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Asymmetric synthesis of α-amino acids via diastereoselective addition of (*R*)-pantolactone to their ketenes

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Abstract: The diastereoselective addition of (*R*)-pantolactone to various amino ketenes derived from phthalylamino acids is reported. The configuration of the newly-generated asymmetric center is dependent on alkyl or aryl Cα substitution. This method constitutes a novel and convenient way of amino acid deracemization. © 1997 Elsevier Science Ltd

Amino ketene derivatives are generally unstable, hence usually they have been generated *in situ*.[1] The only extensively investigated reaction involving amino ketenes concerns the cycloaddition with imines giving amino β-lactames which are constituents of penicillins. Particularly in asymmetric syntheses, the use of chiral Evans's or Oppolzer's ketenes derived from glycine affords high diastereoselectivities.[2] We considered the possiblity of using amino ketenes as intermediates in the asymmetric synthesis of amino acids. Indeed, thirty-five years ago, it was noted[3] that, in the presence of a chiral tertiary amine, addition of an achiral alcohol to the ketene prepared from a phthalylamino acid, afforded the phthalylamino acid ester with modest to 33% diastereomeric excesses, depending on the nature of the chiral base (brucine or acetylquinine) and the temperature (22°C or −96°C).

Recently Hegedus et al.[4,5] have studied the stereoselective addition of achiral alcohols or amines to chiral chromium amino ketenes generated by photolysis of the corresponding chromium amino carbene complexes. High diastereoisomeric excesses were generally obtained.[4] Moreover, we showed that the triethylamine catalyzed diastereoisomeric addition at −78°C of (*R*)-pantolactone to the N-phthalyl phenylglycine ketene affords the corresponding ester with a 98% diastereoisomeric excess. After hydrolysis optically active phenylglycine was isolated without any racemization.[6] This provided a new and convenient asymmetric synthesis of phenylglycine by deracemization of the racemic mixture.

In this work we report the diastereoselective addition of (*R*)-pantolactone **4**, a very efficient chiral auxiliary, to various alkyl phthalylamino ketenes **3** which are not as stable as the phenyl or the very bulky t-butyl phthalylamino ketene.[3]

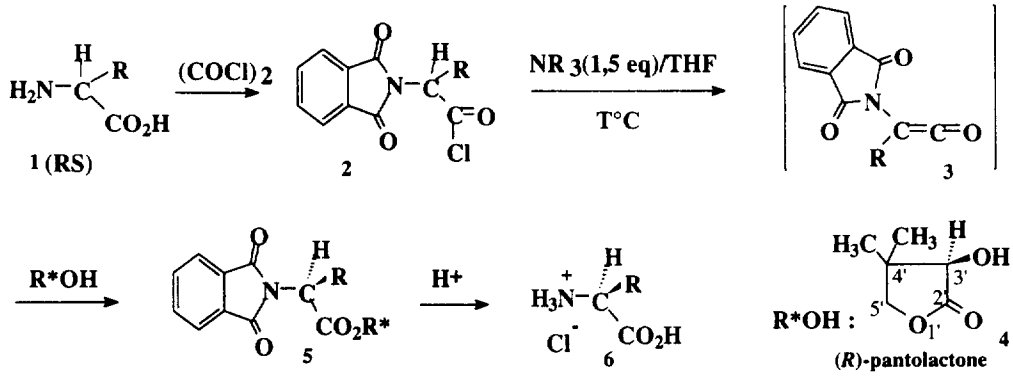

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Table 1. Yield and configuration of the C_α of phthalylamino acid pantolactonyl esters

entries	R (5)	method 1 T°C	yield	*d.e*, config C_α		method 2 T°C	yield	*d.e*, config C_α	
1	C_6H_5 (5a)	-78	96	98%	R	-78	85	36%	R
		0	63	48%	R	0	93	60%	R
						20	94	18%	R
2	4-F-C_6H_4 (5b)	-78	95	97%	R				
3	CH_3 (5c)	-78	78	70%	S	-78	96	91%	S
		0	12	54%	S	0	95	94%	S
						20	90	92%	S
4	CH_2-CH_3 (5d)	-78	80	68%	S	-78	94	72%	S
						0	95	72%	S
5	$(CH_2)_2$-CH_3 (5e)	-78	77	67%	S	0	90	78%	S
6	$(CH_2)_3$-CH_3 (5f)	-78	75	68%	S	0	85	73%	S
7	CH_2-C_6H_5 (5g)	-78	80	64%	S	-78	55	27%	S
		0	14	5%	S	0	98	71%	S
						20	90	80%	S
8	CH_2-β-naphtyl (5h)					0	92	63%	S
9	$CH(CH_3)_2$ (5i)	-78	0*	-		-78	0*	-	
		0	70	41	S	0	70	42%	S
						20	73	22%	S
10	$CH_2CH(CH_3)_2$ (5j)	-78	30	14%	S	-78	39	22%	S
		0	38	16%	S	0	69	33%	S
						20	89	31%	S

* There was no reaction after 3.5h.

