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(*R*)- and (*S*)-3-Hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone as chiral auxiliaries in the enantioselective preparation of α-aryloxypropanoic acid herbicides and α-chlorocarboxylic acids

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Abstract

rac-α-Chlorocarboxylic acids, *rac*-**9a–e**, were formally deracemized by reaction of the corresponding acyl chlorides with the chiral auxiliaries (*R*)- and (*S*)-3-hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone, (*R*)- and (*S*)-**4**, followed by mild alkaline hydrolysis. The highest o.p. (99%) was obtained in the case of (*S*)-α-chloropropanoic acid, a known precursor for the synthesis of (*R*)-α-aryloxypropanoic acid herbicides such as dichlorprop-P, (*R*)-**3a**, or mecoprop-P, (*R*)-**3b**, which, together with their enantiomers, were also obtained in moderate e.e.s by dynamic kinetic resolution from (α*RS*,3*S*)-4,4-dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-bromopropanoate, (α*RS*,3*S*)-**6**, by reaction with the corresponding phenoxide followed by mild acid hydrolysis. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

Some time ago, we described[1] a multigram scale synthesis of both enantiomers of 3-hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone, (*R*)- and (*S*)-**4**, and their use for the formal deracemization of α-arylpropanoic and α-substituted α-arylacetic acids.[2,3] Also, their use in an enantioselective synthesis of α-hydroxyacids based on the dynamic kinetic resolution of α-bromoesters derived from these chiral auxiliaries with *p*-methoxyphenoxide was recently described.[4] Compounds (*R*)- and (*S*)-**4** are easily crystallizable non-hygroscopic solids more lipophilic than pantolactone, which greatly facilitates their recovery. Both enantiomers are readily available and their e.e.s can be easily obtained by chiral HPLC under UV detection.

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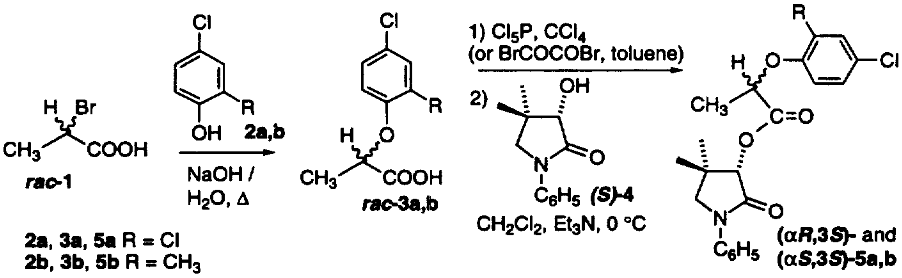
In this paper we describe the application of these chiral auxiliaries for the preparation of α-aryloxypropanoic acid herbicides such as dichlorprop-P, (*R*)-**3a**, mecoprop-P, (*R*)-**3b**, as well as their enantiomers, from racemic precursors.

2. Results and discussion

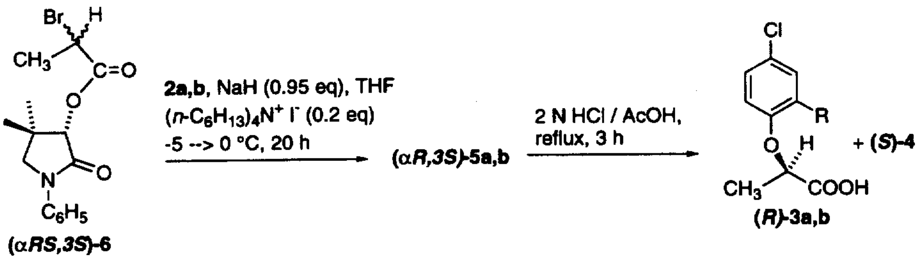
To this end, several possibilities were envisaged. The first one, shown in Scheme 1, consisted of the formal deracemization of the corresponding *rac*-α-aryloxypropanoic acid, in a method similar to that used in the case of α-arylpropanoic[2,5,6] and α-substituted-α-arylacetic acids.[3] Dichlorprop, *rac*-**3a**, and mecoprop, *rac*-**3b**, were prepared by known procedures.[7] Reaction of *rac*-**3a** with phosphorus pentachloride in CCl_4 gave the corresponding acyl chloride which was reacted as a crude product with the chiral auxiliary, (*S*)-**4**, under the standard conditions used for the formal deracemization of α-arylpropanoic acids,[2] to give in low yield a mixture of (α*R*,3*S*)- and (α*S*,3*S*)-**5a** in an approximate ratio of 2:1 (^{1}H NMR). A similar reaction, in which *rac*-**3a** was transformed into the corresponding acyl bromide, by reaction with oxalyl bromide in toluene, and then reacted with (*S*)-**4** gave a mixture of (α*R*,3*S*)- and (α*S*,3*S*)-**5a** in better yield but with practically no diastereoselectivity (^{1}H NMR). A similar result was obtained starting from *rac*-**3b**. These results are in accord with those obtained starting from α-(*p*-methoxyphenoxy)carboxylic acids.[4]



Scheme 1. Attempted diastereoselective syntheses of α-aryloxy esters **5a,b** from *rac*-**3a,b** and (*S*)-**4**

Another approach, shown in Scheme 2, was based on the dynamic kinetic resolution[8–13] of diastereomeric mixtures of α-bromoesters (α*RS*,3*S*)-**6** on reaction with 2,4-dichlorophenol, **2a**, or 4-chloro-2-methylphenol, **2b**. The optimum reaction conditions[4] found in the case of the reaction of *p*-methoxyphenol with diastereomeric ester mixtures derived from different α-bromocarboxylic acids and (*R*)- or (*S*)-**4**, were used. These conditions consist of: (i) the use of a small molar deficiency of sodium hydride with respect to the phenol and α-bromo ester to avoid epimerization of the starting compounds and/or products; (ii) the use of tetra-*n*-hexylammonium iodide (20% molar) as catalyst; and (iii) the control of the temperature of the reaction mixture in the range −5 to 0°C. In this way, esters (α*R*,3*S*)-**5a,b** were obtained in good yield and moderate diastereoselectivities (54% d.e. by ^{1}H NMR). These results are in accord with those previously found by our group in similar reactions using *p*-methoxyphenol.[4]

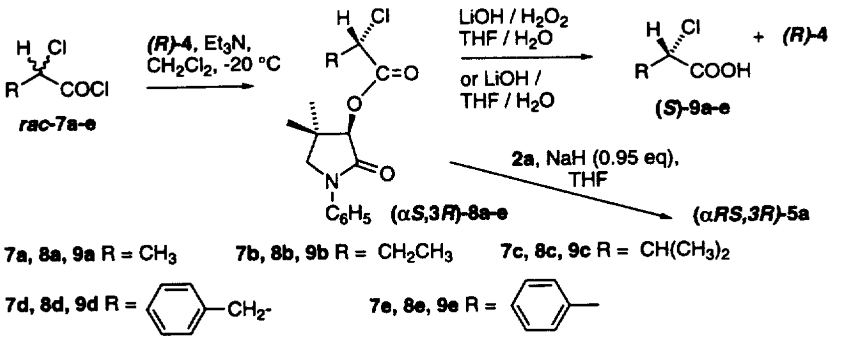
It is worth noting that the dynamic kinetic resolution of esters derived from these chiral auxiliaries and other α-bromocarboxylic acids, such as α-bromo-β-methylbutanoic, α-bromo-α-phenylacetic and α-bromo-β-phenylpropanoic acids, with *p*-methoxyphenoxide gave the corresponding substitution products in good diastereoselectivities (89–98%).[4] The lower diastereoselectivity in the reactions of α-bromopropanoates **6** might then be ascribed to a lower reactivity difference of both diastereomers towards the phenoxides. The d.e.s of the thus-obtained diastereomeric mixtures of esters **5a,b** were increased to 72–85% after one or two crystallizations from methanol. Hydrolysis of these diastereomerically enriched



Scheme 2. Enantioselective synthesis of (*R*)-**3a**,**b** by dynamic kinetic resolution from (α-*RS*,3*S*)-**6**

mixtures under the acid conditions used in related cases[2–5] (3.2 ml 2 N HCl and 8 ml AcOH per mmol of ester, 120°C, 3 h) gave the corresponding acids (*R*)- or (*S*)-**3a**,**b**. From the specific rotation of the thus-obtained acids, their optical purities (o.p.) were calculated, showing that little or no epimerization takes place during hydrolysis.

In a third approach to the enantioselective synthesis of α-aryloxypropanoic acids (*R*)-**3a**,**b**, we studied the enantioselective preparation of (*S*)-α-chloropropanoic acid, (*S*)-**9a** (Scheme 3), since it is a known precursor for this family of herbicides.[7,14] Our previous experience on the enantioselective preparation of α-bromoacids using (*R*)- or (*S*)-**4** as chiral auxiliaries was not too promising,[4] since although the reaction of the chiral auxiliary with an activated form of the α-bromoacid was quite diastereoselective, the thus-obtained esters easily epimerize at the α-ester stereocenter in chloroform solution at room temperature or, especially, under the studied acid or base hydrolysis conditions.



