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Resolution of 5-hydroxymethyl-2-oxazolidinone by preferential crystallization[1] and investigations on the nature of the racemates of some 2-oxazolidinone derivatives

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Abstract—After ascertaining its conglomerate nature by DSC and solid-state IR analyses, 5-hydroxymethyl-2-oxazolidinone **1**, whose enantiomers are very important synthons, was efficiently resolved without chiral auxiliaries by preferential crystallization from a supersaturated isopropanolic solution of the racemate, slightly enriched in one enantiomer (3.7% ee). Favourable conditions to the entrainment were defined utilizing the previously constructed ternary phase diagram {(*R*)-**1**, (*S*)-**1**, 2-propanol}. Furthermore, the investigations were extended to other chiral 2-oxazolidinones with a functionalized methyl at the 5- or 4-position finding that 5-tosyloxymethyl-2-oxazolidinone is a racemic compound, whereas just the corresponding mesylate is a conglomerate as the parent alcohol **1**. Interestingly, 4-hydroxymethyl-2-oxazolidinone **4** proved to be a racemic compound in contrast with its positional isomer **1** demonstrating how a relatively fine variation in the molecular structure can unpredictably influence the crystalline nature of the racemate. The X-ray structure determination carried out on (*S*)-(+)-**1**, (±)-**4** and (*R*)-(+)-**4** enlightened the importance of the hydrogen bond in determining different supramolecular assembling in the two homochiral compounds with respect to the racemic one and allowed a correlation with the stability of the crystal to be made.
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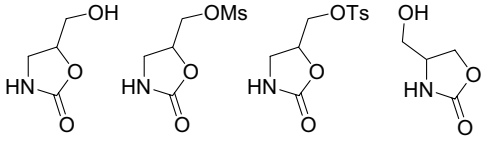
1. Introduction

Homochiral 5-hydroxymethyl-2-oxazolidinone **1** is extensively used to prepare a large number of enantiomerically pure compounds of great biological interest. It can be regarded as a protected 3-amino-1,2-propanediol derivative, which allows, for instance, a variety of functionalized β-aminoalcohols to be synthesized by nucleophilic substitution at the exocyclic carbon, followed by a ring opening.[2,3] Compound **1** is an even more valuable synthon since many novel pharmacological agents are *N*-arylated 2-oxazolidinones bearing a functionalized methyl group at the 5-position. The known antimicrobial linezolid[4] and the antidepressant befloxatone[5] can be cited as examples. For the synthesis of such optically active compounds, the recent methods[6,7] based on the initial coupling of aryl halides with preconstituted oxazolidinones represent an advantageous alternative to the previous ones,[8,9] which defer construction of the oxazolidinone cycle to the last steps of the synthetic pathway. In this context, the O-protected or esterified derivatives of **1**, chiefly its (*R*)-enantiomer, come to assume the role of key intermediates.



1 **2** **3** **4**

It is therefore no wonder that several preparative methods for enantiomerically pure **1** have been developed over the last 20 years, ranging from the enzymatic resolution of racemic esters of **1**[10] to the carbonylation of (*R*)- and (*S*)-3-amino-1,2-propanediol,[11–13] in turn obtained by classical resolution of the racemate[14] or from chiral pool substances.[13] Alternative accesses have

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been offered by the chromatographic separation of diastereomeric pairs of *N*-(α-methylbenzyl)-5-iodomethyl-2-oxazolidinone obtained from (*R*)- or (*S*)-1-phenylethylamine[2] and, more recently, by the Hofmann rearrangement of cyclic boronic acid esters of enantiomerically pure 3,4-dihydroxybutyramide.[15] However, each of these methods has its limitations such as a large number of steps, the poor availability of the enantiomerically pure starting material or laborious separation procedures.

Over the course of our research into new methods for preparing enantiopure protected C_3 synthons, such as glycerol carbonate and its isostere **1**, we noticed that a 71–72 °C melting point had been reported for the racemate of **1**,[11] while the corresponding value for the single enantiomer ranged from 85 to 90 °C according to authors.[10,13,15] The gap is not so wide as to indicate that **1** crystallizes as a conglomerate and to let us hope for the resolution of its racemate by a straightforward procedure of direct crystallization. Nevertheless, we supposed that the low melting point of the racemate could have been overestimated and, consequently, its difference from that of the enantiomer undervalued. On the basis of this hypothesis, we decided to synthesize (±)-**1**, (*S*)-(+)-**1** and (*R*)-(−)-**1** in order to analyze their physical properties. Herein we report the results of these analyses, which clearly show that **1** is a conglomerate, and the successful resolution of (±)-**1** by preferential crystallization according to the entrainment procedure.[16] Furthermore, it seemed pertinent to extend the investigations on the racemate type to other 2-oxazolidinones bearing a functionalized methyl group at the 5-position, such as the important synthons mesylate **2** and tosylate **3**, and to the 4-substituted isomer of **1**, 4-hydroxymethyl-2-oxazolidinone **4**. The results of such supplementary researches are also reported herein and, in particular, the nature of racemic compound of **4** is compared to that of conglomerate of **1** in the light of respective X-ray crystallographic data.

