Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 3701–3718

TETRAHEDRON: *ASYMMETRY*

Controlled racemization and asymmetric transformation of α-substituted carboxylic acids in the melt

Eelco J. Ebbers,[a,†] Gerry J. A. Ariaans,[a] Alle Bruggink [a,b,*,‡] 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]*Chemferm, De Bijster 18, 4800 DX Breda, The Netherlands*

Received 13 July 1999; accepted 1 September 1999

Abstract

The racemization and asymmetric transformation of a series of α-substituted carboxylic acids, viz. mandelic acid, hydratropic acid, ibuprofen and naproxen, were studied. Several racemization methods for mandelic acid were studied and it was found that base-catalyzed racemization in aprotic polar solvents was the most efficient method. Moreover, a fast and mild base-catalyzed racemization reaction in the melt was developed. DBN turned out to be a very efficient racemizing base for the substrates studied. Combination of the base-catalyzed racemization in the melt with known resolution processes resulted in crystallization-induced asymmetric transformations. Treating racemic ibuprofen or hydratropic acid with 1.5–2.5 equivalents of enantiopure α-methylbenzylamine and a catalytic amount of DBN resulted in the isolation of enantiomerically enriched ibuprofen or hydratropic acid with ees of up to 75% and almost quantitative yields.

1. Introduction

Despite great advances in biocatalysis and asymmetric synthesis, the resolution of racemates is still an important approach in the industrial synthesis of enantiomerically pure compounds. It is often the most economical and convenient way to prepare enantiopure compounds. Moreover, resolution procedures meeting the conditions of 100% yield together with 100% ee are gaining increasing importance in the (fine-)chemical industry. Traditional resolutions through selective crystallization of diastereomeric salts imply the introduction of in situ racemization of the unwanted isomer resulting in crystallization-induced asymmetric transformations.[1] For amino acids this is a well-known process whereby in situ racemization is achieved under mild conditions through catalytic amounts of Schiff-bases.[2] Apart from amino acids not

* Corresponding authors. E-mail: zwanenb@sci.kun.nl

† Present address: MercaChem, Toernooiveld 100, PO Box 31070, 6503 CB Nijmegen, The Netherlands.

‡ Present address: DSM Research, Life Sciences R&D, PO Box 18, 6160 MD Geleen, The Netherlands.

0957-4166/99/$ - see front matter
PII: S0957-4166(99)00387-0

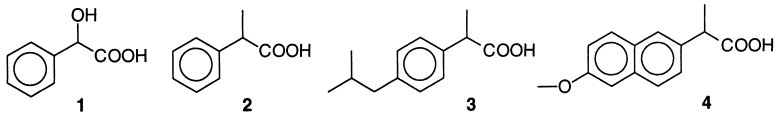


Figure 1.

many compounds can be racemized by a mild and controlled procedure.[3] In order to broaden this scope we made a systematic study of the racemization processes of a series of α-substituted carboxylic acids, viz. mandelic acid **1**, hydratropic acid **2**, ibuprofen **3** and naproxen **4** (Fig. 1). The results obtained were combined with resolution procedures leading to crystallization-induced asymmetric transformations.

2. Results and discussion

2.1. Racemization studies: mandelic acid

From a literature survey on racemizations, it is evident that base catalysis is the most prominent method for α-hydroxycarboxylic acids, e.g. mandelic acid **1**.[4] Some other racemization procedures for mandelic acid **1** are less applicable.[5–8] In order to be compatible with a resolution through diastereomeric salts, our focus was on racemization under basic conditions. Initial results with various bases, including resolving agents, show smooth racemization at 80–130°C (Table 1). Racemization reactions were first order in substrate and base. The observed rate constants (k_{obs}) and half-life periods ($t_{1/2}$) of the racemization were calculated using the least squares method from Eqs. 1 and 2 (pseudo-first order kinetics), where α_0 and α_t are the optical rotations at time zero and t, respectively.

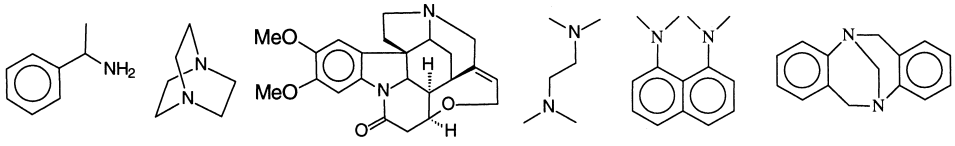
$$\ln\left[\frac{\alpha_0}{\alpha_t}\right] = k_{obs} \cdot t \tag{1}$$

$$t_{1/2} = \frac{\ln 2}{k_{obs}} \tag{2}$$

More detailed studies, including some mandelic acid derivatives, show a preference for aprotic polar solvents such as DMSO in combination with strong organic bases such as DABCO **6** (Table 2). These results are in agreement with studies of Cram et al.[9] Due to differences in solvation, bases are relatively stronger in aprotic polar solvents compared to protic solvents. In aprotic polar solvents, bases are less solvated and relatively 'naked' and therefore more reactive than in protic solvents. Furthermore, it can be concluded that the racemization rate increases with an increase in the electron-withdrawing ability of the substituents at Cα and carboxylic derivative of mandelic acid. Combined with a positive entropy effect, dioxolane **14** is the most easily racemized derivative of mandelic acid.

The racemization results were further improved by employing high concentrations. In fact, the best results were obtained when the reactions were run without solvent at all, i.e. in the melt. When mandelic acid **1** was subjected to racemization by DABCO **6** in the melt at 135°C for 1 h, an acceleration was observed compared to the racemization by DABCO in dimethyl sulfoxide. Mandelic acid **1** is almost completely racemized within 1 h using 1 equiv. of DABCO in the melt at 135°C, while racemization in dimethyl sulfoxide with 10 equiv. of DABCO at 135°C has a half-life of about 1 h. Racemization in the melt also took place using the resolving base MBA **5** with a half-life period of almost 1 h. Thus this method has good promise for a crystallization-induced asymmetric transformation of mandelic acid **1**.

Table 1
Racemization of mandelic acid (*S*)-**1**[a]



5 **6** **(-)-7** **8** **9** **10**

Entry	Base	[Base] (M)	k_{obs} (10^{-4} s^{-1})[b]	$t_{½}$ (h)[b]
1	MBA (**5**)	0.5	0.2	8.9
2	DABCO (**6**)	0.5	0.6	3.1
3	Brucine (**7**)	0.5	1.5	1.3
4	Et_3N	0.5	0.2	12.3
5	dicyclohexylamine	0.4	0.1	15.4
6	TMEDA (**8**)	0.4	0.2	9.3
7	Proton Sponge (**9**)	0.4	N.r.	N.r.
8	Trogers Base (**10**)	0.4	N.r.	N.r.
7	NaOH [c]	0.8	0.1	19.8

a) Conditions: mandelic acid [(S)-**1**] (1.6 mmole), 10 equiv base, hexanol, 130°C. b) N.r. = no reaction. c) 2.3 Equiv base was used in water at 80°C.

Several other bases were investigated to racemize (*S*)-**1** in the melt. The results are summarized in Table 3. These data reveal that TBD **21** gave the best result, followed by DBN **19** and TMEDA **8**. The best racemizing base in solution, i.e. DABCO **6**, gave a homogeneous melt at 130°C and completely racemized mandelic acid **1** at this temperature. The use of DABCO **6** below 130°C resulted in a partly molten mixture and no racemization was observed.

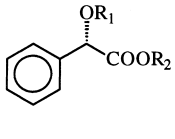
2.2. Racemization studies: α-arylpropionic acids

With the results of mandelic acid in hand and using a dozen different bases, optimal conditions for hydratropic acid **2**, ibuprofen **3** and naproxen **4** were readily found. Complete racemization in the melt was achieved at 90–110°C in no more than 5 h using catalytic amounts of base (1 equiv. of base was required for neutralization). The results are summarized in Tables 4 and 5. The best results were obtained with amidine and guanidine bases **18**, **19** and **21**. A more detailed analysis of these results reveals that there is no linear relationship between the racemization rate and base strength. Based on the equilibria given in Scheme 1, the following explanation can be given: a strong base will shift equilibrium **A** leading to faster racemization, but at the same time decreases the amount of available substrate through shifting equilibrium **B**. Semi-empirical calculations using MOPAC AM1 with the COSMO solvent approximation[12] have been performed on all equilibria. These calculations show a difference between the enthalpies of activation of equilibrium **A** and equilibrium **C** of more than 20 kcal/mol.[13] Equilibrium **C** therefore has almost no influence on the rate of racemization. This strongly suggests that there will be an optimal base strength, which optimally balances the deprotonation at Cα and at the carboxylic acid group.

