Asymmetric Synthesis of (*S*)-β²-Homoarylglycines

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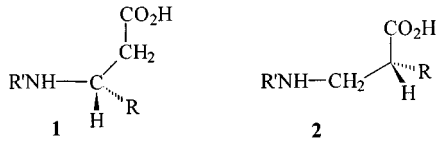
The synthesis of racemic *N*-phthalyl β²-homoarylglycines **5** and their asymmetric transformation have been investigated. The key step is the stereoselective addition of the (*R*)-pantolactone to the corresponding prochiral ketene **7**.

Introduction

β-Amino acids and their derivatives are an important class of compounds in the development of peptidomimetics[1] and functionalized β-lactams.[2] They also show interesting pharmacological effects in their free form.[3]

Many methods have been reported for the synthesis of racemic β-amino acids, but only recently have enantiomerically pure compounds been prepared.[4] However, these syntheses concern principally β³-substituted compounds **1** (Scheme 1), the preparation of β²-substituted analogs **2** still remaining a challenge.



Scheme 1

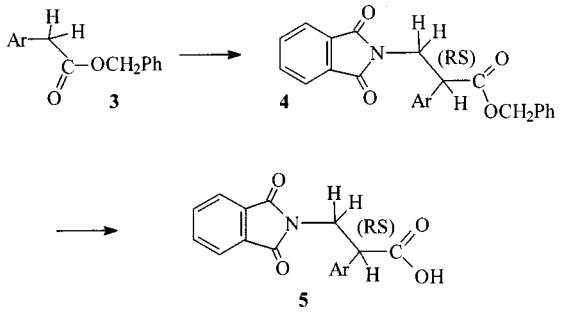
The usual way to prepared β²-substituted compounds involves diastereoselective alkylation of an enolate derived from β-alanine, the synthesis of the latter being the limiting step.[5] An elaborate synthesis[6] using a palladium catalyzed asymmetric allylic substitution and a modified Curtius reaction as key steps to introduce nitrogen has also been proposed. Recently, enantiomerically pure β²-homophenylglycine has been obtained by acylation of metallated phenylacetonitrile with sultam carbonyl chloride.[7]

It has been shown in previous studies[8,9] concerning deracemization reactions, that the asymmetric transformation of racemic mixtures involving prochiral ketenes was a simple, convenient and effective reaction. We have recently successfully applied this method for the preparation of β-amino acids and described a convenient access to (*S*)-β²-homophenylglycine.[9e] Extending our investigations, we wish now to report our results concerning the preparation of optically active β²-homoarylglycines **9a−d** which, for most of them, corresponds to their first asymmetric synthesis.

Results and Discussion

Prior to carrying out the stereoselective transformation (Scheme 3), racemic 3-amino-2-aryl propanoic acid derivatives (that are racemic β²-homoarylglycines) had to be prepared with the amine function fully protected in order to avoid NH addition to the ketene. We developed a convenient method (Scheme 2) that directly produced adequate *N*-protected substrates starting from various aryl acetic acid benzyl esters **3** (easily prepared from the cheap commercially available corresponding acid) and *N*-(bromomethyl)phthalimide.

Alkylation of **3d** was achieved in good yield (70% after purification) using the same experimental conditions as those previously used for the preparation of the racemic *N*-phthalyl-β²-homophenylglycine, i.e. deprotonation in THF at low temperature (−78 °C) by using lithium diisopropylamide as base and DMPU[10] as co-solvent. The same conditions applied to **3a−c**, where the phenyl group contains a fluoro- or one or two methoxy substituents, led to the corresponding esters in only moderate yields (35−40%), even if another additive such as LiCl was used. On the other hand, **4a**, **4b**, and **4c** were obtained in good yield (75, 78,



3-5	a	b	c	d
Ar	4-MeOC$_6$H$_4$	4-F-C$_6$H$_4$	3,4-(MeO)$_2$C$_6$H$_3$	α-naphthyl

Scheme 2. Synthesis of *rac*-**5a−d**

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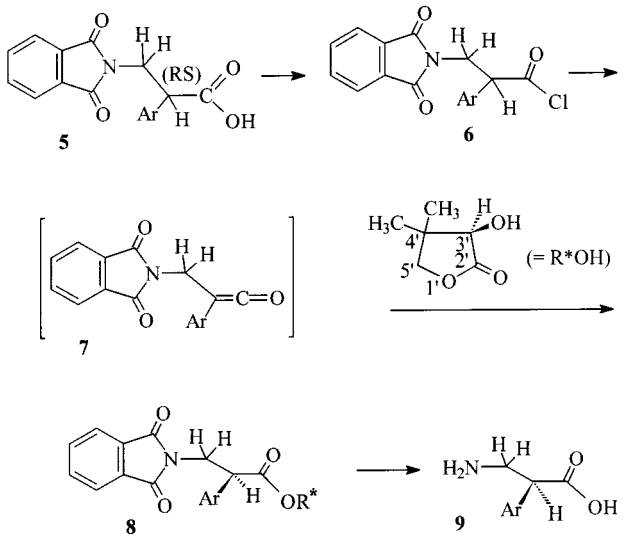
and 68% yields, respectively after purification) in THF at low temperature (−78 °C) when lithium hexamethyldisilazane was used as the base. The benzyl ester was then easily cleaved by hydrogenolysis without degradation of the phthalyl group affording the *N*-phthalyl-3-amino-2-arylpropanoic acids **5a−d** as racemic mixtures, quantitatively.

According to the considered methodology, the asymmetric transformation of **5** involves the stereoselective addition of a chiral alcohol to the *N*-phthalyl-3-aminomethyl-2-aryl ketene (**7**) (Scheme 3). This reaction was performed in THF with (*R*)-pantolactone, a very efficient commercially available chiral auxiliary, used as the chiral alcohol.



Scheme 3. Stereoselective synthesis of **9a−d**

The ketene **7** was obtained in situ by dehydrochlorination of the corresponding acyl chloride **6**, which was obtained from **5** by treatment at room temperature with oxalyl chloride. The tertiary base, used in excess, both catalyzed the diastereoselective addition of an alcohol to a ketene and increased the stereoselectivity.[9,11] Ketene formation and alcohol addition occurred in a one pot procedure.

In the first attempt, we used the same experimental conditions as previously employed for the preparation of the *N*-phthalyl-β^2-homophenylglycine, i.e. generation of the ketene at room temperature by treatment of the acid chloride **6** with triethylamine, followed one hour later by the addition of the (*R*)-pantolactone at the same temperature. Under these experimental conditions, moderate to modest chemical yields and/or stereoselectivities were obtained, depending on the nature of the amino acid aryl side chain (Table 1, entries 1, 5, 9, and 14). However, the generation of the ketene must occur at room temperature, since when a lower temperature (0 °C to −20 °C) was used the ketene was only partly produced. Indeed, at lower temperatures, by trapping the ketene with CH_3OD only a small amount of the corresponding Cα deuterated methyl ester was formed.

To improve chemical yields and stereoselectivities, we tested various tertiary amines, reaction times, and temperatures for each β-amino acid. The most representative results are recorded in Table 1.

