



Deracemization of α -Substituted Arylacetic Acids

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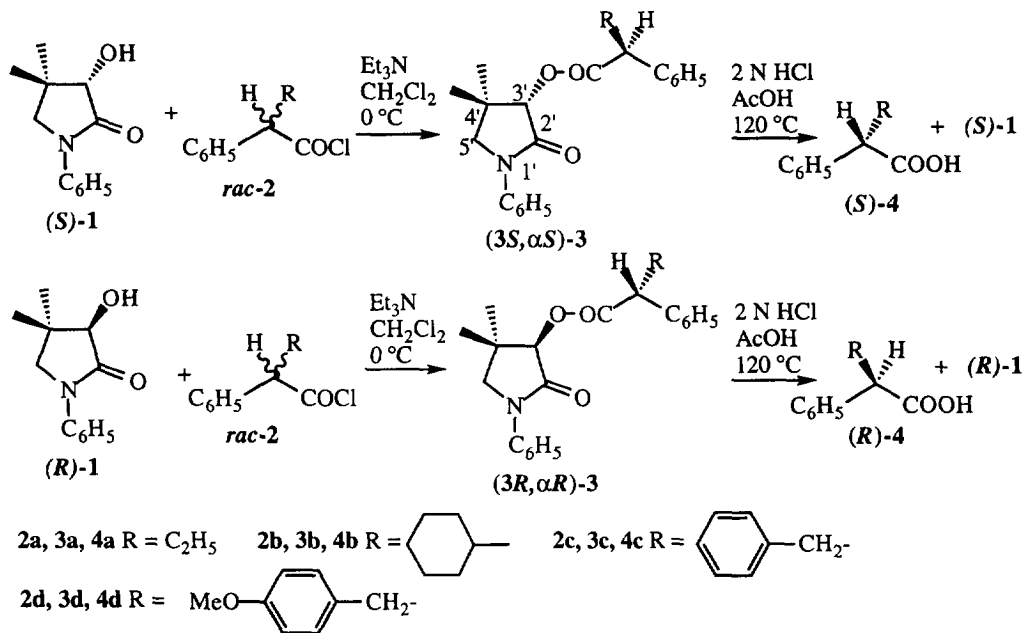
Abstract: Reaction of *rac*- α -substituted arylacetyl chlorides with (*R*)- and (*S*)-3-hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone under standard esterification conditions, gave esters (**3R, α R**)- and (**3S, α S**)-**3**, respectively, with a diastereoselectivity which diminishes on increasing the steric effect of the α -substituent. Controlled acidic hydrolysis of esters **3** afforded the corresponding acids **4** with minimal racemization. Boron tribromide demethylation of (*R*)- and (*S*)-**4d** gave without racemization the hydroxyacids (*R*)- and (*S*)-**4e**, known precursors of (*R*)- and (*S*)-iodoaliphonic acid.

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We recently described¹ a multigram scale synthesis of both enantiomers of 3-hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone, (*R*)- and (*S*)-**1**, and their use for the asymmetric synthesis of α -arylpropanoic acids from the corresponding racemic mixtures². These chiral auxiliaries are easily crystallizable non-hygroscopic solids more lipophilic than pantolactone, which greatly facilitates their recovery. Both enantiomers are readily available and their ee can be easily established by chiral HPLC with UV detection.

In this paper we report the use of (*R*)- and (*S*)-**1** for the asymmetric synthesis of α -substituted arylacetic acids from the corresponding racemic mixtures (Scheme 1). The starting acids were *rac*-2-phenylbutanoic acid, *rac*-**4a**, *rac*- α -cyclohexylphenylacetic acid, *rac*-**4b**, *rac*- α,β -diphenylpropanoic acid, *rac*-**4c**, and *rac*- β -(*p*-methoxyphenyl)- α -phenylpropanoic acid, *rac*-**4d**. *Rac*-**4a,b** were bought from Aldrich, while *rac*-**4c,d** were prepared from diethyl malonate and benzyl chloride or *p*-methoxybenzyl chloride by standard procedures. These acids were transformed into the corresponding *rac*-acid chlorides by reaction with a 10% excess of PCl_5 in CCl_4 , which were reacted with (*R*)- or (*S*)-**1** under the previously described standard conditions (methylene chloride, 0°C, triethylamine)², the corresponding ketene being formed *in situ*. Under these conditions, the diastereoselectivity observed was the same as previously found in the case of α -arylpropanoic acids² (see Table 1), i.e.: starting from (*R*)-**1**, the main diastereomeric ester was always (**3R, α R**)-**3**, while from (*S*)-**1** it was (**3S, α S**)-**3**. As expected, on increasing the steric effect of the R substituent in the starting acid, the diastereoselectivity of the reaction decreased. The de's of esters **3** were acceptable when R was a primary alkyl or aralkyl group (i.e. ethyl, benzyl, *p*-methoxybenzyl). In the case of R being cyclohexyl, both the yield and de were very low (37% yield, 16% de), probably due to steric hindrance during ketene formation.

Worthy of note, when *rac*-**2a** was reacted with *rac*-**1** under the standard conditions except for the use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) instead of triethylamine, a mixture of two pairs of enantiomers was obtained in 92% yield, the (**3RS, α RS**)-pair being formed in only 40% de. A similar reaction carried out by using 4-dimethylaminopyridine (DMAP) instead of DBU gave a mixture in which the (**3RS, α SR**)-pair was the main product (94% yield, 60% de), i.e. the diastereoselectivity of the reaction was reversed. Similarly, reaction of *rac*-**2b** with (*S*)-**1** using DMAP as the base, gave (**3S, α R**)-**3b** in 65% yield and 39% de, which was improved to 60% de (38% yield) on crystallization from abs. ethanol (Table 1).

Scheme 1. Enantioselective synthesis of α -substituted arylacetic acids, 4.Table 1. Yields^[a], diastereomeric (de)^[b] or enantiomeric (ee)^[c] excesses of esters 3, acids 4, and recovered chiral auxiliary, from the reaction of *rac*-2 with (*R*)- or (*S*)-1 under standard conditions.