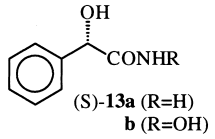
2.3. Asymmetric transformations: mandelic acid

A crystallization-induced asymmetric transformation is also possible while working in a melt. If a 1:1 mixture of two diastereomeric salts is heated there will not be a sharp melting point, but a range in which

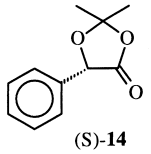
Table 2
Substituent and solvent effects on the racemization rate[a]



(S)-12	R_1	R_2
a	H	Me
b	H	Et
c	H	tBu
d	tBu	tBu
e	COMe	H



(S)-**13a** (R=H)
b (R=OH)



(S)-**14**

Entry	Substrate	Solvent[b]	k_{obs} (10^{-4} s^{-1})[c]	$t_{½}$ (h)[c]
1	(*S*)-**1**	HexOH	0.6	3.1
2	(*S*)-**1**	EtOH[d]	n.r.	n.r.
3	(*S*)-**1**	H_2O[d]	n.r.	n.r.
4	(*S*)-**1**	toluene[e]	n.r.	n.r.
5	(*S*)-**1**	DMSO	1.9	1.0
6	(*S*)-**12a**	DMSO	8.8	0.2
7	(*S*)-**12b**	HexOH	6.1[f]	0.3
8	(*S*)-**12b**	DMSO	13.6	0.1
9	(*S*)-**12b**	DMI	8.9	0.2
10	(*S*)-**12b**	NMP	8.1	0.2
11	(*S*)-**12b**	DMF	8.1	0.2
12	(*S*)- **12c**	DMSO	1.3	1.5
13	(*S*)-**12d**	DMSO	0.3	5.7
14	(*S*)-**12e**	DMSO	19.3	0.1
15	(*S*)-**13a**	DMSO	0.2	9.2
16	(*S*)-**13b**	DMSO	2.6[g]	0.7
17	(*S*)-**14**	DMSO	891	0.002

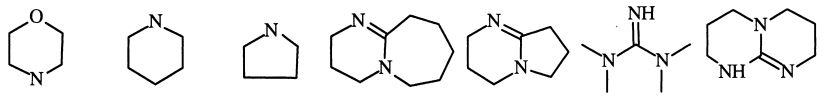
a) Conditions: Substrate (1.8 mmole), DABCO **6** (18 mmole), solvent (35 ml), T=130°C b) Abbreviations: DMI=1,3-dimethyl-2-imidazolidine, NMP=*N*-methyl-2-pyrrolidone, DMF=*N*,*N*-dimethylformamide, DME=1,2-dimethoxyethane. c) n.r.=no reaction. d) T=80°C. e) T=110°C. f) Hexyl mandelate was isolated as the product. g) Racemization also occurred without base under influence of heat (130°C) and after work-up, the substrate could not be isolated..

a melt and the solid salt with the highest melting point are both present (heterogeneous mixture). Within this temperature range an asymmetric transformation is possible.

Many resolving agents for mandelic acid **1** are known,[14,15] of which MBA **5** has been shown to be the most efficient. Initial experiments towards asymmetric transformations in a solvent-free system (heterogeneous melt) using MBA **5** both as the resolving agent and as a racemizing agent met with limited success (quantitative yields but with ees of only 2–5%). Similar results were obtained with brucine and *N*-methylephedrine. Reactions were run in the melt using up to 2 equiv. of base.

As evident from the racemization studies shown above, ‘stronger’ bases are required to achieve efficient racemization during resolution. Thus, more promising results were found when resolving base MBA **5** was combined with racemizing bases DABCO **6**, DBN **19** or TBD **21** (Table 6). Catalytic amounts of additional base are sufficient to reach ees of up to 30% with yields well over 90%. Small amounts (instead of one equiv. or more) of extra base have the advantage of a higher melting temperature range, thus enhancing the rate of racemization. So far for mandelic acid the goal of 100% ee and 100% yield could not be reached. Optimization of reaction conditions should improve these results.

Table 3
Racemization of mandelic acid (*S*)-**1** by 1.1 equiv. of base in the melt[a]



15 **16** **17** **18** **19** **20** **21**

		T=90°C		T=110°C	
Entry	Base	Racemization[b] (%)	Yield (%)	Racemization[b] (%)	Yield (%)
1	Et_3N	4	90	20	95
2	TMEDA **8**	19	93	48	89
3	Proton Sponge **9**	0	95	8	93
4	Trogers base **10**	[c]	95	27[c]	84
5	Morfoline **15**	9	93	25	89
6	Piperidine **16**	0.2[c]	92	1[c]	98
7	Pyrrolidine **17**	11	96	32	90
8	DBU **18**	9	96	28	96
9	DBN **19**	23	99	48	94
10	TMG **20**	0.3	90	5	84
11	TBD **21**	23	95	74	95

a) Conditions: mandelic acid (S)-**1** (1.6 mmole), base (1.8 mmole), under nitrogen, melt, 5 h. b) Determined by HPLC (Chiralcel ODH, ± 0.5%) c) Heterogeneous melt.

Table 4
Racemization of profens (*S*)-**2**–**4** by 1.1 equiv. base in the melt at 110°C[a]

			(*S*)-**2**		(*S*)-**3**		(*S*)-**4**	
Entry	Base	pKa[b]	Racemization (%)[d]	Yield (%)	Racemization (%)[d]	Yield (%)	Racemization (%)[d]	Yield (%)
1	Et_3N	11.0	70	100	67	97	77	100
2	MBA **5**	9.4	2[e]	95	1[e]	96	3[e]	95
3	DABCO **6**	2.8; 8.8	96	97	83	95	4[e]	97
4	TMEDA **8**	5.9; 9.1	89	99	82	96	93	94
5	Proton sponge **9**	9.7; 13.5	89	95	74	97	85	95
6	Morfoline **15**	8.3	67	99	61	95	3[e]	95
7	Piperidine **16**	11.1	82	97	73	98	2[e]	100
8	Pyrrolidine **17**	11.3	95	100	93	98	78	97
9	DBU **18**	(0.214[c])	100	97	100	100	97	100
10	DBN **19**	(0.063[c])	100	97	100	98	100	97
11	TMG **20**	13.6 (<0.06[c])	64	100	43	85	13[e]	98
12	TBD **21**	(9.4[c])	91	91	64	100	68	94

a) Conditions: profen **2-4** (1 mmole), base (1.1 mmole), under nitrogen, melt, 110°C, 5 h. b) Basicity in water.[10] c) Relative basicity in acetonitrile[11] (basicity increases with increasing value). d) Determined by HPLC (Chiralcel ODH). e) Heterogeneous melt.

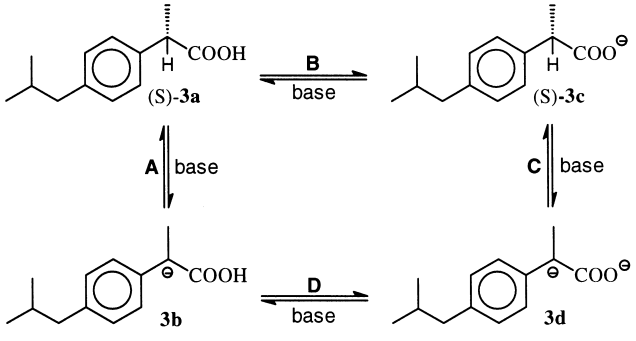
2.4. Asymmetric transformations: α-arylpropionic acids

MBA **5** is also a suitable resolving agent both for hydratropic acid **2**[16] and ibuprofen **3**.[17] Combining this resolving agent with racemization by an additional amount of achiral strong base in the melt gave

Table 5
Racemization of profens (*S*)-**2**–**4** by 1.1 equiv. base in the melt at 90°C[a]

		(S)-**2**		(S)-**3**		(S)-**4**	
Entry	Base	Racemization (%)[b]	Yield (%)	Racemization (%)[b]	Yield (%)	Racemization (%)[b]	Yield (%)
1	Et_3N	39	99	34	95	25	95
2	MBA **5**	[c]		[c]		[c]	
3	DABCO **6**	65	94	28	95	[c]	
4	TMEDA **8**	53	100	27	100	15[c]	88
5	Proton sponge **9**	38	95	36	95	31	95
6	Morfoline **15**	29	96	3[c]	100	[c]	
7	Piperidine **16**	45	93	21	90	2[c]	98
8	Pyrrolidine **17**	66	100	36	87	3[c]	100
9	DBU **18**	89	100	52	96	32	94
10	DBN **19**	100	99	81	97	10[c]	98
11	TMG **20**	22	90	3[c]	97	[c]	
12	TBD **21**	36	97	23	96	28	95

a) Conditions: profen **2**-**4** (1 mmole), base (1.1 mmole), under nitrogen, melt, 90°C, 5 h. b) Determined by HPLC (Chiralcel ODH). c) Heterogeneous melt.



Scheme 1.

