

New resolving bases for ibuprofen and mandelic acid: qualification by binary phase diagrams

Eelco J. Ebbers,^a Bart J. M. Plum,^b Gerry J. A. Ariaans,^a Bernard Kaptein,^b Quirinus B. Broxterman,^b Alle Bruggink*^{a,c} and Binne Zwanenburg*^{a,*}

^a Department of Organic Chemistry, NSR-Center for Molecular Structure, Design and Synthesis, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands

^b DSM Research, Organic Chemistry and Biotechnology Section, P.O. Box 18, 6160 MD Geleen, The Netherlands

^c Chemferm, De Bijster 18, 4800 DX Breda, The Netherlands

Abstract: New resolving bases for ibuprofen **1** and mandelic acid **2** were studied and qualified by their binary phase diagrams of the corresponding salts. It was shown that analysis of the binary phase diagrams gives a good prediction for a resolution process. A comparison of resolving bases revealed that (S)-phenylglycinol (**S-7**) is the best resolving base for ibuprofen **1**. By the same procedure, various resolving bases for mandelic acid **2** were studied. The known resolving base (S)-MBA **9** was found to be the best for this acid. © 1997 Elsevier Science Ltd. All rights reserved.

Introduction

Resolution of enantiomers is an important method for the industrial production of enantiopure compounds. The most frequently applied method is formation and selective crystallization of diastereomeric salts. The major problem of this approach is identifying a suitable resolving agent. Until now, no suitable method is available to predict a resolving agent for a given racemate.¹ The conditions required for an efficient resolution are: the diastereomeric salts consist of a mechanical mixture of crystals of the pure diastereomers (eutectic mixture); both salt pairs can be crystallized separately and have substantial differences in physico-chemical properties, especially solubilities.²

Optimum conditions (e.g. concentration, temperature) for a resolution process can be quantified by construction of the ternary (solubility) phase diagram. However, this requires a large amount of experimental data. It is a well known fact that binary (melting) phase diagrams are often a good approximation for ternary diagrams especially for selection and qualification of a resolving agent for a given substrate.^{3,4} Thus, the efficiency of a resolution depends on the location of the eutectic. The formation or existence of a eutectic mixture, a primary condition for a resolution, can be determined. Moreover, the diagram allows calculation of the maximum yield (R_{\max}) and efficiency⁵ (S). Starting from the racemic composition ($x_{0.5}$) and going to the isolation of a pure diastereomer, the following equations can be used to calculate these parameters:⁶

$$R_{\max} = \frac{0.5 - x_{\text{eu}}}{1 - x_{\text{eu}}} \times 100\% \quad (R_{\max} = 0 - 50\%) \quad (1)$$

$$S = kt = \frac{1 - 2x_{\text{eu}}}{1 - x_{\text{eu}}} \quad (S = 0 - 1) \quad (2)$$

where x is the molar fraction of the less soluble diastereomer, x_{eu} the eutectic composition, k the chemical yield ($k=2$ for 100%) and t the optical purity ($t=1$ for 100% ee). A more successful resolution is expected when the diagram has a steeper slope, i.e. a larger difference between the melting points

* Corresponding author. Email: zwanenb@sci.kun.nl

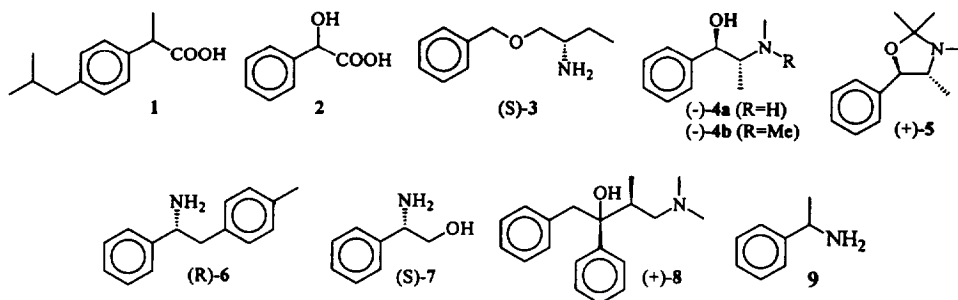


Figure 1. Substrates and resolving bases.

of the pure diastereomers and a more eccentric eutectic. The binary phase diagram of a diastereomeric mixture can be constructed using the Schröder–van Laar equation.⁴

The use of binary phase diagrams for qualification and selection of resolving agents also has some limitations, i.e. diagrams cannot be constructed when thermal decomposition takes place, the role of solvates cannot be observed and both diastereomers are not always available.

Using this approach, five new resolving bases for ibuprofen **1** have been tested, (S)-1-(benzyloxy-methyl)propylamine (BOP) (S)-**3**, (–)-ephedrine (–)-**4a**, (4S,5R)-(+)-1,2,5,5-2,2,3,4-tetramethyl-5-phenyl-1,3-oxazolidine (TPO) (+)-**5**, (R)-1-phenyl-2-*p*-tolylethylamine (PTEA) (R)-**6** and (S)-phenylglycinol (S)-**7**. Also two new resolving bases for mandelic acid **2** were tried, (–)-*N*-methylephedrine (–)-**4b** and (+)-(2S,3R)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol (DMDB) (+)-**8** (Figure 1).

Binary phase diagrams of these ibuprofenates and mandelates were constructed using differential scanning calorimetry (DSC). Experimental data are compared with calculated diagrams using the Schröder–van Laar equation. The diagrams were then used for the qualification of resolving bases for the given substrate. Known resolving agents with well-described physico-chemical data are also included.

Results and discussion

Ibuprofen

According to known methods, ibuprofen **1** can be resolved using either α -methylbenzylamine (MBA)⁷ **9** or lysine.⁸ The binary phase diagram of the ibuprofen·MBA salt **10** has not been reported previously. Therefore, this diagram was constructed revealing a eutectic mixture (Figure 2A). Several of the salt mixtures used to construct this diagram were analyzed by NMR and subjected to elemental analysis. There were no indications for the occurrence of solvates. Both the eutectic point ($x_{eu}=0.66$) and the flat slope are rather unfavorable for a good resolution process. The calculated maximum yield of enantiopure (S)-**9** is limited to 24% starting from the racemic composition. Resolution according to a patent of Ethyl^{7a} confirmed the expected limitations.

Lysine is an interesting resolving base because ibuprofen **1** can be marketed as lysinate salt **11**. The phase diagram of this lysinate **11** could not be constructed as no clear melting behavior of these salts was observed during the DSC experiments. From NMR, DSC and elemental analysis it was concluded that a solvate of salt **11** was formed with 0.5 equiv. of water. Resolution experiments⁸ indicated an efficiency (S_{exp}) of 0.5–0.6.

The binary phase diagram of ibuprofen·(S)-BOP salt **12** is shown in Figure 2B. The conglomerate has an unfavorable eutectic point ($x_{eu}=0.33$) which results in a low maximum yield and efficiency of 25% and 0.5 respectively. Moreover, the small difference between the melting points of the pure diastereomers results in a flat slope and will make a resolution process difficult, which was confirmed by some attempted resolution experiments. Several other 2-amino-1-butanol were investigated but all formed oily ibuprofenates.

