Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 4061–4070

TETRAHEDRON: *ASYMMETRY*

Structural basis of solid solution formation during chiral resolution

Orsolya Barabás,[a] Dóra K. Menyhárd,[a] Zsolt Böcskei,[b] Kálmán Simon,[b,*] Ilona Kiss-Ajzert,[b] Kálmán Takács[b] and István Hermecz[b]

[a]*Department of Theoretical Chemistry, Lorand Eötvös University, POB 32, H-1518 Budapest, Hungary*
[b]*Preclinical Development, Chinoin Pharmaceuticals a member of Sanofi-Synthelabo Group, POB 110, H-1325 Budapest, Hungary*

Received 28 July 2000; accepted 31 August 2000

Abstract

A systematic study of crystal packing in a series of structures is presented: an isostructural triplet of an optically active compound {(*R*)-2-(6,7-diethoxy-1,2,3,4-tetrahydro-1-isoquinolidene)-2-[2-hydroxy-3-(4-morpholinyl)propyl]mercaptoacetonitrile hydrochloride, $C_{22}H_{32}ClN_3O_4S$} **1**, its racemate **2** and their achiral dehydroxy parent compound {2-(6,7-diethoxy-1,2,3,4-tetrahydro-1-isoquinolidene)-2-[3-(4-morpholinyl)propyl]mercaptoacetonitrile hydrochloride, $C_{22}H_{32}ClN_3O_3S$} **3**. Based on the structures we suggest some requirements necessary for an optically active compound and its racemate to be isostructural. A generally used resolving agent D-champhor sulphonic acid was unable to provide full separation of the racemate. The crystal structure of a partially resolved product ($C_{32}H_{47}N_3O_8S_2$) **4** sheds light on the possible reasons of this failure. We suggest a few criteria for solid solution formation of diastereomeric salts.

1. Introduction

Resolution through diastereomeric salt formation is a widely used procedure.[1–3] The method, discovered by Pasteur,[4] rests upon the combination of a racemate with an enantiomerically pure chiral resolving agent and subsequent separation of the mixture of diastereomeric salts by crystallization techniques. The application of the method requires considerable skill and also patience in some cases. Basically it still remains a trial-and-error procedure,[7] because there is no hypothesis, let alone a theory, on which to base a predictable resolution technique. However, it is essential in the pharmaceutical and chemical industry for the production of large amounts of enantiopure compounds.[5,6] This is why many detailed examinations of crystal structures[8] and energy differences[9] of diastereomeric salts have been of remarkable importance. One can find a

* Corresponding author. Tel: +36-1-690900; fax: +36-1-3705597; e-mail: kalman.simon@sanofi-synthelabo.com

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00347-5

large number of examples in the literature where the method of diastereomeric salt formation was found to be fast and effective, there are also many examples of failure.[10,11] This is partly due to co-crystallization of diastereomers as a continuous series of solid solutions.[12]

The underlying structural features have rarely been examined in detail since in most of these cases no crystals of appropriate quality could be prepared. Here we present crystal structures, which shed light on the structural characteristics of a system presenting the solid solution-like behavior.

This group of samples was originally generated because the chiral resolution of the drug candidate material 2-(6,7-diethoxy-1,2,3,4-tetrahydro-1-isoquinolidene)-2-[2-hydroxy-3-(4-morpholinyl)propyl]mercaptoacetonitrile hydrochloride ($C_{22}H_{32}ClN_3O_4S$)[13] has posed a number of difficulties. A generally used resolving agent D-champhor sulphonic acid was unable to provide full separation of the racemate. At an intermediate stage of the project we initiated the crystal structure determination of a partially resolved product **4**. It is our view that the results explain why in this particular case the resolution did not progress further. In addition we have also examined and compared the structures of enantiomerically pure (*R*)-**1** (finally prepared through asymmetric synthesis), that of the racemate **2** and their dehydroxy parent compound {2-(6,7-diethoxy-1,2,3,4-tetrahydro-1-isoquinolidene)-2-[3-(4-morpholinyl)propyl]mercaptoacetonitrile hydrochloride, $C_{22}H_{32}ClN_3O_3S$} **3**. This group of three structures is of outstanding interest: despite the remarkable variations in molecular structure, the optically active material, its racemic form and their achiral dehydroxy parent compound are isostructural. It may be noteworthy, that mostly subtle variations in molecular structure result in remarkable changes of crystal packing. From this respect it is of considerable interest to study cases where variations in molecular structure result in small changes of packing, so that their effects could easily be examined. In particular, investigation of isostructural crystals[14] of different molecules may lead to a better understanding of packing principles.