Table 6
Crystallization-induced asymmetric transformation of mandelic acid **1**[a]

Entry	MBA (**5**) (equiv.)	Achiral base	(equiv.)	T (°C)	Time (h)	Yield (%)	ee[b] (%)
1	S (1)	DABCO **6**	(1)	130	5	100	2 (S)
2	S (1)	DBN **19**	(0.5)	RT-90	[c]		
3	S (5)	DBN **19**	(0.1)	90	20	89	15 (S)
4	S (2.5)	DBN **19**	(0.05)	120	64	97	27 (S)
5	R (2.5)	TBD **21**	(0.05)	120	64	91	24 (R)

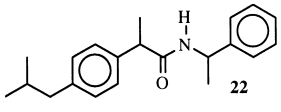
a) Conditions: mandelic acid **1** (6.6 mmole), MBA **5** and achiral base, under nitrogen, heterogeneous melt.
b) Determined by HPLC (Chiralcel ODH). c) Homogeneous melt.

efficient asymmetric transformation with ees of up to 75% and almost quantitative yields (Tables 7 and 8). Several parameters were identified that affect the asymmetric transformation, i.e. base strength, ratio of achiral base:resolving base, reaction temperature, solubility, reaction time and solvent. A good balance between an optimum racemization and resolution was difficult to find. For instance, increasing the amount of DBN results in better racemization in the mother liquor but shows a decrease in yield

Table 7
Crystallization-induced asymmetric transformation of ibuprofen **3**

Entry	MBA **5** (equiv.)	DBN **19** (equiv.)	Method[a]	Time (h)	T (°C)	Yield (%)	Ee (%)[b]	Mother liquor (%ee)[b]
1	R (10)	0.1	A	64	100	92	45 (R)	n.d
2[d]	R (10)	0.1	A	64	100	87	21 (R)	n.d.
3	S (5)	0.5	A	20	90	78	35 (S)	57 (R)
4	S (5)	0.1	A	20	90	98	38 (S)	54 (R)
5	R (5)	0.1	A	64	100	100	37 (R)	n.d.
6	S (2.5)	0.01	A	64	130	84	68 (S)	n.d.
7	R (2.5)	0.01	A	64	135	82	56 (R)	[c]
8	R (2.5)	0.05	A	64	120	91	60 (R)	n.d.
9	R (2.5)	0.05	A	64	130	85	69 (R)	54 (S)
10	R (1)	0.5	A	64	110	92[e]	32 (R)	n.d.
11	S (1)	0.1	A	17	130	91	44 (S)	n.d
12	S (1)	0.1	A	17	130	91	44 (S)	n.d.
13	S (10)	1.0	B	64	80	15	70 (S)	4 (R)
14	S (10)	0.1	B	64	90	88	62 (S)	n.d.
15	S (5)	0.5	B	64	100	49	69 (S)	12 (R)
16	S (2.5)	0.1	B	20	130	60	52 (S)	n.d.
17	R (2.5)	0.05	B	64	110	88	75 (R)	24 (S)
18	S (2.5)	0.05	B	64	130	72	54 (S)	42 (R)
19	R (1.5)	0.5	B	64	120	25	57 (R)	0
20	R (1.5)	0.05	B	112	130	73	73 (R)	32 (S)

a) Method A: a mixture of ibuprofen **3** (1.0 g, 4.9 mmole), MBA **5** (0.64 ml, 5.0 mmole) and an achiral base was stirred at a maximum temperature giving heterogeneous conditions, under nitrogen. The mixture was subsequently cooled to room temperature in about 5 h. Method B: like a) with the exception that the reaction mixture was filtered hot at the reaction temperature. b) Determined by chiral HPLC (Chiralcel ODH) on liberated ibuprofen **3**; n.d.= not determined. c) Formation of amid **22** was observed as a side reaction. d) (*S*)-Ibuprofen was used as substrate. e) The isolated salt consisted of ibuprofen.MBA / ibuprofen.DBN ratio of 2:1.



22

of the final diastereomeric salt. The addition of any polar or apolar solvent has a negative effect on the asymmetric transformation. The best results were obtained by applying 1.5–2.5 equiv. of resolving base together with a catalytic amount of an achiral strong base and using hot filtration during work-up. Long reaction times at 100–130°C are still required to allow sufficient conversion. A net inversion was observed by reacting (*S*)-ibuprofen with the 'wrong' resolving base (*R*)-MBA and DBN. Other resolving agents, e.g. lysine[18] and 1-phenyl-2-*p*-tolyl-ethylamine for ibuprofen **3** and ephedrine[19] for hydratropic acid **2**, in combination with DBN **19**, gave moderate asymmetric transformations in the melt with ees of up to 10% only.

The asymmetric transformation of naproxen **4** was attempted using 1.5–2.5 equiv. of the enantiopure resolving bases MBA **5**,[20] *N*-methyl-glucamine[21] and dehydroabiethylamine[22] in combination with 0.05 equiv. of DBN **19** at 110–130°C. However, no enantiomeric enrichment of naproxen **4** was observed.

3. Scope and limitations

Efficient racemization techniques for various mandelic acid derivatives **1**, **12**–**14** and α-arylpropionic acids **2**–**4** have been found, employing strong organic bases in a solvent-free system (i.e. in the melt).

Table 8
Crystallization-induced asymmetric transformation of hydratropic acid **2**

Entry	MBA **5** (equiv.)	DBN **19** (equiv.)	Method[a]	Time (h)	T (°C)	Yield (%)	Ee (%)[b]	Mother liquor (%ee)[b]
1	S (5)	0.1	A	20	90	90	10 (R)	43 (S)
2	R (2.5)	0.1	B	64	100	72	69 (S)	20 (R)
3	R (1.5)	0.05	B	64	125	94	68 (S)	22 (R)

a) Method A: a mixture of hydratropic acid **2** (2.0 g, 13.4 mmole), MBA **5** and DBN **19** was stirred at a maximum temperature giving heterogeneous conditions, under nitrogen. The mixture was gradually cooled to room temperature and filtered. Method B: like a) with the exception that the reaction mixture was filtered hot at the reaction temperature. b) Determined by chiral HPLC (Chiralcel ODH) on liberated hydratropic acid **4**.

Applying these results in resolution processes has shown the feasibility of asymmetric transformations under these conditions. This method is a useful extension to the asymmetric transformation of chiral carboxylic acids which so far was limited to α-amino acids. A complicating factor is the required amount of resolving agent (1.5–2.5 equiv. are needed for optimal results) and the use of a second (racemizing) base which disturbs the crystallization process. From an industrial point of view the use of excess resolving agent has little relevance as resolving agents have to be recycled anyway. The rather long reaction times combined with relatively high reaction temperatures are more problematic. Higher temperatures are required for fast and efficient racemization. Shorter reaction times and also higher ees can be envisaged by using more efficient resolving bases. The thermal stability of the substrates and resolving agents may also lead to complications. Whereas MBA **5** is completely stable for several days at 120–130°C, other resolving agents, like various alkaloids and glucamines, are less compatible with such conditions. Further research will therefore be directed towards new resolving bases with high thermal stability in combination with high resolution efficiency and good racemization ability. Chiral amidines and guanidines, derived from strong bases which act as efficient racemization catalysts, such as DBU **18**, DBN **19** and TBD **21**, might well provide the compounds in which the desired resolution and racemization properties are combined.

4. Experimental

^{1}H 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 FT-IR 1720-X spectrophotometer. Elemental analysis was performed with a Carlo Erba Instruments CHNSO 1108 elemental analyzer. For mass spectroscopy, a double focusing VG 7070E was used. For the chemical ionization (CI) technique, methane was used as a 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[23] was used with silica gel 60H (Merck) as 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 were a gift from DSM Andeno, Venlo, The Netherlands. (*R*)-Ibuprofen was prepared by purification of diastereomerically enriched (*R*)-ibuprofen, (*R*)-MBA salt **24**[17a] or (*R*)-ibuprofen sodium salt **25**.[24] Enantiomeric excesses of mandelic acid **1**,

hydratropic acid **2**, ibuprofen **3** and naproxen **4** 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): mandelic acid (eluent: hexane:2-propanol:trifluoroacetic acid=875:125:2.5, v/v), hydratropic acid (eluent: hexane:2-propanol:trifluoroacetic acid=950:50:2.5, v/v), ibuprofen (eluent: hexane:2-propanol:trifluoroacetic acid=980:20:2.5, v/v), naproxen (eluent: hexane:2-propanol:trifluoroacetic acid=950:50:2.5, v/v).

*4.1. (*RS*)-Hydratropic acid (*RS*)-**2**

A solution of $NaClO_2$ (179.4 g, 1.6 mol) in water (750 ml) was added dropwise over a period of 3 h to a stirred mixture of hydratropaldehyde 18 (150.5 g, 1.1 mol) in acetonitrile (750 ml) and $NaH_2PO_4 \cdot H_2O$ (35.9 g, 0.26 mol) in water (300 ml) and 35% hydrogen peroxide (112 ml, 1.3 mol) while keeping the temperature at 0–10°C. Oxygen evolved from the solution until the end of the reaction (3 h). To the stirred solution was added Na_2SO_3 (20 g) to destroy unreacted HOCl and H_2O_2, followed by the addition of $NaHCO_3$ until pH 9–10. The resulting mixture was extracted with dichloromethane (three times), acidified with concentrated hydrochloride until pH=1–2 and extracted with dichloromethane (four times). The combined organic layers from the acidic extraction were dried over $MgSO_4$ and concentrated in vacuo to give pure (*RS*)-**2** as an oil (154.3 g, 91%). Calculated for $C_9H_{10}O_2$: 71.98% C, 6.71% H; found: 70.80% C, 6.80% H. IR (CCl_4, cm^{-1}): ν 2500–3500 (OH), 1705 (C=O). ^{1}H NMR ($CDCl_3$, ppm): δ 1.51 (d, 3H, C*H*$_3$, J=7.2 Hz), 3.73 (q, 1H, C*H*, J=7.2 Hz), 7.2–7.4 (m, 5H, Ar*H*).

