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Resolution of (\pm) -mandelic- and (\pm) -2-(chlorophenoxy)propionicacid derivatives by crystallization of their diastereomeric amides with (*R*)- or (*S*)- α -arylethylamines

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Abstract : An alternative and cost effective route for the resolution in high ees (95-99%) of (\pm) -mandelicand (\pm) -2-(chlorophenoxy)propionic- acid derivatives is reported. The key step involves the covalent derivatization and separation of their diastereometric amides with (R)- or (S)- α -arylethylamines. © 1999 Elsevier Science Ltd. All rights reserved.

The optically active acids such as mandelic acid 1, atrolactic acid 2, 2-methoxy-2-phenylacetic acid 3 and 2-(4-chlorophenoxy)propionic acid 4 are used for the synthesis of chiral phosphine ligands,¹ as intermediates for anticholesteremics or herbicides synthesis.^{2, 3} They are also used for NMR analysis of absolute configuration.⁴ Resolution of these acids has therefore presented a significant challenge in recent years.^{5, 6} Atrolactic acid (\pm)-2 can be resolved with phenylglycinol by crystallization of the diastereomeric salts,^{7, 8} or with 1-phenyl-2-(*p*tolyl)ethyl amine (98.8% ee).^{9, 10}



Only a few procedures are available however for the preparation of the enantiomerically pure forms of the 2methoxy-2-phenylacetic acids 3 and 2-(4-chlorophenoxy)propionic acids 4. R-(-)-2-methoxy-2-phenylacetic acid 3 can be prepared by acid-catalyzed reaction of (2*S*-trans)-3-phenyloxiranemethanol with methanol and oxidation of the resulting (2*S*, 3*R*)-3-methoxy-3-phenyl-1,2-propanediol.¹¹ 2-Methoxy-2-phenylacetic acid (\pm)-3 can be resolved by homochiral alcohols (60% ee).¹² R-(+)-2-(4-chlorophenoxy)propionic acid 4 can be prepared by reaction of 4-chlorophenol on the O-*p*-toluenesulfonylester of the *S*-(-)-ethyl lactate, followed by crystallization of its salt with cyclohexylamine.¹³ (\pm)-4 can be resolved by the lipase OF 360, modified by a bioimprinting procedure.¹⁴ The most practical procedure so far described for the preparation in large scale of enantiopure (-)-4 and (+)-4 seems to be the resolution of (\pm)-4 by brucine via diastereomeric salt formation.¹⁵ In light of the large number of reactions, we were prompted to consider a more widely applicable methodology.

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Furthermore, the preparation and separation of diastereomeric amides, applied for the resolution of mandelicand 2-(chlorophenoxy)propionic- acid derivatives has not yet been developed. Enantiopure derivatives of α methylbenzylamine (α -mba) have proved to be valuable resolving agents and various carboxylic acids were resolved via their diastereomeric salts,¹⁶ or through the chromatographic separation of diastereomeric amides.¹⁷ In this paper, we report our efforts regarding the resolution of these racemic acids via the covalent derivatization and separation of diastereomeric amides with optically active α -arylethylamines.

The optically active mandelic acids 1, atrolactic acids 2 and 2-methoxy-2-phenylacetic acids 3 were condensed respectively with the optically active α -methylbenzylamines 8 (R₄ = Ph) or α -(1-naphthyl)-ethylamines 9 (R₄ = 1-naphthyl) using the dicyclohexylcarbodiimide (DCC), *p*-toluenesulfonic acid (pTsOH) or ClCO₂Et as an activating agent (Scheme1).¹⁸ The amine 9 did not allow us to prepare the corresponding amides in satisfactory yields (20-25%). We also prepared for this study the diastereomeric mixtures 13-16 between (±)-2-(4-chlorophenoxy)propionic acid 4 ; (±)-2-(3-chlorophenoxy)propionic acid 5 ; (±)-2-(2-chlorophenoxy)propionic acid 6 ; (±)- 2-(phenoxy)propionic acid 7 and *R*-(+)-and *S*-(-)- α -mba 8.



