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(*R*)- and (*S*)-3-Hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone as chiral auxiliaries for the asymmetric synthesis of α-hydroxy acids

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Abstract: *Rac*-α-bromo acids, ***rac*-4**, have been converted into (*R*)- or (*S*)-α-hydroxy acids, (***R***)- or (***S***)-**9**, by DCC-induced esterification with the chiral auxiliaries (***R***)- or (***S***)-**1**, followed by reaction with sodium *p*-methoxyphenoxide in the presence of tetra-*n*-hexylammonium iodide, conditions of dynamic kinetic resolution, to give quite diastereoselectively the (**α*R*,3*S***)- or (**α*S*,3*R***)-α-(*p*-methoxyphenoxy) esters, **7**, which were then oxidized with ceric ammonium nitrate and hydrolyzed under controlled acid conditions. © 1997 Elsevier Science Ltd

We recently described[1] 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 formal deracemization of α-arylpropanoic and α-substituted arylacetic acids.[2,3] 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 e.e. can be easily obtained by chiral HPLC under UV detection.

The key-step for this formal deracemization of α-arylpropanoic and α-substituted arylacetic acids using these chiral auxiliaries consists of the reaction of the racemic acyl chloride with the enantiopure chiral auxiliary under conditions in which an intermediate ketene seems to be formed in situ. Diastereoselective addition of the enantiopure chiral auxiliary to the prochiral ketene gives rise to a mixture of diastereomeric esters enriched in one of them from which, after mild acid hydrolysis, the enantiomerically enriched acid is obtained.

Application of such a methodology to *rac*-α-bromo acids, **4**, would afford the diastereomerically enriched esters from which the enantiomerically enriched α-bromo acids[4] and other α-substituted acids[4–9] could then be obtained. In practice, reaction of ***rac***-, (***R***)- or (***S***)-**1** with *rac*-α-bromopropanoyl chloride, ***rac*-2a**, *rac*-α-bromo-β-methylbutanoyl chloride, ***rac*-2b**, or *rac*-α-bromo-β-phenylpropanoyl chloride, ***rac*-2c**, gave the corresponding esters **5** quite diastereoselectively (^{1}H NMR) as shown in Table 1 and, for the reactions starting from (***S***)-**1**, in Scheme 1. On the contrary, reaction of ***rac***- or (***S***)-**1** with *rac*-α-bromophenylacetyl chloride, ***rac*-2d**, showed low diastereoselectivity. Worthy of note, the diastereomeric mixtures of esters **5a–c** changed their composition on standing at room temperature in $CDCl_3$ solution to give after 2 or 3 days an essentially 1:1 mixture of the corresponding diastereomers, derived from the epimerization of the α-ester position. According to this, the minimum diastereoselectivity observed in the case of **5d** must be due to the easier epimerization of this ester because of the greater acidity of its α-ester hydrogen which is also benzylic, as also observed in a related case.[4]

Hydrolysis of the diastereomerically enriched α-bromo esters (**α*R*,3*S***)-**5a,c** and (**α*S*,3*R***)-**5b** under the acid conditions previously used for the hydrolysis of the esters derived from (***R***)- and (***S***)-**1** and α-substituted arylacetic acids, gave the corresponding α-bromo acids (***R***)-**4a,c** and (***S***)-**4b** with very low specific rotations (Table 2) as compared with the described values,[10,11] probably due to epimerization

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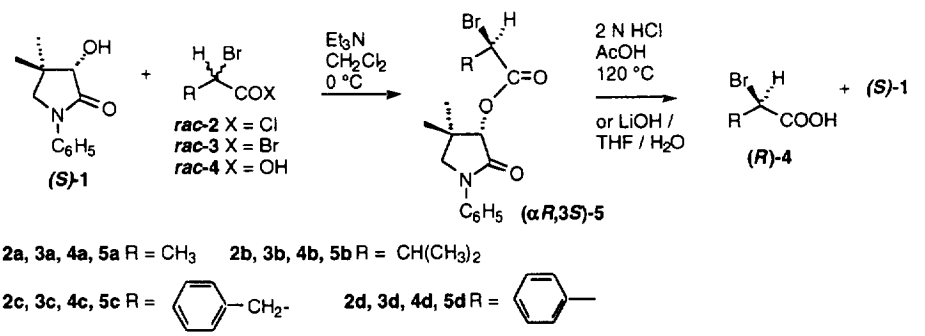
Table 1. Conditions, yields and diastereomeric excesses (d.e.)[a] of esters **5** from the reaction of derivatives of ***rac*-4a–d** with ***rac*-, (*R*)- or (*S*)-1**

Entry	Starting acid derivative	Starting **1**	Reaction conditions		Ester **5**		
			time (h)	temp. (°C)	Main diast.	yield (%)	d.e. (%)
1	***rac*-2a**	***rac*-1**	17	0 / 5	**(αRS,3SR)-5a**	80	80
2	***rac*-2a**	***rac*-1**	24	-78	**(αRS,3SR)-5a**	78	80
3	***rac*-2b**	***rac*-1**	20	-5 / 0	**(αRS,3SR)-5b**	61	60
4	***rac*-2c**	***rac*-1**	16	-5 / 0	**(αRS,3SR)-5c**	79	75
5	***rac*-2d**	***rac*-1**	3	-5 / 0	**(αRS,3SR)-5d**	67	10
6	***rac*-2d**	***rac*-1**	17	-78	**(αRS,3SR)-5d**	36	20
7	***rac*-3a**	**(*S*)-1**	0.16	-20	**(αR,3S)-5a**	99	86
8	***rac*-2b**	**(*R*)-1**	3	-5 / 0	**(αS,3R)-5b**	84	84
9	***rac*-2c**	**(*S*)-1**	3	-5 / 0	**(αR,3S)-5c**	99	82

[a] The d.e. of esters **5** were determined by ^{1}H NMR through the integration of the CHBr signal. In the case of **(αR,3S)-5a** and its **(αS,3S)**-diastereomer, the relative area by achiral HPLC was fully concordant with the d.e. obtained by ^{1}H NMR.



Scheme 1. Diastereoselective synthesis of α-bromo esters **5** and enantioselective synthesis of α-bromo acids **4** from the chiral auxiliary **(*S*)-1**.

of the esters before hydrolysis. By using LiOH in THF/water, as described[4] for a related case, hydrolysis of esters **5** took place with a lower but still important degree of epimerization (Table 2). Although this formal deracemization of α-bromo acids is not too efficient, the configuration of the obtained acids let us establish that of esters **5**, which is in accord with the described results[4] when D-pantolactone had been used as the chiral auxiliary. In our case, however, recovery of the chiral auxiliary was always carried out in high chemical yield without any racemization.

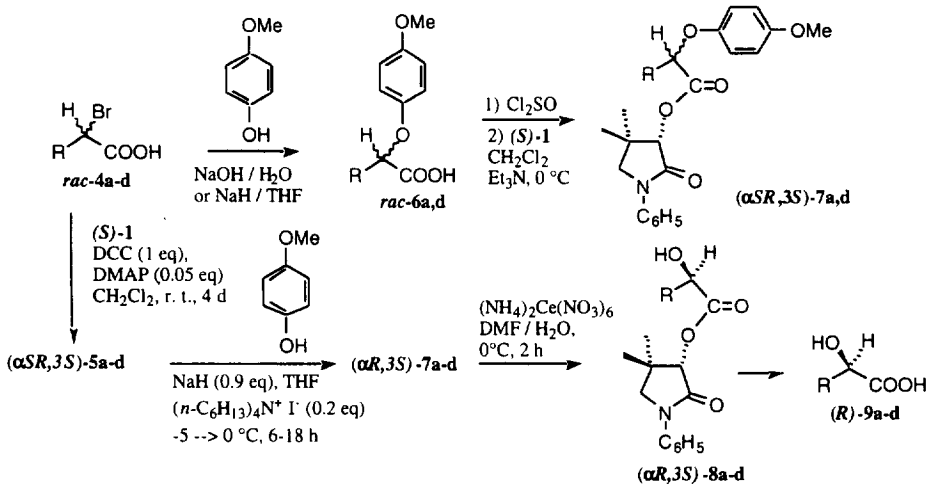
As a second goal, we envisaged the asymmetric synthesis of α-hydroxy acids[12,13] from the same precursors, i.e., ***rac*-4a,d** and **(*R*)-** or **(*S*)-1**, as shown in Scheme 2. As a latent hydroxyl, we chose the *p*-methoxyphenoxy group, which had recently been used for this purpose by Corey and Link,[14] the hydroxyl function being smoothly generated in high yield by ceric ammonium nitrate oxidation of the *p*-methoxyphenoxy group. To this end, *rac*-α-(*p*-methoxyphenoxy) acids, ***rac*-6a,d**, prepared by reaction of the sodium salts of the corresponding *rac*-α-bromo acids, ***rac*-4a,d**, with sodium *p*-methoxyphenoxide, were transformed into the corresponding acyl chlorides (or bromide in the case of ***rac*-6a**) by reaction with thionyl chloride (or thionyl bromide) in a standard way. These acyl chlorides (or bromide) were then reacted with **(*S*)-1** in the standard conditions used for the asymmetric synthesis of other α-substituted esters.[2,3] However, the corresponding esters **7a,d** were obtained in very low yields with poor diastereoselectivity.

Alternatively, esters **7a–d** could be obtained from α-bromo esters **5a–d** by reaction with *p*-

Table 2. Yields and specific rotations[a] of acids **4** obtained by acid or base hydrolysis[b] of esters **5**

Entry	Starting ester		Hydrolysis conditions	Acid **4**				Recovered **1**		
	Main diast.	de (%)		Main enant.	yield (%)	$[\alpha]_D^{20}$		Enant.	yield (%)	e.e. (%)
1	(α*R*,3*S*)-**5a**	86	A	(*R*)-**4a**	66	+5.8	(+29.6)[10]	(*S*)-**1**	93	> 99
2	(α*S*,3*R*)-**5b**	84	A	(*S*)-**4b**	61	-10.1	(+21.1)[10]	(*R*)-**1**	87	> 99
3	(α*R*,3*S*)-**5c**	60	A	(*R*)-**4c**	86	+0.6	(+10.4)[11]	(*S*)-**1**	83	> 99
4	(α*R*,3*S*)-**5a**	82	B1	(*R*)-**4a**	84	+15.4		(*S*)-**1**	89	> 99
5	(α*R*,3*S*)-**5a**	82	B2	(*R*)-**4a**	85	+17.4		(*S*)-**1**	86	> 99
6	(α*R*,3*S*)-**5a**	82	B3	(*R*)-**4a**	83	+18.9		(*S*)-**1**	85	> 99
7	(α*R*,3*S*)-**5b**	80	B1	(*R*)-**4b**	84	+10.6		(*S*)-**1**	83	> 99
8	(α*R*,3*S*)-**5b**	80	B2	(*R*)-**4b**	84	+9.8		(*S*)-**1**	88	> 99
9	(α*R*,3*S*)-**5c**	82	B1	(*R*)-**4c**	84	+4.1		(*S*)-**1**	87	> 99
10	(α*R*,3*S*)-**5c**	82	B2	(*R*)-**4c**	84	+3.8		(*S*)-**1**	86	> 99

[a] Described values for the specific rotations of acids (*R*)-**4** are given in parenthesis. The experimental values were obtained by using the same solvent and concentration close to that described for each case. [b] Acid hydrolysis (Conditions A): 2 N HCl / AcOH, 120 °C, 2 h (for **5a,c**) or 4 h (for **5b**). Base hydrolysis (Conditions B): LiOH (1.5 eq.) / THF (4 mL / mmol) / H_2O (2 mL / mmol). Conditions B1: room temperature, 1 h (for **5a**) or 4 h (for **5b,c**). Conditions B2: 0 °C, 1 h (for **5a**) or 6.5 h (for **5b,c**). Conditions B3: 2 h at - 20 °C and 4 h at -15 °C.