2. Results and discussion

We synthesized (±)-**1** from 3-amino-1,2-propanediol by treatment with diethylcarbonate according to Danielmeier and Steckhan.[13] From the enantiomers of the aminodiol, we analogously prepared (*S*)-(+)-**1** and (*R*)-(−)-**1**, which were crystallized from 2-propanol after chromatographic purification. The melting points of the racemic oxazolidinone and its enantiomers were accurately determined by DSC under identical conditions and it was found that (±)-**1** melts 36 °C lower than (*S*)-(+)-**1** and (*R*)-(−)-**1**. Furthermore, IR spectra of (±)-**1** and (*S*)-(+)-**1** in the crystalline phase proved perfectly superimposable. These data demonstrated that **1** is a member of that minor category of enantiomer systems (5–10% of the totality of chiral organic solids), which are mechanical mixtures or conglomerates of crystals, each of which being made up of homochiral molecules. Consistently with this evidence, the solubility of the racemate was approximately twice that of the constituent enantiomers. In 2-propanol, for instance, we found a 2.6 ratio α_χ between the solubilities, expressed as mole fraction, of (±)-**1** and of (*S*)-(+)-**1**, respectively. Such a value, higher than 2, is typical for conglomerates,[17] whose molecules are not dissociable in solution as it is the case for those of **1**.

On the basis of these results, we decided to try the resolution by direct crystallization according to the entrainment procedure, which involves the preferential precipitation of one enantiomer from a supersaturated solution of the racemate enriched with a slight excess of the same enantiomer. Before performing the crystallization experiments, we determined the binary melting point phase diagram for the enantiomer system (*S*)-(+)-**1**/(*R*)-(−)-**1** and the ternary solubility phase diagram for the system (*S*)-(+)-**1**/(*R*)-(−)-**1**/2-propanol at 22 °C. This solvent was selected as a good candidate for the preferential crystallization considering its reasonable dissolving ability for both (±)-**1** (8.8 mL/g) and (*S*)-(+)-**1** (23.6 mL/g).

The DSC curves for (±)-**1**, (*S*)-(+)-**1** and (*R*)-(−)-**1** showed one peak at 56.8, 93.0 and 93.7 °C, respectively, while two distinct peaks characterized the melting profiles of three differently proportioned (±)-**1**/(*R*)-(−)-**1** mixtures, the first, between 56 and 57 °C, representing the fusion of the eutectic, that is the 1/1 mixture of the two enantiomers, while the second, at temperatures increasing with the *R* enrichment, representing the excess of (*R*)-(−)-**1**. The resultant experimental binary diagram, depicted in Figure 1 for mole fractions of (*R*)-(−)-**1** ranging from 0.5 to 1, is typical of a conglomerate system. As can be seen in the same figure, the experimental values acceptably fit with the theoretical ones (solid curve) calculated on the basis of the melting point of (*R*)-(−)-**1** and of its heat of fusion (166.1 J/g) by the Schröder–van Laar equation.

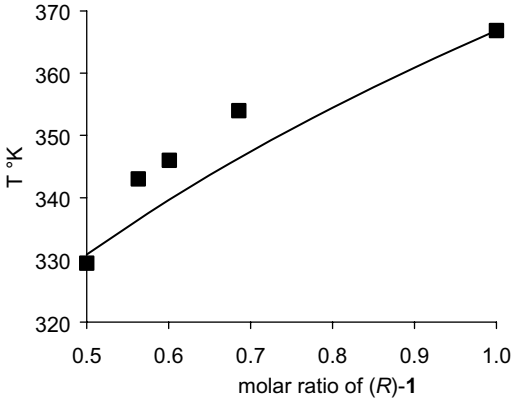


Figure 1. Binary melting-point phase diagram for the enantiomeric system (*R*)-**1**/(*S*)-**1**. The solid curve represents the values calculated on the basis of the Schröder–van Laar equation.