Entry	Starting material		ester 3			acid 4 ^[d]			recovered 1		
	<i>rac</i> -2	1	Conf.	% yield	% de	Conf.	% yield	% ee	Conf.	% yield	% ee
1	<i>rac</i> -2a	<i>R</i> -1	<i>R,R</i>	88	88	<i>R</i>	95	94	<i>R</i>	92	> 99
2	<i>rac</i> -2a	<i>S</i> -1	<i>S,S</i>	91	88	<i>S</i>	95	97	<i>S</i>	96	> 99
3	<i>rac</i> -2b	<i>R</i> -1	<i>R,R</i>	37	16						
4	<i>rac</i> -2b ^[e]	<i>S</i> -1	<i>S,R</i>	65 (38)	39 (60)	<i>R</i>	84	60	<i>S</i>	90	> 99
5	<i>rac</i> -2c	<i>R</i> -1	<i>R,R</i>	87	83	<i>R</i>	98 (73)	73 (> 99)	<i>S</i>	97	> 99
6	<i>rac</i> -2d	<i>R</i> -1	<i>R,R</i>	88	80	<i>R</i>	97 (73)	75 (93)	<i>R</i>	94	> 99
7	<i>rac</i> -2d	<i>S</i> -1	<i>S,S</i>	90	73	<i>S</i>	93 (65)	72 (> 99)	<i>S</i>	95	> 99

[a] Yields refer always to isolated product. For the acids 4, yields correspond to the hydrolysis step. [b] The de's of the esters 3 were determined by HPLC under achiral conditions (see experimental). [c] The ee's of the acids 4 and recovered 1 were determined by chiral HPLC using different columns and conditions (see experimental). [d] Values in parenthesis refer to yields and ee's after crystallization of the acid as cyclohexylamine salt from which the acid was then recovered. [e] In this reaction, DMAP was used instead of triethylamine. Values in parenthesis correspond to the product after crystallization from abs. ethanol.

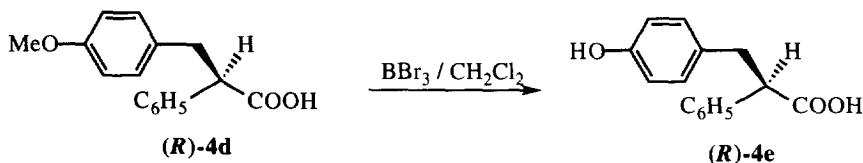
The lower diastereoselectivity of the reactions with DBU and DMAP may be due to the concurrence of other esterification mechanisms. More difficult to explain is the change in diastereoselectivity when DMAP was used as the base. Other authors³ have previously also observed a great influence of the base upon the diastereoselectivity of the reaction of racemic α -arylpropanoyl chlorides with D-pantolactone.

Hydrolysis of esters **3** under the standard conditions used in the case of the esters derived from α -arylpropanoic acids², took place with minimal racemization. Sometimes the ee's of the isolated acids **4** were greater than the de's of the corresponding esters due to enrichment during the isolation of the acids by crystallization as cyclohexylamine salts (entries 1 and 2). The ee's of these acids could be improved (entries 5, 6 and 7) through a second crystallization as cyclohexylamine salt. The chiral auxiliaries were always recovered without racemization (ee's > 99%) normally in high yields.

The de's of esters **3** were obtained by HPLC under achiral conditions, by assuming the ratio of areas to be equal to their molar ratio, in good agreement with the values obtained by ¹H NMR spectroscopy. For the NMR and HPLC study of esters **3**, *rac*-acids **4** were esterified with *rac*-**1** in the presence of dicyclohexylcarbodiimide (DCC) obtaining mixtures of the two enantiomeric pairs (*RS,RS*)-**3** and (*RS,SR*)-**3**, with a small preference for the latter (10-30% ee). The ee's of the acids **4** and of the recovered chiral auxiliaries were established by HPLC using the chiral columns and conditions indicated in the experimental part.

The new compounds, esters (*3R,αR*)-**3a,c,d**, (*3S,αS*)-**3a,d** and (*3R,αS*)-**3b** and acids (*R*)- and (*S*)-**4d**, have been fully characterized through their spectroscopic data and elemental analysis. The NMR spectra of these compounds have been fully assigned on the basis of COSY ¹H/¹H and ¹H/¹³C experiments and of our previous work^{1,2}.

The enantioselective synthesis of the acids herein described opens the way to potential industrial procedures for the preparation of drugs derived from α -substituted arylacetic acids, in which the α -substituent is a primary alkyl or aralkyl group, as it is the case for butethamate, butamirate, fenbutrazate, pheneturide, derived from α -phenylbutanoic acid, which are being marketed as racemates⁴. The enantiomers of this acid had been previously obtained⁵ by resolution of the racemic mixture, each enantiomer being converted into the corresponding enantiomer of pheneturide. Also, a preparation of (*S*)-butethamate and (*S*)-butamirate from (*S*)-(+)-**4b**, obtained by kinetic resolution of the racemic anhydride with chiral alcohols, has been described⁶.



Scheme 2. Enantiospecific demethylation of (*R*)-**4d** to (*R*)-**4e**.

Moreover, the not previously described (*R*)- and (*S*)- β -(*p*-methoxyphenyl)- α -phenylpropanoic acids, (*R*)- and (*S*)-**4d**, on reaction with boron tribromide in methylene chloride⁷ gave in good yields the corresponding (*R*)- and (*S*)- β -(*p*-hydroxyphenyl)- α -phenylpropanoic acids, (*R*)- and (*S*)-**4e**, respectively, as shown in Scheme 2 for the (*R*)-enantiomer. The ee's of these acids were the same as their precursors, showing that no racemization took place during the reaction. These acids had been previously obtained by resolution of the corresponding racemic mixture with quinine⁸, which on iodination gave the corresponding enantiomers of iodoalphonic acid⁸, a known diagnostic aid marketed as the racemate⁴.

In conclusion, (*R*)- or (*S*)-3-hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone, (*R*)- or (*S*)-**1**, have been successfully applied to the enantioselective synthesis of α -primary alkyl or aralkyl-substituted arylacetic acids, from which several drugs can be easily derived.