2. Results and discussion

*2.1. Conformational characteristics of the individual moieties in structures **1**–**4***

First we wish to compare the structures of the isoquinoline based molecules in the four crystal lattices. The conformations of the molecules in the crystals of **1**–**3** (Fig. 1) are very similar due

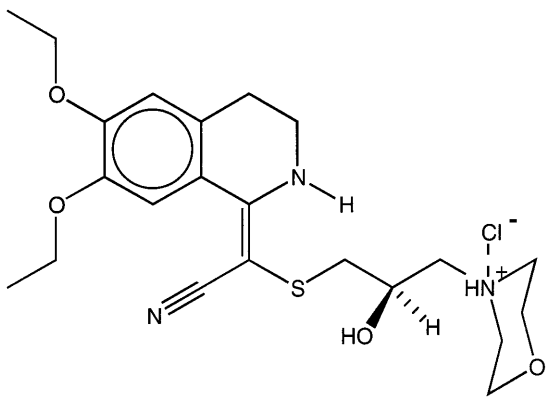

Figure 1. Chemical formula of the optically active compound **1**

to their isostructurality. Therefore we only wish to discuss the structure of **1** (Fig. 2) in detail, while in the other two cases only differences from **1** will be highlighted.

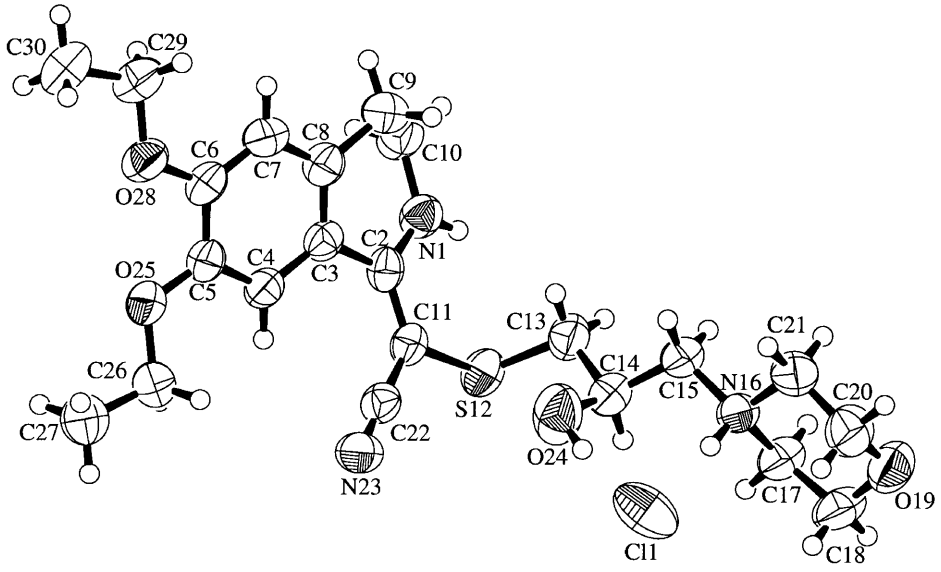

Figure 2. Molecular structure and atomic numbering for **1**. Thermal motion ellipsoids are drawn at the 50% probability level

The ethoxy substituents of the dihydroisoquinoline ring are coplanar with the plane of the isoquinoline ring similarly to a number of other related structures.[15,16] The dihydropyridine ring is in a half chair, while the morpholino group assumes a chair conformation. Bond lengths and angles show delocalization along the N1–C2–C11–C22–N23 chain. The rotation is only free along the torsion angles in the S12–C13–C14–C15–N16 moiety (Table 1). In **1**–**3** this segment is in the same open chain conformation (Fig. 2). The conformation of this part changes in **4** (Fig. 3), so the relative position of the morpholine moiety with respect to the isoquinolidene one is different in **4** from that found in **1**–**3**. The most dominant component of this conformational change is a rotation around the S12–C13 bond (Table 1).