The triangular phase diagram (*S*)-(+)-**1**/(*R*)-(−)-**1**/2-propanol was constructed using values of 0.069 and 0.027, that is the solubilities expressed as mole fractions, which we had previously measured for (±)-**1** and (*S*)-(+)-

1 in 2-propanol at 22 °C, respectively (see Fig. 2). At this temperature, the mole fraction of 2-propanol for a saturated solution of (±)-**1** is 0.931, while it is 0.973 for a saturated solution of (*S*)-(+)-**1**. The resultant solubility curve was constituted by two segments (the red lines in Figure 2) not parallel to the sides of the triangle, which intersect to form a <60° angle.

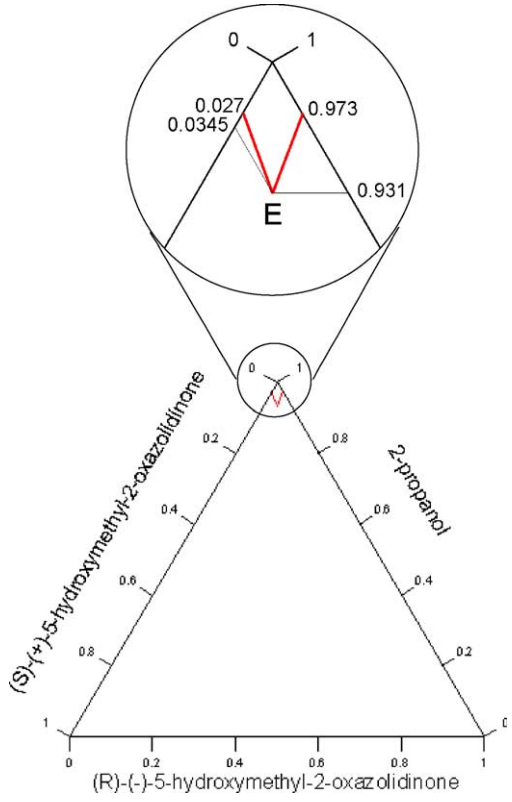
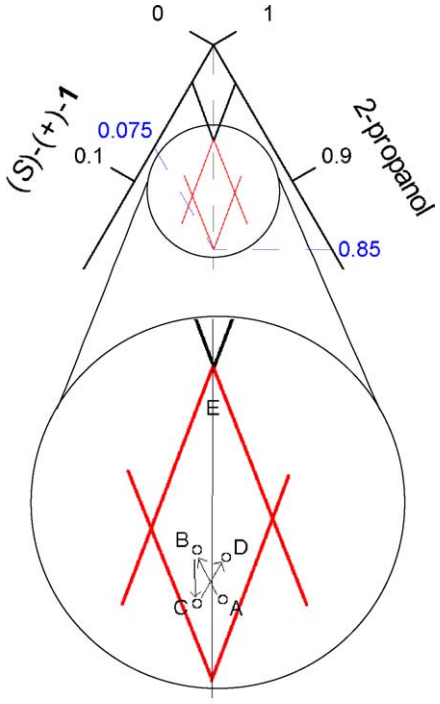


Figure 2. Solubility diagram of **1** in 2-propanol at 22 °C. The concentrations of the components are expressed as mole fractions. The magnified upper part of the diagram shows the composition of the saturated solution of racemate (point E: $0.931\chi_{2\text{-propanol}}$ and $(0.0345 \times 2)\chi_{(\pm)\text{-}\mathbf{1}}$) and of single enantiomer ($0.973\chi_{2\text{-propanol}}$ and $0.027\chi_{(S)\text{-}\mathbf{1}}$).

In this triangular phase diagram we defined the region in which resolution by entrainment is favourable; in other words, the more suitable conditions of supersaturation for an efficient resolution by preferential crystallization. A 0.15 mole fraction of (±)-**1** [0.27 g of (±)-**1** per millilitre of 2-propanol, i.e., more than twice its solubility, which is 0.11 g/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 some days at room temperature. The area of the ternary diagram useful for the entrainment resulting from such a limit of metastable supersaturation is a parallelogram (see Fig. 3) 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 corrresponding to 0.15 mole fraction of (±)-**1** (ternary composition: $0.85\chi_{2\text{-propanol}} - 0.075\chi_{(S)\text{-}\mathbf{1}} - 0.075\chi_{(R)\text{-}\mathbf{1}}$).[18] Within this area, we drew five consecutive crystallization cycles. Figure 3 gives a bird's eye view of the ternary compositions (points A, B, C and D) assumed by the system over the course of the first cycle, which was then reproduced by the successive four.



