Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 493–509

TETRAHEDRON: *ASYMMETRY*

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

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Received 7 December 1998; accepted 14 January 1999

Abstract

rac-α-Amino acids (*rac*-**1a**–**d**) were formally deracemized by a four-step reaction sequence: (a) protection of the amino function as the phthalimido derivative; (b) acyl chloride formation; (c) diastereoselective reaction with the chiral auxiliaries (*R*)- or (*S*)-3-hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone, (*R*)- or (*S*)-**3**; and (d) acid hydrolysis to deprotect both the ester and phthalimido functions. Diastereoselectivities of the intermediate esters **4** were good (82–96% d.e.), except for the case of **4b** (41% d.e.), the precursor of valine. The main diastereoisomer of esters **4** was (α*R*,3*S*)- or (α*S*,3*R*)-, except for **4d**: in this case, working at −78°C, the (α*R*,3*R*)-diastereoisomer was the main product, which epimerizes easily at the α-position when at room temperature. Acid hydrolysis of esters **4** directly gave the deprotected α-amino acids, with little or no epimerization at the α-position of the α-amino acid and complete recovery of the chiral auxiliary. Only (α*R*,3*R*)-**4d** on acid hydrolysis partially epimerized at the α-position. Moreover, some α-amino acids and their *N*,*N*-dibenzyl derivatives were obtained by dynamic kinetic resolution of diastereoisomeric mixtures of α-bromo esters **5** derived from the chiral auxiliaries (*R*)- or (*S*)-**3** during reaction with dibenzylamine.

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*)-**3**, and their use for the formal deracemization of α-arylpropanoic, α-substituted α-arylacetic[2,3] and α-chloro acids.[4] We also described their use in an enantioselective synthesis of α-hydroxy acids[5] and α-aryloxypropanoic acid herbicides, such as dichlorprop-P and mecoprop-P, based on the dynamic kinetic resolution of α-bromo esters derived from

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0957-4166/99/$ - see front matter
PII: S0957-4166(99)00018-X

these chiral auxiliaries on reaction with substituted phenoxides.[4,5] A key point of these transformations is the efficient recovery of the chiral auxiliary.

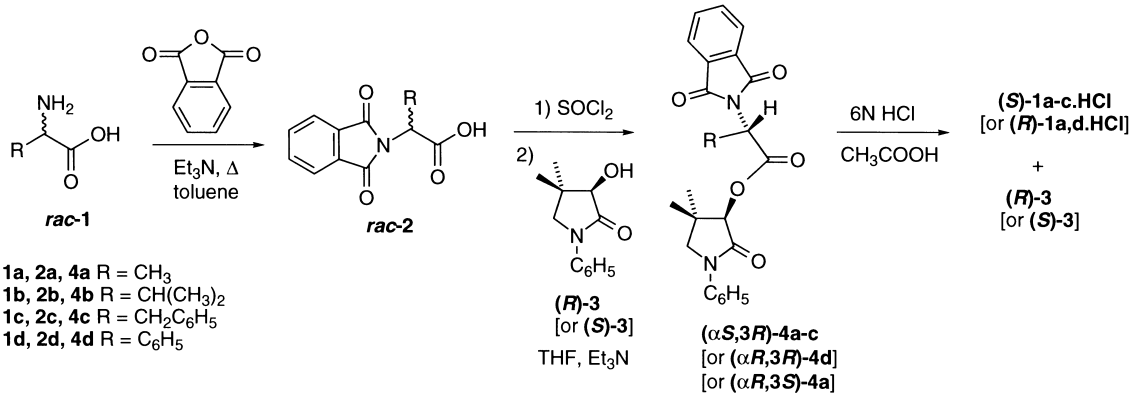
Although natural L-α-amino acids are readily available, there is an increasing demand for enantiopure non-natural α-amino acids, since they are being used as precursors for many drugs[6] and bioactive compounds,[7] as well as intermediates for the preparation of chiral auxiliaries,[8] or important chiral building blocks.[9]

Much work has been done on the asymmetric synthesis of α-amino acids, which has been the subject of many reviews.[10,11] Well-established methods for the synthesis of enantiopure α-amino acids include the enantioselective hydrogenation of α-acylamino dehydroacids;[12] the enzymatic kinetic resolution of racemic mixtures of α-amino esters;[13] the diastereoselective electrophilic amination of acid derivatives;[14,15] the nucleophilic[16–18] and radical[19] additions to C=N bonds, including the asymmetric Strecker synthesis;[20,21] and the α-amino enolate alkylations[22,23] among others. Other procedures imply the formal deracemization of racemic precursors: (a) by reaction of a prochiral ketene intermediate with an enantiopure alcohol such as D-pantolactone[24,25] or (b) by dynamic kinetic resolution[26–30] of diastereoisomeric mixtures of α-substituted acid derivatives derived from chiral auxiliaries such as the Oppolzer's sultam,[31] D-pantolactone,[32,33] imidazolidin-2-ones,[34] oxazolidin-2-ones,[35] etc.

In this paper we describe the application of the chiral auxiliaries (*R*)- and (*S*)-**3** in the preparation of enantioenriched α-amino acids from racemic precursors in two ways: (1) by formal deracemization of *rac*-α-amino acids; and (2) by dynamic kinetic resolution of *rac*-α-halo esters derived from these chiral auxiliaries.

2. Results and discussion

Firstly, we studied the formal deracemization of *rac*-α-amino acids using the chiral auxiliaries (*R*)- or (*S*)-**3** through the four-step reaction sequence shown in Scheme 1 which consists of: (a) the protection of the amino group of *rac*-α-amino acids as the corresponding phthalimido derivative, as described;[24,36] (b) the transformation of the acid function into the corresponding acyl chloride by reaction with thionyl chloride; (c) the diastereoselective reaction of acyl chloride with (*R*)- or (*S*)-**3**; and (d) the controlled acid hydrolysis of both the ester and phthalimido groups to give enantioenriched α-amino acid. The use of the phthalimido protecting group has the advantage of its ease of introduction and removal.



Scheme 1. Formal deracemization of α-amino acids, *rac*-**1a**–**d**, by diastereoselective esterification of the protected racemic acyl chloride with the chiral auxiliaries (*R*)- or (*S*)-**3**

The key step of this reaction sequence, i.e. the diastereoselective reaction of the acyl chloride and (*R*)- or (*S*)-**3**, was carried out in a similar manner to that developed by our group for the formal deracemization of α-arylpropanoic[2] and α-substituted-α-arylacetic acids,[3] which consists of the rapid mixture of the acyl chloride, the chiral auxiliary and triethylamine in the selected solvent (THF, in this case), usually at room temperature, without preformation of the intermediate ketene, in contrast with the method described by Larsen et al.,[37] in which the ketene was previously formed. Under these reaction conditions, a ketene may be formed in situ which could experience a diastereoselective addition of the enantiopure alcohol to give the corresponding diastereoisomerically enriched ester **4**. However, as we pointed out recently,[5] a dynamic kinetic resolution of acylammonium intermediates on reaction with the enantiopure alcohol could also explain the diastereoselectivity of these reactions.

Very recently, Calmes et al.[24,25] described a similar reaction using D-pantolactone as the chiral auxiliary, showing the enormous influence of the tertiary amine,[38,39] solvent and temperature on the diastereoselectivity of these reactions. They used two different procedures to carry out the diastereoselective ester formation. In one of them the ketene was previously formed at −78°C, then D-pantolactone was added, performing the reaction at this temperature or at 0°C. Under these reaction conditions, yields and diastereoselectivities were low, except for the phenylglycine derivative working at −78°C. In another procedure the ketene was not previously generated: a solution of D-pantolactone and triethylamine was added to the acyl chloride solution at the desired temperature. In this case, yields and diastereoselectivities highly increased, except for the phenylglycine derivative. These results may be indicative of a different reaction course or of the concurrence of different reaction mechanisms when the ketene is not previously formed.

As can be seen from Table 1, under our standard conditions, and working at room temperature, yields and diastereoselectivities were high for the derivatives of alanine **4a** and phenylalanine **4c**, the main diastereoisomer being (α*R*,3*S*) or (α*S*,3*R*). The yield was also high for the derivative of valine **4b**, the main diastereoisomer also (α*S*,3*R*) but the diastereoselectivity was low (41% d.e.). In the case of the phenylglycine derivative, (α*R*,3*R*)-**4d** (11% d.e.) was obtained. However, working at −78°C, (α*R*,3*R*)-**4d** was obtained in high yield and diastereoselectivity. In this case, the main diastereoisomer was different from that obtained in the other cases, as had also been observed by Calmes et al. when using D-pantolactone.[24] When the reaction of the acyl chloride derived from *rac*-**2d** and (*R*)-**3** was carried out at −78°C for 2.5 h as usual, and the reaction mixture was allowed to warm to room temperature, then stopped at different times, the d.e. of the isolated (α*R*,3*R*)-**4d** showed lower values at longer reaction times (32, 14 and 12% d.e., after 1, 3 and 18 h at r.t., respectively), demonstrating that this product epimerizes under the reaction conditions. In an attempt to improve the d.e. of (α*S*,3*R*)-**4b**, the reaction of the acyl chloride derived from *rac*-**2b** and (*R*)-**3** was carried out at −78°C. However, no reaction was observed at this temperature after 5 h. Moreover, the reaction of the acyl chloride derived from *rac*-**2a** and (*S*)-**3** using 4-(dimethylamino)pyridine (DMAP) instead of triethylamine in THF at −20°C led to (α*S*,3*S*)-**4a** (22% d.e.), showing the enormous influence of the amine on the diastereoselectivity of this reaction.[25,38,39]

