Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 1511–1518

TETRAHEDRON: *ASYMMETRY*

Resolution of α-phenylethylamine by its acidic derivatives

József Bálint,[a] Gabriella Egri,[a,*] Mátyás Czugler,[b] József Schindler,[a] Violetta Kiss,[a] Zoltán Juvancz[c] and Elemér Fogassy[a]

[a]*Department of Organic Chemical Technology, Budapest University of Technology and Economics, PO Box 91, H-1521 Budapest, Hungary*

[b]*Institute of Chemistry, Chemical Research Center, Hungarian Academy of Science, PO Box 17, H-1525 Budapest, Hungary*

[c]*VITUKI Plc., Kvassay J.u.1, H-1095 Budapest, Hungary*

Received 18 May 2001; accepted 31 May 2001

Abstract—α-Phenylethylamine was resolved by its own derivatives formed with a homologous series of dicarboxylic acids. The structure of the oxalamic acid diastereoisomeric salts was investigated by the single-crystal X-ray diffraction method.

1. Introduction

Separation of the diastereoisomeric salts of a given compound is the main method for enantiomeric resolution.[1–3] A special case is the resolution of a compound by one of its own derivatives. The resolving agent is prepared from one enantiomer of the target compound to give the derivative of opposite acid–base characteristics. Although this is quite a promising method which makes use of the undesired enantiomer, so far only few examples are known in the literature.[4–7]

α-Phenylethylamine is a widely applied resolving agent.[8,9] It has previously been resolved by its succinic acid monoamide.[10] Our aim was to conduct a systematic study of some resolution processes involving monoamides formed with dicarboxylic acids of different chain length. We synthesized the oxalic and malonic acid monoamide-resolving agents, while the succinic acid monoamide has been reported previously in the literature.[10]

2. Results and discussion

2.1. Resolution and enantiomeric enrichment

The resolving agents were synthesized (Fig. 1) by condensing (*R*)-α-phenylethylamine with the dicarboxylic acid diester. The resulting monoamide-monoester was then subjected to alkaline hydrolysis followed by acidification in order to liberate the acids. Synthesis of *N*-(1-phenylethylamine)oxalamic acid has been reported[11] by biocatalytic (*Candida* sp.) hydrolysis of the ester but no analytical data were given.

The resolution experiment was carried out by applying the resolving agent in equivalent quantity. In each case, including literature data ($n=2$), resolution by the (*R*)-monoamide yielded (*S*)-phenylethylamine. That is, the (*S*,*R*)-diastereoisomeric salt is more stable than the (*R*,*R*)-diastereoisomer, which indicates molecular compound-like behavior of the diastereoisomeric mixture; as in the case of molecular compounds heterochiral interactions are stronger than homochiral ones.

The resolution process can be seen in Fig. 2.

The resulting diastereoisomeric salts were enantiomerically enriched by repeated recrystallization. In the liter-

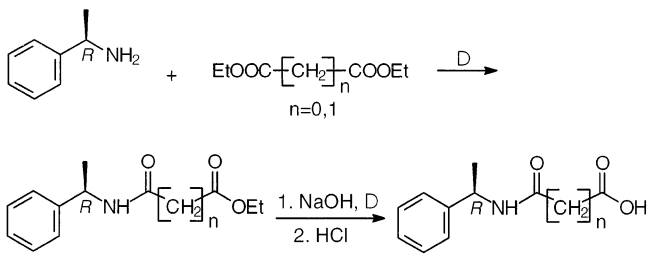


Figure 1. Formation of the resolving agents.

* Corresponding author. Fax: +36 1 4633648; e-mail: h7622egr@ella.hu

0957-4166/01/$ - see front matter
PII: S0957-4166(01)00254-3

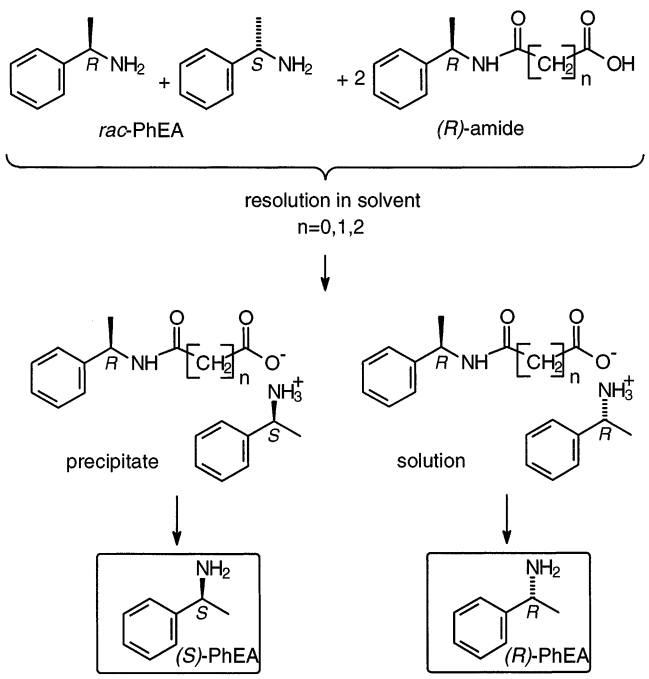


Figure 2. Resolution of α-phenylethylamine by its monoamides.

ature three steps were carried out in butan-2-one. In our case, two recrystallizations from acetone gave good results.