Scheme 3. Enantioselective synthesis of (*S*)-α-chlorocarboxylic acids, (*S*)-**9**

A study of the reaction of *rac*-α-chloropropanoyl chloride, *rac*-**7a**, with (*S*)-**4** in anhydrous methylene dichloride at −20°C using different tertiary amines (2 equiv.) showed the enormous influence of the amine on the diastereoselectivity of this reaction, a fact that had been previously observed by other authors.[15–17] Good yields of esters (92–99%) were attained in a 10 min period, except in the case of N-methylmorpholine (25 min). The greatest diastereoselectivity (96% d.e. by HPLC, >95% by ^{1}H NMR) was obtained by using triethylamine, giving (α*R*,3*S*)-**8a**, the main diastereomer. The same kind but lower diastereoselectivity was observed by using ethyldiisopropylamine (49% d.e.) or N-methylmorpholine (46% d.e.). The use of pyridine and its derived bases 2,6-dimethylpyridine and 4-(dimethylamino)pyridine gave very poor and reversed diastereoselectivities [(α*S*,3*S*)-**8a** in 2, 8 and 9% d.e.s, respectively]. Surprisingly, (α*R*,3*S*)-**8a**, contrary to the corresponding α-bromoester, appeared to be quite stable in chloroform solution.

Hydrolysis of (α*R*,3*S*)-**8a** was studied under basic conditions with lithium hydroxide[18] or hydroperoxide,[19] conditions previously used in related cases. Acid hydrolysis conditions (2 N HCl/AcOH) were not tested since they had been shown to induce nearly complete epimerization of

Table 1

Yields[a] and diastereomeric excesses (d.e.)[a] of α-chloro esters **8** and yields, specific rotations and approx. enantiomeric excesses (o.p.) of α-chloro acids **9**[b]

Entry	Starting **7**	Starting **4**	α-chloroester **8**			α-chlorocarboxylic acid **9**			
			Main diast.	yield (%)	d.e. (%)	Main enant.	yield (%)	$[\alpha]_D^{20}$	e.e. (%)
1	***rac*-7a**	**(*R*)-4**	**(α*S*,3*R*)-8a**	>99 (77)	96 (>99)	**(*S*)-9a**	86	-15.6 (-15.9)[19]	98
2	***rac*-7a**	**(*S*)-4**	**(α*R*,3*S*)-8a**	99 (69)	>99 (>99)	**(*R*)-9a**	85	+15.7 (-15.9)[19]	99
3	***rac*-7b**	**(*S*)-4**	**(α*R*,3*S*)-8b**	>99 (53)	74 (82)	**(*R*)-9b**	87	+10.3 (+12.7)[20]	81
4	***rac*-7c**	**(*S*)-4**	**(α*R*,3*S*)-8c**	>99 (51)	22 (24)	**(*R*)-9c**	89	-0.21 (+ 1.0)[21]	21
5	***rac*-7d**	**(*R*)-4**	**(α*S*,3*R*)-8d**	99	59	**(*S*)-9d**	98	+6.0 (+10.2)[22]	59
6	***rac*-7e**	**(*S*)-4**	**(α*S*,3*S*)-8e**	99 (57)	72 (98)	**(*S*)-9e**	99	+52.4 (-163)[23]	32

[a] Yields and d.e.'s of α-chloroesters **8** correspond to crude material; values in parenthesis correspond to yields or d.e.'s of the crystallized products used in the hydrolysis step, except for the oily **(α*S*,3*R*)-8d**. Crystallizations of esters **8** were carried out in ethyl acetate (0.4 mL ethyl acetate / mmol substrate) for **(α*R*,3*S*)-8b**, **(α*R*,3*S*)-8c** and **(α*S*,3*S*)-8e** and in a mixture of hexane / ethyl acetate (2 mL hexane and 0.2 mL ethyl acetate / mmol substrate) for **(α*S*,3*R*)-** and **(α*R*,3*S*)-8a**. D.e's of esters **8** were obtained by HPLC, assuming the relative areas of the peaks to be equal to their relative molar ratios.

[b] Hydrolysis were carried out by reaction with lithium hydroperoxide in THF / water, except for **(α*S*,3*S*)-8e** where lithium hydroxide in THF / water was used. The described values for the specific rotations of acids **(*R*)-** or **(*S*)-9** are given in parenthesis. In the case of **(*R*)-9a**, **(*R*)-9c** and **(*S*)-9e**, the given values correspond to their enantiomers. The experimental values were obtained by using the same solvent and a concentration close to that described for each case.

the α-ester stereocenter in the case of the corresponding α-bromo esters. Although lithium hydroxide hydrolysis induced partial epimerization, the use of lithium hydroperoxide allowed us to isolate in good yield and without any detectable epimerization the corresponding α-chloropropanoic acid, (*R*)-**9a** (85% yield, 99% o.p.).

The optimum reaction conditions established for the conversion of *rac*-**7a** to (*R*)-**9a** were also applied for the preparation of (*S*)-**9a** and other α-chlorocarboxylic acids, using either (*S*)- or (*R*)-**4** as the chiral auxiliary (see Scheme 3 and Table 1). As can be seen from this table, the d.e.s of esters **8** greatly depend on the steric effect of the R group: 96–99% for R=methyl, 74% for R=ethyl, 59% for R=benzyl, 22% for R=isopropyl. Solid esters **8** were crystallized from ethyl acetate or mixtures of hexane and ethyl acetate which somewhat increases their d.e.s. (see Table 1). The main diastereomer of esters **8** derived from the chiral auxiliary (*R*)-**4** is generally the (α*S*,3*R*) while from (*S*)-**4** it is the (α*R*,3*S*). Curiously, the reaction of α-chloro-α-phenylacetyl chloride, *rac*-**7e**, with (*S*)-**4**, showed reversed diastereoselectivity, giving rise to (α*S*,3*S*)-**8e** as the main diastereomer.

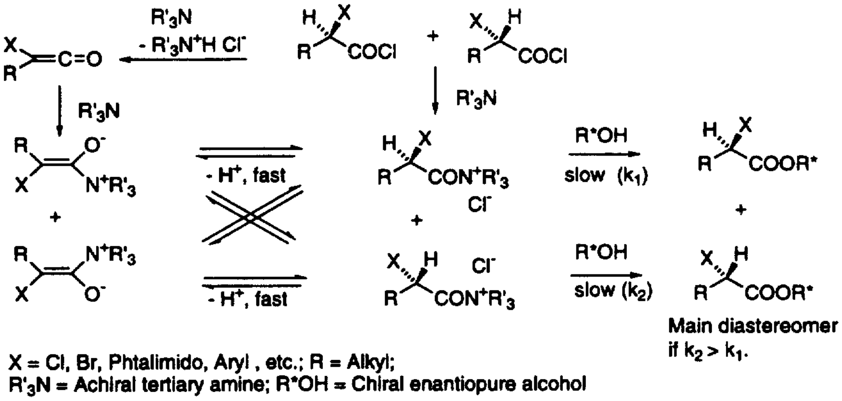
Hydrolysis of the diastereomerically enriched esters **8a–d** was carried out with little or no epimerization by treatment with lithium hydroperoxide as in the case of (*R*)-**9a**. However, hydrolysis of (α*S*,3*S*)-**8e** under these conditions led to the formation of significant amounts of benzoic acid (30%) and *rac*-**9e** (60%). Hydrolysis of this ester using lithium hydroxide in a mixture of THF/water allowed us to obtain (*S*)-**9e** in good yield but low optical purity (32% o.p.), showing that a significant amount of epimerization takes place during hydrolysis, a fact that must be due to the greater acidity of the α-ester hydrogen atom in this case.

After hydrolysis of esters **8** and **5**, the chiral auxiliaries (*R*)- and (*S*)-**4** were always recovered in high yield without epimerization.

Having (α*R*,3*S*)-**8a** (>95% d.e.) in hand, we also tried its conversion into (α*S*,3*S*)-**5a** through an S_N2 mechanism by reaction with the sodium salt of phenol **2a**. When this reaction was carried out in THF at room temperature, the starting compound, partially epimerized at the α-position (74% d.e.), was recovered. At the reflux temperature, a mixture of (α*R*,3*S*)-**5a** and (α*S*,3*S*)-**5a** (39% yield, 22% d.e. by ^{1}H NMR) was obtained with much of the epimerized starting compound also being recovered.

