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Efficient synthesis of orthogonally protected *anti*-2,3-diamino acids

Stefania Capone, Annalisa Guaragna, Giovanni Palumbo and Silvana Pedatella*

Dipartimento di Chimica Organica e Biochimica, Università di Napoli Federico II, Via Cynthia 4, 80126 Napoli, Italy

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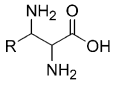
Abstract—An asymmetric synthesis of *anti*-2,3-diamino acids is reported. The enolates of *N*,*N*-dibenzylated β^3-amino esters were treated with di-*tert*-butyl azodicarboxylate (DBAD) to afford their N',N''-di-Boc-2-hydrazino derivatives with excellent *anti* diastereoisomeric ratio. Final Boc removal and reductive cleavage of the hydrazino bond led to the expected 2,3-diamino esters having only one free amino group. In comparison with other asymmetric C-2 amination procedures, this method does not need the use of expensive chiral reagents and/or chiral auxiliaries, while leads to products which can be orthogonally protected.

1. Introduction

2,3-Diamino acids are important non-protein amino acids, usually components of both natural and synthetic bioactive compounds.[1] In fact, they are currently well recognized as key structural moieties in a variety of biologically active molecules: (*S*)-2,3-diamino propanoic acid (DAP, **1**),[2] 2,3-diamino butanoic acids (DAB, **2** and **3**)[3] and (2*S*,3*R*)-2,3-diamino-4-phenylbutanoic acid (**4**)[4] are present in some antifungal dipeptides[5] and in peptide antibiotics, like aspartocin,[3] glumamycin,[6] lavendomycin[7] and aminodeoxybestatin.[8] Furthermore, (2*R*,3*S*)-2,3-diamino-3-phenylpropanoic acid (**5**) has been considered as an alternative side chain in the anticancer drug Taxol.[9]



1 R=H (2*S*)
2 R=CH_3 (2*S*,3*S*)
3 R=CH_3 (2*R*,3*S*)
4 R=CH_2Ph (2*S*,3*R*)
5 R=Ph (2*R*,3*S*)

The elementary, polyfunctional 2,3-diamino acid unit has been frequently used to probe several aspects of peptide and protein structures. In addition, the usefulness of simple chiral 1,2-diamines as auxiliaries and controller groups in asymmetric synthesis (e.g., dihydroxylation,[10] conjugate addition,[11] olefination,[12] allylation,[13] epoxidation,[14] and aldol reaction[15]) is also well documented. Their use to resolve racemic mixtures of chiral allylic alcohols has been reported as well.[16]

The development of simple and efficient methods to produce enantiomerically pure 2,3-diamino acids from readily available starting materials represent a fascinating goal and several asymmetric syntheses have been reported so far. The Mitsunobu reaction on serine,[17] the Hofmann and Curtius rearrangements of asparagine derivatives,[18] and the Schmidt reaction on aspartic acid[19] were used to access chiral 2,3-diaminopropanoic acid. A variety of other syntheses have been also reported: the conjugate addition[20] of homochiral lithium *N*-benzyl-*N*-α-methylbenzylamide to α,β-unsaturated esters and in situ amination with trisyl azide, the asymmetric Rh(I)-phosphine-catalyzed hydrogenation of diastereoisomeric enamides,[21] and the ring opening of *cis*-3-alkylaziridine-2-carboxylates coming from Sharpless asymmetric aminohydroxylation of α,β-unsaturated esters.[22]

In this paper we report a new inexpensive, general and highly stereoselective synthesis of *anti*-2,3-diamino acids via amination of β^3-amino esters.[23]

2. Results and discussion

N,*N*-Dibenzylated β^3-amino esters (**7a–c**), in dry THF at −78 °C and under dry nitrogen stream, were treated with potassium bis(trimethylsilyl)amide (KHMDS) to get the corresponding enolates. The use of more common bases, such as LiHMDS and LDA, for the enolate generation was

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* Corresponding author. Tel.: +39 081 674 118; fax: +39 081 674 102; e-mail: pedatell@unina.it