Table 1. Reaction conditions, yields and (*S*,*R*)/(*R*,*R*) ratio in the diastereoselective addition of (*R*)-pantolactone to aryl ketenes **7a−d**

Entry	Ester	NR_3 1.1 equiv.	Ketene room temp.	ROH *T* [°C]	Yield [%]	(*S*,*R*)/(*R*,*R*)
1	**8a**	NEt_3	1 h	room temp.	75	22:78
2	**8a**	Quinuclidine	1 h	room temp.	88	84:16
3	**8a**	Quinuclidine	2 h	room temp.	85	90:10
4	**8a**	Quinuclidine	2 h	0	80	90:10
5	**8b**	NEt_3	1 h	room temp.	55	75:25
6	**8b**	NEt_3	1 h	0	76	80:20
7	**8b**	NEt_3	2 h	0	78	92:8
8	**8b**	Quinuclidine	1 h	0	70	60:40
9	**8c**	NEt_3	1 h	room temp.	60	87:13
10	**8c**	NEt_3	1 h	0	82	84:16
11	**8c**	NEt_2Me	1 h	0	60	73:27
12	**8c**	NMe_2Et	1 h	0	68	79:21
13	**8c**	Quinuclidine	1 h	0	85	94:6
14	**8d**	NEt_3	1 h	room temp.	65	55:45
15	**8d**	Quinuclidine	1 h	room temp.	88	92:8

The data in Table 1 show that it was preferable to use the tricyclic tertiary amine quinuclidine rather than triethylamine, except in the case of **6b** (entries 3, 7, 13, and 15). It is also clear that the formation rate and the stability of ketenes are dependent on the substitution of the phenyl side chain of the amino acid. The optimum results were obtained for **8a** and **8b** for which the time for ketene formation had been increased from one to two hours (entries 2, 3 and 6, 7). In addition, when the reaction was carried out at 0 °C instead at room temperature, we observed for **8b** and **8c** an improvement in both yield and stereoselectivity (entries 5, 6 and 9, 10).

Although the reaction was not totally diastereoselective, the optically pure *N*-phthalyl pantolactonyl esters **8a−d** could be easily obtained by recrystallisation of the corresponding optically-enriched mixture. The (α*S*,3′*R*) configuration of the main esters form **8a−c** was ascertained from the X-ray diffraction patterns (Figures 1−3).[12] In the case of **8d**, that crystallized as fine needles, the X-ray method could not be applied.

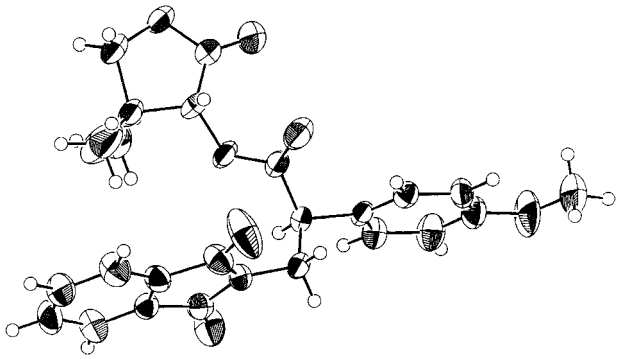


Figure 1. ORTEP drawing of ester **(α*S*,3′*R*)-8a**

Hydrolysis[9c,9d] under acidic conditions of the diastereomerically pure *N*-phthalyl pantolactonyl esters afforded the corresponding β^2-homoarylglycines **9a−d**. The enantiomeric excesses of **9a−d** were determined by NMR analysis after derivatization with Marfey's reagent (1-fluoro-2,4-di-

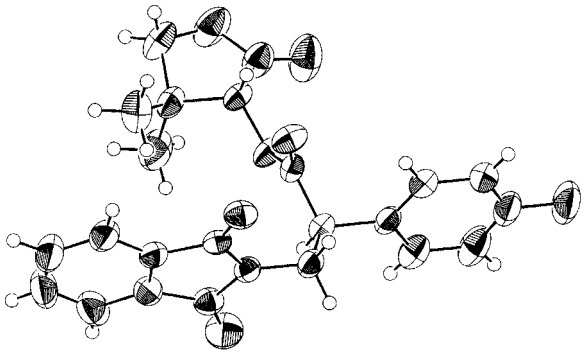


Figure 2. ORTEP drawing of ester **(α*S*,3′*R*)-8b**

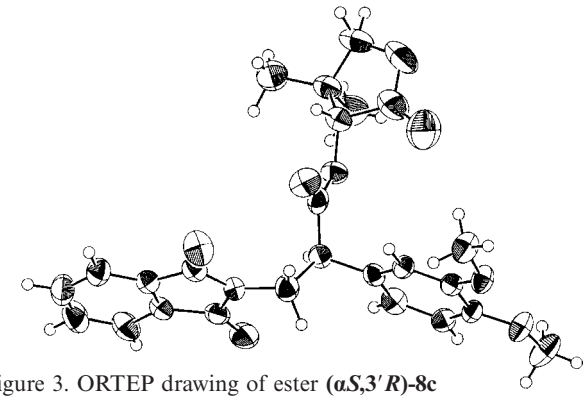


Figure 3. ORTEP drawing of ester **(α*S*,3′*R*)-8c**

nitrophenyl-5-(*S*)-alanine amide).[13] The stereochemistry of **8a−c** allowed us to establish the (*S*) configuration for the compounds **9a−c**.

To define the absolute configuration of the 3-amino-2-(α-naphthyl)propanoic acid **9d**, we prepared its *N*-*tert*-butyloxycarbonyl (Boc) derivative **9d**-Boc, since the physical data of the (*R*) enantiomer have been recently reported by Bower et al.[6b] To our surprise, comparison of the specific rotation values suggested that the (*R*) enantiomer of **9d**-Boc was formed, whereas we expected the (*S*) enantiomer. However, in the study of Bower et al.[6b] the specific rotation value of another compound, the (*R*)-3-amino-2-phenylpropanoic acid, is given as opposite to that previously reported by Wyatt et al.[5e] after determination of the absolute configuration by an unambiguous X-ray crystallographic analysis. So, since in our case compounds **8a−d** have all been prepared starting from similar compounds by using the same reaction scheme, it is reasonable to assume that **8d**, like **8a−c**, has the (α*S*,3′*R*) configuration thus affording **(*S*)-9d**.

Conclusion

In this work, we have established syntheses of some optically active β²-homoarylglycine derivatives, which for most of them correspond to their first asymmetric preparation. This asymmetric transformation by stereoselective addition of the (*R*)-pantolactone to prochiral ketenes proved to be a simple and convenient method for the preparation of particularly interesting β²-substituted β-amino acids.

Experimental Section

Tetrahydrofuran (THF) was freshly distilled under argon from sodium and benzophenone; triethylamine (NEt_3) was distilled from KOH and ninhydrin; 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) was stirred with CaH_2 for 1 h and then distilled at reduce pressure before use. Thin layer chromatography (tlc) was carried out on silica gel (60 F_{254}, Merck 5715) and the spots located with UV light or iodine vapor (eluent A: hexane/AcOEt 9:1; eluent B: hexane/AcOEt 8:2; eluent C: hexane/diethyl ether 2:8; eluent D: hexane/AcOEt 8:3; eluent E: CH_2Cl_2). (*R*)-Pantolactone (chemical and enantiomeric purities > 99%) was purchased from Fluka Chemical Co. All other chemicals were commercially pure compounds. − Melting points were determined with a Büchi apparatus and are uncorrected. − Optical rotations were measured with a Perkin−Elmer, model 241 polarimeter. − IR spectra were recorded with a FT-IR Perkin−Elmer, model 1000 spectrometer. − HPLC analysis were performed with a Waters model 510 with variable detector. − ^{1}H NMR spectra were recorded with a Bruker AC 250 or A DRX 400 spectrometer. Data are reported as follows: chemical shifts (δ) in ppm with respect to TMS, multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, br = broad), coupling constants (*J*) in Hz. − The ESI mass spectra were recorded with a platform II quadrupole mass spectrometry (Micromass, Manchester, UK) fitted with an electrospray source and the voltages were set at 3.5 kV for the capillary and 30 V for the cone. The Fast Atom Bombardment mass spectra were recorded with a SX102 type spectrometer, Jeol Ltd., Tokyo, Japan and 3-nitrobenzyl alcohol was used as matrix. Diastereoisomeric ratios of **8** were determined from crude products from ^{1}H NMR spectra ($CDCl_3$) by integration of the 3′-C*H* signal of the pantolactonyl moiety of the couple of diastereoisomers and/or by HPLC [column chirasphere (Merck), 25 cm × 4 mm, flow: 1 mL/min, hexane/2-propanol: condition A: 95:5, condition B: 90:10]. − To obtain racemic samples of pantolactonyl esters **8**, (*SR*)-**5** was esterified with (*R*)-pantolactone in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP). HPLC and NMR data of compounds **8** were deduced from comparison of the data of the racemic mixtures and optically enriched compounds obtained. Racemization during acid hydrolysis of **8** was controlled by ^{1}H NMR analysis ([D_6]DMSO) after derivatization with Marfey's reagent [FDAA = 1-fluoro-2,4-dinitrophenyl-5-(*S*)-alanine amide].[13] Marfey's reagent induces an adequate chemical shift NMR non-equivalence of aromatic protons of the two diastereoisomers formed from racemic 3-amino-2-arylpropanoic acids, allowing satisfactory enantiomeric excess determination.