Scheme 2. Diastereoselective synthesis of esters **7** and **8** and enantioselective synthesis of α-hydroxy acids **9** from the reaction of diastereomeric mixtures of esters (α*SR*,3*S*)-**5a–d** with *p*-methoxyphenoxide.

methoxyphenoxide. It had been shown that diastereomeric mixtures of α-bromo esters derived from D-pantolactone, can react with nucleophiles, such as *p*-methoxyphenoxide, in the presence of a catalytic amount of tetra-*n*-hexylammonium iodide, to give mainly one of the two possible diastereomers differing in the configuration of the α-ester carbon atom.[5] Under such conditions, the (α*S*,3*S*)- or (α*R*,3*R*)-α-bromo esters seem to react faster than their epimers at Cα to give the corresponding substitution products with inversion of the configuration at the reactive centre, while the less reactive (α*R*,3*S*)- or (α*S*,3*R*)-diastereomers reacting with the iodide anion give rise to the corresponding iodides with inverted configuration at Cα, thus being transformed into the more reactive (α*S*,3*S*)- or (α*R*,3*R*)-α-iodo esters, which are then transformed into the substitution products. Through such a process, which has been defined as dynamic kinetic resolution of diastereomers,[15,16] the (α*R*,3*S*)-

Table 3. Yields, diastereomeric excesses (d.e.) and reaction conditions for the conversion of esters **5**[a] into **7**[b]

Entry	Starting α-bromo ester **5**			Reaction conditions			α-(*p*-methoxyphenoxy) ester **7**		
	Main diast.	yield (%)	d.e. (%)	eq. NaH	Temp. (°C)	time (h)	Main diast.	yield (%)	d.e. (%)
1	(α*RS*,3*RS*)-**5d**	94	10	1.1	-5 / 0	6	(α*RS*,3*SR*)-**7d**	62	42[c]
2	(α*RS*,3*RS*)-**5d**	94	10	1.1	-78	17	(α*RS*,3*SR*)-**7d**	67	42
3	(α*RS*,3*RS*)-**5d**	94	10	1.1	-78	6	(α*RS*,3*SR*)-**7d**	56	60
4	(α*S*,3*S*)-**5d**	94	6	0.9	-5 / 0	6	(α*R*,3*S*)-**7d**	98	84[d]
5	(α*R*,3*R*)-**5d**	92	7	0.9	-5 / 0	6	(α*S*,3*R*)-**7d**	95	94[d]
6	(α*S*,3*S*)-**5a**	77	26	0.9	-5 / 0	18	(α*R*,3*S*)-**7a**	79	54[d]
7	(α*S*,3*S*)-**5b**	92	0	0.9	-5 / 0	18	(α*R*,3*S*)-**7b**	65	98[d]
8	(α*S*,3*S*)-**5c**	86	4	0.9	-5 / 0	18	(α*R*,3*S*)-**7c**	48	89[d]

[a] Obtained by reaction of the corresponding racemic acids ***rac*-4a-d** with (***RS***)-, (***R***)- or (***S***)-**1** and DCC catalyzed by DMAP. [b] All the reactions were carried out in THF using tetra-*n*-hexylammonium iodide (0.2 eq.) as catalyst, except for entry 3 where 1 eq. of catalyst was used; the amount of *p*-methoxyphenol was always slightly higher than that of the NaH, i.e.: 1.2 eq. phenol *vs* 1.1 eq. NaH or 1.0 eq. phenol *vs* 0.9 eq. NaH. [c] The d.e. was obtained by ^{1}H NMR. [d] The d.e. was obtained by achiral HPLC by assuming the area ratio to be equal to the molar ratio.

or (α*S*,3*R*)-diastereomers of the products can be obtained in good yield and high d.e., independently from the diastereomeric ratio of the starting α-bromo esters.

To apply this methodology for the preparation of esters **7a–d**, diastereomeric mixtures of esters **5a–d**, were prepared in good yields but low diastereoselectivity, by reacting the acids ***rac*-4a–d** with (***RS***)-, (***R***)- or (***S***)-**1** induced by dicyclohexylcarbodiimide (DCC) in the presence of 4-(dimethylamino)pyridine (DMAP) (Table 3). Then, the optimum conditions for the diastereoselective reaction of esters **5a–d** with sodium *p*-methoxyphenoxide were studied, selected results being collected in Table 3. In general, 0.2 eq. of tetra-*n*-hexylammonium iodide as catalyst and THF as solvent were used. As can be seen from Table 3, the highest diastereoselectivities were achieved by using a 10% molar defect of base (1.0 eq. *p*-methoxyphenol and 0.9 eq. NaH) while under the conditions described by Durst and Koh[5] for a related case (1.2 eq. *p*-methoxyphenol and 1.1 eq. NaH) the d.e. of esters **7** were lower, probably due to partial epimerization (see entries 1 and 4 from Table 3). The use of lower reaction temperatures combined with longer reaction times (see entries 1 and 2 from Table 3) did not affect the diastereoselectivity, while it was improved by using 1 eq. of catalyst at −78°C (see entries 2 and 3 of Table 3). Under the optimum conditions, the yields were high, except for the case of (α*R*,3*S*)-**7c** (entry 8 from Table 3) due to the formation of important amounts of the elimination product, (*S*)-4,4-dimethyl-2-oxo-1-phenylpyrrolidin-3-yl cinnamate, (***S***)-**10**, (38% isolated yield). Diastereoselectivities were also high, except for (α*R*,3*S*)-**7a** (54% d.e.) (entry 6 from Table 3), a fact that might be due to a lesser reactivity difference of the diastereomers (α*R*,3*S*)- and (α*S*,3*S*)-**5a** towards nucleophiles as a consequence of the lower steric effect of a methyl group as compared with isopropyl, benzyl or phenyl. The d.e. were obtained by achiral HPLC (see experimental) by assuming the relative area ratios to be equal to the molar ratios. In the case of (α*R*,3*S*)-**7a**, where the amount of its diastereomer (α*S*,3*S*)-**7a** was high enough, the d.e. was also obtained by ^{1}H NMR through the integration of the 4-αCH_3 signal, which gave a d.e. very close to that obtained by HPLC. The configuration of the main diastereomer in each case was tentatively assigned by analogy with previous results[5] and later confirmed through the configuration of the obtained α-hydroxy acids **9**.

In the absence of catalyst, reaction of (α*S*,3*R*)-**5a** (86% d.e.) with sodium *p*-methoxyphenoxide [from *p*-methoxyphenol (1 eq.) and NaH (0.9 eq.)] in different solvents (THF, DMSO or acetonitrile) and different temperatures (25 to 80°C) gave, in medium yields (45–89%) with low diastereoselectivities (0–18% d.e.), mixtures of (α*R*,3*R*)- and (α*S*,3*R*)-**7a**, probably as a consequence of a low epimerization of both diastereomers of **5a** combined with a low difference in their reactivity towards

Table 4. Yields[a], d.e.[b] and specific rotations[c] in the preparation of esters **8** and acids **9**

Entry	Starting ester **7**		α-Hydroxy ester **8**			α-Hydroxy acid **9**			
	Main diast.	d.e. (%)	Main diast.	yield (%)	d.e. (%)	Main enant.	yield (%)		$[\alpha]_D^{20}$
1	(α*R*,3*S*)-**7a**	54	(α*R*,3*S*)-**8a**	51	66	(*R*)-**9a**	91	-2.0	(-2.26)[17]
2	(α*R*,3*S*)-**7b**	98	(α*R*,3*S*)-**8b**	65	96	(*R*)-**9b**	94	-18.2	(+19)[18]
3	(α*R*,3*S*)-**7c**	89	(α*R*,3*S*)-**8c**	68	90	(*R*)-**9c**	96	+18.7	(+22.2)[17]
4	(α*R*,3*S*)-**7d**	84	(α*R*,3*S*)-**8d**	64	90	(*R*)-**9d**[d]	81	-157.5	(-158)[17]
				(43)	(>99)				
5	(α*S*,3*R*)-**7d**	94	(α*S*,3*R*)-**8d**	63	86	(*S*)-**9d**[d]	73	+155.2	(+156.6)[17]
				(46)	(>99)				

[a] Yields of esters **7** and **8** correspond to chromatographed products, while those of acids **9** and the values in parenthesis for (α*R*,3*S*)- and (α*S*,3*R*)-**8d** correspond to crystallized products. [b] The d.e. of esters (α*R*,3*S*)-**8a,c** were obtained by ^{1}H NMR and those of (α*R*,3*S*)-**8b,d** and (α*S*,3*R*)-**8d** by achiral HPLC. [c] The described values for the optical rotations of acids (*R*)- or (*S*)-**9** are given in parenthesis. The experimental values were obtained by using the same solvent and a concentration close to that described for each case. For (*R*)-**9b**, the optical rotation in parenthesis correspond to its enantiomer. In the case of (*R*)- and (*S*)-**9d**, the e.e. determined by chiral HPLC was shown to be > 99%. [d] Obtained starting from the crystallized precursors.

p-methoxyphenoxide under the reaction conditions. Starting from (α*RS*,3*RS*)-**5c** (28% d.e.) and using KBr (20 eq.) or NaI (20 eq.) as catalyst in DMSO at 60–100°C, the only isolated product was the elimination product, (*RS*)-**10**. In this case, the use of NaI (20 eq.) in acetonitrile at room temperature gave mainly (*RS*)-**10** and the substitution product in very low yield (16%) with poor diastereoselectivity (33% d.e.). All these facts show the need for an adequate catalyst, such as tetra-*n*-hexylammonium iodide, in order to attain high diastereoselectivities in these reactions and that neither KBr nor NaI are good catalysts.

Oxidation of esters (α*R*,3*S*)-**7a–d** and (α*S*,3*R*)-**7d** with ceric ammonium nitrate gave in medium yields the corresponding α-hydroxy esters **8**, whose configuration was assumed to be the same as their precursors. The d.e.s of esters (α*R*,3*S*)-**8a,c** were obtained by ^{1}H NMR through the integration of the C*H*OH and 4-αCH$_3$ signals, respectively. In the cases of (α*R*,3*S*)-**8b,d** and (α*S*,3*R*)-**8d**, the d.e. was obtained by achiral HPLC, by assuming the relative areas to be equal to the molar ratio.

In general, an increase in the d.e. was observed in passing from esters **7** to **8**, due to enrichment during column chomatography purification of esters **8**, and specially during crystallization in the cases of the solid compounds (α*R*,3*S*)- and (α*S*,3*R*)-**8d** (see entries 4 and 5 from Table 4). Hydrolysis of the above esters **8** under the standard acid conditions used in the case of α-arylpropanoic acids (2 N HCl, AcOH, 120°C)[2] gave the corresponding enantiomerically enriched α-hydroxy acids (*R*)-**9a–d** and (*S*)-**9d** in high yield with little or no epimerization (see Table 4). The specific rotation of these acids, measured under conditions close to those described for each case, showed them to be essentially pure. The e.e. of (*R*)- and (*S*)-**9d** was shown to be >99% by chiral HPLC (see Experimental). As for the case of esters **8**, an increase in the e.e. took place during crystallization of acids **9**. The configuration of the obtained α-hydroxy acids **9a–d** allowed us to establish the configuration of the main diastereomer of their precursors, esters **7a–d** and **8a–d**, which is in accord with previous results using D-pantolactone as the chiral auxiliary.[5]

In order to improve the yield of the conversion of *rac*-α-bromo acids, ***rac*-4a–d**, to the enantiomerically enriched (*R*)- or (*S*)-α-hydroxy acids, (*R*)- or (*S*)-**9a–d**, and increase the recovery of the chiral auxiliary, the whole sequence of reactions were performed without isolating any of the intermediate esters, except for the case of (*R*)-**9c**, where (α*R*,3*S*)-**7c** was separated from the elimination product (*S*)-**10** by column chromatography. Table 5 collects the global yields and the optical rotations for these preparations of α-hydroxy acids **9**. The values in parenthesis correspond to the sequence in which each intermediate was purified before being used in the next step. Also in this Table, the yields of the recovered chiral auxiliary and its e.e. are collected. As can be seen from Table 5, although the