The amide formation between enantiopure acids and amines took places without epimerisation of the acid moiety. The pure amides **10-12** were obtained by recrystallization from an acetone/heptane or a methanol/water mixture with some yields ranging between 56 and 83% (Table 1).

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Entry	Acid	R,	R ₁	R.	Amine	i)	Amide 10 ***	Yield	[α] ₂ ²⁵	M.p.
,		1	2	3		,		(%)	1.10	്റ്
								(10)		(0)
1	(-)-1	OH	Н	Ph	(+)- 8	p-TsOH	(+)-10	21	+52.4	110
2	(+)-1	OH	Н	Ph	(-)- 8	p-TsOH	(-)-10,	20	-52.4	112
3	(-)- 2	OH	CH ₃	Ph	(+)-8	DCC	(+)- 11 ,	57	+87.9	116
4	(+)-2	OH	CH ₃	Ph	(-)-8	DCC	(-)-11 _b	56	-87.9	118
5	(-)-3	OCH ₃	H	Ph	(+)-8	ClCO ₂ Et	(+)-12 _n	83	+30.3	122
6	(+)-3	OCH ₃	Н	Ph	(-)-8	$ClCO_2Et$	(-)-12 _b	82	-30.3	123
7	(-)-3	OCH ₁	Н	Ph	(-)-8	ClCO ₂ Et	(-)-12 [°]	83	-145	105
8	(+)-3	OCH ₃	Н	Ph	(+)-8	ClCO ₂ Et	$(+)-12_{d}$	82	+145	105
9	(±)-4	CH ₃	н	4-ClPhO	(+)-8	$ClCO_2Et$	$(+)-13_{a};(+)-13_{d}$	85 ⁴	ref. 20,	ref.20
10	(±)- 4	CH	Н	4-ClPhO	(-)-8	ClCO ₂ Et	$(-)-13_{b};(-)-13_{c}$	85 ^d	ref.20	ref.20
11	(±)-5	CH ₃	н	3-ClPhO	(-)-8	ClCO ₂ Et	$(-)-14_{b};(-)-14_{c}$	87 ª	e	e
12	(±)-6	CH ₃	н	2-ClPhO	(-)-8	ClCO ₂ Et	(-)-15 _b ; (-)-15 _c	83 d	e	c
13	(±)-7	CH ₃	Н	PhO	(-)-8	ClCO ₂ Et	$(-)-16_{h};(-)-16_{c}$	84 ^d	e	e

Table 1. Preparation of amides 10-16 between acids 1-7 and α -methylbenzylamines 8.

a) The de (%) were determined by HPLC using a chiralcel OD column. Eluent system : 2-propanol/heptane (1:9) and ranged from 97 to 99%; b) The notation a, b, c and d denotes the 2*R*, 1'*R*, 2*S*, 1'*S*, 2*R*, 1'S and 2*S*, 1'*R* amides respectively; c) See ref.19; d) Crude yield; e) SeeTable 2 for the separation of the diastereomeric mixture.

Then, we examined the ability of the diastereomeric mixtures of amides to be separated by crystallization and to determine how efficient this methodology could be for the optical resolution of these carboxylic acids.

Thus (\pm) -2-7 were condensed with optically active α -mba 8. The resulting diastereomeric mixture of amides 11 obtained from the racemic atrolactic acid 2 and R-(+)- α -mba 8 was remarkably separated by one single recrystallization from a mixture of methanol/water : the pure amide (+)- 11_a (99% de) was obtained in 25% yield. The amide (-)-11_b was similarly obtained from (\pm)-2 and S-(-)-8. Successive crystallizations from a mixture of methanol/water of amides 12 afforded (+)- 12_a in 38% yield. The pure (-)- 12_a amide was also obtained in the same conditions from (\pm)-3 and S-(-)-8.