EXPERIMENTAL

Melting points were determined on a MFB 595010 M Gallenkamp melting point apparatus. 500 MHz ¹H NMR spectra and COSY ¹H/¹H and ¹H/¹³C experiments were determined on a Varian VXR 500 MHz

spectrometer, 300 MHz ^1H and 75.4 MHz ^{13}C NMR spectra on a Varian Gemini 300 and 200 MHz ^1H and 50.3 MHz ^{13}C NMR spectra on a Varian Gemini 200, in CDCl_3 , except where otherwise stated. COSY $^1\text{H}/^1\text{H}$ experiments were performed using standard procedures while for the COSY $^1\text{H}/^{13}\text{C}$ experiments, the HMQC sequence with an indirect detection probe was used. Chemical shifts (δ) are reported in ppm related to internal tetramethylsilane. Optical rotations were measured on a Perkin Elmer, model 241 polarimeter. HPLC analyses were performed on a Waters model 600 liquid chromatograph provided with variable λ detector, working at $\lambda = 249$ nm and using column A for the non-stereospecific analyses and columns B and C for the stereospecific HPLC analyses. Column A: Tracer Analytical column ODS-2 (15 x 0.39 cm) 4 μm silica gel; column B: CHIRALCEL OD-H column (25 x 0.46 cm) containing the chiral stationary phase cellulose tris-(3,5-dimethylphenylcarbamate); column C: Chiral-AGP (10 x 0.40 cm, 5 μm) containing the chiral stationary phase silica-bonded α_1 -acid glycoprotein. Conditions A: Column A, H_2O / acetonitrile in a ratio of 45 / 55 as eluent, flow 0.4 ml / min; Conditions B: Column A, H_2O / acetonitrile in a ratio of 40 / 60 as eluent, flow 0.3 ml / min; Conditions C: column B, mixture of hexane / isopropanol / trifluoroacetic acid in the ratio of 93 / 7 / 0.05 as eluent, flow 0.3 ml / min. Conditions D: column B, mixture of hexane / isopropanol / trifluoroacetic acid in the ratio of 93 / 7 / 0.05 as eluent, flow 0.5 ml / min. Conditions E: column B, mixture of hexane / isopropanol / trifluoroacetic acid in the ratio of 93 / 7 / 0.05 as eluent, flow 0.2 ml / min. Conditions F: Column C, sodium phosphate buffer 100 mM, pH = 6.0 / isopropanol in the ratio 95 / 5, flow 0.3 ml / min. Conditions G: column B, mixture of hexane / isopropanol in the ratio of 93 / 7 as eluent, flow 0.5 ml / min. Solvents were of analytical grade.

General procedure for the preparation of rac- α -substituted arylacetyl chlorides.

A mixture of the *rac*- α -substituted arylacetic acid, *rac*-**4**, (1 equiv) and PCl_5 (1.1 equiv) in CCl_4 (1.5 ml / mmol) was stirred at 40 $^\circ\text{C}$ for 30 min. Evaporation of the volatile products gave the corresponding *rac*- α -substituted arylacetyl chloride, *rac*-**2**, that was used as such in the following step.

General procedure for the reaction of rac- α -substituted arylacetyl chlorides with (R)- or (S)-1.

To a dried (1 g of 3 \AA molecular sieves / mmol) and cooled solution (ice-water bath) of (*R*)- or (*S*)-**1** (1 equiv) in CH_2Cl_2 (3 ml / mmol) under an argon atmosphere, dried solutions (1 g of 3 \AA molecular sieves / mmol) of the *rac*- α -substituted arylacetyl chloride, *rac*-**2**, (1 equiv) in CH_2Cl_2 (3 ml / mmol) and triethylamine (2.2 equiv) in CH_2Cl_2 (4 ml / mmol) were successively added and the mixture was magnetically stirred for 3 h at 0 $^\circ\text{C}$. The mixture was washed with N HCl (2 x 5 ml / mmol), saturated aqueous solution of NaHCO_3 (2 x 5 ml / mmol), dried with Na_2SO_4 and concentrated in vacuo. The residue was chromatographed [silica gel (50 g / g residue), hexane / diethyl ether] and the diastereomeric excess of the ester **3** thus obtained was determined by HPLC under conditions A or B.

(3R)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl (αR)- α -phenylbutanoate (3R, αR)-3a.

Following the general procedure, from (*R*)-**1** (514 mg, 2.81 mmol) and *rac*-**2a** (576 mg, 2.81 mmol), (*3R*, αR)-**3a** (872 mg, 88% yield, 88% de, conditions A, r.t. 61.0 min.) was obtained as an oil, $[\alpha]_{\text{D}}^{20}$ ($c = 1.1$, CHCl_3) = +35.2. ^1H NMR (500 MHz) $\delta = 0.99$ (t, $J = 7.5$ Hz, 3 H, CH_3CH_2), 1.04 (s, 3 H, 4' α - CH_3), 1.20 (s, 3 H, 4' β - CH_3), 1.92 (m, 1 H) and 2.23 (m, 1 H) (CH_3CH_2), 3.47 (d, $J = 9.5$ Hz, 1 H, 5' α -H), 3.55 (d, $J = 9.5$ Hz, 1 H, 5' β -H), 3.65 (t, $J = 7.5$ Hz, 1 H, CHCOO), 5.37 (s, 1 H, 3'-H), 7.14 (t, $J = 7.5$ Hz, 1 H, 4-H N-phenyl), 7.25 (tm, $J = 7.5$ Hz, 1 H, 4-H C-phenyl), 7.30-7.39 [m, 6 H, 3(5)-H N-phenyl, 3(5)-H C-phenyl and 2(6)-H C-phenyl], 7.60 [dd, $J = 7.5$ Hz, $J' = 1.0$ Hz, 2 H, 2(6)-H N-phenyl]. ^{13}C NMR (75.4 MHz) $\delta = 12.2$ (CH_3 , CH_3CH_2), 21.0 (CH_3 , 4' α - CH_3), 24.7 (CH_3 , 4' β - CH_3), 26.4 (CH_2 , CH_3CH_2), 37.2 (C, C4'), 53.5 (CH, CHCOO), 57.5 (CH_2 , C5'), 78.1 (CH, C3'), 119.3 [CH, C2(6) N-phenyl], 124.7 (CH, C4 N-phenyl), 127.2 (CH, C4 C-phenyl), 128.0 [CH, C2(6) C-phenyl], 128.4 [CH, C3(5) N-phenyl], 128.8 [CH, C3(5) C-phenyl], 138.3 (C, C1 C-phenyl), 139.0 (C, C1 N-phenyl), 168.6 (C, C2'), 173.1 (C, COO); IR (NaCl) $\nu = 1743$ and 1716 ($\text{C}=\text{O}$ st) cm^{-1} . $\text{C}_{22}\text{H}_{25}\text{NO}_3$ (351.45): calcd. C 75.19% H 7.17% N 3.99%. Found C 75.10% H 7.21% N 3.99%.