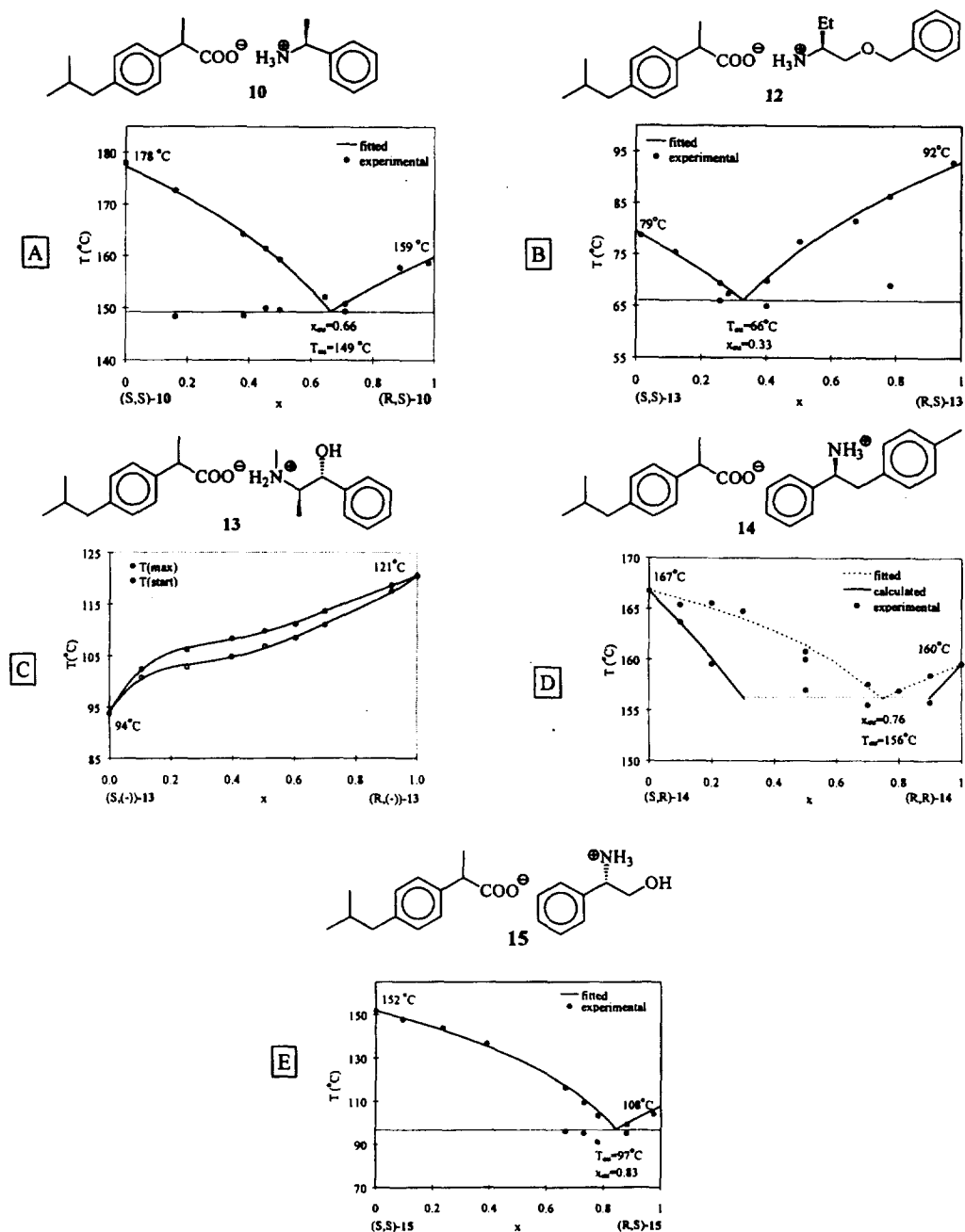


Figure 2. Binary phase diagrams of ibuprofen.

With (–)-ephedrine (–)-4a as a resolving agent the formation of crystalline salt with ibuprofen 1 was achieved. However, this ibuprofenate 13 was not suitable for the resolution of ibuprofen because it exists as a solid solution (Figure 2C) as was deduced from thermograms which showed a single broad peak. A few resolution experiments using (–)-ephedrine (–)-4 in various solvents (e.g. toluene, diisopropyl ether) confirmed the formation of a solid solution as only low des and low yields could be obtained. Several substituted ephedrines were also studied, however all of them failed to crystallize.

Table 1. Resolving agents for ibuprofen **1** and their resolving abilities^a

Salt	Type	ΔH_{exp} (kJ/mole)	ΔH_{calc} (kJ/mole)	T_{exp} (°C)	T_{calc} (°C)	T_{eu} (°C)	x_{eu}	R_{max} (%)	S_{calc}
(S,S)- 10	conglomerate	59.8	61.8	178	178	149	0.66	24	0.48
(R,S)- 10		52.9	58.8	159	159	149			
lysinate 11	solvate								0.5-0.6 ^b
(S,S)- 12	conglomerate	30.0	29.7	80	79	66	0.33	25	0.51
(R,S)- 12		37.4	42.6	93	93				
(S,-)- 13	solid solution	38.5		94					
(R,-)- 13		41.5		121					
(S,R)- 14	partial solid solution / conglomerate	53.5		167					
(R,R)- 14		50.9		160					
(S,S)- 15	conglomerate	44.4	44.2	152	152	97	0.83	40	0.80
(R,S)- 15		20.1	18.5	104	108				

ΔH_{exp} is the experimental heat of fusion, T_{exp} the experimental melting point, ΔH_{calc} and T_{calc} are the calculated values by the Schröder-van Laar equation (5-3), T_{eu} and x_{eu} were determined using the calculated phase diagram, the maximum yield (R_{max}) and efficiency (S) were calculated using equations 5-1, 5-2 and x_{eu} .

Oxazolidine (+)-**5** derived from (-)-ephedrine did produce crystalline salts with ibuprofen **1**, but these salts decomposed during resolution experiments even at room temperature.

Several substituted MBAs[†] were studied as potential resolving agents. Only (R)-PTEA (R)-**6** gave a crystalline ibuprofenate **14**. Constructing the phase diagram of ibuprofenate **14** results in a relatively rare diagram (Figure 2D). Diastereomeric salt mixtures **14** were analyzed by NMR and elemental analysis showing salts in a 1:1 ratio without the inclusion of solvent. Consequently, this diagram is best typified as a solid solution between crystalline diastereomeric salts existing as conglomerates.⁹ The diagram does not represent a complete solid solution because no broad single peaks were observed. Most thermograms showed two overlapping peaks, which could be separated using peak-fitting calculations¹⁰ in some cases. The possibility of the formation of a (1:1) double salt was rejected due to the absence of the typical maximum at $x=0.5$.¹¹ The use of PTEA **6** as a resolving agent for ibuprofen **1** was abandoned because of the above behavior of this ibuprofenate.

