A New Synthetic Route to Protected α-Hydrazinoesters in High Optical Purity Using the Mitsunobu Protocol

Nicolas Brosse, Maria-Fatima Pinto, Jacques Bodiguel, and Brigitte Jamart-Grégoire*

MAEM UMR mixte CNRS-UHP no. 7567, Faculté des Sciences, Université H. Poincaré Nancy I, Bld. des Aiguillettes, BP 239 F-54506 Vandoeuvre-lès-Nancy, France

Brigitte.Jamart@maem.uhp-nancy.fr

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Introduction

Among the variety of amino acid analogues currently investigated in organic chemistry, there is a growing interest in the synthesis of α-hydrazinoacids (2-hydrazinyl acids) which present interesting biological activities[1] and can be used for the preparation of (*N*-aminoamide) peptides[2] or (hydrazide) peptides.[2a,3] A few reaction pathways have been described for the preparation of optically pure α-hydrazinoacids,[1,4] although these involve laborious methods. In addition, the presence of the additional N^{α} sometimes presents difficulties in preparation of these compounds and their incorporation in pseudopeptides design where coupling of α-hydrazinoacids with amino acids is not always regioselective. In that context, the availability of a general method for the production of N^{α}- or N^{β}-protected (*R*)- or (*S*)-α-hydrazinoacids is of great interest.

As part of our research aimed at developing synthetic protocols for the preparation of protected hydrazines,[5] we have demonstrated that *N*-*tert*-butyloxycarbonyl- and *N*-benzyloxycarbonyl-aminophthalimides, efficiently obtained using phthalic anhydride and carbazates as starting materials, are very good acid partners in a Mitsunobu protocol.[5b,c] We demonstrated that primary, secondary alkyl, benzyl groups as well as functionalized groups can be introduced with good overall yields. Furthermore, we showed that a final dephthaloylation step results in an efficient method for the preparation of 1,1-substituted hydrazines.

In this paper, we aim to extend our current method to include the preparation of chiral hydrazinoacid derivatives. We demonstrate that these compounds can be efficiently obtained starting from the corresponding α-hydroxyesters.

Results and Discussion

Mitsunobu Reaction: Formation of 2. The (*R*)- and (*S*)-α-hydroxyesters used in this study are commercially available or prepared from their acid form (see Experimental Section).

As a first step, the reactivity of *N*-*tert*-butyloxycarbonylaminophthalimide (**1**, P = BOC) toward (*S*)-α-hydroxyesters in the Mitsunobu protocol was studied. Shown in the following Scheme 1 (step a) and Table 1 are the results obtained.

The corresponding *N*,*N*-triprotected α-hydrazinoesters **2a**−**d** were obtained with very good yields for R = H and Me. However, for R = CH_2−$CH(CH_3)_2$, the yield of **2e** decreased to 50%. For R = CH_2Ph and $CH(CH_3)_2$ no reaction was observed (unreported results). In comparison, when the less hindered *N*-benzyloxycarbonylaminophthalimide (**1**, P = Z) was used as the acid partner, compounds **2f**−**p** were obtained with good to very good yields regardless of the nature of the side chain group R or of the ester group R′(methyl or benzyl group) used.

The observation of two sets of resonances for some groups in ^1H and ^{13}C NMR spectra (see Experimental Section) suggested that compounds **2** were present as two isomers in a ratio 45/55. We and others have observed this phenomenon before in the preparation of hydrazides derivatives[5c] or amide containing compounds.[6] The different resonances of the isomers arise from a hindered rotation about the nitrogen to carbonyl bond thus allowing one to distinguish between Z and E forms. Complementary studies are under active investigation to fully assign resonance signals.

Preparation of N^{β}-Protected α-Hydrazinoesters. Selective removal of the benzyloxycarbonyl or the *tert*-butyloxycarbonyl group can be readily achieved using HBr/CH_3COOH[7] or HCl/EtOAc,[8] respectively (Scheme 1 (step b), Table 1). These deprotection steps permit the general preparation of N^{β}-protected α-hydrazinoesters. However, during the Z deprotection of compounds **2f**, **2h**, and **2n** (R′ = CH_2Ph), partial proteolysis of the benzylic ester function occurred contributing to a decrease in the yield of compounds **3**. We circumvented this problem by using the corresponding methyl esters as starting materials thus enabling compounds **3** (R′ = Me) to be obtained in good yields.

Preparation of N^{α}-Protected α-Hydrazinoesters. We previously demonstrated that dephthaloylation of *N*-subtituted aminophthalimides could be improved by using methylhydrazine in THF.[5b] Using these conditions, N^{α}-protected hydrazinoesters **4** were obtained, starting from compounds **2**, with very good yields in most cases (Scheme 1 (step c), Table 1). However, dephthaloylation

* To whom correspondence should be addressed. Tel/fax: 33 (0) 383 91 27 48.

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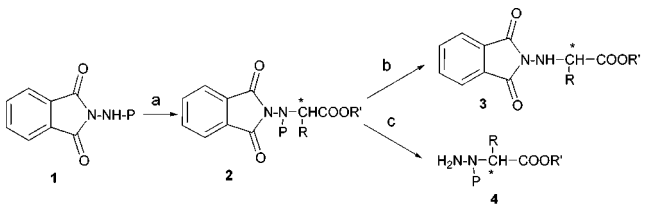
Scheme 1. Formation of 2, 3, and 4



For description of P, R, and R′ and configuration of compounds see Table 1. [a](*R*)- or (*S*)-RCHOHCOOR′, 1 equiv, DEAD, 1.5 equiv, PPh_3, 1.5 equiv, THF; [b]P = BOC: HCl/EtOAc. P = Z: HBr/AcOH. [c]NH_2NHCH_3, 1.5 equiv, THF.

of compound **2j** was less successful resulting in a yield of only 35%. Starting material was recovered, and the yield of **4j** was constant whatever the amount of reactant used.