(3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl (αS)- α -phenylbutanoate (3S, αS)-3a.

Following the general procedure, from (*S*)-**1** (555 mg, 3.04 mmol) and *rac*-**2a** (623 mg, 3.04 mmol), (*3S*, αS)-**3a** (974 mg, 91% yield, 88% de) was obtained as an oil, $[\alpha]_{\text{D}}^{20}$ ($c = 1.0$, CHCl_3) = -34.8. The IR and NMR

data coincide with those of **(3R, α R)**-**3a**. $C_{22}H_{25}NO_3$ (351.45): calcd. C 75.19% H 7.17% N 3.99%. Found C 75.11% H 7.20% N 3.89%.

(3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl (α R)- α -cyclohexylphenylacetate **(3S, α R)-**3b**.**

Following the general procedure, except for the use of DMAP instead of triethylamine as the base, from **(S)**-**1** (472 mg, 2.30 mmol) and *rac*-**2b** (542 mg, 2.30 mmol), **(3S, α R)**-**3b** (600 mg, 65% yield, 39% de, conditions B, r.t. 97.2 min.) was obtained as a solid. On crystallization from ethanol (0.5 ml / mmol), the de of the product increased to 60% (38% global yield), mp = 110–112 °C, $[\alpha]_D^{20}$ (c = 1.0, CH_2Cl_2) = -22.8. 1H NMR (500 MHz) δ = 0.81 (s, 3 H, 4' α -CH₃), 1.07 (s, 3 H, 4' β -CH₃), 0.77 (m, 1 H), 1.16 (m, 3 H), 1.34 (m, 2 H), 1.64 (m, 2 H), 1.79 (m, 1 H), 2.03 (m, 1 H) and 2.10 (m, 1 H) (H cyclohexyl), 3.42 (d, J = 9.5 Hz, 1 H, 5' α -H), 3.44 (d, J = 11.5 Hz, 1 H, CHCOO), 3.54 (d, J = 9.5 Hz, 1 H, 5' β -H), 5.39 (s, 1 H, 3'-H), 7.16 (t, J = 7.5 Hz, 1 H, 4-H N-phenyl), 7.23–7.41 (complex signal, 7 H, H C-phenyl and 3(5)-H N-phenyl), 7.61 (broad d, J = 8.0 Hz, 2 H, 2(6)-H N-phenyl). ^{13}C NMR (75.4 MHz) δ = 20.5 (CH₃, 4' α -CH₃), 24.4 (CH₃, 4' β -CH₃), 25.9 (CH₂, C3 and C5 cyclohexyl), 26.1 (CH₂, C4 cyclohexyl), 30.1 (CH₂) and 31.8 (CH₂) (C2 and C6 cyclohexyl), 37.3 (C, C4'), 40.3 (CH, C1 cyclohexyl), 57.4 (CH₂, C5'), 58.2 (CH, CHCOO), 77.7 (CH, C3'), 119.2 (CH, C2(6) N-phenyl), 124.6 (CH, C4 N-phenyl), 127.1 (CH, C4 C-phenyl), 128.3 (CH) 128.6 (CH) and 128.7 (CH) [C3(5) N-phenyl, C2(6) C-phenyl and C3(5) C-phenyl], 137.8 (C, C1 C-phenyl), 138.9 (C, C1 N-phenyl), 168.7 (C, C2'), 173.1 (C, COO); IR (KBr) ν = 1741 and 1718 (C=O st) cm^{-1} . $C_{26}H_{31}NO_3$ (405.54): calcd. C 77.01% H 7.71% N 3.45%. Found C 76.85% H 7.76% N 3.41%.

*Significant NMR data of **(3S, α S)**-**3b** deduced from the spectra of the above mixture:*

1H NMR (500 MHz) δ = 1.06 (s, 3 H, 4' α -CH₃), 1.21 (s, 3 H, 4' β -CH₃), 3.43 (d, J = 11.5 Hz, 1 H, 2-H), 3.49 (d, J = 9.5 Hz, 1 H, 5' α -H), 3.56 (d, J = 9.5 Hz, 1 H, 5' β -H), 5.36 (s, 1 H, 3'-H). ^{13}C NMR (75.4 MHz) δ = 21.0 (CH₃, 4' α -CH₃), 24.6 (CH₃, 4' β -CH₃), 57.4 (CH₂, C5'), 58.9 (CH, C2), 78.0 (CH, C3'), 168.4 (C, C2'), 172.8 (C, COO).

(3R)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl (α R)- α,β -diphenylpropanoate **(3R, α R)-**3c**.**