In the first attempt we used the same experimental conditions as those used previously for the N-phthalyl phenylglycine[6] (method 1), *i.e.* generation of the ketene at −78°C by treatment of the phthalylamino acid chloride **2** with triethylamine (1.5 equiv) followed, 0.5 hour later, by addition of (*R*)-pantolactone **4** at the same temperature. The results are recorded in Table 1.

The first very surprising feature is that, under the same experimental conditions, the newly generated stereogenic center of all alkyl amino acid esters has the *S* configuration (Table 1: entries 3 to 10) whereas it possesses the *R* configuration in the case of arylglycine esters (Table 1: entries 1 and 2).

The second remark concerns the very low to moderate values of both chemical yields and diastereoisomeric excesses for alkylglycines, whereas both are excellent for arylglycines. The low yields may arise from the instability of the corresponding ketenes which, reacting too slowly with the hindered (*R*)-pantolactone, partially polymerize. In the case of branched amino acids, valine and leucine (Table 1: entries 9 and 10), no ester was formed at −78°C, starting phthalylamino acids being totally recovered after the workup. At this temperature, as in the case of the very hindered ter-leucine,[3] valine and leucine acid chlorides are unable either to react with pantolactone or to afford the corresponding ketene. In order to increase the branched amino acid reactivity, reactions were performed at 0°C. At this temperature the esterification took place but, surprisingly in a chemical yield lower for leucine than for the more hindered valine. The poor selectivity for valine and leucine at 0°C may stem from the competitive reactivities of partially formed ketene and remaining acid chloride towards pantolactone. This agrees with the poor Cα deuteriation of ester when (*R*)-pantolactone was replaced with (*R*)-pantolactone-OD. At the same temperature, the chemical yields dropped drastically for other alkylglycine derivatives, and many by-products were afforded probably because of polymerization of the corresponding ketene.

In order to improve both chemical yields and stereoselectivities, we modified the experimental conditions. First, under Durst and Koh's conditions,[7] the acid chloride **2** was added to a cooled solution of pantolactone **4** and triethylamine, but no marked improvement was observed. In a second attempt we reversed the addition (Table 1: method 2): a THF solution of (*R*)-pantolactone **4** and 1.5

equiv of triethylamine was added slowly to a cooled solution (0°C or −78°C) of the phthalylamino acid chloride **2**. The reaction was preferentially accomplished at 0°C (which is more convenient) in place of −78°C. Indeed for unbranched amino acids (except for arylglycines) no significant change was observed in either the chemical yield or the *d.e.* Conversely yields were slighty lower when we increased the reaction temperature to 20°C. Moreover at 0°C the esterification was very fast and went to completion after about 1 hour whereas, as in the first method, 4 to 5 hours were necessary at −78°C. In the case of branched amino acids (valine and leucine) no pantolactonyl ester was afforded after 3.5h at −78°C, and it was necessary to extend the reaction time overnight to achieve merely a 37% yield. When the reaction was carried out at 20°C instead of 0°C, we observed an improvement in the yield but a decrease in *d.e.* This decrease in selectivity was certainly due to an increase in the competitive reactivity of the acid chloride with (*R*)-pantolactone.

The cleavage of protecting groups should occur without any racemization. In a previous paper concerning N-phthalyl phenylglycine pantolactonyl ester[6] we proposed a two step cleavage consisting first in transesterification with methanol followed by cleavage of the phthalyl group with hydrazine. This method requires very precise conditions to avoid racemization. It is more convenient to perform the simultaneous cleavage of both amine and carboxylic acid protecting groups under acidic conditions by boiling with a 6N HCl/AcOH (4/1) solution for 4 hours. Under these conditions all the tested optically active amino acid hydrochlorides were obtained without additional racemization.

In conclusion, the deracemization of amino acids through the diastereoselective addition of a chiral alcohol to amino ketenes at near room temperature, proves to be a very simple and convenient possible alternative to the present popular methodology using stereoselective protonation of enolates[8] at −78°C. Work is now in progress on improving the diastereoisomeric excesses of the generated esters, particularly by using other amine protecting groups and/or other efficient chiral alcohols and catalysts.