Hydrolysis of the diastereoisomerically enriched esters **4a**–**c** with simultaneous cleavage of the protecting phthalimido group was performed in one step by treatment with a 10:1 mixture of 6 N HCl and acetic acid,[24] leading to the corresponding enantioenriched α-amino acid hydrochlorides **1a**–**c**·HCl with little or no epimerization. However, when this treatment was applied to ester (α*R*,3*R*)-**4d**, (*R*)-**1d**·HCl was obtained in good yield but low enantiomeric excess (55% e.e.), showing that an important degree 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. Curiously, a similar situation had not been previously observed in the hydrolysis of the corresponding D-pantolactone ester.[24] Other procedures to transform (α*R*,3*R*)-

Table 1
Yields[a] and diastereomeric excesses (d.e.s)[a] of α-phthalimido esters **4** and yields, specific rotations and approximate enantiomeric excesses (e.e.) of α-amino acid hydrochlorides **1**·HCl[b]

Entry	Starting	Starting	Reaction	α-phtalimido ester **4**			α-amino acid hydrochloride **1·HCl**			
	2	**3**	Temp.	Main diast.	yield (%)	d.e. (%)	Main enant.	yield (%)	$[\alpha]_D^{20}$	e.e. (%)
1	***rac*-2a**	**(*S*)-3**	room temp.	**(α*R*,3*S*)-4a**	>99	96	**(*R*)-1a·HCl**	94	-7.92	97
			(r.t.)		(71)	(>99)			(+8.2)	
2	***rac*-2a**	**(*R*)-3**	r.t.	**(α*S*,3*R*)-4a**	99	95	**(*S*)-1a·HCl**	95	+8.03	98
					(76)	(>99)			(+8.2)	
3[c]	***rac*-2a**	**(*S*)-3**	-20 °C	**(α*S*,3*S*)-4a**	98	22				
4	***rac*-2b**	**(*R*)-3**	r.t.	**(α*S*,3*R*)-4b**	99	41	**(*S*)-1b·HCl**	92	+5.75	40
					(92)	(39)			(+14.5)	
5	***rac*-2b**	**(*R*)-3**	-78 °C	**(α*S*,3*R*)-4b**	0	--				
6	***rac*-2c**	**(*R*)-3**	r.t.	**(α*S*,3*R*)-4c**	>99	82	**(*S*)-1c·HCl**	94	-11.4	77
					(95)	(78)			(-14.8)	
7	***rac*-2d**	**(*R*)-3**	r.t.	**(α*R*,3*R*)-4d**	99	11				
8	***rac*-2d**	**(*R*)-3**	-78 °C	**(α*R*,3*R*)-4d**	94	86	**(*R*)-1d·HCl**	98	-61.8	55
					(84)	(>99)			(-112.3)	
9	***rac*-2d**	**(*R*)-3**	-78 °C/2.5 h and 1 h r.t.	**(α*R*,3*R*)-4d**	94	32				
10	***rac*-2d**	**(*R*)-3**	-78 °C/2.5 h and 3 h r.t.	**(α*R*,3*R*)-4d**	94	14				
11	***rac*-2d**	**(*R*)-3**	-78 °C/2.5 h and 18 h r.t.	**(α*R*,3*R*)-4d**	94	12				

[a] All these reactions were carried out by the general standard procedure described in Section 3.2 at the indicated temperatures. Yields and d.e.s of α-phthalimido esters **4** correspond to crude material; values in parentheses correspond to yields or d.e.s of the crystallized (**4a**) or chromatographed (**4b–d**) products used in the hydrolysis step. The d.e.s of esters **4** were obtained by HPLC, assuming the relative areas of the peaks to be equal to their relative molar ratios.

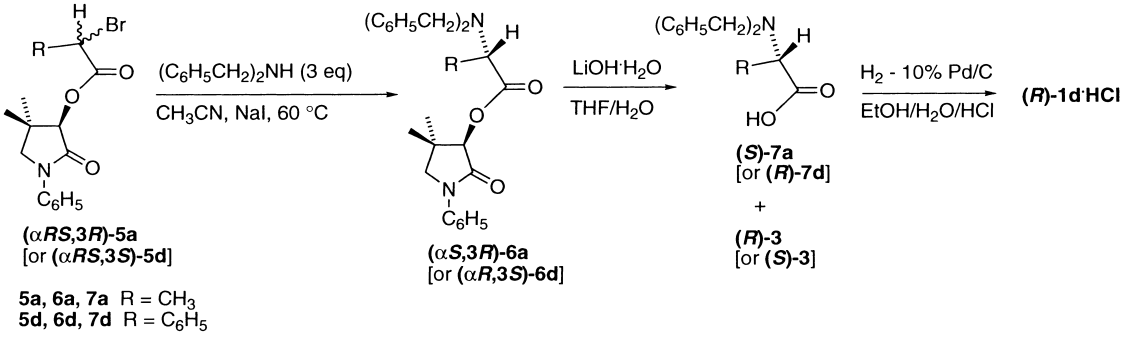
[b] Hydrolysis of the phthalimido esters **4** was carried out by reaction with a mixture of 6 N HCl (30 ml/mmol) and AcOH (3 ml/mmol). The values for the specific rotations of standard α-amino acid hydrochlorides **1**·HCl were obtained from samples prepared from the corresponding commercially available α-amino acids and are given in parentheses. The experimental values were obtained by using the same solvent and a concentration close to that used for the standard sample. In the case of (*R*)-**1a**·HCl, the given value corresponds to its enantiomer.

[c] This reaction was carried out by the standard procedure, except for the use of DMAP instead of triethylamine working at −20°C.

4d into (*R*)-**1d**·HCl gave still worse results. Attempted deprotection of the amino group by reaction with hydrazine following described procedures,[40] led to the recovery of a 1:1 mixture of (α*R*,3*R*)- and (α*S*,3*R*)-**4d**. Basic hydrolysis of the ester function with lithium hydroperoxide, before the cleavage of the protecting group, led mainly to benzoic acid (80% yield), while lithium hydroxide hydrolysis of the ester function followed by 6 N HCl/AcOH hydrolysis of the phthalimido group, did not improve the enantiomeric excess of (*R*)-**1d**·HCl.

Another approach to the preparation of enantioenriched α-amino acids (Scheme 2), was based on the dynamic kinetic resolution[26–35] of diastereoisomeric mixtures of α-bromoesters (α*RS*,3*R*)- or (α*RS*,3*S*)-**5a–d**[5] on reaction with dibenzylamine or potassium phthalimide. Firstly, we carried out a model study using dibenzylamine as the nucleophile and mixtures of α-bromoesters (α*RS*,3*RS*)-/(α*RS*,3*SR*)-**5a–d**.

The reaction of a stereoisomeric mixture of (α*RS*,3*RS*)-/(α*RS*,3*SR*)-**5a** with dibenzylamine was carried out in different solvents (DMSO, acetonitrile and THF) using either NaI (20 equiv., for reactions carried out in DMSO or acetonitrile) or tetrahexylammonium iodide (0.2 equiv., for reactions carried out in THF) as the catalyst (Scheme 2 and Table 2, entry 1). The best diastereoselectivities were attained in acetonitrile or in THF. However, the yield of the reaction carried out in acetonitrile was higher (96%). Better diastereoselectivities but lower yields were obtained in the reaction of the stereoisomeric mixture of (α*RS*,3*RS*)-/(α*RS*,3*SR*)-**5d** with dibenzylamine (Scheme 2 and Table 2, entry 4). The reaction of the stereoisomeric mixtures of (α*RS*,3*RS*)-/(α*RS*,3*SR*)-**5b** and (α*RS*,3*RS*)-/(α*RS*,3*SR*)-**5c** with dibenzylamine always gave the corresponding elimination products, (*RS*)-**8b** and (*RS*)-**8c**, no matter which solvent was used (Scheme 3 and Table 2, entries 2 and 3).



Scheme 2. Dynamic kinetic resolution of α-bromo esters (α*RS*,3*R*)-**5a** and (α*RS*,3*S*)-**5d** on reaction with dibenzylamine

The best reaction conditions [acetonitrile, 60°C, NaI (20 equiv.)] found in the reaction of the stereoisomeric mixtures of (α*RS*,3*RS*)-/(α*RS*,3*SR*)-**5a**,**d** with dibenzylamine, were applied to the dynamic kinetic

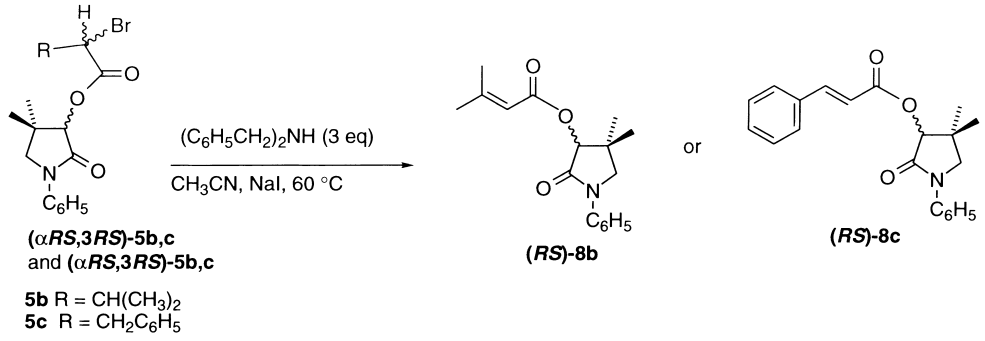
Table 2
Reaction conditions, yields[a] and diastereomeric excesses (d.e.s)[a,b] of α-dibenzylamino esters **6** and yields of esters **8** from the reaction of α-bromoesters **5** and dibenzylamine

Entry	Starting α-bromoester **5**	Reaction conditions				Reaction product		
		Solvent	T (°C)	t (h)	catalyst (eq.)	Diast.	yield (%)	d.e. (%)
1[c]	(α*RS*,3*RS*)- and (α*RS*,3*SR*)-**5a**	DMSO	60	48	NaI (20)	(α*RS*,3*SR*)-**6a**	88	80
2[c]	(α*RS*,3*RS*)- and (α*RS*,3*SR*)-**5b**	THF	reflux	48	$Hex_4N^+I^-$ (0.2)	(*RS*)-**8b**	90	---
3[c]	(α*RS*,3*RS*)- and (α*RS*,3*SR*)-**5c**	DMSO	60	48	NaI (20)	(*RS*)-**8c**	quant.	---
4[c]	(α*RS*,3*RS*)- and (α*RS*,3*SR*)-**5d**	CH_3CN	60	48	NaI (20)	(α*RS*,3*SR*)-**6d**	quant.	98
							(71)	(98)
5	(α*RS*,3*R*)-**5a**	CH_3CN	60	48	NaI (20)	(α*S*,3*R*)-**6a**	quant.	82
							(78)	(81)
6	(α*RS*,3*S*)-**5d**	CH_3CN	60	48	NaI (20)	(α*R*,3*S*)-**6d**	quant.	>99
							(67)	(>99)

[a]Yields and d.e.s of α-dibenzylamino esters **6** correspond to crude material; values in parentheses correspond to yields or d.e.s of the crystallized [(α*R*,3*S*)-**6d**] or chromatographed [(α*RS*,3*SR*)-**6d** and (α*S*,3*R*)-**6a**] products used in the hydrolysis step. The catalyst was always NaI (20 equiv.) for reactions carried out in DMSO or acetonitrile and tetrahexylammonium iodide (0.2 equiv.) for reactions carried out in THF.