Following the general procedure, from **(R)**-**1** (444 mg, 2.17 mmol) and *rac*-**2c** (530 mg, 2.17 mmol), **(3R, α R)**-**3c** (680 mg, 87% yield, 83% de, conditions A, r.t. 83.1 min) was obtained as an oil, $[\alpha]_D^{20}$ (c = 1.8, $CHCl_3$) = +39.1. 1H NMR (500 MHz) δ = 0.75 (s, 3 H, 4' α -CH₃), 1.06 (s, 3 H, 4' β -CH₃), 3.16 (dd, J = 13.5 Hz, J' = 6.0 Hz, 1 H) and 3.49 (dd, J = 13.5 Hz, J' = 10.0 Hz, 1 H) (CH_2 -C₆H₅), 3.40 (d, J = 9.5 Hz, 1 H, 5' α -H), 3.51 (d, J = 9.5 Hz, 1 H, 5' β -H), 4.07 (dd, J = 10.0 Hz, J' = 6.0 Hz, 1 H, CHCOO), 5.29 (s, 1 H, 3'-H), 7.15 (broad t, J = 7.5 Hz, 1 H, 4-H N-phenyl), 7.20 (m, 1 H, 4-H benzyl), 7.26 [complex signal, 5 H, 2(6)-H benzyl, 3(5)-H benzyl and 4-H C-phenyl], 7.34 [m, 2 H, 3(5)-H C-phenyl], 7.35 [CH, 2 H, 3(5)-H N-phenyl], 7.45 [d, J = 7.0 Hz, 2 H, 2(6)-H C-phenyl], 7.58 [dd, J = 8.0 Hz, J' = 1.0 Hz, 2 H, 2(6)-H N-phenyl]. ^{13}C NMR (75.4 MHz) δ = 20.3 (CH₃, 4' α -CH₃), 24.1 (CH₃, 4' β -CH₃), 36.8 (C, C4'), 39.4 (CH₂, C₆H₅-CH₂), 53.5 (CH, CHCOO), 57.0 (CH₂, C5'), 78.0 (CH, C3'), 119.0 (CH, C2(6) N-phenyl), 124.4 (CH, C4 N-phenyl), 126.2 (CH) and 127.2 (CH) (C4 benzyl and C4 C-phenyl) 127.6 [CH, C2(6) C-phenyl], 127.9 (CH) and 128.8 (CH) [C2(6) benzyl and C3(5) benzyl], 128.1 (CH) and 128.3 (CH) [CH, C3(5) N-phenyl and C3(5) C-phenyl], 137.7 (C, C1 benzyl), 138.6 (C), and 138.7 (C) (C1 C-phenyl and C1 N-phenyl), 168.2 (C, C2'), 172.2 (C, COO); IR (NaCl) ν = 1742 and 1717 (C=O st) cm^{-1} . $C_{27}H_{27}NO_3$ (413.52): calcd. C 78.42% H 6.58% N 3.39%. Found C 78.44% H 6.65% N 3.36%.

(3R)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl (α R)- α -phenyl- β -(*p*-methoxyphenyl)propanoate **(3R, α R)-**3d**.**

Following the general procedure, from **(R)**-**1** (1.85 g, 8.60 mmol) and *rac*-**2d** (2.36 mg, 8.60 mmol), **(3R, α R)**-**3d** (3.37 mg, 88% yield, 80% de, conditions A, r.t. 66.1 min.) was obtained as an oil, $[\alpha]_D^{20}$ (c = 1.0, CH_2Cl_2) = +30.6. 1H NMR (500 MHz) δ = 0.77 (s, 3 H, 4' α -CH₃), 1.07 (s, 3 H, 4' β -CH₃), 3.10 (dd, J = 13.5 Hz, J' = 6.0 Hz, 1 H) and 3.44 (dd, J = 13.5 Hz, J' = 10.0 Hz, 1 H) (CH_2 -C₆H₅), 3.41 (d, J = 9.5 Hz, 1 H, 5' α -H), 3.52 (d, J = 9.5 Hz, 1 H, 5' β -H), 3.77 (s, 3 H, OCH₃), 4.01 (dd, J = 10.0 Hz, J' = 6.0 Hz, 1 H, CHCOO), 5.29 (s, 1 H, 3'-H), 6.81 (dd, J = 9.0 Hz, J' = 1.0 Hz, 3(5)-H *p*-methoxyphenyl), 7.16 (broad t, J = 7.5 Hz, 1 H, 4-H N-phenyl), 7.17 (d, J = 9.0 Hz, 2 H, 2(6)-H *p*-methoxyphenyl), 7.27 (m, 1 H, 4-H C-phenyl), 7.33 [m, 2 H, 3(5)-H C-phenyl], 7.35 [m, 2 H, 3(5)-H N-phenyl], 7.44 [d, J = 8.0 Hz, 2 H, 2(6)-H C-phenyl], 7.58 [dd, J = 7.5 Hz, J' =

1.0 Hz, 2 H, 2(6)-H N-phenyl]. ^{13}C NMR (75.4 MHz) δ = 20.7 (CH_3 , 4' α - CH_3), 24.6 (CH_3 , 4' β - CH_3), 37.3 (C, C4'), 38.9 (CH_2 , Ar- CH_2), 54.1 (CH, CHCOO), 55.2 (CH_3 , OCH_3), 57.6 (CH_2 , C5'), 78.3 (CH, C3'), 113.8 [CH, C3(5) *p*-methoxyphenyl], 119.4 [CH, C2(6) N-phenyl], 124.8 (CH, C4 N-phenyl), 127.4 (CH, C4 C-phenyl), 128.0 (CH, C2(6) C-phenyl), 128.6 (CH, C3(5) C-phenyl), 128.9 (CH, C3(5) N-phenyl), 130.1 [CH, C2(6) *p*-methoxyphenyl], 130.8 (C, C1 *p*-methoxyphenyl), 138.0 (C, C1 C-phenyl), 139.0 (C, C1 N-phenyl), 158.3 (C, C4 *p*-methoxyphenyl), 168.6 (C, C2'), 172.7 (C, COO); IR (NaCl) ν = 1741 and 1716 ($\text{C}=\text{O}$ st) cm^{-1} . $\text{C}_{28}\text{H}_{29}\text{NO}_4$ (443.54): calcd. C 75.82% H 6.59% N 3.16%. Found C 75.80% H 6.70% N 3.17%.

*(3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl (α S)- α -phenyl- β -(*p*-methoxyphenyl)propanoate (3S, α S)-3d.*

Following the general procedure, from (*S*)-**1** (410 mg, 2.00 mmol) and *rac*-**2d** (550 mg, 2.00 mmol), (**3S, α S**)-**3d** (800 mg, 90% yield, 73% de) was obtained as an oil, $[\alpha]_{\text{D}}^{20}$ (c = 1.4, CH_2Cl_2) = -28.4. The IR and NMR data coincide with those of (**3R, α R**)-**3d**. $\text{C}_{28}\text{H}_{29}\text{NO}_4$ (443.54): calcd. C 75.82% H 6.59% N 3.16%. Found C 75.86% H 6.60% N 3.05%.