All of the new compounds (esters **5a,b** and **8a,e**) have been fully characterized as diastereomeric mixtures through their spectroscopic data and elemental analysis. The NMR spectra of these compounds have been fully assigned taking into account our previous work.[1,2] The assignment of the signals of the two diastereomers of each mixture could be easily carried out due to their different ratios. The diastereomeric ratio of esters **8**, obtained by HPLC assuming the relative areas of both diastereomers to be equal to their molar ratio, were in good concordance with those obtained from the ^{1}H NMR data, through the integration of the signals of the C*H*Cl protons. For the HPLC analysis of esters (α*R*,3*S*)- and (α*S*,3*R*)-**8a** (>95% d.e.), nearly 1:1 mixtures of (α*R*,3*S*)-**8a**:(α*S*,3*S*)-**8a** and (α*S*,3*R*)-**8a**:(α*R*,3*R*)-**8a** were obtained by reaction of *rac*-**9a** with (*R*)- or (*S*)-**4** induced by DCC. Assignment of the configuration of the α-ester stereocenter of esters **5a,b** and **8a–e** was carried out after their hydrolysis to the corresponding acids **3a,b** and **9a–e**, respectively, of known configuration.

The great influence of the amine on the diastereoselectivity of the amine-catalyzed addition of chiral enantiopure alcohols to ketenes has been explained through the formation of diastereomeric *E*/*Z* enolates derived from the addition of the amine to the previously generated ketene, which then react with the enantiopure alcohol.[15,17] However, under our standard conditions for the deracemization of α-halocarboxylic and α-substituted-α-arylacetic acids,[2,3] a ketene is not previously formed. Usually, the acyl chloride is added to the cold (−20–0°C) solution of the enantiopure alcohol and the amine (2 equiv.). Under such conditions, a possible alternative mechanism to explain the diastereoselectivity of these reactions, which takes into account the important role played by the amine, is shown in Scheme 4.



Scheme 4. Possible mechanism for the diastereoselective formation of esters in the amine-induced reaction of chiral enantiopure alcohols with *rac*-acyl chlorides having a trisubstituted stereogenic center at the α-position, based on the dynamic kinetic resolution of enantiomeric acylammonium intermediates by the enantiopure alcohol

Reaction of the racemic acyl chloride with the amine can give a racemic mixture of acylammonium cations which can be in rapid equilibrium *via* the corresponding *E*- and/or *Z*-enolates. These enolates may alternatively be formed by addition of the amine to the *in situ* generated ketene. A slow reaction of these enantiomeric acylammonium cations with an enantiopure alcohol may result in the diastereoselective formation of one of the two possible esters through a dynamic kinetic resolution process,[8–13] provided the alcohol reacts faster with one of them, in such a way that equilibration of both enantiomeric acylammonium cations can be achieved. This mechanism may be operative not only in the formal deracemization of α-halocarboxylic acids herein described, but also in the formal deracemization of other α-substituted carboxylic acids such as α-arylpropanoic acids, α-phthalimidocarboxylic acids, etc.

In conclusion, the chiral auxiliaries (*R*)- and (*S*)-**4** have shown their value for the formal deracemization of some α-chlorocarboxylic acids, especially for the preparation of (*R*)- and (*S*)-α-chloropropanoic acids, (*R*)- and (*S*)-**9a**, the last one being a key precursor for the synthesis of (*R*)-α-aryloxypropanoic acid herbicides,[24] such as dichlorprop-P,[14] (*R*)-**3a** and mecoprop-P,[7] (*R*)-**3b**. Also, an alternative moderately enantioselective synthesis of acids (*R*)- and (*S*)-**3a**,**b**, based on the dynamic kinetic resolution of a diastereomeric mixture of α-bromo ester **6** by reaction with the corresponding phenoxides, has been developed. Moreover, the synthesis of (*R*)- and (*S*)-α-chlorocarboxylic acids herein described could be of interest for the preparation of other enantiopure compounds such as oxiranes,[25] α-amino acids,[26] and several drugs.[27–30] The increasing interest in enantiopure α-chlorocarboxylic acids is also shown by several recent patent applications claiming the enantiopure preparation of (*R*)- or (*S*)-α-chloropropanoic acids by enzymatic resolution of the racemic mixture.[31–33]

3. Experimental

Melting points were determined on a MFB 595010 M Gallenkamp melting point apparatus. 500 MHz ^{1}H NMR spectra were performed on a Varian VXR 500 spectrometer, while 300 MHz ^{1}H and 75.4 MHz ^{13}C NMR spectra were carried out on a Varian Gemini 300. Except where otherwise stated, ^{1}H NMR spectra were recorded at 500 MHz and ^{13}C NMR spectra at 75.4 MHz, always in $CDCl_3$. Chemical shifts (δ) are reported in ppm referenced to internal tetramethylsilane. IR spectra were recorded on an FT/IR Perkin–Elmer spectrometer, model 1600. 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 λ=249 or 230 nm and always using, for the stereospecific and non-stereospecific analyses, a Chiralcel OD-H column (25×0.46 cm) containing the chiral stationary phase cellulose tris-(3,5-dimethylphenylcarbamate). Conditions A: a mixture of hexane/isopropanol/trifluoroacetic acid in the ratio of 99/1/0.05 as eluent, flow 0.2 ml/min. Conditions B: a mixture of hexane/isopropanol in the ratio of 93/7 as eluent, flow 0.35 ml/min. Solvents were of analytical grade. Elemental analyses were carried out at the Microanalysis Service of the *Centro de Investigación y Desarrollo* (C.I.D.), Barcelona, Spain.

3.1. (αS,3R)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-(2,4-dichlorophenoxy)propanoate, (αS,3R)-5a, from rac-α-(2,4-dichlorophenoxy)propanoic acid, rac-3a, and (R)-4

Method A. A solution of *rac*-**3a** (235 mg, 1.00 mmol) in anhydrous CCl_4 (25 ml) was treated with PCl_5 (209 mg, 1.00 mmol) for 1.5 h under reflux in an argon atmosphere. The volatile products were distilled off at reduced pressure, the residue was taken in anhydrous CH_2Cl_2 (5 ml) and it was added dropwise over a cold (0°C) solution of (*R*)-**4** (195 mg, 0.95 mmol) and triethylamine (0.3 ml, 2 mmol) in CH_2Cl_2 (5 ml) in an argon atmosphere. After addition was completed, stirring was continued for 1 h at 0°C. The reaction mixture was washed with 2 N HCl (4×20 ml) and a saturated aqueous solution of $NaHCO_3$ (4×20 ml). The organic phase was dried with anhydrous Na_2SO_4 and concentrated *in vacuo* to give a residue, which was purified by column chromatography [silica gel (15 g), CH_2Cl_2] to give a mixture of (α*S*,3*R*)-**5a** and (α*R*,3*R*)-**5a** (191 mg, 48% yield, 28% d.e. by ^{1}H NMR).

Method B. A solution of *rac*-**3a** (235 mg, 1.00 mmol) in anhydrous toluene (10 ml) was treated with oxalyl bromide (0.54 g, 2.5 mmol) for 2 h under reflux in an argon atmosphere. The volatile products were distilled off at reduced pressure, the residue was taken in anhydrous CH_2Cl_2 (5 ml) and it was reacted as in Method A with (*R*)-**4** (195 mg, 0.95 mmol) to give, after column chromatography, a mixture of (α*S*,3*R*)-**5a** and (α*R*,3*R*)-**5a** (204 mg, 51% yield, 20% d.e. by ^{1}H NMR).

3.2. *(α*S*,3*R*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-(4-chloro-2-methylphenoxy)propanoate, (α*S*,3*R*)-**5b**, from* rac-*α-(4-chloro-2-methylphenoxy)propanoic acid,* rac-***3b***, and (*R*)-**4***

Method A. Following the same procedure described above under Method A, from *rac*-**3b** (215 mg, 1.00 mmol), a mixture of (α*S*,3*R*)-**5b** and (α*R*,3*R*)-**5b** (189 mg, 49% yield, 42% d.e. by ^{1}H NMR) was obtained.

Method B. Following the same procedure described above under Method B, from *rac*-**3b** (215 mg, 1.00 mmol), a mixture of (α*S*,3*R*)-**5b** and (α*R*,3*R*)-**5b** (171 mg, 45% yield), in the approximate ratio 1:1 (by ^{1}H NMR) was obtained.