General Procedure for the Preparation of Benzyl Arylacetates (3): Benzyl arylacetates **3** were prepared from the corresponding arylacetic acid and benzyl alcohol as previously described in the literature.[14]

Benzyl (4-Methoxyphenyl)acetate (3a): Following the general procedure from (4-methoxyphenyl)acetic acid (1.66 g, 10.00 mmol), **3a** (2.30 g, 9.30 mmol, 93% yield), was obtained as an oil; tlc (eluent D) R_f = 0.42. − IR (KBr): ṽ = 3028 w, 2934 m, 2849 w,1731 s, 1509 m, 1259 s, 1165 s, 1080 m. − ^{1}H NMR ($CDCl_3$): δ = 3.65 [s, 2 H, $(CH_3O)C_6H_4CH_2CO$], 3.80 (s, 3 H, OCH_3), 5.16 (s, 2 H, $OCH_2C_6H_5$), 6.90 [d, *J* = 8.7 Hz, 2 H, $C_6H_4(OCH_3)$], 7.28 [d, *J* = 8.7 Hz, 2 H, $C_6H_4(OCH_3)$], 7.42 (m, 5 H, C_6H_5). − FAB-MS; *m*/*z* (%): 256 (15) [$M^{+\cdot}$], 135 (30), 121 (20), 109 (52), 91 (100). − $C_{16}H_{16}O_3$ (256.3) calcd. C 75.07, H 6.30; found C 75.12, H 6.38.

Benzyl (4-Fluorophenyl)acetate (3b): Following the general procedure from (4-fluorophenyl)acetic acid (1.54 g, 10.00 mmol), **3b**

(2.22 g, 9.10 mmol, 91% yield), was obtained as an oil; tlc (eluent B) R_f = 0.58. − IR (KBr): $\tilde{\nu}$ = 3066 w, 2924 m, 2849 w, 1731 s, 1509 m, 1221 m, 1160 m. − ^{1}H NMR ($CDCl_3$): δ = 3.65 (s, 2 H, F−$C_6H_4CH_2CO$), 5.14 (s, 2 H, O$CH_2C_6H_5$), 7.02 (t, $J_1 = J_2$ = 8.7 Hz, 2 H, C_6H_4F), 7.25 (dd, J = 8.7 Hz and J = 6.8 Hz, 2 H, C_6H_4F), 7.35 (m, 5 H, C_6H_5). − FAB-MS; *m/z* (%): 245 (6) [(M + H)$^+$], 154 (5), 137 (8), 109 (43), 91 (100). − $C_{15}H_{13}FO_2$ (244.3) calcd. C 73.84, H 5.37; found C 73.76, H 5.43.

Benzyl (3,4-Dimethoxyphenyl)acetate (3c): Following the general procedure from (3,4-dimethoxyphenyl)acetic acid (1.96 g, 10.00 mmol), **3c** (2.72 g, 9.50 mmol, 95% yield), was obtained as an oil; tlc (eluent C) R_f = 0.63. − IR (CH_3CN): $\tilde{\nu}$ = 2985 w, 2943 m, 2830 w, 1736 s, 1514 s,.1259 s, 1235 m, 1141 s. − ^{1}H NMR ($CDCl_3$): δ = 3.61 [s, 2 H, $(CH_3O)_2C_6H_3CH_2CO$]), 3.82 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 5.13 (s, 2 H, O$CH_2C_6H_5$), 6.81 [s, 3 H, $C_6H_3(OCH_3)_2$], 7.38 (m, 5 H, C_6H_5). − FAB-MS; *m/z* (%): 286 (60) [M$^+$], 209 (5), 151 (73), 91 (100). − $C_{17}H_{18}O_4$ (286.3) calcd. C 71.39, H 6.34; found C 71.30, H 6.45.

Benzyl (α-Naphthyl)acetate (3d): Following the general procedure from (α-naphthyl)acetic acid (1.86 g, 10.00 mmol), **3d** (2.48 g, 9.00 mmol, 90% yield), was obtained as an oil; tlc (eluent A) R_f = 0.38. − IR (CH_3CN): $\tilde{\nu}$ = 3056 m, 3028 m, 2934 m, 1736s, 1514 w, 1259 m, 1141 s. − ^{1}H NMR ($CDCl_3$): δ = 4.18 (s, 2 H, $C_{10}H_7CH_2CO$), 5.21 (s, 2 H, O$CH_2C_6H_5$), 7.35 (m, 5 H, C_6H_5), 7.50 (m, 2 H, *H*-naphthyl); 7.57 (m, 2 H, *H*-naphthyl), 7.90 (m, 2 H, *H*-naphthyl), 8.07 (m, 1 H, *H*-naphthyl). − FAB-MS; *m/z* (%): 276 (25) [M$^+$], 199 (5), 141 (66), 91 (100). − $C_{19}H_{16}O_2$ (276.33) calcd. C 82.69, H 5.84; found C 82.52, H 5.96.

General Procedure for the Preparation of (*RS*)-Benzyl 2-Aryl-3-phthalimidopropanoates (4). − Method A: A solution of *n*-butyllithium (2.5 M) in hexane (2.4 mL, 6.00 mmol) was added dropwise over 5 min to a stirred solution of diisopropylamine (0.91 mL, 6.50 mmol) in dry THF (12 mL) at −78 °C under an argon atmosphere. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (3.5 mL) was added in one portion, and the mixture was then stirred at −78 °C for 1 h. A solution of **3** (5.00 mmol) in THF (7 mL) was then added over 10 min, keeping the temperature below −78 °C during the addition. After 1 h stirring at −78 °C, the *N*-(bromomethyl)phthalimide (1.44 g, 6.00 mmol) was added dropwise in dry THF (9 mL) at the same temperature. The mixture was stirred for an additional 1 h at −78 °C, and then warmed slowly to room temperature. After 16 h stirring at room temperature the reaction mixture was quenched with 1 N HCl (60 mL), and then extracted with diethyl ether (3 × 100 mL). The combined ether extracts were washed with water, dried (Na_2SO_4), and concentrated in vacuo to afford a yellowish solid. The solid was then purified by chromatography on silica gel to give **4** as colourless crystals.

Method B: A solution of *n*-butyllithium (2.5 M) in hexane (2.4 mL, 6.00 mmol) was added dropwise over 5 min to a stirred solution of hexamethyldisilazane (1.37 mL, 6.50 mmol) in dry THF (12 mL) at −78 °C under argon and the mixture was then stirred for 1 h at −78 °C. A solution of **3** (5.00 mmol) in THF (7 mL) was then added over 10 min, keeping the temperature below −78 °C during the addition. After stirring the mixture for 1 h at −78 °C, the *N*-(bromomethyl)phthalimide (1.44 g, 6.00 mmol), was added dropwise in dry THF (9 mL) at the same temperature. The mixture was stirred for an additional 1 h at −78 °C, and then warmed slowly to room temperature. After 16 h stirring at room temperature, the reaction was treated as described in method A.