General procedure for the reaction of rac- α -substituted arylacetic acids with rac-1.

A mixture of the *rac*- α -substituted arylacetic acid, *rac*-**4** (1 equiv), dicyclohexylcarbodiimide (1 equiv), *rac*-**1** (1 equiv) and 4-dimethylaminopyridine (0.05 equiv) in CH_2Cl_2 (6 ml / mmol) was magnetically stirred at room temperature for 3 h following the reaction by tlc. The mixture was filtered and the filtrate was washed with saturated aqueous solution of citric acid (3 x 6 ml / mmol) and saturated aqueous NaHCO_3 (3 x 6 ml / mmol), dried with Na_2SO_4 and concentrated in vacuo. The residue containing the mixture of (**3RS, α RS**)- and (**3RS, α SR**)-**3** was analyzed by HPLC under conditions A or B, and by NMR spectroscopy.

In all cases, the reaction was performed starting from 200 mg of the acid, the oily stereoisomeric mixtures of esters being obtained in the following yields: **3a** (72%), **3b** (73%), **3c** (62%) and **3d** (70%). The enantiomeric pair (**3RS, α SR**)-**3** was slightly more abundant (10-30% de) in all cases.

HPLC data of the enantiomeric pairs (3RS, α RS)- and (3RS, α SR)-3.

(**3RS, α RS**)-**3a**: r.t. 61.0 min, (**3RS, α SR**)-**3a**: r.t. 57.6 min (conditions A); $k_1' = 20.7$, $k_2' = 22.0$, $\alpha = 1.06$, Res = 1.7.

(**3RS, α RS**)-**3b**: r.t. 102.1 min, (**3RS, α SR**)-**3b**: r.t. 97.2 min (conditions B); $k_1' = 30.7$, $k_2' = 32.2$, $\alpha = 1.05$, Res = 1.3.

(**3RS, α RS**)-**3c**: r.t. 83.1 min, (**3RS, α SR**)-**3c**: r.t. 74.8 min (conditions A); $k_1' = 30.9$, $k_2' = 34.5$, $\alpha = 1.12$, Res = 2.7.

(**3RS, α RS**)-**3d**: r.t. 66.2 min, (**3RS, α SR**)-**3d**: r.t. 63.6 min (conditions A); $k_1' = 25.6$, $k_2' = 26.7$, $\alpha = 1.04$, Res = 1.4.

Significant NMR data of the enantiomeric pairs (3RS, α SR)-3, deduced from the data of the above mixtures:

(**3RS, α SR**)-**3a**: ^1H NMR (300 MHz) δ : = 0.77 (s, 3 H, 4' α - CH_3), 0.93 (t, $J = 7.5$ Hz, CH_3CH_2), 1.08 (s, 3 H, 4' β - CH_3), 3.39 (d, $J = 9.6$ Hz, 1 H, 5' α -H), 3.52 (d, $J = 9.6$ Hz, 1 H, 5' β -H), 3.65 (t, $J = 7.5$ Hz, CHCOO), 5.40 (s, 1 H, 3'-H). ^{13}C NMR (75.4 MHz) δ = 11.9 (CH_3 , CH_3CH_2), 20.5 (CH_3 , 4' α - CH_3), 24.6 (CH_3 , 4' β - CH_3), 26.1 (CH_2 , CH_3CH_2), 37.5 (C, C4'), 52.9 (CH, CHCOO), 57.5 (CH_2 , C5'), 77.9 (CH, C3'), 168.9 (C, C2'), 173.4 (C, COO).

(**3RS, α SR**)-**3c**: ^1H NMR (200 MHz) δ : = 0.66 (s, 3 H, 4' α - CH_3), 1.03 (s, 3 H, 4' β - CH_3), 5.37 (s, 1 H, 3'-H). ^{13}C NMR (50.3 MHz) δ = 20.4 (CH_3 , 4' α - CH_3), 24.3 (CH_3 , 4' β - CH_3), 37.4 (C, C4'), 38.7 (CH_2 , $\text{C}_6\text{H}_5\text{CH}_2$), 52.6 (CH, CHCOO), 57.3 (CH_2 , C5'), 78.2 (CH, C3'), 168.6 (C, C2'), 172.8 (C, COO).

(**3RS, α SR**)-**3d**: ^1H NMR (200 MHz) δ : = 0.69 (s, 3 H, 4' α - CH_3), 1.07 (s, 3 H, 4' β - CH_3), ^{13}C NMR (50.3 MHz) δ = 20.4 (CH_3 , 4' α - CH_3), 24.6 (CH_3 , 4' β - CH_3), 38.0 (CH_2 , Ar CH_2 -), 53.0 (CH, CHCOO), 57.6 (CH_2 , C5'), 78.1 (CH, C3'), 169.0 (C, C2'), 173.0 (C, COO).

General procedure for the hydrolysis of esters 3: Preparation of acids (S)- and (R)-4 and recovery of the chiral auxiliaries (S)- and (R)-1.

A mixture of the ester **3** (1 equiv), acetic acid (8 ml / mmol) and 2 N HCl (3.2 ml / mmol) was heated at 120°C (bath temperature) till completion of the hydrolysis (2.5 h), following the reaction by tlc. The mixture was allowed to cool to room temperature and the volatile products were distilled at reduced pressure. Water (8 ml / mmol) was added to the residue, and the mixture was extracted with CH₂Cl₂ (3 x 8 ml / mmol). The combined organic phases were treated with cyclohexylamine (1 equiv) and the precipitate thus formed was filtered. The crystallization as cyclohexylamine salt was repeated in some cases to improve the ee of the acid.

The solid was treated with N HCl until pH = 1, and the mixture was extracted with CH₂Cl₂ (3 x 8 ml / mmol). The combined organic extracts were washed with water (2 x 8 ml / mmol), dried with Na₂SO₄ and concentrated in vacuo to give the (*S*)- or (*R*)- α -substituted arylacetic acid.

The filtrate was concentrated in vacuo and the residue consisting of the chiral auxiliary (*S*)- or (*R*)-**1** was crystallized from ethanol (0.2 ml / mmol).