Table 1
Characteristic freely rotatable torsion angles in the crystal structures of compounds **1**–**4**

	1		**2**	**3**	**4**	
Torsion angles (°)	A	B			A	B
C(2)–C(11)–S(12)–C(13)	−72.8(9)	76(1)	75.2(3)	77.6(7)	−97.1(8)	92.7(8)
C(11)–S(12)–C(13)–C(14)	−99.2(9)	103(1)	95.5(3)	88.6(7)	160.6(7)	176.4(8)
S(12)–C(13)–C(14)–C(15)	178.9(8)	166(1)	177.6(3)	−176.9(6)	170.4(7)	179.4(7)
C(13)–C(14)–C(15)–N(16)	169.9(9)	−175(1)	−167.1(3)	−165.9(7)	−174.6(8)	−171.3(9)
C(14)–C(15)–N(16)–C(21)	165.6(9)	−146(2)	−162.9(4)	−165.2(8)	−169.2(8)	168.2(9)

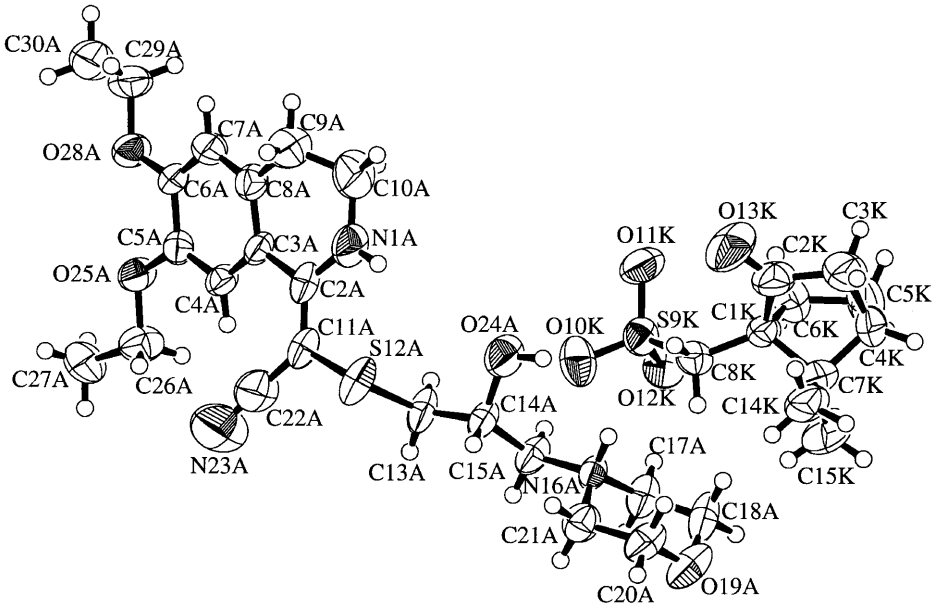

Figure 3. Molecular structure and atomic numbering for **4**. Thermal motion ellipsoids are drawn at the 50% probability level. The atoms of other molecule in the asymmetric unit are labeled B with the disordered OH group labeled C and those of its counter ion labeled L

From the isostructurality of structures of **1**–**3** it follows that in the crystal of **1** the two crystallographically independent chiral molecules (A and B) will have to assume conformations related by a (pseudo)center of inversion which relate the two molecules if we ignore the O24–H24 group on the stereogenic C14 carbon. This way the inversion center present in the structures of **2** and **3** is, in fact, mimicked. The positions of the chloride ions are determined in all three structures by the restraint that they have to be close to the protonated positively charged N16 atoms, while the chloride ions are hydrogen bonded to N16 atoms in all three structures (Table 2). Apart from N16–H16···Cl1 there is one more hydrogen bond shared by all three structures: N1–H1···N23 which runs through the crystal interconnecting molecules in a chain-like fashion (Table 2).