Experimental

Tetrahydrofuran (THF) was freshly distilled under argon from sodium and benzophenone; triethylamine (NEt_3) was distilled from KOH and ninhydrin. Thin layer chromatography (tlc) was carried out on silica gel (60 F_{254}, Merck 5715) and spots located with UV light or iodine vapors (eluent A: hexane/AcOEt/AcOH 5/5/0.1; eluent B: ether/hexane 8/2). (*R*)-Pantolactone (chemical and enantiomeric purities >99%) was purchased from Fluka Chemical Co. All other chemicals were commercially pure compounds and were used as received. Melting points were determined with a Büchi apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC 250 spectrometer. Data are reported as follows: chemical shifts (δ) in ppm with respect to TMS, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad), coupling constants (J) in Hz. Diastereoisomeric excesses (*d.e.*) of **5** were determined from crude products from ^{1}H NMR spectra (DMSO-d_6) 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: 1ml/min, hexane/*iso*propanol: condition A: 80/20, condition B: 85/15, condition C: 90/10). To obtain samples of **5**, (*RS*) and (*S*) equimolecular mixtures of **1** were esterified with (*R*)-pantolactone in the presence of dicyclohexylcarbodiimide (DCC) affording 75/25 diastereoisomeric mixtures. In all cases, the 3′-C*H* signal of the alcohol moiety in (*S,R*)-**5** appears upfield shifted with respect to the corresponding signal of (*R,R*)-**5**. Racemization during acid hydrolysis of **5** was controlled by HPLC analysis (column nucleosil C_{18}, 25 cm × 4 mm, flow 1 ml/min, gradient water/acetonitrile) after derivatization with Marfey's reagent (1-fluoro 2,4-dinitrophenyl 5-(*S*) alanine amide).[9]

General procedure for the preparation of phthalyl-(RS)*-amino acids* ***1a–j***

Phthalyl-(*RS*)-amino acids **1a–j** were prepared by using free amino acids and phthalic anhydride as previously described in the literature.[10]

*N-Phthalyl-(*RS*)-phenylglycine* ***1a***

Following the general procedure from (*RS*)-phenylglycine (151 mg, 1 mmol), **1a** (258 mg, 0.92 mmol, 92% yield), was obtained as a solid, m.p. 164–166°C; tlc (eluent A) Rf=0.47; ^{1}H NMR ($CDCl_3$) δ=6.05 (s, 1H, C*H*CO_2H), 7.29 (m, 3H, *H*-phenyl), 7.51 (m, 2H, *H*-phenyl), 7.67 (m, 2H, *H*-phthalyl), 7.77 (m, 2H, *H*-phthalyl), 8.65 (br, 1H, CO_2*H*).

*N-Phthalyl-4-fluoro-(*RS*)-phenylglycine* ***1b***

Following the general procedure from 4-fluoro-(*RS*)-phenylglycine (169 mg, 1 mmol), **1b** (284 mg, 0.95 mmol, 95% yield), was obtained as a solid, m.p. 176°C; tlc (eluent A) Rf=0.44; ^{1}H NMR ($CDCl_3$) δ=6.05 (s, 1H, C*H*CO_2H), 6.98 (m, 2H, *H*-phenyl), 7.51 (m, 2H, *H*-phenyl), 7.68 (m, 2H, *H*-phthalyl), 7.79 (m, 2H, *H*-phthalyl), 6.75 (br, 1H, CO_2*H*).

*N-Phthalyl-(*RS*)-alanine* ***1c***

Following the general procedure from (*RS*)-alanine (89 mg, 1 mmol), **1c** (166 mg, 0.76 mmol, 76% yield), was obtained as a solid, m.p. 152–154°C; tlc (eluent A) Rf=0.50; ^{1}H NMR ($CDCl_3$) δ=1.70 (d, J=7.5 Hz, 3H, C*H*$_3$), 5.04 (q, J=7.5 Hz, 1H, C*H*CO_2H), 7.73 (m, 2H, *H*-phthalyl), 7.85 (m, 2H, *H*-phthalyl), 9.25 (br, 1H, CO_2*H*).

*Phthalyl-(*RS*)-amino butyric acid* ***1d***

Following the general procedure from (*RS*)-amino butyric acid (103 mg, 1 mmol), **1d** (186 mg, 0.8 mmol, 80% yield), was obtained as a solid, m.p 93–95°C; tlc (eluent A) Rf=0.50; ^{1}H NMR ($CDCl_3$) δ=0.87 (t, J=7.5 Hz, 3H, CH_2CH_3), 2.18 (m, 2H, CH_2CH_3), 4.75 (t, J=7.5 Hz, 1H, C*H*CO_2H), 7.68 (m, 2H, *H*-phthalyl), 7.80 (m, 2H, *H*-phthalyl), 8.80 (br, 1H, CO_2*H*).

*N-Phthalyl-(*RS*)-norvaline* ***1e***

Following the general procedure from (*RS*)-norvaline (117 mg, 1 mmol), **1e** (215 mg, 0.87 mmol, 87% yield), was obtained as a solid, m.p 103–105°C; tlc (eluent A) Rf=0.50; ^{1}H NMR ($CDCl_3$) δ=0.95 (t, J=7.5 Hz, 3H, $CH_2CH_2CH_3$), 1.35 (m, 2H, $CH_2CH_2CH_3$), 2.22 (m, 2H, $CH_2CH_2CH_3$), 4.94 (dd, J=4.8 Hz and J=11 Hz, C*H*CO_2H), 7.74 (m, 2H, *H*-phthalyl), 7.88 (m, 2H, *H*-phthalyl), 9.80 (br, 1H, CO_2*H*).

