-**4**/(*S*)-**4**. The solid curve represents the values calculated on the basis of the Prigogine–Defay and the Schröder–van Laar equations.

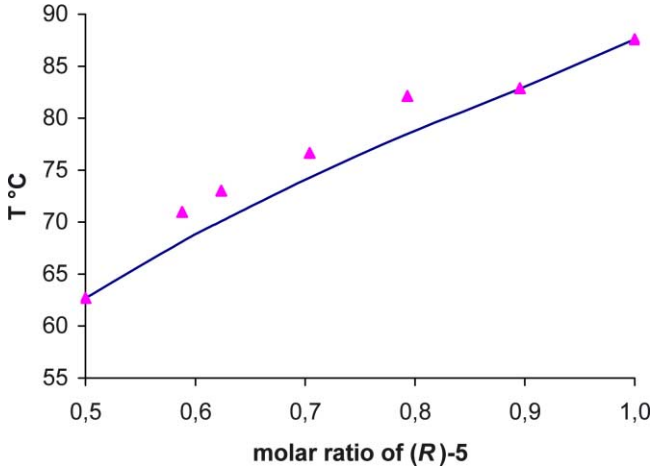


Figure 4. Binary melting-point phase diagram for the enantiomeric system (*R*)-**5**/(*S*)-**5**. The solid curve represents the values calculated on the basis of the Schröder–van Laar equation.

expected in the case of a conglomerate which is not ionised in solution, the solubility of the racemate is sensibly higher than the double of the solubility of the enantiomers. For instance, 1 mL of isopropanol dissolves, at 25°C, 20.3 mg of **5** and 9.0 mg of (*R*)-**5**.

3. Discussion and conclusion

Contrary to what has been reported in the literature, the present results demonstrate that the resolution of 1,4-benzodioxane-2-carboxylic acid **1** with dehydroabietylamine (+)-**2** is a simple and very efficient procedure.

The use of one equivalent of resolving free amine in methanol (method A) led to the isolation of (*R*)-**1**·(+)-**2** salt with a 0.54 experimental efficiency, which is consistent with 0.62 maximum theoretical resolvability calculated from the solubilities of (*R*)-**1**·(+)-**2** and (*S*)-**1**·(+)-**2** diastereomeric salts in the same alcohol. The main disadvantage of this method is the need for a large volume of crystallisation solvent in consequence of the low solubility of the more soluble (*S*)-**1**·(+)-**2** salt (19.3 mg/mL).

The second type of procedure (method B), which implies the treatment of **1** sodium salt with stoichiometric (+)-**2** acetate in methanol and the recystallisation of the resulting precipitate from the same solvent, shows a little better resolution efficiency (0.59) while allowing the large methanol volume of the preceding method to be substantially reduced. This is presumably due to the presence of water, produced by the salification of **1** with sodium hydroxide, and of sodium acetate in the first precipitation, which occurred with a considerable 0.44 efficiency in spite of the very high C_0 (306 mg/mL). The method A was not tried at so high concentration, but it was very unlikely to show similar resolution efficiency considering that a value of 0.08 can be calculated for the maximum theoretical resolvability of **1** with stoichiometric (+)-**2** at 306 mg/mL C_0 by using the equation $S=(k_n-k_p)/\frac{1}{2}C_0$.

With less than stoichiometric resolving agent (0.6 equiv., method C), the efficiency is significantly higher than in the two previous methods. In fact, at the end of the procedure nearly 76% of the theoretical quantity of (*R*)-**1**·(+)-**2** salt was yielded, while the (*S*)-acid was liberated from the mother liquors with a considerable 67.2% e.e., which could be increased to >99% by two recrystallisations from toluene. Interestingly, the former of these consisted in an (*S*)-enrichment of the toluenic mother liquors kinetically surpassing the composition of the eutecticum E^- and the latter in the precipitation of enantiopure (*S*)-**1**. The overall yield of enantiopure (*S*)-acid was a satisfactory 36.8% of the half of starting racemic acid.

This yield value can be doubled (74.2%) if the (*S*)-enriched acid from the mother liquors of the resolution with (+)-**2** is converted into methyl ester and simply recrystallised from diisopropyl ether (method D). Undoubtedly, such a strategy of enrichment is preferable considering the much higher yield and the fact that the methyl ester, contrary to the acid, can be easily reduced to alcohol **4**, at whose enantiomers the resolution of the acid is aimed.