We found it advantageous during the workup of the reaction to first remove the resolving agent by acidification followed by organic solvent extraction. Using this method, around 90% of the resolving agent can be recovered from the organic phase. The phenylethylamine is then liberated by adjusting the pH of the aqueous phase to alkaline and isolated by straightforward extraction.

The resolution and enrichment results are summarized in Table 1. In contrast to expectations, the best results came from the resolving agent having the longest side chain and thus the largest distance of the carboxylic group from the stereogenic center.

For a better interpretation of the resolution results, single-crystal X-ray crystal structure determinations were undertaken for the (*R*)- and (*S*)-1-phenylethylamine-(*R*)-1-phenylethylamine oxalamic acid monoamide diastereoisomeric salts (**1a** and **1b**, respectively). In this case both diastereoisomeric salts gave suitable crystals for single-crystal structural studies.

For the diastereoisomeric salts of the malonamic and succinamic acid compounds attempts at obtaining single crystals were not successful.

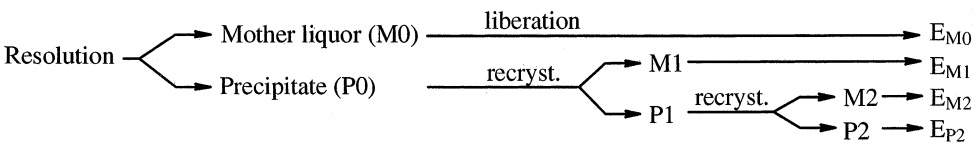
2.2. X-Ray crystallography

The structure model of the (*R*)-salt **1a** is shown in Fig. 3.

Solid state models resulting from single-crystal X-ray structure determinations (Table 2) of **1a** (Fig. 3) and **1b** (Fig. 4) indicate overall shapes of the associations of the acid and base molecules forming the crystallographic asymmetric units. The intramolecular geometry has bonding dimensions as expected.

It is also apparent (Table 3) that the conformations of both the (*R*)-PEA and the (*S*)-PEA bases are identical, except for the sign change due to the (*R*)/(*S*) switch. There is only one difference in the conformation of the (*R*)-oxalamic acid moieties (cf. Table 3). This is a roughly 75° rotation discrepancy around the N(1)–C(7) bond. This twist can be interpreted as a shift in the eclipsing C and H atomic positions in the vicinity of the amide group. C(1) eclipses with H1 and the amide C(8) with C(7)H in **1a**. In **1b** the C(10)H atom turns, eclipsing with C(1)H. Though the amide C(8) stays eclipsed with C(7)H in **1b** it is now placed symmetrically on the other side of C(7)H (cf. the Newman projection insets in Figs. 3 and 4).

Table 1. Resolution and enantiomeric enrichment of α-phenylethylamine



	Res. agent	PhEA oxalamic acid			PhEA malonamic acid			PhEA succinamic acid[b]		
	Conf.	*Y* (%)	Ee[a] (%)	*S*[c]	*Y* (%)	Ee[a] (%)	*S*[c]	*Y* (%)	OP (%)	*S*[c]
E_{M0}	*R*	83	32	0.27	94	61	0.57	110	54	0.56
E_{M1}	*R*	17	14		16	17				
E_{M2}	*S*	4	19		6	67				
E_{P2}	*S*	38	98	0.37	56	99	0.55	61	100	0.61

[a] Ee determined by chiral GC; see Experimental section.
[b] Literature data source,[10] OP based on optical rotatory power.
[c] $S = Y \times$ee or $Y \times$OP (efficiency of the resolution).

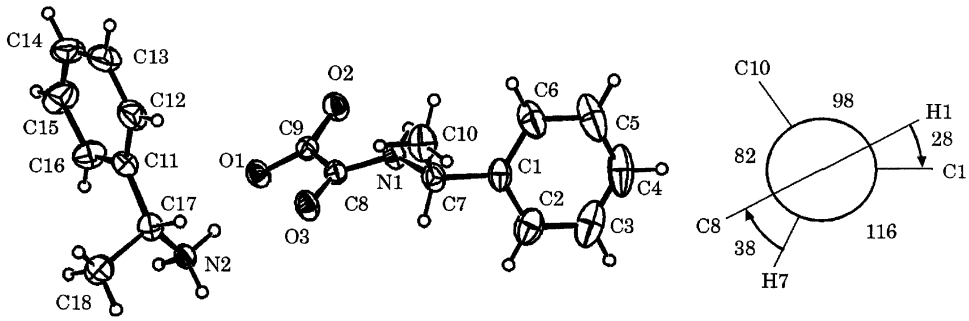


Figure 3. X-Ray structure model of **1a** with atomic displacement parameters. The Newman projection inset is along the N(1)–C(7)–C(1) bonds; arrows indicate rotations to next-neighbors on the wheel.