Determination of the Optical Purity. Starting from **4h**, **4j**, **4l**, **4n**, or **4p**, the corresponding amino acids can be obtained by hydrogenolysis with an excess of Raney nickel[9] (50 bar of H_2, 24 h, 25 °C). These conditions allowed simultaneous cleavage of the N−N bond, deprotection of the Z group, and conversion of the benzylester group into the corresponding acid form. For compounds **4c** and **4e**, a preliminary deprotection of the BOC group with CF_3COOH was necessary. The enantiomeric purities of amino acids were determined by HPLC after derivatization of the free amine with *o*-phthalaldehyde and the chiral thiol *N*-isobutyryl-D-cysteine.[10] The very high chiral purities obtained (ee > 97%, see Table 1) established that the conversion of the α-hydrazinoesters to the corresponding amino acids via the illustrated steps sequence proceed with complete inversion of configuration and were accompanied by a negligible loss of enantiomeric purity (<1% compared to enantiomeric purities of commercial hydroxyesters or hydroxyacids, see Experimental Section).

Conclusion

We have demonstrated that *N*-*tert*-butyloxycarbonyl- and *N*-benzyloxycarbonyl-aminophthalimides can be reacted with commercially available (*S*)- and (*R*)-α-hydroxyesters for an efficient preparation of either N^{α}-protected, N^{β}-bisprotected or orthogonal N^{α}, N^{β}-triprotected, respectively, (*R*)- and (*S*)-α-hydrazinoesters with high optical purity. It follows that these procedures represent an attractive alternative to the methods currently used for the preparation of α-hydrazinoacid derivatives. Application of this protocol to the synthesis of more complex varieties of hydrazinoacids is under active investigation.

Experimental Section

General. Melting points were obtained on a hot-stage apparatus and were uncorrected. NMR spectra were recorded on spectrometers operating at 400 or 250 MHz. Optical rotations were measured in a 1 dm cell at 20 °C. Electron Impact Mass Spectra were performed by the ULIRS Mass Spectrometry Facility (the School of Pharmacy, London). Tetrahydrofuran was dried by distillation over sodium−benzophenone. Column chromatography was performed using silica gel 60 of 0.063−0.200 mm particle size. α-Hydroxyacids ((*S*)-(+)-2-hydroxy-3-methylbutyric acid (ee: 98%) and (*S*)-(−)-2-hydroxyisocaproic acid (ee: 99%)) or α-hydroxyesters (benzyl-(*S*)-(−)-2-hydroxy-3-phenylpropionate (ee: 97%), (benzyl-(*R*)-(+)-2-hydroxy-3-phenylpropionate (ee: 97%), benzylglycolate, (*S*)-benzyllactate (ee: 98%), and (*S*)-methyllactate (ee: 97%)) were purchased from Aldrich. Benzylation of α-hydroxyacids was accomplished using benzyl bromide in accordance with previously described procedure[11] and methylation by reaction with diazomethane.[12]

General Procedure for the Alkylation of *N*-Acyl or *N*-Alkoxycarbonylaminophthalimides via Mitsunobu Protocol. To a solution of **1** (5 mmol), PPh_3 (7.5 mmol), and α-hydroxyester RCH(OH)COOR′, 5 mmol) in dry THF (50 mL) and under Nitrogen was added in one portion DEAD (diethylazodicarboxylate, 7.5 mmol) with stirring at −20 °C or 0−5 °C (see Table 1). The resulting solution was stirred at room temperature (monitored by TLC until completion) and concentrated in vacuo. The residue was triturated in EtOAc and most of the triphenylphosphine oxide and diethylhydrazinedicarboxylate was removed by filtration. The filtrate was evaporated and the residue was chromatographed on silica gel.

***N*-*tert*-Butyloxycarbonyl-*N*-phthalimidoglycine Benzyl Ester. 2a P = Boc, R = H, R′ = CH_2Ph.** Mp 94−98 °C; *Rf* = 0.55 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 1798, 1745; ^{1}H NMR (250 MHz, $CDCl_3$) 7.96−7.70 (m, 4 H), 7.47−7.23 (m, 5 H), 5.21 and 5.18 (2 s, 2 H), 4.50 and 4.41 (2 s, 2 H), 1.44 and 1.35 (2 s, 9 H); ^{13}C NMR ($CDCl_3$) 168.2, 165.3, 165.0, 153.2, 135.7, 135.1, 130.3, 130.2, 129.0, 128.9, 128.7, 124.3, 84.3, 83.6, 67.5, 52.6, 50.5, 28.3; HRMS Calcd for $C_{22}H_{26}N_3O_6$ [M+NH_4^+] *m*/*z* 428.1821, found 428.1815.

***N*-*tert*-Butyloxycarbonyl-*N*-phthalimidoglycine Methyl Ester. 2b P = Boc, R = H, R′ = CH_3.** Mp 117−118 °C; *Rf* = 0.60 (EtOAc/Hexane 4/6); IR (KBr) ν_{max}/cm^{-1} 1797, 1758, 1722; ^{1}H NMR (250 MHz, $CDCl_3$) 7.95−7.73 (m, 4 H), 4.47 and 4.41 (2 s, 2 H), 3.78 and 3.75 (2 s, 3 H), 1.53 and 1.35 (2 s, 9 H); ^{13}C NMR ($CDCl_3$) 168.7, 165.9, 153.1, 130.2, 130.1, 124.3, 84.2, 83.5, 52.6, 52.3, 50.2, 28.3, 28.1; HRMS Calcd for $C_{16}H_{22}N_3O_6$ [M+NH_4^+] *m*/*z* 352.1509, found 352.1519.