*N-Phthalyl-(*RS*)-norleucine* ***1f***

Following the general procedure from (*RS*)-norleucine (131 mg, 1 mmol), **1f** (216 mg, 0.83 mmol, 83% yield), was obtained as a solid, m.p 105–107°C; tlc (eluent A) Rf=0.39; ^{1}H NMR ($CDCl_3$) δ=0.81 (t, J=7 Hz, 3H, $(CH_2)_3CH_3$), 1.26 (m, 4H, $CH_2(CH_2)_2CH_3$), 2.20 (m, 2H, $CH_2(CH_2)_2CH_3$), 4.85 (dd, J=5 Hz and J=10.5 Hz, 1H, C*H*CO_2H), 7.67 (m, 2H, *H*-phthalyl), 7.88 (m, 2H, *H*-phthalyl), 9.10 (br, 1H, CO_2*H*).

*N-Phthalyl-(*RS*)-phenylalanine* ***1g***

Following the general procedure from (*RS*)-phenylalanine (165 mg, 1 mmol), **1g** (177 mg, 0.6 mmol, 60% yield), was obtained as a solid, m.p. 172–174°C; tlc (eluent A) Rf=0.53; ^{1}H NMR ($CDCl_3$) δ=3.50 (d, J=8.5 Hz, 2H, C*H*$_2$), 5.10 (t, J=8.5 Hz, 1H, C*H*CO_2H), 7.11 (m, 5H, *H*-phenyl), 7.67 (m, 2H, *H*-phthalyl), 7.70 (m, 2H, *H*-phthalyl), 8.50 (br, 1H, CO_2*H*).

*N-Phthalyl-(*RS*)-β-naphthylalanine* ***1h***

Following the general procedure from (*RS*)-β-naphthylalanine (215 mg, 1 mmol), **1h** (304 mg, 0.88 mmol, 88% yield), was obtained as a solid, m.p. 156–158°C; tlc (eluent A) Rf=0.45; ^{1}H NMR ($CDCl_3$) δ=3.75 (m, 2H, C*H*$_2$), 5.33 (dd, J=7 Hz and J=10 Hz, 1H, C*H*CO_2H), 7.33 (m, 2H, *H*-phthalyl), 7.62 (m, 9H, *H*-phthalyl and *H*-naphthyl), 9.10 (br, 1H, CO_2*H*).

N-Phthalyl-(RS)-valine ***1i***

Following the general procedure from (*RS*)-valine (117 mg, 1 mmol), **1i** (227 mg, 0.92 mmol, 92% yield), was obtained as a solid, m.p. 98–100°C; tlc (eluent A) Rf=0.60; ^{1}H NMR ($CDCl_3$) δ=0.84 (d, J=6.8 Hz, 3H, $CHCH_3$), 1.10 (d, J=6.8 Hz, 3H, $CHCH_3$), 2.65 (m, 1H, $CH(CH_3)_2$), 4.55 (d, J=8.5 Hz, 1H, $CHCO_2H$), 7.67 (m, 2H, *H*-phthalyl), 7.80 (m, 2H, *H*-phthalyl), 7.80 (br, 1H, CO_2H).

N-Phthalyl-(RS)-leucine ***1j***

Following the general procedure from (*RS*)-leucine (131 mg, 1 mmol), **1j** (245 mg, 0.94 mmol, 94% yield), was obtained as a solid, m.p. 138–140°C; tlc (eluent A) Rf=0.42; ^{1}H NMR ($CDCl_3$) δ=0.85 (d, J=6.5 Hz, 3H, $CHCH_3$), 0.88 (d, J=5.6 Hz, 3H, $CHCH_3$), 1.45 (m, 1H, $CH(CH_3)_2$), 1,88 (m, 1H, $CHCH_2$), 2.30 (m, 1H, $CHCH_2$), 4.90 (dd, J=4.4 Hz and J=11.5 Hz, 1H, $CHCO_2H$), 7.67 (m, 2H, *H*-phthalyl), 7.79 (m, 2H, *H*-phthalyl), 8.80 (br, 1H, CO_2H).

General procedure for the preparation of phthalyl-(RS)-amino acid chlorides ***2a–j***

A mixture of the phthalyl-(*RS*)-amino acid (1 equiv.) and oxalyl chloride (10 equiv.) was stirred under argon at 30°C for 12 h. Evaporation of oxalyl chloride excess gave the corresponding phthalyl-(*RS*)-amino acid chloride that was used as such in the following step.