(*RS*)-Benzyl 2-(4-Methoxyphenyl)-3-phthalimidopropanoate (4a): Following method B from benzyl (4-methoxyphenyl)acetate (1.23 g, 5.00 mmol), **4a** (1.49 g, 3.60 mmol, 72% yield), was obtained as a colourless solid after chromatography, (eluent E) R_f = 0.34. − m.p. 148 °C. − IR (KBr): $\tilde{\nu}$ = 2990 w, 2952 m, 2830 w, 1773 m, 1707s, 1613 m, 1509 m. − ^{1}H NMR ($CDCl_3$): δ = 3.75 (s, 3 H, 0CH_3), 4.16 (m, 3 H, CH−CH_2−N and CH−CH_2−N), 5.02 (d, J = 12.4 Hz, 1 H, $HCHC_6H_5$), 5.08 (d, J = 12.4 Hz, 1 H, $HCHC_6H_5$), 6.75 [d, J = 10.3 Hz, 2 H, $C_6H_4(OCH_3)$], 7.20 [m, 7 H, C_6H_5 and $C_6H_4(OCH_3)$], 7.67 (m, 2 H, *H*-phthalyl), 7.75 (m, 2 H, *H*-phthalyl). − ESI-MS; *m/z* (%): 415.9 (50) [(M + H)$^+$], 269.9 (100). − $C_{25}H_{21}NO_5$ (415.4) calcd. C 72.36, H 5.10, N 3.38; found C 72.16, H 5.26, N 3.28.

(*RS*)-Benzyl 2-(4-Fluorophenyl)-3-phthalimidopropanoate (4b): Following method B from benzyl (4-fluorophenyl)acetate (1.21 g, 5.00 mmol), **4b** (1.51 g, 3.70 mmol, 75% yield), was obtained as a colourless solid after chromatography, (eluent E) R_f = 0.65. − m.p. 107 °C. − IR (KBr): $\tilde{\nu}$ = 3047 w, 2924 m, 2849 w, 1773 m, 1731 s, 1707 s, 1603 m, 1509 m. − ^{1}H NMR ($CDCl_3$): δ = 4.18 (m, 3 H, CH−CH_2−N and CH−CH_2−N), 5.08 (d, J = 12.3 Hz, 1 H, $HCHC_6H_5$), 5.12 (d, J = 12.3 Hz, 1 H, $HCHC_6H_5$), 6.94 (t, $J_1 = J_2$ = 8.7 Hz, 2 H, C_6H_4F), 7.24 (m, 7 H, C_6H_5 and C_6H_4F), 7.63 (m, 2 H, *H*-phthalyl), 7.71 (m, 2 H, *H*-phthalyl). − ESI-MS; *m/z* (%): 404.3 (100) [(M + H)$^+$], 312.9 (72). − $C_{24}H_{18}FNO_4$ (403.4) calcd. C 71.53, H 4.50, N 3.48; found C 71.45, H 4.38, N 3.25.

(*RS*)-Benzyl 2-(3,4-Dimethoxyphenyl)-3-phthalimidopropanoate (4c): Following method B from benzyl (3,4-dimethoxyphenyl)acetate (1.43 g, 5.00 mmol), **4c** (1.38 g, 3.10 mmol, 62% yield), was obtained as a colourless solid after chromatography, (eluent E) R_f = 0.35. − m.p. 144 °C. − IR (KBr): $\tilde{\nu}$ = 2988 w, 2934 m, 2839 m, 1769 m, 1736 s, 1712 s, 1594 m, 1514 m. − ^{1}H NMR ($CDCl_3$): δ = 3.77 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 4.20 (m, 3 H, CH−CH_2−N and CH−CH_2−N), 5.07 (d, J = 12.3 Hz, 1 H, $HCHC_6H_5$), 5.13 (d, J = 12.3 Hz, 1 H, $HCHC_6H_5$), 6.80 [m, 3 H, $C_6H_3(OCH_3)_2$], 7.22 (m, 5 H, C_6H_5), 7.68 (m, 2 H, *H*-phthalyl), 7.77 (m, 2 H, *H*-phthalyl). − ESI-MS; *m/z* (%): 446.1 (100) [(M + H)$^+$]. − $C_{26}H_{23}NO_6$ (445.5) calcd. C 70.18, H 5.21, N 3.15; found C 70.10, H 5.34, N 3.18.

(*RS*)-Benzyl 2-(α-Naphthyl)-3-phthalimidopropanoate (4d): Following method A from benzyl (α-naphthyl)acetate (1.38 g, 5.00 mmol), **4d** (1.52 g, 3.50 mmol, 70% yield), was obtained as a colourless solid after chromatography, (eluent E) R_f = 0.59. − m.p. 129 °C. − IR (KBr): $\tilde{\nu}$ = 3056 m, 2934 m, 1773 m, 1736 s, 1709 s, 1594 w, 1500 m. − ^{1}H NMR ($CDCl_3$): δ = 4.15 (dd, J = 6.7 Hz and J = 13.8 Hz, 1 H, HCH−N), 4.53 (dd, J = 8.8 Hz and J = 13.8 Hz, 1 H, HCH−N), 5.13 (s, 2 H, $CH_2C_6H_5$), 5.23 (dd, J = 6.7 Hz and J = 8.8 Hz, 1 H, CH−CH_2−N), 7.18 (m, 5 H, C_6H_5), 7.50 (m, 4 H, *H*-naphthyl), 7.70 (m, 2 H, *H*-phthalyl), 7.85 (m, 4 H, *H*-naphthyl and *H*-phthalyl), 8.30 (m, 1 H, *H*-naphthyl). − ESI-MS; *m/z* (%): 436.1 (100) [(M + H)$^+$]. − $C_{28}H_{21}NO_4$ (435.5) calcd. C 77.31, H 4.87, N 3.22; found C 77.23, H 4.92, N 3.35.

General Procedure for the Preparation of (*RS*)-2-Aryl-3-phthalimidopropanoic Acids (5): (*RS*)-Benzyl 2-aryl-3-phthalimidopropanoates **4** (1.50 mmol) were added to a cooled (−20 °C) solution of 20% palladium hydroxide on charcoal (0.01 g) in ethyl acetate (4 mL). The mixture was then stirred for 5−6 h at room temperature under H_2 (the reaction was monitored by tlc). After filtration through Celite, concentration of the filtrate yielded the expected compounds **5**.

(*RS*)-2-(3-Methoxyphenyl)-3-phthalimidopropanoic Acid (5a): Following the general procedure from (*RS*)-benzyl 2-(4-methoxyphenyl)-3-phthalimidopropanoate (0.63 g, 1.50 mmol), **5a** (0.45 g, 1.40 mmol, 97% yield), was obtained as a colourless solid, m.p.

186° C. − IR (KBr): ṽ = 3500−2500 br, 2952 w, 2839 w, 1773 m, 1707 s, 1509 m, 1179 m, 709 m. − ^{1}H NMR ($CDCl_3$): δ = 3.74 (s, 3 H, OCH_3), 4.24 (m, 3 H, CH_2−N and CH−CH_2−N), 6.80 [d, J = 8.7 Hz, 2 H, $C_6H_4(OCH_3)$], 7.23 [d, J = 8.7 Hz, 2 H, $C_6H_4(OCH_3)$], 7.68 (m, 2 H, *H*-phthalyl), 7.77 (m, 2 H, *H*-phthalyl). − ESI-MS; *m*/*z* (%): 326.2 (45) [(M + H)$^+$], 307.9 (15), 280 (100). − $C_{18}H_{15}NO_5$ (325.3) calcd. C 66.52, H 4.65, N 4.31; found C 66.58, H 4.55, N 4.42.

(*RS*)-2-(4-Fluorophenyl)-3-phthalimidopropanoic Acid (5b): Following the general procedure from (*RS*)-benzyl 2-(4-fluorophenyl)-3-phthalimidopropanoate (0.60 g, 1.50 mmol), **5b** (0.42 g, 1.40 mmol, 92% yield), was obtained as a colourless solid, m.p. 175° C. − IR (KBr): ṽ = 3500−2500 br, 2950 w, 2924 w, 1769 m, 1707 s, 1500 m, 1221 m, 716 m. − ^{1}H NMR ($CDCl_3$): δ = 4.27 (m, 3 H, CH_2−N and CH−CH_2−N), 6.96 (t, J_1 = J_2 = 8.6 Hz, 2 H, C_6H_4F), 7.30 (dd, J = 8.6 Hz and J = 5.2 Hz, 2 H, C_6H_4F), 7.68 (m, 2 H, *H*-phthalyl), 7.76 (m, 2 H, *H*-phthalyl). − ESI-MS; *m*/*z* (%): 313.9 (82) [(M + H)$^+$], 296.1 (65), 268.2 (45). − $C_{17}H_{12}FNO_4$ (313.3) calcd. C 65.24, H 3.86, N 4.47; found C 65.13, H 3.75, N 4.52.