Table 5. Yields[a] and specific rotations[b] for the conversion of acids *rac*-**4** into acids (*R*)- or (*S*)-**9**

Entry	Starting acid **4**	Starting **1**	α-Hydroxy acid **9**			recovered **1**	
			Main enant.	yield (%)	$[\alpha]_D^{20}$	yield (%)	e.e. (%)
1	*rac*-**4a**	(*S*)-**1**	(*R*)-**9a**	36 (28)	-1.6	(-2.26)[17]	40 > 99
2	*rac*-**4b**	(*S*)-**1**	(*R*)-**9b**	47 (37)	-18.6	(+19)[18]	58 > 99
3	*rac*-**4c**	(*S*)-**1**	(*R*)-**9c**	31 (27)	+18.9	(+22.2)[17]	33 > 99
4	*rac*-**4d**	(*S*)-**1**	(*R*)-**9d**	62 (48)	-154	(-158)[17]	58 > 99
5	*rac*-**4d**	(*R*)-**1**	(*S*)-**9d**	59 (40)	+155.3	(+156.6)[17]	63 > 99

[a] Yields of acids **9** correspond to crystallized products, after having carried out the whole sequence of reactions without any intermediate purification step, except for (*R*)-**9c** for which ester (**αR,3S**)-**7c** was separated from the elimination product (*S*)-**10** by column chromatography. Values in parenthesis refer to the same sequence in which all the intermediates were purified. [b] The described values for the specific rotations of acids (*R*)- or (*S*)-**9** are given in parenthesis. In the case of (*R*)-**9b**, the value in parenthesis correspond to the specific rotation of its enantiomer. The experimental values were obtained by using the same solvent and a concentration close to that described for each case.

global yield is medium, a significant increase in the yield of α-hydroxy acids **9** was observed when the sequence of reactions was carried out without purification of the intermediate esters. The optical purity of the products obtained in this way were high, except for the case of (*R*)-**9a** in accord with the lower diastereoselectivity observed during the formation of ester (**αR,3S**)-**7a** (54% d.e.). The yields of the different steps in each sequence were usually high, except for the preparation of (**αR,3S**)-**7c**, due to the competitive formation of important amounts of the elimination product (*S*)-**10**, and for the oxidation of the *p*-methoxyphenoxy group which was always medium and is the main factor for the global medium yields of the whole sequences. The yields of the recovered chiral auxiliary were medium, in general slightly higher than the yields of the obtained α-hydroxy acids, but the e.e. were always >99%, showing the configuration of the chiral auxiliary to be unaffected during the whole sequence of reactions.

All of the new compounds (esters **5a–d**, **7a–d** and **8a–d** as diastereomeric mixtures, (*S*)-**10**) and *rac*-**6a,d** 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 $^1H/^{13}C$ experiments carried out on esters **5a–d**, **7a–d** and **8d** and taking into account our previous work.[1,2] The assignment of the signals of the two diastereomers of each mixture could be carried out due to their different ratio.

In conclusion, the chiral auxiliaries (*R*)- and (*S*)-**1** have shown their possibilities for the asymmetric synthesis of α-substituted carboxylic acids. The asymmetric synthesis of α-hydroxy acids, **9**, is based on the dynamic kinetic resolution of a diastereomeric mixture of α-bromo esters **5**, derived from the chiral auxiliary, with *p*-methoxyphenoxide in the presence of tetra-*n*-hexylammonium iodide, which formally facilitates the rapid epimerization of the α-bromo esters at the α-position. Diastereoselectivities are high except for the esters derived from the α-bromopropanoic acid, probably due to a lower reactivity difference of both diastereomers with this nucleophile. The method could be applied to the asymmetric synthesis of other α-substituted acids, such as α-amino acids or α-aryloxy acids, a matter which is under study.

Experimental

Melting points were determined on a MFB 595010 M Gallenkamp melting point apparatus. 500 MHz ^1H NMR spectra and COSY $^1H/^1H$ and $^1H/^{13}C$ experiments were performed on a Varian VXR 500 spectrometer, while 300 MHz ^1H and 75.4 MHz ^{13}C NMR spectra on a Varian Gemini 300. Except where otherwise stated, ^1H NMR spectra were recorded at 500 MHz and ^{13}C NMR spectra at 75.4 MHz, always in $CDCl_3$. COSY $^1H/^1H$ experiments were carried out by using standard procedures

while for the COSY $^{1}H/^{13}C$ experiments, the HMQC sequence with an indirect detection probe was used. Chemical shifts (δ) are reported in ppm related to internal tetramethylsilane. IR spectra were recorded on a 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 using column A for the non-stereospecific analyses and column B for the chiral HPLC analyses. Column A: Waters C_{18} column Nova-Pak 60 Å (15×0.39 cm) 4 μm silica gel; column B: CHIRALCEL OD-H column (25×0.46 cm) containing the chiral stationary phase cellulose tris-(3,5-dimethylphenylcarbamate). Conditions A: Column A, H_2O/acetonitrile as eluent with eluent ratios (e.r.) from 50/50 to 65/35 and flows from 0.2 to 0.7 mL/min; Conditions A1: e.r. 55/45, flow 0.7; Conditions A2: e.r. 55/45, flow 0.5; Conditions A3: e.r. 50/50, flow 0.3; Conditions A4: e.r. 50/50, flow 0.5; Conditions A5: e.r. 50/50, flow 0.4; Conditions A6: e.r. 60/40, flow 0.4; Conditions A7: e.r. 65/35, flow 0.2. Conditions B: column B, mixture of hexane/isopropanol/trifluoroacetic acid in the ratio of 93/7/0.05 as eluent, flow 0.5 mL/min. Conditions C: column B, 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.

General procedure for the preparation of the diastereomeric mixtures of α-bromo esters ***5***

A mixture of the ***rac*-4** (1.0 mmol), DCC (1.0 mmol), DMAP (0.05 mmol) and (***R*)-** or (***S*)-1** (1.0 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature under an argon atmosphere for 4 days. The mixture was filtered, the filtrate was washed with saturated aqueous solution of citric acid (3×8 mL) and saturated aqueous $NaHCO_3$ (3×8 mL), dried with anh. Na_2SO_4 and concentrated *in vacuo* and the residue was submitted to column chromatography [silica gel (20 g), CH_2Cl_2] to give pure esters **5** as diastereomeric mixtures.

(αRS,3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-bromopropanoate, ***(αRS,3S)-5a***

Following the general procedure, from ***rac*-4a** (0.60 g, 3.9 mmol) and ***(S)*-1** (0.80 g, 3.9 mmol), ***(αRS,3S)*-5a** (1.03 g, 77% yield) was obtained as an oil, $[\alpha]_D^{20}$ (c=1.02, $CHCl_3$)=−42.4. HPLC (conditions A1): Main diastereomer ***(αS,3S)*-5a**, r.t. 23.1 min, 63% relative area; ***(αR,3S)*-5a**, r.t. 21.8 min, 37% relative area. The integral of the $CHCH_3$ group in both diastereomers (δ 1.87 and 1.92) gave a ratio ***(αS,3S)*-5a/*(αR,3S)*-5a**=64/36. IR (NaCl) ν: 1748 and 1716 (C=O st) cm^{-1}. $C_{15}H_{18}BrNO_3$ (340.23): calcd. C 52.95% H 5.34% N 4.12% Br 23.49%. Found C 52.99% H 5.45% N 4.11% Br 23.75%.

Spectroscopic data of ***(αS,3S)-5a*** *obtained from the spectra of the mixture.* ^{1}H NMR, δ: 1.19 (s, 3 H, 4-αCH_3), 1.32 (s, 3 H, 4-βCH_3), 1.87 (d, J=7.0 Hz, 3 H, $CHCH_3$), 3.51 (d, J=9.5 Hz, 1 H, 5α-H), 3.62 (d, J=9.5 Hz, 1 H, 5β-H), 4.55 (q, J=7.0 Hz, 1 H, $CHCH_3$), 5.41 (s, 1 H, 3-H), 7.16 (tm, J=7.5 Hz, 1 H, Ar-H*para*), 7.36 (m, 2 H, Ar-H*meta*), 7.59 (dm, J=8.8 Hz, 2 H, Ar-H*ortho*). ^{13}C NMR, δ: 20.9 (CH_3, 4-αCH_3), 21.9 (CH_3, $CHCH_3$), 24.7 (CH_3, 4-βCH_3), 37.9 (C, C4), 39.1 (CH, $CHCH_3$), 57.75 (CH_2, C5), 79.1 (CH, C3), 119.5 (CH, Ar-C*ortho*), 125.1 (CH, Ar-C*para*), 129.0 (CH, Ar-C*meta*), 138.9 (C, Ar-C*ipso*), 168.3 (C, COO), 170.0 (C, C2).

Significant spectroscopic data of ***(αR,3S)-5a*** *obtained from the spectra of the mixture.* ^{1}H NMR, δ: 1.18 (s, 3 H, 4-αCH_3), 1.31 (s, 3 H, 4-βCH_3), 1.92 (d, J=7.0 Hz, 3 H, $CHCH_3$), 3.53 (d, J=9.5 Hz, 1 H, 5α-H), 3.61 (d, J=9.5 Hz, 1 H, 5β-H), 4.51 (q, J=7.0 Hz, 1 H, $CHCH_3$), 5.38 (s, 1 H, 3-H). ^{13}C NMR, δ: 20.8 (CH_3, 4-αCH_3), 21.3 (CH_3, $CHCH_3$), 24.7 (CH_3, 4-βCH_3), 37.5 (C, C4), 40.2 (CH, $CHCH_3$), 57.68 (CH_2, C5), 79.1 (CH, C3).

(αRS,3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-bromo-β-methylbutanoate, ***(αRS,3S)-5b***

Following the general procedure, from ***rac*-4b** (0.71 g, 3.9 mmol) and **(*S*)-1** (0.80 g, 3.9 mmol), **(α*RS*,3*S*)-5b** (1.32 g, 92% yield) was obtained as a solid, m.p. 61–63°C (ethyl acetate/hexane), $[\alpha]_D^{20}$ (c=1.02, $CHCl_3$)=−43.9. The integral of the C*H*Br proton in both diastereomers (δ 4.15 and 4.24) gave a ratio **(α*S*,3*S*)-5b/(α*R*,3*S*)-5b**=50 / 50. This mixture could not be separated by HPLC using different conditions A. IR (KBr) ν: 1750 and 1709 (C=O st) cm^{-1}. $C_{17}H_{22}BrNO_3$ (368.29): calcd. C 55.44% H 6.03% N 3.80% Br 21.70%. Found C 55.34% H 5.96% N 3.79% Br 21.76%.

Spectroscopic data of ***(αS,3S)-5b*** *obtained from the spectra of the mixture.* ^{1}H NMR, δ: 1.11 (d, J=7.0 Hz, 3 H) and 1.15 (d, J=6.5 Hz, 3 H) [CH(C*H*$_3$)$_2$], 1.18 (s, 3 H, 4-αCH$_3$), 1.31 (s, 3 H, 4-βCH$_3$), 2.30 [m, 1 H, C*H*(CH$_3$)$_2$], 3.52 (d, J=9.5 Hz, 1 H, 5α-H), 3.61 (d, J=9.5 Hz, 1 H, 5β-H), 4.24 (d, J=7.5 Hz, 1 H, C*H*-Br), 5.43 (s, 1 H, 3-H), 7.16 (broad t, J=7.5 Hz, 1 H, Ar-H*para*), 7.36 (m, 2 H, Ar-H*meta*), 7.60 (dm, J=8.0 Hz, 2 H, Ar-H*ortho*). ^{13}C NMR, δ: 19.7 (CH$_3$) and 20.1 (CH$_3$) [CH(*C*H$_3$)$_2$], 21.0 (CH$_3$, 4-αCH$_3$), 24.7 (CH$_3$, 4-βCH$_3$), 32.0 [CH, *C*H(CH$_3$)$_2$], 37.6 (C, C4), 53.8 (CH, CHBr), 57.7 (CH$_2$, C5), 79.0 (CH, C3), 119.4 (CH, Ar-C*ortho*), 125.0 (CH, Ar-C*para*), 128.9 (CH, Ar-C*meta*), 138.9 (C, Ar-C*ipso*), 168.2 (C) and 169.1 (C) (COO and C2).