The ee of the α -substituted arylacetic acids were obtained by HPLC under the chiral conditions indicated in each case, while the ee of the recovered chiral auxiliaries were obtained by HPLC under the chiral conditions G.

(R)- α -Phenylbutanoic acid (R)-4a.

Following the general procedure, from (**3R, α R**)-**3a** (691 mg, 1.96 mmol), (**R**)-**4a** (307 mg, 95% yield, 94% ee) and (**S**)-**1** (370 mg, 92% yield, > 99% ee) were obtained. (**R**)-**4a**: bp 102-104 °C / 0.4 Torr, $[\alpha]_D^{20}$ (methanol, c = 1.0) = - 78.0; Lit.⁹: $[\alpha]_D^{25}$ (methanol, c = 1.0) = - 81.0. HPLC (conditions C): (**S**)-**4a**: r.t. 17.94 min; (**R**)-**4a**: r.t. 15.93 min; $k_1' = 0.45$, $k_2' = 0.64$, $\alpha = 1.42$, Res = 2.0.

(S)- α -Phenylbutanoic acid (S)-4a.

Following the general procedure, from (**3S, α S**)-**3a** (706 mg, 2.01 mmol), (**S**)-**4a** (313 mg, 95% yield, 97% ee) and (**S**)-**1** (400 mg, 96% yield, > 99% ee) were obtained. (**S**)-**4a**: bp 97 °C / 0.1 Torr, $[\alpha]_D^{20}$ (methanol, c = 1.0) = + 79.1.

(R)- α -Cyclohexylphenylacetic acid (R)-4b.

Following the general procedure, from (**3S, α R**)-**3b** (100 mg, 0.25 mmol), (**R**)-**4b** (45 mg, 84% yield, 60% ee) and (**S**)-**1** (46 mg, 90% yield, > 99% ee) were obtained. (**R**)-**4b**: mp 99-102 °C (abs. ethanol), $[\alpha]_D^{20}$ (CHCl₃, c = 1.0) = - 22.3. Lit.¹⁰: $[\alpha]_D^{25}$ (CHCl₃, c = 20.0) = - 38.8. HPLC (conditions D): (**S**)-**4b**: r.t. 10.15 min; (**R**)-**4b**: r.t. 8.76 min; $k_1' = 0.27$, $k_2' = 0.47$, $\alpha = 1.74$, Res = 2.3.

(R)- α,β -Diphenylpropanoic acid (R)-4c.

Following the general procedure, from (**3R, α R**)-**3c** (400 mg, 0.96 mmol), (**R**)-**4c** (213 mg, 98% yield, 73% ee) and (**R**)-**1** (191 mg, 97% yield, > 99% ee) were obtained. On crystallization of the above acid as cyclohexylamine salt [cyclohexylamine (93 mg, 0.94 mmol) in CH₂Cl₂ (0.4 ml)], after a standard work-up, (**R**)-**4c** (158 mg, 73% global yield, > 99% ee) was isolated: mp 88-90 °C (abs. ethanol), Lit.¹¹: 88-90 °C, $[\alpha]_D^{20}$ (methanol, c = 1.0) = - 93.2. Lit.¹¹: $[\alpha]_D^{20}$ (methanol, c = 1.0) = - 94.0. HPLC (conditions E): (**S**)-**4c**: r.t. 30.18 min; (**R**)-**4c**: r.t. 28.95 min; $k_1' = 0.87$, $k_2' = 0.95$, $\alpha = 1.10$, Res = 0.9.

*(S)- β -(*p*-Methoxyphenyl)- α -phenylpropanoic acid (S)-4d.*

Following the general procedure, from (**3S, α S**)-**3d** (800 mg, 1.80 mmol), (**S**)-**4d** (430 mg, 93% yield, 72% ee) and (**S**)-**1** (350 mg, 95% yield, > 99% ee) were obtained. On crystallization of the above acid as cyclohexylamine salt [cyclohexylamine (166 mg, 1.68 mmol) in CH₂Cl₂ (0.5 ml)], after a standard work-up, (**S**)-**4d** (301 mg, 65% global yield, > 99% ee) was isolated: mp 124-127 °C (abs. ethanol), $[\alpha]_D^{20}$ (CH₂Cl₂, c = 1.0) = + 65.0. HPLC (conditions E): (**S**)-**4d**: r.t. 93.13 min; (**R**)-**4d**: r.t. 82.89 min; $k_1' = 3.98$, $k_2' = 4.59$, $\alpha = 1.15$, Res = 2.7. ¹H NMR (500 MHz) δ = 2.99 (dd, J = 13.5 Hz, J' = 7.0 Hz, 1 H) and 3.36 (dd, J = 13.5 Hz, J' = 8.5 Hz, 1 H) (CH₂-C₆H₅), 3.77 (s, 3 H, OCH₃), 3.83 (dd, J = 8.5 Hz, J' = 7.0 Hz, 1 H, CHCOO), 6.78 [d, J = 8.5 Hz, 3(5)-H *p*-methoxyphenyl], 7.03 [d, J = 8.5 Hz, 2 H, 2(6)-H *p*-methoxyphenyl], 7.30 (m, 5 H, C₆H₅). ¹³C NMR (75.4 MHz) δ = 38.4 (CH₂, Ar-CH₂), 53.7 (CH, CHCOO), 55.1 (CH₃, OCH₃), 113.7 [CH, C3(5) *p*-methoxyphenyl], 127.6 (CH, C4 phenyl), 128.1 (CH) and 128.6 (CH) [C2(6) and C3(5) phenyl], 129.9 [CH, C2(6) *p*-methoxyphenyl], 130.7 (C, C1 *p*-methoxyphenyl), 137.9 (C, C1 phenyl), 158.1 (C, C4 *p*-methoxyphenyl), 179.4 (C, COO); IR (KBr) ν = 3500-2500 (OH st) 1708 (CO st) cm⁻¹. C₁₆H₁₆O₃ (256.30): calcd. C 74.98% H 6.30%. Found C 74.90% H 6.41%.

(R)-β-(p-Methoxyphenyl)-α-phenylpropanoic acid (R)-4d.