Finally, (S)-phenylglycinol (S)-**7** was studied as a possible resolving agent for ibuprofen **1**. The melting diagram (Figure 2E) of the ibuprofenate salt **15** indicated the formation of a diastereomeric mixture with a favorable eutectic composition, moreover the diagram has a steep slope. The calculated diagram based on the pure diastereomers is in full agreement with the experimental results. Hence, phenylglycinol **7** can be qualified as a potentially suitable resolving base for ibuprofen **1**. Based on the eutectic point ($x_{\text{eu}}=0.83$) a resolution with a maximum yield of 40% and efficiency of 0.8 is possible. Resolution experiments of ibuprofen **1** with (S)-phenylglycinol (S)-**7** in acetone or toluene/hexane mixtures resulted in the isolation of (S,S)-**15** as crystalline salt with des up to 53%, yields above 50% and efficiencies of about 0.5. Several other substituted phenylglycinols were synthesized but all of them formed oily ibuprofenates.

The results of the various resolving bases investigated for ibuprofen **1** are summarized in Table 1 showing phenylglycinol **7** as the most promising resolving agent for ibuprofen **1**. Currently, phenylglycinol **7** is further developed as a resolving base for ibuprofen **1**.

Mandelic acid

Mandelic acid **2** is a widely applied resolving agent for various amines.¹² Both antipodes are commercially available at low prices in enantiopure form.¹³ Physico-chemically well-studied

[†] Enantiopure substituted MBAs *N*-(*p*-hydroxybenzyl)-1-(R)-*p*-tolyl-ethylamine, 1-(R)-phenyl-2-*p*-tolylethylamine (R)-**6** and *N*-(*p*-methoxy-*o*-hydroxybenzyl)-1-(R)-*p*-tolyl-ethylamine were kind gifts from Sumitomo Chemical Company, Ltd, Japan.

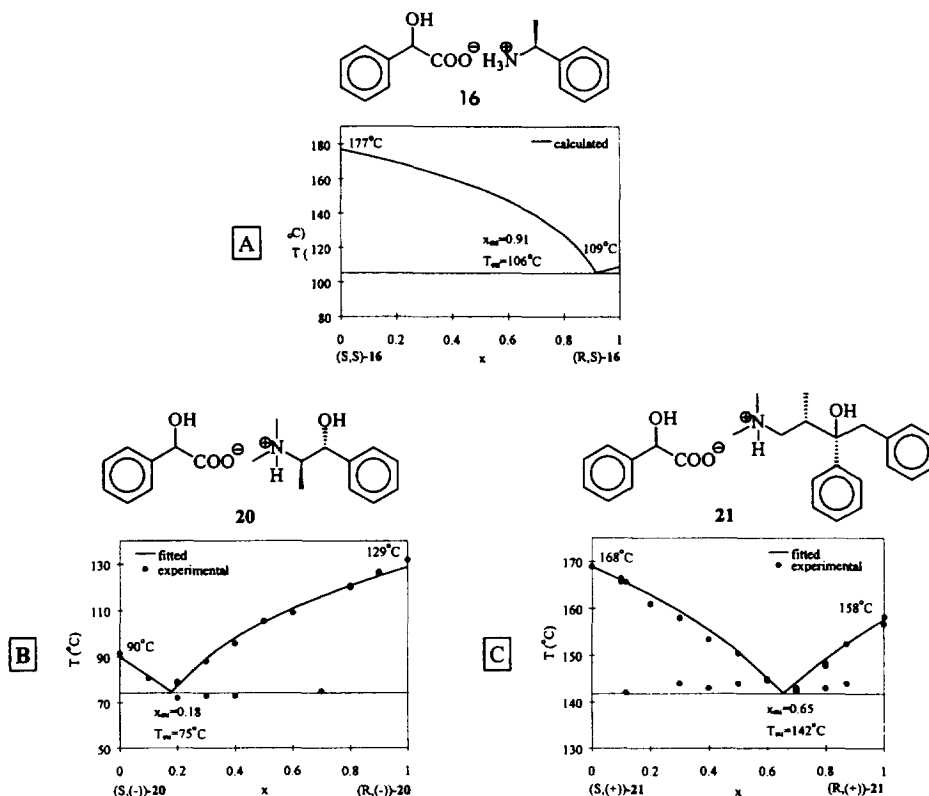


Figure 3. Binary phase diagrams of mandelates.

mandelate salts used for resolution purposes are MBA mandelate **16** (Figure 3A),¹⁴ 2-benzylamino-1-butanol mandelate **17**,^{3,15} (R)-2-*tert*-butyl-3-methylimidazolidin-4-one (BMI) mandelate **18**,^{3,16} and (+)-cinchonine mandelate **19**.¹⁷ Other known resolving agents are brucine,¹⁸ quinine,¹⁸ quinidine,¹⁸ (-)-ephedrine,¹⁹ (-)-2-amino-1-butanol,²⁰ amphetamine^{14c} and adrenaline.^{14c}

Two new resolving bases (-)-*N*-methylephedrine (-)-**4b** and (+)-DMDB (+)-**8**, formed crystalline mandelates **20** and **21** respectively. Their resolving ability was studied by their binary phase diagrams which showed the formation of eutectic mixtures (Figure 3B and 3C). The physico-chemical properties of these mixtures are summarized in Table 2 and were compared with known mandelates **16–19**. The experimental results of mandelates **20** and **21** are in good agreement with the calculated diagrams. However, two deviations were observed when comparing the experimental and calculated heats of fusion of (S,-)-**20** and (R,+)-**21**. In both cases a difference of about 15 kJ/mol was observed. This may imply that the simplified Schröder–van Laar equation is not valid for these sections of the diagrams. This deviation may be attributed to several effects, e.g. the specific heat capacities of the pure diastereomers cannot be neglected, the mixtures of diastereomers do not show ideal behavior in the solid or liquid phase, polymorphism or incongruent melting.²¹

The results in Table 2 clearly reveal MBA **9** as the most appropriate resolving base for mandelic acid **2** (Figure 3A). The eutectic composition of the corresponding mandelate salt **16** lies toward the end of the diagram resulting in an almost ideal efficiency and yield. Moreover, the large difference between the melting points of the pure salts results in a steep slope of the diagram. Also, both enantiomers of MBA **9** are readily available at the same price allowing straightforward preparation of either enantiomer of mandelic acid **2**. Only when the primary amine MBA **9** is not preferred (for example because of amide formation) tertiary amines (-)-*N*-methylephedrine (-)-**4b** and BMI **18** are good alternatives.