3.3. *General procedure for the reactions of α-bromo esters **6** with sodium 2,4-dichlorophenoxide or 4-chloro-2-methylphenoxide*

A THF solution of sodium 2,4-dichlorophenoxide or 4-chloro-2-methylphenoxide was prepared by adding sodium hydride (0.95 mmol) to a stirred solution of 2,4-dichlorophenol or 4-chloro-2-methylphenol (1.00 mmol) in dry THF (7 ml) at room temperature under an argon atmosphere. Stirring was continued until evolution of hydrogen ceased. The resulting solution was then added dropwise *via* cannula to a stirred, dried (1.0 g of 4 Å molecular sieves) THF solution (9 ml) of α-bromo ester **6** (1.00 mmol) and tetra-*n*-hexylammonium iodide (0.20 mmol) at −5 to 0°C under an argon atmosphere and the solution was stirred at this temperature for 20 h. The mixture was concentrated *in vacuo*, CH_2Cl_2 (8 ml) was added to the residue and the solution was washed with water (3×5 ml) and saturated aqueous $NaHCO_3$ (3×5 ml), dried with anh. Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed [silica gel (30 g) hexane/ethyl acetate] and the thus-obtained α-phenoxy ester **5a**,**b** was characterized as a diastereomeric mixture. Chemical yields refer to the total yield of both diastereomers.

3.4. *(α*S*,3*R*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-(2,4-dichlorophenoxy)propanoate, (α*S*,3*R*)-**5a***

Following the above general procedure, from (α*RS*,3*R*)-**6** (1.36 g, 4.00 mmol), (α*S*,3*R*)-**5a** (1.57 g, 93% yield, 52% d.e. by ^{1}H NMR, 54% d.e. by HPLC) was isolated. After two crystallizations from methanol (6 and 3 ml, respectively) solid (α*S*,3*R*)-**5a** was obtained (0.25 g, 15% yield), m.p. 83–85°C, $[\alpha]_D^{20}$=+41.1 (c=0.94, $CHCl_3$), 82% d.e. by ^{1}H NMR, 83% d.e. by HPLC [conditions B: main diastereomer (α*S*,3*R*)-**5a**, r.t. 68.7 min; (α*R*,3*R*)-**5a**, r.t. 77.8 min]. The integral of the 4-αCH_3 group in both diastereomers (δ 1.06 and 1.09) allows us to calculate the ratio (α*S*,3*R*)-**5a**/(α*R*,3*R*)-**5a** in each case. IR (KBr) ν: 1761 and 1716 (C=O st) cm^{-1}. $C_{21}H_{21}Cl_2NO_4$ (422.32): calcd C 59.72%, H 5.02%, N 3.32%, Cl 16.79%. Found C 59.67%, H 5.20%, N 3.31%, Cl 16.59%.

3.4.1. *Spectroscopic data of (α*S*,3*R*)-**5a** obtained from the spectra of the crystallized sample*

^{1}H NMR, δ: 1.06 (s, 3H, 4-αCH_3), 1.21 (s, 3H, 4-βCH_3), 1.79 (d, J=7.0 Hz, 3H, CHC*H*$_3$), 3.51 (d, J=9.5 Hz, 1H, 5α-H), 3.61 (d, J=9.5 Hz, 1H, 5β-H), 4.92 (q, J=7.0 Hz, 1H, C*H*CH_3), 5.42 (s, 1H, 3-H), 6.93 (d, J=9.0 Hz, 1H, 6-H $C_6H_3Cl_2O$–), 7.18 (m plus dd, J=9.0 Hz, J′=2.5 Hz, 2H, H_{para} N-phenyl and 5-H $C_6H_3Cl_2O$–), 7.38 (m plus d, J=2.5 Hz, 3H, H_{meta} N-phenyl and 3-H $C_6H_3Cl_2O$–), 7.60 (dm, J=8.5 Hz, 2H, H_{ortho} N-phenyl). ^{13}C NMR, δ: 18.6 (CH_3, CHCH_3), 21.0 (CH_3, 4-αCH_3), 24.5 (CH_3, 4-βCH_3), 37.3

(C, C4), 57.6 (CH_2, C5), 73.7 (CH, *C*HCH$_3$), 78.7 (CH, C3), 115.4 (CH, C6 $C_6H_3Cl_2O$–), 119.4 (CH, C_{ortho} N-phenyl), 124.2 (C, C2 $C_6H_3Cl_2O$–), 125.1 (CH, C_{para} N-phenyl), 126.8 (C, C4 $C_6H_3Cl_2O$–), 127.6 (CH, C5 $C_6H_3Cl_2O$), 129.0 (CH, C_{meta} N-phenyl), 130.2 (CH, C3 $C_6H_3Cl_2O$–), 138.8 (C, C_{ipso} N-phenyl), 152.0 (C, C1 $C_6H_3Cl_2O$–), 168.1 (C, C2), 170.6 (C, COO).

3.4.2. *Significant spectroscopic data of (αR,3R)-**5a** obtained from the spectra of (αS,3R)-**5a** of 54% d.e.*

^{1}H NMR, δ: 1.09 (s, 3H, 4-αCH_3), 1.28 (s, 3H, 4-βCH_3), 1.78 (d, J=7.0 Hz, 3H, CHC*H*$_3$), 3.51 (d, J=9.5 Hz, 1H, 5α-H), 3.60 (d, J=9.5 Hz, 1H, 5β-H), 4.90 (q, J=7.0 Hz, 1H, C*H*CH$_3$), 5.41 (s, 1H, 3-H), 6.96 (d, J=9.0 Hz, 1H, 6-H $C_6H_3Cl_2O$–). ^{13}C NMR, δ: 18.5 (CH_3, CHCH$_3$), 21.2 (CH_3, 4-αCH_3), 24.7 (CH_3, 4-βCH_3), 37.3 (C, C4), 57.6 (CH_2, C5), 74.4 (CH, *C*HCH$_3$), 79.0 (CH, C3).

3.5. *(αR,3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-(2,4-dichlorophenoxy)propanoate, (αR,3S)-**5a***

Following the above general procedure, from (α*RS*,3*S*)-**6** (1.19 g, 3.50 mmol), (α*R*,3*S*)-**5a** (1.35 g, 91% yield, 54% d.e. by ^{1}H NMR, 58% d.e. by HPLC) was isolated. After one crystallization from methanol (5 ml), solid (α*R*,3*S*)-**5a** was obtained (0.38 g, 26% yield), m.p. 81–83°C, $[\alpha]_D^{20}=-41.3$ (c=1.00, $CHCl_3$), 82% d.e. by ^{1}H NMR, 85% d.e. by HPLC. $C_{21}H_{21}Cl_2NO_4$ (422.32): calcd C 59.72%, H 5.02%, N 3.32%, Cl 16.79%. Found C 59.52%, H 5.20%, N 3.23%, Cl 17.01%. The IR and ^{1}H and ^{13}C NMR data coincide with those of their enantiomers.

3.6. *(αS,3R)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-(4-chloro-2-methylphenoxy)propanoate, (αS,3R)-**5b***

Following the above general procedure, from (α*RS*,3*R*)-**6** (0.68 g, 2.0 mmol), (α*S*,3*R*)-**5b** (0.65 g, 86% yield, 62% d.e. by ^{1}H NMR, 64% d.e. by HPLC) was isolated. After one crystallization from methanol (5 ml), solid (α*S*,3*R*)-**5b** was obtained (0.31 g, 41% yield), m.p. 91–93°C, $[\alpha]_D^{20}=+30.1$ (c=1.03, $CHCl_3$), 76% d.e. by ^{1}H NMR, 78% d.e. by HPLC [conditions B: main diastereomer (α*S*,3*R*)-**5b**, r.t. 55.0 min; (α*R*,3*R*)-**5b**, r.t. 65.1 min]. The integral of the 4-αC*H*$_3$ group in both diastereomers (δ 0.94 and 1.10) gave the ratio (α*S*,3*R*)-**5b**/(α*R*,3*R*)-**5b** in each case. IR (KBr) ν: 1763 and 1714 (C=O st) cm^{-1}. $C_{22}H_{24}ClNO_4$ (401.91): calcd C 65.75%, H 6.02%, N 3.49%, Cl 8.82%. Found C 65.66%, H 6.06%, N 3.47%, Cl 9.37%.

