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(*S*)-(3-Hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl) acetic acid as a solid supported chiral auxiliary in the asymmetric synthesis of β^2-homoarylglycines

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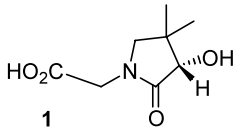
Abstract—Diastereoselective additions of the resin-supported (*S*)-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl) acetic acid to phthalimidomethyl aryl ketenes allow solid phase preparation of β^2-homoarylglycines with reasonable degrees of stereoselectivity.

1. Introduction

Solid-phase synthesis of small molecules has been recognized as an efficient tool to prepare chemical libraries.[1] However, asymmetric reactions[2–4] on a solid support have not been widely explored so far except when a solid supported chiral reagent or catalyst was used.[2] The use of a supported chiral auxiliary[3] is an attractive approach since it allows simple isolation of the desired non-racemic compound, easy elimination of by-products and excess reagents, and facile separation and recovery of the chiral material.

We have recently described[5] the preparation of a new enantiomerically pure auxiliary **1** with a carboxylic function that allowed its attachment to an amine-functionalized insoluble polymer to form **2**. Its efficiency as a polymer-supported chiral auxiliary has been first demonstrated by asymmetric transformation of two racemic aryl propionic acids via ketene formation.[5]



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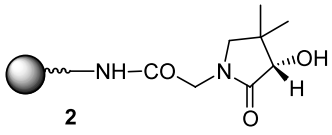

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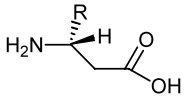
During the last few years, the preparation of enantiopure β-amino acids has gained considerable attention.[6,7] They are components of a variety of natural products[6,8] and show interesting pharmacological properties in free form or as their cyclized derivatives (β-lactam).[9] Although numerous methodologies have emerged to prepare enantiomerically pure β-amino acids in solution, these syntheses principally concern β^3-substituted compounds **3** but the preparation of enantiomerically pure β^2-substituted analogs **4** still remain a challenge.[10]

We have previously found[11] that stereoselective addition of the chiral alcohol **5** to a prochiral ketene was a



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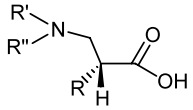
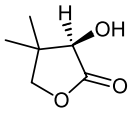


4a R' = R'' = H; R = alkyl, aryl...
4b R',R'' = Pht; R = C_6H_5
4c R',R'' = Pht; R = 4-F-C_6H_4
4d R',R'' = Pht; R = 3,4-$(CH_3O)_2C_6H_3$



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convenient method for the synthesis of (*S*)-β²-homoarylglycines **4** (R = aryl). As part of our program directed toward the development of asymmetric solid-phase reactions, we decided to examine this method for the solid-phase preparation of these compounds using the polymer-supported chiral auxiliary **2**. To our knowledge, there are no examples to date of asymmetric preparation of β²-amino acids using an insoluble polymer.

2. Results and discussion

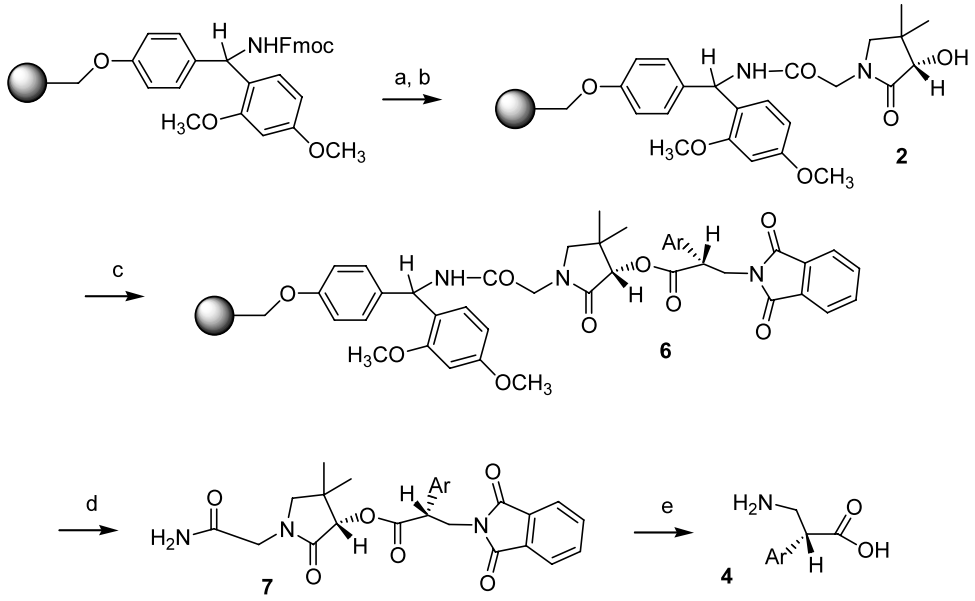
The starting β²-amino acids were *rac*-2-phenyl-3-phthalimidopropanoic acid: *rac*-**4b**, *rac*-2-(4-fluorophenyl)-3-phthalimidopropanoic acid: *rac*-**4c**, and *rac*-2-(3,4-dimethoxyphenyl)-3-phthalimidopropanoic acid: *rac*-**4d**. The phthalimido group, which totally protected the amine function, avoids the NH addition to the intermediate ketene. The *N*-protected compounds **4b–d** were obtained directly, as previously described,[11] starting from the corresponding aryl acetic acid benzyl esters and *N*-(bromomethyl) phthalimide.