Significant spectroscopic data of ***(αR,3S)-5b*** *obtained from the spectra of the mixture.* ^{1}H NMR, δ: 1.11 (d, J=7.0 Hz, 3 H) and 1.15 (d, J=6.5 Hz, 3 H), [CH(C*H*$_3$)$_2$], 1.19 (s, 3 H, 4-αCH$_3$), 1.30 (s, 3 H, 4-βCH$_3$), 2.30 [m, 1 H, C*H*(CH$_3$)$_2$], 3.53 (d, J=9.5 Hz, 1 H, 5α-H), 3.61 (d, J=9.5 Hz, 1 H, 5β-H), 4.15 (d, J=7.5 Hz, 1 H, CHBr), 5.43 (s, 1 H, 3-H). ^{13}C NMR, δ: 19.9 (CH$_3$) and 20.0 (CH$_3$) [CH(*C*H$_3$)$_2$], 21.0 (CH$_3$, 4α-CH$_3$), 24.7 (CH$_3$, 4β-CH$_3$), 32.5 [CH, *C*H(CH$_3$)$_2$], 37.6 (C, C4), 54.6 (CH, CHBr), 57.6 (CH$_2$, C5), 78.9 (CH, C3).

(αRS,3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-bromo-β-phenylpropanoate, ***(αRS,3S)-5c***

Following the general procedure, from ***rac*-4c** (1.00 g, 4.4 mmol) and **(*S*)-1** (0.89 g, 4.4 mmol), **(α*RS*,3*S*)-5c** (1.56 g, 86% yield) was obtained as an oil, $[\alpha]_D^{20}$ (c=1.21, $CHCl_3$)=−43.3. The integral of the C*H*Br proton in both diastereomers (δ 4.62 and 4.49) gave a ratio **(α*S*,3*S*)-5c/(α*R*,3*S*)-5c**=52/48. This mixture could not be separated by HPLC using different conditions A. IR (NaCl) ν: 1749 and 1718 (C=O st) cm^{-1}. $C_{21}H_{22}BrNO_3$ (416.33): calcd. C 60.58% H 5.33% N 3.36% Br 19.19%. Found C 60.64% H 5.36% N 3.37% Br 19.09%.

Spectroscopic data of ***(αS,3S)-5c*** *obtained from the spectra of the mixture.* ^{1}H NMR, δ: 1.18 (s, 3 H, 4-αCH$_3$), 1.31 (s, 3 H, 4-βCH$_3$), 3.27 (dd, J=8.5 Hz, J′=14.5 Hz, 1 H) and 3.56 (m, 1 H) (C$_6$H$_5$-C*H*$_2$), 3.50 (d, J=9.5 Hz, 1 H, 5α-H), 3.61 (d, J=9.5 Hz, 1 H, 5β-H), 4.62 (dd, J=6.5 Hz, J′=8.8 Hz, 1 H, CHBr), 5.41 (s, 1 H, 3-H), 7.16 (tm, J=7.0 Hz, 1 H, H*para* N-phenyl), 7.25 (m, 2 H), 7.31 (m, 3 H), 7.36 (m, 2 H) (CH$_2$-C$_6$*H*$_5$ and H*meta* N-phenyl), 7.59 (m, 2 H, H*ortho* N-phenyl). ^{13}C NMR, δ: 20.9 (CH$_3$, 4-αCH$_3$), 24.8 (CH$_3$, 4-βCH$_3$), 37.9 (C, C4), 40.3 (CH$_2$, Ar-*C*H$_2$), 45.2 (CH, CHBr), 57.7 (CH$_2$, C5), 79.2 (CH, C3), 119.5 (CH, C*ortho* N-phenyl), 125.0 (CH, C*para* N-phenyl), 127.3 (CH, C*para* benzyl), 128.6 (CH) and 129.2 (CH) (C*ortho* and C*meta* benzyl), 128.9 (CH, C*meta* N-phenyl), 136.4 (C, C*ipso* benzyl), 138.8 (C, C*ipso* N-phenyl), 168.1 (C) and 168.7 (C) (COO and C2).

Significant spectroscopic data of ***(αR,3S)-5c*** *obtained from the spectra of the mixture.* ^{1}H NMR, δ: 0.99 (s, 3 H, 4α-CH$_3$), 1.18 (s, 3 H, 4-βCH$_3$), 3.30 (dd, J=6.5 Hz, J′=14.0 Hz, 1 H) and 3.56 (m, 1 H) (C$_6$H$_5$-C*H*$_2$), 3.47 (d, J=9.5 Hz, 1 H, 5α-H), 3.54 (d, J=9.5 Hz, 1 H, 5β-H), 4.49 (dd, J=7.0 Hz, J′=9.0 Hz, 1 H, CHBr), 5.34 (s, 1 H, 3-H). ^{13}C NMR, δ: 20.8 (CH$_3$, 4-αCH$_3$), 24.6 (CH$_3$, 4-βCH$_3$), 37.6 (C, C4), 41.3 (CH$_2$, Ar-*C*H$_2$), 45.0 (CH, CHBr), 57.6 (CH$_2$, C5), 79.2 (CH, C3).

(αRS,3R)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-bromo-α-phenylacetate, ***(αRS,3R)-5d***

Following the general procedure, from ***rac*-4d** (1.57 g, 7.3 mmol) and ***(R)*-1** (1.50 g, 7.3 mmol), **(α*RS*,3*R*)-5d** (2.71 g, 92% yield) was obtained as a solid, m.p. 94–96°C (methanol), $[\alpha]_D^{20}$ (c=1.18, $CHCl_3$)=+24.2. The integral of the C*H*Br proton in both diastereomers (δ 5.54 and 5.57) gave a ratio **(α*R*,3*R*)-5d/(α*S*,3*R*)-5d**=53/47. This mixture could not be separated by HPLC using different conditions A. IR (KBr) ν: 1748 and 1712 (C=O st) cm^{-1}. $C_{20}H_{20}BrNO_3$ (402.30): calcd. C 59.71% H 5.01% N 3.48% Br 19.86%. Found C 59.70% H 4.99% N 3.44% Br 19.65%.

Spectroscopic data of ***(αR,3R)-5d*** *obtained from the spectra of the mixture.* ^{1}H NMR (300 MHz) δ: 1.21 (s, 3 H, 4-αCH_3), 1.34 (s, 3 H, 4-βCH_3), 3.46 (d, J=9.6 Hz, 1 H, 5α-H), 3.59 (d, J=9.6 Hz, 1 H, 5β-H), 5.44 (s, 1 H, 3-H), 5.58 (s, 1 H, CHBr), 7.18 (tm, J=7.4 Hz, 1 H, H*para* N-phenyl), 7.38 (m, 5 H) and 7.60 (m, 4 H) (rest of Ar-H). ^{13}C NMR, δ: 20.9 (CH_3, 4-αCH_3), 24.7 (CH_3, 4-βCH_3), 37.7 (C, C4), 45.1 (CH, CHBr), 57.6 (CH_2, C5), 79.5 (CH, C3), 119.4 (CH, C*ortho* N-phenyl), 125.0 (CH, C*para* N-phenyl), 128.6 (CH), 128.9 (CH), 129.3 (CH) (CH, CH-phenyl), 129.0 (CH, C*meta* N-phenyl), 134.9 (C, C*ipso* CH-phenyl), 138.8 (C, C*ipso* N-phenyl), 167.8 (C) and 168.0 (C) (COO and C2).

Significant spectroscopic data of ***(αS,3R)-5d*** *obtained from the spectra of the mixture.* ^{1}H NMR (300 MHz) δ: 0.91 (s, 3 H, 4-αCH_3), 1.20 (s, 3 H, 4-βCH_3), 3.53 (d, J=9.6 Hz, 1 H, 5α-H), 3.64 (d, J=9.6 Hz, 1 H, 5β-H), 5.43 (s, 1 H, 3-H), 5.54 (s, 1 H, CHBr). ^{13}C NMR, δ: 20.6 (CH_3, 4-αCH_3), 24.6 (CH_3, 4-βCH_3), 37.6 (C, C4), 47.1 (CH, CHBr), 57.4 (CH_2, C5), 79.7 (CH, C3).

(αRS,3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-bromo-α-phenylacetate, ***(αRS,3S)-5d***

Following the general procedure, from ***rac*-4d** (3.00 g, 13.9 mmol) and ***(S)*-1** (2.85 g, 13.9 mmol), **(α*RS*,3*S*)-5d** (5.26 g, 94% yield) was obtained as a solid, m.p. 97–99°C (methanol), $[\alpha]_D^{20}$ (c=1.04, $CHCl_3$)=−25.3. The integral of the C*H*Br proton in both diastereomers (δ 5.54 and 5.57) gave a ratio **(α*S*,3*S*)-5d/(α*R*,3*S*)-5d**=53/47. IR (KBr) ν: 1748 and 1712 (C=O st) cm^{-1}. $C_{20}H_{20}BrNO_3$ (402.30): calcd. C 59.71% H 5.01% N 3.48% Br 19.86%. Found C 59.74% H 5.01% N 3.53% Br 19.78%. The NMR data coincide with those of their enantiomers.

General procedure for the preparation of rac-α-*bromoacyl chlorides*

A mixture of the *rac*-α-bromo acid, ***rac*-4** (1.0 mmol) and thionyl chloride (3 mL) was heated under reflux for an hour. Evaporation of the volatile products gave the corresponding *rac*-α-bromoacyl chloride, ***rac*-2**, which was used as such in the following step.

General procedure for the reaction of rac-α-*bromoacyl chlorides,* **rac-2**, *or* rac-α-*bromopropanoyl bromide* **rac-3a**, *with* **(R)-** *or* **(S)-1**

To a dried (1.5 g of 4 Å molecular sieves) and cooled solution (ice-water bath) of **(*S*)-1** (1.0 mmol) in CH_2Cl_2 (3 mL) under an argon atmosphere, dried solutions (1.5 g of 4 Å molecular sieves) of ***rac*-2** or ***rac*-3a** (1.2–1.4 mmol) in CH_2Cl_2 (3 mL) and triethylamine (2.0–3.4 mmol) in CH_2Cl_2 (3 mL) were successively added and the mixture was magnetically stirred for 10 min to 3 h at 0°C. The mixture was washed with N HCl (3×5 mL), saturated aqueous solution of $NaHCO_3$ (3×5 mL), dried with anh. Na_2SO_4 and concentrated *in vacuo*.

(αR,3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-bromopropanoate, ***(αR,3S)-5a***

Following the above general procedure, from **(*S*)-1** (2.05 g, 10 mmol), ***rac*-3a** (1.3 mL, 12 mmol) and triethylamine (2.8 mL, 20 mmol) after 2 h reaction, **(α*R*,3*S*)-5a** (3.38 g, 99% yield, 86% d.e. by ^{1}H NMR) was obtained as a solid, m.p. 59–61°C (hexane/ethyl acetate), $[\alpha]_D^{20}$ (c=1.06, $CHCl_3$)=+32.2. HPLC (conditions A6): **(α*R*,3*S*)-5a**, r.t. 48.6 min, **(α*S*,3*S*)-5a**, r.t. 51.9 min., relative area **(α*R*,3*S*)-5a/(α*S*,3*S*)-5a**=93/7.

(αR,3S)-4,4-Dimethyl-2-oxo-1-phenylpirrolidin-3-yl α-bromo-β-methylbutyrate, ***(αS,3R)-5b***

Following the general procedure, from ***(R)*-1** (0.30 g, 1.46 mmol), ***rac*-2b** (0.39 g, 1.95 mmol) and triethylamine (0.7 mL, 4.9 mmol) after 4 h reaction, **(αS,3R)-5b** (0.39 g, 84% yield, 84% d.e. by ^{1}H NMR) was obtained as a solid.