3.6.1. *Spectroscopic data of (αS,3R)-**5b** obtained from the spectra of the crystallized sample*

^{1}H NMR, δ: 0.94 (s, 3H, 4-αCH_3), 1.13 (s, 3H, 4-βCH_3), 1.74 (d, J=6.5 Hz, 3H, CHC*H*$_3$), 2.23 [s, 3H, $C_6H_3Cl(CH_3)O$–], 3.45 (d, J=9.5 Hz, 1H, 5α-H), 3.58 (d, J=9.5 Hz, 1H, 5β-H), 4.88 (q, J=6.5 Hz, 1H, C*H*CH$_3$), 5.39 (s, 1H, 3-H), 6.71 [d, J=8.5 Hz, 1H, 6-H $C_6H_3Cl(CH_3)O$–], 7.06–7.11 [compl. signal, 2H, 3-H and 5-H $C_6H_3Cl(CH_3)O$–], 7.16 (tm, J=7.5 Hz, 1H, H_{para} N-phenyl) 7.36 (m, 2H, H_{meta} N-phenyl), 7.59 (dm, J=8.0 Hz, 2H, H_{ortho} N-phenyl). ^{13}C NMR, δ: 16.2 (CH_3, $C_6H_3Cl(CH_3)O$–), 18.8 (CH_3, CHCH$_3$), 20.8 (CH_3, 4-αCH_3), 24.4 (CH_3, 4-βCH_3), 37.2 (C, C4), 57.5 (CH_2, C5), 72.6 (CH, *C*HCH$_3$), 78.5 (CH, C3), 112.5 (CH, C6 $C_6H_3Cl(CH_3)O$–), 119.4 (CH, C_{ortho} N-phenyl), 125.0 (CH, C_{para} N-phenyl), 125.8 [C, C4 $C_6H_3Cl(CH_3)O$–], 126.3 [CH, C5 $C_6H_3Cl(CH_3)O$–], 129.0 (CH, C_{meta} N-phenyl), 130.7 [CH, C3 $C_6H_3Cl(CH_3)O$–], 138.8 (C, C_{ipso} N-phenyl), 154.3 [C, C1 $C_6H_3Cl(CH_3)O$–], 168.2 (C, C2), 171.4 (C, COO). The signal of C2 was not observed.

3.6.2. *Significant spectroscopic data of (αR,3R)-**5b** obtained from the spectra of (αS,3R)-**5b** of 62% d.e.*

^{1}H NMR, δ: 1.10 (s, 3H, 4-αCH$_3$), 1.25 (s, 3H, 4-βCH$_3$), 1.73 (d, J=7.0 Hz, 3H, CHC*H*$_3$), 2.24 [s, 3H, $C_6H_3Cl(CH_3)O$–], 3.50 (d, J=9.5 Hz, 1H, 5α-H), 3.60 (d, J=9.5 Hz, 1H, 5β-H), 4.86 (q, J=7.0 Hz, 1H, C*H*CH$_3$), 5.40 (s, 1H, 3-H), 6.68 [d, J=8.5 Hz, 1H, 6-H $C_6H_3Cl(CH_3)O$–]. ^{13}C NMR, δ: 16.2 [CH$_3$, $C_6H_3Cl(CH_3)O$–], 18.6 (CH$_3$, CH*C*H$_3$), 21.1 (CH$_3$, 4-αCH$_3$), 24.7 (CH$_3$, 4-βCH$_3$), 37.2 (C, C4), 57.6 (CH$_2$, C5), 72.8 (CH, *C*HCH$_3$), 78.7 (CH, C3).

3.7. *(αR,3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-(4-chloro-2-methylphenoxy)propanoate, (αR,3S)-**5b***

Following the above general procedure, from (α*RS*,3*S*)-**6** (0.85 g, 2.5 mmol), (α*R*,3*S*)-**5b** (0.85 g, 89% yield, 46% d.e. by ^{1}H NMR, 48% d.e. by HPLC) was obtained, which after one crystallization from methanol (7 ml) gave a solid (0.36 g, 38% yield), m.p. 92–94°C, $[\alpha]_D^{20}=-29.8$ (c=1.02, CHCl$_3$), 72% d.e. by ^{1}H NMR, 74% d.e. by HPLC. The integral of the 4-αC*H*$_3$ group in both diastereomers (δ 0.97 and 1.13) gave the ratio (α*R*,3*S*)-**5b**/(α*S*,3*S*)-**5b** in each case. $C_{22}H_{24}ClNO_4$ (401.91): calcd C 65.75%, H 6.02%, N 3.49%, Cl 8.82%. Found C 65.52%, H 6.27%, N 3.43%, Cl 8.58%. The IR and NMR data coincide with those of their enantiomers.

3.8. *General procedure for the hydrolysis of α-phenoxy esters **5***

A mixture of the α-phenoxy ester **5** (1.0 mmol), acetic acid (8 ml) and 2 N HCl (3.2 ml) was heated at 120°C (bath temperature) until completion of the hydrolysis (3 h), this was followed by thin layer chromatography (TLC). The mixture was allowed to cool to room temperature and the volatile products were distilled off at reduced pressure. Water (10 ml) was added to the residue, the mixture was treated with saturated aqueous NaHCO$_3$ until a basic pH was achieved and it was extracted with CH$_2$Cl$_2$ (2×10 ml). The combined organic extracts were dried with anh. Na$_2$SO$_4$ and concentrated *in vacuo* to give the chiral auxiliary, (*R*)- or (*S*)-**4**. The aqueous phase was acidified with 2 N HCl and extracted with ethyl acetate (3×10 ml). The combined organic phases were dried with anh. Na$_2$SO$_4$ and concentrated *in vacuo* to give the (*R*)- or (*S*)-α-phenoxypropanoic acid, (*R*)- or (*S*)-**3**. Chemical yields refer to the total yield of both enantiomers.

3.9. *(R)-α-(2,4-Dichlorophenoxy)propanoic acid, (R)-**3a***

From (α*R*,3*S*)-**5a** (0.29 g, 0.69 mmol, 85% d.e. by HPLC), (*R*)-**3a** (0.15 g, 93% yield) was obtained as a solid, m.p. 108–110°C (hexane/ethyl acetate) (described: 116–117.5°C),[24] $[\alpha]_D^{20}=+22.3$ (c=1.00, ethanol) [described: $[\alpha]_D^{20}=+26.6$ (c=1.23, ethanol)],[24] approx. 84% o.p., 84% e.e. by HPLC [conditions A: main enantiomer (*R*)-**3a**, r.t. 121.1 min; (*S*)-**3a**, r.t. 111.2 min].

3.10. *(S)-α-(2,4-Dichlorophenoxy)propanoic acid, (S)-**3a***

From (α*S*,3*R*)-**5a** (0.21 g, 0.50 mmol, 83% d.e. by HPLC), (*S*)-**3a** (0.11 g, 94% yield) was obtained as a solid, m.p. 107–109°C (hexane/ethyl acetate), $[\alpha]_D^{20}=-19.7$ (c=1.18, ethanol), 74% approx. o.p., 70% e.e. by HPLC [conditions A: main enantiomer (*S*)-**3a**, r.t. 116.0 min, (*R*)-**3a**, r.t. 128.1 min].

3.11. *(*R*)-α-(4-Chloro-2-methylphenoxy)propanoic acid, (*R*)-**3b***

From (α*R*,3*S*)-**5b** (0.15 g, 0.37 mmol, 78% d.e. by HPLC), (*R*)-**3b** (0.07 g, 92% yield) was obtained as a solid, m.p. 89–91°C (hexane/ethyl acetate) (described: 95°C),[24] $[\alpha]_D^{20}$=+20.8 (c=1.03, ethanol), [described: $[\alpha]_D^{20}$=+28.1 (ethanol)],[24] 74% approx. o.p.

3.12. *(*S*)-α-(4-Chloro-2-methylphenoxy)propanoic acid, (*S*)-**3b***

From (α*S*,3*R*)-**5b** (0.26 g, 0.65 mmol, 76% d.e. by ^{1}H NMR), (*S*)-**3b** (0.13 g, 90% yield) was obtained as a solid, m.p. 89.5–91.5°C (hexane/ethyl acetate) $[\alpha]_D^{20}$=−21.3 (c=1.00, ethanol), 76% approx. o.p.

3.13. *General procedure for the reaction of* rac-*α-chloroacyl chlorides with (*R*)- or (*S*)-**4***

To a dried and cooled solution (−20°C) of (*R*)- or (*S*)-**4** (1.00 mmol) and triethylamine (2.0 mmol) in CH_2Cl_2 under an argon atmosphere, a solution of *rac*-**7** (1.05 mmol) in CH_2Cl_2 was added dropwise over a period of 10 min and the mixture was magnetically stirred for 10 min at −20°C. The mixture was washed with 1 N HCl (3×3.75 ml), a saturated aqueous solution of $NaHCO_3$ (3×3.75 ml), dried (anh. Na_2SO_4) and concentrated *in vacuo*.