Table 2. Summary of crystallographic data and structure model refinement for **1a** and **1b**

	1a	**1b**
Empirical formula (F_w)	$C_{18}H_{22}N_2O_3$, 314.38	$C_{18}H_{22}N_2O_3$, 314.38
Temperature (K)	293(2)	295(2)
Radiation and wavelength	Mo Kα, $\lambda = 0.710730$ Å	Mo Kα, $\lambda = 0.710730$ Å
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1$	$P2_1$
Unit cell dimensions		
a (Å)	9.869(1)	11.478(1)
b (Å)	6.750(1)	6.660(2)
c (Å)	13.548(1)	11.593(1)
β (°)	101.38(1)	103.06(1)
V (Å^3)	884.8(2)	863.3(3)
Z	2	2
D_{calcd} (Mg m^{-3})	1.1801(2)	1.2094(4)
Absorption coefficient, μ (mm^{-1})	0.081	0.083
Crystal color	Colorless	Colorless
Crystal description	Block	Block
Crystal size (mm)	$0.40 \times 0.35 \times 0.15$	$0.40 \times 0.30 \times 0.25$
Reflections collected	6973	6873
Decay (%)	8	3
Independent reflections	6117 [$R_{int} = 0.011$]	5975 [$R_{int} = 0.023$]
Reflections $I > 2\sigma(I)$	3576	3386
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	6117/139/212	5975/1/211
Goodness-of-fit on F^2	0.977	0.941
Extinction coefficient	0.013(5)	–
Final R indices R_1, wR^2 [$I > 2\sigma(I)$]	0.0411, 0.1042	0.0473, 0.1113
R indices (all data) R_1, wR^2	0.0843, 0.1126	0.0937, 0.1212
Max. and mean shift (e.s.d.)	0.000, 0.000	0.002, 0.000
Largest diff. peak and hole (e Å^{-3})	0.142/−0.133	0.224/0.133

Intra-associate parameters show the usual bonding and H-bonding characteristics (Table 4) as anticipated for these types of salts. The fairly uniform hydrogen bonding defines the salt link and an infinite one-dimensional chain along the crystallographic {0,1,0} base vector. In essence it can be summarized that the intra-associate conformation remains stable and the same, as far as H-bonding between the PEA-ammonium cation and the (*R*)-PEA-oxalamic anion is concerned.

As the differing *a* and *c* cell parameters clearly indicate, the (*S*)- and (*R*)-PEA salts of (*R*)-*N*-(1-phenylethylamine)oxalamic acid monoamide are not isostructural. Though slightly surprising, it shows that (in spite of the similar H-bonding and the same space group symmetry) other weaker forces define the crystal lattices. The packing energies of the two salts are comparable (–31.0 kJ mol^{-1} for **1a**, –31.6 kJ mol^{-1} for **1b**, summed[12] for 96 and 98 interactions, respectively), and also show that this approach does not reflect well upon the differing lattice stability. To aid interpretation of the physical properties of these two solids, their crystal packing was further investigated. This showed some further differences. Firstly, the small but significant differences in the calculated densities of **1a** ($D_c = 1.1801(2)$ (Mg m^{-3})) and **1b** ($D_c = 1.2094(4)$ (Mg m^{-3})), reflecting the overall balance of repulsive and attractive forces in the two crystals. Since strong H-bonding does not show up differences between **1a** and **1b**, much weaker interactions should be sought after. These are partly seen in the interesting, and yet again very similar, pattern of C–H···π interactions and aromatic ring center distances (Tables 4 and 5).

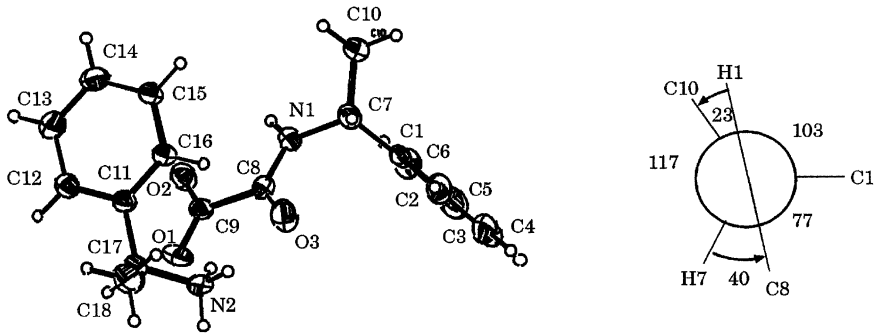


Figure 4. X-Ray structure model of **1b** with atomic displacement parameters. The Newman projection inset is along the N(1)–C(7)–C(1) bonds; arrows indicate rotations to next-neighbors on the wheel.

As the packings (Fig. 5) indicate, aside from the identical H-bonding the intermolecular conformations are somewhat different. Both **1a** and **1b** have two identical C-H···π ring center distances (Table 5). One of these comes in both cases from the same methyl group hydrogen atom of the oxalamic anion component, while the other is from a phenyl-hydrogen of the base. However, these differ in that in **1a** a *meta*-moiety acts as the donor, while in **1b** an *ortho*-position C–H acts as the donor. All of these shortest C–H···π ring contacts are virtually of equal strength. A probably more relevant difference is seen in the geometry of the aromatic ring center distances (Table 6).