[b]The d.e.s were obtained by HPLC, assuming the relative areas of the peaks to be equal to their relative molar ratios.

[c]The same products were obtained in any one of the three solvents (DMSO, THF or acetonitrile) used. Yields were somewhat higher in acetonitrile.



Scheme 3. Attempted dynamic kinetic resolution of α-bromo esters (α*RS*,3*SR*)-/(α*RS*,3*SR*)-**5b**,**c** on reaction with dibenzylamine: formation of the elimination products (*RS*)-**8b**,**c**

resolution of (α*RS*,3*R*)-**5a** and (α*RS*,3*S*)-**5d**, thus obtaining (α*S*,3*R*)-**6a** and (α*R*,3*S*)-**6d**, respectively, in good yields and d.e.s (Scheme 2 and Table 2, entries 5 and 6).

Hydrolysis of the α-dibenzylamino ester (α*S*,3*R*)-**6a** was carried out by reaction with lithium hydroxide[41] without noticeable epimerization to give the α-dibenzylamino acid (*S*)-**7a** in high yield. The sign of the specific rotation of (*S*)-**7a**[42] established its configuration and that of its precursor (α*S*,3*R*)-**6a**. The e.e. of (*S*)-**7a** could be easily increased to >99% by crystallization from a mixture of ethyl acetate/hexane. In the case of (α*R*,3*S*)-**6d**, lithium hydroxide hydrolysis gave an α-dibenzylamino acid, (*R*)-**7d**, whose configuration and e.e. could not be established since, to the best of our knowledge, it had not been previously described. However, partial epimerization during hydrolysis was evident since the specific rotation of the crude product was lower than that of the crystallized product. A higher degree of epimerization (lower specific rotation of the crude acid) was observed when hydrolysis was carried out by heating (α*R*,3*S*)-**6d** with a mixture of 2 N HCl in AcOH at 120°C for 18 h. We were not able to establish the e.e. of this product by chiral HPLC under different conditions. Hydrogenolysis of the benzyl groups of (*R*)-**7d** in a mixture of ethanol and water in the ratio of 1:1, containing an excess of HCl, 10% Pd–C as catalyst and working at 1 atm gave α-amino acid hydrochloride (*R*)-**1d**·HCl, whose specific rotation let us assign its configuration and that of its precursors, (α*R*,3*S*)-**6d** and (*R*)-**7d**. Comparison of the specific rotation of the obtained (*R*)-**1d**·HCl with that of a standard sample showed a 67% e.e., thus confirming partial epimerization during ester hydrolysis which does not preclude possible epimerization during hydrogenolysis.

When potassium phthalimide was used as the nucleophile in the dynamic kinetic resolution of the model stereoisomeric mixture of esters (α*RS*,3*RS*)-/(α*RS*,3*SR*)-**5a**, diastereoselectivities were always low. The corresponding reaction of potassium phthalimide with the stereoisomeric mixtures of (α*RS*,3*RS*)-/(α*RS*,3*SR*)-**5b** and (α*RS*,3*RS*)-/(α*RS*,3*SR*)-**5c** led mainly or exclusively to the elimination products (*RS*)-**8b** and (*RS*)-**8c** (Scheme 3), respectively, while the reaction with the stereoisomeric mixture of (α*RS*,3*RS*)-/(α*RS*,3*SR*)-**5d**, where elimination of hydrogen bromide cannot take place, led in medium yield to alcohol (*RS*)-**3** as the only isolated neutral product, showing that hydrolysis of the starting ester had taken place, probably via an elimination process through a ketene intermediate, due to the greater acidity in this case of the α-ester hydrogen atom, which is also benzylic.

After hydrolysis of esters **4** and **6**, the chiral auxiliaries (*R*)- and (*S*)-**3** were always recovered in high yield without epimerization.

The new compounds (esters **4a**–**d**, **6a**,**d** as diastereoisomeric mixtures and ester **8b** as a racemic mixture) have been fully characterized through their spectroscopic data and elemental analysis. The ^{1}H and ^{13}C NMR spectra of these compounds have been fully assigned taking into account our previous work.[1,2] The assignment of the signals of the diastereoisomeric mixtures could be easily carried out due

to their different ratio. The diastereoisomeric ratio of esters **4a**–**d** and **6a**,**d**, obtained by HPLC assuming the relative areas of both diastereoisomers to be equal to their molar ratio, were in good agreement with those obtained from the ^{1}H NMR data, through the integration of the signals of the 3-H protons for **4a**,**d** and **6a**,**d**, 4α-CH_3 protons for **4c** and C*H*N proton for **4b**. Nearly 1:1 mixtures of esters **4a**–**d** and **6a**,**d** were prepared by standard procedures (see Experimental, Sections 3.8 and 3.11) for the HPLC analysis and to facilitate the assignment of the spectroscopic data, in cases where the diastereoisomeric excesses of the diastereoselectively obtained products were high. Assignment of the configuration of the α-ester stereocenter of esters **4a**–**d** and **6a**,**d** was carried out after their hydrolysis to the corresponding α-amino acid hydrochlorides, **1a**–**d**·HCl and **7a**, of known configuration.

In conclusion, the chiral auxiliaries (*R*)- and (*S*)-**3** have shown their value for the formal deracemization of several α-amino acids, via the corresponding phthalimido derivatives. Enantiomeric excesses are mainly dependent on the bulk of the alkyl substituent at the α-stereocenter: the e.e. was high for alanine (R=Me), not so high for phenylalanine (R=benzyl), and low for valine (R=*i*-Pr). Phenylglycine is a special case since the corresponding ester **4d** epimerizes rapidly at the α-position under the reaction conditions at room temperature and thus, working at −78°C was required. Moreover, diastereoselectivity was reversed in this case, the main diastereoisomer having the (α*R*,3*R*) configuration, while for the rest of the studied cases it was (α*R*,3*S*) or (α*S*,3*R*). In addition, the enantioselective synthesis of α-amino acids based on the dynamic kinetic resolution of diastereoisomeric mixtures of α-bromoesters (α*RS*,3*R*)- or (α*RS*,3*S*)-**5** derived from the chiral auxiliaries (*R*)- or (*S*)-**3** by reaction with dibenzylamine, seems to have a limited scope due to the competitive elimination of hydrogen bromide, which depends on the acidity of the β-hydrogen atom (phenylalanine) and the steric crowding around the α-carbon atom (valine). The dynamic kinetic resolution works well for the enantioselective preparation of alanine where the steric crowding at the α-position is low and of phenylglycine, where HBr elimination cannot take place, although in this case, an important degree of epimerization takes place during hydrolysis of the ester function. According to the results of O'Meara et al.[33] using (*R*)-pantolactone, this reaction must also work for other α-amino acids having primary alkyl substituents at the α-stereocenter different from benzyl.

3. Experimental

Melting points were determined on an MFB 595010 M Gallenkamp melting point apparatus. 500 MHz ^{1}H NMR spectra were performed on a Varian VXR 500 spectrometer and 300 MHz ^{1}H and 75.4 MHz ^{13}C NMR spectra 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 related 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 nm and using column A: Chiralcel OD-H column (25×0.46 cm) containing the chiral stationary phase cellulose tris-(3,5-dimethylphenylcarbamate) or column B: a (15×0.46 cm) column, containing cellulose bis-(3,5-dichlorophenylcarbamate), covalently bonded to silica Nucleosil (100 Å–5 μm), prepared by Prof. C. Minguillón's research group. Condition A: column A, mixture of hexane:isopropanol in the ratio of 75:25 as eluent, flow 0.60 ml/min. Condition B: column 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. General procedure for the preparation of rac-α-phthalimido acyl chlorides

A solution of the *rac*-α-phthalimido acid (10 mmol), prepared by previously described procedures,[24,36] in thionyl chloride (15 ml) was heated under reflux for 15 h and concentrated in vacuo to give *rac*-α-phthalimido acyl chloride as a solid, which was used without further purification in the following step.

3.2. General procedure for the reaction of rac-α-phthalimidoacyl chlorides with (R)- or (S)-3

Solid *rac*-α-phthalimido acyl chloride (1.2 mmol) was added to a dried solution (4 Å molecular sieves, 1.5 g) of (*R*)- or (*S*)-**3** (1.0 mmol) and triethylamine (2.5 mmol) in anhydrous THF (14 ml) under an argon atmosphere, at room temperature and the mixture was magnetically stirred for 2.5 h. After adding CH_2Cl_2 (20 ml), the mixture was washed with 1 N HCl (3×20 ml) and saturated aqueous solution of $NaHCO_3$ (3×20 ml), dried with anh. Na_2SO_4, and concentrated in vacuo to give the α-phthalimidoesters **4**. Chemical yields refer to the total yield of both diastereoisomers.