We used a rink amide resin[12] since the benzhydrylamine bond created between the chiral auxiliary and the polymer was stable under the employed reaction conditions and it could be selectively cleaved after reaction of the ketene with the supported chiral auxiliary.

The four step reaction sequence involved during the asymmetric transformation of *rac*-**4b–d** are: (a) attachment of the chiral auxiliary to the solid support after removal of the Fmoc group of the linker; (b) diastereoselective addition of the supported alcohol to the ketene generated in solution by treatment with a tertiary amine of the corresponding acyl chloride; (c) benzhydrylamine bond cleavage; (d) acid hydrolysis of both the ester and the phtalimido group to yield enantioenriched β²-homoarylglycines **4** (Scheme 1).

The key step of this reaction sequence, i.e. diastereoselective addition of the supported chiral auxiliary (*S*)-**2** to the ketene, was carried out in a similar manner to that developed by our group for the solid phase asymmetric transformation of α-arylpropionic acids.[11] This consisted in the addition of an excess of the preformed intermediate ketene to the supported chiral auxiliary suspended in THF in the presence of the tertiary amine catalyst at the selected temperature (Table 1). The mixture was then left overnight at the same temperature. The excess of the tertiary base used both catalyzed the diastereoselective addition of the auxiliary to the ketene and increased the stereoselectivity.[13]

The intermediate ketenes were generated using different optimized experimental conditions as both their formation rate and their stability are dependent on the substitution of the phenyl side chain of the amino acid (Table 1).



Scheme 1. *Reagents*: (a) piperidine, DMF; (b) (*S*)-**1**, BOP, DIEA, DMF; (c) $PhtNCH_2(Ar)C{=}C{=}O$, NR_3, THF; (d) TFA, CH_2Cl_2; (e) 6N HCl/AcOH–propylene oxide.

Table 1.

Ester	Ar	NR_3	t_1, ketene room temp.	ROH T°C	Yield % ()[a]	(*S*,*R*)/(*S*,*S*)
7b	C_6H_5	NEt_3	1 h	Room temp.	95 (65)	93/7
7c	4-F-C_6H_4	NEt_3	2 h	0°C	98 (68)	92/8
7d	3,4-$(CH_3O)_2C_6H_3$	Quinuclidine	2 h	Room temp.	90 (63)	85/15

[a] After chromatography on silica gel.

After cleavage of the benzhydrylamine bond, the corresponding crude esters **7b–d** were obtained in high yields[14] and with good diastereoselectivities (Table 1). The diastereoisomeric ratios of **7b–d** were determined from crude products from ^{1}H NMR spectra by integration of the C*H*-3 signal of the ester moiety of the couple of diastereoisomers and/or by HPLC.[15]

Hydrolysis of the esters **7b–d** under acidic conditions[11] afforded, after propylene oxide treatment, the corresponding free (*R*)-β^2-homoarylglycines: (*R*)-**4b–d**. The (*R*) configuration was assigned by comparison of the specific rotation values of **4** with the literature data[11] indicating that in each case the (*S*,*R*) esters **7** were mainly formed when using the supported auxiliary (*S*)-(3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl) acetic acid.