Table 2. Resolving agents for mandelic acid 2 and their resolving abilities^a

Salt	Type	ΔH_{exp} (kJ/mole)	ΔH_{calc} (kJ/mole)	T_{exp} (°C)	T_{calc} (°C)	T_{eu} (°C)	x_{eu}	R_{max} (%)	S_{calc}	S_{exp}
(S,S)-16 ³	conglomerate	48.9		177	106	108	0.09	45	0.9	0.86
(R,S)-16		30.3		109						
(p)-17 ³	conglomerate	32.1		108		69	0.32	26	0.45	0.32
(n)-17		28.8		84						
(R,R)-18 ³	conglomerate	51.5		118		76	0.15	41	0.82	0.82
(S,R)-18		30.6		79						
19	solvate								0.3-0.5	
(S,-)-20	conglomerate	30.0	13.5	91	90	75	0.18	39	0.78	
(R,-)-20		40.9	36.9	132	129					
(S,+)-21	conglomerate	59.2	60.0	169	168	142	0.65	23	0.46	
(R,+)-21		55.9	40.0	158	158					

a) ΔH_{exp} is the experimental heat of fusion, T_{exp} the experimental melting point and S_{exp} the experimental efficiency, ΔH_{calc} and T_{calc} are the calculated values by the Schröder-van Laar equation, T_{eu} and x_{eu} were determined by using the calculated phase diagram, the maximum yield (R_{max}) and efficiency (S_{calc}) were calculated by equations 5-1, 5-2 and x_{eu} .

Experimental

¹H-NMR spectra were recorded on a Bruker AC-100 (100 MHz, FT) spectrometer with tetramethylsilane as internal standard. IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer or Perkin-Elmer FTIR 1720-X spectrophotometer. Elemental analyses were performed with a Carlo Erba CHNSO 1108 elemental analyzer. For mass spectroscopy, a double focusing VG 7070E was used. For the chemical ionization (CI) technique, methane was used as the reacting gas. Melting points were measured on a Reichert Thermopan microscope (uncorrected) or on a Perkin-Elmer DSC7 instrument. Optical rotations were determined on a Perkin-Elmer 241 polarimeter at 589 nm, equipped with a quartz cell of 1.00 dm path length. The polarimeter was connected with a thermostat for exact temperature control. For column chromatography, the 'flash technique'²² was used with silica gel 60H (Merck) as the stationary phase and a pressure of about 1.5 bar. Tetrahydrofuran was distilled from lithium aluminum hydride. All other solvents and reagents were either p.a. or 'reinst' quality and used as obtained from the supplier.

Racemic and enantiopure (S)-ibuprofen was a gift from DSM Andeno, Venlo, The Netherlands. (R)-ibuprofen was prepared by purification of diastereomerically enriched (R)-ibuprofen·(R)-MBA salt^{7a} or (R)-ibuprofen sodium salt.²³ The chiral bases *N*-(*p*-hydroxybenzyl)-1-(*R*)-*p*-tolyl-ethylamine, 1-(*R*)-phenyl-2-*p*-tolyl-ethylamine and *N*-(*p*-methoxy-*o*-hydroxybenzyl)-1-(*R*)-*p*-tolyl-ethylamine were a gift from Sumitomo Chemical Co. Ltd, Japan.

Enantiomeric excesses of ibuprofen and mandelic acid were determined using chiral HPLC (performed on a Spectra Physics HPLC system equipped with a chiral Daicel Chiralcel ODH column, 25×0.46 cm, particle size: 5 μm, ambient temperature): ibuprofen (eluent: hexane:2-propanol:trifluoroacetic acid=980:20:2.5, v/v), mandelic acid (eluent: hexane:2-propanol:trifluoroacetic acid=875:125:2.5, v/v).

DSC thermograms were determined using a Perkin-Elmer DSC7 instrument, calibrated with In and Zn or Sn. Samples (2–10 mg) were weighed with an accuracy of 0.01 mg and encapsulated in stainless steel large volume pans (75 μl). Thermograms were recorded at a scanning rate of 10°C/min, a data rate of 0.4–0.8 sec/point and with an empty pan as reference under a nitrogen atmosphere. Melting points are given as the top of the peaks because of broad peaks. If necessary, deconvolution of peaks was performed using PeakFit[®] version 4 for Win32 (Jandel Scientific Software). Pearson IV peaks were used as the peak description. Solid solution diagrams were constructed using the beginning and maximum of the broad peaks for the *solidus* and *liquidus* curves, respectively. The start temperature for

melting mixtures of diastereomers was corrected with the width of the peaks of the pure diastereomers ($T_{\max} - T_{\text{start}}$).

Preparation of salts

Pure diastereomeric salts were prepared by mixing equimolar amounts of enantiopure base and acid **1** or **2** in ethanol. The salts obtained were allowed to crystallize, filtered and dried in vacuo.

Diastereomeric salt mixtures were prepared as described by Jacques, Collet and Wilen.²⁴ Accurately weighed amounts of the pure salts were dissolved in ethanol and the solution obtained was concentrated and dried in vacuo. The composition of mixtures obtained were analyzed by chiral HPLC on liberated ibuprofen **1** or mandelic acid **2**.

Hydrolysis of ibuprofen and mandelic acid salts (general procedure)

Ibuprofenates were hydrolyzed with 1 N aqueous sulfuric acid at pH 1–2, stirred for 0.5 h at room temperature and extracted with dichloromethane (three times). The combined organic layers were extracted with brine, dried over MgSO_4 and concentrated in vacuo to give ibuprofen **1**.

Mandelates were hydrolyzed with 2 N aqueous hydrochloric acid at pH 1–2, stirred for 0.5 h at room temperature and extracted with ethyl acetate (three times). The combined organic layers were extracted with brine, dried over MgSO_4 and concentrated in vacuo to give mandelic acid **2**.

(S)-1-(Benzyloxymethyl)propylamine (S)-3

Amine (S)-**3** was prepared using the Williamson reaction.²⁵ To a slurry of sodium hydride (6.6 g, 120 mmol) in dry tetrahydrofuran (50 ml) under a nitrogen atmosphere, (S)-2-amino-1-butanol (10.0 g, 110 mmol) was gradually added. The mixture was stirred for 17 h at 80°C and then a solution of benzylchloride (15.6 g, 250 mmol) in dry tetrahydrofuran (100 ml) was added dropwise. The resulting solution was stirred for 20 h at 70°C and subsequently cooled to room temperature. Ethyl acetate (100 ml), methanol (100 ml) and water (100 ml) were added and the resulting solution was concentrated to a volume of about 100 ml. Water (200 ml) was added, the mixture was acidified to pH 1–2 and extracted twice with dichloromethane. The water layer was treated with sodium hydrogen carbonate until pH 11–12 and extracted with dichloromethane (three times). The combined organic layers were dried over MgSO_4 and concentrated in vacuo to give pure (S)-**3** as an oil (15.2 g, 77%). $[\alpha]_{\text{D}}^{25} -18.1$ (methanol, $c=1.0$). IR (CCl_4 , cm^{-1}): ν 3400–2800 (NH), 1100 (C–O). $^1\text{H-NMR}$ (CDCl_3 , ppm): δ 0.85 (t, 3H, CH_3CH_2 , $J=7.0$ Hz), 1.0–1.8 (m, 4H, CH_2CH_3 , NH_2) 2.8–3.0 (m, 1H, CH), 3.1–3.5 (m, 2H, OCH_2CH), 4.52 (s, 2H, OCH_2Ar), 7.1–7.4 (m, 5H, ArH). Literature:²⁶ $[\alpha]_{\text{D}}^{25} -15.7$ and -18.9 (ethanol, $c=1.5$), IR and $^1\text{H-NMR}$ were identical with those described above.