According to the two shortest such contacts for both crystals, **1b** obviously packs better. In **1a** one of the two longer contacts is to the base's phenyl, while in **1b** both shorter and equal contacts are to and between the acid aromatic rings. This pattern corroborates a somewhat closer packing in **1b** than in **1a**.

Table 3. Essential torsion angles in the (*S*)-PEA **1a** and (*R*)-PEA **1b** salts of (*R*)-*N*-(1-phenylethylamine)oxalamic acid monoamide, with deviations greater than 20° marked

Torsion angle (°)	**1a** (°)	**1b** (°)	Δ>20 (°)
(*R*)-*N*-(1-PEA)-Oxalamic acid			
O(3)–C(8)–C(9)–O(1)	−12.9	−2.0	
O(3)–C(8)–C(9)–O(2)	168.8	179.6	
N(1)–C(8)–C(9)–O(1)	164.4	176.8	
N(1)–C(8)–C(9)–O(2)	−13.9	−1.5	
C(2)–C(1)–C(7)–N(1)	−100.5	−116.6	
C(7)–N(1)–C(8)–O(3)	5.2	3.7	
C(8)–**N(1)**–**C(7)**–C(1)	152.5	77.4	**75.1**
C(9)–C(8)–N(1)–C(7)	−172.0	−175.1	
C(10)–C**(7)**–**N(1)**–C(8)	−81.8	−157.4	**75.6**
(*S*/*R*)-*N*-(1-PhEA)			
C(10)–C(7)–C(1)–C(2)	135.3	119.8	
C(12)–C(11)–C(17)–N(2)	−134.4	138.2	
C(18)–C(17)–C(11)–C(12)	102.6	−99.2	

3. Experimental

3.1. Materials and methods

The ^{1}H NMR spectra were recorded at 250 MHz on a Bruker WM250 spectrometer. Chemical shift values are expressed in ppm values on the δ scale. IR spectra of thin film samples were taken on a Perkin–Elmer 1600 Series FTIR spectrophotometer. Optical rotations were determined on a Perkin–Elmer 241 polarimeter. Thin-layer chromatography was carried out using POLYGRAM® SIL G/UV$_{254}$ sheets. Spots were visualized by UV light or by treatment with 5% ethanolic phosphomolybdic acid solution and heating of the dried plates. Chemicals were products of Aldrich. All solvents used were freshly distilled. GC analyses were done on a Hewlett–Packard 5890/II instrument equipped with FID at 120°C. Column was a 20×0.200 mm ID fused silica tubing, coated with ChNEB (naphthylethylamide chiral group containing silicone polymer[xy]) stationary phase at 0.2 μm film thickness. Carrier gas was H_2 with 1:100 split ratio. Samples were derivatized with trifluoroacetic anhydride according to the standard procedure.[13,14]

3.2. *N*-(1-Phenylethylamine)oxalamic acid

A mixture of (*R*)-1-phenylethylamine (35.0 g, 289 mmol) and diethyl oxalate (127.0 g, 869 mmol) was stirred at 110°C (oil bath temperature) for 3 h. Excess

Table 4. Dimensions of hydrogen bonds (Å, °) in **1a** and **1b**[a]

1a/**1b** D–H···A	**1a**/**1b** D–H (Å)	**1a**/**1b** H···A (Å)	**1a**/**1b** D···A (Å)	**1a**/**1b** D–H···A (°)
N1–H1···O2	0.86	2.25/2.30	2.640(2)/2.668(2)	107.8/106.0
N2–H2A···O2*i*	0.89	1.95/1.92	2.814(2)/2.811(2)	163.1/175.2
N2–H2B···O1	0.89	2.02/2.15	2.868(2)/2.914(2)	158.5/143.4
N2–H2B···O3	0.89	2.42/2.17	3.024(2)/2.898(2)	125.6/138.9
N2–H2C···O1*j*/*k*	0.89	1.98/1.93	2.836(2)/2.784(2)	160.7/160.2

[a] Translation of symmetry code to equiv. pos. $i=x, -1+y, z$; $j=1-x, -1/2+y, 1-z$; $k=-x, -1/2+y, 2-z$.

Table 5. Analysis of X–H···Cg (π-ring) interactions (H···Cg < 3.0 Å, $\gamma < 30.0°$) (distances to centers of gravities (Cg), indicated by their acid–base type, are in Å)

X···H	Cg(J)	*d* H···Cg (Å)	X–H···Cg (°)	X···Cg (Å)	Compound
C(10)–H(10a) acid-methyl-H	2756 **base**	2.99	135	3.73	**1a**[a]
C(15)–H(15) base-*meta*-H	1556 **acid**	2.87	160	3.75	**1a**
C(10)–H(10c) acid-methyl-H	2657 **base**	2.92	131	3.63	**1b**[b]
C(12)–H(12) base-*ortho*-H	1556 **acid**	2.92	164	3.83	**1b**

[a] **1a**: Calculated density = 1.1801(2) (Mg m^{-3}): (2756) = 2–*x*, 1/2+*y*, 1–*z*; (1556) = *x*, *y*, 1+*z*, H-bond symops: (1545) = *x*, –1+*y*, *z*; (2646) = 1–*x*, –1/2+*y*, 1–*z*.