These results demonstrate that the polymer-bound chiral auxiliary (*S*)-**2** has significant potential in the asymmetric preparation on solid phase of β^2-homoarylglycines using ketene chemistry. Both stereoselectivity and chemical yields are comparable to those obtained in the corresponding solution reactions. This method represents the first solid-phase protocol for the asymmetric preparation of β^2-aminoacids.

3. Experimental

3.1. General

All reagents were used as purchased from commercial suppliers without further purification except triethylamine (NEt_3) which was distilled from KOH and ninhydrin. Solvents were dried and purified by conventional methods prior to use; THF was freshly distilled under argon from sodium and benzophenone. Melting points were determined with a Kofler Heizbank apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 341 polarimeter. ^{1}H or ^{13}C NMR spectra (DEPT, ^{1}H/^{13}C 2D-correlations) were recorded with a Bruker A DRX 400 spectrometer. Data are reported as follows: chemical shifts (δ) in ppm with respect to TMS, coupling constants (J) in Hz. The ESI mass spectra were recorded with a platform II quadrupole mass spectrometer (Micromass, Manchester, UK) fitted with an electrospray source. HPLC analysis were performed with a Waters model 510 instrument with variable detector at 214 nm using: column A: reversed phase Nucleosil C_{18}, 5μ, (250×10 mm), flow: 1 ml/min, H_2O/CH_3CN/0.1% TFA gradient 0→100% (15 min) and 100% (4 min); column B: Chirasphere, 5μ, (250×10 mm), flow: 1 ml/min, hexane/2-propanol, 90/10.

The chiral auxiliary: (*S*)-3-hydroxy-4,4-dimethyl-2-oxopyrrolidin-1-yl) acetic acid, its attachment on a rink resin, the (*RS*)-3-phthalimido-2-arylpropanoic acids and the (*RS*)-3-phthalimido-2-aryl propanoic acid chlorides were prepared as previously described.[5,11]

3.2. General procedure for the diastereoselective addition of the supported chiral auxiliary (*S*)-2 to phthalimidomethyl aryl ketenes

To a stirred solution of (*RS*)-3-phthalimido-2-arylpropanoic acid chlorides (2.70 mmol, 3.0 equiv.) in 20 ml of anhydrous THF cooled to 0°C and under argon, was slowly (5 min) added 3.3 equiv. of NR_3 in 5 ml of THF (2.97 mmol). After t_1 hours stirring at room temperature, the resulting ketene was added at the selected temperature T°C to the solvent-swollen supported chiral alcohol (1.24 g, 0.90 mmol) in 20 ml of anhydrous THF. The suspension was stirred for 18 h at the same temperature and the solution was removed from the resin by filtration. After washing with THF (3×30 ml), CH_2Cl_2 (3×30 ml), CH_2Cl_2/CH_3OH (8/2) (3×30 ml), CH_2Cl_2 (3×30 ml), diethyl ether (3×30 ml) the expected resin **6** was dried under reduced pressure.

3.3. Preparation of the supported 3-phthalimido-2-phenylpropionic acid 6b

The supported 3-phthalimido-2-phenylpropionic acid **6b** (1.48 g, 0.9 mmol), was obtained following the general procedure (NR_3 = NEt_3 (414 μl, 2.97 mmol, 3.3 equiv.), t_1 = 1 h; T°C = room temperature) from (*RS*)-3-phthalimido-2-phenylpropanoic acid chloride (846 mg, 2.7 mmol, 3.0 equiv.).

3.4. Preparation of the supported 3-phthalimido-2-(4-fluorophenyl)propionic acid 6c

The supported 3-phthalimido-2-(4-fluorophenyl)propionic acid **6c** (1.50 g, 0.9 mmol), was obtained following the general procedure (NR_3 = NEt_3 (414 μl, 2.97 mmol, 3.3 equiv.), t_1 = 2 h; T°C = 0°C) from (*RS*)-3-phthalimido-2-(4-fluorophenyl)propanoic acid chloride (895 mg, 2.7 mmol, 3.0 equiv.).