(4S,5R)-2,2,3,4-Tetramethyl-5-phenyl-oxazolidine (+)-(4S,5R)-5

A solution of (–)-ephedrine **4a** (24 g, 140 mmol) and *p*-toluenesulfonic acid (2.5 g, 14 mmol) in a mixture of chloroform (100 ml) and 2,2-dimethoxypropane (90 ml, 700 mmol) was refluxed for one week. The mixture was then cooled to room temperature, concentrated and dissolved in dichloromethane (100 ml). This solution was extracted twice with 1 N aqueous sodium hydroxide and concentrated in vacuo. The product was purified by column chromatography (flash, silica gel 60H, dichloromethane:methanol: Et_3N =600:100:2, v/v) to give pure (+)-(4S,5R)-**5** (4.4 g, 15%). Mp 40–42°C, $[\alpha]_{\text{D}}^{25} +17.7$ (ethanol, $c=1.0$). Literature:²⁷ Mp 39–43°C, $[\alpha]_{\text{D}}^{25} +22.0$ (ethanol). Calculated for $\text{C}_{13}\text{H}_{19}\text{NO}$: 76.06% C, 9.33% H, 6.82% N; found: 75.76% C, 9.19% H, 6.88% N. $^1\text{H-NMR}$ (CDCl_3 , ppm): δ 0.63 (d, 3H, CH_3CH , $J=6.4$ Hz), 1.21 (s, 3H, CH_3C), 1.52 (s, 3H, CH_3C), 2.26 (s, 3H, CH_3N), 3.14 (dq, 1H, CHN , $J=6.4, 8.0$ Hz), 5.03 (d, 1H, CHO , $J=8.0$ Hz), 7.2–7.4 (m, 5H, ArH). MS (EI): m/e (%) 206 (M^++1 , 18), 190 (M^+-Me , 33), 148 (206-acetone, 100), 133 (148-Me, 6).

Ibuprofen·(S)- α -methylbenzylamine salt **10**

(S,S)-**10**: Mp 178.0°C, $[\alpha]_{\text{D}}^{25} +0.89$ (ethanol, $c=1.0$). Calculated for $\text{C}_{21}\text{H}_{29}\text{NO}_2$: 77.03% C, 8.93% H, 4.28% N; found: 76.77% C, 8.84% H, 4.37% N. $^1\text{H-NMR}$ (CDCl_3 , ppm): δ 0.87 (d, 6H, $(\text{CH}_3)_2\text{CH}$,

J=6.5 Hz), 1.32 and 1.35 (2d, 6H, CH_3CHN and CH_3CHCO , J=6.9 Hz), 1.6–1.9 (m, 1H, CHCH_2), 2.41 (d, 2H, CH_2 , J=7.1 Hz), 3.48 (q, 1H, CHCO , J=7.0 Hz), 4.00 (q, 1H, CHN , J=6.9 Hz), 5.96 (s, 3H, NH_3^+), 7.0–7.4 (m, 9H, ArH). IR (KBr, cm^{-1}): ν 3100–2500, 2220 (NH), 1625, 1545 (C=O).

(R,S)-**10**: Mp 158.6°C, $[\alpha]_{\text{D}}^{25} = -40.0$ (ethanol, $c=0.1$). Calculated for $\text{C}_{21}\text{H}_{29}\text{NO}_2$: 77.03% C, 8.93% H, 4.28% N; found: 77.07% C, 8.76% H, 4.39% N. $^1\text{H-NMR}$ (CDCl_3 , ppm): δ 0.83 (d, 6H, $(\text{CH}_3)_2\text{CH}$, J=6.4 Hz), 1.32 and 1.38 (2d, 6H, CH_3CHCO and CH_3CHN , J=6.9 Hz), 1.6–1.9 (m, 1H, CHCH_2), 2.38 (d, 2H, CH_2 , J=7.1 Hz), 3.55 (q, 1H, CHCO , J=6.9 Hz), 4.02 (q, 1H, CHN , J=6.9 Hz), 5.04 (s, 3H, NH_3^+), 7.0–7.4 (m, 9H, ArH). IR (KBr, cm^{-1}): ν 3100–2300, 2200 (NH), 1630, 1550 (C=O).

Resolution of ibuprofen **1** by (S)- α -methylbenzylamine(S)-**9**

Ibuprofen **1** was resolved following a procedure of Ethyl.^{7a} Racemic ibuprofen (RS)-**1** (1.03 g, 5.0 mmol) and triethylamine (0.7 ml, 5.0 mmol) were dissolved in octane (1 ml) under a nitrogen atmosphere. The stirred mixture was heated to 125°C and to the clear solution obtained, (S)-MBA (S)-**9** (0.32 ml, 2.5 mmol) was added dropwise. The white heterogeneous mixture was stirred for 3 h at 125°C and slowly cooled to room temperature. The precipitate was filtered off, washed with octane, dried in vacuo and weighed. A fraction of the salt was hydrolyzed and the ee of liberated ibuprofen **1** was analyzed by chiral HPLC. The principal part of the obtained salt was recrystallized twice from 2-propanol to give pure (S)-ibuprofen·(S)-MBA (S,S)-**10** as white crystals (0.6 g, 1.95 mmol) in 78% yield and with a de of 80.6%. The $^1\text{H-NMR}$ was in full accordance with **10**. The aforementioned patent claims the isolation of optically pure salt **10** in 69% yield after three crystallizations.

(S)-Lysine ibuprofenate **11**

The salts were prepared according to the general procedure using a mixture of water:ethanol=95:5 (v/v) as the solvent.

(S,S)-**11**: Calculated for $\text{C}_{19}\text{H}_{32}\text{N}_2\text{O}_4 \cdot 0.5 \text{H}_2\text{O}$: 63.13% C, 9.20% H, 7.75% N; found: 63.20% C, 9.06% H, 7.63% N. $^1\text{H-NMR}$ (D_2O , ppm): δ 0.84 (d, 6H, $(\text{CH}_3)_2\text{CH}$, J=6.6 Hz), 1.2–2.0 (m, 10H, $(\text{CH}_2)_3$, CH_3CH , $\text{CH}(\text{CH}_3)_2$), 2.45 (d, 2H, CH_2Ar , J=6.9 Hz), 2.97 (t, 2H, CH_2N , J=7.2 Hz), 3.4–3.8 (m, 2H, CHN , CHAr), 7.0–7.4 (m, 4H, ArH).