(*R*)-*N*-*tert*-Butyloxycarbonyl-*N*-phthalimidoalanine Benzyl Ester. 2c P = Boc, R = CH_3, R′ = CH_2Ph. Mp 110−112 °C; $[\alpha]_D$ = −1.5 (c 1.12, $CHCl_3$); *Rf* = 0.55 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 1799, 1742; ^{1}H NMR (400 MHz, $CDCl_3$) 7.90−7.69 (m, 4 H), 7.49−7.19 (m, 5 H), 5.20 and 5.19 (2 s, 2 H), 5.09 and 4.85 (2 q, *J* = 7 Hz, 1 H), 1.47−1.16 (m with 2 s at 1.35 and 1.26, 12 H); ^{13}C NMR ($CDCl_3$) 170.6, 166.4, 166.2, 166.0, 165.7, 152.5, 136.1, 135.2, 130.2, 130.0, 128.9, 128.7, 128.5, 124.3, 84.0, 83.1, 67.7, 67.4, 57.2, 55.4, 28.1, 15.0, 14.6; HRMS Calcd for $C_{23}H_{28}N_3O_6$ [M+NH_4^+] *m*/*z* 442.1974, found 442.1978.

(*R*)-*N*-*tert*-Butyloxycarbonyl-*N*-phthalimidoalanine Methyl Ester. 2d P = Boc, R = CH_3, R′ = CH_3. Mp 91−92 °C; $[\alpha]_D$ = +20.10 (c 0.78, $CHCl_3$); *Rf* = 0.50 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 1799, 1741; ^{1}H NMR (400 MHz, $CDCl_3$) 7.76−7.64 (m, 4 H), 4.94 and 4.70 (2 q, 1 H, *J* = 7 Hz), 3.68 and 3.64 (2 s, 3 H), 1.42−1.07 (m with 2 s at 1.37 and 1.17 and with 2 d at 1.29 and 1.25, *J* = 8 Hz, 12 H); ^{13}C NMR ($CDCl_3$) 171.1, 166.3 166.1, 165.5, 152.5, 135.3, 130.2, 124.2, 83.9, 83.1, 57.2, 55.0, 52.6, 28.2, 28.0, 15.0, 14.6; HRMS Calcd for $C_{17}H_{21}N_2O_6$ [M+H^+] *m*/*z* 349.1400, found 349.1426.

(*R*)-*N*-*tert*-Butyloxycarbonyl-*N*-phthalimidoleucine Benzyl Ester. 2e P = Boc, R = CH_2−$CH(CH_3)_2$, R′ = CH_2Ph. Oil; $[\alpha]_D$ = +14.3 (c 0.91, $CHCl_3$); *Rf* = 0.70 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 1799, 1737; ^{1}H NMR (400 MHz, $CDCl_3$) 7.91−7.83 (m, 4 H), 7.46−7.20 (m, 5 H), 5.26−5.10 and 4.9 (m with s at 5.17 and t at 4.94, *J* = 9 Hz, 3 H), 1.94−1.54 (m, 3 H), 1.40 and 1.26 (2 s, 9 H), 1.00−0.80 (m, 6 H); ^{13}C NMR ($CDCl_3$) 170.1, 166.3, 165.0, 165.3, 152.7, 135.9, 135.1, 130.2, 130.1, 128.9, 128.7, 128.5, 124.2, 84.0, 83.1, 67.7, 67.5, 59.5, 57.5, 38.3, 28.2, 28.1, 24.9, 24.7, 22.8, 22.6; HRMS Calcd for $C_{26}H_{31}N_2O_6$ [M+H^+] *m*/*z* 467.2182, found 467.2174.

***N*-Benzyloxycarbonyl-*N*-phthalimidoglycine Benzyl Ester. 2f P = Z, R = H, R′ = CH_2Ph.** Oil; *Rf* = 0.35 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 1805, 1742; ^{1}H NMR (400 MHz, $CDCl_3$) 7.85−7.64 (m, 4 H), 7.45−7.06 (m, 10 H), 5.23−5.05 (m,

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Table 1. Preparation of Orthogonal N^{α},N^{β}-Triprotected 2, N^{β}-Bisprotected 3, or N^{α}-Monoprotected α-Hydrazinoesters 4

R	R′	P	Configuration of **2**, **3**, **4**	Time (h)	Yields, **2** (%)	Time (h)	Yields, **3** (%)	Time (h)	Yields, **4** (%)	ee (%)
H	CH_2−Ph	BOC		1	**2a** 85	15	**3a** 84	2.5[a]	**4a** 90	
H	CH_3	BOC		0.5	**2b** 70					
CH_3	CH_2−Ph	BOC	R	4	**2c** 94	15	**3c** 72	1.5[a]	**4c** 87	>99
CH_3	CH_3	BOC	R	4	**2d** 82					
CH_2−$CH(CH_3)_2$	CH_2−Ph	BOC	R	18	**2e** 50	72	**3e** 63	24[a]	**4e** 55	98
H	CH_2−Ph	Z		0.5	**2f** 93	2	**3a** 61	1[b]	**4f** 92	
H	CH_3	Z		2.5	**2g** 81		**3g** 93			
CH_3	CH_2−Ph	Z	R	0.25	**2h** 87	1	**3c** 60	1[b]	**4h** 86	>99
CH_3	CH_3	Z	R	1	**2i** 90	1	**3i** 81			
$CH(CH_3)_2$	CH_2−Ph	Z	R	5[a]	**2j** 74			24[a]	**4j** 35	>99
$CH(CH_3)_2$	CH_3	Z	R	0.75	**2k** 54	4	**3k** 65			
CH_2−$CH(CH_3)_2$	CH_2−Ph	Z	R	0.2	**2l** 80			60[a]	**4l** 73	98
CH_2−$CH(CH_3)_2$	CH_3	Z	R	0.25	**2m** 77	1	**3m** 80			
CH_2−Ph	CH_2−Ph	Z	R	1.5[a]	**2n** 92	4	**3n** 57	5[a]	**4n** 68	97
CH_2−Ph	CH_3	Z	R	0.25	**2o** 64	2	**3o** 60			
CH_2−Ph	CH_2−Ph	Z	S	2	**2p** 77			5[a]	**4p** 73	99

[a] The reaction mixture was stirred at −20 °C for 30 min before raising to room temperature. [b] The reaction mixture was stirred at 0 °C for 30 min before raising to room temperature.