3.5. Preparation of the supported 3-phthalimido-2-(3,4-dimethoxyphenyl)propionic acid 6d

The supported 3-phthalimido-2-(3,4-dimethoxyphenyl)-propionic acid **6d** (1.54 g, 0.9 mmol), was obtained following the general procedure (NR_3 = quinuclidine (330 mg, 2.97 mmol, 3.3 equiv.), t_1 = 2 h; T°C = room temperature) from (*RS*)-3-phthalimido-2-(3,4-dimethoxyphenyl)propanoic acid chloride (1.0 g, 2.7 mmol, 3.0 equiv.).

3.6. General procedure for the benzhydrylamine bond hydrolysis of the resin 6

To the resin **6** (0.9 mmol) was added 50 ml of a solution of 5% TFA in dry CH_2Cl_2 and the suspension was stirred for 40 min. The solution was removed from the resin by filtration and the resin was washed with CH_2Cl_2 (3×30 ml), CH_2Cl_2/CH_3OH (8/2) (3×30 ml), CH_2Cl_2 (3×30 ml). A second cleavage was realized using the same conditions. Evaporation of the combined filtrates in vacuo afforded the expected ester **7**.

3.7. (1-Carbamoylmethyl-4,4-dimethyl-2-oxopyrrolidinyl) 3-phthalimido-2-phenylpropionate 7b

Following the general procedure from the supported 3-phthalimido-2-phenylpropionic acid **6b** (1.48 g), compound (*S*,*R*)-**7b** (396 mg, 86% d.e., 95% yield) was obtained as a crude product which after purification by column chromatography (silica gel, CH_2Cl_2/MeOH/AcOH 9.5/0.5/0.1 or ethyl acetate alone) yielded (*S*,*R*)-**7b** as a white solid (271 mg, 86% d.e., 65% yield); mp 70–72°C; $[\alpha]_D^{20}=+21$ (*c* 2 in AcOEt); HPLC: column A rt 10.3 min; MS (ESI) *m*/*z*: 464.3 [(M+H)$^+$], 928.5.

The main diastereoisomer (*S*,*R*)-**7b**: HPLC: column B rt 115.1 min; ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 3H, C*H*$_3$-C), 1.04 (s, 3H, C*H*$_3$-C), 3.05 (d, $J=9.6$ Hz, 1H, HC*H*-5), 3.15 (d, $J=9.6$ Hz, 1H, HC*H*-5), 3.74 (d, $J=16.1$, 1H, N-HC*H*-CO), 3.83 (d, $J=16.1$ Hz, 1H, N-HC*H*-CO), 4.03 (dd, $J=8.0$ Hz and $J=13.7$ Hz, 1H, HC*H*-N), 4.26 (dd, $J=8.0$ Hz and $J=13.7$ Hz, 1H, HC*H*-N), 4.39 (t, $J_1=J_2=8.0$ Hz, 1H, *H*C-C_6H_5), 5.10 (s, 1H, C*H*-3), 6.02 (br, 1H, CO-*H*NH), 6.48 (br, 1H, CO-*H*NH), 7.17 (m, 3H, C_6H_5), 7.27 (m, 2H, C_6H_5), 7.58 (m, 2H, *H*-phthalyl), 7.68 (m, 2H, *H*-phthalyl); ^{13}C NMR ($CDCl_3$) δ 21.54 (*C*H$_3$-C), 25.66 (*C*H$_3$-C), 38.01 (*C*-(CH$_3$)$_2$), 40.70 (*C*H$_2$-N), 46.85 (N-*C*H$_2$-CO), 49.72 (H*C*-C_6H_5), 58.81 (*C*H$_2$-5), 78.88 (*C*H-3), 123.72, 128.53, 128.77, 129.20 (*C*H-arom.), 132.14 (*C*-arom.), 134.47 (*C*H-arom.), 135.39 (*C*-arom.), 168.34, 170.46, 171.26 (*C*O).