A total separation of the diastereomeric mixture 13 between (\pm) -2-(4-chlorophenoxy)propionic acid 4 and S-(-)- 8 was efficiently achieved. Thus, (-)-13_e amide was obtained by crystallization of the mixture 13 from a mixture of methanol/water in 38% yield. The recovery of (-)-13_b from the mother liquor of the crystallization of (-)-13_e was carried out by evaporating the solution to dryness, thus producing a residue which was recrystallized from a toluene/heptane mixture. Similar results were obtained when R-(+)-8 is used for resolution. A total separation of the mixture 16 between (±)-7 and S-(-)-8 was also carried out. Both of the (-)-16_b and (-)-16_e amides were obtained : crystallization from ethanol/water provided (-)-16_e in 37% yield, and the suspension in the mother liquor was found to be the pure (-)-16_b amide. Recrystallization of the mixture 14 from ethanol/methanol afforded (-)-14_e in 39% yield. Repeated recrystallization of the diastereomeric mixture of amides 15 prepared from (±)-6 and S-(-)-8 did not lead to any significant separation of either (-)-15_b or (-)-15_e.

A notable advantage is that a variation of the molar ratio solvent/amides did not greatly affect the resolution efficiency unlike what was often observed for diastereometric salts.²¹ The hydrolysis (75%) of the amides **12-16**

Acid	Resolving agent	Condensing agent	Solvent of crystallization	Separated amide (yield %) ^{a, b}	Hydrolysis conditions	Resolved acid	ee (%) ^c	Overall yield	М.р. (°С)	[α] _D ²⁵
(±)- 2	(+)-8	DCC or p-TsOH	$MeOH/H_2O(2:1)$	(+)- 11 _a (25)	d	-	-	-	-	-
(±)- 2	(-)- 8	DCC	$MeOH/H_2O(2:1)$	(-) -11 _b (26)	d	-	-	-	-	-
(±)- 3	(+)- 8	ClCO ₂ Et	$MeOH/H_2O(2:1)$	(+) -12 , (38)	HCl 6N, 20h	(-)-3	95	29	67	-145
(±)-3	(-) -8	ClCO ₂ Et	$MeOH/H_2O(2:1)$	(-) -12 _b (38)	HCl 6N, 20h	(+)-3	96	29	68	+146
(±) -4	(+)-8	ClCO₂Et or <i>p</i> -TsOH	MeOH/H ₂ O (1 : 1)	(+) -13 _d (38)	HCl 6N, 17h	(-)-4	98	28	103	-36
		-	Toluene/heptane (3: 1) ^e	(+) -13 , (30)	HCl 6N, 17h	(+)-4	97	24	102	+35
(±)- 4	(-)-8	ClCO2Et or p-TsOH	$MeOH/H_2O(1:1)$	(-)- 13 _c (38)	HCl 6N, 17h	(+)-4	97	29	103	+36
			Toluene/heptane (3: 1) ^e	(-)- 13 _b (32)	HCl 6N, 17h	(-)-4	97	24	103	-36
(±)- 5	(-)-8	ClCO2Et or p-TsOH	EtOH/MeO (1: 1)	(-)- 14 _c (39)	HCl 6N, 17h	(+)-5	99	33	91	+31
(±)- 7	(-)-8	ClCO₂Et	EtOH/H ₂ O (10 : 1) suspension ^e	(-)- 16 _c (37) (-)- 16 _b (25)	HCl 6N, 17h HCl 6N, 17h	(+)- 7 (-)- 7	98 98	30 21	88 87	+39 -38

Table 2. Resolution of mandelic- and 2-(chlorophenoxy)propionic- acid derivatives

a) The notation a, b, c and d denotes the 2*R*, 1'*R*, 2*S*, 1'*S*, 2*R*, 1'*S* and 2*S*, 1'*R* amides respectively; b) yield from the racemic acid; c) The ee (%) was determined by HPLC analysis using a chiralpak-WH column with 2mM CuSO₄ aq. solution; d) the hydrolysis conditions were not determined; e) See text.