*4.2. (*R*)-α-Methylbenzylamine salt of (*S*)-hydratropic acid (*R,S*)-**23**

Racemic hydratropic acid (*RS*)-**2** (75 g, 0.5 mol) and (*R*)-MBA (*R*)-**5** (60.5 g, 0.5 mol) were dissolved in a hot mixture of toluene (1 l) and ethanol (250 ml) and allowed to crystallize. The precipitate was filtered off, washed with cold toluene, dried in vacuo and weighed. A fraction of the salt obtained was hydrolyzed with 1N aqueous sulfuric acid, extracted with dichloromethane, dried over $MgSO_4$ and concentrated in vacuo. The ee of liberated **2** was measured using HPLC (Chiralcel ODH, eluent: hexane:2-propanol:trifluoroacetic acid=950:50:2.5, v/v). The main part of the salt obtained was recrystallized three times from toluene:ethanol=4:1 (v/v) to give pure (*R,S*)-**23** as white needles (27 g, 0.1 mol) in 40% theoretical yield and 94% ee. Mp 162.6°C, $[\alpha]_D^{25}$ −19.0 (ethanol, c=1.0). Calculated for $C_{17}H_{21}NO_2$: 75.25% C, 7.80% H, 5.16% N; found: 75.11% C, 7.87% H, 5.20% N. FT-IR (KBr, cm^{-1}): ν 2500–3000, 2223 (NH), 1656, 1562 (C=O). ^{1}H NMR ($CDCl_3$, ppm): δ 1.37 (d, 3H, C*H*$_3$CN, J=6.7 Hz), 1.40 (d, 3H, C*H*$_3$CCO, J=7.1 Hz), 3.55 (q, 1H, C*H*CO, J=7.1 Hz), 4.07 (q, 1H, C*H*N, J=6.7 Hz), 5.6 (s, NH_3^+), 7.1–7.4 (m, 10H, Ar*H*).

*4.3. (*S*)-α-Methylbenzylamine salt of (*R*)-hydratropic acid (*S,R*)-**23**

Hydratropic acid **2** (17.8% ee (*R*), 65.3 g, 0.43 mol) and (*S*)-MBA (*S*)-**5** (52.7 g, 0.43 mol) were dissolved in a hot mixture of toluene:ethanol=4:1 (v/v, 1100 ml) and allowed to crystallize. The precipitate was filtered off, washed with cold toluene, dried in vacuo and weighed. A fraction of the salt obtained was hydrolyzed with 1N aqueous sulfuric acid, extracted with dichloromethane, dried over $MgSO_4$ and concentrated in vacuo. The ee of the liberated **2** was measured using HPLC (Chiralcel ODH, eluent: hexane:2-propanol:trifluoroacetic acid=950:50:2.5, v/v). The principal part of the salt obtained was recrystallized from toluene:ethanol=4:1 (v/v, 600 ml) to give pure (*S,R*)-**23** as white needles (31.8 g, 0.12 mol) in 55% theoretical yield and 98% ee. Mp 163.5°C. Calculated for $C_{17}H_{21}NO_2$: 75.25%

C, 7.80% H, 5.16% N; found: 75.05% C, 7.80% H, 5.18% N. FT-IR and ^{1}H NMR data were in full accordance with (*R*,*S*)-**23**.

*4.4. (*S*)-Hydratropic acid (*S*)-**2***

The (*R*)-MBA·(*S*)-hydratropic acid salt (*R*,*S*)-**23** (20 g, 74 mmol, 94% ee) was hydrolyzed with 1N aqueous sulfuric acid for 1 h at room temperature. The resulting mixture was extracted with dichloromethane (four times). The combined organic layers were extracted with brine, dried over $MgSO_4$ and concentrated in vacuo to give an oil (10.3 g, 93%) which crystallized on standing. Recrystallization from hexane (10 ml) gave pure (*S*)-**2** (7.0 g, 63%). Mp 30–31°C, $[\alpha]_D^{25}$ +79.2 (ethanol, c=1.0). HPLC (Chiralcel ODH, eluent: hexane:2-propanol:trifluoroacetic acid=950:50:2.5, v/v): 99% ee. Calculated for $C_9H_{10}O_2$: 71.98% C, 6.71% H; found: 72.22% C, 6.50% H. FT-IR and ^{1}H NMR data were in full accordance with (*S*)-**2**.

*4.5. (*R*)-Hydratropic acid (*R*)-**2***

The (*S*)-MBA·(*R*)-hydratropic acid salt (*S*,*R*)-**23** (20 g, 74 mmol, 98% ee) was hydrolyzed with 1N aqueous sulfuric acid for 1 h at room temperature. The resulting mixture was extracted with dichloromethane (four times). The combined organic layers were extracted with brine, dried over $MgSO_4$ and concentrated in vacuo to give an oil (9.4 g, 85%) which crystallized on standing. Recrystallization from hexane (20 ml) gave pure (*R*)-**2** in two crops (8.4 g, 76%). Mp 30–31°C, $[\alpha]_D^{25}$ −80.0 (ethanol, c=1.0). HPLC (Chiralcel ODH, eluent: hexane:2-propanol:trifluoroacetic acid=950:50:2.5, v/v): 99% ee. Calculated for $C_9H_{10}O_2$: 71.98% C, 6.71% H; found: 72.40% C, 6.63% H. FT-IR and ^{1}H NMR data were in full accordance with (*R*)-**2**.

*4.6. (*RS*)-2-(6-Methoxy-2-naphthyl)propionic acid (naproxen) (*RS*)-**4***

A mixture of enantiopure (*S*)-**4** (15.0 g, 65.1 mmol) and DBN **19** (8.9 ml, 71.6 mmol) was heated to 120°C under a nitrogen atmosphere. The homogeneous mixture was stirred for 5 h at 120°C and subsequently cooled to room temperature. The salt obtained was dissolved in water (500 ml) and hydrolyzed with 2N aqueous hydrochloric acid (75 ml) for 0.5 h at room temperature. The obtained mixture was extracted with dichloromethane (four times). The combined organic layers were extracted with water and brine, dried over $MgSO_4$ and concentrated in vacuo to give pure (*RS*)-**4** (14.5 g, 97%). Mp 157°C. HPLC (Chiralcel ODH, eluent: hexane:2-propanol:trifluoroacetic acid=950:50:2.5, v/v): 0% ee. Calculated for $C_{14}H_{14}O_3$: 73.03% C, 6.13% H; found: 72.88% C, 5.92% H. IR (KBr, cm^{-1}): ν 2500–3400 (OH), 1700 (C=O). ^{1}H NMR ($CDCl_3$, ppm): δ 1.58 (d, 3H, C*H*$_3$C, J=7.1 Hz), 3.87 (q, 1H, C*H*, J=7.1 Hz), 3.90 (s, 3H, C*H*$_3$O), 7.1–7.8 (m, 6H, Ar*H*).

*4.7. Optical stability of (*S*)-α-methylbenzylamine (*S*)-**5***

(*S*)-MBA (*S*)-**5** (5 ml, 39 mmol, 100% ee) was heated at 125°C for 64 h under a nitrogen atmosphere. The light yellow mixture was cooled to room temperature. A fraction of obtained **5** (100 μl, 0.8 mmol) was dissolved in diethyl ether. $MgSO_4$ (100 mg) and benzaldehyde (200 μl, 2 mmol) were added and the mixture was shaken for 0.5 h. The formed imine was analyzed by HPLC (Chiralpak AD, eluent: hexane:2-propanol=99:1, v/v): 100% ee (*S*).

4.8. Methyl (S)-mandelate (S)-**12a**

(*S*)-Mandelic acid (*S*)-**1** (5.0 g, 33 mmol) was refluxed in a mixture of benzene (25 ml), methanol (3 ml) and concentrated sulfuric acid (0.05 ml) while removing water using a Dean–Stark trap. After completion of the reaction the mixture was cooled to room temperature and washed with a saturated aqueous solution of $NaHCO_3$ (three times) and the combined water layers with diethyl ether (three times). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo to yield a yellow oil (5.1 g, 92%). Distillation (90°C, 0.1 mm Hg) provided a white solid which was recrystallized from hexane giving pure (*S*)-**12a** as white needles (55%). HPLC (Chiralcel ODH, hexane:2-propanol=8:2, v/v): 100% ee (*S*). Mp 55–56°C, $[\alpha]_D^{25}$ +137 (methanol, c=1.5). Calculated for $C_9H_{10}O_3$: 65.05% C, 6.07% H; found: 64.86% C, 5.96% H. IR (KBr, cm^{-1}): ν 3615, 3515 (OH), 2820–3060 (CH), 1735 (C=O). ^1H NMR ($CDCl_3$, ppm): δ 3.46 (d, 1H, O*H*, J=5.1 Hz), 3.76 (s, 3H, OCH_3), 5.18 (d, 1H, C*H*, J=5.1 Hz), 7.2–7.4 (m, 5H, Ar*H*). MS (CI^+): m/e (%) 167 (M^++1, 31), 166 (M^+, 10), 150 (−OH, 10), 149 (−H_2O, 100), 121 (23).

4.9. Ethyl (S)-mandelate (S)-**12b**

(*S*)-Mandelic acid (10.0 g, 66 mmol) (*S*)-**1** was refluxed for 4 h in a mixture of toluene (50 ml), ethanol (16 ml) and concentrated sulfuric acid (0.1 ml) under azeotropic removal of water using a Dean–Stark trap. The mixture was cooled to room temperature and washed with a saturated aqueous solution of $NaHCO_3$ (three times) and the combined water layers with diethyl ether (three times). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo to give an oil (11.6 g, 97%). Recrystallization from hexane provided pure (*S*)-**12b** as a white solid (92%). HPLC (Chiralcel ODH, hexane:2-propanol=8:2, v/v): 100% ee (*S*). Mp 33–34°C, $[\alpha]_D^{25}$ +132.9 (chloroform, c=1.0). Calculated for $C_{10}H_{12}O_3$: 66.65% C, 6.71% H; found: 65.86% C, 6.54% H. IR (KBr, cm^{-1}): ν 3520 (OH), 2900–3080 (CH), 1730 (C=O). ^1H NMR ($CDCl_3$/DMSO-d_6, ppm): δ 1.12 (t, 3H, CH_3, J=6 Hz), 4.06 (dq, 2H, CH_2, J=6 Hz, 1.3 Hz), 5.11 (d, 1H, C*H*, J=5 Hz), 6.05 (d, 1H, O*H*, J=5 Hz), 7.2–7.5 (m, 5H, Ar*H*). MS (CI^+): m/e (%) 181 (M^++1, 8), 180 (M^+, 7), 163 (−H_2O, 35), 107 (−COOEt, 100).