4 H), 4.56 and 4.47 (2 s, 2 H); ^{13}C NMR ($CDCl_3$) 167.7, 164.9, 164.6, 135.6, 135.3, 130.1, 130.0, 128.9, 128.8, 128.7, 128.5, 127.7, 124.4, 69.7, 69.1, 67.6, 52.4, 51.2; HRMS Calcd for $C_{25}H_{24}N_3O_6$ [M+NH_4^+] *m*/*z* 462.1665, found 462.1660.

***N*-Benzyloxycarbonyl-*N*-phthalimidoglycine Methyl Ester. 2g P = Z, R = H, R′ = CH_3.** Mp 100 °C; *Rf* = 0.25 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 1799, 1742; ^{1}H NMR (400 MHz, $CDCl_3$) 7.81−7.60 (m, 4 H), 7.32−7.02 (m, 5 H), 5.15 and 5.05 (2 s, 2 H), 4.42 and 4.38 (2 s, 2 H), 3.62 and 3.59 (2 s, 3 H); ^{13}C NMR ($CDCl_3$) 168.3, 164.9, 164.6, 154.5, 154.0, 135.6, 135.3, 130.0, 129.9, 129.0, 128.8, 128.4, 127.6, 124.3, 69.6, 69.1, 52.6, 52.1, 51.0; HRMS Calcd for $C_{19}H_{16}N_2O_6$ *m*/*z* 368.1008, found 368.1007.

(*R*)-*N*-Benzyloxycarbonyl-*N*-phthalimidoalanine Benzyl Ester. 2h P = Z, R = CH_3, R′ = CH_2Ph. Oil; [α]$_D$ = +3.47 (c 1.9, $CHCl_3$); *Rf* = 0.25 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 1798, 1745; ^{1}H NMR (400 MHz, $CDCl_3$) 7.92−7.70 (m, 4 H), 7.49−7.19 (m, 10 H), 5.35−4.96 (m, 5 H), 1.53−1.38 (m, 3 H); ^{13}C NMR ($CDCl_3$) 170.3, 166.2, 165.9, 165.8, 165.3, 154.0, 136.0, 135.7, 135.3, 130.2, 130.0, 128.9, 128.7, 128.5, 127.5, 124.3, 69.7, 67.7, 57.2, 56.4, 14.7; HRMS Calcd for $C_{26}H_{26}N_3O_6$ [M+NH_4^+] *m*/*z* 476.1821, found 476.1814.

(*R*)-*N*-Benzyloxycarbonyl-*N*-phthalimidoalanine Methyl Ester. 2i P = Z, R = CH_3, R′ = CH_3. Oil; [α]$_D$ = +22.1 (c 1.45, $CHCl_3$); *Rf* = 0.40 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 1799, 1747; ^{1}H NMR (250 MHz, $CDCl_3$) 8.00−7.82 (m, 4 H), 7.36−7.12 (m, 5 H), 5.39−4.97 (m, 3 H), 3.85 and 3.73 (2 s, 3 H), 1.45 (d, *J* = 8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 170.8, 165.8, 154.2, 135.7, 135.3, 129.0, 128.7, 128.4, 127.6, 124.4, 69.7, 67.0, 57.1, 56.0, 52.6, 15.6.

(*R*)-*N*-Benzyloxycarbonyl-*N*-phthalimidovaline Benzyl Ester. 2j P = Z, R = $CH(CH_3)_2$, R′ = CH_2Ph. Mp 80 °C; [α]$_D$ = +31.8 (c 1.29, $CHCl_3$); *Rf* = 0.60 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 1799, 1746; ^{1}H NMR (400 MHz, $CDCl_3$) 7.94−7.73 (m, 4 H), 7.45−7.06 (m, 10 H), 5.30−5.06 (m, 4 H), 4.88 and 4.64 (2 d, *J* = 11 Hz, 1 H), 2.18−2.03 (m, 1 H), 1.36−1.20 and 0.97−0.82 (2 m, 6 H); ^{13}C NMR ($CDCl_3$) 168.9, 168.7, 166.0, 165.6, 154.5, 154.3, 135.2, 135.3, 130.3, 130.2, 128.9, 128.7, 128.5, 127.4, 124.3, 69.7, 67.8, 67.6, 66.6, 67.6, 29.35, 29.1, 19.8, 19.3; HRMS Calcd for $C_{28}H_{27}N_2O_6$ [M+H^+] *m*/*z* 487.1869, found 487.1867.

(*R*)-*N*-Benzyloxycarbonyl-*N*-phthalimidovaline Methyl Ester. 2k P = Z, R = $CH(CH_3)_2$, R′ = CH_3. Oil; *Rf* = 0.45 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 1799, 1741; ^{1}H NMR (400 MHz, $CDCl_3$) 7.91−7.69 (m, 4 H), 7.41−7.06 (m, 5 H), 5.30−5.06 (m, 2 H) 4.88 and 4.64 (2 d, *J* = 12 Hz, 1 H), 3.71 (s, 3 H), 2.18−2.03 (m, 1 H), 1.28 and 1.22, 0.90 and 0.87 (4 d, *J* = 8 Hz, 6 H); ^{13}C NMR ($CDCl_3$) 169.5, 166.4, 165.9, 165.5, 154.5, 135.7, 135.2, 130.3, 130.0,129.0, 128.7, 128.4, 127.4, 124.3, 69.7, 69.1, 67.6, 66.2, 52.9, 29.1, 19.7, 19.3; HRMS Calcd for $C_{22}H_{22}N_2O_6$ *m*/*z* 410.1478, found 410.1475.

