Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 1038–1041

Resolution of 2-substituted 1,4-benzodioxanes by entrainment

Cristiano Bolchi,* Marco Pallavicini, Laura Fumagalli, Chiara Rusconi, Matteo Binda and Ermanno Valoti

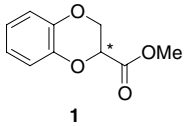
Istituto di Chimica Farmaceutica e Tossicologica, Università di Milano, viale Abruzzi 42, I-20131 Milano, Italy

Received 5 April 2007; accepted 24 April 2007
Available online 1 June 2007

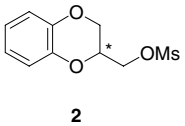
Abstract—The methyl ester of 1,4-benzodioxane-2-carboxylic acid **1** and the mesylate of 2-hydroxymethyl-1,4-benzodioxane **2** are synthetic intermediates whose enantiomers can be advantageously used to prepare a number of enantiopure 2-substituted 1,4-benzodioxanes from readily accessible (±)-1,4-benzodioxane-2-carboxilic acid. We have previously demonstrated the conglomerate nature of the enantiomeric systems of **1** and **2**. Herein, we report the resolution of their racemates by preferential crystallization according to an entrainment procedure. In particular, the entrainment resolution of **1** showed good efficiency, which makes the present method a competitive alternative to the classical resolutions of 1,4-benzodioxane-2-carboxylic acid with dehydroabietylamine and para-substituted 1-phenylethylamines that we have recently reported.

1. Introduction

The chiral 2-substituted 1,4-benzodioxane system is a recurrent substructure in therapeutic agents while the absolute configuration of its stereogenic C_2 often strongly influences the biological activity of molecules containing such a system. This is the main reason why a number of methods have been developed over the last 30 years for the preparation of enantiopure 1,4-benzodioxanes bearing, at the 2-position, substituents easily susceptible to further synthetic transformations, such as carboxyl, alkoxycarbonyl, vinyl or suitably functionalized methyl. These methods are based on resolution of the respective racemates, catalyzed by enzymes[1,2] or accomplished after conversion into diastereomeric mixtures,[3,4] or on syntheses, which utilize asymmetric catalysts or start from non-racemic precursors belonging to the 'chiral pool', such as glycerol or glycidol derivatives.[5–8] The most recent examples, reported after 2000, are the palladium-catalyzed asymmetric cyclization of benzene-1,2-diol with allylic biscarbonates,[9] the palladium-catalyzed intramolecular cyclization of non-racemic 1-(2-bromophenyl)glycerol[10] and the enzymatic resolutions of 1,4-benzodioxane-2-carboxylic acid,[11] its ethyl ester[12] and 2-hydroxymethyl-1,4-benzodioxane.[13] In 2003, we developed some efficient resolution methods for 1,4-benzodioxane-2-carboxylic acid with (+)-dehydroabietylamine, giving access to both enantiopure (*R*)- and (*S*)-acids.[14] Two years later, we reported two new resolution procedures, which were more efficient, of the same acid using 1-(*p*-nitrophenyl)ethylamine and 1-(*p*-methylphenyl)ethylamine.[15] Over the course of our studies on the resolution with (+)-dehydroabietylamine, we were able to demonstrate by DSC and IR analyses that 1,4-benzodioxane-2-carboxylic acid and 2-hydroxymethyl-1,4-benzodioxane are racemic compounds, whereas the respective methyl ester **1** and mesylate **2** form conglomerates.[14]



1



2

On the basis of this latter observation, and of our previous successful experiences in resolving conglomerates[16–18] by entrainment, we planned to apply this resolution method to **1** and **2**. In fact, we consider that preferential crystallization represents, among the stereotechnologies, an additional option, which is not as familiar to researchers, since conglomerates are relatively rare, and neglected, because the process needs optimization and careful control of conditions. This notwithstanding, the fact that chiral auxiliaries are not required makes such a procedure attractive and really advantageous. Here, we report the

* Corresponding author. Tel.: +39 02 50317553; fax: +39 02 50317565; e-mail: cristiano.bolchi@unimi.it

0957-4166/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2007.04.026

entrainment resolution of **1** and **2**, supported by solubility characterization and enantiomeric excess analysis of the two substrates. The results are compared with those of our previous classical resolutions via diastereomeric salts of 1,4-benzodioxane-2-carboxylic acid.