4.10. tert-Butyl (S)-mandelate (S)-**12c**

In a closed flask (*S*)-**1** (3.0 g, 20 mmol) was dissolved in dioxane (50 ml) and concentrated sulfuric acid (3 ml) and then cooled to 0°C. Isobutene (30 ml, 315 mmol) was added and the mixture was stirred for 2 days while warming to room temperature. The resulting mixture was cooled to 0°C and poured into a solution of diethyl ether (200 ml) and 1N aqueous NaOH (125 ml) at 0°C. The layers were separated and the water layer was extracted with diethyl ether (three times). The combined organic layers were dried over $MgSO_4$ and concentrated to give a yellow oil (3.3 g, 80%). The product was purified by column chromatography (silica gel 60H, ethyl acetate:hexane=1:3, v/v) and provided (*S*)-**12c** (1.8 g, 35%) and (*S*)-**12d** (350 mg, 8%). (*S*)-**12c**: mp 69–70°C, $[\alpha]_D^{25}$ +97.4 (methanol, c=1.0), literature[25] (*R*)-**5c**: $[\alpha]_D^{25}$ −119.1 (CCl_4, c=1.05). Calculated for $C_{12}H_{16}O_3$: 69.21% C, 7.74% H; found: 68.56% C, 7.82% H. IR (KBr, cm^{-1}): ν 3610, 3500 (OH), 2800–3100 (CH), 1730 (C=O). ^1H NMR ($CDCl_3$, ppm): δ 1.41 (s, 9H, C(CH_3)$_3$), 3.53 (d, 1H, O*H*, J=6 Hz), 5.03 (d, 1H, C*H*, J=6 Hz), 7.2–7.5 (m, 5H, Ar*H*). MS (CI^+): m/e (%) 209 (M^++1, 2), 153 (−C_4H_9, 12), 135 (153−H_2O, 56), 107 (135−CO, 66), 57 ($C_4H_9^+$, 100). (*S*)-**12d**: mp 34°C, $[\alpha]_D^{25}$ +51.0 (methanol, c=1.3). Calculated for $C_{16}H_{24}O_3$: 72.70% C, 9.15% H; found: 72.72% C, 9.25% H. IR (KBr, cm^{-1}): ν 2850–3100 (CH), 1750, 1715 (C=O). ^1H NMR ($CDCl_3$, ppm): δ 1.26 (s, 9H, CO_2C(CH_3)$_3$), 1.4 (s, 9H, COC(CH_3)$_3$), 4.92 (s, 1H, C*H*), 7.2–7.5 (m, 5H, Ar*H*). MS (CI^+):

m/e (%) 265 (M^++1, 2), 209 (−C_4H_9, 33), 163 (209−CH_2O_2, 82), 135 (163−H_2O, 60), 107 ($PhCHOH^+$, 100).

4.11. O-*Acetyl-(S)-mandelic acid (S)-**12e***

(*S*)-**1** (2.0 g, 13.2 mmol) was added to a cooled mixture (0°C) of pyridine (5 ml), acetic anhydride (1.3 ml, 14.3 mmol), 4-dimethylaminopyridine (10 mg), and dry diethyl ether (20 ml). The mixture was stirred overnight while warming to room temperature. The mixture was acidified with 2 M aqueous hydrochloride and washed with diethyl ether (four times). The combined organic layers were extracted with water and brine, and concentrated in vacuo to give crude (*S*)-**12e** (2.4 g). Recrystallization from water gave pure (*S*)-**12e** as white needles in 91% yield. HPLC (Chiralcel ODH, hexane:2-propanol:trifluoroacetic acid=875:125:2.5, v/v): 100% ee (*S*). Mp 79–80°C, $[\alpha]_D^{25}$ +107.8 (chloroform, c=1.25). Calculated for $C_{10}H_{10}O_4$: 61.85% C, 5.19% H; found: 61.75% C, 5.07% H. IR (KBr, cm^{-1}): ν 2500–3300 (OH, CH), 1755, 1725 (C=O). ^{1}H NMR ($CDCl_3$, ppm): δ 2.16 (s, 3H, C*H*$_3$), 3.76 (s, 3H, OC*H*$_3$), 5.81 (s, 1H, C*H*), 7.2–7.6 (m, 5H, Ar*H*), 11.6 (s, 1H, O*H*). MS (CI^+): m/e (%) 195 (M^++1, 6), 194 (M^+, 2), 177 (−H_2O, 4), 152 (−$COCH_3$, 17), 149 (177−CO, 36), 135 (−CH_3COOH, 100), 107 ($PhCHOH^+$, 93).

4.12. (S)-*Mandelamide (S)-**13a***

Ethyl (*S*)-mandelate (*S*)-**12b** (6.0 g, 33 mmol) was added to a cooled solution (0°C) of 25% ammonia (60 ml) and stirred for 2.5 h while warming to room temperature. The mixture was concentrated and the remaining solid was recrystallized from ethanol to give pure (*S*)-**13a** as white crystals (2.5 g, 52%). From the mother liquor, another fraction (*S*)-**13a** crystallized (0.8 g, 16%). Mp 118–120°C, $[\alpha]_D^{25}$ +94.7 (water, c=2.4), literature[26] [(*R*)-**13a**]: $[\alpha]_D^{25}$ −95.5 (water, c=1.8). Calculated for $C_8H_9NO_2$: 63.57% C, 9.27% N, 6.00% H; found: 63.42% C, 8.98% N, 5.87% H. IR (KBr, cm^{-1}): ν 3100–3500 (OH, NH), 1650 (C=O). ^{1}H NMR (DMSO-d_6, ppm): δ 4.87 (d, 1H, C*H*, J=4.5 Hz), 6.05 (d, 1H, O*H*, J=4.5 Hz), 6.86 (s, 1H, N*H*), 7.06 (s, 1H, N*H*), 7.2–7.7 (m, 5H, Ar*H*). MS (CI^+): m/e (%) 152 (M^++1, 31), 134 (−H_2O, 75), 107 (−$CONH_2$, 100), 77 ($C_6H_5^+$, 19).

4.13. (S)-2-Hydroxy-2-phenylacetohydroxamic acid (S)-*13b*

To a stirred solution of $NH_2OH\cdot HCl$ (4.0 g, 57 mmol) in methanol (20 ml), kept under nitrogen at room temperature, was added a solution of potassium hydroxide (4.8 g, 85 mmol) in methanol (15 ml). The resulting mixture was cooled to 0°C and filtered under a nitrogen atmosphere. To the stirred filtrate under nitrogen ethyl (*S*)-mandelate (*S*)-**12b** (5.0 g, 28 mmol) was added and the solution was immediately filtered under a nitrogen atmosphere. The remaining filtrate was kept at room temperature for 1 h with nitrogen flushing. The solution was acidified with 2 M aqueous acetic acid to pH 5–6 and stirred for 1 h. The resulting mixture was extracted with ethyl acetate (nine times). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo to give a white solid. Recrystallization from ethyl acetate provided pure (*S*)-**13b** as a white crystalline solid (2.6 g, 56%). Mp 114–116°C, $[\alpha]_D^{25}$ +63.4 (water, c=2.4), literature (*S*)-**13b**: $[\alpha]_D^{25}$ +164 (water, c=2.5),[27] [(*R*)-**13b**]: $[\alpha]_D^{25}$ −46 (methanol, c=0.6).[28] Calculated for $C_8H_9NO_3$: 57.48% C, 8.38% N, 5.43% H; found: 57.31% C, 8.13% N, 5.31% H. FT-IR (KBr, cm^{-1}): ν 2500–3500 (OH, NH), 1676 (C=O). ^{1}H NMR (DMSO-d_6, ppm): δ 4.93 (d, 1H, C*H*, J=5 Hz), 6.00 (d, 1H, CHO*H*, J=5 Hz), 7.2–7.5 (m, 5H, Ar*H*), 8.81 (s, 1H, NHO*H*), 10.77 (s, 1H, N*H*). MS (CI^+): m/e (%) 168 (M^++1, 5), 150 (−H_2O, 21), 132 (−2H_2O, 21), 107 (−CONHOH, 100), 77 ($C_6H_5^+$, 27).