3.14. *(α*S*,3*R*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-chloropropanoate, (α*S*,3*R*)-**8a***

Following the above general procedure, from (*R*)-**4** (4.10 g, 20.0 mmol) and *rac*-**7a** (2.0 ml, 20.6 mmol), (α*S*,3*R*)-**8a** (5.90 g, >99% yield, 96% d.e. by HPLC) was obtained as a solid. Crystallization from a mixture of hexane (40 ml) and ethyl acetate (4 ml) gave the analytical sample (4.55 g, 77% global yield), m.p. 79–80°C, $[\alpha]_D^{20}$=+50.3 (c=1.05, $CHCl_3$), >99% d.e. by HPLC [conditions B: main diastereomer (α*S*,3*R*)-**8a**, r.t. 59.0 min; (α*R*,3*R*)-**8a**, r.t. 57.0 min]. IR (KBr) ν: 1770, 1756 and 1703 (C=O st) cm^{-1}. $C_{15}H_{18}ClNO_3$ (295.78): calcd C 60.91%, H 6.14%, N 4.74%, Cl 11.99%. Found C 61.02%, H 6.21%, N 4.76%, Cl 12.00%. ^{1}H NMR, δ: 1.16 (s, 3H, 4-αCH_3), 1.31 (s, 3H, 4-βCH_3), 1.79 (d, J=7.0 Hz, 3H, $CHCH_3$), 3.53 (d, J=9.5 Hz, 1H, 5α-H), 3.62 (d, J=9.5 Hz, 1H, 5β-H), 4.56 (q, J=7.0 Hz, 1H, CHCl), 5.40 (s, 1H, 3-H), 7.16 (tm, J=7.5 Hz, 1H, H_{para}), 7.37 (m, 2H, H_{meta}), 7.60 (dm, J=8.0 Hz, 2H, H_{ortho}). ^{13}C NMR, δ: 21.0 (CH_3, 4-αCH_3), 21.8 (CH_3, $CHCH_3$), 24.8 (CH_3, 4-βCH_3), 37.5 (C, C4), 52.8 (CH, CHCl), 57.7 (CH_2, C5), 79.3 (CH, C3), 119.4 (CH, C_{ortho}), 125.0 (CH, C_{para}), 128.9 (CH, C_{meta}), 138.8 (C, C_{ipso}), 168.0 (C, C2), 169.4 (C, COO).

3.15. *(α*R*,3*S*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-chloropropanoate, (α*R*,3*S*)-**8a***

Following the above general procedure, from (*S*)-**4** (0.41 g, 2.0 mmol) and *rac*-**7a** (0.2 ml, 2.1 mmol), (α*R*,3*S*)-**8a** (0.59 g, 99% yield, >99% d.e. by HPLC) was obtained as a solid. Crystallization from a mixture of hexane (4.5 ml) and ethyl acetate (0.5 ml) gave the analytical sample (0.41 g, 69% global yield), m.p. 79.5–80°C, $[\alpha]_D^{20}$=−51.0 (c=1.03, $CHCl_3$), >99% by HPLC [conditions B: main diastereomer (α*R*,3*S*)-**8a**, r.t. 37.0 min; (α*S*,3*S*)-**8a**, r.t. 32.7 min]. $C_{15}H_{18}ClNO_3$ (295.78): calcd C 60.91%, H 6.14%, N 4.74%, Cl 11.99%. Found C 60.92%, H 6.13%, N 4.78%, Cl 11.99%. The IR and NMR spectra are coincident with those of its enantiomer.

3.16. (αR,3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-chlorobutanoate, (αR,3S)-8b

Following the above general procedure, from (*S*)-**4** (4.10 g, 20.0 mmol) and *rac*-**7b** (2.96 g, 21.0 mmol), (α*R*,3*S*)-**8b** (6.19 g, >99% yield, 74% d.e. by HPLC) was obtained as a solid. Crystallization from ethyl acetate (8 ml) gave the analytical sample (3.30 g, 53% global yield), m.p. 49.5–50°C, $[\alpha]_D^{20}=-50.5$ (c=1.12, $CHCl_3$), 82% d.e. by HPLC [conditions B: main diastereomer (α*R*,3*S*)-**8b**, r.t. 32.5 min; (α*S*,3*S*)-**8b**, r.t. 29.4 min]. IR (KBr) ν: 1750 and 1711 (C=O st) cm^{-1}. $C_{16}H_{20}ClNO_3$ (309.81): calcd C 62.03%, H 6.51%, N 4.52%, Cl 11.44%. Found C 61.92%, H 6.63%, N 4.53%, Cl 11.51%.

3.16.1. Spectroscopic data of (αR,3S)-8b obtained from the spectra of the mixture

^1H NMR, δ: 1.10 (t, J=7.5 Hz, 3H, CH_3CH_2), 1.16 (s, 3H, 4-αCH_3), 1.30 (s, 3H, 4-βCH_3), 2.04 (m, 1H) and 2.10 (m, 1H) (CH_3CH_2), 3.53 (d, J=9.5 Hz, 1H, 5α-H), 3.62 (d, J=9.5 Hz, 1H, 5β-H), 4.40 (dd, J=5.5 Hz, J′=7.5 Hz, 1H, CHCl), 5.42 (s, 1H, 3-H), 7.16 (tm, J=7.5 Hz, 1H, H_{para}), 7.36 (m, 2H, H_{meta}), 7.60 (dm, J=7.5 Hz, 2H, H_{ortho}). ^{13}C NMR, δ: 10.4 (CH_3, CH_3CH_2), 21.0 (CH_3, 4-αCH_3), 24.8 (CH_3, 4-βCH_3), 28.5 (CH_2, CH_3CH_2), 37.5 (C, C4), 57.6 (CH_2, C5), 59.0 (CH, CHCl), 79.1 (CH, C3), 119.4 (CH, C_{ortho}), 125.0 (CH, C_{para}), 128.9 (CH, C_{meta}), 138.8 (C, C_{ipso}), 168.0 (C, C2), 168.9 (C, COO).

3.17. (αR,3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-chloro-β-methylbutanoate, (αR,3S)-8c

Following the above general procedure, from (*S*)-**4** (2.87 g, 14.0 mmol) and *rac*-**7c** (2.33 g, 15.0 mmol), (α*R*,3*S*)-**8c** (4.52 g, >99% yield, 22% d.e. by HPLC) was obtained as a solid. Crystallization from ethyl acetate (6 ml) gave the analytical sample (2.31 g, 51% global yield), m.p. 69–70°C, $[\alpha]_D^{20}=-50.1$ (c=1.05, $CHCl_3$), 24% d.e. by HPLC [conditions B: main diastereomer (α*R*,3*S*)-**8c**, r.t. 27.8 min; (α*S*,3*S*)-**8c**, r.t. 25.7 min]. IR (KBr) ν: 1756 and 1708 (C=O st) cm^{-1}. $C_{17}H_{22}ClNO_3$ (323.84): calcd C 63.05%, H 6.85%, N 4.33%, Cl 10.95%. Found C 62.85%, H 6.84%, N 4.31%, Cl 10.88%.

3.17.1. Spectroscopic data of (αR,3S)-8c obtained from the spectra of the mixture

^1H NMR, δ: 1.09 (d, J=7.0 Hz, 3H) and 1.12 (d, J=7.0 Hz, 3H) [$CH(CH_3)_2$], 1.163 (s, 3H, 4-αCH_3), 1.298 (s, 3H, 4-βCH_3), 2.38 (oct., J=7.0 Hz, 1H, $CH(CH_3)_2$), 3.52 (d, J=9.5 Hz, 1H, 5α-H), 3.62 (d, J=9.5 Hz, 1H, 5β-H), 4.27 (d, J=7.0 Hz, 1H, CHCl), 5.439 (s, 1H, 3-H), 7.16 (tm, J=7.5 Hz, 1H, H_{para}), 7.36 (m, 2H, H_{meta}), 7.60 (dm, J=8.5 Hz, 2H, H_{ortho}). ^{13}C NMR, δ: 18.0 (CH_3) and 19.6 (CH_3) [$CH(CH_3)_2$], 21.06 (CH_3, 4-αCH_3), 24.7 (CH_3, 4-βCH_3), 32.7 (CH, $CH(CH_3)_2$), 37.5 (C, C4), 57.58 (CH_2, C5), 64.5 (CH, CHCl), 79.1 (CH, C3), 119.4 (CH, C_{ortho}), 125.0 (CH, C_{para}), 129.0 (CH, C_{meta}), 138.9 (C, C_{ipso}), 168.1 (C, C2), 168.7 (C, COO).

3.17.2. Significant spectroscopic data of (αS,3S)-8c obtained from the spectra of the mixture

^1H NMR, δ: 1.107 (d, J=7.0 Hz, 3H) and 1.110 (d, J=7.0 Hz, 3H) [$CH(CH_3)_2$], 1.160 (s, 3H, 4-αCH_3), 1.304 (s, 3H, 4-βCH_3), 2.42 (oct., J=7.0 Hz, 1H, $CH(CH_3)_2$), 3.52 (d, J=9.5 Hz, 1H, 5α-H), 3.62 (d, J=9.5 Hz, 1H, 5β-H), 4.29 (d, J=6.0 Hz, 1H, CHCl), 5.436 (s, 1H, 3-H). ^{13}C NMR, δ: 17.8 (CH_3), 19.6 (CH_3) [$CH(CH_3)_2$], 21.1 (CH_3, 4-αCH_3), 24.7 (CH_3, 4-βCH_3), 32.5 (CH, $CH(CH_3)_2$), 37.4 (C, C4), 57.6 (CH_2, C5), 63.8 (CH, CHCl), 79.2 (CH, C3), 168.1 (C, C2), 168.9 (C, COO).