	χ (*R*)-(-)-1	χ (*S*)-(+)-**1**	χ 2-PrOH
A	0,0671	0,0626	0,8703
B	0,0549	0,0621	0,8830
C	0,0618	0,0689	0,8693
D	0,0624	0,0564	0,8812

Figure 3. Area (red quadrilateral) of the solubility diagram of (±)-**1** usable for the entrainment and, in the magnified part, the first cycle of resolution of (±)-**1**. A and C are the ternary compositions of the supersaturated solutions of (±)-**1**, *R* and *S* enriched, respectively, where the crystallization takes place; B and D those of mother liquors remaining from the crystallizations of (*R*)-(−)- and (*S*)-(+)-**1**, respectively.

In the first cycle, a highly supersaturated solution of (±)-**1** (4.4 g in 20 mL of 2-propanol), enriched with a slight excess of (*R*)-(−)-**1** (0.17 g) (see ternary composition A in Fig. 3), was seeded with crystals of this latter enantiomer, vigorously stirred for 1 h and then allowed to stand over night at room temperature. After this time, we only decanted the mother liquors isolating a precipitate of the laevorotatory enantiomer, which was, after drying, about the triple of the initial enrichment and had a 77% optical purity. Concomitantly, the sign of the optical rotation of the mother liquors, now having composition B, had changed to positive. This *S* enriched solution was added with (±)-**1** to restore the initial supersaturation (composition C) and the procedure repeated for the (*S*)-enantiomer. Again, a crystalline, but now destrorotatory precipitate was isolated in analogous yield with 94% optical purity from mother liquors, which

had meantime assumed composition D. For each crystallization, two or three times the amount of the initial excess of the enantiomerically pure compound was separated; after five cycles, for both enantio-mers we obtained a 2.6 g amount with near 90% optical purity (see Table 1). Finally, these two quantities were recrystallized from 2-propanol yielding about 2 g of each enantiomer, more than 11 times the amount of the initial investment in (*R*)-(−)-**1**, with >99.6% optical purity.

Prompted by the successful resolution of (±)-**1** by preferential crystallization, we successively considered other 2-oxazolidinones bearing a functionalized methyl group at the 5-position. In the case of the 5-halomethyl-2-oxazolidinones, the literature data indicated that the single enantiomers melt at the same temperature or at lower temperatures than the respective racemates, thus excluding the possibility of forming conglomerates for such compounds.[13] For 5-mesyloxymethyl-2-oxazolidinone **2**, the melting point of the single enantiomer (118–120 °C) was reported in the literature,[13] but not that of the racemate; vice versa, for 5-tosyloxymethyl-2-oxazolidinone **3**, the melting point of the racemate (98–99 °C),[11] but not that of the single enantiomer. Therefore, we prepared (±)-**2** and (±)-**3** from (±)-**1** and (*R*)-(−)-**2** and (*S*)-(+)-**3** from (*R*)-(−)- and (*S*)-(+)-**1**, respectively. The DSC and IR analyses of the tosylate allowed its nature of racemic compound to be ascertained on the basis of the melting point of (*S*)-(+)-**3** exceeding that of (±)-**3** by only 17 °C (118.5 vs 101.2 °C) and of the respective solid-state spectra, which are not superimposable. On the contrary, the more relevant difference (30 °C) between the melting point of (*R*)-(−)-**2** (117.7 °C) and that of (±)-**2** (87.9 °C) and the identity of the respective IR spectra in the crystalline phase demonstrated that the mesylate is a conglomerate like its parent alcohol **1** implying the resolvability of the racemic mixture by direct crystallization. Consistently with these data, we determined a 2.35 ratio α_χ between the solubilities, expressed as a mole fraction, of (±)-**2** and of (*R*)-(−)-**2**, respectively, in methanol.

Finally, we took into account 4-hydroxymethyl-2-oxazolidinone **4**, another important chiral derivative of 2-oxazolidinone, in order to verify whether it formed a conglomerate as its 5-hydroxymethyl substituted isomer **1**. Similarly to the case of this latter, the nature of the enantiomeric system has been never examined and the physical data available from the literature [96–99 and 77–81 °C melting point for (*R*)-(+)-**4**[19] and (±)-**4**,[20] respectively] were not informative. Therefore, we prepared (*R*)-(+)-**4** and (±)-**4** from (*S*)-serine methyl ester hydrochloride and its racemate, respectively, according to literature methods:[19,21] reaction with triphosgene gave (*S*)-(−)- and (±)-4-methoxycarbonyloxazolidin-2-one, which were successively reduced to the corresponding hydroxymethyl derivatives by treatment with sodium borohydride. On the contrary, an alternative synthetic route, involving an initial reaction of glycidol with benzyl isocyanate to give *N*-benzyl-4-hydroxymethyl-2-oxazolidinone,[22] was left due to the difficulty in debenzylating such an intermediate. DSC analyses showed that (*R*)-(+)-**4** melts at 103.4 °C, while (±)-**4** at 85.6 °C; the solid-state IR spectra of the single enantiomer is not superimposable to that of the racemate. On the basis of these results, we concluded that **4** is not a conglomerate like **1**, but a racemic compound. This means that the shift of the hydroxymethyl residue from the 5 to the 4 position of the 2-oxazolidinone ring hinders, in the case of the racemate, the transfer of chirality from molecular to supramolecular level. It was presumable that such a dramatic change, due to simple positional isomerism, resulted from a variation of the hydrogen-bonded molecular assembly, considering the hydrogen bond acceptor and donor nature of both the hydroxymethyl group and the cyclic carbamate. The X-ray analysis of the solid-state structures of (*S*)-(+)-**1**, (*R*)-(+)-**4** and (±)-**4** confirmed this hypothesis revealing that the hydrogen bond pattern of the racemic compound substantially