2.2. Crystal packing considerations

Now we wish to discuss the intermolecular relationships and packing principles of **1**–**4**. In the unit cell of the crystal of **4** two layers of molecules are separated (Fig. 4). One is in the *bc* plane, while the other is parallel to the first, but runs through the middle of the unit cell. The latter contains a disordered site where both enantiomers may occur.

The relative positions of the molecules in the two layers are very similar. The camphor sulphonate ions are in identical relative positions in the two layers, while the molecules to be resolved are related by approximate mirror symmetry. The occurrence of the disorder in one of the two layers may be explained on the basis of the structure. The layer running parallel with the *bc* plane in the middle of the unit cell offers the formation of a hydrogen bond of the O24–H24 group in both positions. The OH group of the *S* enantiomer (O24B–H24B) can form

Table 2
Hydrogen bond characteristics in the crystal structures of compounds **1**–**3**

Compound	*d*(H1···N23) (Å)	∠NHN (°)	*d*(N1···N23) (Å)	Symmetry transformations
N1–H1···N23				
1A	2.33(1)	142.5(4)	3.06(1)	N23B [*x*, *y*, *z*−1]
1B	2.35(1)	142.5(4)	3.08(1)	N23A [*x*, *y*, *z*]
2	2.343(4)	141.3(1)	3.062(4)	N23 [*x*, −*y*+1/2, *z*−1/2]
3	2.39(1)	142.0(3)	3.11(1)	N23 [*x*, −*y*+1/2, *z*−1/2]
	d(H16···Cl1) (Å)	∠NHCl (°)	*d*(N16···Cl1) (Å)	
N16–H16···Cl1				
1A	2.146(8)	171.1(3)	3.059(8)	
1B	2.15(2)	164.2(7)	3.04(1)	
2	2.145(3)	171.73(9)	3.048(3)	
3	2.122(7)	166.3(2)	3.014(7)	
	d(H24···Cl1) (Å)	∠OHCl (°)	*d*(O24···Cl1) (Å)	
O24–H24···Cl1				
1A	2.121(7)	173.5(2)	3.077(7)	Cl1A [*x*, *y*, *z*]
1B	2.52(2)	128.9(9)	3.21(3)	Cl1B [−*x*+2, *y*−1/2, −*z*+1]
2	2.119(4)	170.7(1)	3.070(4)	Cl1 [*x*, *y*, *z*]
3	–	–	–	

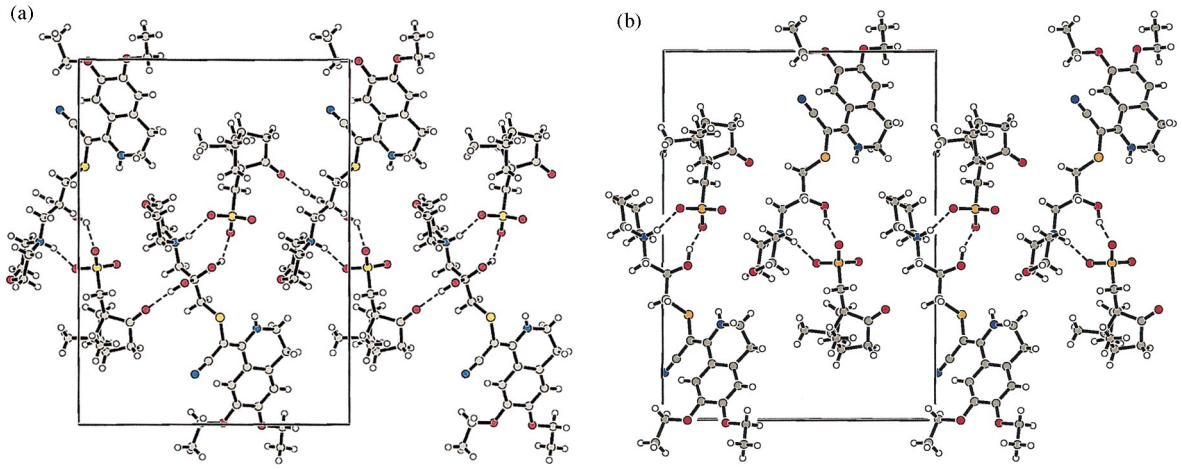

Figure 4. Crystal packing of **4** projected along the *a* axis (*b* is running horizontally, while *c* is running vertically). (a) shows the layer containing the disordered OH group with the two alternative hydrogen bonding possibilities for the two enantiomers, while in (b) (in the ordered layer) there is no hydrogen bond acceptor atom available for the OH group of the *S* enantiomer