(*RS*)-2-(3,4-Dimethoxyphenyl)-3-phthalimidopropanoic Acid (5c): Following the general procedure from (*RS*)-benzyl 2-(3,4-dimethoxyphenyl)-3-phthalimidopropanoate (0.67 g, 1.50 mmol), **5c** (0.46 g, 1.40 mmol, 96% yield), was obtained as a white solid, m.p. 149 °C. − IR (KBr): ṽ = 3500−2500 br, 2952 w, 2924 w, 2839 w, 1760 m, 1707 s, 1584 m, 1514 m, 718 m. − ^{1}H NMR ($CDCl_3$): δ = 3.80 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 4.23 (m, 3 H, CH_2−N and CH−CH_2−N), 6.74 [d, J = 8.0 Hz, 1 H, $C_6H_3(OCH_3)_2$], 6.84 [s, 1 H, $C_6H_3(OCH_3)_2$], 6.87 [d, J = 8.0 Hz, 1 H, $C_6H_3(OCH_3)_2$], 7.66 (m, 2 H, *H*-phthalyl), 7.71 (m, 2 H, *H*-phthalyl). − ESI-MS; *m*/*z* (%): 356.1 (64) [(M + H)$^+$], 309.9 (100). − $C_{19}H_{17}NO_6$ (355.3) calcd. C 64.29, H 4.83, N 3.95; found C 64.20, H 4.90, N 3.83.

(*RS*)-2-(α-Naphthylphenyl)-3-phthalimidopropanoic Acid (5d): Following the general procedure from (*RS*)-benzyl 2-(α-naphthyl)-3-phthalimidopropanoate (0.65 g, 1.50 mmol), **5d** (0.48 g, 1.40 mmol, 92% yield), was obtained as a colourless solid, m.p. 164° C. − IR (KBr): ṽ = 3500−2500 br, 2945 w, 2924 w, 1764 m, 1740 s, 1707 s, 1688 m, 1537 m, 1198 m, 720 m. − ^{1}H NMR ($CDCl_3$): δ = 4.16 (dd, J = 7.3 Hz and J = 13.8 Hz, 1 H, *H*CH−N), 4.48 (dd, J = 8.3 Hz and J = 13.8 Hz, 1 H, *H*CH−N), 5.20 (dd, J = 7.3 Hz and J = 8.3 Hz, 1 H, CH−CH_2−N), 7.50 (m, 10 H, *H*-naphthyl and *H*-phthalyl), 8.19 (m, 1 H, *H*-naphthyl). − ESI-MS; *m*/*z* (%): 345.9 (85) [(M + H)$^+$], 328.1 (100), 299.9 (58). − $C_{21}H_{15}NO_4$ (345.4) calcd. C 73.11, H 4.38, N 4.06; found C 73.03, H 4.44, N 3.95.

General Procedure for the Preparation of (*RS*)-2-Aryl-3-phthalimidopropanoic Acid Chlorides (6): A mixture of the (*RS*)-2-aryl-3-phthalimidopropanoic acid (1 equiv.) and oxalyl chloride (10 equiv.) was stirred under argon at 30 °C for 12 h. Evaporation of excess oxalyl chloride yielded the corresponding (*RS*)-2-aryl-3-phthalimidopropanoic acid chloride **6** that was used without further purification in the following step.

General Procedure for the Preparation of the Racemic Pantolactonyl Esters (8): To (*RS*)-2-aryl-3-phthalimidopropanoic acids **5** (1.0 mmol), (*R*)-pantolactone (0.13 g, 1.00 mmol) and 4-(dimethylamino)pyridine (0.12 g, 1 equiv) in 6 mL of CH_2Cl_2 was added 1 equiv. of dicyclohexylcarbodiimide (0.21 g) at 0° C. The mixture was then stirred at room temp. for an additional 12 h. The resulting mixture was filtered and washed successively with saturated aqueous solutions of citric acid (3 × 6 mL) and saturated $NaHCO_3$ solution (3 × 6 mL), dried with Na_2SO_4, and concentrated in vacuo. The racemic mixtures (α*S*,3*R*)/(α*R*,3*R*) of the pantolactonyl esters **8** were analyzed by NMR and HPLC.

General Procedure for the Diastereoselective Addition of (*R*)-Pantolactone to Aryl Phthalimidomethyl Ketenes (7): To a stirred solution of (*RS*)-2-aryl-3-phthalimidopropanoic acid chlorides **6** (0.60 mmol) in 5 mL of anhydrous THF cooled to 0° C under argon, was added 1.1 equivalents of NR_3 in THF (0.3 mL). After t_1 hours stirring at room temperature, a solution of 1.2 equivalents of (*R*)-pantolactone in 0.3 mL of THF was added. After t_2 hours at T °C (monitoring the reaction by tlc), a 1 N citric acid solution (5 mL) was added at 0 °C and the solution was extracted with AcOEt (3 × 10 mL). The organic layer was washed successively with water, sodium bicarbonate solution and dried with sodium sulfate. Evaporation in vacuo yielded the pantolactonyl esters **8**.

4′,4′-Dimethyl-γ-butyrolacton-3′-yl 2-(4-Methoxyphenyl)-3-phthalimidopropanoate (8a): Following the general procedure (NR_3 = quinuclidine, t_1 = 2 h; t_2 = 5 h; T = room temp.) from (*RS*)-2-(4-methoxyphenyl)-3-phthalimidopropanoic acid chloride (0.20 g, 0.60 mmol), **(α*S*,3′*R*)-8a** (0.24 g, 80% *de*) was obtained as a crude product, which after purification by column chromatography (silica gel, ethyl acetate/hexane 1:1) yielded **(α*S*,3′*R*)-8a** as a colourless solid (0.19 g, 75% yield, 80% *de*). Crystallisation from a mixture of ethyl acetate and hexane gave optically pure **(α*S*,3′*R*)-8a** (0.11 g, 45% yield, >99% *de*). − m.p. 130 °C; $[\alpha]_D^{20}$ = −95 (*c* = 2 in CH_2Cl_2). − IR (KBr): ṽ = 2943 m, 2896 m, 2830 m, 1798 s, 1775 s, 1745 s, 1717 s, 1613 m, 1504 m, 1151 m, 717 s. − ESI-MS; *m*/*z* (%): 438.1 (100) [(M + H)$^+$], 308.2 (18), 280.0 (22). − $C_{24}H_{23}NO_7$ (437.4) calcd. C 65.97, H 5.31, N 3.21; found C 65.91, H 5.16, N 3.21.

Main Diastereoisomer (α*S*,3′*R*)-8a: HPLC (condition B): ret. time = 39.6 min. − ^{1}H NMR ($CDCl_3$): δ = 1.01 (s, 3 H, 4′−CH_3), 1.13 (s, 3 H, 4′-CH_3), 3.76 (s, 3 H, OCH_3), 3.91 (d, J = 8.9 Hz, 1 H, 5′-HC*H*), 3.95 (d, J = 8.9 Hz, 1 H, 5′-HC*H*), 4.12 (dd, J = 7.4 Hz and J = 13.6 Hz, 1 H, HC*H*−N), 4.27 (dd, J = 7.4 Hz and J = 13.6 Hz, 1 H, HC*H*−N), 4.43 [t, J_1 = J_2 = 7.4 Hz, 1 H, *H*C−$C_6H_4(OCH_3)$], 5.30 (s, 1 H, 3′-C*H*), 6.77 [d, J = 8.7 Hz, 2 H, $C_6H_4(OCH_3)$], 7.24 [d, J = 8.7 Hz, 2 H, $C_6H_4(OCH_3)$], 7.70 (m, 2 H, *H*-phthalyl), 7.77 (m, 2 H, *H*-phthalyl).