3.3. (αR,3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-phthalimidopropanoate, (αR,3S)-4a

Following the above general procedure, from (*S*)-**3** (1.02 g, 5.00 mmol) and *rac*-**2a** (1.42 g, 6.00 mmol), (α*R*,3*S*)-**4a** (2.02 g, >99% yield, 96% d.e. by HPLC) was obtained as a solid. Crystallized from a mixture of hexane (30 ml) and ethyl acetate (20 ml), (α*R*,3*S*)-**4a** (1.43 g, 71% yield) showed m.p. 187–189°C, $[\alpha]_D^{20}$=−35.5 (c=1.02, $CHCl_3$), >99% d.e. by HPLC [Condition A: main diastereoisomer (α*R*,3*S*)-**4a**, r.t. 26.4 min; (α*S*,3*S*)-**4a**, r.t. 30 min, k_1'=3.9, k_2'=4.6, α=1.2, Rs=1.8]. IR (KBr) ν: 1776, 1751 and 1709 (C=O st) cm^{-1}. $C_{23}H_{22}N_2O_5$ (406.45): calcd C, 67.97%; H, 5.46%; N, 6.89%. Found: C, 67.86%; H, 5.43%; N, 6.87%. ^{1}H NMR δ: 1.18 (s, 3H, 4α-CH_3), 1.34 (s, 3H, 4β-CH_3), 1.77 (d, J=7.5 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), 5.20 (q, J=7.5 Hz, 1H, CHN), 5.44 (s, 1H, 3-H), 7.15 (tm, J=7.0 Hz, 1H, H*para N*-phenyl), 7.36 (dd, J=8.5 Hz, J′=7.0 Hz, 2H, H*meta N*-phenyl), 7.59 (dm, J=8.5 Hz, 2H, H*ortho N*-phenyl), 7.72 [m, 2H, 5(6)-H phthalimido], 7.85 [m, 2H, 4(7)-H phthalimido]. ^{13}C NMR δ: 15.4 (CH_3, CH*C*H$_3$), 21.1 (CH_3, 4α-CH_3), 24.8 (CH_3, 4β-CH_3), 37.7 (C, C4), 47.7 (CH, CHN), 57.7 (CH_2, C5), 79.4 (CH, C3), 119.5 (CH, C*ortho N*-phenyl), 123.5 [CH, C4(7) phthalimido], 125.0 (CH, C*para N*-phenyl), 128.9 (CH, C*meta N*-phenyl), 131.9 [C, C3a(7a) phthalimido], 134.1 [CH, C5(6) phthalimido], 138.9 (C, C*ipso N*-phenyl), 167.3 (C), 168.2 (C) and 169.2 (C) [C1(3) phthalimido, COO and C2].

3.4. (αS,3R)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-phthalimidopropanoate, (αS,3R)-4a

Following the above general procedure, from (*R*)-**3** (0.50 g, 2.40 mmol) and *rac*-**2a** (0.70 g, 2.90 mmol), (α*S*,3*R*)-**4a** (0.98 g, 99% yield, 95% d.e. by HPLC) was obtained as a solid. Crystallized from a mixture of hexane (25 ml) and ethyl acetate (12 ml), (α*S*,3*R*)-**4a** (0.75 g, 76% yield) showed m.p. 187–189°C, $[\alpha]_D^{20}$=+34.9 (c=1.00, $CHCl_3$), >99% d.e. by HPLC [Condition A: main diastereoisomer (α*S*,3*R*)-**4a**, r.t. 30.5 min; (α*R*,3*R*)-**4a**, r.t. 44.7 min, k_1'=4.6, k_2'=7.3, α=1.6, Rs=4.7]. $C_{23}H_{22}N_2O_5$ (406.45): calcd C, 67.97%; H, 5.46%; N, 6.89%. Found: C, 67.79%; H, 5.44%; N, 6.89%. The IR and NMR spectra are coincidental with those of its enantiomer.

3.5. (αS,3R)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-phthalimido-β-methylbutanoate, (αS,3R)-4b

Following the above general procedure, from (*R*)-**3** (0.50 g, 2.40 mmol) and *rac*-**2b** (0.78 g, 2.90 mmol), (α*S*,3*R*)-**4b** (1.05 g, 99% yield, 41% d.e. by HPLC) was obtained as an oil. After column chromatography [alumina (25 g), CH_2Cl_2], (α*S*,3*R*)-**4b** (0.98 g, 92% yield) showed $[\alpha]_D^{20}$=+3.2 (c=1.02, $CHCl_3$), 39% d.e. by HPLC [Condition A: main diastereoisomer (α*S*,3*R*)-**4b**, r.t. 23.8 min; (α*R*,3*R*)-**4b**, r.t. 40.9 min, k_1'=3.4, k_2'=6.6, α=1.9, Rs=7.1]. IR (KBr) ν: 1755 and 1719 (C=O st) cm^{-1}. $C_{25}H_{26}N_2O_5$ (434.51): calcd C, 69.11%; H, 6.04%; N, 6.45%. Found: C, 68.93%; H, 6.04%; N, 6.25%.

3.5.1. Spectroscopic data of (αS,3R)-4b obtained from the spectra of the mixture

^{1}H NMR δ: 0.96 (d, J=7.0 Hz, 3H) and 1.22 (d, J=7.0 Hz, 3H) [CH(CH_3)$_2$], 1.17 (s, 3H, 4α-CH_3), 1.32 (s, 3H, 4β-CH_3), 2.85 [d heptet, J=8.5 Hz, J′=7.0 Hz, 1H, C*H*(CH_3)$_2$], 3.49 (d, J=9.5 Hz, 1H, 5α-H), 3.59 (d, J=9.5 Hz, 1H, 5β-H), 4.76 (d, J=8.5 Hz, 1H, CHN), 5.436 (s, 1H, 3-H), 7.13 (tm, J=7.5 Hz, 1H, H*para N*-phenyl), 7.33 (dd, J=8.5 Hz, J=7.5 Hz, 2H, H*meta N*-phenyl), 7.56 (dm, J=8.5 Hz, 2H, H*ortho N*-phenyl), 7.72 [m, 2H, 5(6)-H phthalimido], 7.86 [m, 2H, 4(7)-H phthalimido]. ^{13}C NMR δ: 19.5 (CH_3) and 21.1 (CH_3) [CH(*C*H_3)$_2$], 21.2 (CH_3, 4α-CH_3), 24.7 (CH_3, 4β-CH_3), 28.4 [CH, *C*H(CH_3)$_2$], 37.6 (C, C4), 57.6 (CH_2, C5), 58.0 (CH, CHN), 79.3 (CH, C3), 119.4 (CH, C*ortho N*-phenyl), 123.5 [CH, C4(7) phthalimido], 124.8 (CH, C*para N*-phenyl), 128.9 (CH, C*meta N*-phenyl), 131.7 [C, C3a(7a) phthalimido], 134.1 [CH, C5(6) phthalimido], 138.9 (C, C*ipso N*-phenyl), 167.62 (C), 168.1 (C) and 168.3 (C) [C1(3) phthalimido, COO and C2].

3.6. (αS,3R)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-phthalimido-β-phenylpropanoate, (αS,3R)-4c

Following the above general procedure, from (*R*)-**3** (1.02 g, 5.00 mmol), and *rac*-**2c** (1.90 g, 6.00 mmol), (α*S*,3*R*)-**4c** (2.40 g, quantitative yield, 82% d.e. by HPLC) was obtained as an oil. After column chromatography [silica gel (80 g), CH_2Cl_2], (α*S*,3*R*)-**4c** (2.29 g, 95% yield) showed $[\alpha]_D^{20}$=−65.1 (c=1.00, $CHCl_3$), 78% d.e. by HPLC [Condition A: main diastereoisomer (α*S*,3*R*)-**4c**, r.t. 38.3 min; (α*R*,3*R*)-**4c**, r.t. 64.7 min, k_1'=6.1, k_2'=11.0, α=1.8, Rs=5.6]. IR (KBr) ν: 1781, 1756 and 1716 (C=O st) cm^{-1}. $C_{29}H_{26}N_2O_5$ (482.55): calcd C, 72.18%; H, 5.43%; N, 5.81%. Found: C, 72.31%; H, 5.64%; N, 5.52%.

3.6.1. Spectroscopic data of (αS,3R)-4c obtained from the spectra of the mixture

^{1}H NMR δ: 1.20 (s, 3H, 4α-CH_3), 1.36 (s, 3H, 4β-CH_3), 3.53 (d, J=9.5 Hz, 1H, 5α-H), 3.616 (dd, J=11.5 Hz, J′=14.0 Hz, 1H) and 3.68 (dd, J=5.0 Hz, J′=14.0 Hz, 1H) (Ar–CH_2), 3.623 (d, J=9.5 Hz, 1H, 5β-H), 5.38 (dd, J=11.5 Hz, J′=5.0 Hz, 1H, CHN), 5.48 (s, 1H, 3-H), 7.14–7.18 (complex signal, 6H, H*para N*-phenyl and Ar–H *C*-phenyl), 7.36 (dd, J=7.5 Hz, J′=8.5 Hz, 2H, H*meta N*-phenyl), 7.60 (dm, J=8.5 Hz, 2H, H*ortho N*-phenyl), 7.65 [m, 2H, 5(6)-H phthalimido], 7.75 [m, 2H, 4(7)-H phthalimido]. ^{13}C NMR δ: 21.2 (CH_3, 4α-CH_3), 24.9 (CH_3, 4β-CH_3), 34.5 (CH_2, Ar–CH_2), 37.7 (C, C4), 53.4 (CH, CHN), 57.7 (CH_2, C5), 79.6 (CH, C3), 119.5 (CH, C*ortho N*-phenyl), 123.4 [CH, C4(7) phthalimido], 125.0 (CH, C*para N*-phenyl), 126.9 (CH, C*para C*-phenyl), 128.6 (CH), 128.8 (CH) and 129.0 (CH) [C*ortho C*-phenyl, C*meta N*-phenyl and C*meta C*-phenyl), 131.5 [C, C3a(7a) phthalimido], 134.0 [CH, C5(6) phthalimido], 136.3 (C, C*ipso C*-phenyl), 138.9 (C, C*ipso N*-phenyl), 167.3 (C), 168.1 (C), 168.2 (C) [C1(3) phthalimido, COO and C2].