The minor diastereoisomer (*S*,*S*)-**7b** has the following HPLC and NMR physical data:[15,16] HPLC: column B rt 133.7 min; ^{1}H NMR ($CDCl_3$) δ 0.58 (s, 3H, C*H*$_3$-C), 0.95 (s, 3H, C*H*$_3$-C), 2.97 (d, $J=9.2$ Hz, 1H, HC*H*-5), 3.18 (d, $J=9.2$ Hz, 1H, HC*H*-5), 3.74 (d, $J=16.1$, 1H, N-HC*H*-CO), 3.83 (d, $J=16.1$ Hz, 1H, N-HC*H*-CO), 4.10 (dd, $J=8.5$ Hz and $J=13.7$ Hz, 1H, HC*H*-N), 4.22 (dd, $J=8.5$ Hz and $J=13.7$ Hz, 1H, HC*H*-N), 4.37 (t, $J_1=J_2=7.8$ Hz, 1H, *H*C-C_6H_5), 5.18 (s, 1H, C*H*-3), 6.06 (br, 1H, CO-*H*NH), 6.40 (br, 1H, CO-*H*NH), 7.17 (m, 3H, C_6H_5), 7.27 (m, 2H, C_6H_5), 7.58 (m, 2H, *H*-phthalyl), 7.68 (m, 2H, *H*-phthalyl); ^{13}C NMR ($CDCl_3$) δ 21.47 (*C*H$_3$-C), 25.33 (*C*H$_3$-C), 38.20 (*C*-(CH$_3$)$_2$), 40.76 (*C*H$_2$-N), 46.85 (N-*C*H$_2$-CO), 49.72 (H*C*-C_6H_5), 58.07 (*C*H$_2$-5), 78.64 (*C*H-3), 123.72, 128.43, 128.84, 129.10 (*C*H-arom.), 132.14 (*C*-arom.), 134.36 (*C*H-arom.), 135.37 (*C*-arom.), 168.23, 170.31, 171.32 (*C*O).

3.8. (1-Carbamoylmethyl-4,4-dimethyl-2-oxopyrrolidinyl) 3-phthalimido-2-(4-fluorophenyl)propionate 7c

Following the general procedure from the supported 3-phthalimido-2-(4-fluorophenyl)propionic acid **6c** (1.5 g), compound (*S*,*R*)-**7c** (425 mg, 84% de, 98% yield) was obtained as a crude product which after purification by column chromatography (silica gel, ethyl acetate) yielded (*S*,*R*)-**7c** as a white solid (295 mg, 84% d.e., 68% yield). Mp 83–84°C; $[\alpha]_D^{20}=+25$ (*c* 2 in AcOEt); HPLC: column A rt 10.4 min; MS (ESI) *m*/*z*: 482.3 [(M+H)$^+$], 963.4.

The main diastereoisomer (*S*,*R*)-**7c**: HPLC: column B rt 121.9 min ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 3H, C*H*$_3$-C), 1.06 (s, 3H, C*H*$_3$-C), 3.05 (d, $J=9.5$ Hz, 1H, HC*H*-5), 3.19 (d, $J=9.5$ Hz, 1H, HC*H*-5), 3.79 (s, 2H, N-C*H*$_2$-CO), 4.05 (dd, $J=8.1$ Hz and $J=13.7$ Hz, 1H, HC*H*-N), 4.20 (dd, $J=8.1$ Hz and $J=13.7$ Hz, 1H, HC*H*-N), 4.37 (t, $J_1=J_2=8.1$ Hz, 1H, *H*C-C_6H_4F), 5.13 (s, 1H, C*H*-3), 5.84 (br, 1H, CO-*H*NH), 6.43 (br, 1H, CO-*H*NH), 6.88 (t, $J_1=J_2=8.6$ Hz, 2H, C_6H_4F), 7.24 (dd, $J=8.6$ Hz and $J=5.2$ Hz, 2H, C_6H_4F), 7.60 (m, 2H, *H*-phthalyl), 7.69 (m, 2H, *H*-phthalyl); ^{13}C NMR ($CDCl_3$) δ 21.57 (*C*H$_3$-C), 25.53 (*C*H$_3$-C), 38.07 (*C*-(CH$_3$)$_2$), 40.63 (*C*H$_2$-N), 46.83 (N-*C*H$_2$-CO), 48.89 (H*C*-C_6H_4F), 58.72 (*C*H$_2$-5), 78.72 (*C*H-3), 116.12 (d, $J=21.6$ Hz), 123.77, 130.55 (d, $J=8.4$ Hz), (*C*H-arom.), 131.13, 132.03 (*C*-arom.), 134.55 (*C*H-arom.), 162.81 (*C*F, d, $J=247$ Hz), 168.29, 170.31, 171.20 (*C*O).