(αR,3S)-4,4-Dimethyl-2-oxo-1-phenylpirrolidin-3-yl α-bromo-β-phenylpropanoate, ***(αR,3S)-5c***

Following the general procedure, from ***(S)*-1** (0.38 g, 1.85 mmol), ***rac*-2c** (0.61 g, 2.47 mmol) and triethylamine (0.9 mL, 6.2 mmol) after 2 h reaction, **(αR,3S)-5c** (0.75 g, 99% yield, 82% d.e. by ^{1}H NMR) was obtained as a solid.

General procedure for the acid hydrolysis of α-bromo esters ***5***

A mixture of the α-bromo ester (1.0 mmol), acetic acid (8 mL) and 2 N HCl (3.2 mL) was heated at 120°C (bath temperature) till completion of the hydrolysis (2–4 h), following the reaction by TLC. The mixture was allowed to cool to room temperature and the volatile products were distilled at reduced pressure. Aqueous 2 N NaOH was added to the residue until alkaline pH, and the mixture was extracted with ethyl acetate (3×15 mL). The combined organic phases were dried with 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 2 N HCl and extracted with ethyl acetate (3×15 mL). The combined organic phases were dried with anh Na_2SO_4 and concentrated *in vacuo* to give the (*R*)- or (*S*)-α-bromo acid ***(R)*-** or ***(S)*-4**.

(R)-α-Bromopropanoic acid, ***(R)*-4a**

From **(αR,3S)-5a** (0.20 g, 0.6 mmol, 86% d.e.), after 2 h reaction, ***(R)*-4a** (62 mg, 66% yield) was isolated as an oil, $[\alpha]_D^{20}$ (c=1.5, $CHCl_3$)=+5.8, (described $[\alpha]_D^{20}$ (c=1.3, $CHCl_3$)=+29.6).[10]

(S)-α-Bromo-β-methylbutanoic acid, ***(S)*-4b**

From **(αS,3R)-5b** (0.45 g, 1.2 mmol, 84% d.e.), after 4 h reaction, ***(S)*-4b** (134 mg, 61% yield) was isolated as a solid, $[\alpha]_D^{20}$ (c=1.3, $CHCl_3$)=−10.1, (described for ***(R)*-4b** $[\alpha]_D^{20}$ (c=1.0, $CHCl_3$)=+21.1).[10]

(R)-α-Bromo-β-phenylpropanoic acid, ***(R)*-4c**

From **(αR,3S)-5c** (0.13 g, 0.3 mmol, 60% d.e.), after 2 h reaction, ***(R)*-4c** (61 mg, 86% yield) was isolated as an oil, $[\alpha]_D^{20}$ (c=3.1, MeOH)=+0.58, (described $[\alpha]_D^{20}$ (c=2, MeOH)=+10.4).[11]

General procedure for the base hydrolysis of α-bromo esters ***5***

To a solution of the α-bromo ester **5** (1.0 mmol) in a mixture of THF (4 mL) and water (2 mL), solid $LiOH.H_2O$ (1.5 mmol) was added and the mixture was stirred at a temperature between −20°C and room temperature till completion of the hydrolysis (1–6.5 h), following the reaction by TLC. The mixture was allowed to warm to room temperature and part of the organic solvents was distilled at reduced pressure. The mixture was extracted with ethyl acetate (3×10 mL). The combined organic phases were dried with 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 2 N HCl and extracted with ethyl acetate (3×10 mL). The combined organic phases were dried with anh. Na_2SO_4 and concentrated *in vacuo* to give the (*R*)- or (*S*)-α-bromo acid, ***(R)*-** or ***(S)*-4**.

(R)-α-Bromopropanoic acid, ***(R)*-4a**

From **(αR,3S)-5a** (0.34 g, 1.0 mmol, 82% d.e.), after 2 h reaction at −20°C and 4 h at −15°C, ***(R)*-4a** (127 mg, 83% yield) was isolated as an oil, $[\alpha]_D^{20}$ (c=0.98, $CHCl_3$)=+18.9.

(S)-α-Bromo-β-methylbutanoic acid, **(R)-4b**

From **(αR,3S)-5b** (0.34 g, 0.91 mmol, 88% d.e.), after 3.5 h reaction at room temperature, **(R)-4b** (138 mg, 84% yield) was isolated as a solid, $[\alpha]_D^{20}$ (c=0.97, $CHCl_3$)=+10.6.

(R)-α-Bromo-β-phenylpropanoic acid, **(R)-4c**

From **(αR,3S)-5c** (0.35 g, 0.85 mmol, 82% d.e.), after 4 h reaction at room temperature, **(R)-4c** (164 mg, 84% yield) was isolated as an oil, $[\alpha]_D^{20}$ (c=1.91, MeOH)=+4.1.

General procedure for the reactions of α-bromo esters **5** *with sodium* p-*methoxyphenoxide*

A THF solution of sodium *p*-methoxyphenoxide was prepared by adding sodium hydride (0.9 mmol) to a stirred solution of *p*-methoxyphenol (1.0 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 esters **5** (1.0 mmol) with tetra-*n*-hexylammonium iodide (0.2 mmol) at −5 to 0°C under an argon atmosphere and the solution was stirred at this temperature for 6–18 h. The mixture was concentrated *in vacuo*, CH_2Cl_2 (14 mL) was added to the residue and the solution was washed with water (2×9 mL) and saturated aqueous $NaHCO_3$ (2×9 mL), dried with anh. Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed [silica gel (40 g) hexane/ethyl acetate] and the *p*-methoxyphenoxy ester, **7**, thus obtained was characterized as a diastereomeric mixture. Chemical yields refer to the total yield of both isomers.

*(αR,3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-(*p-*methoxyphenoxy)propanoate,* **(αR,3S)-7a**

From **(αRS,3S)-5a** (0.80 g, 2.4 mmol), after 18 h reaction, **(αR,3S)-7a** (0.64 g, 79% yield) was obtained as an oil, $[\alpha]_D^{20}$ (c=1.02, $CHCl_3$)=−23.9. HPLC (conditions A5): Main diastereomer **(αR,3S)-7a**, r.t. 27.3 min, 77% relative area; **(αS,3S)-7a**, r.t. 26.2 min, 23% relative area. The integral of the 4-αCH_3 group in both diastereomers (δ 0.98 and 1.09) gave a ratio **(αR,3S)-7a/(αS,3S)-7a**=78/22. IR (NaCl) ν: 1744 and 1716 (C=O st) cm^{-1}. $C_{22}H_{25}NO_5$ (383.46): calcd. C 68.91% H 6.58% N 3.65%. Found C 68.81% H 6.56% N 3.66%.

Spectroscopic data of **(αR,3S)-7a** *obtained from the spectra of the mixture.* ^{1}H NMR, δ: 0. 98 (s, 3 H, 4-αCH_3), 1.16 (s, 3 H, 4-βCH_3), 1.70 (d, J=7.0 Hz, 3 H, CHCH_3), 3.46 (d, J=9.5 Hz, 1 H, 5α-H), 3.57 (d, J=9.5 Hz, 1 H, 5β-H), 3.74 (s, 3 H, OCH_3), 4.85 (q, J=7.0 Hz, 1 H, C*H*CH_3), 5.41 (s, 1 H, 3-H), 6.81 (dm, J=9.0 Hz, 2 H) and 6.88 (dm, J=9.0 Hz, 2 H) (Ar-H *p*-methoxyphenoxy), 7.16 (tm, J=7.0 Hz, 1 H, H*para* N-phenyl), 7.36 (m, 2 H, H*meta* N-phenyl), 7.59 (dm, J=8.0 Hz, 2 H, H*ortho* N-phenyl). ^{13}C NMR, δ: 18.9 (CH_3, CH*C*H_3), 20.9 (CH_3, 4-α*C*H_3), 24.5 (CH_3, 4-β*C*H_3), 37.3 (C, C4), 55.7 (CH_3, O*C*H_3), 57.6 (CH_2, C5), 72.9 (CH, *C*HCH$_3$), 78.4 (CH, C3), 114.7 (CH) and 115.9 (CH) (C*ortho* and C*meta p*-methoxyphenoxy), 119.4 (CH, C*ortho* N-phenyl), 125.0 (CH, C*para* N-phenyl), 128.9 (CH, C*meta* N-phenyl), 138.9 (C, C*ipso* N-phenyl), 151.5 (C, C*ipso p*-methoxyphenoxy), 154.3 (C, C*para p*-methoxyphenoxy), 168.3 (C, COO), 171.8 (C, C2).

Significant ^{1}*H NMR data of* **(αS,3S)-7a** *obtained from the spectrum of the mixture.* δ: 1.09 (s, 3 H, 4-αCH_3), 1.25 (s, 3 H, 4-βCH_3), 1.70 (d, J=7.0 Hz, 3 H, CHCH_3), 3.49 (d, J=9.5 Hz, 1 H, 5α-H), 3.58 (d, J=9.5 Hz, 1 H, 5β-H), 3.74 (s, 3 H, OCH_3), 4.81 (q, J=7.0 Hz, 1 H, C*H*CH_3), 5.41 (s, 1 H, 3-H).

*(αR,3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-(*p-*methoxyphenoxy)-β-methylbutanoate,* **(αR,3S)-7b**

From **(αRS,3S)-5b** (0.84 g, 2.3 mmol), after 18 h reaction, **(αR,3S)-7b** (0.55 g, 65% yield) was obtained as an oil, $[\alpha]_D^{20}$ (c=1.01, $CHCl_3$)=+3.4. HPLC (conditions A5): Main diastereomer **(αR,3S)-7b**, r.t. 76.9 min, 99% relative area; **(αS,3S)-7a**, r.t. 71.2 min, 1% relative area. IR (NaCl) ν: 1743 and

1717 (C=O st) cm^{-1}. $C_{24}H_{29}NO_5$ (411.52): calcd. C 70.05% H 7.11% N 3.40%. Found C 70.11% H 7.15% N 3.39%. ^1H NMR, δ: 0.98 (s, 3 H, 4-αCH$_3$), 1.13 (s, 3 H, 4-βCH$_3$), 1.165 (d, J=7.0 Hz, 3 H) and 1.17 (d, J=7.0 Hz, 3 H) [CH(C*H*$_3$)$_2$], 2.37 [m, 1 H, C*H*(CH$_3$)$_2$], 3.46 (d, J=9.5 Hz, 1 H, 5α-H), 3.58 (d, J=9.5 Hz, 1 H, 5β-H), 3.76 (s, 3 H, OCH$_3$), 4.49 (d, J=5.5 Hz, 1 H, CHOAr), 5.46 (s, 1 H, 3-H), 6.83 (dm, J=9.5 Hz, 2 H) and 6.91 (dm, J=9.5 Hz, 2 H) (Ar-H *p*-methoxyphenoxy), 7.17 (tm, J=7.5 Hz, 1 H, H*para* N-phenyl), 7.37 (m, 2 H, H*meta* N-phenyl), 7.60 (dm, J=8.0 Hz, 2 H, H*ortho* N-phenyl). ^{13}C NMR, δ: 17.6 (CH$_3$) and 18.8 (CH$_3$) [CH(*C*H$_3$)$_2$], 21.0 (CH$_3$, 4-αCH$_3$), 24.3 (CH$_3$, 4-βCH$_3$), 31.7 (CH, *C*H(CH$_3$)$_2$], 37.3 (C, C4), 55.7 (CH$_3$, OCH$_3$), 57.5 (CH$_2$, C5), 78.3 (CH, C3), 82.0 (CH, CHOAr), 114.7 (CH) and 115.9 (CH) (C*ortho* and C*meta* *p*-methoxyphenoxy), 119.4 (CH, C*ortho* N-phenyl), 124.9 (CH, C*para* N-phenyl), 128.9 (CH, C*meta* N-phenyl), 138.9 (C, C*ipso* N-phenyl), 152.3 (C, C*ipso* *p*-methoxyphenoxy) and 154.2 (C, C*para* *p*-methoxyphenoxy), 168.4 (C, COO), 170.9 (C, C2).