2. Results and discussion

We prepared (±)-**1** and small quantities of its enantiomers according to previously reported methods.[14] Solubility tests of (±)-**1** in various solvents indicated 2-propanol as a good candidate for the preferential crystallization by entrainment considering its reasonable dissolving ability for (±)-**1** (51 mg/mL) at room temperature (21 °C). Before performing the crystallization experiments, we determined the ternary solubility phase diagram for the system (*S*)-(−)-**1**/(*R*)-(+)-**1**/2-propanol at 21 °C. The triangular diagram was constructed using values of 6.12% (51 mg/mL) and 2.67% (21.5 mg/mL), namely, the solubilities expressed as weight/weight percentages, which we had previously measured for (±)-**1** and (*S*)-(−)-**1** in 2-propanol at 21 °C, respectively (see Fig. 1).

The slightly higher than 2 ratio (α) of racemate solubility to enantiomer solubility is typical for conglomerates, whose molecules are not dissociable in solution as is the case for those of **1**.[19] As can be seen from Figure 1, such an α value results in an unsaturation area, which is not represented by a parallelogram, that is a rhomb (α = 2), but by a quadrilateral, where the solubility curve is made up of two segments (the red lines) not parallel to the sides of the triangle, and intersecting to form a <60° angle. In this triangular phase diagram, we defined the region in which the resolution by entrainment is favourable; in other words, the more suitable conditions of supersaturation for an efficient resolution by preferential crystallization (see Fig. 2). A 13 wt % of (±)-**1** [117 mg of (±)-**1** per millilitre of 2-propanol, that is, more than twice its solubility, which is 51 mg/mL] was empirically established as a concentration corresponding to a sufficiently high, but nevertheless even metastable supersaturation, since without seeding, no crystallization took place in a solution with such a concentration during several hours at room temperature. The area of the ternary diagram useful for entrainment resulting from this limit of metastable saturation is a parallelogram (see Fig. 2) whose sides are formed by the prolongations of the two segments of the solubility curve and by the respective parallel lines intersecting at the point corresponding to

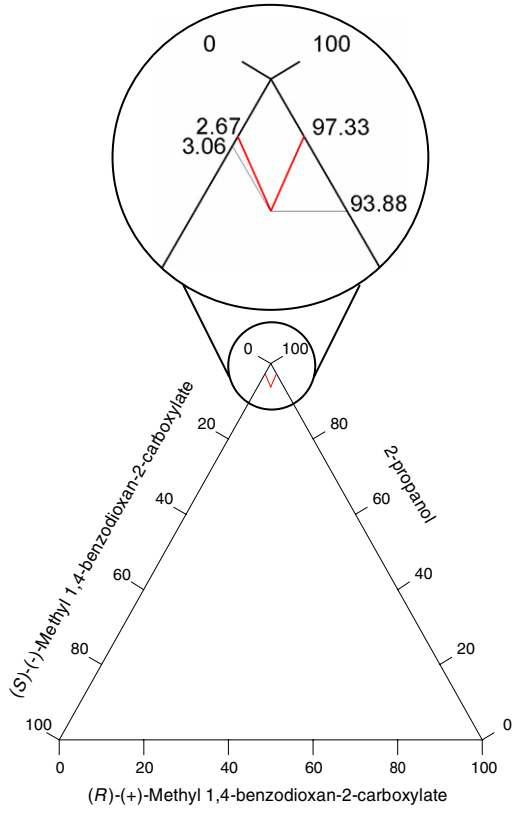
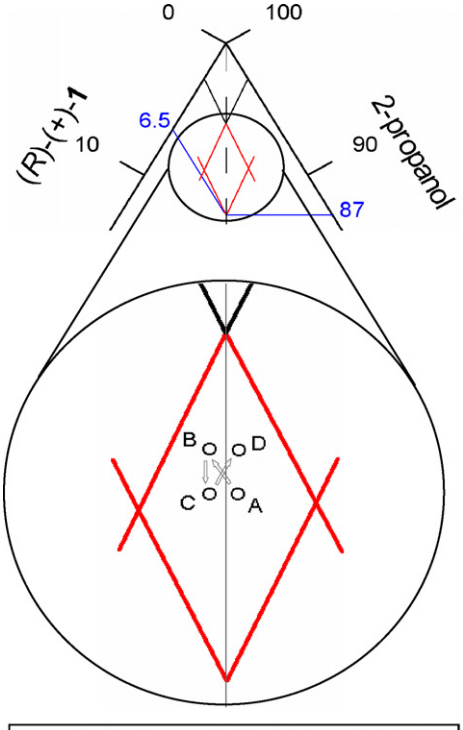