4.14. 2,2-Dimethyl-5-(S)-phenyl-1,3-dioxolan-4-one (S)-**14**

A mixture of (*S*)-mandelic acid (*S*)-**1** (10.0 g, 66 mmol) in 2,2-dimethoxypropane (150 ml) and *p*-toluenesulfonic acid (20 mg) was stirred for 2 days at room temperature. The mixture was concentrated to 50 ml and diethyl ether (50 ml) was added. The resulting solution was extracted with 1 M aqueous $NaHCO_3$, water (twice) and brine, dried over $MgSO_4$ and concentrated in vacuo to give crude (*S*)-**7** (13.8 g). Recrystallization from hexane gave pure (*S*)-**14** as white needles (9.8 g, 77%). GC (B-DEX 120, T=80°C): 100% ee (*S*). Mp 72–73°C, $[\alpha]_D^{25}$ +84.0 (chloroform, c=1.0). Calculated for $C_{11}H_{12}O_3$: 68.74% C, 6.29% H; found: 68.09% C, 6.33% H. FT-IR (KBr, cm^{-1}): ν 2870–3070 (CH), 1800 (C=O), 1130 (C–O). ^{1}H NMR ($CDCl_3$, ppm): δ 1.68 (s, 3H, *trans*-C*H*$_3$), 1.73 (s, 3H, *cis*-C*H*$_3$), 5.40 (s, 1H, C*H*), 7.3–7.5 (m, 5H, Ar*H*). MS (CI^+): m/e (%) 193 (M^++1, 2), 163 (−CH_2O, 8), 148 (−COOH, 52), 135 (−acetone, 100), 107 ($PhCHOH^+$, 17).

4.15. Enantiomeric purification of partially enriched (R)-ibuprofen·(R)-MBA (R,R)-**24**

Partly diastereomerically enriched ibuprofen·(*R*)-MBA salt **24** with a de of 69.1% (*R*,*R*) was recrystallized from a hot 2-propanol solution. A fraction of the salt obtained was hydrolyzed with 1N aqueous sulfuric acid, extracted with dichloromethane, dried over $MgSO_4$ and concentrated in vacuo. The ee of liberated **3** was measured using HPLC (Chiralcel ODH, eluent: hexane:2-propanol:trifluoroacetic acid=980:20:2.5, v/v). This procedure was repeated three times to give enantiomerically pure (*R*,*R*)-**24** as a white crystalline solid with 98% ee (*R*). Mp 178°C. Calculated for $C_{21}H_{29}NO_2$: 77.03% C, 8.93% H, 4.28% N; found: 77.02% C, 8.84% H, 4.35% N. ^{1}H NMR ($CDCl_3$, ppm): δ 0.87 (d, 6H, (C*H*$_3$)$_2$CH, J=6.3 Hz), 1.32 and 1.35 (2d, 6H, C*H*$_3$CHN and C*H*$_3$CHCO, J=6.9 Hz), 1.6–1.9 (m, 1H, C*H*CH_2), 2.41 (d, 2H, C*H*$_2$, J=7.0 Hz), 3.47 (q, 1H, C*H*CO, J=6.9 Hz), 4.0 (q, 1H, C*H*N, J=6.9 Hz), 5.8 (s, 3H, N*H*$_3^+$), 7.0–7.4 (m, 9H, Ar*H*).

Enantiomerically pure (*R*,*R*)-**24** salt was hydrolyzed with 1N aqueous sulfuric acid for 1 h at room temperature. The resulting mixture was extracted with dichloromethane (four times). The combined organic layers were extracted with brine, dried over $MgSO_4$ and concentrated in vacuo to give enantiopure (*R*)-ibuprofen (*R*)-**3**.

4.16. Enantiomeric purification of partially enriched (R)-ibuprofen sodium salt (R)-**25**

This method was performed according to a literature procedure. Partially enantiomerically enriched (*R*)-ibuprofen (*R*)-**3** (8.15 g, 39.5 mmol, 67.8% ee) and sodium hydroxide pellets (1.3 g, 32.5 mmol) were dissolved in refluxing acetone (100 ml) and allowed to crystallize at room temperature. The precipitate was filtered off, washed with diethyl ether, dried in vacuo and weighed. Two fractions of the ibuprofen sodium salt **25** were obtained which were combined (5.8 g, 64% total). A fraction of the salt obtained was hydrolyzed with 1N aqueous sulfuric acid, extracted with dichloromethane, dried over $MgSO_4$ and concentrated in vacuo. HPLC (Chiralcel ODH, eluent: hexane:2-propanol:trifluoroacetic acid=980:20:2.5, v/v): 85.5% ee (*R*). The main part of the salt obtained was recrystallized from acetone to give pure (*R*)-**25** as a white solid in three fractions in 32% yield and 96% ee. Mp 229–230°C. $[\alpha]_D^{25}$ +4.6 (ethanol, c=0.5). ^{1}H NMR (DMSO-d_6/D_2O=1/1 (v/v), ppm): δ 0.71 (d, 6H, (C*H*$_3$)$_2$CH, J=3.3 Hz), 1.17 (d, 3H, C*H*$_3$CH, J=7.1 Hz), 1.4–1.9 (m, 1H, C*H*CH_2), 2.28 (d, 2H, C*H*$_2$, J=6.9 Hz), 3.34 (q, 1H, C*H*CO, J=7.1 Hz), 6.97 (d, 2H, ArH, J=8.1 Hz), 7.10 (d, 2H, ArH, J=8.1 Hz). IR (KBr, cm^{-1}): ν 3600–2800 (COO^-Na^+), 1590 (C=O).

Enantiomerically pure (*R*)-**25** salt was hydrolyzed with 1N aqueous sulfuric acid for 1 h at room temperature. The resulting mixture was extracted with dichloromethane (three times). The combined organic layers were extracted with brine, dried over $MgSO_4$ and concentrated in vacuo to give optically pure (*R*)-ibuprofen (*R*)-**3** in quantitative yield. HPLC (Chiralcel ODH, eluent: hexane:2-propanol:trifluoroacetic acid=980:20:2.5, v/v): 96.4% ee (*R*). Mp 49–50°C. $[\alpha]_D^{25}$ −57.5 (ethanol, c=1.0). Calculated for $C_{13}H_{18}O_2$: 75.69% C, 8.80% H; found: 75.87% C, 8.82% H. ^{1}H NMR ($CDCl_3$, ppm): δ 0.89 (d, 6H, $(CH_3)_2CH$, J=6.5 Hz), 1.49 (d, 3H, CH_3CH, J=7.1 Hz), 1.6–2.0 (m, 1H, $CHCH_2$), 2.44 (d, 2H, CH_2, J=7.2 Hz), 3.70 (q, 1H, CHCO, J=7.1 Hz), 7.0–7.4 (m, 5H, ArH, OH). IR (KBr, cm^{-1}): ν 3500–2300 (OH), 1720 (C=O).

*4.17. Racemization of (S)-mandelic acid (S)-**1** by base in solution*

As a typical procedure, (*S*)-**1** (258 mg, 1.7 mmol) was dissolved in dimethyl sulfoxide (35 ml) at 130°C, followed by the addition of DABCO **6** (1.9 g, 17 mmol) and stirred at 130°C under a nitrogen atmosphere. A 1 ml aliquot was taken from the solution by a syringe at appropriate time intervals and was cooled immediately to 0°C. To this 1 ml aliquot, ethanol (1 ml) and 6 M hydrochloric acid (0.2 ml) were added. This mixture was shaken at room temperature (0.5 h) and the optical rotation of the filtrate was measured at 589 nm at 25°C.

*4.18. Racemization of (S)-mandelic acid (S)-**1** in the melt*

As a typical example, a sealed tube, charged with (*S*)-**1** (250 mg, 1.6 mmol) and DBN **19** (223 μl, 1.8 mmol) under nitrogen, was heated at 90°C with stirring for 5 h. The mixture was cooled to 0°C. Water (5 ml) and 2N aqueous hydrochloric acid (2.4 ml) were added to hydrolyze the salt and stirred for 30 min at room temperature. The resulting mixture was extracted with ethyl acetate (three times) and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to give pure **1** in 94% yield. HPLC (Chiralcel ODH, eluent: hexane:2-propanol:trifluoroacetic acid=875/125:2.5, v/v): 52.5% ee (*S*).

*4.19. Racemization of profens (S)-**4**–**6** by DBN **19** in the melt*

As a typical procedure, a sealed tube, charged with (*S*)-**3** (250 mg, 1.2 mmol) and DBN **19** (164 μl, 1.3 mmol) under nitrogen, was stirred at 90°C for 5 h. The mixture was cooled to 0°C. Water (5 ml) and 1 M aqueous sulfuric acid (2 ml) were added to hydrolyze the salt and stirred for 0.5 h at room temperature. The resulting mixture was extracted with dichloromethane (three times). The combined organic layers were extracted with water and brine, dried over $MgSO_4$ and concentrated in vacuo to give pure **3** as an oil which solidified on standing (243 mg, 97%). ^{1}H NMR ($CDCl_3$, ppm): δ 0.89 (d, 6H, $(CH_3)_2C$, J=6.5 Hz), 1.49 (d, 3H, CH_3CHCO, J=7.1 Hz), 1.5–2.0 (m, 1H, $CHCH_2$), 2.44 (d, 2H, CH_2, J=7.1 Hz), 3.69 (q, 1H, CHN, J=7.1 Hz), 7.0–7.4 (m, 4H, ArH), 10.08 (broad s, 1H, OH). HPLC (Chiralcel ODH, eluent: hexane:2-propanol:trifluoroacetic acid=980:20:2.5, v/v): 18.8% ee (*S*).