with hydrochloric acid led to the desired (+)- and (-)-acids in high ees (95-99%; Table 2). It should be emphasized that for the resolutions of both acids 4 and 7, one resolving agent S-(-)-8 afforded both enantiomers in optically pure forms from the same resolving agent without seeding. The resolution of the acids 3-5 and 7 was carried out in 1mmol as well as in 0.1 mol scale, using this procedure.²² In summary, we have developed an alternative method for the resolution of 2-methoxy-2-phenylacetic acid, 2-(4-chlorophenoxy)-, 2-(3-chlorophenoxy)- and 2-(phenoxy)- propionic acids in high ees (95-99%) and relatively good overall yield (25-30%), through the preparation and facile separation of the corresponding diastereomeric mixtures of amides with (R)- or (S)- α -methylbenzylamine. These results confirm the advantages of the α -methylbenzylamine as a simple, yet powerful resolving agent. This procedure is inexpensive since the α -meth is recovered, and seems to be a complementary route to resolve these acids.

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References

- 1. Valentine Jr., D.; Johnson, K. K.; Priester, W.; Sun, R. C.; Toth, K. and Saucy, G. J. Org. Chem., 1980, 45, 3698-703.
- 2. Armani, G.; Bottari, F.; Saettone, M. F. and Serafini, M. F. Farmaco Ed. Sci., 1972, 27 (10), 870-5.
- 3. Bodgan, T. Pestycydy (Warsaw), 1996, 1, 5-9.
- 4. Trost, B. M. and Curran, D. P. Tetrahedron Lett., 1981, 22, 4929-32.
- 5. Tanaka, A.; Kawamoto, T. Nippon Nogei Kagaku Kaishi, 1991, 65 (7), 1115-18.
- 6. Chinchilla, R.; Najera, C.; Yus, M.and Heumann, A. Tetrahedron : Asymmetry, 1991, 2(2), 101-4.
- 7. Hiroyaki, N. Japanese Patent 81 127325 810814.
- 8. Saigo, K.; Miura, H.; Ishizaki, K. and Nohira, H. Bull. Chem. Soc. Jpn, 1982, 55(4), 1188-90.
- 9. Patent JP 91-249373, 910927, Yamakawa Chemical Ind. Japan (1991).
- 10. Jacques, J.; Collet, A. and Wilen, S. H. Enantiomers, racemates and resolution, Krieger Publishing Company,
- Malabar, Florida, 1994. 11. Toa Eiyo Co. Ltd. Japan. Japanese Patent 88 206353, 880822.
- 12. Mazon, A.; Najera, C.; Yus, M. and Heuman, A. Tetrahedron : Asymmetry, 1992, 3 (11), 1455-66.
- 13. Gabard, J. and Collet, A. New J. Chem., 1986, 10, 685-90.
- 14. Ampon, K.; Kawamoto, T.; Fukui, T.; Tanaka, A. J. Biosci. (Penang Malays), 1995, 6 (1), 35-9.
- 15. Witiak, D.T., Ho, T. and Hackney, R. E. J. Med. Chem. 1968, 11, 1086-89.
- 16. Juaristi, E.; Escalante, J.; Leon-Romo, J. L. and Reyes, A. Tetrahedron : Asymmety, 1998, 9, 715-40 and references therein.
- 17. Oi, N.; Kitahara, H.; Aoki. F. J. Chromatogr., 1994, 666 (1-2), 457-62.
- 18. Okumura, K.; Shigekuni, M.; Nakamura, Y. and Shin, C. Chem. Lett., 1996, 1025-26.