General procedure for the esterification of (RS) and (S) phthalylamino acid mixtures with (R)-pantolactone ***4***

To an equimolecular mixture of (*RS*) and (*S*) phthalylamino acids (1 mmol), (*R*)-pantolactone **4** (130 mg, 1 mmol) and 4-dimethylaminopyridine (0.05 equiv.) in 6 ml of CH_2Cl_2 was added 1 equivalent of dicyclohexylcarbodiimide (206 mg) at 0°C. The mixture was then stirred at room temperature for an additional 12 h. The resulting mixture was filtered and washed with saturated aqueous solutions of citric acid (3×6 ml) and saturated $NaHCO_3$ (3×6 ml) dried over Na_2SO_4 and concentrated in vacuo. The stereoisomeric mixtures (*S,R*)/(*R,R*) of esters **5**, close to 75/25, was analyzed by NMR spectroscopy and HPLC.

HPLC and NMR data of the compounds ***5*** *deduced from the data of the diastereoisomeric mixtures obtained above*

N-Phthalyl phenylglycine pantolactonyl ester ***5a***

(*R,R*)-5a: HPLC (condition A), r.t. 15.9 min; ^{1}H NMR (DMSO-d_6) δ=0.71 (s, 3H, 4′-CH_3), 1.12 (s, 3H, 4′-CH_3), 4.00 (d, J=8.5 Hz, 1H, 5′-HC*H*), 4.15 (d, J=8.5 Hz, 1H, 5′-HC*H*), 5.75 (s, 1H, 3′-C*H*), 6.39 (s, 1H, C*H*-COO), 7.38 (m, 3H, *H*-phenyl), 7.54 (m, 2H, *H*-phenyl), 7.95 (m, 4H, *H*-phthalyl).

(*S,R*)-5a: HPLC (condition A), r.t. 14.14 min; ^{1}H NMR (DMSO-d_6) δ=0.77 (s, 3H, 4′-CH_3), 1.16 (s, 3H, 4′-CH_3), 4.00 (d, J=8.5 Hz, 1H, 5′-HC*H*), 4.15 (d, J=8.5 Hz, 1H, 5′-HC*H*), 5.68 (s, 1H, 3′-C*H*), 6.37 (s, 1H, C*H*-COO), 7.38 (m, 3H, *H*-phenyl), 7.54 (m, 2H, *H*-phenyl), 7.95 (m, 4H, *H*-phthalyl).

$C_{22}H_{19}NO_6$ (393.40): calcd. C 67.17% H 4.87% N 3.56%. Found: C 67.25% H 4.72% N 3.47%.

N-Phthalyl 4-fluorophenylglycine pantolactonyl ester ***5b***

(*R,R*)-5b: HPLC (condition A), r.t. 17.14 min; ^{1}H NMR (DMSO-d_6) δ=0.70 (s, 3H, 4′-CH_3), 1,11 (s, 3H, 4′-CH_3), 4.00 (d, J=8.6 Hz, 1H, 5′-HC*H*), 4.12 (d, J=8.6 Hz, 1H, 5′-HC*H*), 5.74 (s, 1H, 3′-C*H*), 6.46 (s, 1H,C*H*-COO), 7.24 (m, 2H, *H*-phenyl), 7.60 (m, 2H, *H*-phenyl), 7.95 (m, 4H, *H*-phthalyl).

(*S,R*)-5b: HPLC (condition A), r.t. 15.84 min; ^{1}H NMR (DMSO-d_6) δ=0.79 (s, 3H, 4′-CH_3), 1,16 (s, 3H, 4′-CH_3), 4.02 (d, J=8.6 Hz, 1H, 5′-HC*H*), 4.14 (d, J=8.6 Hz, 1H, 5′-HC*H*), 5.67 (s, 1H, 3′-C*H*), 6.43 (s, 1H,C*H*-COO), 7.24 (m, 2H, *H*-phenyl), 7.60 (m, 2H, *H*-phenyl), 7.95 (m, 4H, *H*-phthalyl).

$C_{22}H_{18}NO_6F$ (411.39): calcd. C 64.23% H 4.41% N 3.40%. Found: C 64.11% H 4.56% N 3.25%.

N-Phthalylalanine pantolactonyl ester ***5c***

(***R,R***)-**5c**: HPLC (condition B), r.t. 16.74 min; ^{1}H NMR (DMSO-d_6) δ=0.66 (s, 3H, 4′-CH_3), 1.03 (s, 3H, 4′-CH_3), 1.54 (d, J=7.2 Hz, 3H, CHCH_3), 3.94 (d, J=8.6 Hz, 1H, 5′-HC*H*), 4.08 (d, J=8.6 Hz, 1H, 5′-HC*H*), 5.19 (q, J=7.2 Hz, 1H, C*H*-COO), 5.65 (s, 1H, 3′-C*H*), 7.90 (m, 4H, *H*-phthalyl).

(***S,R***)-**5c**: HPLC (condition B), r.t. 15.00 min; ^{1}H NMR (DMSO-d_6) δ=0.95 (s, 3H, 4′-CH_3), 1.13 (s, 3H, 4′-CH_3), 1.63 (d, J=7.2 Hz, 1H, CHCH_3), 4.00 (d, J=8.6 Hz, 1H, 5′-HC*H*), 4.07 (d, J=8.6 Hz, 1H, 5′-HC*H*), 5.19 (q, J=7.2Hz, 1H, C*H*-COO), 5.61 (s, 1H, 3′-C*H*), 7.90 (m, 4H, *H*-phthalyl).