In this context, our DSC studies provide a useful insight into the nature of the racemates of some 2-substituted 1,4-benzodioxanes. In particular, they demonstrate the alternate occurrence of racemic compound and conglomerate in the synthetic sequence 'acid-ester-alcohol-mesylate', **1** and **4** being racemic compounds, whereas **3** and **5** conglomerates. This gives two advantageous opportunities of effecting enantiomeric enrichments in the course of such a synthesis, one, as described in this paper, of nonracemic **3**, the other of nonracemic **5**, in both cases by solubilisation of the racemate and crystallisation of the exceeding enantiomer.

In summary, we have described a new diversified approach to resolve 1,4-benzodioxane-2-carboxilic acid with (+)-dehydroabietylamine efficiently. The best options were found to be (i) the precipitation of the dehydroabietylamine salt of the (*R*)-acid using 0.6 equiv. of the resolving agent acetate per 1 equiv. of the racemic acid sodium salt and the (*S*)-enrichment of the nonracemic acid isolated from the mother liquors by recrystallisations and (ii) the same procedure, but converting the acid from the mother liquors into methyl ester before the (*S*)-enrichment by a single crystallisation. Such strategies, which give access to the enantiomers of valuable 2-substituted derivatives of 1,4-benzodioxane, were theoretically supported by the identification of the types of racemate formed by these latter and by the knowledge of the solubility differences determinant for their separation.

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 DSC analysis, taking the temperature of the end of the melting peak. The DSC curves were recorded and integrated with the aid of a TA Instruments DSC 2010 apparatus.

The resolving agent (+)-**2** acetate was prepared from commercial (+)-**2** (Merck) as previously reported.[14] Racemic acid **1** was synthesised by condensation of catechol with ethyl 2,3-dibromopropionate and successive saponification of the intermediate ester according to a literature method.[15]

4.1. Resolution of 1 with (+)-2

4.1.1. Method A. A solution of (+)-**2** (4.91 g, 17.2 mmol) in methanol (100 mL) was added to a solution of **1** (3.1 g, 17.2 mmol) in methanol (107 mL). The immediately formed white precipitate redissolved by heating the suspension to boiling temperature for a few minutes. The resultant solution was cooled to room temperature, whereupon the precipitation took place again. After stirring for 15 h, the solid was isolated by filtration, rinsed with cold methanol, and dried to give (*R*)-**1**·(+)-**2** (2.2 g, 54.9%): mp 225.5°C; $[\alpha]_D^{25}=+44.4$; the e.e. of the acid liberated from a sample of the salt was 99.2% (by HPLC on a Chiracel 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 0.9 (s, 3H), 1.10 (s, 3H), 1.13 (d, 6H), 1.10–1.40 (m, 4H), 1.50–1.75 (m, 4H), 2.23 (m, 1H), 2.58–2.87 (m, 5H), 4.09 (dd, 1H), 4.24 (dd, 1H), 4.32 (dd, 1H), 6.68–6.84 (m, 5H), 6.92 (dd, 1H), 7.12 (dd, 1H), 8.10 (bs, 3H). The salt was treated with 1 M NaOH (11 mL), water (25 mL) and toluene (50 mL) at 60°C for 30 min. 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 yielding (*R*)-**1** (0.85 g, 54.5%) as a white solid: mp 97.5°C (125.4°C for the racemate); $[\alpha]_D^{25}=+63.0$ (*c* 1, $CHCl_3$); the e.e. was identical to that previously determined for the acid liberated from a sample of the salt with (+)-**2**; ^{1}H NMR ($CDCl_3$) δ 4.38 (dd, 1H, $J=2.9$ Hz, 11.4 Hz), 4.44 (dd, 1H, $J=4.4$ Hz, 11.4 Hz), 4.90 (dd, 1H, $J=2.9$ Hz, 4.4 Hz), 6.88–6.97 (m, 3H), 6.99–7.02 (m, 1H).