(RS,S)-**11**: Calculated for $\text{C}_{19}\text{H}_{32}\text{N}_2\text{O}_4 \cdot 0.5 \text{H}_2\text{O}$: 63.13% C, 9.20% H, 7.75% N; found: 63.34% C, 8.84% H, 7.73% N. $^1\text{H-NMR}$ (D_2O , ppm): δ 0.85 (d, 6H, $(\text{CH}_3)_2\text{CH}$, J=6.6 Hz), 1.2–2.0 (m, 10H, $(\text{CH}_2)_3$, CH_3CH , $\text{CH}(\text{CH}_3)_2$), 2.45 (d, 2H, CH_2Ar , J=7.1 Hz), 2.99 (t, 2H, CH_2N , J=7.6 Hz), 3.4–3.8 (m, 2H, CHN , CHAr), 7.0–7.4 (m, 4H, ArH).

(S)-1-Benzylloxymethylpropylamine ibuprofenate **12**

(S,S)-**12**: Calculated for $\text{C}_{24}\text{H}_{35}\text{NO}_3$: 74.77% C, 9.15% H, 3.63% N; found: 74.58% C, 9.17% H, 3.58% N. IR (KBr, cm^{-1}): ν 3100–2500, 2190 (NH), 1640, 1550, 1520 (C=O), 1100 (C–O). $^1\text{H-NMR}$ (CDCl_3 , ppm): δ 0.7–1.0 (m, 9H, $(\text{CH}_3)_2\text{CH}$, CH_3CH_2), 1.2–1.6 (m, 5H, CH_2CH_3 , CH_3CHCO) 1.6–2.0 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 2.40 (d, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, J=7.0 Hz) 2.8–3.1 (m, 1H, CHN), 3.1–3.7 (m, 3H, CHCO , OCH_2CH), 4.46 (s, 2H, OCH_2Ar), 5.43 (s, 3H, NH_3^+), 6.9–7.5 (m, 9H, ArH).

(RS,S)-**12**: Calculated for $\text{C}_{24}\text{H}_{35}\text{NO}_3$: 74.77% C, 9.15% H, 3.63% N; found: 74.55% C, 9.16% H, 3.60% N. IR (KBr, cm^{-1}): ν 3100–2200, 2100 (NH), 1630, 1550, 1530 (C=O). $^1\text{H-NMR}$ (CDCl_3 , ppm): δ 0.7–1.0 (m, 9H, $(\text{CH}_3)_2\text{CH}$, CH_3CH_2), 1.2–1.5 (m, 5H, CH_2CH_3 , CH_3CHCO) 1.6–1.9 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 2.40 (d, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, J=7.0 Hz) 2.8–3.0 (m, 1H, CHN), 3.1–3.7 (m, 3H, CHCO , OCH_2CH), 4.46 (s, 2H, OCH_2Ar), 5.84 (s, 3H, NH_3^+), 6.9–7.5 (m, 9H, ArH).

(-)-Ephedrine ibuprofenate **13**

(S,(-))-**13**: Calculated for $\text{C}_{23}\text{H}_{34}\text{NO}_3$: 74.16% C, 9.20% H, 3.76% N; found: 74.56% C, 9.06% H, 3.86% N. IR (KBr, cm^{-1}): ν 3500–2000 (OH, NH), 1580–1560 (C=O). $^1\text{H-NMR}$ (CDCl_3 , ppm): δ 0.83 (d, 6H, $(\text{CH}_3)_2\text{CH}$, J=6.4 Hz), 0.86 (d, 3H, CH_3CHN , J=6.6 Hz), 1.41 (d, 3H, CH_3CHCO , J=7.1 Hz), 1.5–1.9 (m, 1H, CHCH_2), 2.28 (s, 3H, CH_3N), 2.37 (d, 2H, CH_2 , J=7.1 Hz), 2.76 (dq, 1H,

CHN, $J=6.6, 1.7$ Hz), 3.55 (q, 1H, CHCO, $J=7.1$ Hz), 5.06 (d, 1H, CHOH, $J=1.7$ Hz), 6.9–7.4 (m, 9H, ArH), 7.6 (s, 3H, NH_2^+ , OH).

(RS,(-))-13: Calculated for $\text{C}_{23}\text{H}_{34}\text{NO}_3$: 74.16% C, 9.20% H, 3.76% N; found: 74.08% C, 8.89% H, 3.76% N. IR (KBr, cm^{-1}): ν 3500–2100 (OH, NH), 2490 (NH), 1560 (C=O). $^1\text{H-NMR}$ (CDCl_3 , ppm): δ 0.83 (d, 6H, $(\text{CH}_3)_2\text{CH}$, $J=6.4$ Hz), 0.86 (d, 3H, CH_3CHN , $J=6.6$ Hz), 1.39 (d, 3H, CH_3CHCO , $J=7.1$ Hz), 1.5–1.9 (m, 1H, CHCH₂), 2.24 (s, 3H, CH_3N), 2.35 (d, 2H, CH_2 , $J=7.1$ Hz), 2.76 (dq, 1H, CHN, $J=6.6, 1.7$ Hz), 3.52 (q, 1H, CHCO, $J=7.1$ Hz), 5.07 (d, 1H, CHOH, $J=1.7$ Hz), 6.9–7.4 (m, 9H, ArH), 8.2 (s, 3H, NH_2^+ , OH).

(R)-1-Phenyl-2-p-tolyethylamine ibuprofenate 14

(S,R)-14: $[\alpha]_{\text{D}}^{25} +70.9$ (ethanol, $c=1.0$). Calculated for $\text{C}_{28}\text{H}_{35}\text{NO}_2$: 80.54% C, 8.45% H, 3.35% N; found: 80.30% C, 8.41% H, 3.42% N. IR (KBr, cm^{-1}): ν 3200–2300 (NH), 1625 (C=O). $^1\text{H-NMR}$ (CDCl_3 , ppm): δ 0.89 (d, 6H, $(\text{CH}_3)_2\text{CH}$, $J=6.0$ Hz), 1.47 (d, 3H, CH_3CHCO , $J=7.1$ Hz), 1.6–2.0 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 2.31 (s, 3H, CH_3Ar), 2.44 (d, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $J=7.0$ Hz), 2.8–3.0 (m, 2H, CH_2CHN), 3.65 (q, 1H, CHCO, $J=7.1$ Hz), 4.14 (dd, 1H, CHN, $J=7.8, 8.0$ Hz), 5.16 (s, 3H, NH_3^+), 7.0–7.4 (m, 13H, ArH).

(R,R)-14: $[\alpha]_{\text{D}}^{25} +27.3$ (ethanol, $c=0.3$). Calculated for $\text{C}_{28}\text{H}_{35}\text{NO}_2$: 80.54% C, 8.45% H, 3.35% N; found: 79.83% C, 8.29% H, 3.51% N. IR (KBr, cm^{-1}): ν 3200–2300, 2200–2100 (NH), 1615 (C=O). $^1\text{H-NMR}$ (CDCl_3 , ppm): δ 0.88 (d, 6H, $(\text{CH}_3)_2\text{CH}$, $J=6.5$ Hz), 1.43 (d, 3H, CH_3CHCO , $J=7.1$ Hz), 1.6–2.0 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 2.30 (s, 3H, CH_3Ar), 2.42 (d, 2H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$, $J=7.1$ Hz), 2.8–3.0 (m, 2H, CH_2CHN), 3.60 (q, 1H, CHCO, $J=7.2$ Hz), 4.12 (dd, 1H, CHN, $J=7.8, 7.8$ Hz), 5.17 (s, 3H, NH_3^+), 6.9–7.4 (m, 13H, ArH).