3.7. (αR,3R)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-phthalimido-α-phenylacetate, (αR,3R)-**4d**

Following the above general procedure except for the temperature (−78°C), from (*R*)-**3** (0.50 g, 2.40 mmol) and *rac*-**2d** (0.88 g, 2.91 mmol), (α*R*,3*R*)-**4d** (1.07 g, 94% yield, 86% d.e. by HPLC) was obtained as an oil. After column chromatography [silica gel (50 g), CH_2Cl_2], (α*R*,3*R*)-**4d** (0.96 g, 84% yield) showed $[\alpha]_D^{20}$=+3.5 (c=0.57, $CHCl_3$), >99% d.e. by HPLC [Condition A: main diastereoisomer (α*R*,3*R*)-**4d**, r.t. 67.5 min; (α*S*,3*R*)-**4d**, r.t. 39.6 min, k_1'=6.3, k_2'=11.5, α=1.8, Rs=5.1]. IR (KBr) ν: 1760, 1772 and 1718 (C=O st) cm^{-1}. $C_{28}H_{24}N_2O_5 \cdot 0.5H_2O$ (477.53): calcd C, 70.43%; H, 5.28%; N, 5.87%. Found: C, 70.50%; H, 5.16%; N, 5.97%.

3.7.1. Spectroscopic data of (αR,3R)-**4d** obtained from the spectra of the mixture

^{1}H NMR δ: 0.93 (s, 3H, 4α-CH_3), 1.32 (s, 3H, 4β-CH_3), 3.43 (d, J=9.5 Hz, 1H, 5α-H), 3.59 (d, J=9.5 Hz, 1H, 5β-H), 5.54 (s, 1H, 3-H), 6.20 (s, 1H, CHN), 7.13 (tm, J=7.5 Hz, 1H, H*para N*-phenyl), 7.30–7.38 (complex signal, 5H, H*meta N*-phenyl and H*meta* and H*para C*-phenyl), 7.56 (dm, J=8.5 Hz, 2H, H*ortho C*-phenyl), 7.60 (dm, J=8.5 Hz, 2H, H*ortho N*-phenyl), 7.71 [m, 2H, 5(6)-H phthalimido], 7.85 [m, 2H, 4(7)-H phthalimido]. ^{13}C NMR δ: 20.9 (CH_3, 4α-CH_3), 24.4 (CH_3, 4β-CH_3), 37.4 (C, C4), 55.5 (CH, CHN), 57.5 (CH_2, C5), 79.6 (CH, C3), 119.4 (CH, C*ortho N*-phenyl), 123.6 [CH, C4(7) phthalimido], 124.9 (CH, C*para N*-phenyl), 128.6 (CH), 128.7 (CH), 128.9 (CH) 129.7 (CH) [C*ortho C*-phenyl, C*para C*-phenyl, C*meta N*-phenyl and C*meta C*-phenyl), 131.7 [C, C3a(7a) phthalimido], 134.1 (C, C*ipso C*-phenyl), 134.3 [CH, C5(6) phthalimido], 138.9 (C, C*ipso N*-phenyl), 166.9 (C), 167.5 (C), 168.0 (C) [C1(3) phthalimido, COO and C2].

3.8. General procedure for the preparation of the diastereoisomeric mixtures of α-phthalimido esters **4**

A mixture of *rac*-**2** (1.0 mmol), dicyclohexylcarbodiimide (DCC, 1.0 mmol), DMAP (0.05 mmol) and (*R*)- or (*S*)-**3** (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 a saturated aqueous solution of citric acid (3×8 ml) and saturated aqueous $NaHCO_3$ (3×8 ml), dried with anh. Na_2SO_4, concentrated in vacuo and the residue was submitted to column chromatography [silica gel (20 g), CH_2Cl_2], to give pure esters **4** as diastereoisomeric mixtures.

3.8.1. (αRS,3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-phthalimidopropanoate, (αRS,3S)-**4a**

Following the above general procedure, from *rac*-**2a** (0.11 g, 0.5 mmol) and (*S*)-**3** (0.10 g, 0.5 mmol), (α*RS*,3*S*)-**4a** (0.20 g, 99% yield) was obtained. For the spectroscopic data of (α*R*,3*S*)-**4a** see Section 3.3.

3.8.1.1. *Significant spectroscopic data of (αS,3S)-**4a**, obtained from the spectra of the mixture.* ^{1}H NMR δ: 0.89 (s, 3H, 4α-CH_3), 1.25 (s, 3H, 4β-CH_3), 1.74 (d, J=7.5 Hz, 3H, CH*C*H_3), 3.41 (d, J=9.5 Hz, 1H, 5α-H), 3.56 (d, J=9.5 Hz, 1H, 5β-H), 5.16 (q, J=7.5 Hz, 1H, CHN), 5.430 (s, 1H, 3-H). ^{13}C NMR δ: 15.3 (CH_3, CH*C*H_3), 20.8 (CH_3, 4α-CH_3), 24.4 (CH_3, 4β-CH_3), 37.3 (C, C4), 47.4 (CH, CHN), 57.5 (CH_2, C5), 79.1 (CH, C3).

3.8.2. (αRS,3R)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-phthalimidopropanoate, (αRS,3R)-**4a**

Following the above general procedure, from *rac*-**2a** (0.11 g, 0.5 mmol) and (*R*)-**3** (0.10 g, 0.5 mmol), (α*RS*,3*R*)-**4a** (0.19 g, 95% yield) was obtained. The ^{1}H and ^{13}C NMR spectra are coincidental with those of (α*RS*,3*S*)-**4a**.

*3.8.3. (αRS,3R)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-phthalimido-β-methylbutanoate, (αRS,3R)-**4b***

Following the above general procedure, from *rac*-**2b** (0.12 g, 0.5 mmol) and (*R*)-**3** (0.10 g, 0.5 mmol), (α*RS*,3*R*)-**4b** (0.22 g, 99% yield) was obtained. For the spectroscopic data of (α*S*,3*R*)-**4b** see Section 3.5.1.

3.8.3.1. *Significant spectroscopic data of (αR,3R)-**4b**, obtained from the spectra of the mixture.* ^{1}H NMR δ: 0.85 (s, 3H, 4α-CH_3), 0.95 (d, J=7.0 Hz, 3H) and 1.20 (d, J=7.0 Hz, 3H) [CH(CH_3)$_2$], 1.22 (s, 3H, 4β-CH_3), 2.83 (d heptet, J=8.5 Hz, J=7.0 Hz, 1H [C*H*(CH_3)$_2$], 3.40 (d, J=9.5 Hz, 1H, 5α-H), 3.55 (d, J=9.5 Hz, 1H, 5β-H), 4.78 (d, J=8.5 Hz, 1H, CHN), 5.438 (s, 1H, 3-H). ^{13}C NMR δ: 19.3 (CH_3) and 20.8 (CH_3) [CH(*C*H_3)$_2$], 21.2 (CH_3, 4α-CH_3), 24.3 (CH_3, 4β-CH_3), 28.8 [CH, *C*H(CH_3)$_2$], 37.3 (C, C4), 57.4 (CH_2, C5), 58.0 (CH, *C*HN), 78.8 (CH, C3).

*3.8.4. (αRS,3R)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-phthalimido-β-phenylpropanoate, (αRS,3R)-**4c***

Following the above general procedure, from *rac*-**2c** (0.15 g, 0.5 mmol) and (*R*)-**3** (0.10 g, 0.5 mmol), (α*RS*,3*R*)-**4c** (0.21 g, 88% yield) was obtained. For the spectroscopic data of (α*S*,3*R*)-**4c** see Section 3.6.1.

3.8.4.1. *Significant spectroscopic data of (αR,3R)-**4c**, obtained from the spectra of the mixture.* ^{1}H NMR δ: 0.89 (s, 3H, 4α-CH_3), 1.27 (s, 3H, 4β-CH_3), 3.42 (d, J=9.5 Hz, 1H, 5α-H), 3.57 (d, J=9.5 Hz, 1H, 5β-H), 3.58 (dd, J=14.0 Hz, J′=11.5 Hz, 1H), 3.67 (dd, J=14.0 Hz, J′=5.5 Hz, 1H) (Ar–CH_2), 5.34 (dd, J=11.0 Hz, J′=5.5 Hz, 1H, CHN), 5.46 (s, 1H, 3-H). ^{13}C NMR δ: 20.7 (CH_3, 4α-CH_3), 24.4 (CH_3, 4β-CH_3), 34.8 (CH_2, Ar–CH_2), 37.2 (C, C4), 53.0 (CH, CHN), 57.4 (CH_2, C5), 79.3 (CH, C3).

*3.8.5. (αRS,3R)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-phthalimido-α-phenylacetate, (αRS,3R)-**4d***

Following the above general procedure, from *rac*-**2d** (0.14 g, 0.5 mmol) and (*R*)-**3** (0.10 g, 0.5 mmol), (α*RS*,3*R*)-**4d** (0.23 g, 98% yield) was obtained. For the spectroscopic data of (α*R*,3*R*)-**4d** see Section 3.7.1.