a hydrogen bond with the camphor carbonyl oxygen, while that of the *R* enantiomer (O24C–H24C) with one of the oxygens of the SO_3^- group (Fig. 4a, Table 3). On the contrary, in the layer lying in the *bc* plane no hydrogen bond possibilities are offered for the OH group

belonging to the *S* enantiomer (O24A–H24A) (Fig. 4b, Table 3). This explains on a qualitative energetical basis why the *S* enantiomer is not present in the given layer leading to a partial resolution of the base.

Table 3
Hydrogen bond possibilities offered for the O24–H24 group in the crystal structure of compound **4**

Layer	Hydrogen bond	*d*(H···O) (Å)	∠OHO (°)	*d*(O···O) (Å)	Symmetry transformations
In the ordered layer	O24A–H24A···O10K	1.879(9)	146.5(3)	2.731(9)	O10K [*x*, *y*, *z*]
In the disordered layer	O24B–H24B···O13L	1.96(3)	164.3(5)	2.89(3)	O13L [$-x+1$, $y+1/2$, $-z$]
	O24C–H24C···O11L	2.17(1)	148.1(4)	3.03(1)	O11L [*x*, *y*, *z*]

The presence of both enantiomers in the same crystallographic position in different unit cells, i.e. the formation of a solid solution of the two enantiomers, explains why full separation could not be achieved.

Finally, it is worth analyzing the possible reasons for the isostructurality presented by the crystal structures **1**–**3**. The easiest case to discuss is perhaps the isostructurality of **2** and **3** (Figs. 5 and 6).

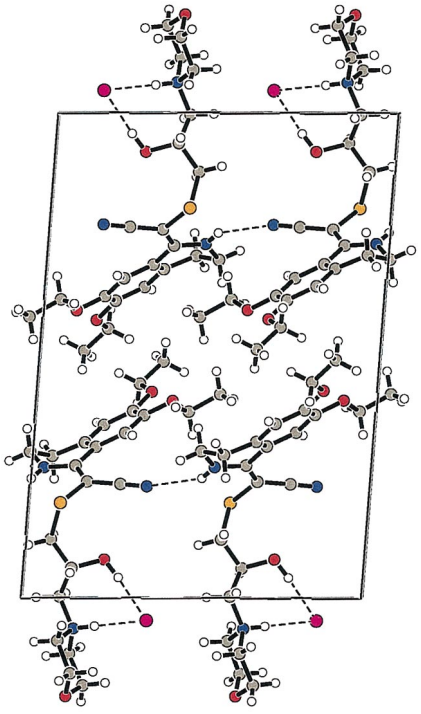

Figure 5. Crystal packing of **2** shown along the *b* axis (*a* is running vertically, while *c* is running horizontally)

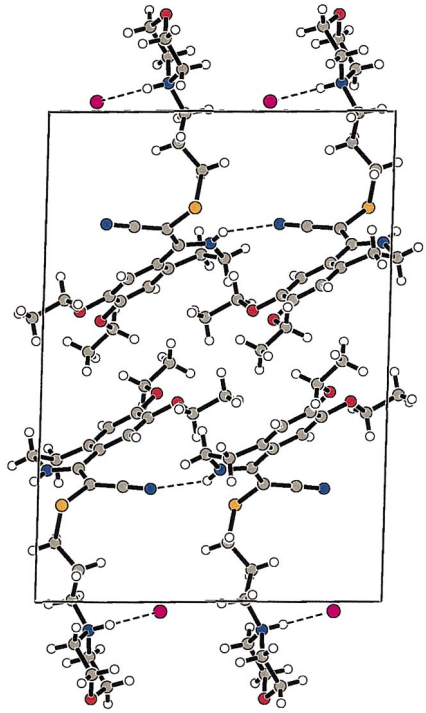

Figure 6. Crystal packing of **3** shown along the *b* axis (*a* is running vertically, while *c* is running horizontally)