- The (S)-N-(α-methylbenzyl)-(S)-2-methoxy-2-phenylacetamide 12, was also prepared using oxalylchloride as condensing agent in 77% yield after purification by chromatography : Trost, B. M., Bunt, R. C. and Pulley, S. R. J. Org. Chem., 1994, 59, 4202-05.
- 20. A Typical procedure for the preparation of these new amides is the following : to a solution of (\pm) -4 acid (40 g, 0.2 mol) in THF (300 mL) was added dropwise triethylamine (21.3 g, 0.21 mol) and ClCO₂Et (22.8 g, 0.21 mol) at 0 °C over a period of 20m. Then S-(-)- 8 (25.4 g, 0.21 mol) was added and the reaction was stirred for 3h at 0 °C. After filtration, concentration and recrystallization from MeOH/H₂O (1 : 1), 23.3 g (38%) of 13_c were obtained. $[\alpha]_D^{25}$ = -22.1 (c 0.48, MeOH); mp = 127 °C ; ¹H NMR (CDCl₃) δ : 1.40 (CH₃CH, d, J = 6.83); 1.54 (OCHCH₃, d, J = 6.83); 4.64 (OCHCH₃, qd, J = 6.83); 5.13 (NCHCH₃, qt, J = 7.32); 6.57 (NH, d, J = 6.83); 6.86 7.36 (Ph, 9H, m). ¹³C NMR (CDCl₃) δ : 18.6 (OCHCH₃); 21.6 (NCHCH₃); 48.2 (NCHCH₃); 75.5 (OCHCH₃); 116.8 155.4 (12C, Ph); 170.9 (C=O). IR (KBr) v : 3332 (NH); 1655 (C=O). MS : 304 (MH*). Anal. Calc. for C_{17H₁₈NO₂Cl : C 67.21; H 5.97; N 4.61; % found : C 67.15; H 6.18; N 4.46. **13**_b was obtained from the filtrate of the crystallization of (-)- **13**_c : thus the filtrate was evaporated to dryness and the residue recrystallized from toluene/heptane (3 : 1) to afford 20.5 g (32.5%) of **13**_b (α]₀²⁵= -60.2 (c 0.5, MeOH); mp = 130 °C. (98.1% de); ¹H NMR (CDCl₃) δ : 1.49 (CH₂CH, d, J = 6.83); 1.57 (OCHCH₃, d, J = 6.83); 4.61 (OCHCH₃, q, J = 6.34); 5.11 (NCHCH₃, q, J = 7.32); 6.53 (NH, d, J = 6.83); 6.78 7.22 (Ph, 9H,m). ¹³C NMR (CDCl₃) δ : 1.86 (OCHCH₃); 21.8 (NCHCH₃); 75.5 (OCHCH₃); 116.9 155.4 (12C, Ph); 1659 (C=O). MS : 304 (MH*). Anal. Calc. for C₁₇H₁₈NO₂Cl : C 67.21; H 5.97; N 4.61 (OCHCH₃, q, J = 6.34); 5.11 (NCHCH₃, q, J = 7.32); 6.53 (NH, d, J = 6.83); 6.78 7.22 (Ph, 9H,m). ¹³C NMR (CDCl₃) δ : 1.86 (OCHCH₃); 21.8 (NCHCH₃); 75.5 (OCHCH₃); 116.9 155.4 (12C, Ph); 170.9 (C=O). IR (KBr) v : 3267 (NH); 1659 (C=O). MS : 304 (MH*). Anal. Calc. for C₁₇H₁₈NO₂Cl : C 67.21; H 5.97; N 4.61; % found : C 67.27; H 5.89; N 4.51. Anal. Calc. for C₁₇H₁₈NO}
- 21. Sakai, K.; Hashimoto, Y.; Kinbara, K.; Saigo, K.; Murakami, H. and Nohira, H. Bull. Chem. Soc. Jpn. 1993, 66, 3414-18.
- 22. Typical procedure for the resolution of (±)-4-5 and 7 acids: the resolution of (±)-4 with S-(-)- α-methylbenzylamine 8 afforded R-(+)-2-(4-chlorophenoxy)propionic acid 4 : the hydrolysis of (-)- 13_e (21 g, 0.07 mol) with 450 mL of HCl (6 mol dm⁻³) under reflux for 17h led to 10.3 g (74%) of pure R-(+)-4 (97% ee). mp = 103 °C, [α]_D²⁵ = +36 (c 0.5, MeOH) after recrystallization from petroleum ether.