3.18. (αS,3R)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-chloro-β-phenylpropanoate, (αS,3R)-8d

Following the above general procedure, from (*R*)-**4** (4.68 g, 22.8 mmol) and *rac*-**7d** (4.74 g, 23.3 mmol), (α*S*,3*R*)-**8d** (8.43 g, 99% yield, 59% d.e. by HPLC) was obtained as an oil, $[\alpha]_D^{20}=+60.6$

(c=1.21, $CHCl_3$). HPLC (conditions B): main diastereomer (α*S*,3*R*)-**8d**, r.t. 70.3 min; (α*R*,3*R*)-**8d**, r.t. 77.9 min. IR (NaCl) ν: 1754 and 1716 (C=O st) cm^{-1}. $C_{21}H_{22}ClNO_3$ (371.88): calcd C 67.83%, H 5.97%, N 3.77%, Cl 9.53%. Found C 67.75%, H 5.98%, N 3.75%, Cl 9.57%.

3.18.1. Spectroscopic data of (αS,3R)-8d obtained from the spectra of the mixture

^1H NMR, δ: 0.98 (s, 3H, 4-αCH_3), 1.18 (s, 3H, 4-βCH_3), 3.24 (dd, J=14.0 Hz, J′=7.0 Hz, 1H) and 3.47 (dd, J=14.0 Hz, J′=7.5 Hz, 1H) (C_6H_5–C*H*$_2$), 3.48 (d, J=9.5 Hz, 1H, 5α-H), 3.58 (d, J=9.5 Hz, 1H, 5β-H), 4.56 (pseudo t, J=7.5 Hz, 1H, C*H*Cl), 5.37 (s, 1H, 3-H), 7.17 (tm, J=7.5 Hz, 1H, H_{para} N-phenyl), 7.23–7.34 (compl. signal, 5H, C_6H_5–CH_2), 7.36 (m, 2H, H_{meta} N-phenyl), 7.59 (dm, J=9.0 Hz, 2H, H_{ortho} N-phenyl). ^{13}C NMR, δ: 20.7 (CH_3, 4-αCH_3), 24.5 (CH_3, 4-βCH_3), 37.4 (C, C4), 41.3 (CH_2, Ar–*C*H_2), 57.3 (CH, *C*HCl), 57.5 (CH_2, C5), 79.2 (CH, C3), 119.4 (CH, C_{ortho} N-phenyl), 124.9 (CH, C_{para} N-phenyl), 127.3 (CH, C_{para} benzyl), 128.6 (CH), 128.9 (CH), 129.3 (CH) (rest of Ar–CH), 135.5 (C, C_{ipso} benzyl), 138.8 (C, C_{ipso} N-phenyl), 167.9 (C, C2), 168.5 (C, COO).

3.18.2. Significant spectroscopic data of (αR,3R)-8d obtained from the spectra of the mixture

^1H NMR, δ: 1.15 (s, 3H, 4-αCH_3), 1.30 (s, 3H, 4-βCH_3), 3.22 (dd, J=14.5 Hz, J′=9.0 Hz, 1H) and 3.49 (dd, J=14.5 Hz, J′=5.5 Hz, 1H) (C_6H_5–C*H*$_2$), 3.52 (d, J=9.5 Hz, 1H, 5α-H), 3.62 (d, J=9.5 Hz, 1H, 5β-H), 4.64 (dd, J=9.0 Hz, J′=5.5 Hz, 1H, C*H*Cl), 5.42 (s, 1H, 3-H). ^{13}C NMR, δ: 20.8 (CH_3, 4-αCH_3), 24.7 (CH_3, 4-βCH_3), 37.5 (C, C4), 40.3 (CH_2, Ar–*C*H_2), 57.1 (CH, *C*HCl), 57.6 (CH_2, C5), 79.4 (CH, C3), 168.0 (C, C2), 168.8 (C, COO).

3.19. (αS,3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-chloro-α-phenylacetate, (αS,3S)-8e

Following the above general procedure, from (*S*)-**4** (1.03 g, 5.02 mmol) and *rac*-**7e** (0.8 ml, 5.2 mmol), (α*S*,3*S*)-**8e** (1.69 g, 95% yield, 72% d.e. by HPLC) was obtained as a solid. Crystallization from ethyl acetate (2 ml) gave the analytical sample (1.01 g, 57% global yield), m.p. 65–66°C, $[\alpha]_D^{20}=-20.2$ (c=1.62, $CHCl_3$), 98% d.e. by HPLC [conditions B: main diastereomer (α*S*,3*S*)-**8e**, r.t. 71.6 min; (α*R*,3*S*)-**8e**, r.t. 56.7 min]. IR (KBr) ν: 1761 and 1716 (C=O st) cm^{-1}. $C_{20}H_{20}ClNO_3$ (357.85): calcd C 67.13%, H 5.64%, N 3.91%, Cl 9.91%. Found C 67.25%, H 5.71%, N 3.88%, Cl 10.24%. ^1H NMR, δ: 1.13 (s, 3H, 4-αCH_3), 1.29 (s, 3H, 4-βCH_3), 3.51 (d, J=9.5 Hz, 1H, 5α-H), 3.60 (d, J=9.5 Hz, 1H, 5β-H), 5.39 (s, 1H, 3-H), 5.51 (s, 1H, C*H*Cl), 7.15 (tm, J=7.0 Hz, 1H, H_{para} N-phenyl), 7.33–7.42 (comp. signal, 5H), 7.55–7.60 (compl. signal, 4H) (rest of Ar–H). ^{13}C NMR, δ: 20.8 (CH_3, 4-αCH_3), 24.6 (CH_3, 4-βCH_3), 37.3 (C, C4), 57.4 (CH_2, C5), 58.1 (CH, *C*HCl), 79.6 (CH, C3), 119.3 (CH, C_{ortho} N-phenyl), 124.8 (CH, C_{para} N-phenyl), 128.0 (CH), 128.6 (CH), 128.8 (CH), 129.2 (CH) (rest of Ar–CH), 134.8 (C, C_{ipso} C–phenyl), 138.7 (C, C_{ipso} N-phenyl), 167.6 (C), 167.8 (C) (COO and C2).

3.20. General procedure for the hydrolysis of α-chloro esters 8

Method A:[18] To a cooled solution (0°C) of α-chloro ester **8** (1.0 mmol) in a mixture of THF (1.9 ml) and water (0.6 ml), H_2O_2 (0.35 ml, 33% w/v) and $LiOH\cdot H_2O$ (2.0 mmol) were added and the mixture was magnetically stirred at 0°C till completion of the hydrolysis (15 min), following the reaction by TLC. An aqueous solution of $Na_2S_2O_3$ (6.0 ml, 10%) was added to the mixture and it was extracted with ether (3×10 ml). The combined organic phases were dried (anh. Na_2SO_4) and concentrated *in vacuo* to give the chiral auxiliary which was crystallized from ethanol (0.2 ml). The aqueous phase was acidified with 35% HCl (until pH=1), saturated aqueous solution of NaCl (10 ml) was added and it was extracted with ether (5×10 ml). The combined organic phases were dried (anh. Na_2SO_4) and concentrated *in vacuo* to give the (*R*)- or (*S*)-α-chloro acid, (*R*)- or (*S*)-**9**.

Method B:[19] To a cooled solution (0°C) of α-chloro ester **8** (1.0 mmol) in a mixture of THF (4 ml) and water (2 ml), solid $LiOH{\cdot}H_2O$ (1.5 mmol) was added and the mixture was magnetically stirred at 0°C until completion of the hydrolysis (15 min), following the reaction by TLC. Water (6 ml) was added to the mixture and it was extracted with ether (3×10 ml). The combined organic phases were dried (anh. Na_2SO_4) and concentrated *in vacuo* to give the chiral auxiliary which was crystallized from ethanol (0.2 ml). The aqueous phase was acidified with 35% HCl (until pH=1), solid NaCl (3 g) was added and it was extracted with ether (5×10 ml). The combined organic phases were dried (anh. Na_2SO_4) and concentrated *in vacuo* to give the (*R*)- or (*S*)-α-chloro acid, (*R*)- or (*S*)-**9**.

*3.21. (S)-α-Chloropropanoic acid, (S)-**9a***

Following method A, from (α*S*,3*R*)-**8a** (4.43 g, 15.0 mmol, >99% d.e. by HPLC), (*S*)-**9a** (1.40 g, 86% yield) was isolated as an oil, $[\alpha]_D^{20}=-15.6$ (c=1.09, $CHCl_3$), described[19] $[\alpha]_D^{20}=-15.9$ (c=1.0, $CHCl_3$), 98% approx. o.p.