The minor diastereoisomer (*S*,*S*)-**7c** has the following HPLC and NMR physical data:[15,16] HPLC: column B rt 145.3 min; ^{1}H NMR ($CDCl_3$)) δ 0.63 (s, 3H, C*H*$_3$-C), 0.97 (s, 3H, C*H*$_3$-C), 2.96 (d, $J=9.5$ Hz, 1H, HC*H*-5), 3.19 (d, $J=9.5$ Hz, 1H, HC*H*-5), 3.75 (s, 2H, N-C*H*$_2$-CO), 4.11 (dd, $J=8.1$ Hz and $J=13.7$ Hz, 1H, HC*H*-N), 4.18 (dd, $J=8.1$ Hz and $J=13.7$ Hz, 1H, HC*H*-N), 4.38 (t, $J_1=J_2=8.1$ Hz, 1H, *H*C-C_6H_4F), 5.21 (s, 1H, C*H*-3), 5.84 (br, 1H, CO-*H*NH), 6.38 (br, 1H, CO-*H*NH), 6.87 (t, $J_1=J_2=8.6$ Hz, 2H, C_6H_4F), 7.21 (dd, $J=8.6$ Hz and $J=5.2$ Hz, 2H, C_6H_4F), 7.60 (m, 2H, *H*-phthalyl), 7.69 (m, 2H, *H*-phthalyl); ^{13}C NMR ($CDCl_3$) δ 21.10 (*C*H$_3$-C), 25.21 (*C*H$_3$-C), 38.59 (*C*-(CH$_3$)$_2$), 40.09 (*C*H$_2$-N), 46.83 (N-*C*H$_2$-CO), 48.46 (H*C*-C_6H_4F), 58.52 (*C*H$_2$-5), 78.30 (*C*H-3), 116.16 (d, $J=21.6$ Hz), 123.77, 130.55 (d, $J=8.4$ Hz), (*C*H-arom.), 131.13,, 132.03 (*C*-arom.), 134.47 (*C*H-arom.), 162.81 (*C*F, d, $J=247$ Hz), 168.29, 170.70, 171.51 (*C*O).

3.9. (1-Carbamoylmethyl-4,4-dimethyl-2-oxopyrrolidinyl) 3-phthalimido-2-(3,4-dimethoxyphenyl) propionate 7d

Following the general procedure from the supported 3-phthalimido-2-(3,4-dimethoxyphenyl)propionic acid **6d** (1.54 g), compound (*S*,*R*)-**7d** (424 mg, 70% de, 90% yield) was obtained as a crude product which after purification by column chromatography (silica gel, ethyl acetate) yielded (*S*,*R*)-**7d** as a pale yellow solid (330 mg, 70% d.e., 63% yield); mp 95–98°C; $[\alpha]_D^{20}=+18$ (*c* 2 in AcOEt); HPLC: column A rt 9.76 min**;** MS (ESI) *m*/*z:* 524.4 [(M+H)$^+$].

The main diastereoisomer (*S*,*R*)-**7d**: ^{1}H NMR ($CDCl_3$): δ 0.89 (s, 3H, C*H*$_3$-C), 1.03 (s, 3H, C*H*$_3$-C), 3.02 (d, $J=9.5$, 1H, HC*H*-5), 3.17 (d, $J=9.5$ Hz, 1H, HC*H*-5), 3.72 (s, 3H, OC*H*$_3$), 3.74 (s, 3H, OC*H*$_3$), 3.78 (d, $J=10.0$ Hz, 1H, N-HC*H*-CO), 3.82 (d, $J=10.0$ Hz, 1H, N-HC*H*-CO), 4.06 (dd, $J=8.1$ Hz and $J=13.7$ Hz, 1H, HC*H*-N), 4.20 (dd, $J=8.1$ Hz and $J=13.7$ Hz, 1H, HC*H*-N), 4.32 (t, $J_1=J_2=8.1$ Hz, 1H, *H*C-C_6H_3(OCH$_3$)$_2$), 5.12 (s, 1H, C*H*-3), 6.19 (br, 1H, CO-*H*NH), 6.66 (m, 2H, CO-*H*NH and C_6H_3(OCH$_3$)$_2$), 6.78 (m, 2H, C_6H_3(OCH$_3$)$_2$), 7.59 (m, 2H, *H*-phthalyl),