(αR,3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-(p-methoxyphenoxy)-β-phenylpropanoate, ***(αR,3S)-7c*** *and (S)-4,4-dimethyl-2-oxo-1-phenylpyrrolidin-3-yl cinnamate,* ***(S)-10***

From **(α*RS*,3*S*)-5c** (1.00 g, 2.4 mmol), after 18 h reaction **(α*R*,3*S*)-7c** (0.48 g, 48% yield) and **(*S*)-10** (0.31 g, 38% yield) were obtained in pure form as oils by column chromatography.**(α*R*,3*S*)-7c**: $[\alpha]_D^{20}$ (c=1.05, $CHCl_3$)=−18.6. HPLC (conditions A4): Main diastereomer **(α*R*,3*S*)-7c**, r.t. 76.2 min, 94.5% relative area; **(α*S*,3*S*)-7c**, r.t. 68.5 min, 5.5% relative area. IR (NaCl) ν: 1761 and 1715 (C=O st) cm^{-1}. $C_{28}H_{29}NO_5$ (459.56): calcd. C 73.18% H 6.37% N 3.05%. Found C 73.18% H 6.46% N 3.16%. ^1H NMR, δ: 0.87 (s, 3 H, 4-αCH$_3$), 1.08 (s, 3 H, 4-βCH$_3$), 3.32 (m, 2 H, C$_6$H$_5$C*H*$_2$), 3.43 (d, J=9.5 Hz, 1 H, 5α-H), 3.55 (d, J=9.5 Hz, 1 H, 5β-H), 3.72 (s, 3 H, OCH$_3$), 4.87 (dd, J=5.5 Hz, J'=8.0 Hz, 1 H, CHOAr), 5.41 (s, 1 H, 3-H), 6.78 (dm, J=9.0 Hz, 2 H) and 6.85 (dm, J=9.0 Hz, 2 H) (Ar-H *p*-methoxyphenoxy), 7.16 (tm, J=7.5 Hz, 1 H, H*para* N-phenyl), 7.22 (m, 1 H), 7.29 (m, 2 H), 7.35 (m, 4 H) (C$_6$*H*$_5$CH$_2$ and H*meta* N-phenyl), 7.59 (m, 2 H, H*ortho* N-phenyl). ^{13}C NMR, δ: 20.8 (CH$_3$, 4-αCH$_3$), 24.3 (CH$_3$, 4-βCH$_3$), 37.3 (C, C4), 39.3 (CH$_2$, C$_6$H$_5$*C*H$_2$), 55.7 (CH$_3$, OCH$_3$), 57.6 (CH$_2$, C5), 78.5 (CH, CHOAr and C3), 114.6 (CH) and 116.2 (CH) (C*ortho* and C*meta* *p*-methoxyphenoxy), 119.5 (CH, C*ortho* N-phenyl), 125.0 (CH, C*para* N-phenyl), 126.8 (CH, C*para* benzyl), 128.5 (CH), 129.0 (CH) and 129.5 (CH) (C*ortho* and C*meta* benzyl and C*meta* N-phenyl), 136.2 (C, C*ipso* benzyl), 138.9 (C, C*ipso* N-phenyl), 151.7 (C, C*ipso* *p*-methoxyphenoxy), 154.4 (C, C*para* *p*-methoxyphenoxy), 168.3 (C, COO), 170.9 (C, C2).

(*S*)-10: $[\alpha]_D^{20}$ (c=1.04, $CHCl_3$)=+29.4. IR (NaCl) ν: 1711 (C=O st) 1636 (C=C st) cm^{-1}. $C_{21}H_{21}NO_3$ (335.42): calcd. C 75.20% H 6.32% N 4.18%. Found C 75.10% H 6.35% N 4.13%. ^1H NMR, δ: 1.18 (s, 3 H, 4-αCH$_3$), 1.33 (s, 3 H, 4-βCH$_3$), 3.54 (d, J=9.5 Hz, 1 H, 5α-H), 3.64 (d, J=9.5 Hz, 1 H, 5β-H), 5.53 (s, 1 H, 3-H), 6.57 (d, J=16.0 Hz, 1 H, α-H cinnamate), 7.16 (tm, J=7.5 Hz, 1 H, H*para* N-phenyl), 7.38 (m, 5 H) and 7.54 (m, 2 H) (H*meta* N-phenyl and C$_6$*H*$_5$ cinnamate), 7.64 (d, J=8.0 Hz, 2 H, H*ortho* N-phenyl), 7.79 (d, J=16.0 Hz, 1 H, β-H cinnamate). ^{13}C NMR, δ: 21.2 (CH$_3$, 4-αCH$_3$), 24.9 (CH$_3$, 4-βCH$_3$), 37.6 (C, C4), 57.8 (CH$_2$, C5), 78.3 (CH, C3), 117.0 (CH, Cα cinnamate), 119.4 (CH, C*ortho* N-phenyl), 124.9 (CH, C*para* N-phenyl), 128.2 (CH), 128.89 (CH), 128.94 (CH) and 130.5 (CH) (C*ortho*, C*meta* and C*para* C$_6$H$_5$ cinnamate and C*meta* N-phenyl), 134.2 (C, C*ipso* C$_6$H$_5$ cinnamate), 139.1 (C, C*ipso* N-phenyl), 146.2 (CH, Cβ cinnamate), 166.2 (C, COO), 169.1 (C, C2).

(αR,3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-(p-methoxyphenoxy)-α-phenylacetate, ***(αR, 3S)-7d***

From **(α*RS*,3*S*)-5d** (5.19 g, 12.9 mmol), after 6 h reaction, **(α*R*,3*S*)-7d** (5.08 g, 98% yield) was obtained as a solid, m.p. 152–153.5°C (hexane/ethyl acetate) $[\alpha]_D^{20}$ (c=1.07, $CHCl_3$)=−4.6. HPLC (conditions A3): Main diastereomer **(α*R*,3*S*)-7d**, r.t. 78.9 min, 92% relative area; **(α*S*,3*S*)-7d**, r.t. 76.3 min, 8% relative area. IR (KBr) ν: 1761 and 1709 (C=O st) cm^{-1}. $C_{27}H_{27}NO_5$ (445.53): calcd. C

72.79% H 6.11% N 3.14%. Found C 72.74% H 6.20% N 3.11%. ^{1}H NMR (300 MHz), δ: 0.72 (s, 3 H, 4-αCH$_3$), 1.03 (s, 3 H, 4-βCH$_3$), 3.39 (d, J=9.6 Hz, 1 H, 5α-H), 3.54 (d, J=9.6 Hz, 1 H, 5β-H), 3.75 (s, 3 H, OCH$_3$), 5.45 (s, 1 H, 3-H), 5.74 (s, 1 H, CHOAr), 6.83 (dm, J=9.2 Hz, 2 H) and 6.97 (dm, J=9.2 Hz, 2 H) (Ar-H *p*-methoxyphenoxy), 7.17 (tm, J=7.4 Hz, 1 H, H*para* N-phenyl), 7.39 (m, 5 H), 7.58 (m, 2 H), 7.63 (m, 2 H) (C$_6$*H*$_5$CH, H*meta* and H*ortho* N-phenyl). ^{13}C NMR, δ: 20.5 (CH$_3$, 4-αCH$_3$), 24.4 (CH$_3$, 4-βCH$_3$), 37.6 (C, C4), 55.6 (CH$_3$, OCH$_3$), 57.5 (CH$_2$, C5), 78.6 (CH) and 79.0 (CH) (CHOAr and C3), 114.7 (CH) and 116.6 (CH) (C*ortho* and C*meta* *p*-methoxyphenoxy), 119.5 (CH, C*ortho* N-phenyl), 125.0 (CH, C*para* N-phenyl), 127.5 (CH), 128.8 (CH), 129.0 (CH) and 129.1 (CH) (C*para*, C*meta* and C*ortho* C$_6$H$_5$CH and C*meta* N-phenyl), 135.7 (C, C*ipso* C$_6$H$_5$CH), 138.9 (C, C*ipso* N-phenyl), 151.2 (C, C*ipso* *p*-methoxyphenoxy), 154.5 (C, C*para* *p*-methoxyphenoxy), 168.3 (C, COO), 169.6 (C, C2).

(αS,3R)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-(p-methoxyphenoxy)-α-phenylacetate, ***(αS, 3R)-7d***

From **(α*RS*,3*R*)-5d** (2.59 g, 6.45 mmol), after 6 h reaction, **(α*S*,3*R*)-7d** (2.45 g, 95% yield) was obtained as a solid, m.p. 151–152°C (hexane / ethyl acetate) $[\alpha]_D^{20}$ (c=1.04, CHCl$_3$)=+3.4. HPLC (conditions A3): Main diastereomer **(α*S*,3*S*)-7d**, r.t. 78.9 min, 97% relative area; **(α*S*,3*S*)-7d**, r.t. 76.3 min, 3% relative area. IR (KBr) ν: 1761 and 1709 (C=O st), cm^{-1}. C$_{27}$H$_{27}$NO$_5$ (445.53): calcd. C 72.79% H 6.11% N 3.14%. Found C 72.75% H 6.14% N 3.11%.

rac-α-(p-*Methoxyphenoxy)propanoic acid,* **rac-*6a***

A solution of *p*-methoxyphenol (4.09 g, 33 mmol) in aqueous 2 N NaOH (16.5 mL) was added to a solution of ***rac*-4a** (5.05 g, 33 mmol) in aqueous 2 N NaOH (16.5 mL) and the solution was heated under reflux for 1 h. The mixture was acidified with 5 N HCl until pH=1 and it was extracted with CH$_2$Cl$_2$ (3×50 mL). The combined organic extracts were dried with anh. Na$_2$SO$_4$ and concentrated *in vacuo*, to give ***rac*-6a** (4.96 g, 77% yield) as a solid, m.p. 86–88°C (hexane/ethyl acetate). IR (KBr) ν: 2946 (O-H st), 1717 (C=O st) cm^{-1}. C$_{10}$H$_{12}$O$_4$ (196.21): calcd. C 61.24% H 6.17%. Found C 61.36% H 6.19%. ^{1}H NMR (300 MHz) δ: 1.64 (d, J=6.9 Hz, 3 H, CHC*H*$_3$), 3.77 (s, 3 H, OC*H*$_3$), 4.70 (d, J=6.9 Hz, 1 H, CHOAr), 6.84 (m, 4 H) (Ar-H). ^{13}C NMR, δ: 18.4 (CH$_3$, C3), 55.6 (CH$_3$, OCH$_3$), 73.0 (CH, C2), 114.7 (CH) and 116.5 (CH) (Ar-C*ortho* and Ar-C*meta*), 151.2 (C, Ar-C*ipso*) and 154.5 (C, Ar-C*para*), 178.3 (C, COO).

rac-α-(p-*Methoxyphenoxy)phenylacetic acid,* **rac-*6d***

Sodium hydride (0.2 g of a 55% dispersion in mineral oil, approx. 2.3 mmol) was added to a stirred solution of *p*-methoxyphenol (288 mg, 2.3 mmol) in dry THF (10 mL) at room temperature under an argon atmosphere. A solution ***rac*-4d** (500 mg, 2.3 mmol) in dry THF (10 mL) was reacted with NaH (0.2 g of a 55% dispersion in mineral oil, approx. 2.3 mmol) at room temperature under and argon atmosphere. Anh. HMPA (2 mL) was added until complete dissolution of the precipitated salt. Then, a solution of sodium *p*-methoxyphenoxide (prepared by adding NaH (0.2 g of a 55% dispersion in mineral oil, approx. 2.3 mmol) to a stirred solution of *p*-methoxyphenol (288 mg, 2.3 mmol) in dry THF (10 mL) at room temperature under an argon atmosphere] was added dropwise via cannula and the mixture was stirred at this temperature for 15 h. The precipitated sodium salt of ***rac*-6d** was filtered and treated with an ethereal solution of HCl (0.38 N, 20 mL). The organic solution was washed with water (3×20 mL), dried with anh. Na$_2$SO$_4$ and concentrated *in vacuo* to give ***rac*-6d** (467 mg, 78% yield) as a solid, m.p. 106–108°C (hexane/ethyl acetate), IR (KBr) ν: 2904 (O-H st), 1699 (C=O st) cm^{-1}. C$_{15}$H$_{14}$O$_4$ (258.38): calcd. C 69.75% H 5.47%. Found C 69.70% H 5.44%. ^{1}H NMR (300 MHz) δ: 3.74 (s, 3H, OC*H*$_3$), 5.55 (s, 1 H, 2-H), 6.79 (dm, J=9.0 Hz, 2 H) and 6.89 (dm, J=9.0 Hz, 2 H) (Ar-H *p*-methoxyphenoxy), 7.38 (m, 3 H) and 7.55 (m, 2 H) (Ar-H phenyl). ^{13}C NMR, δ: 55.6 (CH$_3$, OCH$_3$), 79.1 (CH, C2), 114.7 (CH) and 116.9 (CH) (C*ortho* and C*meta* *p*-methoxyphenoxy), 127.1

(CH), 128.8 (CH), (C*ortho* and C*meta* phenyl) 129.1 (CH, C*para* phenyl), 134.9 (C, C*ipso* phenyl), 150.9 (C, C*ipso p*-methoxyphenoxy) and 154.7 (C, C*para p*-methoxyphenoxy) 175.6 (C, COO).