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

Cycle no	**1** added (mg)		Recovery of resolved **1** (mg)		α_D^{30} of the mother liquors
	(±)	(−)	(−)[a]	(+)[a]	
1	4400	170	524 (77.2%)		+0.397
	550			480 (93.7%)	−0.485
2	500		480 (>99.6%)		+0.381
	480			500 (98.0%)	−0.427
3	500		610 (87.1%)		+0.507
	610			805 (70.5%)	−0.331
4	810		480 (92.8%)		+0.391
	480			460 (92.8%)	−0.259
5	460		510 (77.5%)		+0.360
	510			370 (>99.6%)	−0.280
Total	9300	170	2604[b]	2615[c]	
Residue (mg)[d]	4140 (*R* enriched; 4.2% ee)				

[a] Between brackets, the optical purity resulting from the percent ratio of the observed specific rotation to the specific rotation $\{[\alpha]_D^{25} = +30.4$, (*c* 2, isopropanol)} of pure (*S*)-**1** (>99.6% ee).

[b] 1905 mg (o.p. > 99.6%) after recrystallization from 2-propanol.

[c] 2037 mg (o.p. > 99.6%) after recrystallization from 2-propanol.

[d] Recovered by concentration of the mother liquors remaining from the last crystallization.

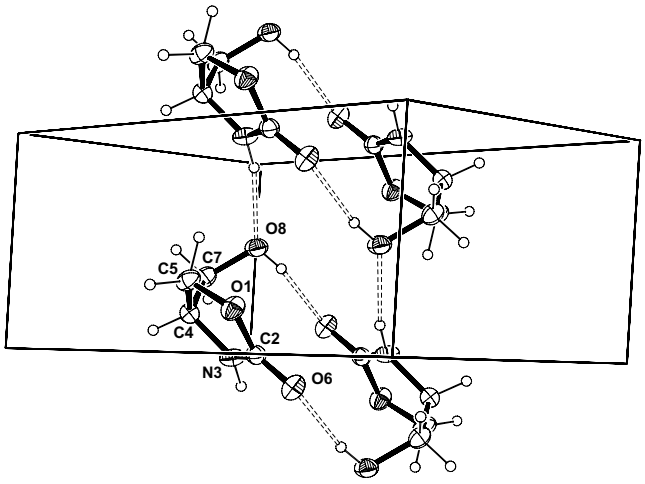


Figure 4. ORTEP partial drawing of the crystal packing for (±)-**4**, showing the hydrogen bond pattern.

differs from those of the two homochiral ones, which are instead quite similar.

A view of a significant portion of the crystal packing of (±)-**4** is reported in Figure 4. Here, pairs of enantiomeric molecules, located about crystallographic inversion centres, are held together via hydrogen bonds between the donor OH(8) and the acceptor carbonylic O(6) with a O(6)···O(8) interaction of 2.766(1) Å, and a O(6)···H(8)–O(8) angle of 163.9(2)°. These dimeric units are stacked to form chains extending along [1 0 0] because they interact through a further hydrogen bond between the O(8) hydroxyl atom, which acts, in this case, as an acceptor, and the donor N(3) atom. The O(8)···N(3) interaction is 2.882(1) Å, while the O(8)···H(3)–N(3) angle is 162.15(2)°. As a result, each molecule is hydrogen bonded to *three* other molecules. The whole crystal is therefore derived by the assembling of chains among which only weak van der Waals interactions occur.