[b] **1b**: (2657) = 1–*x*, 1/2+*y*, 2–*z*←*j* = –*x*, –1/2+*y*, 2–*z*; (1556) = *x*, *y*, 1+*z*←*i* = *x*, –1+*y*, *z*.

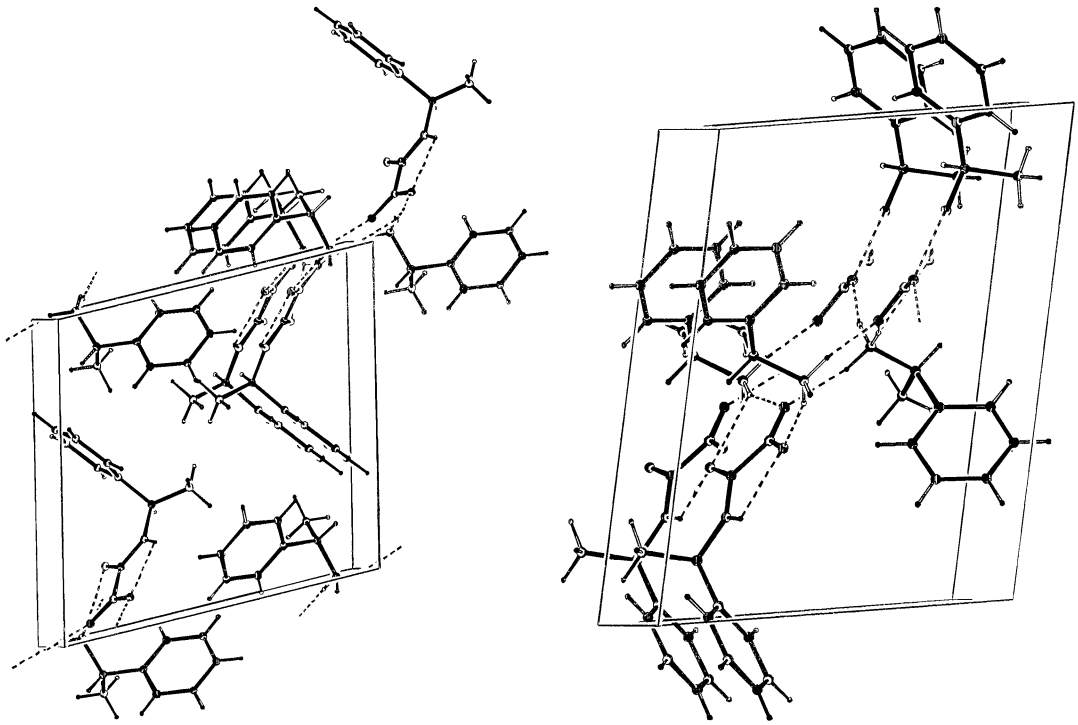


Figure 5. Packing motifs in the crystals of **1a** and **1b** with the unit cell box and with the principal H-bonding shown as broken lines. The view is a projection near to the *b* axis.

diethyl oxalate was removed by distillation in vacuo. The residue (57.8 g of oily material) was treated with water (175 mL) and NaOH (23 g) and the resultant mixture was stirred under reflux for 2 h. After cooling the mixture and stirring for 1 h at 0–5°C the precipitated diamide was collected by filtration. To the mother liquor 37% aqueous HCl (55 mL) was added and the mixture was left to crystallize for 2 h at 0–5°C. The crystals were filtered and washed with water (3×10 mL) and dried to afford a white crystalline solid of *N*-(1-phenylethyl)oxalamic acid (31.2 g, 161 mmol, 56%); mp 128–130°C; $[\alpha]_D^{20} = +125.7$ (*c* 1, methanol); ^{1}H NMR ($CDCl_3$): δ 1.62 (d, 3H, CH_3), 5.11 (m, 1H, CH), 7.33–7.41 (m, 5H, Ar), 7.61 (s, br, 1H, NH); FT-IR (KBr, cm^{-1}): 3304, 1764, 1680, 1544, 1436, 1360, 1352, 1304, 1240, 1176, 1116, 880, 776, 740, 696. Anal. calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.87; H, 7.06; N, 8.90%.

3.3. *N*-(1-Phenylethyl)malonamic acid

A mixture of (*R*)-1-phenylethylamine (70.0 g, 578 mmol) and diethyl malonate (139.0 g, 868 mmol) was stirred at 145–155°C (oil bath temperature) for 3 h. Excess diethyl malonate was removed by distillation in vacuo. To the residue (116.5 g of brown oil), water (350 mL) and NaOH (35 g) were added and the mixture was stirred under reflux for 2 h. After cooling and stirring overnight at 0–5°C the precipitated diamide was collected by filtration. The mother liquor was washed with dichloromethane (4×200 mL), then 37% aqueous HCl

Table 6. Analysis of short ring interactions with Cg–Cg distances < 6.0 Å and $\beta < 60.0°$. **1a** (calculated density = 1.1801(2) (Mg m^{-3}))

Cg(I) type	Cg(J) type	*D* (Å)	Compound
Acid	Acid[a]	5.118	**1a**
Acid	Base[b]	5.084	**1a**
Acid	Acid[c]	4.704	**1b**
Acid	Acid[d]	4.704	**1b**

[a] 1–*x*, 1/2+*y*, –*z*.