Minor Diastereoisomer (α*R*,3′*R*)-8a: HPLC (condition B): ret. time = 36.7 min. − ^{1}H NMR ($CDCl_3$): δ = 0.75 (s, 3 H, 4′-CH_3), 1.01 (s, 3 H, 4′-CH_3), 3.76 (s, 3 H, OCH_3), 3.94 (s, 2 H, 5′-CH_2), 4.21 (d, J = 8.4 Hz, 1 H, HC*H*−N), 4.22 (d, J = 7.3 Hz, 1 H, HC*H*−N), 4.46 [dd, J = 7.3 Hz and J = 8.4 Hz, 1 H, *H*C−$C_6H_4(OCH_3)$], 5.34 (s, 1 H, 3′-C*H*), 6.77 [d, J = 8.7 Hz, 2 H, $C_6H_4(OCH_3)$], 7.24 [d, J = 8.7 Hz, 2 H, $C_6H_4(OCH_3)$], 7.70 (m, 2 H, *H*-phthalyl), 7.77 (m, 2 H, *H*-phthalyl).

4′,4′-Dimethyl-γ-butyrolacton-3′-yl 2-(4-Fluorophenyl)-3-phthalimidopropanoate (8b): Following the general procedure (NR_3 = NEt_3, t_1 = 2 h; t_2 = 15 h; T = 0 °C) from (*RS*)-2-(4-fluorophenyl)-3-phthalimidopropanoic acid chloride (0.20 g, 0.60 mmol), **(α*S*,3′*R*)-8b** (0.23 g, 84% *de*) was obtained as a crude product, which after purification by column chromatography (silica gel, ethyl acetate/hexane 3:7) yielded **(α*S*,3′*R*)-8b** as a colourless solid (0.18 g, 72% yield, 84% *de*). Crystallisation from diethyl ether gave optically pure **(α*S*,3′*R*)-8b** (0.14 g, 52% yield, >99% *de*); m.p. 127 °C. − $[\alpha]_D^{20}$ = −90 (*c* = 2 in CH_2Cl_2). − IR (KBr): ṽ = 3056 w, 2943 m, 2877 m, 1788 s, 1750 s, 1712 s, 1610 m, 1504 m, 1160 m, 727 s. − ESI-MS; *m*/*z* (%): 426.2 (100) [(M + H)$^+$], 296 (28), 267.8 (6). − $C_{23}H_{20}FNO_6$ (425.4) calcd. C 65.00, H 4.74, N 3.30; found C 64.83, H 4.63, N 3.28.

Main Diastereoisomer (α*S*,3′*R*)-8b: HPLC (condition B): ret. time = 29.8 min. − ^{1}H NMR ($CDCl_3$): δ = 1.01 (s, 3 H, 4′-CH_3), 1.14 (s, 3 H, 4′-CH_3), 3.97 (d, J = 9.0 Hz, 1 H, 5′-HC*H*), 3.99 (d,

J = 9.0 Hz, 1 H, 5′-HC*H*), 4.18 (dd, J = 8.6 Hz and J = 13.6 Hz, 1 H, HC*H*−N), 4.28 (dd, J = 7.2 Hz and J = 13.6 Hz, 1 H, HC*H*−N), 4.46 (dd, J = 7.2 Hz and J = 8.6 Hz, 1 H, *H*C−C_6H_4F), 5.27 (s, 1 H, 3′-C*H*), 6.95 (t, $J_1 = J_2$ = 8.6 Hz, 2 H, C_6H_4F), 7.30 (dd, J = 8.6 Hz and J = 5.2 Hz, 2 H, C_6H_4F), 7.64 (m, 2 H, *H*-phthalyl), 7.73 (m, 2 H, *H*-phthalyl).

Minor Diastereoisomer (α*R*,3′*R*)-8b: HPLC (condition B): ret. time = 27.2 min. − ^{1}H NMR ($CDCl_3$): δ = 0.71 (s, 3 H, 4′-CH_3), 0.99 (s, 3 H, 4′-CH_3), 3.91 (s, 2 H, 5′-CH_2), 4.21 (d, J = 8.0 Hz, 2 H, CH_2−N), 4.45 (t, J = 8.0 Hz, 1 H, *H*C−C_6H_4F), 5.31 (s, 1 H, 3′-C*H*), 6.95 (t, $J_1 = J_2$ = 8.6 Hz, 2 H, C_6H_4F), 7.30 (dd, J = 8.6 Hz and J = 5.2 Hz, 2 H, C_6H_4F), 7.64 (m, 2 H, *H*-phthalyl), 7.73 (m, 2 H, *H*-phthalyl).

4′,4′-Dimethyl-γ-butyrolacton-3′-yl 2-(3,4-Dimethoxyphenyl)-3-phthalimidopropanoate (8c): Following the general procedure (NR_3 = quinuclidine, t_1 = 1 h; t_2 = 15 h; T = 0 °C) from (*RS*)-2-(3,4-dimethoxyphenyl)-3-phthalimidopropanoic acid (0.22 g, 0.60 mmol), **(α*S*,3′*R*)-8c** (0.25 g, 88% *de*) was obtained as a crude product, which after purification by column chromatography (silica gel, ethyl acetate/hexane 1:1) yielded **(α*S*,3′*R*)-8c** (as a colourless solid (0.19 g, 70% yield, 88% *de*). Crystallisation from diethyl ether yielded optically pure **(α*S*,3′*R*)-8c** (0.15 g, 55% yield, >99% *de*); m.p. 124 °C; $[\alpha]_D^{20} = -99$ (c = 2 in CH_2Cl_2). − IR (KBr): ṽ = 2967 m, 2952 m, 2917 m, 1787 s, 1740 s, 1712 s, 1594 m, 1509 m, 1151 m, 717 s. − ESI-MS; *m*/*z* (%): 935.0 (13), 468.2 (100) [(M + H)$^+$], 337.9 (12), 309.9 (20). $C_{25}H_{25}NO_8$ (467.5) calcd. C 64.30, H 5.40, N 3.00; found C 64.20, H 5.46, N 3.11.

Main Diastereoisomer (α*S*,3′*R*)-8c: HPLC (condition B): ret. time = 58.8 min. − ^{1}H NMR ($CDCl_3$): δ = 1.01 (s, 3 H, 4′-CH_3), 1.13 (s, 3 H, 4′-CH_3), 3.81 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.96 (d, J = 9.0 Hz, 1 H, 5′-HC*H*), 3.98 (d, J = 9.0 Hz, 1 H, 5′-HC*H*), 4.25 (dd, J = 7.3 Hz and J = 8.0 Hz, 2 H, CH_2−N), 4.44 (dd, J = 7.3 Hz and J = 8.0 Hz, 1 H, *H*C−$C_6H_3(OCH_3)_2$), 5.31 (s, 1 H, 3′-C*H*), 6.74 [d, J = 8.4 Hz, 1 H, $C_6H_3(OCH_3)_2$], 7.84 [s, 1 H, $C_6H_3(OCH_3)_2$], 7.87 [d, J = 8.4 Hz, 1 H, $C_6H_3(OCH_3)_2$], 7.69 (m, 2 H, *H*-phthalyl), 7.78 (m, 2 H, *H*-phthalyl).

Minor Diastereoisomer (α*R*,3′*R*)-8c: HPLC (condition B): ret. time = 55.5 min. − ^{1}H NMR ($CDCl_3$): δ = 0.77 (s, 3 H, 4′-CH_3), 1.04 (s, 3 H, 4′-CH_3), 3.81 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.95 (s, 2 H, 5′-CH_2), 4.19 (dd, J = 8.0 Hz and J = 13.8 Hz, 1 H, HC*H*−N), 4.27 (dd, J = 8.0 Hz and J = 13.8 Hz, 1 H, HC*H*−N), 4.46 [t, $J_1 = J_2$ = 8.0 Hz, 1 H, *H*C−$C_6H_3(OCH_3)_2$], 5.36 (s, 1 H, 3′-C*H*), 6.74 [d, J = 8.4 Hz, 1 H, $C_6H_3(OCH_3)_2$], 7.84 [s, 1 H, $C_6H_3(OCH_3)_2$], 7.87 [d, J = 8.4 Hz, 1 H, $C_6H_3(OCH_3)_2$], 7.69 (m, 2 H, *H*-phthalyl), 7.78 (m, 2 H, *H*-phthalyl).