The difference between **2** and **3** is a substitution of the H14 atom in **3** with an OH group in **2**. It is important to notice that in the crystal of **2** the OH group participates in an 'intermolecular' ring formed by hydrogen bonds, i.e. it is not part of an endless chain, which could increase the stability of the crystal (Fig. 5). So the hydrogen bonds formed by the OH groups play only a minor role in the stabilization of the crystal contrary to the N1–H1···N23 hydrogen bonds, mentioned above, which run through the crystal interconnecting molecules in a chain-like fashion. The OH group is just in an appropriate position to donate a hydrogen bond toward the chloride, which has to be there anyway since it is the counterion of the positively charged protonated N16 atom (Fig. 5). The O–H···Cl hydrogen bond is not very strong however (Table 2), since its linearity is hindered by an eclipsed conformation of H14 and H24 atoms around the C14–O24 bond. So the crystal does not seem to lose an essential stability component by the replacement of the OH group in **2** with the H atom in **3**. It is also important, that the relative change in molecular volume is very small. As a result of these effects the packing efficiency (density) in the crystal of **3** is not dangerously small ($Dx(\mathbf{2}) = 1.295$ g cm^{-3}, $Dx(\mathbf{3}) = 1.257$ g cm^{-3}).

Next we compared the structures of **1** and **2** (Figs. 5 and 7). Above we have analyzed one aspect of the conformational constraints **1** has to fulfil so that it becomes able to form a quasi-centrosymmetric crystal isostructural to **2**. This ability, we believe, can be attributed to the relatively small size of both the hydrogen atom and the hydroxyl group as compared to the size of the other two groups bonded to the C14 chiral carbon. The chirality of **1** in the crystals can be inverted by simply swapping the hydrogen atom and the hydroxyl group of the C14 center. If these two latter substituents are small, compared to the other two of a stereogenic carbon,

then the change in chirality may not hinder the inclusion of the two enantiomers on the same crystallographic position in different unit cells, i.e. the formation of a solid solution of two enantiomers shown in the crystals of **4**. This is, however, only the necessary but not the satisfactory condition. It also looks desirable that similar possibilities be available in terms of energetics (secondary interactions) in both positions. In the case of the disordered layer of **4**, there are hydrogen bond acceptor atoms close to both positions, so that whichever enantiomer is present it is able to form hydrogen bonds of similar strengths.

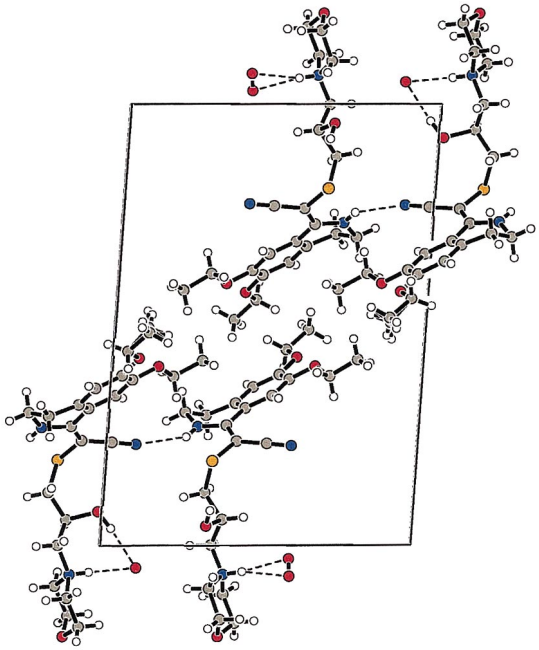

Figure 7. Crystal packing of **1** shown along the *b* axis (*a* is running vertically, while *c* is running horizontally)

3. Conclusions

A rare example of the structure of a partially resolved diastereomeric salt gave us insight into the prerequisites of the formation of solid solution type diastereomeric salt mixtures. The formation of such a continuous series of solid solutions is relatively common and is the reason for the unsuitability of certain systems for chiral resolution at least in the context of commercial processes. We have suggested a rule when such behavior may be expected, i.e. in cases when swapping of two small substituents of a stereogenic atom does not interfere with crystal packing due to the shadowing effect of the other two bulky substituents of the stereogenic atom. A similar effect may be behind the formation of isostructural crystals of an optically active compound, its racemate and their achiral dehydroxy parent compound. We believe that these observations are of importance from the point of view of the design of industrial resolution processes.