General procedure for the preparation of chiral α-hydroxy esters ***8***

A solution of diastereomerically enriched esters **7** (1.0 mmol) in DMF (3 mL) was added dropwise by cannula over 15 min to a cold (−20°C) well-stirred solution of ceric ammonium nitrate (5 mmol) in a 4:1 mixture DMF–H_2O (20 mL). After 2 h reaction at −20°C the solution was maintained at 0°C for 2 h and then diluted with ether–hexane (1:1, 8 mL)) and water (8 mL) with stirring at 0°C. Water (9 mL) was added and the mixture was extracted with a 1:1 mixture of ether–hexane (5×17 mL). The organic extracts were washed with aqueous 0.5 M Na_2CO_3 (2×20 mL), dried with anh. Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed [silica gel (30 g) ethyl acetate/hexane] and the products were characterized as diastereomerically enriched mixtures. Chemical yields refer to the total yield of both isomers.

(αR,3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-hydroxypropanoate, ***(αR,3S)-8a***

From **(α*R*,3*S*)-7a** (0.35 g, 0.9 mmol), **(α*R*,3*S*)-8a** (0.13 g, 51% yield) was obtained as an oil, $[\alpha]_D^{20}$ (c=1.02, $CHCl_3$)=−15.6. The integral of the C*H*OH proton in both diastereomers (δ 4.51 and 4.42) gave a ratio **(α*R*,3*S*)-8a/(α*S*,3*S*)-8a**=83/17. This mixture could not be separated by HPLC using different conditions A. IR (NaCl) ν: 3431 (O-H st), 1755 and 1712 (C=O st) cm^{-1}. $C_{15}H_{19}NO_4.1/2\ H_2O$ (286.34): calcd. C 64.18% H 6.73% N 4.99%. Found C 64.18% H 6.73% N 4.99%.

Spectroscopic data of ***(αR,3S)-8a*** *obtained from the spectra of the mixture.* ^{1}H NMR, δ: 1.13 (s, 3 H, 4-αCH_3), 1.30 (s, 3 H, 4-βCH_3), 1.50 (d, J=7.0 Hz, 3 H, CHCH_3), 3.52 (d, J=9.5 Hz, 1 H, 5α-H), 3.63 (d, J=9.5 Hz, 1 H, 5β-H), 4.51 (q, J=7.0 Hz, 1 H, C*H*CH_3), 5.44 (s, 1 H, 3-H), 7.17 (tm, J=7.5 Hz, 1 H, Ar-H*para*), 7.37 (m, 2 H, Ar-H*meta*), 7.59 (dm, J=8.5 Hz, 2 H, Ar-H-*ortho*). ^{13}C NMR, δ: 20.3 (CH_3, 4-αCH_3), 21.1 (CH_3, CHCH_3), 24.8 (CH_3, 4-βCH_3), 37.4 (C, C4), 57.7 (CH_2, C5), 66.7 (CH, *C*HCH_3), 79.0 (CH, C3), 119.5 (CH, Ar-C*ortho*), 125.1 (CH, Ar-C*para*), 129.0 (CH, Ar-C*meta*), 138.8 (C, Ar-C*ipso*), 168.3 (C, COO), 175.1 (C, C2).

Significant ^{1}H NMR data of ***(αS,3S)-8a*** *obtained from the spectra of the mixture.* δ: 1.23 (s, 3 H, 4-αCH_3), 1.30 (s, 3 H, 4-βCH_3), 1.54 (d, J=7.0 Hz, 3 H, CHCH_3), 3.53 (d, J=9.5 Hz, 1 H, 5α-H), 3.62 (d, J=9.5 Hz, 1 H, 5β-H), 4.42 (q, J=7.0 Hz, 1 H, C*H*CH_3), 5.42 (s, 1 H, 3-H).

(αR,3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-hydroxy-β-methylbutanoate, ***(αR,3S)-8b***

From **(α*R*,3*S*)-7b** (0.30 g, 0.7 mmol), **(α*R*,3*S*)-8b** (0.15 g, 65% yield) was obtained as an oil, $[\alpha]_D^{20}$ (c=1.04, $CHCl_3$)=−41.4. HPLC (conditions A7): Main diastereomer **(α*R*,3*S*)-8b**, r.t. 63.6 min, 98% relative area; **(α*S*,3*S*)-8b**, r.t. 67.6 min, 2% relative area. IR (NaCl) ν: 3458 (O-H st), 1770 and 1718 (C=O st) cm^{-1}. $C_{17}H_{23}NO_4.1/2\ H_2O$ (314.40): calcd. C 65.65% H 7.53% N 4.54%. Found C 65.65% H 7.53% N 4.54%. ^{1}H NMR, δ: 0.92 (d, J=7.0 Hz, 3 H) and 1.08 (d, J=7.0 Hz, 3 H) [CH(CH_3)$_2$], 1.14 (s, 3 H, 4-αCH_3), 1.30 (s, 3 H, 4-βCH_3), 2.18 [m, 1 H, C*H*(CH_3)$_2$], 3.51 (d, J=9.5 Hz, 1 H, 5α-H), 3.64 (d, J=9.5 Hz, 1 H, 5β-H), 4.29 (d, J=3.0 Hz, 1 H, C*H*OH), 5.49 (s, 1 H, 3-H), 7.16 (tm, J=7.5 Hz, 1 H, Ar-H*para*), 7.36 (m, 2 H, Ar-H*meta*), 7.59 (dm, J=7.5 Hz, 2 H, Ar-H*ortho*). ^{13}C NMR, δ 15.7 (CH_3) and 19.0 (CH_3) [CH(*C*H_3)$_2$], 21.2 (CH_3, 4-αCH_3), 24.6 (CH_3, 4-βCH_3), 31.9 [CH, *C*H(CH_3)$_2$], 37.5 (C, C4), 57.5 (CH_2, C5), 74.9 (CH, CHOH), 78.9 (CH, C3), 119.4 (CH, Ar-C*ortho*), 125.0 (CH, Ar-C*para*), 128.9 (CH, Ar-C*meta*), 138.8 (C, Ar-C*ipso*), 168.2 (C, COO), 174.3 (C, C2).

(αR,3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-hydroxy-β-phenylpropanoate, ***(αR,3S)-8c***

From **(α*R*,3*S*)-7c** (0.32 g, 0.7 mmol), **(α*R*,3*S*)-8c** (0.16 g, 68% yield) was obtained as an oil, $[\alpha]_D^{20}$ (c=1.02, $CHCl_3$)=−22.2. The integral of the 4-αCH_3 protons in both diastereomers (δ 0.99 and

1.18) gave a ratio (**αR,3S**)-**8c**/(**αS,3S**)-**8c**=95/5. This mixture could not be separated by HPLC using different conditions A. IR (NaCl) ν: 3441 (O-H st), 1753 and 1713 (C=O st) cm^{-1}. $C_{21}H_{23}NO_4.1/2\ H_2O$ (362.44): calcd. C 70.05% H 6.49% N 3.88%. Found C 70.02% H 6.46% N 3.85%.

^1H NMR, δ: 0.99 (s, 3 H, 4-αCH$_3$), 1.16 (s, 3 H, 4-βCH$_3$), 2.96 (dd, J=7.5 Hz, J′=14.0 Hz, 1 H) and 3.16 (dd, J=4.5 Hz, J′=14.0 Hz) ($C_6H_5CH_2$), 3.42 (d, J=9.5 Hz, 1 H, 5α-H), 3.54 (d, J=9.5 Hz, 1 H, 5β-H), 4.60 (dd, J=4.5 Hz, J′=7.5 Hz, 1 H, C*H*OH), 5.36 (s, 1 H, 3-H), 7.10 (tm, J=7.5 Hz, 1 H, H*para* N-phenyl), 7.17 (m, 1 H, H*para* benzyl), 7.22 (m, 4 H, H*meta* and H*ortho* benzyl), 7.30 (m, 2 H, H*meta* N-phenyl), 7.59 (m, 2 H, H*ortho* N-phenyl). ^{13}C NMR, δ: 21.0 (CH$_3$, 4-αCH$_3$), 24.5 (CH$_3$, 4-βCH$_3$), 37.4 (C, C4), 40.3 (CH$_2$, ($C_6H_5CH_2$), 57.6 (CH$_2$, C5), 71.4 (CH, CHOH), 79.2 (CH, C3), 119.5 (CH, C*ortho* N-phenyl), 125.1 (CH, C*para* N-phenyl), 126.9 (CH, C*para* benzyl), 128.5 (CH), 129.0 (CH) and 129.4 (CH) (C*meta* N-phenyl and C*ortho* and C*meta* benzyl), 136.3 (C, C*ipso* benzyl), 138.8 (C, C*ipso* N-phenyl), 168.3 (C, COO), 173.7 (C, C2).

*(αR,3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-hydroxy-α-phenylacetate, (**αR,3S**)-**8d***

From (**αR,3S**)-**7d** (4.00 g, 8.99 mmol), (**αR,3S**)-**8d** (1.95 g, 64% yield) was obtained as a solid. HPLC (conditions A2): Main diastereomer (**αR,3S**)-**8d**, r.t. 10.5 min, 95% relative area; (**αS,3S**)-**8d**, r.t. 11.2 min, 5% relative area. After crystallization from a mixture ethyl acetate/hexane, m.p. 121–123°C, $[\alpha]_D^{20}$ (c=1.01, $CHCl_3$)=−0.6, d.e. >99% (by HPLC). IR (KBr) ν: 3425 (O-H st), 1752 and 1710 (C=O st) cm^{-1}. $C_{20}H_{21}NO_4$ (339.41): calcd. C 70.78% H 6.24% N 4.13%. Found C 70.79% H 6.32% N 4.20%.

^1H NMR (300 MHz) δ: 0.68 (s, 3 H, 4-αCH$_3$), 1.05 (s, 3 H, 4-βCH$_3$), 3.39 (d, J=9.6 Hz, 1 H, 5α-H), 3.54 (d, J=9.6 Hz, 1 H, 5β-H), 3.5–3.7 (broad signal, 1 H, OH), 5.41 (s, 1 H, CHOH), 5.42 (s, 1 H, 3-H), 7.18 (tm, J=7.4 Hz, 1 H, H*para* N-phenyl), 7.38 (m, 5 H, H*meta* N-phenyl, H*para* and H*meta* C_6H_5CH), 7.49 (dm, J=7.7 Hz, 2 H, H*ortho* C_6H_5CH), 7.58 (broad d, J=7.7 Hz, 2 H, H*ortho* N-phenyl). ^{13}C NMR, δ: 20.4 (CH$_3$, 4-αCH$_3$), 24.4 (CH$_3$, 4-βCH$_3$), 37.5 (C, C4), 57.5 (CH$_2$, C5), 72.9 (CH, CHOH), 79.3 (CH, C3), 119.5 (CH, C*ortho* N-phenyl), 125.1 (CH, C*para* N-phenyl), 126.8 (CH, C*para* C_6H_5CH), 128.6 (CH) and 129.0 (CH) (C*ortho* and C*meta* C_6H_5CH and C*meta* N-phenyl), 138.3 (C) and 138.8 (C) (C*ipso* N-phenyl and C*ipso* C_6H_5CH), 168.1 (C, COO), 173.4 (C, C2).