3.8.5.1. *Significant spectroscopic data of (αS,3R)-**4d**, obtained from the spectra of the mixture.* ^{1}H NMR δ: 0.88 (s, 3H, 4α-CH_3), 1.33 (s, 3H, 4β-CH_3), 3.42 (d, J=9.5 Hz, 1H, 5α-H), 3.57 (d, J=9.5 Hz, 1H, 5β-H), 5.50 (s, 1H, 3-H), 6.24 (s, 1H, CHN). ^{13}C NMR δ: 20.8 (CH_3, 4α-CH_3), 24.2 (CH_3, 4β-CH_3), 37.3 (C, C4), 56.1 (CH, CHN), 57.4 (CH_2, C5), 79.6 (CH, C3).

*3.9. General procedure for the hydrolysis of α-phthalimidoesters **4***

A mixture of the α-phthalimidoester **4** (1.0 mmol), acetic acid (3.0 ml), and 6 N HCl (30 ml) was heated at 120°C (bath temperature) till completion of the hydrolysis (4 h), following the reaction by thin layer chromatography (TLC). The mixture was allowed to cool to room temperature and the volatile product distilled off at reduced pressure. Water (30 ml) was added to the residue and extracted with ethyl acetate (3×30 ml). The aqueous layer was concentrated in vacuo to give (*R*)- or (*S*)-**1**·HCl. The combined organic layers were dried with anh. Na_2SO_4 and concentrated in vacuo. The residue was taken up in CH_2Cl_2 (10 ml) and filtered. The filtrate was concentrated in vacuo to give (*R*)- or (*S*)-**3**.

*3.9.1. (S)-α-Aminopropanoic acid hydrochloride (L-alanine hydrochloride), (S)-**1a**·HCl*

From (α*S*,3*R*)-**4a** (0.60 g, 1.48 mmol, >99% d.e. by HPLC), (*S*)-**1a**·HCl (0.18 g, 95% yield) was obtained as a solid, m.p. 207–209°C (dec.), $[\alpha]_D^{20}$=+8.03 (c=1.01, H_2O), approx. 98% o.p. A standard sample of (*S*)-**1a**·HCl, obtained from L-alanine (Fluka), showed $[\alpha]_D^{20}$=+8.2 (c=1.02, H_2O).

*3.9.2. (R)-α-Aminopropanoic acid hydrochloride (D-alanine hydrochloride), (R)-**1a**·HCl*

From (α*R*,3*S*)-**4a** (1.00 g, 2.46 mmol, >99% d.e. by HPLC), (*R*)-**1a**·HCl (0.29 g, 94% yield) was obtained as a solid, m.p. 206–208°C (dec.), $[\alpha]_D^{20}$=−7.92 (c=1.00, H_2O), approx. 97% o.p.

*3.9.3. (S)-α-Amino-β-methylbutanoic acid hydrochloride (L-valine hydrochloride), (S)-**1b**·HCl*

From (α*S*,3*R*)-**4b** (0.37 g, 0.85 mmol, 39% d.e. by HPLC), (*S*)-**1b**·HCl (0.12 g, 92% yield) was obtained as a solid, m.p. 228–230°C (dec.), $[\alpha]_D^{20}$=+5.75 (c=1.04, H_2O), approx. 40% o.p. A standard sample of (*S*)-**1b**·HCl, obtained from L-valine (Fluka), showed $[\alpha]_D^{20}$=+14.5 (c=1.01, H_2O).

*3.9.4. (S)-α-Amino-β-phenylpropanoic acid hydrochloride (L-phenylalanine hydrochloride), (S)-**1c**·HCl*

From (α*S*,3*R*)-**4c** (0.85 g, 1.76 mmol, 78% d.e. by HPLC), (*S*)-**1c**·HCl (0.33 g, 94% yield) was obtained as a solid, m.p. 229–231°C (dec.), $[\alpha]_D^{20}$=−11.4 (c=0.98, H_2O), approx. 77% o.p. A standard sample of (*S*)-**1c**·HCl, obtained from L-phenylalanine (Sigma), showed $[\alpha]_D^{20}$=−14.8 (c=1.01, H_2O).

*3.9.5. (R)-α-Amino-α-phenylacetic acid hydrochloride (D-phenylglycine hydrochloride), (R)-**1d**·HCl*

From (α*R*,3*R*)-**4d** (0.70 g, 1.50 mmol, >99% d.e. by HPLC), (*R*)-**1d**·HCl (0.27 g, 98% yield) was obtained as a solid, m.p. 254–256°C (dec.), $[\alpha]_D^{20}$=−61.1 (c=1.15, H_2O), approx. 54% o.p. A standard sample of (*R*)-**1d**·HCl, obtained from D-phenylglycine (Fluka), showed $[\alpha]_D^{20}$=−112.3 (c=1.01, H_2O).

*3.10. General procedure for the reaction of α-bromoesters **5** with dibenzylamine*

A mixture of α-bromoester **5**[5] (1.0 mmol), dibenzylamine (3.0 mmol) and sodium iodide (20 mmol) in anh. acetonitrile (60 ml) was heated under reflux in an argon atmosphere for 48 h. The mixture was concentrated in vacuo, CH_2Cl_2 (100 ml) was added to the residue and the solution was washed with 5% aqueous citric acid solution (3×30 ml) and saturated aqueous $NaHCO_3$ solution (3×30 ml). The organic layer was dried with anh. Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography [alumina, CH_2Cl_2] or by crystallization.

*3.10.1. (αS,3R)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-(N,N-dibenzylamino)propanoate, (αS,3R)-**6a***

Following the above general procedure, from (α*RS*,3*R*)-**5a** (1.70 g, 5.00 mmol), (α*S*,3*R*)-**6a** (2.79 g, 82% d.e. by HPLC) was obtained as a crude product which after purification by column chromatography [alumina (50 g), CH_2Cl_2] gave analytical grade oily (α*S*,3*R*)-**6a** [1.77 g, 78% yield, 81% d.e. by HPLC, Condition A: main diastereoisomer (α*S*,3*R*)-**6a**, r.t. 13.1 min; (α*R*,3*R*)-**6a**, r.t. 21.1 min, k_1'=1.4, k_2'=2.9, α=2.1, Rs=7.3]. $[\alpha]_D^{20}$=−54.7 (c=1.07, $CHCl_3$). IR (NaCl) ν: 1737 and 1716 (C=O st) cm^{-1}. $C_{29}H_{32}N_2O_3$ (456.60): calcd C, 76.28%; H, 7.07%; N, 6.14%. Found: C, 76.21%; H, 7.13%; N, 6.07%.

Main diastereoisomer: ^{1}H NMR δ: 1.16 (s, 3H, 4α-CH_3), 1.29 (s, 3H, 4β-CH_3), 1.39 (d, J=7.0 Hz, 3H, C*H*$_3$CH), 3.55 (d, J=9.5 Hz, 1H, 5α-H), 3.63 (d, J=9.5 Hz, 1H, 5β-H), 3.65 (q, J=7.0 Hz, 1H, CHN), 3.79 (d, J=14.0 Hz, 2H) and 3.89 (d, J=14.0 Hz, 2H) (2CH_2 *N*-benzyl), 5.50 (s, 1H, 3-H), 7.17 (tm, J=7.5 Hz, 1H, H*para N*-phenyl), 7.20 (tm, J=7.5 Hz, 2H, H*para N*-benzyl), 7.28 (tm, J=7.5 Hz, 4H,

H*meta N*-benzyl), 7.38 (dd, J=7.5 Hz, J′=8.5 Hz, 2H, H*meta N*-phenyl), 7.41 (broad d, J=7.5 Hz, 4H, H*ortho N*-benzyl), 7.64 (dm, J=8.5 Hz, 2H, H*ortho N*-phenyl). ^{13}C NMR δ: 15.7 (CH_3, *C*H_3CH), 21.4 (CH_3, 4α-CH_3), 24.7 (CH_3, 4β-CH_3), 37.2 (C, C4), 54.1 (CH_2, *N*-benzyl), 55.9 (CH, CHN), 57.7 (CH_2, C5), 78.1 (CH, C3), 119.5 (CH, C*ortho N*-phenyl), 124.9 (CH, C*para N*-phenyl), 126.8 (CH, C*para N*-benzyl), 128.1 (CH, C*ortho N*-benzyl), 128.7 (CH, C*meta N*-benzyl), 129.0 (CH, C*meta N*-phenyl), 139.1 (C, C*ipso N*-phenyl), 139.9 (C, C*ipso N*-benzyl), 168.8 (C, C2), 172.7 (C, COO).

*3.10.2. (*RS*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl β-methyl-α-butenoate, (*RS*)-**8b***

Following the above general procedure, from a mixture of (α*RS*,3*RS*)-/(α*RS*,3*SR*)-**5b** (0.18 g, 0.49 mmol) and after purification by column chromatography [silica gel (15 g), CH_2Cl_2], (*RS*)-**8b** (0.16 g, 90% yield) was isolated as a solid, m.p. 71–73°C (ethyl acetate/hexane). IR (NaCl) ν: 1713 (C=O st), 1648 (C=C st) cm^{-1}. $C_{17}H_{21}NO_3$ (287.37): calcd C, 71.05%; H, 7.37%; N, 4.87%. Found: C, 70.89%; H, 7.34%; N, 4.87%. ^{1}H NMR (300 MHz) δ: 1.13 (s, 3H, 4α-CH_3), 1.31 (s, 3H, 4β-CH_3), 1.94 (d, J=1.3 Hz, 3H, CH=C–C*H*$_3$-*anti*), 2.22 (d, J=1.2 Hz, 3H, CH=C–C*H*$_3$-*syn*), 3.51 (d, J=9.5 Hz, 1H, 5α-H), 3.62 (d, J=9.5 Hz, 1H, 5β-H), 5.45 (s, 1H, 3-H), 5.85 (m, 1H, α-H), 7.16 (tm, J=7.5 Hz, 1H, H*para N*-phenyl), 7.38 (dd, J=8.5 Hz, J′=7.5 Hz, 2H, H*meta N*-phenyl), 7.64 (dm, J=8.5 Hz, 2H, H*ortho N*-phenyl). ^{13}C NMR δ: 20.5 (CH_3, CH=C*C*H$_3$-*syn*), 21.2 (CH_3, 4α-CH_3), 24.9 (CH_3, 4β-CH_3), 27.5 (CH_3, CH=C*C*H$_3$-*anti*), 37.4 (C, C4), 57.7 (CH_2, C5), 77.3 (CH, C3), 115.1 (CH, Cα) 119.4 (CH, C*ortho N*-phenyl), 124.7 (CH, C*para N*-phenyl), 128.9 (CH, C*meta N*-phenyl), 139.1 (C, C*ipso N*-phenyl), 158.9 (C, Cβ), 165.5 (C, COO), 169.4 (C, C2).