4.1.2. Method B. A stirred solution of **1** (13 g, 72.2 mmol) in methanol (110 mL) was added with sodium hydroxide (2.89 g, 72.2 mmol). After 15 min, the resulting solution was heated to 50°C and added with (+)-**2** acetate (24.93 g, 72.2 mmol). The mixture was refluxed for 8 h, stirred for additional 15 h at rt, and filtered to give a white solid (22.2 g), which was dried and refluxed with methanol (400 mL) for 8 h. The suspension was cooled to rt, stirred overnight and filtered yielding (*R*)-**1**·(+)-**2** (10.22 g, 60.8%) as a white crystalline solid. The enantiomeric excess of the acid liberated from a sample of the salt was 96.9% (33.0% before the treatment with boiling methanol). The salt was decomposed as described in method A obtaining (*R*)-**1** (3.9 g, 60.0%) as a white solid: e.e. identical to that previously determined for the acid liberated from a sample of (*R*)-**1**·(+)-**2**.

4.1.3. Method C. A stirred solution of **1** (20 g, 111.0 mmol) in methanol (170 mL) was added with sodium hydroxide (4.44 g, 111.0 mmol). After 15 min, the resulting solution was heated to 50°C and added with (+)-**2** acetate (23.0 g, 66.6 mmol). The mixture was refluxed for 8 h, stirred for additional 15 h at rt, and filtered to give a white solid (21.9 g), which was dried and refluxed with methanol (80 mL) for 8 h. The suspension was cooled to rt, stirred overnight and filtered yielding (*R*)-**1**·(+)-**2** (19.61 g, 75.9%) as a white crystalline solid. The enantiomeric excess of the acid liberated from a sample of the salt was 99.2% (85.6% before the treatment with boiling methanol). The salt was decomposed as described in method A obtaining (*R*)-**1** (7.56 g, 75.6%) as a white solid: e.e. identical to that previously determined for the acid liberated from a sample of (*R*)-**1**·(+)-**2**.

The methanolic filtrate resulting from the isolation of the first precipitate was concentrated and the residue decomposed in the same way as reported for (*R*)-**1**·(+)-**2** (see method A) to give (*S*)-**1** (11.4 g) with 67.2% e.e. The liberated (*S*)-acid was treated with boiling toluene (65 mL) to give a clear solution. The heating was stopped and, after crystallisation started, the mixture was rapidly cooled to 0°C and filtered. The filtrate was concentrated obtaining (*S*)-**1** (4.8 g) with 94.6% e.e. This latter was recrystallised from toluene (21 mL) to give a precipitate of (*S*)-**1** (3.68 g, 36.8%) with >99.0% e.e.: $[\alpha]_D^{25}=-63.8$ (*c* 1, $CHCl_3$); mp and ^{1}H NMR spectrum identical to that of (*R*)-**1**.

4.1.4. Method D. A solution of **1** (20 g, 111.0 mmol) in methanol (170 mL) was submitted to the same resolution procedure described in method C obtaining 7.32 g (73.2%) of (*R*)-**1** with 98.9% e.e. and, from the mother liquors of the first crystallisation of (*R*)-**1**·(+)-**2**, 11.04 g of (*S*)-enriched acid (69.0% e.e.), which was dissolved in methanol (100 mL) and slowly added with conc. H_2SO_4 (7.2 mL) and trimethyl orthoformate (15 mL). The mixture was refluxed for 4 h and concentrated. The resultant residue was dissolved in ethyl acetate and washed with saturated aqueous $NaHCO_3$ three times. The organic phase was separated and concentrated yielding the methyl ester of the (*S*)-enriched acid (11.7 g) with unchanged enantiomeric excess (69%; by HPLC on a Chiracel OD column; hexane/2-propanol 85/15; 1.2 mL/min; (***R***)-**3**: $k'=3.17$; (***S***)-**3**: $k'=2.19$). Crystallisation from diisopropyl ether (45 mL) and filtration at rt afforded (*S*)-**3** (7.95 g; 74.2% of half of the starting racemic acid) as a white solid: mp 78.1°C; $[\alpha]_D^{25}=-56.4$ (*c* 1, $CHCl_3$); e.e. 98.9%; ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H), 4.38 (d, 2H, $J=4.0$ Hz), 4.85 (t, 1H, $J=4.0$ Hz), 6.86-6.92 (m, 3H), 6.99–7.02 (m, 1H).

(*RS*)-Methyl 1,4-benzodioxan-2-carboxylate 3. Obtained, in nearly quantitative yield, by treatment of racemic acid **1** with methanol, concentrated sulfuric acid and trimethyl orthoformate as described in method D. The crude ester was recrystallised from diisopropyl ether: mp 53.7°C; ^{1}H NMR identical to that of (*S*)-**3** (see method D).