4′,4′-Dimethyl-γ-butyrolacton-3′-yl 2-(α-Naphthyl)-3-phthalimidopropanoate (8d): Following the general procedure (NR_3 = quinuclidine, t_1 = 1 h; t_2 = 5 h; T = room temperature) from (*RS*)-2-(α-naphthylphenyl)-3-phthalimidopropanoic acid (0.22 g, 0.60 mmol), **(α*S*,3′*R*)-8d** (0.26 g, 84% *de*) was obtained as a crude product, which after purification by column chromatography (silica gel, ethyl acetate/hexane 1:1) yielded **(α*S*,3′*R*)-8d** as a colourless solid (0.2 g, 72% yield, 84% *de*). A second column chromatography (silica gel CH_2Cl_2/ethyl acetate 9.5:0.5) yielded optically pure **(α*S*,3′*R*)-8d** (0.14 g, 52% yield, >99% *de*); m.p. 88 °C. − $[\alpha]_D^{20}$ = −115 (c = 2 in CH_2Cl_2). − IR (KBr): ṽ = 3047 w, 2962 m, 2915 m, 2868 m, 1789 s, 1744 s, 1710 s, 1453 m, 717 m. − ESI-MS; *m*/*z* (%): 458.3 (100) [(M + H)$^+$], 328.2 (22), 300.1 (12). $C_{27}H_{23}NO_6$ (457.5) calcd. C 70.96, H 5.07, N 3.06; found C 70.64, H 4.91, N 2.99.

Main Diastereoisomer (α*S*,3′*R*)-8d: HPLC (condition B): ret. time = 32.6 min. − ^{1}H NMR ($CDCl_3$): δ = 0.89 (s, 3 H, 4′-CH_3), 1.08 (s, 3 H, 4′-CH_3), 3.97 (s, 2 H, 5′-CH_2), 4.25 (dd, J = 6.7 Hz and J = 13.8 Hz, 1 H, HC*H*−N), 4.59 (dd, J = 8.9 Hz and J = 13.8 Hz, 1 H, HC*H*−N), 5.34 (s, 1 H, 3′-C*H*), 5.39 (dd, J = 6.7 Hz and J = 8.9 Hz, 1 H, *H*C-naphthyl), 7.50 (m, 3 H, *H*-naphthyl), 7.63 (m, 3 H, *H*-naphthyl and *H*-phthalyl), 7.82 (m, 4 H, *H*-naphthyl and *H*-phthalyl), 8.20 (d, J = 8.4 Hz, 1 H, *H*-naphthyl).

Minor Diastereoisomer (α*R*,3′*R*)-8d: HPLC (condition B): ret. time = 30.20 min. − ^{1}H NMR ($CDCl_3$): δ = 0.47 (s, 3 H, 4′-CH_3), 0.93 (s, 3 H, 4′-CH_3), 3.85 (d, J = 8.9 Hz, 1 H, 5′-HC*H*), 4.05 (d, J = 8.9 Hz, 1 H, 5′-HC*H*), 4.19 (dd, J = 6.5 Hz and J = 13.9 Hz, 1 H, HC*H*−N), 4.52 (dd, J = 8.7 Hz and J = 13.9 Hz, 1 H, HC*H*−N), 5.38 (s, 1 H, 3′-C*H*), 5.40 (dd, J = 6.5 Hz and J = 8.7 Hz, 1 H, *H*C-naphthyl), 7.50 (m, 3 H, *H*-naphthyl); 7.63 (m, 3 H, *H*-naphthyl and *H*-phthalyl); 7.82 (m, 4 H, *H*-naphthyl and *H*-phthalyl); 8.20 (d, J = 8.4 Hz, 1 H, *H*-naphthyl).

General Procedure for the Hydrolysis of 4′,4′-Dimethyl-γ-butyrolacton-3′-yl 2-Aryl-3-phthalimidopropanoate (8): A mixture of the pantolactonyl esters **8** (0.50 mmol), acetic acid (1.4 mL) and a 6 N HCl solution (14 mL) was heated under reflux 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). Concentration in vacuo of the aqueous layer followed by propylene oxide treatment yielded the free amino acids **9**.

(*S*)-(−)-3-Amino-2-(4-methoxyphenyl)propanoic Acid (9a): From **(α*S*,3′*R*)-8a** (0.22 g, >99% *de*), **(*S*)-9a** (0.08 g, 85% yield, 95% *ee*) was obtained as a solid m.p. >260 °C. − $[\alpha]_D^{20} = -89$ (c = 2 in 0.1 N HCl). − IR (KBr): ṽ = 3000−2500 br, 2190 m, 1556 s, 1514 s, 1258 m, 1030 m, 830 s. − ^{1}H NMR (D_2O): δ = 3.16 (dd, J = 7.5 Hz and J = 12.8 Hz, 1 H, HC*H*−N), 3.34 (dd, J = 7.5 Hz and J = 12.8 Hz, 1 H, HC*H*−N), 3.65 [t, $J_1 = J_2$ = 7.5 Hz, 1 H, *H*C−$C_6H_4(OCH_3)$], 3.74 (s, 3 H, OCH_3), 6.92 (d, J = 8.5 Hz, 2 H, *H* arom.), 7.18 (d, J = 8.5 Hz, 2 H, *H* arom.). − ESI-MS; *m*/*z* (%): 196.1 (100) [(M + H)$^+$], 178.1 (48), 149.9 (26). − $C_{10}H_{13}NO_3$ (195.2) calcd. C 61.60, H 6.72, N 7.18; found C 61.68, H 6.63, N 7.10.

(*S*)-(−)-3-Amino-2-(4-fluorophenyl)propanoic Acid (9b): From **(α*S*,3′*R*)-8b** (0.21 g, >99% *de*), **(*S*)-9b** (0.07 mg, 82% yield, 92% *ee*) was obtained as a solid m.p. >260 °C. − $[\alpha]_D^{20}$ = − 78 (c = 2 in 0.1 N HCl). − IR (KBr): ṽ =3000−2500 br, 2100 m, 1551 s, 1500 s, 1382 m, 830 s. − ^{1}H NMR (D_2O): δ = 3.18 (dd, J = 7.3 Hz and J = 12.8 Hz, 1 H, HC*H*−N), 3.36 (dd, J = 7.3 Hz and J = 12.8 Hz, 1 H, HC*H*−N), 3.70 (t, $J_1 = J_2$ = 7.3 Hz, 1 H, *H*C−C_6H_4F), 7.06 (t, $J_1 = J_2$ = 8.5 Hz, 2 H, C_6H_4F), 7.23 (dd, J = 5.5 Hz and J = 8.5 Hz, 2 H, C_6H_4F). − ESI-MS; *m*/*z* (%): 183.9 (100) [(M + H)$^+$], 166.1 (8), 138.1 (5). − $C_9H_{10}FNO_2$ (183.2) calcd. C 59.07, H 5.51, N 7.65; found C 59.19, H 5.63, N 7.50.

(*S*)-(−)-3-Amino-2-(3,4-dimethoxyphenyl)propanoic Acid (9c): From **(α*S*,3′*R*)-8c** (0.23 g, >99% *de*), **(*S*)-9c** (0.09 g, 84% yield, 94% *ee*) was obtained as a solid m.p. >260 °C. − $[\alpha]_D^{20} = -75$ (c = 2 in 0.1 N HCl). − IR (KBr): ṽ = 3000−2500 br, 2180 w, 1731 w, 1632 m, 1552 s, 1514 s, 1030 m, 830 m. − ^{1}H NMR (D_2O): δ = 3.30 (dd, J = 7.4 Hz and J = 12.6 Hz, 1 H, HC*H*−N), 3.50 (dd, J = 7.4 Hz and J = 12.6 Hz, 1 H, HC*H*−N), 3.79 [t, $J_1 = J_2$ = 7.4 Hz, 1 H, *H*C−$C_6H_3(OCH_3)_2$], 3.89 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 7.05 (m, 3 H, *H* arom.). − ESI-MS; *m*/*z* (%): 451.2 (8), 225.9 (100) [(M + H)$^+$], 207.9 (25), 179.8 (18). − $C_{11}H_{15}NO_4$ (225.2) calcd. C 58.72, H 6.70, N 6.23; found C 58.66, H 6.78, N 6.17.