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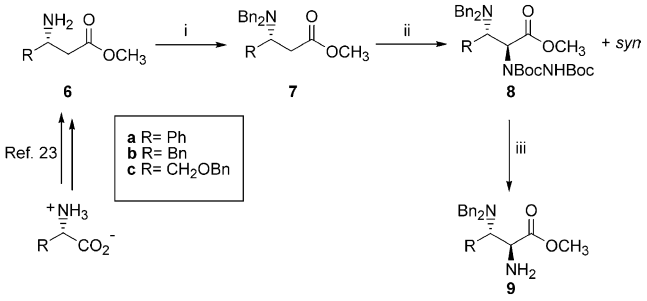
neglected since in our experience[24] such bases lead to significantly poorer results. After 1 h, solid di-*tert*-butyl azodicarboxylate (DBAD) was added to the reaction mixture that was kept at −78 °C for an additional hour. Under such conditions, the Boc-diprotected hydrazino derivatives of the starting **7a–c** were obtained.

The double protection of the amino group is necessary to avoid formation of by-products coming from the abstraction of the N–H proton in the enolate production step. Consequently, common protecting groups that are stable under basic conditions, such as either Boc or Cbz, could not be used under our reaction conditions. Therefore, in a first attempt, the 4-methoxybenzyl group, we had already used elsewhere,[24] was chosen for its peculiar removal conditions (CAN, CH_3CN/H_2O). Unfortunately, although the group turned out to be stable under the reaction conditions, we could not use it because the deprotection of the final 3-[di(4-methoxybenzyl)amino]-2,3-diamino esters led to a plethora of products coming from oxidative cleavage of the C2–C3 bond. Eventually, we used a double benzylic protection that eliminated such deprotection problems and represented at the same time a very bulky nitrogen substituent, suitable to affect the stereochemical outcome[25] of the enolate coupling with the electrophile DBAD. As a matter of fact, the coupling afforded a mixture of *anti*:*syn* Boc protected 2-hydrazino derivatives of **7a–c** with excellent diastereoisomeric ratio. Due to the complexity of the ^{1}H NMR spectra of the Boc containing hydrazino derivatives, they were converted into the corresponding diastereoisomeric mixtures of diamino esters (e.g., **9**) to determine accurately the diastereoisomeric ratio.

The synthetic path is depicted in Scheme 1 and the results obtained for selected β^3-amino esters, namely the methyl esters of β^3-phenylglycine (**6a**), β^3-phenylalanine (**6b**), and β^3-serine (**6c**), are reported in Table 1.



i. BnBr, DIPEA, toluene, reflux; ii. KHMDS, DBAD, dry THF, -78 °C;
iii. a) TFA, CH_2Cl_2; b) H_2, Ni(Ra), MeOH, ultrasound

Scheme 1. Conversion of α-amino acids into monoprotected 2,3-diamino esters.

The more abundant *anti* diastereoisomers were submitted to removal of the Boc protections (TFA in CH_2Cl_2) and cleavage of the N–N bond by hydrogenolysis with Ni(Ra) at low pressure and room temperature in an ultrasound bath.

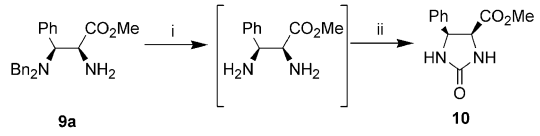
The reduction of hydrazines to amines is reported to be accomplished at high temperature, under high hydrogen pressure.[26] The use of ultrasound reduces significantly both temperature and pressure.[27] As a matter of fact, the hydrogenolysis under such conditions was complete after only 4 h and no traces of C-2 epimerization products could be detected by ^{1}H NMR spectroscopic analysis.

Table 1. Functionalization at C-2 of the fully protected β^3-amino esters **7a–c**

Protected β^3-amino ester	R	Boc protected 2-hydrazino derivatives of **7a–c**		*anti*-2,3-Diamino esters (**9a–c**), yield (%)[a]
		Yield (%)[b]	*anti*/*syn*	
7a	Ph	92	93:7	70
7b	Bn	90	97:3	78
7c	CH_2OBn	90	94:6	65

[a] Overall yield after Boc removal and reductive cleavage of the hydrazine moiety in the *anti* diastereoisomers **8a–c**.
[b] Yield of both diastereoisomers.

The *anti* configuration of the more abundant diastereoisomers coming from the couplings of **7a–c** with DBAD could be attributed, in the case of **8a**, as follows: the final product **9a** was debenzylated and treated, without isolation, with 1,1′-carbonyldiimidazole to afford the imidazolidinone **10** (Scheme 2).



i. Pd/C, H_2, AcOH, 50 °C, 90%; ii. 1,1'-carbonyldiimidazole, TEA, THF, 0 °C, 85%

Scheme 2. Synthesis of *cis*-imidazolidinone (**10**).