$C_{17}H_{17}NO_6$ (331.33): calcd. C 61.63% H 5.17% N 4.23%. Found: C 61.75% H 5.02% N 4.35%.

Phthalyl-2-aminobutyric pantolactonyl ester ***5d***

(***R,R***)-**5d**: HPLC (condition C), r.t. 19.94 min; ^{1}H NMR (DMSO-d_6) δ=0.65 (s, 3H, 4′-CH_3), 0.89 (t, J=7.4 Hz, 3H, CH_2CH_3), 0.94 (s, 3H, 4′-CH_3), 2.15 (m, 2H, CH_2CH_3), 3.97 (d, J=7.6 Hz, 1H, 5′-HC*H*), 4.11 (d, J=7.6 Hz, 1H, 5′-HC*H*), 5.00 (dd, J=6.4 Hz and J=9.2 Hz, 1H, C*H*-COO), 5.66 (s, 1H, 3′-C*H*), 7.93 (m, 4H, *H*-phthalyl).

(***S,R***)-**5d**: HPLC (condition C), r.t. 17.60 min; ^{1}H NMR (DMSO-d_6) δ=0.89 (t, J=7.4 Hz, 3H, CH_2CH_3), 0,95 (s, 3H, 4′-CH_3), 1.13 (s, 3H, 4′-CH_3), 2.15 (m, 2H, CH_2CH_3), 4.03 (d, J=8.6 Hz, 1H, 5′-HC*H*), 4.12 (d, J=8.6 Hz, 1H, 5′-HC*H*), 5.00 (dd, J=6.4 Hz and J=9.2 Hz, 1H, C*H*-COO), 5.62 (s, 1H, 3′-C*H*), 7.93 (m, 4H, *H*-phthalyl).

$C_{18}H_{19}NO_6$ (345.35): calcd. C 62.60% H 5.55% N 4.06%. Found: C 62.47% H 5.43% N 4.17%.

N-Phthalylnorvaline pantolactonyl ester ***5e***

(***R,R***)-**5e**: HPLC (condition C), r.t. 17.50 min; ^{1}H NMR (DMSO-d_6) δ=0,74 (s, 3H, 4′-CH_3), 1,02 (s, 3H, 4′-CH_3), 1.88 (t, J=7.2 Hz, 3H, CH_2CH_3), 1.28 (m, 2H, CH_2CH_3), 2.10 (m, 2H, CH_2CH_2), 3.94 (d, J=8.6 Hz, 1H, 5′-HC*H*), 4.11 (d, J=8.6 Hz, 1H, 5′-HC*H*), 5.06 (dd, J=6 Hz and J=9.8 Hz, 1H, C*H*-COO), 5.64 (s, 1H, 3′-C*H*), 7.94 (m, 4H, *H*-phthalyl).

(***S,R***)-**5e**: HPLC (condition C), r.t. 15.48 min; ^{1}H NMR (DMSO-d_6) δ=0,95 (s, 3H, 4′-CH_3), 1,12 (s, 3H, 4′-CH_3), 1.88 (t, J=7.2 Hz, 3H, CH_2CH_3), 1.28 (m, 2H, CH_2CH_3), 2.10 (m, 2H, CH_2CH_2), 4.04 (d, J=8.6 Hz, 1H, 5′-HC*H*), 4.12 (d, J=8.6 Hz, 1H, 5′-HC*H*), 5.04 (dd, J=5.2Hz and J=10.5 Hz, 1H,C*H*-COO), 5.61 (s, 1H, 3′-C*H*), 7.94 (m, 4H, *H*-phthalyl).

$C_{19}H_{21}NO_6$ (359.38): calcd. C 63.50% H 5.89% N 3.90%. Found: C 63.39% H 5.77% N 3.99%.

N-Phthalylnorleucine pantolactonyl ester ***5f***

(***R,R***)-**5f**: HPLC (condition B), r.t. 15.56 min; ^{1}H NMR (DMSO-d_6) δ=0,65 (s, 3H, 4′-CH_3), 0.82 (t, J=6.5 Hz, 3H, CH_2CH_3), 1,03 (s, 3H, 4′-CH_3), 1.23 (m, 4H, $CH_2CH_2CH_3$), 2.08 (m, 2H, CHCH_2), 3.97 (d, J=8.6 Hz, 1H, 5′-HC*H*), 4.12 (d, J=8.6 Hz, 1H, 5′-HC*H*), 5.03 (dd, J=6 Hz and J=9.5 Hz, 1H, C*H*-COO), 5.64 (s, 1H, 3′-C*H*), 7.92 (m, 4H, *H*-phthalyl).