(RS,R)-14: Calculated for $\text{C}_{28}\text{H}_{35}\text{NO}_2$: 80.54% C, 8.45% H, 3.35% N; found: 80.61% C, 8.41% H, 3.42% N. IR (KBr, cm^{-1}): ν 3200–2300, 2200–2100 (NH), 1620 (C=O). $^1\text{H-NMR}$ was identical to (S,R)- and (R,R)-19.

(S)-Phenylglycinol ibuprofenate 15

(S,S)-15: Calculated for $\text{C}_{21}\text{H}_{29}\text{NO}_3$: 73.44% C, 8.51% H, 4.08% N; found: 73.29% C, 8.50% H, 4.25% N. IR (KBr, cm^{-1}): ν 3500–2200, 2180 (OH, NH), 1640, 1550–1520 (C=O). $^1\text{H-NMR}$ (CDCl_3 , ppm): δ 0.88 (d, 6H, $(\text{CH}_3)_2\text{CH}$, $J=6.7$ Hz), 1.45 (d, 3H, CH_3CHCO , $J=7.1$ Hz), 1.6–2.0 (m, 1H, CHCH₂), 2.42 (d, 2H, CH_2Ar , $J=7.1$ Hz), 3.4–3.8 (m, 3H, CH_2OH , CHCO), 4.10 (dd, 1H, CHN, $J=8.5, 4.3$ Hz), 4.76 (s, 4H, OH, NH_3^+), 6.9–7.5 (m, 9H, ArH).

(RS,S)-15: Calculated for $\text{C}_{21}\text{H}_{29}\text{NO}_3$: 73.44% C, 8.51% H, 4.08% N; found: 72.85% C, 8.37% H, 4.06% N. IR (KBr, cm^{-1}): ν 3500–2200, 2160 (OH, NH), 1660, 1550 (C=O). $^1\text{H-NMR}$ (CDCl_3 , ppm): δ 0.89 (d, 6H, $(\text{CH}_3)_2\text{CH}$, $J=6.5$ Hz), 1.46 (d, 3H, CH_3CHCO , $J=7.2$ Hz), 1.6–2.0 (m, 1H, CHCH₂), 2.43 (d, 2H, CH_2Ar , $J=7.0$ Hz), 3.5–3.8 (m, 3H, CH_2OH , CHCO), 4.11 (dd, 1H, CHN, $J=8.5, 4.2$ Hz), 4.76 (s, 4H, OH, NH_3^+), 6.9–7.5 (m, 9H, ArH).

Resolution of ibuprofen 1 by (S)-phenylglycinol (S)-7

Racemic ibuprofen (RS)-1 (0.5 g, 2.4 mmol) and (S)-phenylglycinol (S)-7 (0.33 g, 2.4 mmol) were dissolved in hot acetone (5 ml) or a hot mixture of toluene:hexane=2:1 (v/v) and gradually cooled. The formed crystalline salt (S,S)-15 was filtered off, washed with cold solvent, dried in vacuo and weighed. A fraction of the salt was hydrolyzed and the ee of liberated ibuprofen 1 was analyzed by chiral HPLC. Results: acetone as solvent: 0.52 g (1.5 mmol, 63%), 39.4% de, S=0.50; toluene:hexane=2:1 (v/v) as solvent: 0.60 g (1.8 mmol, 73%), 37% de, S=0.54.

(-)-N-Methylephedrine mandelate 20

(S,(-))-20: $[\alpha]_{\text{D}}^{25} +24.6$ (ethanol, $c=1.0$). Calculated for $\text{C}_{19}\text{H}_{25}\text{NO}_4$: 68.86% C, 7.60% H, 4.23% N; found: 68.59% C, 7.55% H, 4.26% N. IR (KBr, cm^{-1}): ν 3500–3000 (OH), 3000–2100 (NH), 1600 (C=O). $^1\text{H-NMR}$ (CDCl_3 , ppm): δ 1.00 (d, 3H, CH_3CH , $J=6.9$ Hz), 2.67 (s, 6H, $\text{N}(\text{CH}_3)_2$),

3.14 (dq, 1H, $CHCH_3$, $J=2.1, 6.9$ Hz), 4.97 (s, 1H, $CHCO$), 5.41 (d, 1H, CHO , $J=2.1$ Hz), 7.0–7.5 (m, 13H, ArH , NH^+ , 2OH).

(R, $-$)-**20**: $[\alpha]_D^{25} +65.8$ (ethanol, $c=1.0$). Calculated for $C_{19}H_{25}NO_4$: 68.86% C, 7.60% H, 4.23% N; found: 68.67% C, 7.61% H, 4.25% N. IR (KBr, cm^{-1}): ν 3500 (OH), 3400–2200 (NH), 1600 (C=O). 1H -NMR ($CDCl_3$, ppm): δ 1.00 (d, 3H, CH_3CH , $J=7.1$ Hz), 2.70 (s, 6H, $N(CH_3)_2$), 3.12 (dq, 1H, $CHCH_3$, $J=2.0, 7.1$ Hz), 4.94 (s, 1H, $CHCO$), 5.36 (d, 1H, CHO , $J=2.1$ Hz), 7.0–7.5 (m, 13H, ArH , NH^+ , 2OH).

(RS, $-$)-**20**: Calculated for $C_{19}H_{25}NO_4$: 68.86% C, 7.60% H, 4.23% N; found: 68.49% C, 7.58% H, 4.26% N. IR (KBr, cm^{-1}): ν 3500–3000 (OH), 3000–2100 (NH), 1600 (C=O). 1H -NMR ($CDCl_3$, ppm): δ 1.00 (d, 3H, CH_3CH , $J=6.7$ Hz), 2.69 (s, 6H, $N(CH_3)_2$), 3.13 (dq, 1H, $CHCH_3$, $J=2.0, 6.7$ Hz), 4.96 (s, 1H, $CHCO$), 5.39 (d, 1H, CHO , $J=2.0$ Hz), 7.0–7.5 (m, 13H, ArH , NH^+ , 2OH).

(+)-(2*S*,3*R*)-4-Dimethylamino-3-methyl-1,2-diphenyl-2-butanol mandelate **21**

(S,(+))-**21**: $[\alpha]_D^{25} +47.8$ (ethanol, $c=1.0$). Calculated for $C_{27}H_{33}NO_4$: 74.76% C, 7.64% H, 3.22% N; found: 74.36% C, 7.58% H, 3.23% N. FTIR (KBr, cm^{-1}): ν 3500–3000, 3401, 3162 (OH), 3000–2000, 2640, 2400 (NH), 1617 (C=O). 1H -NMR ($CDCl_3$, ppm): δ 0.96 (d, 3H, CH_3CH , $J=6.7$ Hz), 1.9–2.8 (m, 3H, $CHCH_3$, CH_2Ar), 2.40 (s, 6H, $N(CH_3)_2$), 3.0–3.4 (m, 2H, CH_2N), 4.96 (s, 1H, CHO), 7.0–7.6 (m, 15H, ArH), 8.06 (s, 3H, NH^+ , 2OH).