[b] *x*, *y*, –1+*z*.

[c] –*x*, –1/2+*y*, 1–*z*.

[d] –*x*, 1/2+*y*, 1–*z*.

(80 mL) was added and the mixture was extracted with dichloromethane (4×200 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was evaporated. The oily residue crystallized on standing for 3 days to a pink solid of *N*-(1-phenylethyl)malonamic acid (63.4 g, 306 mmol, 53%); mp 65–68°C; $[\alpha]_D^{20}=+114.1$ (*c* 1, methanol). The product was suitable for use in resolution experiments without further purification. The analytical sample was prepared by three recrystallizations from toluene: mp 69–71°C; $[\alpha]_D^{20}=+116.1$ (*c* 1, methanol); ^{1}H NMR ($CDCl_3$): δ 1.48 (d, 3H, CH_3), 3.20–3.30 (m, 2H, CH_2), 5.07 (m, 1H, CH), 7.23–7.32 (m, 5H, Ar), 7.35 (d, 1H, NH); FT-IR (KBr, cm^{-1}): 3384, 3288, 1724, 1620, 1576, 1552, 1496, 1324, 1240, 1204, 1128, 740, 680. Anal. calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53. Found: C, 69.40; H, 7.38; N, 8.55%.

3.4. Resolution of 1-phenylethylamine using *N*-(1-phenylethyl)oxalamic acid

(±)-1-Phenylethylamine (6.10 g, 50 mmol) and *N*-(1-(*R*)-phenylethyl)oxalamic acid (9.70 g, 50 mmol) were dissolved in hot acetone (25 mL) and the mixture was left to crystallize overnight. The crystals were filtered, washed with acetone (3×2 mL) and dried to afford product (5.82 g). The product was recrystallized twice from acetone (first recrystallization: 30 mL acetone; second recrystallization: 20 mL acetone) to give the diastereoisomeric salt as a white solid (3.62 g); mp 127–130°C; $[\alpha]_D^{20}=+66.4$ (*c* 1, methanol). The diastereoisomeric salt was dissolved in water (10 mL), 37% aqueous HCl (1.5 mL) was added and the mixture was washed with dichloromethane (3×10 mL). (The organic phase contains the resolving agent, which can be recovered by evaporation of the solvent.) The aqueous phase was treated with NaOH (1.5 g) and the mixture was extracted with dichloromethane (4×10 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was evaporated. The residue was distilled in vacuo yielding (*S*)-1-phenylethylamine as an oil (1.17 g), $[\alpha]_D^{20}=-29.8$ (*c* 10, ethanol).

The mother liquor of the resolution was evaporated. To the residue were added water (20 mL) and 37% aqueous HCl (3 mL) and the mixture was washed with dichloromethane (3×10 mL). (The organic phase contains the resolving agent.) To the aqueous phase was added NaOH (3 g) and the mixture was extracted with dichloromethane (4×10 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was evaporated. The residue was distilled in vacuo yielding (*R*)-1-phenylethylamine as an oil (2.53 g), $[\alpha]_D^{20}=+10.2$ (*c* 10, ethanol). The mother liquor of the first recrystallization was evaporated and the residue treated with water (10 mL) and 37% aqueous HCl (0.6 mL). The mixture was washed with dichloromethane (3×10 mL). After adding NaOH (0.6 g) to the aqueous phase, it was extracted with dichloromethane (4×10 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was evaporated, yielding (*R*)-1-phenylethylamine as an oil (0.53 g), $[\alpha]_D^{20}=+4.0$ (*c* 10, ethanol).

The mother liquor of the second recrystallization was evaporated. To the residue water (5 mL) and 37% aqueous HCl (0.2 mL) were added and the mixture was extracted with dichloromethane (3×5 mL). After adding NaOH (0.2 g) to the aqueous phase, it was extracted with dichloromethane (4×5 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was evaporated, yielding (*S*)-1-phenylethylamine as an oil (0.13 g), $[\alpha]_D^{20}=-5.2$ (*c* 10, ethanol).

3.5. Resolution of 1-phenylethylamine by *N*-(1-phenylethyl)malonamic acid

(±)-1-Phenylethylamine (6.10 g, 50 mmol) and *N*-(1-(*R*)-phenylethyl)malonamic acid (10.4 g, 50 mmol) were dissolved in hot ethyl acetate (25 mL) and the mixture was left to crystallize overnight. The crystals were filtered, washed with ethyl acetate (3×2 mL) and dried to afford product (7.46 g). The residue was recrystallized twice from acetone (20 mL acetone per recrystallization. Yield from first recrystallization = 5.93 g), affording product (5.34 g), $[\alpha]_D^{20}=+49.5$ (*c* 1, methanol), mp 124–127°C. The diastereoisomeric salt was dissolved in water (20 mL), 37% aqueous HCl (1.5 mL) was added and the mixture was washed with dichloromethane (4×10 mL). (The organic phase contains the resolving agent.) To the aqueous phase NaOH (1.5 g) was added and it was extracted with dichloromethane (4×10 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was evaporated. The residue was distilled in vacuo, yielding (*S*)-1-phenylethylamine as an oil (1.72 g), $[\alpha]_D^{20}=-30.0$ (*c* 10, ethanol).