In each of the homochiral (*S*)-(+)-**1** and (*R*)-(+)-**4** compounds, the hydrogen bond pattern gives rise to a tridimensional assemblage of molecules, extending all over the crystal, where each molecule is hydrogen bonded to four neighbouring molecules (see Figs. 5 and 6). In all cases OH(8) acts as donor towards O(6) and acceptor from N(3). The O(8)···O(6) and O(8)···N(3) interactions are 2.712(3) and 2.886(4) Å for (*S*)-(+)-**1**, and 2.735(1) and 2.871(1) Å for (*R*)-(+)-**4**. The different pattern of the hydrogen bonds, tridimensionally extended in (*S*)-(+)-**1** and (*R*)-(+)-**4**, but not in (±)-**4**, is consistent with the higher stability of the homochiral crystals with respect to the racemic compound, as indicated by the respective melting points.

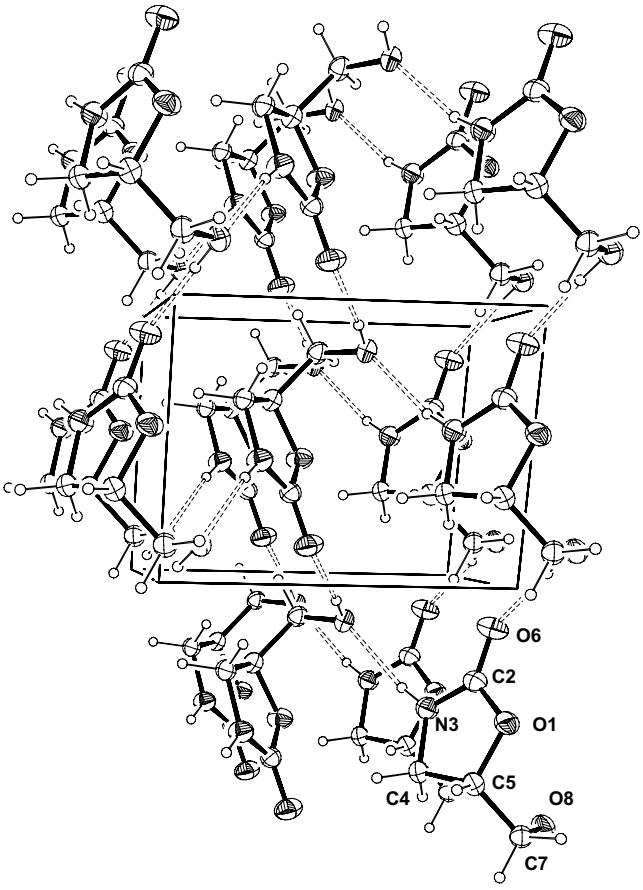


Figure 5. ORTEP partial drawing of the crystal packing for (*S*)-(+)-**1**, showing the hydrogen bond pattern.

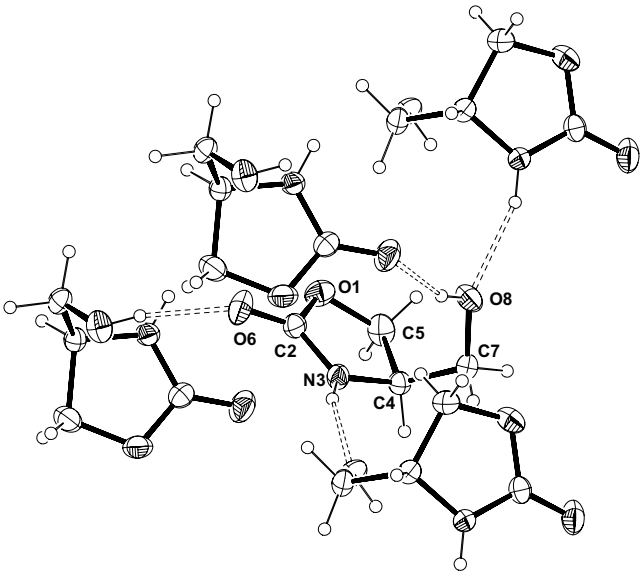


Figure 6. ORTEP drawing of a molecule with its neighbours for (*R*)-(+)-**4**.

3. Conclusion

To the best of our knowledge, the conglomerate nature of the enantiomeric mixtures of **1** and of its mesylate **2** has been first ascertained by us. As proof of the relative rarity of this type of enantiomeric system, 5-chloromethyl-, 5-bromomethyl-, 5-iodomethyl-2-oxazolid-

inone and 2-oxazolidinones **3** and **4**, though structurally close to **1** and **2**, do not form conglomerates. For the halomethyl derivatives, this is unambiguously indicated by the literature data, while, in the case of **3** and **4**, has been disclosed by the present investigations, which have demonstrated their nature of racemic compounds.