*3.10.3. (*RS*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl cinnamate, (*RS*)-**8c***

Following the above general procedure, from (α*RS*,3*RS*)-/(α*RS*,3*SR*)-**5c** (0.42 g, 1.01 mmol), and after purification by column chromatography [silica gel (20 g), CH_2Cl_2], (*RS*)-**8c** (0.34 g, >99% yield) was isolated as a solid.[5]

*3.10.4. (*αR,*3*S*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-(*N,N*-dibenzylamino)-α-phenylacetate, (*αR,*3*S*)-**6d***

Following the above general procedure, from (α*RS*,3*S*)-**5d** (2.40 g, 5.97 mmol), (α*S*,3*R*)-**6d** (3.89 g, >99% d.e. by HPLC) was obtained as a crude product which, after purification by crystallization [ethyl acetate (70 ml)], gave analytical grade (α*R*,3*S*)-**6d** [2.08 g, 67% yield, >99% d.e. by HPLC, Condition B: main diastereoisomer (α*R*,3*S*)-**6d**, r.t. 25.4 min; (α*S*,3*S*)-**6d**, 35.9 min, k_1'=1.5, k_2'=2.7, α=1.8, Rs=7.8], m.p. 181–183°C (ethyl acetate), $[\alpha]_D^{20}$=−13.4 (c=1.19, $CHCl_3$). IR (KBr) ν: 1738 and 1708 (C=O st) cm^{-1}. $C_{34}H_{34}N_2O_3$ (518.68): calcd. C, 78.73%; H, 6.61%; N, 5.40%. Found: C, 79.01%; H, 6.70%; N, 5.44%. ^{1}H NMR δ: 0.99 (s, 3H, 4α-CH_3), 1.28 (s, 3H, 4β-CH_3), 3.50 (d, J=9.5 Hz, 1H, 5α-H), 3.63 (d, J=9.5 Hz, 1H, 5β-H), 3.83 (s, 4H, 2CH_2 *N*-benzyl), 4.75 (s, 1H, CHN), 5.62 (s, 1H, 3-H), 7.17 (tm, J=7.5 Hz, 1H, H*para N*-phenyl), 7.20 (tm, J=7.0 Hz, 2H, H*para N*-benzyl), 7.26–7.44 (complex signal, 15H, H*ortho N*-benzyl, H*ortho C*-phenyl, H*para C*-phenyl, H*meta N*-phenyl, H*meta N*-benzyl and H*meta C*-phenyl), 7.64 (dm, J=8.5 Hz, 2H, H*ortho N*-phenyl). ^{13}C NMR δ: 21.2 (CH_3, 4α-CH_3), 24.7 (CH_3, 4β-CH_3), 37.2 (C, C4), 54.0 (CH_2, *N*-benzyl), 57.7 (CH_2, C5), 65.5 (CH, CHN), 78.2 (CH, C3), 119.5 (CH, C*ortho N*-phenyl), 124.9 (CH, C*para N*-phenyl), 126.9 (CH, C*para N*-benzyl), 127.8 (CH, C*para C*-phenyl), 128.2 (CH, C*ortho N*-benzyl), 128.3 (CH), 128.7 (CH) and 128.97 (CH) (C*ortho C*-phenyl, C*meta C*-phenyl, C*meta N*-phenyl), 129.01 (CH, C*meta N*-benzyl), 136.6 (C, C*ipso C*-phenyl), 139.0 (C, C*ipso N*-phenyl), 139.4 (C, C*ipso N*-benzyl), 168.6 (C, C2), 171.1 (C, COO).

*3.11. Procedure for the preparation of diastereoisomeric mixtures of α-(N,N-dibenzylamino) esters (αRS,3R)-**6a** and (αRS,3S)-**6d***

Diastereoisomeric mixtures of α-(*N*,*N*-dibenzylamino) esters, (α*RS*,3*R*)-**6a** and (α*RS*,3*S*)-**6d**, in a ratio close to 1:1, were prepared from mixtures of α-bromo esters (α*RS*,3*R*)-**5a** or (α*RS*,3*S*)-**5d** by a variation of the general procedure given in Section 3.10, in which sodium iodide was not added, toluene was used as the solvent, and the reaction was carried out at the reflux temperature.

*3.11.1. (αRS,3R)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-(N,N-dibenzylamino)propanoate, (αRS,3R)-**6a***

From a mixture of (α*RS*,3*R*)-**5a** (340 mg, 1.0 mmol), (α*RS*,3*R*)-**6a** (410 mg, 91% yield) was obtained. The spectroscopic data of (α*S*,3*R*)-**6a** were described in Section 3.10.1.

3.11.1.1. *Significant spectroscopic data of (αR,3R)-**6a**, obtained from the spectra of the mixture.* ^{1}H NMR δ: 1.24 (s, 3H, 4α-CH_3), 1.34 (s, 3H, 4β-CH_3), 1.43 (d, J=7.5 Hz, 3H, C*H*$_3$CH), 3.53 (d, J=9.5 Hz, 1H, 5α-H), 3.629 (d, J=9.5 Hz, 1H, 5β-H), 3.68 (q, J=7.0 Hz, 1H, CHN), 3.74 (d, J=14.0 Hz, 2H) and 3.91 (d, J=14.0 Hz, 2H) (2C*H*$_2$ *N*-benzyl), 5.47 (s, 1H, 3-H). ^{13}C NMR δ: 15.4 (CH_3, *C*H_3CH), 21.5 (CH_3, 4α-CH_3), 24.8 (CH_3, 4β-CH_3), 37.2 (C, C4), 54.4 (CH_2, *N*-benzyl), 56.4 (CH, CHN), 57.74 (CH_2, C5), 78.1 (CH, C3).

*3.11.2. (αRS,3S)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl α-(N,N-dibenzylamino)-α-phenylacetate, (αRS,3S)-**6d***

From a mixture of (α*RS*,3*S*)-**5d** (300 mg, 0.8 mmol), (α*RS*,3*S*)-**6d** (360 mg, 92% yield) was obtained. The spectroscopic data of (α*R*,3*S*)-**6d** were described in Section 3.10.4.

3.11.2.1. *Significant spectroscopic data of (αS,3S)-**6d**, obtained from the spectra of the mixture.* ^{1}H NMR δ: 1.09 (s, 3H, 4α-CH_3), 1.39 (s, 3H, 4β-CH_3), 3.51 (d, J=9.5 Hz, 1H, 5α-H), 3.65 (d, J=9.5 Hz, 1H, 5β-H), 3.80 (d, J=14.5 Hz, 2H) and 3.90 (d, J=14.5 Hz, 2H) (2CH_2 *N*-benzyl), 4.81 (s, 1H, α-H), 5.64 (s, 1H, 3-H). ^{13}C NMR δ: 21.4 (CH_3, 4α-CH_3), 24.8 (CH_3, 4β-CH_3), 37.2 (C, C4), 54.2 (CH_2, *N*-benzyl), 57.7 (CH_2, C5), 65.7 (CH, Cα), 78.3 (CH, C3).

*3.12. General procedure for the reaction of α-bromo esters **5** with potassium phthalimide*

A mixture of α-bromo ester **5** (1.0 mmol), potassium phthalimide (1.0 mmol) and sodium iodide (20 mmol) in acetonitrile (80 ml) was heated at 60°C in an argon atmosphere for 48 h. The mixture was concentrated in vacuo, CH_2Cl_2 (100 ml) was added to the residue and the solution was then washed with H_2O (3×30 ml). The organic layer was dried with anh. Na_2SO_4 and concentrated in vacuo and the residue purified by column chromatography [silica gel (20 g), CH_2Cl_2]. A similar procedure was used for the reactions carried out in DMSO as solvent. For the reactions carried out in THF, tetrahexylammonium iodide (0.2 mmol) was used as a catalyst instead of sodium iodide.

*3.13. General procedure for the hydrolysis of α-(N,N-dibenzylamino) esters **6***

Solid LiOH·H_2O (1.5 mmol) was added to a solution of α-(*N*,*N*-dibenzylamino) ester **6** (1.0 mmol) in a mixture of THF (20 ml) and water (5 ml), and the mixture magnetically stirred at room temperature

until completion of the hydrolysis (3 days), following the reaction by thin layer chromatography (TLC). The mixture was concentrated in vacuo, 0.5 N NaOH (30 ml) was added to the residue and then the mixture was extracted with CH_2Cl_2 (2×10 ml).

Work-up A [for (α*S*,3*R*)-**6a**]: the combined organic layers were dried with anh. Na_2SO_4 and concentrated in vacuo to give (*R*)-**3**. The aqueous layer was made acidic with acetic acid and extracted with CH_2Cl_2 (5×20 ml). The combined organic layers were dried with anh. Na_2SO_4, concentrated in vacuo and dried for 8 h at 60°C/1 torr to give (*S*)-**7a**.

Work-up B [for (α*R*,3*S*)-**6d**]: the combined organic layers were dried with anh. Na_2SO_4 and concentrated in vacuo to give a mixture of (*S*)-**3** and (*R*)-**7d**. Column chromatography [alumina (7 g)] of this mixture gave (*S*)-**3** on elution with a mixture of CH_2Cl_2/methanol in the ratio of 99.5:0.5, and (*R*)-**7d** on elution with a mixture of CH_2Cl_2:methanol:acetic acid in the ratio of 99:0.5:0.5.