The mother liquor of the resolution was evaporated. To the residue were added water (20 mL) and 37% aqueous HCl (3 mL) and the mixture was washed with dichloromethane (3×20 mL). (The organic phase contains the resolving agent.) To the aqueous phase NaOH (3 g) was added and it was extracted with dichloromethane (4×10 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was evaporated. The residue was distilled in vacuo, yielding (*R*)-1-phenylethylamine as an oil (2.88 g), $[\alpha]_D^{20}=+19.0$ (*c* 10, ethanol).

The mother liquor of the first recrystallization was evaporated. To the residue were added water (10 mL) and 37% aqueous HCl (0.5 mL) and the mixture was washed with dichloromethane (3×10 mL). (The organic phase contains the resolving agent.) After adding NaOH (0.5 g) to the aqueous phase, it was extracted with dichloromethane (4×10 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was evaporated, yielding (*R*)-1-phenylethylamine as an oil (0.49 g), $[\alpha]_D^{20}=+4.8$ (*c* 10, ethanol).

The mother liquor of the second recrystallization was evaporated. To the residue were added water (5 mL) and 37% aqueous HCl (0.2 mL) and the mixture was extracted with dichloromethane (3×10 mL). (The organic phase contains the resolving agent.) After adding NaOH (0.2 g) to the aqueous phase, it was extracted with dichloromethane (3×10 mL). The com-

bined organic phase was dried over Na_2SO_4 and the solvent was evaporated, yielding (*S*)-1-phenylethylamine as an oil (0.18 g), $[\alpha]_D^{20} = -19.8$ (*c* 10, ethanol).

3.6. X-Ray crystallography

Single crystals were obtained from their optically pure components by crystallization from acetone.

Compound **1a**. Crystal data: $C_{18}H_{22}N_2O_3$, F_w 314.38, colorless block, size: 0.40×0.35×0.15 mm, monoclinic, space group $P2_1$, $a = 9.869(1)$, $b = 6.750(1)$, $c = 13.548(1)$ Å, $\beta = 101.38(1)°$, $V = 884.77(17)$ Å^3, $T = 566(2)$ K, $Z = 2$, $F(000) = 336$, $D_{calcd} = 1.180$ Mg m^{-3}, $\mu = 0.081$ mm^{-1}. A crystal of **1a** was mounted on a glass fiber. Cell parameters were determined by least-squares of the setting angles of 25 ($14.59 \leq \theta \leq 16.70°$) reflections. Intensity data were collected on an Enraf–Nonius CAD4 diffractometer (graphite monochromator; Mo Kα radiation, $\lambda = 0.710730$ Å) at 293(2) K in the range $2.35 \leq \theta \leq 31.97°$ using ω–2θ scans. The scan width was 0.54+0.54tg(θ)° in ω. Backgrounds were measured 1/2 the total time of the peak scans. The intensities of three standard reflections were monitored regularly (every 60 min). The intensities of the standard reflections indicated a crystal decay of 8% (the data were corrected for decay). A total of 6973 reflections[15] were collected of which 6117 were unique [$R_{int} = 0.0110$, $R(\sigma) = 0.0402$]; intensities of 3576 reflections were greater than $2\sigma(I)$. Completeness to $2\theta = 0.998$. Empirical absorption correction[16] was applied. The structure was solved by direct methods[17] and subsequent difference syntheses. Anisotropic full-matrix least-squares refinement[18] on F^2 for all non-hydrogen atoms yielded $R_1 = 0.0411$ and $wR^2 = 0.1042$ for 3576 [$I > 2\sigma(I)$] and $R_1 = 0.0843$ and $wR^2 = 0.1126$ for all (6117) intensity data (goodness-of-fit = 0.977; the maximum and mean shift/e.s.d. 0.000 and 0.000; extinction coefficient = 0.013(5)). The maximum and minimum residual electron density in the final difference map was 0.142 and −0.133 e Å^{-3}. Hydrogen atomic positions were calculated from assumed geometries. Hydrogen atoms were included in structure-factor calculations but they were not refined. The isotropic displacement parameters of the hydrogen atoms were approximated from the *U*(eq.) value of the atom they were bonded to.