(*R*)-*N*-Benzyloxycarbonyl-*N*-phthalimidoleucine Benzyl Ester. 2l P = Z, R = CH_2-$CH(CH_3)_2$, R′ = CH_2Ph. Oil; [α]$_D$ = +19.2 (c 1.13, $CHCl_3$); *Rf* = 0.60 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 1799, 1751; ^{1}H NMR (400 MHz, $CDCl_3$) 7.89−7.68 (m, 4 H), 7.46−7.06 (m, 10 H), 5.33−4.97 (m, 5 H), 1.92−1.53 (m, 3 H), 1.04−0.77 (m, 6 H); ^{13}C NMR ($CDCl_3$) 169.8, 166.2, 165.9, 165.5, 154.1, 135.9, 135.7, 130.1, 128.9, 128.7, 128.5, 127.5, 124.3, 69.7, 69.0, 67.9, 67.7, 59.6, 58.6, 38.4, 24.9, 24.7, 22.8, 22.7; HRMS Calcd for $C_{29}H_{32}N_3O_6$ [M + NH_4^+] *m*/*z* 518.2291, found 518.2281.

(*R*)-*N*-Benzyloxycarbonyl-*N*-phthalimidoleucine Methyl Ester. 2m P = Z, R = CH_2-$CH(CH_3)_2$, R′ = CH_3. Oil; [α]$_D$ = +45.96 (c 0.57, $CHCl_3$); *Rf* = 0.55 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 1800, 1746; ^{1}H NMR (400 MHz, $CDCl_3$) 7.91−7.70 (m, 4 H), 7.44−7.06 (m, 5 H), 5.27, 5.23, 5.12, 5.01 (2 s, 2 t, *J* = 6 Hz, 3 H), 3.75 and 3.72 (2 s, 3 H), 1.87−1.59 (m, 3 H), 1.02−0.81 (m, 6 H); ^{13}C NMR ($CDCl_3$) 170.4, 165.9, 135.9, 135.3, 130.1, 129.0, 128.7, 128.4, 127.5, 124.4, 69.7, 69.1, 59.4, 58.2, 52.8, 38.4, 38.2, 24.8, 24.7, 23.0, 22.7; HRMS Calcd for $C_{23}H_{24}N_2O_6$ *m*/*z* 424.1634, found 424.1644.

(*R*)-*N*-Benzyloxycarbonyl-*N*-phthalimidophenylalanine Benzyl Ester. 2n P = Z, R = $CH_2C_6H_5$, R′ = CH_2Ph. Oil; [α]$_D$ = +28.9 (c 0.56, $CHCl_3$); *Rf* = 0.50 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 1799, 1745; ^{1}H NMR (400 MHz, $CDCl_3$) 7.96−7.70 (m, 4 H), 7.48−7.00 (m, 15 H), 5.51 and 5.27 (2 dd, *J* = 10 Hz, 5 Hz, 1H), 5.25−5.06 (m, 4 H), 3.40−3.22 (m, 2 H); ^{13}C NMR ($CDCl_3$) 168.9, 166.3, 166.0, 165.4, 154.0, 153.8, 136.4, 136.2, 135.6, 135.4, 130.3, 130.1, 129.0, 128.9, 128.7, 128.5, 127.7, 127.4, 124.5, 69.9, 69.2, 67.9, 67.7, 62.9, 61.8, 36.4; HRMS Calcd for $C_{32}H_{30}N_3O_6$ [M+NH_4^+] *m*/*z* 552.2135, found 552.2120.

(*R*)-*N*-Benzyloxycarbonyl-*N*-phthalimidophenylalanine Methyl Ester. 2o P = Z, R = $CH_2C_6H_5$, R′ = CH_3. Oil; *Rf* = 0.50 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 1799, 1744; ^{1}H NMR (400 MHz, $CDCl_3$) 7.94−7.66 (m, 4 H), 7.44−7.10 (m, 10 H), 5.45 and 5.31−5.10 (dd and m, *J* = 12 Hz, 6 Hz, 3 H), 3.66 and 3.62 (2 s, 3 H), 3.34−3.19 (m, 2 H); ^{13}C NMR ($CDCl_3$) 169.5, 169.4, 166.2, 165.9, 165.7, 165.3, 154.0, 153.7, 136.6, 136.4, 135.6, 135.4, 130.2, 130.1, 129.7, 129.0, 128.8, 128.5, 127.7, 127.3, 124.5, 69.8, 69.2, 62.8, 61.5, 52.8, 36.5, 36.1; HRMS Calcd for $C_{26}H_{22}N_2O_4$ *m*/*z* 458.1478, found 458.1482.

(*S*)-*N*-Benzyloxycarbonyl-*N*-phthalimidophenylalanine Benzyl Ester. 2p P = Z, R = $CH_2C_6H_5$, R′ = CH_2Ph. Oil; [α]$_D$ = −28.2 (c 0.56, $CHCl_3$); *Rf* = 0.50 (EtOAc/Hexane 4/6).

General Procedure for the Removal of the Carbamate Group (BOC or Z). A solution of dry hydrobromic acid in glacial acetic acid (33%, 5 mL) (for P = Z) or of dry hydrochloric acid in EtOAc (3 N, 5 mL) (for P = BOC) was added to the carbamate **2** (5 mmol). The mixture was stirred at room temperature for the time indicated in Table 1 (monitored by TLC). The mixture was poured into a saturated solution of $NaHCO_3$ (50 mL) (CAUTION required) and extracted 3 times with EtOAc. The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. The residue was chromatographed on silica gel.

***N*-Phthalimidoglycine Benzyl Ester. 3a P = H, R = H, R′ = CH_2Ph.** Mp 92 °C; *Rf* = 0.30 (EtOAc/Hexane 4/6); IR (KBr) ν_{max}/cm^{-1} 3302, 1780, 1768, 1727; ^{1}H NMR (250 MHz, $CDCl_3$) 7.86−7.66 (m, 4 H), 7.40−7.24 (m, 5 H), 5.30−5.07 (m, 3 H), 3.91

(s, 2 H); ^{13}C NMR ($CDCl_3$) 169.5, 166.5, 135.5, 134.7, 130.5, 128.9, 67.5, 52.0; HRMS Calcd for $C_{17}H_{14}N_2O_4$ *m/z* 310.0953, found 310.095.