*(αS,3R)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-hydroxy-α-phenylacetate, (**αS,3R**)-**8d***

From (**αS,3R**)-**7d** (1.06 g, 2.38 mmol), (**αS,3R**)-**8d** (0.51 g, 63% yield) was obtained as a solid. HPLC (conditions A6): Main diastereomer (**αS,3R**)-**8d**, r.t. 32.4 min, 93% relative area; (**αR,3R**)-**8d**, r.t. 34.7 min, 7% relative area. After crystallization from a mixture ethyl acetate/hexane, m.p. 121–123°C, $[\alpha]_D^{20}$ (c=1.04, $CHCl_3$)=+0.8, d.e. >99% (by HPLC). IR (KBr) ν: 3411 (O-H st), 1752 and 1710 (C=O st) cm^{-1}. $C_{20}H_{21}NO_4$ (339.41): calcd. C 70.78% H 6.24% N 4.13%. Found C 70.84% H 6.29% N 4.08%. The NMR data are coincident with those of its enantiomer.

General procedure for the acid hydrolysis of α-hydroxy esters 8

A mixture of the α-hydroxy ester **8** (1.0 mmol), acetic acid (8 mL) and 2 N HCl (3.2 mL) was heated at 120°C (bath temperature) till completion of the hydrolysis (2.5–4 h), following the reaction by TLC. The mixture was allowed to cool to room temperature and the volatile products were distilled at reduced pressure.

Work-up A: Water (8 mL) was added to the residue, and the mixture was extracted with CH_2Cl_2 (3×8 mL). The combined organic phases were treated with cyclohexylamine (1.0 mmol) and the precipitate thus formed was filtered. The filtrate was concentrated *in vacuo* and the residue consisting of the chiral auxiliary was crystallized from ethanol (0.2 mL). The solid was treated with N HCl until pH=1, and the mixture was extracted with CH_2Cl_2 (3×8 mL). The combined organic extracts were washed with water (2×8 mL), dried with anh. Na_2SO_4 and concentrated *in vacuo* to give the (*R*)- or (*S*)-α-hydroxy acid, (***R***)- or (***S***)-**9**.

Work-up B: A 1:1 mixture ether/hexane (7.5 mL) was added to the residue, and the solution was treated with cyclohexylamine (1.0 mmol). The precipitate was filtered and the filtrate was concentrated *in vacuo* to give a residue consisting of the chiral auxiliary which was crystallized from ethanol (0.2 mL). The precipitate was treated with an ethereal solution of HCl (0.38 N, 25 mL), the precipitated cyclohexylammonium chloride was filtered and the filtrate was concentrated *in vacuo* to give the (*R*)- or (*S*)-α-hydroxy acid.

Work-up C: The residue was made alkaline with 2 N NaOH, and the mixture was extracted with ethyl acetate (3×25 mL). The combined organic phases were dried with 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 concentrated *in vacuo* and the residue was treated with an ethereal solution of HCl (0.38 N, 25 mL). The precipitated NaCl was filtered and the filtrate was concentrated *in vacuo* to give the (*R*)- or (*S*)-α-hydroxy acid.

(R)-α-Hydroxypropanoic acid, **(R)-9a**

From **(αR,3S)-8a** (107 mg, 0.39 mmol), after work-up C, **(*R*)-9a** (31.6 mg, 91% yield) was obtained as a solid, m.p. 50–52°C (hexane / ethyl acetate) (described: 53°C),[17] $[\alpha]_D^{20}$ (c=1.03, H_2O)=−2.0 [described: $[\alpha]_D^{20}$ (c=1.24, H_2O)=−2.26],[17] approx. o.p.=88%.

(R)-α-Hydroxy-β-methylbutanoic acid, **(R)-9b**

From **(αR,3S)-8b** (115 mg, 0.38 mmol), after work-up C, **(*R*)-9b** (41.8 mg, 94% yield) was obtained as a solid, m.p. 68–69.5°C (hexane / ethyl acetate) (described for **(*S*)-9b**: 68–70°C),[18] $[\alpha]_D^{20}$ (c=1.02, $CHCl_3$)=−18.2 [described for **(*S*)-9b**: $[\alpha]_D^{20}$ (c=1, $CHCl_3$)=+19],[18] o.p. 96%.

(R)-α-Hydroxy-β-phenyl propanoic acid, **(R)-9c**

From **(αR,3S)-8c** (150 mg, 0.42 mmol), after work-up B, **(*R*)-9c** (68.2 mg, 96% yield) was obtained as a solid, m.p. 114–115.5°C (chloroform), [described: 124–126°C(water)],[17] $[\alpha]_D^{20}$ (c=1.92, H_2O)=+18.7 [described: $[\alpha]_D^{20}$ (c=2.2, H_2O)=+22.2],[17] approx. o.p. 84%.

(R)-α-Hydroxy-α-phenylacetic acid, **(R)-9d**

From **(αR,3S)-8d** (408 mg, 1.20 mmol), after work-up A, **(*R*)-9d** (148 mg, 81% yield) was obtained as a solid, m.p. 110–112°C (chloroform), (described: 133–135°C),[17] $[\alpha]_D^{20}$ (c=2.67, H_2O)=−157.1 [described: $[\alpha]_D^{20}$ (c=2.5, H_2O)=−158].[17] Chiral HPLC (conditions B), e.e. >99%, **(*R*)-9d**, r.t. 24.6 min, **(*S*)-9d**, r.t. 23.6 min.

(S)-α-Hydroxy-α-phenylacetic acid, **(S)-9d**

From **(αS,3R)-8d** (332 mg, 0.98 mmol), after work-up A, **(*S*)-9d** (109 mg, 73% yield) was obtained as a solid, m.p. 110–112°C (chloroform), $[\alpha]_D^{20}$ (c=2.92, H_2O)=+155.2 [described: $[\alpha]_D^{20}$ (c=2.9, H_2O)=+156.6].[17] e.e. >99% by chiral HPLC (conditions B).

General procedure for the preparation of (R)- *or* (S)-α-*hydroxy acids* **(R)-** *or* **(S)-9** *from* rac-α-*bromo acids,* **rac-4**, *without isolation of any intermediate product*

All the reactions were performed following the experimental procedures described above, but each intermediate product was used without being purified in the following reaction, except in the case of **(αR,3S)-7c** which was separated by column chromatography from important amounts of the elimination by-product **(*S*)-10**. The global yields of the obtained acids **(*R*)-** or **(*S*)-9** as well as the yields of the recovered chiral auxiliary **(*R*)-** or **(*S*)-1** together with the optical rotations for the acids and the e.e. of the recovered **(*R*)-** or **(*S*)-1** (obtained by chiral HPLC under conditions C) are collected in Table 5.

From ***rac*-4a** (460 mg, 3.0 mmol) and **(*S*)-1** (0.62 g, 3.0 mmol), **(*R*)-9a** (90 mg, 36% global yield) was obtained as a solid, m.p. 48–50°C (hexane/ethyl acetate) and **(*S*)-1** (220 mg, 40% yield) was recovered.

From ***rac*-4b** (540 mg, 3.0 mmol) and **(*S*)-1** (0.62 g, 3.0 mmol), **(*R*)-9b** (150 mg, 47% global yield) was obtained as a solid, m.p. 68.5–70.5°C (hexane/ethyl acetate) and **(*S*)-1** (360 mg, 58% yield) was recovered.

From ***rac*-4c** (1.6 g, 7.0 mmol) and **(*S*)-1** (1.43 g, 7.0 mmol), **(*R*)-9c** (360 mg, 31% global yield) was obtained as a solid, m.p. 114–116°C (chloroform) and **(*S*)-1** (470 mg, 33% yield) was recovered.

From ***rac*-4d** (1.50 mg, 7.0 mmol) and **(*S*)-1** (1.43 g, 7.0 mmol), **(*R*)-9d** (590 mg, 62% global yield) was obtained as a solid, m.p. 112–114°C (chloroform) and **(*S*)-1** (830 mg, 58% yield) was recovered.

From ***rac*-4d** (1.87 mg, 8.7 mmol) and **(*R*)-1** (1.78 g, 8.7 mmol), **(*S*)-9d** (710 mg, 59% global yield) was obtained as a solid, m.p. 110–112°C (chloroform) and **(*R*)-1** (1.12 g, 63% yield) was recovered.

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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. Durst, T.; Koh, K.; *Tetrahedron Lett.*, **1992**, *33*, 6799–6802.
5. Koh, K.; Durst, T.; *J. Org. Chem.*, **1994**, *59*, 4683–4686.
6. Ward, R. S.; Pelter, A.; Goubet, D.; Pritchard, M. C.; *Tetrahedron: Asymmetry*, **1995**, *6*, 93–96.
7. Ward, R. S.; Pelter, A.; Goubet, D.; Pritchard, M. C.; *Tetrahedron: Asymmetry*, **1995**, *6*, 469–498.
8. Kubo, A.; Takahashi, M.; Kubota, H.; Nunami, K.; *Tetrahedron Lett.*, **1995**, *36*, 6251–6252.
9. Kubota, H.; Kubo, A.; Takahashi, M.; Shimizu, R.; Da-te, T.; Okamura, K.; Nunami, K.; *J. Org. Chem.*, **1995**, *60*, 6776–6784.
10. Watabe, K.; Chang, S. -C.; Gil-Av, E.; Koppenhoefer, B.; *Synthesis*, **1987**, 225–228.
11. Saito, K.; Harada, K.; *Bull. Chem. Soc. Japan*, **1989**, *62*, 2562–2566.
12. For some enantioselective reduction of α-keto esters to α-hydroxy esters, see: a) Singh, V. K.; *Synthesis*, **1992**, 605–617. b) Hapiot, F.; Agbossou, F.; Morteux, A.; *Tetrahedron: Asymmetry*, **1995**, *6*, 11–14. For some diastereoselective reduction of α-keto esters derived from enantiopure alcohols, to the corresponding α-hydroxy esters, see: a) Akiyama, T.; Nishimoto, H.; Ozaki, S.; *Tetrahedron Lett.* **1991**, *32*, 1335–1338. b) Xiang, Y. B.; Snow, K.; Belley, M.; *J. Org. Chem.*, **1993**, *58*, 993–994.
13. For another enantioselective approach to α-hydroxy acids, see: Evans, D. A.; Morrissey, M. M.; Dorow, R. L.; *J. Am. Chem. Soc.*, **1985**, *107*, 4346–4348.
14. Corey, E. J.; Link, J. O.; *Tetrahedron Lett.*, **1992**, *33*, 3431–3434.
15. For reviews on dynamic kinetic resolution see: a) Noyori, R.; Tokunaga, M.; Kitamura, M.; *Bull. Chem. Soc. Jpn.*, **1995**, *68*, 36–56. b) Ward, R. S.; *Tetrahedron: Asymmetry*, **1995**, *6*, 1475–1490.
16. For a related case of dynamic kinetic resolution see: Matteson, D. S.; Man, H. W.; *J. Org. Chem.*, **1994**, *59*, 5734–5741.
17. Weast, R. C.; *Handbook of Chemistry and Physics*, 69th ed., The Chemical Rubber Publishing Co., Boca Raton, Florida, 1988–89.

18. Aldrich, *Catálogo de Química Fina*, 1996–97, Aldrich Chemical Co., Sigma-Aldrich Química, S.A., Spain.

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