On the basis of this evidence and considering the intrinsic value of the enantiomers of **1** as synthetic intermediates, the resolution of (±)-**1** by preferential crystallization according to the entrainment procedure was tried and successfully developed. The main advantages of such a new procedure over those described in the literature (enzymatic or classical resolution and synthesis from homochiral precursors) can be summarized as follows: (i) the only necessary material, in addition to the solvent, is (±)-**1**, which is easily prepared from largely available racemic 3-amino-1,2-propanediol; (ii) chiral auxiliaries are not needed, excepting the minimum initial enantiomeric enrichment; (iii) the procedure is very simple, not implying laborious working up and separations, but only consisting of reiterated crystallizations and removals of the mother liquor. Furthermore, compared to the other known resolutions of nondissociable racemates by entrainment,[23] this shows an excellent efficiency of ca. 20% (chemical yield, relative to half of the starting racemate, of each crystallization × optical purity) and a good productivity of ca. 2.5% (percent ratio of the weight of the precipitate to that of the mother solution).

4. Experimental

4.1. Materials and methods

^{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. IR spectra were recorded with a FT-IR Paragon 1000 PC Perkin–Elmer spectrometer. Melting points were determined by DSC analysis, taking the temperature of the maximum of the peak. The DSC curves were recorded and integrated with the aid of a TA Instruments DSC 2010 apparatus. For DSC analyses, samples of 2–5 mg were run in crimped aluminium pans. The enantiomeric mixtures of (*S*)-(+)-**1** and (*R*)-(−)-**1** with different molar ratios were prepared by mixing (±)-**1** with increasing quantities of (*R*)-(−)-**1**. All the analyses were performed with a heating rate of 1 °C min^{-1}.

(±)-**1**, (*S*)-(+)-**1** and (*R*)-(−)-**1** were prepared from (±)-, (*S*)-(−)- and (*R*)-(+)-3-amino-1,2-propanediol, respectively, by treatment with diethyl carbonate according to Ref. 13. (±)-**1**: mp 56.8 °C; (*S*)-(+)-**1**: mp 93.0 °C; (*R*)-(−)-**1**: mp 93.7 °C. (±)-**2** and (*R*)-(−)-**2** were obtained from (±)-**1** and (*R*)-(−)-**1** by the method described in Ref. 13. (±)-**2**: mp 87.9 °C; (*R*)-(−)-**2**: mp 117.7 °C. (±)-**3** and (*S*)-(+)-**3** were synthesized from (±)-**1** and (*S*)-(+)-**1** following the procedure reported in Ref. 11. (±)-**3**: mp 101.2 °C; (*S*)-(+)-**3**: mp 118.5 °C. For the preparation of (*R*)-(+)-**4** and (±)-**4**, (*S*)-serine methyl ester hydrochloride and its racemate were respectively used as starting materials. The oxazolidinone cycle was formed by treatment with triphosgene as described in Ref. 21; the ester function was then reduced to an alcohol with $NaBH_4$ according to Ref. 19. The only variant was, in the case of (*R*)-(+)-**4**, an additional recrystallization of the reduction product isolated by silica gel chromatography and crystallized from methanol in order to eliminate traces of eutectic (mp 81.7 °C), revealed by the DSC curve and resulting in lower specific optical rotation {+26.2 vs +32.2 $[\alpha]_D^{25}$ (*c* 1, MeOH) of recrystallized (*R*)-(+)-**4**} and melting point [102.4 vs 103.4 °C for recrystallized (*R*)-(+)-**4**]. (±)-**4**: mp 85.6 °C.

4.2. Typical entrainment procedure

The operation was carried out in a three-necked round-bottom flask equipped with a condenser, a thermometer and a magnetic stirrer.