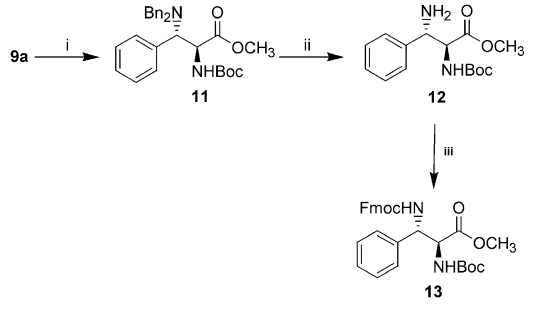
The ^{1}H NMR spectroscopy coupling constant of 9.6 Hz supported[28] the *cis*-configuration of the H-4 and H-5 protons and, thus, the *anti*-configuration of the starting diamino compound.

In the light of this result and in agreement with our previous work on the hydroxylation at C-2 of β^3-amino esters, it seems likely that the stereochemical outcome of the functionalization at C-2 is independent of the nature of the electrophile used, being only a function of the relative stabilities of the enolate conformations.[24]

3. Conclusion

This amination procedure of β^3-amino esters offers several advantages, if compared with many other reported procedures. First of all, it does not require the use of either chiral reagents or chiral auxiliaries: in fact, the observed selection in the coupling step is merely due to the influence of the existing chiral center of the starting β^3-amino ester, enhanced by the presence of two bulky substituents on the nitrogen atom. Moreover, it is noteworthy that the amino groups in the final 2,3-diamino esters have a different protection status: this implies a broad flexibility of their use in peptide synthesis. For instance, the free amino group can be Boc protected and the benzyl groups then removed hydrogenolitically to host an Fmoc protecting group, or vice

versa should either Boc- or Fmoc-strategy be used. Accordingly, in connection with our current interest in the synthesis of glycosyl amino acids, we have prepared the compound **13** as shown in Scheme 3.



Scheme 3. Preparation of the orthogonally protected 2,3-diamino acid **13**.

4. Experimental

4.1. General

NMR spectra were recorded on Varian Inova 500 MHz, Varian Gemini 200 MHz, Varian Gemini 300 MHz, Bruker DRX 400 MHz spectrometers: chemical shifts are in ppm (δ) and J coupling constants in Hz; solvent $CDCl_3$, unless otherwise specified. GC/MS analyses were performed on Hewlett–Packard 6890 GC/5973N MS. Optical rotations were determined on Jasco P-1010 polarimeter (1.0 dm cell); solvent $CHCl_3$, unless otherwise specified. Infrared spectra were recorded using JASCO FT/IR-430 Spectrometer. Mps were taken on a Gallenkamp apparatus. Elemental analyses were performed on a Perkin–Elmer Series II 2400, CHNS analyzer. TLC were carried out on silica gel Merck 60 F_{254} plates (0.2 mm layer) and column chromatographies on Merck Kieselgel 60 (70–230 mesh). Dry solvents were distilled immediately before use.

4.1.1. *N,N*-Dibenzyl protections of 6a–c. *Methyl (R)-3-(dibenzylamino)-3-phenylpropanoate* (**7a**): *typical procedure*. A magnetically stirred suspension of β^3-phenylglycine methyl ester **6a** (1.50 g; 8.38 mmol) and diisopropylethylamine (DIPEA, 7.3 mL; 41.90 mmol) in toluene (18.0 mL) was warmed gently until a clear solution was obtained. Then, benzyl bromide (6.0 mL; 50.28 mmol) was added in one portion and the resulting solution was refluxed for 4 h. The reaction mixture was then cooled in an ice bath, diluted with EtOAc (2×100 mL) and extracted with 10% aq NH_4Cl. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure to afford a crude reaction product whose chromatography on silica gel (petroleum ether/EtOAc, 95:5) gave the pure crystalline compound **7a**, after recrystallization from hexane (2.56 g; 7.12 mmol; 85%). Mp 51.8–53.0 °C. $[\alpha]_D^{20}$ +71.6 (c 2.0). ^{1}H NMR (500 MHz): δ 2.73 (dd, J=7.3, 14.6 Hz, 1H, H-2a), 3.14 (dd, J=8.8, 14.6 Hz, 1H, H-2b), 3.18 (d, J=13.7 Hz, 2H, NC*H*Ph), 3.64 (s, 3H, OCH_3), 3.78 (d, J=13.7 Hz, 2H, NC*H*Ph), 4.33 (dd, J=7.3, 8.8 Hz, 1H, H-3), 7.20–7.41 (m, 15H, *H*-Ar). ^{13}C NMR (125 MHz): δ 36.9, 51.8, 53.9, 59.1, 127.2, 127.7, 128.3, 128.4, 128.8, 129.1, 137.6, 139.8, 172.3. IR (KBr, cm^{-1}): ν 1714. Anal. Calcd for $C_{24}H_{25}NO_2$: C 80.19, H 7.01, N 3.90. Found: C 80.30, H 7.05, N 3.92.