4. Experimental

Syntheses of compounds **1**–**4** are described in Ref. 13. Crystals **1**–**3** were obtained by dissolving the appropriate compounds in ethanol followed by heating and slow cooling. Crystals of **4** were taken from the mixture, which evolved as the product during chiral resolution of **2**. Data collections were carried out at room temperature on a Rigaku AFC6S diffractometer, apart from **2**, which was collected on a CAD-4 diffractometer. All crystallographic data were collected with graphite-monochromated Cu Kα ($\lambda=1.5418$ Å) radiation. All structures were solved by the TEXSAN package[17] (Molecular Structure Corporation, 1992), and refined using SHELXL-93[18,19] (Sheldrick, 1993). Atomic coordinates, bond lengths, bond angles, torsion angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

Crystal data for **1**. Monoclinic, $P2_1$. $a=20.0348(12)$, $b=8.636(2)$, $c=14.0685(14)$ Å, $\beta=94.153(6)°$, $V=2427.8(7)$ Å^3, $Z=4$, $d=1.286$ g cm^{-3}, μ(Cu Kα)$=2.462$ mm^{-1}, $F(000)=1000$. Theta range for data collection: 2.21–75.16°. Index ranges $-25\leq h\leq 25$, $-10\leq k\leq 10$, $-17\leq l\leq 17$. Reflections collected: 9614. Full-matrix least-squares on F^2. Data/restraints/parameters 9608/80/584. Restraints: corresponding bonds of molecules A and B were restrained to the same bond length with standard deviation of 0.03. Goodness-of-fit on F^2: 1.018. Final R indices [$I>2\sigma(I)$ 3275 reflections]: $R_1=0.0676$, $wR_2=0.1641$. Final R indices (all reflections): $R_1=0.2278$, $wR_2=0.2593$. Absolute structure parameter: 0.07(5):0. Extinction coefficient: 0.0018(2). Largest diff. peak and hole 0.446 and −0.300 e Å^{-3}.

Crystal data for **2**. Monoclinic, $P2_1/c$. $a=20.054(3)$, $b=8.5780(10)$, $c=14.0500(10)$ Å, $\beta=94.28(2)°$, $V=2410.2(5)$ Å^3, $Z=4$, $d=1.295$ g cm^{-3}, μ(Cu Kα)$=2.480$ mm^{-1}, $F(000)=1000$. Theta range for data collection: 2.21–75.01°. Index ranges $0\leq h\leq 25$, $-10\leq k\leq 0$, $-17\leq l\leq 17$. Reflections collected 4963. Full-matrix least-squares on F^2. Data/restraints/parameters 4963/0/284. Goodness-of-fit on F^2: 0.967. Final R indices [$I>2\sigma(I)$ 3506 reflections]: $R_1=0.0572$, $wR_2=0.1439$. Final R indices (all reflections): $R_1=0.0811$, $wR_2=0.1455$. Extinction coefficient: 0.0020(4). Largest diff. peak and hole 0.558 and −0.174 e Å^{-3}.

Crystal data for **3**. Monoclinic, $P2_1/c$. $a=19.930(3)$, $b=8.542(3)$, $c=14.104(3)$ Å, $\beta=91.757(14)°$, $V=2400.0(10)$ Å^3, $Z=4$, $d=1.257$ g cm^{-3}, μ(Cu Kα)$=2.440$ mm^{-1}, $F(000)=968$. Theta range for data collection: 2.22–75.15°. Index ranges $-24\leq h\leq 24$, $-10\leq k\leq 6$, $-17\leq l\leq 17$. Reflections collected 5417. Full-matrix least-squares on F^2. Data/restraints/parameters 4781/0/277. Goodness-of-fit on F^2: 1.060. Final R indices [$I>2\sigma(I)$ 1904 reflections]: 0.0831, $wR_2=0.2497$. Final R indices (all reflections): $R_1=0.2101$, $wR_2=0.3872$. Largest diff. peak and hole 0.604 and −0.478 e Å^{-3}.