(±)-**1** (4.4 g, 37.6 mmol) was suspended in 15.7 g of 2-propanol together with 0.17 g (1.45 mmol) of (*R*)-(−)-**1**. The stirred suspension was heated at boiling temperature for 5 min to ensure complete dissolution of the solid [possible insoluble particles had been previously removed from (±)-**1** and (*R*)-(−)-**1** by filtration of respective unsatured solutions in 2-propanol on filter paper] and then slowly cooled to 31 °C. Seeds of (*R*)-(−)-**1** (5 mg ca.) were added under stirring. The temperature was let down to 25 °C in 60–90 min ca. after which stirring was stopped. The mixture, which still had the appearance of a clear solution with the previously added seeds settled to bottom, was allowed to stand overnight at 22 °C. During this period, a white precipitate of (*R*)-(−)-**1** was formed, which adhered to the inner side of the flask and could be easily recovered by decanting the mother liquor. After drying under vacuum, such a precipitate amounted to 524 mg: $[\alpha]_D^{20} = -23.5$ (*c* 2, 2-propanol); ^{1}H NMR (DMSO-d_6) δ 3.21 (pseudo t, 1H, C(4)H, $J = 8.0$), 3.39–3.55 (m, 3H, C(4)H and CH_2–OH), 4.49 (m, 1H, C(5)H), 5.05 (t, 1H, OH; $J = 5.7$), 7.38 (br s, 1H, NH). The mother liquor, which showed $\alpha_D^{30} = +0.397$, was diluted with a little 2-propanol so that the initial content of solvent (15.7 g) was exactly restored. (±)-**1** (550 mg) was then added. The suspension was boiled for 5 min and the resultant solution slowly cooled to 31 °C under stirring and seeded with 5 mg of (*S*)-(+)-**1**. Again, the temperature was let down to 25 °C in 60–90 min ca. Stirring was stopped and the clear solution, containing the undissolved crystals used as seeds, allowed to stand overnight at 22 °C. After this period, isolation and drying of the precipitate as above gave (*S*)-(+)-**1** (480 mg) as a white solid: $[\alpha]_D^{20} = +28.5$ (*c* 2, 2-propanol); ^{1}H NMR was identical to that of (*R*)-(−)-**1**. The same cycle of operation was carried out four more times, yielding a total of 2.615 g of (*S*)-(+)-**1** and 2.604 g of (*R*)-(−)-**1** with 88% and 87% optical purity, respectively (see Table 1). These two quantities were recrystallized from 2-propanol yielding 2.037 g of (*S*)-(+)-**1** {mp identical to that of the synthesized sample; $[\alpha]_D^{25} = +30.4$ (*c* 2, isopropanol); $[\alpha]_D^{25} = +38.2$ (*c* 1.85, ethanol); lit.[15] $[\alpha]_D^{25} = +38.4$ (*c* 1.35, ethanol) for >99.9%

ee} and 1.905 g of (*R*)-(−)-**1** (mp identical to that of the synthesized sample; $[\alpha]_D^{25} = -30.4$ (*c* 2, isopropanol); $[\alpha]_D^{25} = -38.3$ (*c* 1.85, ethanol).

The mother liquor of the last crystallization had $\alpha_D^{30} = -0.280$ and, after concentration, afforded 4.14 g of *R* enriched **1** with ca. 4% enantiomeric excess. These data were consistent with the amount initially submitted to resolution (4.57 g) and its optical purity (3.7%).

4.3. X-ray structure determination

Crystal data for (*S*)-(+)-**1**: $C_4H_7NO_3$, f.w. 117.11, monoclinic, space group $P2_1$ (no 4), $a = 5.566(1)$, $b = 7.900(1)$, $c = 6.243(1)$ Å, $\beta = 104.98(1)°$, $Z = 2$, $d_{calcd} = 1.467\ Mg\,m^{-3}$, $\mu = 1.258\ cm^{-1}$, $F(000)$ 124, $R = 0.0304$, $R_w = 0.0772$ for 1287 observed reflections $[I > 2\sigma(I)]$.

Crystal data for (±)-**4**: $C_4H_7NO_3$, f.w. 117.11, monoclinic, space group $P2_1/c$ (no 14), $a = 5.131(2)$, $b = 8.207(4)$, $c = 12.246(4)$ Å, $\beta = 92.56(3)°$, $Z = 4$, $d_{calcd} = 1.510\ Mg\,m^{-3}$, $\mu = 1.300\ cm^{-1}$, $F(000)$ 248, $R = 0.0300$, $R_w = 0.0818$ for 1238 observed reflections $[I > 2\sigma(I)]$.

Crystal data for (*R*)-(+)-**4**: $C_4H_7NO_3$, f.w. 117.11, orthorhombic, space group $P2_12_12_1$ (no 19), $a = 6.909(3)$, $b = 8.083(3)$, $c = 9.209(4)$ Å, $Z = 4$, $d_{calcd} = 1.512\ Mg\,m^{-3}$, $\mu = 1.302\ cm^{-1}$, $F(000)$ 248, $R = 0.0248$, $R_w = 0.0675$ for 1075 observed reflections $[I > 2\sigma(I)]$.

Intensity data collection were performed with graphite monochromatized MoKα radiation ($\lambda = 0.71073$ Å) on an Enraf-Nonius CAD4 up to $2\theta = 56°$. Data sets were corrected for Lorentz-polarization effects and absorption.[24] Structure solution was carried out by direct methods using SHELXS86[25] and full-matrix least-squares refinements on F^2 were performed using SHELXL97.[26] All non-H atoms were refined anisotropically and H atoms isotropically.

Crystallographic data (excluding structure factors) for the structure herein have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 233909-233911. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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