Under the same conditions, the following *N,N*-diprotected esters were also obtained.

Methyl (S)-3-(dibenzylamino)-4-phenylbutanoate (**7b**). Oil (83%). $[\alpha]_D^{20}$ −5.4 (c 1.0). ^{1}H NMR (500 MHz): δ 2.33 (dd, J=6.4, 14.2 Hz, 1H, H-2a), 2.56 (dd, J=8.8, 13.2 Hz, 1H, H-4a), 2.65 (dd, J=8.3, 14.2 Hz, 1H, H-2b), 3.12 (dd, J=5.7, 13.2 Hz, 1H, H-4b), 3.40–3.50 (m, 1H, H-3), 3.56 (s, 3H, OCH_3), 3.62 (d, J=13.7 Hz, 2H, NC*H*Ph), 3.76 (d, J=13.7 Hz, 2H, NC*H*Ph), 7.20–7.70 (m, 15H, *H*-Ar). ^{13}C NMR (125 MHz): δ 35.9, 36.3, 51.6, 53.7, 57.8, 126.4, 127.2, 128.4, 128.6, 129.1, 129.5, 139.7, 139.8, 172.9. IR (KBr, cm^{-1}): ν 1712. Anal. Calcd for $C_{25}H_{27}NO_2$: C 80.40, H 7.29, N 3.75. Found: C 80.25, H 7.32, N 3.77.

Methyl (R)-4-(benzyloxy)-3-(dibenzylamino)butanoate (**7c**). Oil (86%). $[\alpha]_D^{20}$ +31.6 (c 1.8). ^{1}H NMR (500 MHz): δ 2.55 (dd, J=6.3, 14.6 Hz, 1H, H-2a), 2.68 (dd, J=7.8, 14.6 Hz, 1H, H-2b), 3.47–3.54 (m, 1H, H-3), 3.56–3.62 (m, 4H, H-4a and OCH_3), 3.66 (d, J=13.7 Hz, 2H, NC*H*Ph), 3.71 (dd, J=9.8, 5.4 Hz, 1H, H-4b), 3.75 (d, J=13.7 Hz, 2H, NC*H*Ph), 4.49 (d, J=12.7 Hz, 1H, OC*H*Ph), 4.52 (d, J=12.7 Hz, 1H, OC*H*Ph), 7.20–7.45 (m, 15H, *H*-Ar). ^{13}C NMR (125 MHz): δ 34.7, 51.7, 54.5, 55.2, 70.3, 73.3, 127.1, 127.8, 128.4, 128.6, 129.1, 138.6, 140.1, 173.0. IR (KBr, cm^{-1}): ν 1715. Anal. Calcd for $C_{26}H_{29}NO_3$: C 77.39, H 7.24, N 3.47. Found: C 77.25, H 7.27, N 3.48.