Following the general procedure, from **(3R,αR)-3d** (1.60 g, 3.60 mmol), **(R)-4d** (900 mg, 97% yield, 75% ee) and **(R)-1** (698 mg, 94% yield, > 99% ee) were obtained. On crystallization of the above acid as cyclohexylamine salt [cyclohexylamine (350 mg, 3.50 mmol) in CH₂Cl₂ (1.0 ml)], after a standard work-up, **(R)-4d** (678 mg, 73% global yield, 93% ee) was isolated: mp 124–126 °C (abs. ethanol), [α]_D²⁰ (CH₂Cl₂, c = 1.0) = - 62.0. The IR and NMR data coincide with those of **(S)-4d**. C₁₆H₁₆O₃ (256.30): calcd. C 74.98% H 6.30%. Found C 74.96% H 6.36%.

(S)-β-(p-Hydroxyphenyl)-α-phenylpropanoic acid (S)-4e.

Boron tribromide (0.2 ml, 2.1 mmol) was added dropwise to a solution of **(S)-4d** (300 mg, 1.17 mmol) in anhydrous CH₂Cl₂ (15 ml) and the mixture was stirred for 2 h at room temperature. Water (15 ml) was added, the organic phases were separated and the aqueous one was extracted with diethyl ether (2 x 15 ml). The combined organic phase and extracts were washed with water (2 x 15 ml), dried with Na₂SO₄ and concentrated in vacuo to give **(S)-4e** (245 mg, 87% yield, > 99% ee) as a solid, mp 198–200 °C, Lit.⁸: 201–202 °C. [α]_D²⁰ (ethanol, c = 1.5) = + 109; Lit.⁸: [α]_D²⁰ (ethanol, c = 1.50) = + 111. HPLC (conditions F): **(S)-4e**: r.t. 14.85 min; **(R)-4e**: r.t. 13.43 min; k₁' = 1.07, k₂' = 1.29, α = 1.20, Res = 1.5. ¹H NMR (500 MHz, CD₃OD) δ = 2.82 (dd, J = 14.0 Hz, J' = 7.0 Hz, 1 H) and 3.25 (dd, J = 14.0 Hz, J' = 8.5 Hz, 1 H) (CH₂-C₆H₅), 3.76 (dd, J = 8.5 Hz, J' = 7.0 Hz, 1 H, CHCOO), 4.80 (broad s, COOH and OH), 6.62 [d, J = 8.5 Hz, 3(5)-H *p*-hydroxyphenyl], 6.94 [d, J = 8.5 Hz, 2 H, 2(6)-H *p*-hydroxyphenyl], 7.20–7.30 (m, 5 H, C₆H₅). ¹³C NMR (75.4 MHz) δ = 40.0 (CH₂, Ar-CH₂), 55.4 (CH, CHCOO), 116.0 [CH, C3(5) *p*-hydroxyphenyl], 128.2 (CH, C4 phenyl), 129.1 (CH) and 129.5 (CH) [C2(6) and C3(5) phenyl], 131.0 [CH, C2(6) *p*-hydroxyphenyl], 131.4 (C, C1 *p*-hydroxyphenyl), 140.6 (C, C1 phenyl), 156.8 (C, C4 *p*-hydroxyphenyl), 177.2 (C, COO); IR (KBr) ν = 3700–2500 (OH st) 1706 (CO st) cm⁻¹.

(R)-β-(p-Hydroxyphenyl)-α-phenylpropanoic acid (R)-4e.

This compound was prepared in a similar manner to that described for **(S)-4e**. From **(R)-4d** (524 mg, 2.04 mmol), **(R)-4e** (430 mg, 87% yield, 93% ee) was obtained as a solid, mp 199–200 °C, Lit.⁸: 201–202 °C. [α]_D²⁰ (ethanol, c = 1.5) = - 102. Lit.⁸: [α]_D²⁰ (ethanol, c = 1.50) = - 111. The IR and NMR data coincide with those of **(S)-4e**.

Acknowledgments: A fellowship from the *Generalitat de Catalunya* to S. Giménez and financial support from the *Comisión Interministerial de Ciencia y Tecnología* and the *Generalitat de Catalunya (Programa de Química Fina, Project QFN93-4403)* are gratefully acknowledged. We thank the *Serveis Científico-Tècnics of the Universitat de Barcelona* for recording the NMR spectra, and P. Domènech from the *Centro de Investigación y Desarrollo (C.I.D.) of Barcelona*, for carrying out the elemental analyses.

REFERENCES

1. Camps, P.; Giménez, S.; Font-Bardia, M.; Solans, X. *Tetrahedron: Asymmetry*, **1995**, *6*, 985–990.
2. Camps, P.; Giménez, S. *Tetrahedron: Asymmetry*, **1995**, *6*, 991–1000.
3. a) Larsen, R. D.; Corley, E. G.; Davis, P.; Reider, P. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.*, **1989**, *111*, 7650–7651. b) Calmes, M.; Daunis, J.; Jacquier, R.; Natt, F. *Tetrahedron*, **1994**, *50*, 6875–6880.
4. Budavari, S.; O'Neil, M. J.; Smith, A.; Heckelmsan, P. E. *The Merck Index*, 11th ed., Merck and Co., Inc., Rahway, New Jersey, U.S.A., 1989.
5. Gold-Aubert, Ph. *Helv. Chim. Acta*, **1958**, *41*, 1512–1515.
6. Noe, C. R.; Knollmueller, M.; Letschnig, M.; Holzner, A. *PCT Int. Appl. WO 90 12,788* (1990); *Chem. Abst.*, **1991**, *114*, 247116s.
7. Paquette, L. A. *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons Ltd., Chichester, England, **1995**, vol 1, p. 645.
8. Tullar, B. F.; Hoppe, J. O. *US patent 2,552,696* (1951); *Chem. Abst.*, **1952**, *46*, 1592.
9. Delèpine, H.; Laréze, F. *Bull. Soc. Chim. France*, **1955**, 104–108.
10. Barlow, R. B.; Franks, F. M.; Pearson, J. D. M. *J. Med. Chem.*, **1973**, *16*, 439–446.
11. Cervinka, O.; Hub, L. *Collect. Czech. Chem. Commun.*, **1967**, *32*, 2295–2300.