(*R*)-*N*-Phthalimidoalanine Benzyl Ester. 3c P = H, R = CH_3, R′ = CH_2Ph. Mp 77−78 °C; $[\alpha]_D = +24.0$ (c 0.96, $CHCl_3$); *Rf* = 0.38 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 3298, 1786, 1729; ^{1}H NMR (250 MHz, $CDCl_3$) 7.86−7.64 (m, 4 H), 7.37−7.21 (m, 5 H), 5.25 (d, *J* = 6 Hz, 1 H), 5.15 (d, *J* = 6 Hz, 2 H), 4.11−3.98 (m, 1 H), 1.40 (d, *J* = 8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 171.9, 166.5, 135.4, 134.4, 130.1, 128.6, 128.4, 67.2, 57.5, 16.2; HRMS Calcd for $C_{18}H_{16}N_2O_4$ *m/z* 324.1109, found 324.1110.

(*R*)-*N*-Phthalimidoleucine Benzyl Ester. 3e P = H, R = CH_2−$CH(CH_3)_2$, R′ = CH_2Ph. Oil; *Rf* = 0.45 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 3298, 1788, 1727; ^{1}H NMR (400 MHz, $CDCl_3$) 7.83−7.58 (m, 4 H), 7.53−7.14 (m, 5 H), 5.22−5.00 (m, 3 H), 4.11 and 3.89 (2 m, 1 H), 1.97−1.78 (m, 1 H), 1.67 (t, *J* = 9 Hz, 2 H), 1.04−0.77 (m, 6 H); ^{13}C NMR ($CDCl_3$) 172.9, 166.3, 135.7, 135.6, 130.5, 128.8, 128.6, 123.7, 67.5, 61.8, 40.4, 25.2, 22.9, 22.6.

***N*-Phthalimidoglycine Methyl Ester. 3g P = H, R = H, R′ = CH_3.** Mp 147−148 °C; *Rf* = 0.20 (EtOAc/Hexane 4/6); IR (KBr) ν_{max}/cm^{-1} 3307, 1778, 1746, 1712; ^{1}H NMR (400 MHz, $CDCl_3$) 7.86−7.62 (m, 4 H), 5.22−5.07 (m, 1 H), 3.81 (d, *J* = 6 Hz, 2 H), 3.70 (s, 3H); ^{13}C NMR ($CDCl_3$) 170.1, 166.5, 134.7, 130.5, 123.9, 52.6, 51.8; HRMS Calcd for $C_{11}H_{10}N_2O_4$ *m/z* 234.0640, found 234.0643.

(*R*)-*N*-Phthalimidoalanine Methyl Ester. 3i P = H, R = CH_3, R′ = CH_3. Mp 82 °C; $[\alpha]_D = +32.8$ (c 0.73, $CHCl_3$); *Rf* = 0.35 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 3302, 1783, 1710; ^{1}H NMR (400 MHz, $CDCl_3$) 7.71−7.55 (m, 4 H), 5.13 (d, *J* = 7 Hz, 1 H), 3.90−3.77 (m, 1 H), 3.58 (s, 3 H), 1.26 (d, *J* = 8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) 170.7, 166.8, 136.6, 130.3, 123.7, 57.6, 52.6, 16.4; HRMS Calcd for $C_{12}H_{13}N_2O_4$ [M+H$^+$] *m/z* 249.0868, found 249.0875.

(*R*)-*N*-Phthalimidovaline Methyl Ester. 3k P = H, R = $CH(CH_3)_2$, R′ = CH_3. Oil; *Rf* = 0.50 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 3297, 1787, 1728; ^{1}H NMR (400 MHz, $CDCl_3$) 7.81−7.64 (m, 4 H), 5.10 (d, *J* = 7 Hz, 1 H) 3.71 (s, 3 H), 3.43 (t, *J* = 7 Hz, 1 H), 2.09−1.96 (m, 1 H), 1.10 and 0.98 (2 d, *J* = 7 Hz, 6 H); ^{13}C NMR ($CDCl_3$) 173.2, 166.5, 134.6, 130.5, 123.7, 69.5, 52.3, 30.9, 19.2; HRMS Calcd for $C_{14}H_{16}N_2O_4$ *m/z* 276.1110, found 276.1107.

(*R*)-*N*-Phthalimidoleucine Methyl Ester. 3m P = H, R = CH_2-$CH(CH_3)_2$, R′ = CH_3. Oil; $[\alpha]_D = +45.96$ (c 0.57, $CHCl_3$); *Rf* = 0.50 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 3300, 1787, 1727; ^{1}H NMR (400 MHz, $CDCl_3$) 7.76−7.59 (m, 4 H), 5.04 (d, *J* = 10 Hz, 1 H), 3.73 (q, *J* = 9 Hz, 1 H), 3.62 (s, 3 H), 1.85−1.70 (m, 1 H), 1.56 (t, *J* = 9 Hz, 2 H), 0.88 and 0.85 (2 d, *J* = 9 Hz, 6 H); ^{13}C NMR ($CDCl_3$) 173.4, 166.4, 134.6, 130.4, 123.7, 61.8, 52.5, 40.3, 25.6, 22.8 and 22.6; HRMS Calcd for $C_{15}H_{18}N_2O_4$ *m/z* 290.1267, found 290.1269.

(*R*)-*N*-Phthalimidophenylalanine Benzyl Ester. 3n P = H, R = $CH_2C_6H_5$, R′ = $CH_2C_6H_5$. Oil; *Rf* = 0.45 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 3298, 1787, 1725; ^{1}H NMR (400 MHz, $CDCl_3$) 7.83−7.63 (m, 4 H), 7.40−7.04 (m, 10 H), 5.20−5.03 (m, 3 H), 4.37−4.25 (m, 1 H), 3.20 and 3.13 (2 dd, *J* = 8 Hz, 14 Hz, 2 H); ^{13}C NMR ($CDCl_3$) 171.5, 166.6, 136.4, 135.5, 134.6, 130.4, 129.6, 128.9, 128.7, 127.3, 123.8, 67.6, 63.5, 36.5; HRMS Calcd for $C_{24}H_{20}N_2O_4$ *m/z* 400.1423, found 400.1424.