*3.13.1. (S)-α-(*N,N-*Dibenzylamino)propanoic acid, (S)-**7a***

From (α*S*,3*R*)-**6a** (603 mg, 1.30 mmol, 81% d.e.), following the above reaction procedure and work-up A, (*S*)-**7a** [334 mg, 94% yield, $[\alpha]_D^{20}$=−34.5 (c=2.01, methanol)] was obtained as a solid, which was crystallized from a mixture of ethyl acetate (2 ml) and hexane (15 ml) to give (*S*)-**7a** (207 mg, 59% yield), m.p. 84–86°C, $[\alpha]_D^{20}$=−44.9 (c=2.00, methanol) [described in Velluz et al.[42] $[\alpha]_D^{20}$=−45 (c=2.00 methanol)] >99% o.p. IR (KBr) ν: 3500–2000 (O–H st), 1719 and 1617 (C=O st) cm^{-1}. ^{1}H NMR (300 MHz) δ: 1.40 (d, J=7.1 Hz, 3H, C*H*$_3$CH), 3.58 (q, J=7.1 Hz, 1H, CHN), 3.67 (d, J=13.5 Hz, 2H) and 3.88 (d, J=13.5 Hz, 2H) (2CH_2 *N*-benzyl), 7.34 (complex signal, 10H, Ar–H *N*-benzyl), 9.1–9.8 (broad s, 1H, $^+$NH). ^{13}C NMR δ: 11.2 (CH_3, *C*H_3CH), 54.5 (CH_2, *N*-benzyl), 57.5 (CH, CHN), 127.8 (CH, C*para N*-benzyl), 128.6 (CH, C*ortho N*-benzyl), 129.0 (CH, C*meta N*-benzyl), 137.0 (C, C*ipso N*-benzyl), 175.3 (C, COO).

*3.13.2. (*R*)-α-(*N,N-*Dibenzylamino)-α-phenylacetic acid, (*R*)-**7d***

From (α*R*,3*S*)-**6d** (518 mg, 1.00 mmol, >99% d.e.), following the above general procedure and work-up B, (*R*)-**7d** [309 mg, 93% yield, $[\alpha]_D^{20}$=−49.2 (c=0.22, $CHCl_3$)] was obtained as a solid, which was crystallized from a mixture of ethyl acetate (2.5 ml) and hexane (17 ml) to give (*R*)-**7d** (234 mg, 71% yield), m.p. 78–79.5°C, $[\alpha]_D^{20}$=−56.6 (c=0.20, $CHCl_3$). The e.e. of this product could not be established by chiral HPLC using columns A and B, under several different conditions. IR (KBr) ν: 3500–2200 (O–H st), 1713 and 1622 (C=O st) cm^{-1}. $C_{22}H_{21}NO_2$ (331.43): calcd. C, 79.73%; H, 6.39%; N, 4.23%. Found: C, 79.73%; H, 6.48%; N, 4.34%. ^{1}H NMR (300 MHz) δ: 3.60 (d, J=13.7 Hz, 2H) and 3.92 (d, J=13.7 Hz, 2H) (2 CH_2 *N*-benzyl), 4.71 (s, 1H, CHN), 7.34 (complex signal, 15H, Ar–H), 9.0–10.0 (broad s, 1H, $^+$NH). ^{13}C NMR δ: 54.5 (CH_2, *N*-benzyl), 66.8 (CH, CHN), 127.7 (CH, C*ortho C*-phenyl), 128.4 (CH, C*para C*-phenyl), 128.5 (CH, C*para N*-benzyl), 128.6 (CH, C*ortho N*-benzyl), 129.0 (CH, C*meta N*-benzyl), 129.7 (CH, C*meta C*-phenyl), 133.8 (C, C*ipso C*-phenyl), 137.3 (C, C*ipso N*-benzyl), 174.6 (C, COO).

*3.14. (*R*)-α-Amino-α-phenylacetic acid hydrochloride (*D*-phenylglycine hydrochloride), (*R*)-**1d**·HCl*

A mixture of (*R*)-**7d** (140 mg, 0.42 mmol), conc. HCl (0.2 ml), 10% Pd–C (0.5 g) in a mixture of ethanol/water in the ratio of 1:1 (20 ml) was hydrogenated at 1 atm for 1 h. The mixture was filtered and the filtrate was concentrated in vacuo to give (*R*)-**1d**·HCl (77 mg, 98% yield), $[\alpha]_D^{20}$=−75.5 (c=1.07, H_2O), o.p. 67%.

Acknowledgements

A fellowship from the Comissionat per a Universitats i Recerca (CUR) of the Generalitat de Catalunya (GC) to N. Soldevilla and financial support from the Comisión Interministerial de Ciencia y Tecnología (CICYT) (Programa Nacional de Tecnología de los Procesos Químicos, Project QUI96-0828) and the CUR (Project 1997SGR 00140) are gratefully acknowledged. We thank the Serveis Científico-Tècnics of the Universitat de Barcelona for recording the NMR spectra, and P. Domènech from the Centro de Investigación y Desarrollo (CID) of Barcelona, for carrying out the elemental analyses. We also thank Professor Dr. Cristina Minguillón for her advice and HPLC facilities for the analysis of compound **7d**.

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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* **1998**, *9*, 2065–2079.
5. Camps, P.; Pérez, F.; Soldevilla, N. *Tetrahedron: Asymmetry* **1997**, *8*, 1877–1894.
6. Ng, J. S.; Przybyla, C. A.; Liu, C.; Yen, J. C.; Muellner, F. W.; Weyker, C. L. *Tetrahedron* **1995**, *51*, 6397–6410.
7. Denis, J. N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1991**, *56*, 6939–6942.
8. Studer, A. *Synthesis* **1996**, 793–815.
9. Reetz, M. T. *Angew. Chem., Int. Ed. Engl*. **1991**, *30*, 1531–1546.
10. *Houben-Weyl: Stereoselective Synthesis*, Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds. Georg Thieme Verlag: Stuttgart, 1996.
11. Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539–1650, and references cited therein.
12. Kreuzfeld, H. J.; Döbler, C.; Schmidt, U.; Krause, H. W. *Amino Acids* **1996**, *11*, 269–282.
13. Beller, M.; Eckert, M.; Geissler, H.; Napierski, B.; Rebenstock, H. P.; Holla, E. W. *Chem. Eur. J*. **1998**, *4*, 935–941.
14. Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc*. **1990**, *112*, 4011–4030.
15. Oppolzer, W.; Cintas-Moreno, P.; Tamura, O.; Cardinaux, F. *Helv. Chim. Acta* **1993**, *76*, 187–196.
16. Badorrey, R.; Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron* **1997**, *53*, 1411–1416.
17. Moody, C. J.; Lightfoot, A. P.; Gallagher, P. T. *Synlett* **1997**, 659–660.
18. Pandey, G.; Reddy, P. Y.; Das, P. *Tetrahedron Lett*. **1996**, *37*, 3175–3178.
19. Miyabe, H.; Ushiro, C.; Naito, T. *J. Chem. Soc., Chem. Commun*. **1997**, 1789–1790.
20. Chakraborty, T. K.; Azhar Hussain, K.; Venkat Reddy, G. *Tetrahedron* **1995**, *51*, 9179–9190.
21. Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc*. **1996**, *118*, 4910–4911.
22. Yeh, T.-L.; Liao, C.-C.; Uang, B.-J. *Tetrahedron* **1997**, *51*, 11141–11152.
23. Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc*. **1997**, *119*, 656–673.
24. Calmes, M.; Daunis, J.; Mai, N. *Tetrahedron: Asymmetry* **1997**, *8*, 1641–1648.
25. Calmes, M.; Daunis, J.; Mai, N. *Tetrahedron* **1997**, *53*, 13719–13726.
26. Koh, K.; Durst, T. *J. Org. Chem*. **1994**, *59*, 4683–4686.
27. Kubo, A.; Takahashi, M.; Kubota, H.; Nunami, K. *Tetrahedron Lett*. **1995**, *36*, 6251–6252.
28. Matteson, D. S.; Man, H. W. *J. Org. Chem*. **1994**, *59*, 5734–5741.
29. Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 36–56.
30. Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475–1490.
31. Ward, R. S.; Pelter, A.; Goubet, D.; Pritchard, M. C. *Tetrahedron: Asymmetry* **1995**, *6*, 469–498.
32. Koh, K.; Ben, R. N.; Durst, T. *Tetrahedron Lett*. **1993**, *34*, 4473–4476.
33. O'Meara, J. A.; Gardee, N.; Jung, M.; Ben, R. N.; Durst, T. *J. Org. Chem*. **1998**, *63*, 3117–3119.
34. Caddick, S.; Jenkins, K. *Tetrahedron Lett*. **1996**, *37*, 1301–1304.
35. Kubota, H.; Kubo, A.; Takahashi, M.; Shimizu, R.; Da-te, T.; Okamura, K.; Nunami, K. *J. Org. Chem*. **1995**, *60*, 6776–6784.
36. Bose, A. K. *Org. Synth. Coll. Vol. V* **1973**, 973–975.
37. Larsen, R. D.; Corley, E. G., Davis, P.; Reider, P. J.; Grabowski, E. J. J. *J. Am. Chem. Soc*. **1989**, *111*, 7650–7651.

38. Jähme, J.; Rüchardt, C. *Angew. Chem., Int. Ed. Engl*. **1981**, *20*, 885–887.
39. Bellucci, G.; Berti, G.; Bianchini, R.; Vecchiani, S. *Gazz. Chim. Ital*. **1988**, *118*, 451–456.
40. Sasaki, T.; Minamoto, K.; Itoh, H. *J. Org. Chem*. **1978**, *43*, 2320–2325.
41. Durst, T.; Koh, K. *Tetrahedron Lett*. **1992**, *33*, 6799–6802.
42. Velluz, L.; Amiard, G.; Heymès, R. *Bull. Soc. Chim. France* **1955**, *22*, 201–204.