Crystal data for **4**. Monoclinic, $P2_1$. $a=10.127(4)$, $b=15.881(6)$, $c=21.667(3)$ Å, $\beta=99.36(2)°$, $V=3438.4(19)$ Å^3, $Z=4$, $d=1.286$ g cm^{-3}, μ(Cu Kα)$=1.838$ mm^{-1}, $F(000)=1424$. Theta range for data collection: 2.07–69.64°. Index ranges $-11\leq h\leq 11$, $-12\leq k\leq 19$, $-26\leq l\leq 26$. Reflections collected 6695. Full-matrix least-squares on F^2. Data/restraints/parameters 6306/121/825. Restraints: corresponding bonds of cations A and B and anion K and L were restrained to the same bond length with standard deviation of 0.03. Goodness-of-fit on F^2: 1.034. Final R indices [$I>2\sigma(I)$ 3096 reflections]: 0.0540, $wR_2=0.1432$. Final R indices (all reflections): $R_1=0.1401$, $wR_2=0.1990$. Absolute structure parameter: 0.07(5):0. Largest diff. peak and hole 0.434 and −0.300 e Å^{-3}.

References

1. Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*; John Wiley: New York, 1981.
2. Jacques, J.; Collet, A. *Reissue with corrections*; Krieger: Malabar, FL, USA, 1994.
3. Eliel, E. L.; Wilen, S. H.; Mander, N. *Stereochemistry of Organic Compounds*; John Wiley: New York, 1994.
4. Pasteur, L. C. R. *Hebd. Seances Acad. Sci.* **1953**, *37*, 162.
5. Harrington, P. J.; Lodewijk, E. *Org. Process Res. Dev.* **1997**, *1*, 72.
6. Kamphuis, J.; Boesten, W. H. J.; Kaptein, B.; Hermes, H. F. M.; Sonke, T.; Broxterman, Q. B.; van denTweel, W. J. J.; Schoemaker, H. E. In *Chirality in Industry*; Collins, A. N.; Sheldrake, G. N.; Crosby, J., Eds.; John Wiley: New York, 1994.
7. Sheldon, R. A. *Chirotechnology*; Marcel Dekker: New York, 1993; Chapter 6.
8. Gould, R. O.; Walkinshaw, M. D. *J. Am. Chem. Soc.* **1984**, *106*, 7840.
9. Zingg, S. P.; Arnett, E. M.; McPhail, A. T.; Bother-By, A. A.; Gilkerson, W. R. *J. Am. Chem. Soc.* **1988**, *110*, 1565.
10. Wilen, S. H. In *Tables of Resolving Agents and Optical Resolutions*; Eliel, E. L., Ed.; University of Notre Dame Press: Notre Dame, IN, 1972.
11. Collet, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 3239.
12. Costante, J.; Ehlinger, N.; Perrin, M.; Collet, A. *Enantiomer* **1996**, *1*, 377.
13. Takács, K. et al. Eur. Patent Appl. No. 0 486 211 A1, Paris, 1991.
14. Kálmán, A.; Párkányi, L.; Argay, Gy. *Acta Crystallogr., Sect. B* **1993**, *49*, 1039.
15. Korbonits, D.; Horvath, G.; Kiss, P.; Simon, K.; Kolonits, P. *Chem. Ber.* **1990**, *123*, 493.
16. Böcskei, Zs.; Simon, K.; Friesz, A.; Hermecz, I. *Acta Crystallogr., Sect. C* **1995**, *51*, 1587.
17. Sheldrick, G. M. *Acta Crystallogr., Sect. A* **1990**, *46*, 467.
18. Sheldrick, G. M. SHELXL-93, Program for the Refinement of Crystal Structures; University of Göttingen: Germany, 1993.
19. Molecular Structure Co. TEXSAN: Crystal Structure Analysis Package; MSC: 3200 Research Forest Drive, The Woodlands, TX 77381, USA, 1985, 1992.