*4.20. Asymmetric transformation of mandelic acid **1** in the melt by (S)-MBA (S)-**5** and DBN **19***

A mixture of (*RS*)-**1** (1.0 g, 6.6 mmol), (*S*)-MBA (*S*)-**5** (2.2 ml, 17.1 mmol) and DBN **19** (41 μl, 0.33 mmol) was stirred under nitrogen and heated to 140°C. The homogeneous mixture was cooled to 130°C and seeded with a few crystals of pure (*S*)-**1**·(*S*)-**5** salt. The heterogeneous mixture was stirred at 120°C for 64 h and gradually cooled to room temperature in 5 h. The resulting mixture was filtered, washed with

hexane and dried in vacuo providing pure mandelic acid·(*S*)-MBA salt (1.74 g, 97%). ^{1}H NMR ($CDCl_3$, ppm): δ 1.40 (d, 3H, C*H*$_3$, J=6.8 Hz), 4.25 (q, 1H, C*H*NH, d=6.8 Hz), 4.52 (s, 1H, C*H*OH), 6–7 (4H, N*H*$_3^+$, O*H*), 7.1–7.6 (m, 10H, Ar*H*). A fraction of the salt obtained was hydrolyzed with 2N aqueous HCl at pH 2, stirred for 30 min at room temperature and extracted with ethyl acetate (three times). The combined organic layers were dried over $MgSO_4$ and evaporated to give pure **1** (white solid). The ^{1}H NMR data were in agreement with pure **1**. HPLC (Chiralcel ODH, hexane:2-propanol:trifluoroacetic acid=875:125:2.5, v/v): 27.3% ee (*S*).

*4.21. Hydrolysis of profen salts **2–4**: general procedure*

As a typical procedure, a fraction of ibuprofen·MBA salt **24** was hydrolyzed with 1N 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 pure ibuprofen **3** as a white solid.

*4.22. Crystallization-induced asymmetric transformation of ibuprofen **3** by 2.5 equiv. of (*R*)-MBA (*R*)-**5** and 0.05 equiv. of DBN **19** in the melt (method A)*

A mixture of racemic ibuprofen (*RS*)-**3** (1.0 g, 4.9 mmol), (*R*)-MBA (*R*)-**5** (1.6 ml, 12.5 mmol) and DBN **19** (30 μl, 0.24 mmol) was heated to 140°C under a nitrogen atmosphere. The almost homogeneous mixture was cooled to 130°C and the resulting heterogeneous mixture was stirred for 64 h. The mixture was cooled to room temperature in 5 h and the crystallized salt was filtered, washed with hexane and dried to give 1.35 g (85%) of pure ibuprofen·(*R*)-MBA salt **24**. The ^{1}H NMR data were in full agreement with **24**. A fraction of the salt obtained was hydrolyzed according to the general procedure to give pure ibuprofen **3** as a white solid. The ^{1}H NMR data were in full agreement with **3**. HPLC (Chiralcel ODH, eluent: hexane:2-propanol:trifluoroacetic acid=980:20:2.5, v/v): 69.1% ee (*R*). By the same procedure, impure ibuprofen **3** was isolated from a fraction of the mother liquor. HPLC (Chiralcel ODH, eluent: hexane:2-propanol:trifluoroacetic acid=980:20:2.5, v/v): 53.8% ee (*S*).

*4.23. Crystallization-induced asymmetric transformation of ibuprofen **3** by one equiv. of (*R*)-MBA (*R*)-**5** and 0.01 equiv. of DBN **19** in the melt (method A)*

A mixture of racemic ibuprofen (*RS*)-**3** (2.0 g, 9.7 mmol), (*R*)-MBA (*R*)-**5** (3.2 ml, 24.8 mmol) and DBN **19** (12 μl, 0.1 mmol) was heated to 150°C under a nitrogen atmosphere. The homogeneous mixture was cooled to 135°C and the resulting heterogeneous mixture was stirred for 64 h. The mixture was cooled to room temperature in 5 h and the crystallized salt was filtered, washed with hexane and dried to give 2.58 g (82%) of pure ibuprofen·(*R*)-MBA salt **24**. The ^{1}H NMR data were in full agreement with **24**. A fraction of the salt obtained was hydrolyzed according to the general procedure to give pure ibuprofen **3** as a white solid. The ^{1}H NMR data were in full agreement with **3**. HPLC (Chiralcel ODH, eluent: hexane:2-propanol:trifluoroacetic acid=980:20:2.5, v/v): 37.5% ee (*S*). A similar work-up procedure for the mother liquor resulted in the isolation of 0.45 g (15%) of pure amide **22**. ^{1}H NMR ($CDCl_3$, ppm): δ 0.89 (d, 6H, (C*H*$_3$)$_2$CH, J=6.5 Hz), 1.34 (d, 1.5H, C*H*$_3$CHCO, J=6.9 Hz), 1.38 (d, 1.5H, C*H*$_3$CHCO, J=6.9 Hz), 1.50 (d, 3H, C*H*$_3$CHN, J=7.1 Hz), 1.6–2.1 (m, 1H, C*H*CH$_2$), 2.46 (d, 2H, C*H*$_2$, J=7.1 Hz), 3.52 (q, 0.5H, C*H*CO, J=7.1 Hz), 3.55 (q, 0.5H, C*H*CO, J=7.1 Hz), 5.07 (dq, 1H, C*H*N, J=7.1 Hz, 6.5 Hz), 5.65 (broad d, 1H, N*H*, J=6.5 Hz), 7.0–7.4 (m, 9H, Ar*H*). Literature[29] racemic amide (*RS*,*S*)-**22** ([a]resonances due to the (*S*,*S*)-diastereomer **22**): ^{1}H NMR ($CDCl_3$, ppm): δ 1.27[a] (d, 1.5H, C*H*$_3$CHCO,

J=6.9 Hz), 1.31 (d, 1.5H, C*H*$_3$CHCO, J=6.9 Hz), 1.43[a] (d, 1.5H, C*H*$_3$CHN, J=7.1 Hz), 1.44 (d, 1.5H, C*H*$_3$CHN, J=7.2 Hz), 3.45 (q, 0.5H, C*H*CO, J=7.3 Hz), 3.48[a] (q, 0.5H, C*H*CO, J=7.1 Hz).

*4.24. Inversion of (S)-ibuprofen (S)-**3** by 10 equiv. of (R)-MBA (R)-**5** and 0.1 equiv. of DBN **19** in the melt*

A mixture of (*S*)-ibuprofen (*S*)-**3** (1.0 g, 4.9 mmol), (*R*)-MBA (*R*)-**5** (6.4 ml, 49.6 mmol) and DBN **19** (65 μl, 0.53 mmol) was heated to 120°C under a nitrogen atmosphere. The homogeneous mixture was cooled to 100°C and the resulting heterogeneous mixture was stirred for 64 h. The mixture was cooled to room temperature in 5 h and the crystallized salt was filtered, washed with hexane and dried to give 1.37 g (87%) of pure ibuprofen·(*R*)-MBA salt **24**. The ^{1}H NMR data were in full agreement with **24**. A fraction of the salt obtained was hydrolyzed according to the general procedure to give ibuprofen **3** as a white solid. The ^{1}H NMR data were in full agreement with **3**. HPLC (Chiralcel ODH, eluent: hexane:2-propanol:trifluoroacetic acid=980:20:2.5, v/v): 20.8% ee (*R*). By the same procedure, ibuprofen **3** was isolated from a fraction of the mother liquor. HPLC (Chiralcel ODH, eluent: hexane:2-propanol:trifluoroacetic acid=980:20:2.5, v/v): 51.1% ee (*S*).

*4.25. Crystallization-induced asymmetric transformation of ibuprofen **3** by 2.5 equiv. of (S)-MBA (S)-**5** and 0.05 equiv. of DBN **19** in the melt: use of hot filtration (method B)*

A mixture of racemic ibuprofen (*RS*)-**3** (2.0 g, 9.7 mmol), (*S*)-MBA (*S*)-**5** (3.2 ml, 24.8 mmol) and DBN **19** (65 μl, 0.53 mmol) was heated to 110°C under a nitrogen atmosphere. The heterogeneous mixture was stirred for 64 h. The resulting mixture was filtered hot at 110°C, washed with octane and dried to give 2.77 g (88%) of pure ibuprofen·(*S*)-MBA salt **24**. The ^{1}H NMR data were in full agreement with **24**. A fraction of the salt obtained was hydrolyzed according to the general procedure to give pure ibuprofen **3** as a white solid. The ^{1}H NMR data were in full agreement with **3**. HPLC (Chiralcel ODH, eluent: hexane:2-propanol:trifluoroacetic acid=980:20:2.5, v/v): 74.9% ee (*S*). By the same procedure, ibuprofen **3** was isolated from a fraction of the mother liquor. HPLC (Chiralcel ODH, eluent: hexane:2-propanol:trifluoroacetic acid=980:20:2.5, v/v): 24.1% ee (*R*).

*4.26. Crystallization-induced asymmetric transformation of hydratropic acid **2** by 1.5 equiv. of (R)-MBA (R)-**5** and 0.05 equiv. of DBN **19** in the melt (method B)*

A mixture of racemic hydratropic acid (*RS*)-**2** (2.0 g, 13.3 mmol), (*R*)-MBA (*R*)-**5** (2.5 ml, 19.6 mmol) and DBN **19** (81 μl, 0.66 mmol) was heated to 130°C under a nitrogen atmosphere. The almost homogeneous solution was cooled to 125°C and the resulting heterogeneous solution was stirred for 64 h. The mixture was filtered hot at 125°C, washed with octane and dried to give 3.4 g (94%) of pure hydratropic acid·(*R*)-MBA salt **25**. The ^{1}H NMR data were in agreement with **25**. A fraction of the salt obtained was hydrolyzed according to the general procedure to give pure hydratropic acid **2**. The ^{1}H NMR data were in agreement with **2**. HPLC (Chiralcel ODH, eluent: hexane:2-propanol:trifluoroacetic acid=950:50:2.5, v/v): 68.3% ee (*S*). By the same procedure, impure hydratropic acid **2** was isolated from a fraction of the mother liquor. HPLC (Chiralcel ODH, eluent: hexane:2-propanol:trifluoroacetic acid=950:50:2.5, v/v): 22.2% ee (*R*).