Figure 1. Solubility diagram of **1** in 2-propanol at 21 °C. The concentrations of the components are expressed as weight percentages. The magnified upper part of the diagram shows the composition of the saturated solution of racemate [point E: 93.88% 2-propanol and 3.06% × 2 (±)-**1**] and of single enantiomer [97.33% 2-propanol and 2.67% (*S*)-**1** or (*R*)-**1**].



	% (*S*)-(-)-**1**	% (*R*)-(+)-**1**	% 2-PrOH
A	4.84	4.46	90.70
B	3.95	4.46	91.59
C	4.40	4.90	90.70
D	4.41	4.02	91.57

Figure 2. Area (red quadrilateral) of the solubility diagram of (±)-**1** usable for the entrainment and, in the magnified part, the third cycle of resolution of (±)-**1** (see Table 1). A and C are the ternary compositions of the supersaturated solutions of (±)-**1**, (*S*) and (*R*)-enriched, respectively, where the crystallization takes place; B and D those of the mother liquors remaining from the crystallizations of (*S*)-(−)- and (*R*)-(+)-**1**, respectively.

13% of (±)-**1** [ternary composition: 87% 2-propanol, 6.5% (*S*)-(−)-**1**, 6.5% (*R*)-(+)-**1**].[20] Within this area, we drew five consecutive crystallization cycles. Figure 2 shows a clear view of the ternary compositions (points A–D) assumed by the system over the course of the third cycle.

In the first cycle, (±)-**1** (4 g), enriched with a slight excess of (*S*)-(−)-**1** (0.2 g), was dissolved in 2-propanol (40.95 g), (ternary composition almost identical to the starting composition A of the third cycle, shown in Fig. 2) and slowly cooled to 25 °C while stirring. The resulting supersaturated solution was seeded with crystals of (*S*)-(−)-**1**, cooled further to 21 °C and, after 10 min, filtered to isolate a laevorotatory precipitate, containing an excess of (*S*)-(−)-**1**, which was almost twice the initial (*S*)-enrichment. The filtrated mother liquors, now having a composition similar to B but with the specific rotation changed to a positive value because of the (*R*)-enrichment, were added with (±)-**1** to restore the initial supersaturation (composition ≈ C) and the procedure was repeated for the (*R*)-enantiomer. Again, we isolated a crystalline, but now, destrorotatory precipitate containing an almost double excess of (*R*)-(+)-**1** to the initial (*S*)-enrichment, from mother liquors, which had now assumed a composition similar to D. As shown in Table 1, two or a little more than two times the amount of the initial excess of the enantiomerically pure compound was separated for each of the subsequent eight crystallizations; after five cycles, we obtained 2.3 g of (*R*)-(+)-**1** with 92.2% enantiomeric excess and 3.1 g of (*S*)-(−)-**1** with 68.3% enantiomeric excess. Finally, these two quantities were recrystallized from 2-propanol to yield about 2 g of each enantiomer, 10 times the amount of the initial investment in (*S*)-(−)-**1**, with >99% enantiomeric excess. All the enantiomeric compositions were determined by HPLC on chiral stationary phase according to our previously reported method.[14]