(R,(+))-**21**: $[\alpha]_D^{25} -28.9$ (ethanol, $c=1.0$). Calculated for $C_{27}H_{33}NO_4$: 74.76% C, 7.64% H, 3.22% N; found: 74.36% C, 7.59% H, 3.23% N. FTIR (KBr, cm^{-1}): ν 3500–3000, 3372, 3244 (OH), 3000–2000 (NH), 1623 (C=O). 1H -NMR ($CDCl_3$, ppm): δ 0.95 (d, 3H, CH_3CH , $J=6.5$ Hz), 1.9–2.9 (m, 3H, $CHCH_3$, CH_2Ar), 2.40 (s, 6H, $N(CH_3)_2$), 3.0–3.4 (m, 2H, CH_2N), 4.96 (s, 1H, CHO), 6.28 (s, 3H, NH^+ , 2OH), 7.0–7.6 (m, 15H, ArH).

(RS,(+))-**21**: Calculated for $C_{27}H_{33}NO_4$: 74.76% C, 7.64% H, 3.22% N; found: 74.36% C, 7.58% H, 3.23% N. FTIR (KBr, cm^{-1}): ν 3500–3000, 3372, 3164 (OH), 3000–2100 (NH), 1617 (C=O). 1H -NMR ($CDCl_3$, ppm): δ 0.97 (d, 3H, CH_3CH , $J=6.5$ Hz), 1.9–2.9 (m, 3H, $CHCH_3$, CH_2Ar), 2.41 (s, 6H, $N(CH_3)_2$), 3.0–3.4 (m, 2H, CH_2N), 4.96 (s, 1H, CHO), 6.65 (s, 3H, NH^+ , 2OH), 7.1–7.5 (m, 15H, ArH).

References

1. a) Van der Haest, A. D.; Wijnberg, H.; Leusen, F. J. J.; Bruggink, A. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 523. b) Leusen, F. J. J. *Rationalization of Racemate Resolution: A Molecular Modelling Study*; Ph.D. Thesis: University of Nijmegen, The Netherlands, 1993. c) Van der Haest, A. D. *Classical Resolutions; Design of Resolving Agents and Studies of Diastereomeric Salts*; Ph.D. Thesis: University of Groningen, The Netherlands, 1992.
2. Kozma, D.; Acs, M.; Fogassy, E. *Tetrahedron* **1994**, *50*, 6907 and references cited herein.
3. Kozma, D.; Pokol, G.; Acs, M. *J. Chem. Soc., Perkin Trans. 2* **1992**, 435.
4. Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolution*; John Wiley & Sons: New York, 1981, chap. 2.2.3.
5. Fogassy, E.; Faigl, F.; Darvas, F.; Acs, M.; Toke, L. *Tetrahedron Lett.* **1980**, *21*, 2841.
6. Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994, chap. 7.3.b.
7. a) Manimaran, T.; Impastato, F. J. US 5015764, Ethyl Corp., USA, 18-06-90; *Chem. Abstr.* **115**:135162. b) Nicholson, J. S.; Tantum, J. G. US 4209638, 1980. c) Lukas, H.; Schuster, O.; Rau, G. US 4983765, 1991. d) WO 9315039, Ethyl Corp., USA, 18-12-92; *Chem. Abstr.* **119**:270637.
8. a) Tung, H.; Waterson, S.; Reynolds, S. US 4994604, Merck, 10-01-90. b) Bhattacharya, A.; Fritch, J. R.; Murphy, C. D.; Zeugler, L. D.; McAdams, C. A. US 5380867, Hoechst, 19-10-93.
9. Ref. 4, chap. 2.4.8.
10. Peak-fitting was performed using PeakFit[®] version 4 for Win32 (Jandel Scientific Software). Pearson IV peaks were used as peak descriptors.

11. Ref. 4, chap. 5.1.13.
12. a) Optical Resolution of Amines with Mandelic Acid; Yamakawa Technical Bulletin No. 1, Yamakawa Chemical Industry Co. Ltd: Tokyo, Japan, 1991. b) Ref. 6, pp. 329–344. c) Newman, P. *Optical Resolution Procedures for Chemical Compounds*; Optical Resolution Information Center: New York, 1981.
13. Sheldon, R. A. *Chirotechnology, Industrial Synthesis of Optically Active Compounds*; Marcel Dekker: New York, 1993; p. 156.
14. a) Ingersoll, A. W.; Babcock, S. H.; Burns, F. B. *J. Am. Chem. Soc.* **1933**, *55*, 411. b) Leclerq, M.; Jaques, J. *Bull. Soc. Chim. Fr.* **1975**, *9–10*, 2052. c) Becket, A. H. Chaulis, N. H. *J. Pharm. Sci.* **1966**, *55*, 1155. d) Smith, L. *J. Prakt. Chem.* **84**, 743. e) De Diego, H. L. *Acta Chem. Scand.* **1995**, *49*, 459. f) Larsen, S.; De Diego, H. L. *Models in Chemistry* **1995**, *132*, 441.
15. a) Stoll, A.; Preyer, J.; Hofmann, A. *Helv. Chim. Acta* **1943**, *26*, 929. b) DE 2838882, 15-03-79 (06-09-77), American Cyanamid, USA; *Chem. Abstr.* **90**:203672
16. Acs, M.; Novotny-Bregger, E.; Simon, K.; Argay, G. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2011.
17. Kozma, D.; Nyeki, A.; Acs, M.; Fogassy, E. *Tetrahedron: Asymmetry* **1994**, *5*, 315.
18. Bergman, S. *Arkiv Kemi* **1926**, *9*, 1.
19. a) Jarowski, C.; Hartung, W. H. *J. Org. Chem.* **1947**, *8*, 564. b) Skita; Keil; Meinev, *Berichte* **1933**, 974.
20. Kazan, J.; Chen, S. US 4259521, 31-03-81 (09-10-79), American Cyanamid, USA; *Chem. Abstr.* **95**:6842.
21. Ref. 4, chap. 2.2.3–2.2.4.
22. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
23. Manimaran, T.; Stahly, G. P. *Tetrahedron: Asymmetry* **1993**, *4*, 1949.
24. Ref. 4, pp. 35–36.
25. March, J. *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*; 4th Edn, John Wiley & Sons: New York, 1992, pp. 386–387.
26. a) Touet, J.; Ruault, T.; Brown, E. *Synth. Commun.* **1994**, *24*, 293. b) Touet, J.; Faveriel, L.; Brown, E. *Tetrahedron Lett.* **1993**, *34*, 2957.
27. Hyne, J. B. *J. Am. Chem. Soc.* **1959**, *81*, 6058.

(Received in UK 9 October 1997)