Compound **1b**. Crystal data: $C_{18}H_{22}N_2O_3$, F_w 314.38, colorless block, size: 0.40×0.30×0.25 mm, monoclinic, space group $P2_1$, $a = 11.478(1)$, $b = 6.660(2)$, $c = 11.593(1)$ Å, $\beta = 103.06(1)°$, $V = 863.3(3)$ Å^3, $T = 295(2)$ K, $Z = 2$, $F(000) = 336$, $D_{calcd} = 1.209$ Mg m^{-3}, $\mu = 0.083$ mm^{-1}. A crystal of **1b** was mounted on a glass fiber. Cell parameters were determined by least-squares of the setting angles of 25 ($17.02 \leq \theta \leq 19.86°$) reflections. Intensity data were collected on an Enraf–Nonius CAD4 diffractometer (graphite monochromator; Mo Kα radiation, $\lambda = 0.710730$ Å) at 295(2) K in the range $3.55 \leq \theta \leq 32.00°$ using ω–2θ scans. The scan width was 0.033° in ω. Backgrounds were measured 1/2 the total time of the peak scans. The intensities of 3 standard reflections were monitored regularly (every 60 min). The intensities of the standard reflections indicated a crystal decay of 3% (the data were corrected for decay). A total of 6873 reflections were collected of which 5975 were unique [$R_{int} = 0.0231$, $R(\sigma) = 0.0539$]; intensities of 3386 reflections were greater than $2\sigma(I)$. Completeness to $2\theta = 0.998$. An empirical absorption correction was applied to the data (the minimum and maximum transmission factors were 0.934 and 1.00). The structure was solved by direct methods. Anisotropic full-matrix least-squares refinement on F^2 for all non-hydrogen atoms yielded $R_1 = 0.0473$ and $wR^2 = 0.1113$ for 3386 [$I > 2\sigma(I)$] and $R_1 = 0.0937$ and $wR^2 = 0.1212$ for all (5975) intensity data (goodness-of fit = 0.941; the maximum and mean shift/e.s.d. 0.002 and 0.000). The maximum and minimum residual electron density in the final difference map was 0.224 and −0.133 e Å^{-3}. Hydrogen atomic positions were calculated from assumed geometries. Hydrogen atoms were included in structure-factor calculations but they were not refined. The isotropic displacement parameters of the hydrogen atoms were approximated from the *U*(eq.) value of the atom they were bonded to.

Acknowledgements

The Hungarian OTKA Foundation (Project No. T29251) is gratefully acknowledged for financial support. J.B. and G.E. would like to thank the OTKA (D32705 and D 29445, respectively) for Postdoctoral Fellowships. M.C. would also like to thank the OTKA (T25910) for partial support with the X-ray crystallography measurements.

References

1. Sheldon, R. A. *Chirotechnology*; Marcel Dekker: New York, 1993.
2. Collins, A. N.; Sheldrake, G. N.; Crosby, J. *Chirality in Industry*; John Wiley and Sons, 1992; pp. 69–77.
3. Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolution*; Wiley: New York, 1981; pp. 253–328.
4. Bálint, J.; Egri, G.; Vass, G.; Schindler, J.; Gajáry, A.; Friesz, A.; Fogassy, E.: *Tetrahedron: Asymmetry* **2000**, *11*, 809–813.
5. Schneider, G.; Feller, A.; Greff, Z.; Lempert, K.; Fetter, J.; Hornyák, G.; Sohár, P.; Fogassy, E.; Ács, M.; Kürthy, M.; Fekete, M. 2069/91 Hungarian Patent Application.
6. Faigl, F.; Fogassy, E.; Ács, M. *Hungarian Patent* 1984, 193199 (*Chem. Abstr.* **1984**, *104*, 190891).
7. Fogassy, E.; Orbán, I.; Faigl, F.; Kiss, C. *Hungarian Patent* 1984, 195174 (*Chem. Abstr.* **1984**, *113*, 23378).
8. Newman, P. *Optical Resolution Procedures for Chemical Compounds, Parts I and II*; Optical Resolution Inf. Center, Manhattan College: Riverdale, New York, 1981; Vol. 2.
9. Juaristi, E.; Escalante, J.; León-Romo, J. L.; Reyes, A. *Tetrahedron: Asymmetry* **1998**, *9*, 715–740.
10. Felder, E.; Pitrè, D.; Boveri, S. *Helv. Chim. Acta* **1969**, *52*, 331.
11. Chapman, D. T.; Crout, D. H. G.; Mahmoudian, M.; Scopes, D. I. C.; Smith, P. W. *J. Chem. Soc., Chem.*

Commun **1996**, *21*, 2415–2416.
12. Gavezzotti, A. *Acc. Chem. Res.* **1994**, *27*, 309–314.
13. Juvancz, Z.; Bradshaw, J. S.; Aggarwal, S. K.; Rouse, C. A.; Tarbet, B. J.; Markides, K. E.; Lee, M. L. *Enantiomer* **1998**, *3*, 89.
14. Knapp, D. R. *Handbook of Analytical Derivatization Reactions*; Wiley: New York, 1979.
15. Harms, K. *XCAD*4 *Data Reduction Program for CAD*4 *Diffractometers*; Philipps-Universität: Marburg, Germany, 1996.
16. (a) North, A. C.; Philips, D. C.; Mathews, F. *Acta Crystallogr.* **1968**, *A24*, 350–359; (b) Reibenspies, J. *DATCOR Program for Empirical Absorption Correction*; Texas A&M University: College Station, TX, USA, 1989.
17. Sheldrick, G. M. *SHELXS*-97 *Program for Crystal Structure Solution*; University of Göttingen: Germany, 1997.
18. Sheldrick, G. M. *SHELXL*-97 *Program for Crystal Structure Refinement*; University of Göttingen: Germany, 1997.