(*R*)-Methyl 1,4-benzodioxan-2-carboxylate (*R*)-3. Obtained, in nearly quantitative yield, by treatment of (*R*)-**1** with methanol, concentrated sulfuric acid and trimethyl orthoformate as described in method D. The crude ester was recrystallised from diisopropyl ether: mp 78.5°C; $[\alpha]_D^{25}=+57.0$ (*c* 1, $CHCl_3$); e.e. 99.4% (by HPLC under the analytical conditions described for (*S*)-**3** in method D); ^{1}H NMR identical to that of (*S*)-**3** (see method D).

(*S*)-Methyl 1,4-benzodioxan-2-carboxylate (*S*)-3. See the resolution method D of the racemic acid **1**.

(*RS*)-2-Hydroxymethyl-1,4-benzodioxane 4. Prepared by reduction of racemic methyl ester **3** according to the method previously reported.[16] Crystallisation of the crude alcohol from diisopropyl ether gave **4** in 89.0% yield: mp 89.2°C; ^{1}H NMR ($CDCl_3$) δ 2.03 (bs, 1H), 3.81–3.93 (m, 2 H), 4.07–4.14 (m, 1H), 4.24–4.32(m, 2 H), 6.83–6.92 (m, 4 H).

(*S*)-2-Hydroxymethyl-1,4-benzodioxane (*S*)-4. Prepared by reduction of (*R*)-**3** according to the method previously reported.[16] Crystallisation of the crude alcohol from diisopropyl ether gave (*S*)-**4** in 90.1% yield: mp 75.5°C; $[\alpha]_D^{20} = -36.5$ (*c* 0.1, ethanol) {lit.[12] $[\alpha]_D^{20} = -34.7$ (*c* 0.1, ethanol)}; ^{1}H NMR identical to that of the racemate.

(*R*)-2-Hydroxymethyl-1,4-benzodioxane (*R*)-4. Prepared by reduction of (*S*)-**3** according to the method previously reported.[16] Crystallisation of the crude alcohol from diisopropyl ether gave (*R*)-**4** in 88.7% yield: $[\alpha]_D^{20} = +36.8$ (*c* 0.1, ethanol) {lit.[4] $[\alpha]_D^{20} = +36.2$ (*c* 0.1, ethanol)}; mp and ^{1}H NMR identical to that of the racemate.

(*RS*)-2-Mesyloxymethyl-1,4-benzodioxane 5. Mesyl chloride (1 mL, 12 mmol) was added dropwise to a solution of **4** (2 g, 12 mmol) and triethylamine (1.7 mL, 12 mmol) in dichloromethane (15 mL) at −10°C. After stirring at rt for 1 h, the mixture was acidified with 1N HCl and extracted with dichloromethane. The organic layer was separated, filtered, and concentrated to give a solid residue, which was crystallised from 2-propanol yielding **5** (2.63 g, 90%) as a white solid: mp 62.7°C; ^{1}H NMR ($CDCl_3$) δ 3.09 (s, 3H), 4.20 (dd, 1H, $J = 5.6$ Hz, 11.2 Hz), 4.32 (dd, 1H, $J = 1.8$ Hz, 11.7 Hz), 4.43–4.55 (m, 3H), 6.89 (m, 3H).

(*R*)-2-Mesyloxymethyl-1,4-benzodioxane (*R*)-5. Prepared from (*S*)-**4** as described for the racemate: mp 87.6°C; $[\alpha]_D^{25} = -17.2$ (*c* 1, $CHCl_3$); ^{1}H NMR identical to that of the racemate.

(*S*)-2-Mesyloxymethyl-1,4-benzodioxane (*S*)-5. Prepared from (*R*)-**4** as described for the racemate: $[\alpha]_D^{25} = +17.3$ (*c* 1, $CHCl_3$); mp and ^{1}H NMR identical to that of the racemate.

Thermal analyses. For DSC analyses, samples of 2–5 mg were run in crimped aluminium pans. The enantiomer mixtures with different molar ratios were prepared by mixing (*R*)-**1**, (*R*)-**3**, (*S*)-**4** and (*R*)-**5** with increasing quantities of the respective racemates. All the analyses were performed with a heating rate of 5°C min^{-1} excepting those of the (*R*)-**1**/(*S*)-**1** system (2°C min^{-1}) and of the (*R*)-**4**/(*S*)-**4** system (1°C min^{-1}).

Acknowledgements

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

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