Prompted by the successful resolution of (±)-**1** by preferential crystallization, we considered mesyloxymethylbenzodioxane **2**, the second conglomerate occurring in the 2-substituted benzodioxane synthetic sequence 'carboxylic acid–methyl ester–alcohol–mesylate', where racemic compounds and conglomerates are in alternate succession.[14] The racemate and small quantities of the two enantiomers were synthesized from racemic and enantiopure **1**, respectively, as previously described.[14] Solubility tests indicated ethanol as the most suitable solvent for the entrainment procedure due to its moderate ability at dissolving both (±)-**2** (56.3 mg/mL at 30 °C; 31.5 mg/mL at 21 °C) and its enantiomers (22.0 mg/mL at 30 °C; 14.5 mg/mL at 21 °C). Again, as expected since **2** is not a dissociable compound, little higher than 2 ratios of racemate solubility to enantiomer solubility were found. An analytical method using chiral HPLC (Chiralcel OJ column; water saturated hexane/ethanol 60:40; 0.8 mL/min; (*S*)-**2**: $k' = 5.13$; (*R*)-**2**: $k' = 4.63$) was developed for the enantiomeric excess determination before performing the resolution experiments. These succeeded under the following conditions: (a) solution of (±)-**2** (3 g) and (*R*)-(−)-**2** (0.15 g) in ethanol (25.6 g) at 40 °C; (b) cooling to 35 °C and seeding with crystals of (*R*)-(−)-**2** at this temperature, (c) further cooling to 30 °C while stirring and, after 15 min at this temperature, recovery of the precipitate by filtration. Such a precipitate (0.36 g) was laevorotatory and showed a 75.0% enantiomeric excess, thus containing an excess of (*R*)-(−)-**2** (0.27 g), which was almost twice the initial (*R*)-enrichment. The successive specular procedure, accomplished by seeding the filtrate with crystals of (*S*)-(+)-**2** after restoring the initial supersaturation by addition of (±)-**2** (0.36 g), afforded a destrorotatory precipitate (0.38 g) with a 54.0% enantiomeric excess. These results demonstrated that (±)-**2** can be resolved by entrainment and the process carried out in a cyclic manner.

3. Conclusion

The resolution of (±)-**1** was accomplished by preferential crystallization applying an entrainment procedure under conditions optimized and validated through five consecutive crystallization cycles, which showed an 18–25% efficiency (chemical yield, relative to half of the

Table 1. Resolution of (±)-**1** by entrainment

Cycle	**1** Added (mg)		Recovery of resolved **1** (mg)		ee of recovered precipitate[a]
	(±)	(−)	(−)	(+)	
1	4000	200	890		41.3
	890			405	89.3
2	405		760		52.8
	760			430	88.9
3	430		440		92.2
	440			430	93.6
4	430		470		94.7
	470			530	93.2
5	530		510		93.4
	510			480	86.8
Total	8865	200	3070[b] (68.3% ee[a])	2275[c] (92.2% ee[a])	
Residue[d]	3650				

[a] Enantiomeric excess determined by HPLC (Chiralcel OD column; hexane/2-propanol 85:15; 1.2 mL/min; (*R*)-**1**: $k' = 3.17$; (*S*)-**1**: $k' = 2.19$).
[b] 2060 mg {$[\alpha]_D^{25} = -57$ (*c* 1, $CHCl_3$); ee >99%} after recrystallization from 2-propanol.
[c] 2050 mg {$[\alpha]_D^{25} = +57$ (*c* 1, $CHCl_3$); ee >99%} after recrystallization from 2-propanol.
[d] Recovered, with 5.4% ee [(*S*) enriched], by concentration of the mother liquors remaining from the last crystallization.

starting racemate, of each crystallization × enantiomeric excess), an excellent value compared to the other known resolutions of non-dissociable racemates by entrainment. The same technique was employed to resolve (±)-**2**, completing only one crystallization cycle. In this latter case, the efficiency was slightly lower, but the conditions should be susceptible to optimization. This notwithstanding, the experiments conducted on (±)-**2** demonstrated that the initial enantiomeric enrichment, which is the driving force of the entrainment, was preserved after the whole crystallization cycle and thus the cyclic alternate crystallizations of the two enantiomers, could in theory, be repeated an unlimited number of times.