(*S*)-(−)-3-Amino-2-(α-naphthyl)propanoic Acid (9d): From **(α*S*,3′*R*)-8d** (0.23 g, >99% *de*), **(*S*)-9d** (0.08 mg, 79% yield, 94% *ee*) was obtained as a solid m.p. >260 °C. − $[\alpha]_D^{20}$ = − 90 (*c* = 0.8 in 0.1 N HCl). − IR (KBr): $\tilde{\nu}$ = 3000−2500 br, 1735 m, 1551 s, 1504 m, 1367 m, 750 m. − ^{1}H NMR ([D$_6$]DMSO): δ = 3.15 (dd, *J* = 4.8 Hz and *J* = 12.8 Hz, 1 H, HC*H*−N), 3.57 (dd, *J* = 9.2 Hz and *J* = 12.8 Hz, 1 H, HC*H*−N), 4.77 (dd, *J* = 4.8 Hz and *J* = 9.2 Hz, 1 H, *H*C-naphthyl), 7.48 (d, *J* = 7.0 Hz, 1 H, *H*-naphthyl), 7.62 (m, 3 H, *H*-naphthyl), 8.05 (d, *J* = 8.0 Hz, 1 H, *H*-naphthyl), 8.26 (d, *J* = 8.4 Hz, 1 H, *H*-naphthyl). − ESI-MS; *m*/*z* (%): 216.0 (100) [(M + H)$^+$], 198.6 (18), 169.9 (12). − $C_{13}H_{13}NO_2$ (215.3) calcd. C 72.63, H 6.09, N 6.51; found C 72.68, H 6.15, N 6.42.

(*S*)-(−)-3-(*tert*-butoxycarbonylamino-(α-naphthyl)propanoic Acid (10d): 3-Amino-2-(α-naphthyl)propanoic acid **9d** (0.06 g, 0.30 mmol), 0.65 mmol of aqueous 1 N NaOH (0.65 mL), $(Boc)_2O$ (0.09 g, 0.40 mmol) and THF (1 mL) were stirred at room temperature for 48 h. The mixture was then diluted with water (1 mL) and washed with diethyl ether (3 × 1 mL). The aqueous extract was acidified to pH 4 and extracted with diethyl acetate. The organic layer was dried (Na_2SO_4) and after concentration in vacuo a colourless solid was obtained (0.06 g, 65% yield); m.p. 139 °C. − $[\alpha]_D^{20}$ = −128 (*c* = 1.2 in $CHCl_3$). − ^{1}H NMR ($CDCl_3$) (some of the signals were doublet up probably due to the presence of rotamers) δ = 1.38 and 1.52 [s, 9 H, $NHCO_2C(CH_3)_3$], 3.46 and 3.64 (m, 2 H, CH_2−NHBoc), 4.63 and 4.75 (m, 1 H, C*H*-naphthyl), 5.10 (br, 1 H, N*H*Boc), 7.46 (m, 4 H, *H*-naphthyl), 7.78 (m, 2 H, *H*-naphthyl), 8.16 (d, *J* = 8.4 Hz, 1 H, *H*-naphthyl).

General Procedure for the Preparation of FDAA Derivatives:[13] To an aqueous solution of 5.0 μmol of the β-amino acid (**9a−d**) was added 200 μL of 1% acetone solution of FDAA [1-fluoro-2,4-dinitrophenyl-(5*S*)-alanine amide] (2 mg, 7.2 μmol) followed by 40 μL of 1 M $NaHCO_3$ (40.0 μmol). The mixture was heated at 30−40 °C for 1 hour with frequent mixing. After cooling to room temperature, 40 μL of 1 N HCl (40.0 μmol) was added. The mixture was concentrated and dried in vacuo over phosphorus pentoxide. The residue dissolved in 0.5 mL of [D$_6$]DMSO was analysed by ^{1}H NMR and the enantiomeric excess of the β-amino acid was determined using aromatic proton signals of the DFAA derivative.

Crystal Data for (α*S*,3′*R*)-8a: $C_{24}H_{23}NO_7$ *M* = 437.4, triclinic, space group *P*1, *Z* = 2, *a* = 8.9602(6), *b* = 10.4005 (7), *c* = 11.9365(5) Å, *V* = 1102.6(2) Å^3, $d_{calcd.}$ = 1.32 mg cm^{-3}, λ(Mo-*K*α) = 0.71073 Å, μ = 0.097 mm^{-1}. Intensity data were measured with a Enraf−Nonius Kappa CCD diffractometer using graphite-monochromate Mo-*K*α radiation and the φ-scan technique up to θ = 25.45; 4084 collected reflections, 4084 unique (R_{int} = 0.032) of which 3470 were considered as observed having $I \geq 3\sigma(I)$. The hydrogen atoms are in theoretical positions. Refinement was carried out by minimizing the function $w(F_o^2 - |F_c|^2)^2$, *R* = 0.046 and wR_2 = 0.069 goodness of fit 1.036. The residual electron density in the final difference map was located between −0.19 and 0.16 eÅ^3.

Crystal Data for (α*S*,3′*R*)-8b: $C_{23}H_{20}FNO_6$ *M* = 425.4, orthorhombic, space group $P2_1\,2_1\,2_1$, *Z* = 4, *a* = 9.5666(3), *b* = 11.1026(2), *c* = 20.3200(6) Å, *V* = 2158.3(2) Å^3, $d_{calcd.}$ = 1.31 mg cm^{-3}, λ(Mo-*K*α) = 0.71 Å, μ = 0.1 mm^{-1}. Intensity data were measured with a Enraf−Nonius Kappa CCD diffractometer using graphite-monochromate Mo-*K*α radiation and the φ-scan technique up to θ = 25.41; 2379 collected reflections, 2362 unique (R_{int} = 0.028) of which 2209 were considered as observed having $I \geq 3\sigma(I)$. The hydrogen atoms are in the theoretical positions. Refinement was carried out by minimizing the function $w(F_o^2 - |F_c|^2)^2$, *R* = 0.033 and wR_2 = 0.052 goodness of fit 1.220. The residual electron density in the final difference map was located between −0.10 and 0.10 eÅ^3.

Crystal Data for (α*S*,3′*R*)-8c: $C_{25}H_{25}NO_8$ *M* = 467.5, monoclinic, space group $P2_1$, *Z* = 2, *a* = 11.560(1), *b* = 8.400 (1), *c* = 13.954(1) Å, *V* = 1318.1(4) Å^3, $d_{calcd.}$ = 1.29 mg cm^{-3}, λ(Mo-*K*α) = 0.71073 Å, μ = 0.088 mm^{-1}. Intensity data were measured with a Enraf−Nonius Kappa CCD diffractometer using graphite-monochromate Mo-*K*α radiation and the φ-scan technique up to θ = 25.41; 2742 collected reflections, 2742 unique (R_{int} = 0.062) of which 2547 were considered as observed having $I \geq 1\sigma(I)$. The hydrogen atoms are in the theoretical positions. Refinement was carried out by minimizing the function $w(F_o^2 - |F_c|^2)^2$, *R* = 0.076 and wR_2 = 0.097 goodness of fit 1.428. The residual electron density in the final difference map was located between −0.27 and 0.30 eÅ^3. Computer program: maXus.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-136875 and with the International Union of Crystallography (refGS1061).[12] Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44(1223)336−033; E-mail: deposit@ccdc.cam.ac.uk].[12]

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