(***S,R***)-**5f**: HPLC (condition B), r.t. 13.79 min; ^{1}H NMR (DMSO-d_6) δ=0.82 (t, J=6.5 Hz, 3H, CH_2CH_3), 0,94 (s, 3H, 4′-CH_3), 1,13 (s, 3H, 4′-CH_3), 1.23 (m, 4H, $CH_2CH_2CH_3$), 2.08 (m, 2H, CHCH_2), 4.03 (d, J=8.6 Hz, 1H, 5′-HC*H*), 4.11 (d, J=8.6 Hz, 1H, 5′-HC*H*), 5.01 (dd, J=5.6 Hz and J=9.8 Hz, 1H, C*H*-COO), 5.61 (s, 1H, 3′-C*H*), 7.92 (m, 4H, *H*-phthalyl).

$C_{20}H_{23}NO_6$ (373.41): calcd. C 64.33% H 6.21% N 3.75%. Found: C 64.45% H 6.08% N 3.64%.

N-Phthalylphenylalanine pantolactonyl ester ***5g***

(***R,R***)-**5g**: HPLC (condition A), r.t. 15.53 min; ^{1}H NMR (DMSO-d_6) δ=0.59 (s, 3H, 4′-CH_3), 1.00 (s, 3H, 4′-CH_3), 3.40 (m, 1H, CH_2-phenyl), 3.93 (d, J=8.6 Hz, 1H, 5′-HC*H*), 3.98 (d, J=8.6 Hz, 1H, 5′-HC*H*), 5.41 (m, 1H, C*H*-COO), 5.66 (s, 1H, 3′-C*H*), 7.12 (m, 5H, *H*-phenyl), 7.80 (m, 4H, *H*-phthalyl).

(***S,R***)-**5g**: HPLC (condition A), r.t. 13.83 min; ^{1}H NMR (DMSO-d_6) δ=0.90 (s, 3H, 4′-CH_3), 1.06 (s, 3H, 4′-CH_3), 3.40 (m, 1H, CH_2-phenyl), 3.99 (d, J=8.6 Hz, 1H, 5′-HC*H*), 4.08 (d, J=8.6 Hz,

1H, 5′-HC*H*), 5.41 (m, 1H, C*H*-COO), 5.61 (s, 1H, 3′-C*H*), 7.12 (m, 5H, *H*-phenyl), 7.80 (m, 4H, *H*-phthalyl).

$C_{23}H_{21}NO_6$ (407.43): calcd. C 67.81% H 5.20% N 3.44%. Found: C 67.93% H 5.31% N 3.32%.

N-Phthalyl-β-naphthylalanine pantolactonyl ester ***5h***

(*R,R*)-5h: HPLC (condition B), r.t. 21.43 min; ^{1}H NMR (DMSO-d_6) δ=0.66 (s, 3H, 4′-CH_3), 1.09 (s, 3H, 4′-CH_3), 3.60 (m, 2H, CHCH_2), 3.95 (d, J=8.6 Hz, 1H, 5′-HC*H*), 4.10 (d, J=8.6 Hz, 1H, 5′-HC*H*), 5.62 (dd, J=5.4 Hz and J=11.2 Hz, 1H, C*H*-COO), 5.74 (s, 1H, 3′-C*H*), 7.42 (m, 4H, *H*-phthalyl), 7.78 (m, 7H, *H*-naphthyl).

(*S,R*)-5h: HPLC (condition B), r.t. 18.73 min; ^{1}H NMR(DMSO-d_6) δ=0,96 (s, 3H, 4′-CH_3), 1.18 (s, 3H, 4′-CH_3), 3.60 (m, 2H, CHCH_2), 4.04 (d, J=8.6 Hz, 1H, 5′-HC*H*), 4.11 (d, J=8.6 Hz, 1H, 5′-HC*H*), 5.60 (dd, J=4.9 Hz and J=11 Hz, 1H,C*H*-COO), 5.69 (s, 1H, 3′-C*H*), 7.42 (m, 4H, *H*-phthalyl), 7.78 (m, 7H, *H*-naphthyl).

$C_{27}H_{23}NO_6$ (457.49): calcd. C 70.89% H 5.07% N 3.06%. Found: C 70.76% H 5.20% N 3.12%.

N-Phthalylvaline pantolactonyl ester ***5i***

(*R,R*)-5i: HPLC (condition C), r.t. 15.75 min; ^{1}H NMR (DMSO-d_6) δ=0.66 (s, 3H, 4′-CH_3), 0.90 (d, J=6.8 Hz, 3H, CHCH_3), 1.05 (s, 3H, 4′-CH_3), 1.12 (d, J=6.8 Hz, 3H, CHCH_3), 2.66 (m, 1H, C*H*(CH_3)$_2$), 3.97 (d, J=8.6 Hz, 1H, 5′-HC*H*), 4.11 (d, J=8.6 Hz, 1H, 5′-HC*H*), 4.76 (d, J=7.6 Hz, 1H, C*H*-COO), 5.70 (s, 1H, 3′-C*H*), 7.97 (m, 4H, *H*-phthalyl).