7.68 (m, 2H, *H*-phthalyl); ^{13}C NMR ($CDCl_3$) δ 21.53 (CH_3-C), 25.45 (CH_3-C), 38.07 (CH_2-N), 40.49 (C-$(CH_3)_2$), 46.68 (N-CH_2-CO), 49.23 (HC-$C_6H_3(OCH_3)_2$), 56.14, 56.25 (OCH_3) 58.71 (CH_2-5), 78.69 (CH-3), 111.50, 111.72, 121.23, 123.75 (CH-arom.), 127.60, 132.05 (C-arom.), 134.52 (CH-arom.), 149.06, 149.30 (C-arom.), 168.43, 170.73, 171.59 (CO).

The minor diastereoisomer (*S*,*S*)-**7d** has the following NMR physical data:[15,16] ^{1}H NMR ($CDCl_3$): δ 0.69 (s, 3H, CH_3-C), 0.94 (s, 3H, CH_3-C), 2.91 (d, $J=9.5$ Hz, 1H, HC*H*-5), 3.17 (d, $J=9.5$ Hz, 1H, HC*H*-5), 3.72 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.78 (d, $J=10.0$ Hz, 1H, N-HC*H*-CO), 3.82 (d, $J=10.0$ Hz, 1H, N-HC*H*-CO), 4.04 (dd, $J=8.1$ Hz and $J=13.7$ Hz, 1H, HC*H*-N), 4.23 (dd, $J=8.1$ Hz and $J=13.7$ Hz, 1H, HC*H*-N), 4.32 (t, $J_1=J_2=8.1$ Hz, 1H, *H*C-$C_6H_3(OCH_3)_2$), 5.21 (s, 1H, C*H*-3), 6.19 (br, 1H, CO-*H*NH), 6.66 (m, 2H, CO-*H*NH and $C_6H_3(OCH_3)_2$), 6.78 (m, 2H, $C_6H_3(OCH_3)_2$), 7.59 (m, 2H, *H*-phthalyl), 7.68 (m, 2H, *H*-phthalyl); ^{13}C NMR ($CDCl_3$) δ 21.07 (CH_3-C), 25.08 (CH_3-C), 38.62 (CH_2-N), 40.00 (C-$(CH_3)_2$), 46.68 (N-CH_2-CO), 48.61 $C_6H_3(OCH_3)_2$), 56.14, 56.25 (OCH_3), 58.51 (CH_2-5), 78.24 (CH-3), 111.42, 111.72, 121.34, 123.75 (CH-arom.), 127.89, 132.07, 134.51 (C-arom.), 134.52 (CH-arom.), 149.06, 149.30 (C-arom.), 171.09, 171.21, 172.04 (CO).

3.10. General procedure for the hydrolysis of (1-Carbamoylmethyl-4,4-dimethyl-2-oxopyrrolidinyl)-3-phthalimido-2-arylpropanoate 7

A mixture of the esters **7** (0.50 mmol), acetic acid (1.4 ml) and a 6N HCl solution (14 ml) was refluxed until completion of the hydrolysis (4–5 h), monitoring the reaction by TLC. The mixture was allowed to warm to room temperature and the volatile products were distilled at reduced pressure. Water (15 ml) was added to the residue and the mixture was washed with AcOEt (3×15 ml). After concentration in vacuo of the aqueous layer the remaining chiral auxiliary was solubilized in refluxing acetone while the insoluble collected by filtration yielded the free aminoacids (*R*)-**4b–d** after propylene oxide treatment.

The characterization of compounds **4b–d** has been reported in previous papers.[11]

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14. As previously in solution[11] and probably due to a low stability of the intermediates involved, a rapid chromatography on silica gel of the crude esters **7b–d** was necessary to obtain pure compounds.
15. To obtain equimolar diastereomeric samples of **7b–d**, (*SR*)-**4b–d** were first esterified with the supported chiral alcohol in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 and then the benzhydrylamine bond was cleaved using the conventional method.
16. HPLC and NMR data of the minor diastereoisomers **7b–d** were deduced from comparison of the data of the equimolar diastereomeric mixtures[15] and diastereomerically enriched compounds.