(*R*)-*N*-Phthalimidophenylalanine Methyl Ester. 3o P = H, R = $CH_2C_6H_5$, R′ = CH_3. Mp 80−82 °C; *Rf* = 0.40 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 3294, 1787, 1726; ^{1}H NMR (400 MHz, $CDCl_3$) 7.77−7.59 (m, 4 H), 7.31−6.88 (m, 5 H), 4.99 (d, *J* = 5 Hz, 1 H), 4.19 (m, 1 H), 3.63 (s, 3 H), 3.15 and 3.05 (2 dd, *J* = 14 Hz, 8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) 172.0, 166.5, 136.5, 134.5, 130.4, 129.5, 128.8, 127.2, 123.7, 63.4, 52.6, 37.5; HRMS Calcd for $C_{18}H_{16}N_2O_4$ *m/z* 324.1110, found 324.1098.

General Procedure for the Dephthaloylation Reaction. To a solution of compound **2** (3 mmol) in THF (20 mL) was added $MeNHNH_2$ (4.5 mmol) at −20 °C or 0 °C (see Table 1) and the mixture was stirred at this temperature for 30 mn. The solution was then allowed to warm to room temperature, stirred for the time indicated in the table, and then concentrated in vacuo. EtOAc was added and the white precipitate was filtered off. The filtrate was evaporated and the residue was chromatographed on neutral alumina gel.

***N*-Amino-*N*-*tert*-butyloxycarbonylglycine Benzyl Ester. 4a P = Boc, R = H, R′ = CH_2Ph.** Oil; *Rf* = 0.45 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 3337, 1747, 1712; ^{1}H NMR (400 MHz, $CDCl_3$) 7.37−7.20 (m, 5 H), 5.12 (s, 2 H), 4.40−4.02 (m, 4 H), 1.54−1.26 (m, 9 H); ^{13}C NMR ($CDCl_3$) 170.1, 157.7, 135.8, 128.9, 128.7, 128.6, 81.5, 67.1, 53.8, 28.5; HRMS Calcd for $C_{14}H_{21}N_2O_4$ [M+H$^+$] *m/z* 281.1501, found 281.1507.

(*R*)-*N*-Amino-*N*-*tert*-butyloxycarbonylalanine Benzyl Ester. 4c P = Boc, R = CH_3, R′ = CH_2Ph. Oil; $[\alpha]_D = +21.5$ (c 2.03, $CHCl_3$); *Rf* = 0.65 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 3351, 1743, 1702; ^{1}H NMR (400 MHz, $CDCl_3$) 7.36−7.18 (m, 5 H), 5.09 (s, 2 H), 4.92−4.74 and 4.74−4.54 (2 m, 1 H), 3.98−3.73 (2 m, 2 H), 1.43 (d, *J* = 10 Hz, 3 H), 1.36 (s, 9 H); ^{13}C NMR ($CDCl_3$) 172.3, 157.7, 136.1, 128.9, 128.5, 128.4, 81.3, 67.2, 57.5, 28.8, 15.2; HRMS Calcd for $C_{15}H_{23}N_2O_4$ [M+H$^+$] *m/z* 295.1657, found 295.1652.

(*R*)-*N*-Amino-*N*-*tert*-butyloxycarbonylleucine Benzyl Ester. 4e P = Boc, R = CH_2-$CH(CH_3)_2$, R′ = CH_2Ph. Mp 50 °C; *Rf* = 0.75 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 3351, 1737, 1702; ^{1}H NMR (400 MHz, $CDCl_3$) 7.48−7.21 (m, 5 H), 5.18 (s, 2 H), 5.00−4.85 and 4.82−4.60 (2 m, 1 H), 3.97−3.70 (m, 2 H), 2.12−1.97 (m, 1 H), 1.70−1.35 (m with s at 1.45, 11 H), 0.97 and 0.91 (2 d, *J* = 13 Hz, 6 H); ^{13}C NMR ($CDCl_3$) 172.4, 159.0, 136.1, 128.9, 128.6, 128.3, 81.4, 67.0, 59.2, 37.6, 28.6, 25.2, 23.7, 21.3; HRMS Calcd for $C_{18}H_{29}N_2O_4$ [M+H$^+$] *m/z* 337.2127 found 337.2128.

N-Amino-*N*-benzyloxycarbonylglycine Benzyl Ester. 4f P = Z, R = H, R′ = CH_2Ph. Mp 66 °C; *Rf* = 0.35 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 3355, 1723, 1700; ^{1}H NMR (400 MHz, $CDCl_3$) 7.60−7.14 (m, 10 H), 5.34 and 5.06 (m, 4 H), 5.51−4.14 (m, 4 H); ^{13}C NMR ($CDCl_3$) 169.8, 158.5, 136.4, 135.7, 129.0, 128.8, 128.4, 68.6, 67.4, 53.5; HRMS Calcd for $C_{17}H_{19}N_2O_4$ [M+H$^+$] *m/z* 315.1345, found 315.1339.

(*R*)-*N*-Amino-*N*-benzyloxycarbonylalanine Benzyl Ester. 4h P = Z, R = CH_3, R′ = CH_2Ph. Oil; $[\alpha]_D = +3.3$ (c 1.5, $CHCl_3$); *Rf* = 0.53 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 3355, 1723, 1700; ^{1}H NMR (400 MHz, $CDCl_3$) 7.46−7.20 (m, 10 H), 5.14 and 5.09 (2 s, 4 H), 5.05−4.90 and 4.90−4.60 (2 m, 1 H), 4.14−3.8 (m, 2 H), 1.4 (d, 3 H, *J* = 11 Hz); ^{13}C NMR ($CDCl_3$) 172.0, 158.7, 136.6, 136.2, 129.0, 128.9, 128.7, 128.6, 128.5, 128.4, 68.3, 67.2, 57.3, 15.3; HRMS Calcd for $C_{18}H_{20}N_2O_4$ *m/z* 328.1423, found 328.1420.