*3.22. (R)-α-Chloropropanoic acid, (R)-**9a***

Following method A, from (α*R*,3*S*)-**8a** (1.50 g, 5.08 mmol, >99% d.e. by HPLC), (*R*)-**9a** (0.47 g, 85% yield) was isolated as an oil, $[\alpha]_D^{20}=+15.7$ (c=1.12, $CHCl_3$), 99% approx. o.p.

*3.23. (R)-α-Chlorobutanoic acid, (R)-**9b***

Following method A, from (α*R*,3*S*)-**8b** (1.30 g, 4.20 mmol, 82% d.e. by HPLC), (*R*)-**9b** (0.45 g, 87% yield) was isolated as an oil, $[\alpha]_D^{20}=+10.3$ (c=0.84, methanol), described[20] $[\alpha]_D^{20}=+12.7$ (c=0.4, methanol), 81% approx. o.p.

*3.24. (R)-α-Chloro-β-methylbutanoic acid, (R)-**9c***

Following method A, from (α*R*,3*S*)-**8c** (3.24 g, 10.0 mmol, 24% d.e. by HPLC), (*R*)-**9c** (1.21 g, 89% yield) was isolated as an oil, $[\alpha]_D^{20}=-0.44$ (c=8.01, ethanol), described for (*S*)-**9c**[21], $[\alpha]_D^{20}=2.12$ (c=8.7, ethanol), 21% approx. o.p.

*3.25. (S)-α-Chloro-β-phenylpropanoic acid, (S)-**9d***

Following method A, from (α*S*,3*R*)-**8d** (0.56 g, 1.51 mmol, 59% d.e. by HPLC), (*S*)-**9d** (0.27 g, 98% yield) was isolated as an oil, $[\alpha]_D^{20}=+6.0$ (c=2.09, benzene), described[22] $[\alpha]_D^{20}=+10.2$ (c=2.8, benzene), 59% approx. o.p.

*3.26. (S)-α-Chloro-α-phenylacetic acid, (S)-**9e***

Following method B, from (α*S*,3*S*)-**8e** (0.24 g, 0.67 mmol, 98% d.e. by HPLC), (*S*)-**9e** (0.11 g, 99% yield) was isolated as a solid, $[\alpha]_D^{20}=+52.4$ (c=2.99, ethanol), described for (*R*)-**9e**[23], $[\alpha]_D^{20}=-163$ (ethanol), 32% approx. o.p.

3.27. Attempted preparation of (αS,3S)-5a, by reaction of (αR,3S)-4,4-dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-chloropropanoate, (αR,3S)-8a, with sodium 2,4-dichlorophenoxide

To a cold (0°C) mixture of (α*R*,3*S*)-**8a** (250 mg, 0.85 mmol, >99% d.e. by HPLC) in anhydrous THF (10 ml) under an argon atmosphere, a THF suspension of the sodium salt of **2a** [prepared by reacting **2a** (139 mg, 0.85 mmol) with NaH (33 mg, 0.77 mmol) in anhydrous THF (9 ml) until hydrogen formation ceased] was added, and the mixture was heated under reflux for 20 h. The solvent was evaporated *in vacuo*, the residue was taken in CH_2Cl_2 (50 ml), washed with water (3×50 ml), then a saturated solution of Na_2CO_3 (3×50 ml), dried with anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed [silica gel (20 g), CH_2Cl_2] to give 106 mg (42% yield) of a mixture of (α*R*,3*S*)-**8a** and (α*S*,3*S*)-**8a** in the approximate ratio 1:1 (by ^{1}H NMR), and 132 mg of a mixture of (α*R*,3*S*)-**5a** and (α*S*,3*S*)-**5a** (39% yield, 22% d.e. by ^{1}H NMR).

When this reaction was carried out at room temperature for 15 h, only the starting (α*R*,3*S*)-**8a** (90 mg, 65% yield, 74% d.e. by ^{1}H NMR) was obtained.

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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. Camps, P.; Giménez, S. *Tetrahedron: Asymmetry*, **1996**, *7*, 1227–1234.
4. Camps, P.; Pérez, F.; Soldevilla, N. *Tetrahedron: Asymmetry*, **1997**, *8*, 1877–1894.
5. Larsen, R. D.; Corley, E. G.; Davis, P.; Reider, P. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.*, **1989**, *111*, 7650–7651.
6. Calmes, M.; Daunis, J.; Jacquier, R.; Natt, F. X. *Tetrahedron*, **1994**, *50*, 6875–6880.
7. Koch, M. (Hoechst A.-G.), *Ger. Offen.* 2,854,542 (1980); *Chem. Abstr.* **1980**, *93*, 204280w.
8. Koh, K.; Durst, T. *J. Org. Chem.*, **1994**, *59*, 4683–4686.
9. Kubo, A.; Takahashi, M.; Kubota, H.; Nunami, K. *Tetrahedron Lett.*, **1995**, *36*, 6251–6252.
10. Kubota, H.; Kubo, A.; Takahashi, M.; Shimizu, R.; Da-te, T.; Okamura, K.; Nunami, K. *J. Org. Chem.*, **1995**, *60*, 6776–6784.
11. Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn*, **1995**, *68*, 36–56.
12. Ward, R. S. *Tetrahedron: Asymmetry*, **1995**, *6*, 1475–1490.
13. Matteson, D. S.; Man, H. W. *J. Org. Chem.*, **1994**, *59*, 5734–5741.
14. Gras G. (Rhône-Poulenc Agrochimie) *Ger. Offen.* 3,024,265 (1981); *Chem. Abstr.* **1981**, *94*, 191956q.
15. Jähme, J.; Rüchardt, C. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 885–887.
16. Bellucci, G.; Berti, G.; Bianchini, R.; Vecchiani, S. *Gazz. Chim. Ital.*, **1988**, *118*, 451–456.
17. Calmes, M.; Daunis, J.; Mai, N. *Tetrahedron*, **1997**, *53*, 13719–13726, and references cited therein.
18. Durst, T.; Koh, K. *Tetrahedron Lett.*, **1992**, *33*, 6799–6802.
19. Angibaud, P.; Chaumette, J. L.; Desmurs, J. R.; Duhamel, L.; Plé, G.; Duhamel, P. *Tetrahedron: Asymmetry*, **1995**, *6*, 1919–1932.
20. Shibata, S.; Matsuchita, H.; Kaneko, H.; Naguchi, M.; Saburi, M.; Yoshikawa, S. *Bull. Chem. Soc. Jpn*, **1982**, *55*, 3546–3551.

21. Klebe, J. F.; Finkbeiner, H. *J. Am. Chem. Soc.*, **1968**, *90*, 7255–7261.
22. Boit, H.-G. *Beilsteins Handbuch der Organischen Chemie*, 4th edn, 3rd supplement, Vol. 9, Part 3, Springer-Verlag, Berlin, 1971, p. 2398.
23. Buckingham, J. *Dictionary of Organic Compounds*, 5th edn, 5th supplement, Chapman and Hall, London, 1983, pp. 114–115.
24. Tomlin, C. *The Pesticide Manual*, 10th edn, British Crop Protection Council, Farnham, UK, 1995.
25. Koppenhoefer, B.; Schurig, V. *Org. Synth. Coll. Vol. VIII*, **1993**, 434–441.
26. Paul, A.; Peter, T.; Roske, E.; Siegel, H. (BASF A.-G.), *Eur. Pat. Appl.* EP 295,550 (1988); *Chem. Abstr.* **1989**, *110*, 135721w.
27. Biedermann, J.; León-Lomelí, A.; Borbe, H. O.; Prop, G. *J. Med. Chem.* **1986**, *29*, 1183–1188.
28. Nishama, H.; Oogaki, M. (Fujisawa Pharmaceutical Co.), *Jpn Kokai Tokkyo Koho* JP 05,229,997 (1993); *Chem. Abstr.* **1994**, *120*, 135149x.
29. Scherkenbeck, J.; Plant, A.; Harder, A.; Mencke, N. *Tetrahedron*, **1995**, *51*, 8459–8470.
30. Bold, G.; Capraro, H. G.; Faessler, A.; Lang, M.; Bhagwat, S. S.; Khanna, S. C.; Lazdins, J. K.; Mestan, J. (Ciba-Geigy A.-G.) *Eur. Pat. Appl.* EP 708,085 (1996).
31. Nakayama, K.; Wada, T. (Bio Le Kk), *Jpn Kokai Tokkyo Koho* JP 05,49,498 (1993); *Chem. Abstr.*, **1993**, *119*, 26848h.
32. Ladner, W.; Rettenmaier, H.; Zipperer, B.; Hansen, H. (BASF A.-G.), *Ger.* DE 4,328,231 (1994); *Chem. Abstr.*, **1994**, *121*, 203551v.
33. Merkle, H. R.; Fretschner, E.; Hansen, H.; Zipperer, B. (BASF A.-G.), *Ger. Offen.* DE 19,501,452 (1996); *Chem. Abstr.*, **1996**, *125*, 142121p.