Acknowledgements

The authors would like to thank DSM Research for the financial support of the research described.

References

1. Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*; John Wiley & Sons: New York, 1981; Chapter 6.
2. (a) Yamada, S.; Hongo, C.; Yoshioka, R.; Chibata, I. *J. Org. Chem*. **1983**, *48*, 843. (b) Hongo, C.; Yoshioka, R.; Tohyama, M.; Yamada, S.; Chibata, I. *Bull. Chem. Soc. Jpn*. **1983**, *56*, 3744. (c) Yoshioka, R.; Ohtsuki, O.; Senuma, M.; Tosa, T. *Chem. Pharm. Bull*. **1989**, *37*, 883. (d) Bhattacharya, A.; Araullo-McAdams, C.; Meier, M. B. *Synth. Commun*. **1994**, 2449. (e) Yoshioka, R.; Tohyama, M.; Ohtsuki, O.; Yamada, S.; Chibata, I. *Bull. Chem. Soc. Jpn*. **1987**, *60*, 649, 4321. (f) Hongo, C.; Tohyama, M.; Yoshioka, R.; Yamada, S.; Chibata, I. *Bull. Chem. Soc. Jpn*. **1985**, *58*, 433. (g) Shiraiwa, T.; Sjinjo, K.; Kurokawa, H. *Bull. Chem. Soc. Jpn*. **1991**, *64*, 3251, 3741. (h) Miyzaki, H.; Ohta, A.; Kawakatsu, N.; Waki, Y.; Gogun, Y.; Shiraiwa, T.; Kurokawa, H. *Bull. Chem. Soc. Jpn*. **1993**, *66*, 536.
3. Ebbers, E. J.; Ariaans, G. J. A.; Houbiers, J. P. M.; Bruggink, A.; Zwanenburg, B. *Tetrahedron* **1997**, *53*, 9417–9476.
4. (a) DE 2838882, 790315 (770906), American Cyanamid Co., USA, 1979; *Chem. Abstr*. **1979**, *90*, 203672. (b) US Patent 4259521, 810331 (791009), American Cyanamid Co., USA, 1981; *Chem. Abstr*. **1981**, *95*, 6842. (c) Campbell, A. N.; Campbell, A. J. R. *J. Am. Chem. Soc*. **1932**, *54*, 4581. (d) Winther, C. *Phys. Chem*. **56**, 540. (e) Kresge, A. J. *Pure Appl. Chem*. **1991**, *63*, 213. (f) Chiang, Y.; Kresge, A. J.; Praszynsky, P.; Schepp, N. P.; Wirz, J. *Angew. Chem*. **1990**, *102*, 810.
5. Racemization by treatment of talc: Akekawa, A.; Hayakawa, S. *Bull. Chem. Soc. Jpn*. **1987**, *60*, 19.
6. Racemization by treatment of racemate: (a) Kenyon, G. L.; Hegeman, G. D. *Adv. Enzymol*. **1979**, *50*, 325. (b) Gerlt, J. A.; Kozarich, J. W. *J. Am. Chem. Soc*. **1991**, *113*, 9667. (c) Gerlt, J. A.; Gassman, P. G. *J. Am. Chem. Soc*. **1992**, *114*, 5928. (d) Gerlt, J. A.; Gassman, P. G. *J. Am. Chem. Soc*. **1993**, *115*, 11552. (e) Guthrie, J. P.; Kluger, R. *J. Am. Chem. Soc*. **1993**, *115*, 11569. (f) Kenyon, G. L.; Gerlt, J. A.; Petsko, G. A.; Kozarich, J. W. *Acc. Chem. Res*. **1995**, *28*, 178. (g) Babbitt, P. C.; Mrachko, G. T.; Hasson, M. S.; Huisman, G. W.; Kolter, R.; Ringe, D.; Petsko, G. A.; Kenyon, G. L. *Science* **1995**, *267*, 1159. (h) Westheimer, F. H. *Tetrahedron* **1995**, *51*, 3.
7. *O*-Acetyl-mandelic acid was racemized under acidic conditions using NaOAc:AcOH:Ac_2O=10:30:3 at 150°C in dimethyl sulfoxide. Under the same conditions mandelic acid was racemized accompanied by oxidation to benzoic acid.
8. Ethyl mandelate racemized quantitatively under Oppenauer oxidation conditions. However, it was proven that racemization was induced by the base catalyst instead of the oxidation mechanism. Mandelic acid did not racemize under these conditions.
9. (a) Cram, D. J.; Rickborn; Kingsbury, C. A.; Haberfield, P. *J. Am. Chem. Soc*. **1961**, *83*, 3678. (b) Cram, D. J.; Gosser *J. Am. Chem. Soc*. **1963**, *85*, 3890; idem *J. Am. Chem. Soc*. **1964**, *86*, 5457. (c) Roitman, Cram, D. J. *J. Am. Chem. Soc*. **1971**, *93*, 2225.
10. Data obtained from *Beilstein's Handbook of Organic Chemistry*; Springer Verlag: New York, 1986; 4th ed., Parts I–IV.
11. Schwesinger, R. *Chimia* **1985**, *39*, 269.
12. Steward, J. J. P. *MOPAC 93 Manual*; Fujitsu Limited, 1993
13. Ebbers, E. J.; Ariaans, G. J. A.; Bruggink, A.; Zwanenburg, B. In preparation.
14. (a) Kozma, D.; Pokol, G.; Acs, M. *J. Chem. Soc., Perkin Trans. 2* **1992**, 435. (b) Stoll, A.; Preyer, J.; Hofmann, A. *Helv. Chim. Acta* **1943**, *26*, 929. (c) Acs, M.; Novotny-Bregger, E.; Simon, K.; Argay, G. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2011. (d) Kozma, D.; Nyeki, A.; Acs, M.; Fogassy, E. *Tetrahedron: Asymmetry* **1994**, *5*, 315. (e) Bergman, S. *Arkiv Kemi*, **1926**, *9*, 1. (f) Jarowski, C.; Hartung, W. H. *J. Org. Chem*. **1947**, *8*, 564. (g) Skita, A.; Keil, F.; Meiner, H. *Berichte* **1933**, 974. (h) Kazan, J.; Chen, S. US Patent 4259521, 31-03-81 (09-10-79), Am. Cyanamid, USA, 1981; *Chem. Abstr*. **1981**, *95*, 6842.
15. Ebbers, E. J.; Plum, B. J. M.; Ariaans, G. J. A.; Kaptein, B.; Broxterman, Q. B.; Bruggink, A.; Zwanenburg, B. *Tetrahedron: Asymmetry* **1997**, *8*, 4047.
16. (a) Pettersson, K. *Arkiv Kemi* **1956**, *10*, 283. (b) Leclerq, M.; Jacques, J. *Bull. Soc. Chim. Fr*. **1975**, 2052.
17. (a) Manimaran, T.; Impastato, F. J. US Patent 5015764, Ethyl Corp., USA, 18-06-90, 1991; *Chem. Abstr*. **1991**, *115*, 135162. (b) Nicholson, J. S.; Tantum, J. G. US Patent 4209638, 1980. (c) Lukas, H.; Schuster, O.; Rau, G. US Patent 4983765, 1991. (d) WO 9315039, Ethyl Corp., USA, 18-12-92, 1993; *Chem. Abstr*. **1993**, *119*, 270637.
18. (a) Tung, H.; Waterson, S.; Reynolds, S. US Patent 4994604, Merck, 10-01-90. (b) Bhattacharya, A.; Fritch, J. R.; Murphy, C. D.; Zeugler, L. D.; McAdams, C. A. US Patent 5380867, Hoechst, 19-10-93.

19. Roger, R.; Neilson, D. G. *J. Chem. Soc*. **1960**, 627.
20. Kozma, D.; Acs, M.; Fogassy, E. *Tetrahedron* **1994**, *50*, 6907. (b) EP Patent 0132854, Blaschim S.p.A., 19-04-84, 1985; *Chem. Abstr*. **1985**, *103*, 6055
21. Felder, E.; Pitre, D.; Zutter, H. EP Patent 0007116, Syntex, 17-07-79.
22. US Patent 3904683, Syntex, 09-09-75, *Chem. Abstr*. *83*, 206011.
23. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923.
24. Manimaran, T.; Stahly, G. P. *Tetrahedron: Asymmetry* **1993**, *4*, 1949.
25. Brown, H. C.; Pai, G. G. *J. Org. Chem*. **1985**, *50*, 1384.
26. McKenzie, A.; Smith, I. A. *J. Chem. Soc*. **121**, 1353.
27. Kirby, G. W.; Nazeer, M. *Tetrahedron Lett*. **1988**, *29*, 6173.
28. Defoin, A.; Brouillard-Poichet, A.; Streith, J. *Helv. Chim. Acta* **1992**, *75*, 109.
29. Sen, S. E.; Anliker, K. S. *J. Chem. Educ*. **1996**, *73*, 569.