(*S,R*)-5i: HPLC (condition C), r.t. 13.95 min; ^{1}H NMR (DMSO-d_6) δ=0.98 (s, 3H, 4′-CH_3), 1.16 (s, 3H, 4′-CH_3), 0.90 (d, J=6.8 Hz, 3H, CHCH_3), 1.12 (d, J=6.8 Hz, 3H, CHCH_3), 2.66 (m, 1H, C*H*(CH_3)$_2$), 4.02 (d, J=8.6 Hz, 1H, 5′-HC*H*), 4.12 (d, J=8.6 Hz, 1H, 5′-HC*H*), 4.76 (d, J=7.6 Hz, 1H, C*H*-COO), 5.65 (s, 1H, 3′-C*H*), 7.97 (m, 4H, *H*-phthalyl).

$C_{19}H_{21}NO_6$ (359.38): calcd. C 63.50% H 5.89% N 3.90%. Found: C 63.41% H 5.73% N 3.97%.

N-Phthalylleucine pantolactonyl ester ***5j***

(*R,R*)-5j: HPLC (condition A), r.t. 10.85 min; ^{1}H NMR (DMSO-d_6) δ=0.62 (s, 3H, 4′-CH_3), 0.91 (d, J=6.5 Hz, 6H, CH(CH_3)$_2$), 1.02 (s, 3H, 4′-CH_3), 1.48 (m, 1H, C*H*(CH_3)$_2$), 1.85 (m, 1H, HC*H*-CH(CH_3)$_2$), 2.18 (m, 1H, HC*H*-CH(CH_3)$_2$), 3.97 (d, J=8.6 Hz, 1H, 5′-HC*H*), 4.11 (d, J=8.6 Hz, 1H, 5′-HC*H*), 5.08 (dd, J=4.7 Hz and J=11 Hz, 1H, C*H*-COO), 5.63 (s, 1H, 3′-C*H*), 7.94 (m, 4H, *H*-phthalyl).

(*S,R*)-5j: HPLC (condition A), r.t. 9.82 min; ^{1}H NMR (DMSO-d_6) δ=0.87 (s, 3H, 4′-CH_3), 0.91 (d, J=6.5 Hz, 6H, CH(CH_3)$_2$), 1.12 (s, 3H, 4′-CH_3), 1.48 (m, 1H, C*H*(CH_3)$_2$), 1.85 (m, 1H, HC*H*-CH(CH_3)$_2$), 2.18 (m, 1H, HC*H*-CH(CH_3)$_2$), 4.04 (d, J=8.6 Hz, 1H, 5′-HC*H*), 4.10 (d, J=8.6 Hz, 1H, 5′-HC*H*), 5.08 (dd, J=4.7 Hz and J=11 Hz, 1H, C*H*-COO), 5.60 (s, 1H, 3′-C*H*), 7.94 (m, 4H, *H*-phthalyl).

$C_{20}H_{23}NO_6$ (373.41): calcd. C 64.33% H 6.21% N 3.75%. Found: C 64.42% H 6.33% N 3.82%.

General procedure for the diastereoselective addition of (R)*-pantolactone* ***4*** *to phthalylamino ketenes* ***5a–j***

Method 1: To a stirred solution of phthalyl-(*RS*)-amino acid chloride (1 mmol) in 3 ml of anhydrous THF, cooled to −78°C (or 0°C) under argon, was first added 0.21 ml (1.5 equiv) of NEt_3 followed by, after 30 minutes, a precooled solution of 0.14 g (1.1 mmol) of (*R*)-pantolactone in 2 ml of THF. After 6 h at this temperature (monitoring the reaction by tlc: eluent B), a 1N citric acid solution (5 ml) was added and the reaction mixture was allowed to warm to room temperature. The solution was extracted with AcOEt (10 ml) and the organic layer was washed successively with water and a sodium bicarbonate solution and then dried over sodium carbonate. Evaporation under vacuum gave the pantolactonyl ester.

Method 2: Addition of a THF solution of 1.1 equiv of (*R*)-pantolactone (140 mg) and 1.5 equiv of triethylamine (0.21 ml) to a THF solution of 1 mmol of phthalyl-(*RS*)-amino acid chloride. After 4 to 5 h at −78°C or only 1 hour at 0°C, the solution was treated as previously.

General procedure for the hydrolysis of N-phthalyl pantolactonyl esters ***5a–j***

A mixture of the N-phthalyl pantolactonyl ester (0.5 mmol), acetic acid (1.4 ml) and a 6N HCl solution (14 ml) was refluxed till completion of the hydrolysis (4 h), monitoring the reaction by tlc (eluent A). The mixture was allowed to cool 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). Evaporation under vacuum of the aqueous layer gave free aminoacids **6**.

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