(*R*)-*N*-Amino-*N*-benzyloxycarbonylvaline Benzyl Ester. 4j P = Z, R = $CH(CH_3)_2$, R′ = CH_2Ph. Oil; $[\alpha]_D = +33.0$ (c 1.14, $CHCl_3$); *Rf* = 0.55 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 3353, 1741, 1707; ^{1}H NMR (400 MHz, $CDCl_3$) 7.34−7.11 (m, 10 H), 5.17−4.97 (m, 4 H), 4.57−4.20 (2 m, 1 H), 4.06−3.80 (m, 2 H), 2.49−2.31 (m, 1 H), 1.00 and 0.91 (2 d, *J* = 6 Hz, 6 H); ^{13}C NMR ($CDCl_3$) 171.2, 158.7, 136.5, 136.0, 129.0, 128.9, 128.7, 128.6, 128.4, 128.3, 68.4, 67.0, 28.5, 20.2; HRMS Calcd for $C_{20}H_{24}N_2O_4$ *m/z* 356.1736, found 356.1737.

(*R*)-*N*-Amino-*N*-benzyloxycarbonylleucine Benzyl Ester. 4l P = Z, R = CH_2-$CH(CH_3)_2$, R′=CH_2Ph. Mp 59−62 °C; $[\alpha]_D = +12.9$ (c 1.08, $CHCl_3$); *Rf* = 0.65 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 3353, 1739, 1702; ^{1}H NMR (250 MHz, $CDCl_3$) 7.42−7.16 (m, 10 H), 5.16 and 5.13 (2 s, 4 H), 5.00−4.84 and 4.84−4.64 (m, 1 H), 4.03−3.77 (m, 2 H), 2.16−1.93 (m, 1 H), 1.81−1.45 (m, 2 H), 0.93 (d, *J* = 6 Hz, 6 H); ^{13}C NMR ($CDCl_3$) 172.2, 159.0, 136.5, 136.1, 129.0, 128.9, 128.7, 128.5, 68.5, 67.2, 59.7, 59.2, 37.5, 37.2, 25.1, 23.7, 21.4; HRMS Calcd for $C_{21}H_{26}N_2O_4$ *m/z* 370.1893, found 370.1893.

(*R*)-*N*-Amino-*N*-benzyloxycarbonylphenyalanine Benzyl Ester. 4n P = Z, R = $CH_2C_6H_5$, R′ = CH_2Ph. Mp 44 °C; $[\alpha]_D = +20.8$ (c 1.63, $CHCl_3$); *Rf* = 0.60 (EtOAc/Hexane 4/6); IR (NaCl) ν_{max}/cm^{-1} 3345, 1741, 1702; ^{1}H NMR (400 MHz, $CDCl_3$) 7.31−6.89 (m, 15 H), 5.22−4.77 (m, 5 H), 3.97−3.70 (m, 2 H), 3.28 (d, *J* = 7 Hz, 2 H); ^{13}C NMR ($CDCl_3$) 171.0, 158.5, 138.2, 136.5, 136.0, 129.4, 129.1, 129.0, 128.9, 128.6, 128.4, 128.1, 127.1, 68.3, 67.5, 63.0, 35.1; HRMS Calcd for $C_{24}H_{24}N_2O_4$ *m/z* 404.1736, found 404.1733.

(*S*)-*N*-Amino-*N*-benzyloxycarbonylphenyalanine Benzyl Ester. 4p P = Z, R = $CH_2C_6H_5$, R′ = CH_2Ph. Mp 44 °C; $[\alpha]_D = -20.4$ (c 1.84, $CHCl_3$); *Rf* = 0.60 (EtOAc/Hexane 4/6).

Determination of Enantiomeric Purity: Deprotection of Hydrazinoacids 4. A solution of hydrazinoacid **4** (**4h**, **4j**, **4l**, **4n**, or **4p**, 1 mmol) in ethanol was hydrogenated with Raney nickel (50 bar of H_2, 18 h, 25 °C, 6 mmol). In the cases of

compounds **4c** and **4e**, a preliminary removal of the BOC group with CF_3COOH in CH_2Cl_2 was necessary. The amino acid was obtained after filtration over Celite and evaporation of the solvent. **Derivatization and HPLC Analysis.** A solution of amino acid (40 μL of approximatively 1 mg/mL) was mixed with borate buffer (80 μL of a 0.133 M solution in borate buffer pH 10.4), *o*-phthalaldehyde (40 μL of a 5 mg/mL solution in a borate buffer), and *N*-isobutyryl-D-cysteine (40 μL of a 20 mg/mL solution in a borate buffer). After 5 min, 25 μL of this solution was injected onto a Merck LichroCart 250−4 Purospher RP-18e (5 μm). The mobile phase was acetonitrile/ammonium acetate (50 mM, pH 7.0) at 1 mL/min under isocratic conditions (27/73 for leucine, retention time for DD isomer 4.34 and 4.91 min for LD); (20/80 for alanine, retention time for DD and LD isomers is respectively 3.64 min and 4.00 min); (25/75 for valine, retention time for DD and LD isomers is respectively 3.80 and 4.80 min); (25/75 for phenylalanine, retention time for DD and LD isomers is respectively 10.42 min and 11.72 min). The derivatives were identified by comparison with authentic samples. Chiral purity was determined by integration of HPLC profile monitored at 338 nm and comparison to the peaks of authentic samples.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra of **2a**, **2c**, **2e**, **2g**, **2k**, and **2n**. This material is available free of charge via the Internet at http://pubs.acs.org.

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