Our previous methods of resolution of benzodioxane-2-carboxylic acid with dehydroabietylamine showed efficiencies ranging between 54% and 75%[14] while those with para-substituted phenylethylamines showed values between 79% and 92%.[15] It is evident that at least three crystallization cycles of (±)-**1** by entrainment are necessary to achieve similar resolution efficiencies. However, in spite of such a number of crystallizations, the entrainment resolution of the methyl ester could still be convenient in comparison with the classical resolutions of the carboxylic acid, considering that the work-up is extremely simple and the chiral auxiliaries are not needed in preferential crystallization, whose most interesting feature remains in the fact that the enantiomers themselves are their own resolving agents.

Acknowledgment

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

References

1. Ennis, M. D.; Old, D. W. *Tetrahedron Lett.* **1992**, *33*, 6283.
2. Antus, S.; Gottsegen, A.; Kajtar, J.; Kovacs, T.; Toth, T. S.; Wagner, H. . *Tetrahedron: Asymmetry* **1993**, *4*, 339.
3. Khouili, M.; Guillaumet, G.; Coudert, G. *Farmaco* **1996**, *51*, 185.
4. Bolognesi, M. L.; Budriesi, R.; Cavalli, A.; Chiarini, A.; Gotti, R.; Leonardi, A.; Minarini, A.; Poggesi, E.; Recanatini, M.; Rosini, M.; Tumiatti, V.; Melchiorre, C. *J. Med. Chem.* **1999**, *42*, 4214.
5. Nelson, W. L.; Wennerstrom, J. E. *J. Med. Chem.* **1977**, *20*, 880.
6. Villa, L.; Valoti, E.; Villa, A. M.; Pallavicini, M.; Ferri, V.; Iuliano, E.; Brunello, N. *Farmaco* **1994**, *49*, 587.
7. Valoti, E.; Pallavicini, M.; Villa, L.; Pezzetta, D. *J. Org. Chem.* **2001**, *66*, 1018.
8. Delgado, A.; Leclerc, G.; Cinta Lobato, M.; Mauleon, D. *Tetrahedron Lett.* **1988**, *29*, 3671.
9. Massacret, M.; Lakhmiri, R.; Lhoste, P.; Nguefack, C.; Ben Abdelouahab, F. B.; Fadel, R.; Sinou, D. *Tetrahedron: Asymmetry* **2000**, *11*, 3561.
10. Kuwabe, S.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202.
11. Kasture, S. M.; Varma, R.; Kalkote, U. R.; Nene, S.; Kulkarni, B. D. *Biochem. Eng. J.* **2005**, *27*, 66.
12. Fang, Q. K.; Grover, P.; Han, Z.; McConville, F. X.; Rossi, R. F.; Olsson, D. J.; Kessler, D. W.; Wald, S. A.; Senanayake, C. H. *Tetrahedron: Asymmetry* **2001**, *12*, 2169.
13. Sakai, T.; Hayashi, K.; Yano, F.; Takami, M.; Ino, M.; Korenaga, T.; Ema, T. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1441.
14. Bolchi, C.; Fumagalli, L.; Moroni, B.; Pallavicini, M.; Valoti, E. *Tetrahedron: Asymmetry* **2003**, *14*, 3779.
15. Bolchi, C.; Pallavicini, M.; Fumagalli, L.; Marchini, N.; Moroni, B.; Rusconi, C.; Valoti, E. *Tetrahedron: Asymmetry* **2005**, *16*, 1639.
16. Pallavicini, M.; Bolchi, C.; Di Pumpo, R.; Fumagalli, L.; Moroni, B.; Valoti, E.; Demartin, F. *Tetrahedron: Asymmetry* **2004**, *15*, 1659.
17. Pallavicini, M.; Valoti, E.; Bolchi, C.; Fumagalli, L.; Piccolo, O. EP 6425304.0, 2006.
18. Pallavicini, M.; Bolchi, C.; Fumagalli, L.; Piccolo, O.; Valoti, E. *Tetrahedron: Asymmetry* **2007**, *18*, 906.
19. Jacques, J.; Collet, A.; Wilen, S. *Enantiomers, Racemates and Resolutions*; Wiley: New York, 1981, p 188.
20. For this empirical manner of determining the region, which is useful for the entrainment, see Ref. 19, p 236.