4.1.2. Reactions of 7a–c with DBAD. *Methyl (2S,3S)-3-(dibenzylamino)-2-[N′,N″-(di-tert-butoxycarbonyl)-hydrazino]-3-phenylpropanoate* (**8a**): *typical procedure*. To a magnetically stirred solution of **7a** (2.56 g; 7.12 mmol) in dry THF (75 mL), at −78 °C and under dry argon atmosphere, 0.5 M KHMDS in toluene (28.5 mL; 14.24 mmol) was added dropwise. After 1 h solid di-*tert*-butyl azodicarboxylate (2.85 g; 12.82 mmol) was added in one portion to the reaction mixture kept at −78 °C under stirring. Within 1 h the reaction was quenched by addition of glacial AcOH (1.1 mL) and diluted with EtOAc. The organic layer was washed with brine until neutral, dried (Na_2SO_4), and the solvents evaporated in vacuo. The oily residue, after chromatography on silica gel (hexane/EtOAc, 9:1), afforded the pure title compound **8a** (foam; 3.86 g; 6.55 mmol; 92%). $[\alpha]_D^{20}$ +65.7 (c 1.6). The ^{1}H NMR data were not significant, apparently due to the occurrence of mixtures of rotamers. IR (KBr, cm^{-1}): ν 3260, 1740, 1720. Anal. Calcd for $C_{34}H_{43}N_3O_6$: C 69.25, H 7.35, N 7.13. Found: C 69.17, H 7.31, N 7.15.

Under the same conditions, the following Boc diprotected 2-hydrazino derivatives were also obtained.

Methyl (2S,3S)-3-(dibenzylamino)-2-[N′,N″-(di-tert-butoxycarbonyl)-hydrazino]-4-phenylbutanoate (**8b**). Foam (90%). $[\alpha]_D^{20}$ −2.3 (c 0.3). IR (KBr, cm^{-1}): ν 3250, 1730, 1712. Anal. Calcd for $C_{35}H_{45}N_3O_6$: C 69.63, H 7.51, N 6.96. Found: C 69.60, H 7.49, N 7.01.

Methyl (2S,3R)-4-(benzyloxy)-3-(dibenzylamino)-2-[N′,N″-(di-tert-butoxycarbonyl)-hydrazino]butanoate (**8c**). Foam

(90%). $[\alpha]_D^{20}$ +45.0 (*c* 1.5). IR (KBr, cm^{-1}): ν 3270, 1728, 1715. Anal. Calcd for $C_{36}H_{47}N_3O_7$: C 68.22, H 7.47, N 6.63. Found: C 68.19, H 7.40, N 6.68.

4.1.3. Reductive cleavages of the hydrazino bond in 8a–c. *Methyl (2S,3S)-2-amino-3-(dibenzylamino)-3-phenylpropanoate* (**9a**): *typical procedure*. To a magnetically stirred solution of **8a** (3.86 g; 6.55 mmol) in dry CH_2Cl_2 (54 mL), TFA (54 mL) was added in one portion. After 2 h, the solvent was evaporated under reduced pressure. The crude reaction product, redissolved in MeOH (26 mL), was transferred into a flask containing W-2 Raney nickel (3.86 g, wet) and equipped with a hydrogen inflated balloon. The flask was dipped into an ultrasound bath filled with water and sonicated for 4 h at rt till the starting product was completely consumed (TLC). The reaction mixture was then filtered through Celite® washing with MeOH (100 mL). Removal of the solvents under reduced pressure gave a residue that was redissolved in EtOAc (200 mL), washed with 10% aq Na_2CO_3 (2×100 mL), dried (Na_2SO_4), and evaporated in vacuo, to afford an oil whose chromatography on silica gel (hexane/EtOAc, 7:3) led to the pure title compound **9a** (oil; 1.71 g; 4.58 mmol; 70%). $[\alpha]_D^{20}$ +62.4 (*c* 1.1). ^{1}H NMR (300 MHz): δ 1.97 (bs, 2H, NH_2), 3.05 (d, J=13.5 Hz, 2H, NC*H*Ph), 3.82 (s, 3H, OCH_3), 3.83–3.88 (m, 3H, H-2 and NC*H*Ph), 4.26 (d, J=10.3 Hz, 1H, H-3), 7.20–7.60 (m, 15H, *H*-Ar). ^{13}C NMR (50 MHz): δ 51.7, 54.0, 56.3, 67.3, 126.9, 128.1, 128.3, 128.8, 129.7, 133.5, 139.0, 174.1. IR (KBr, cm^{-1}): ν 3500–3200, 1714. Anal. Calcd for $C_{24}H_{26}N_2O_2$: C 76.98, H 7.00, N 7.48. Found: C 76.81, H 7.06, N 7.52.

Under the same conditions, the following 2-amino esters were also obtained.

Methyl (2S,3S)-2-amino-3-(dibenzylamino)-4-phenylbutanoate (**9b**). Oil (78%). $[\alpha]_D^{20}$ +7.9 (*c* 0.4, MeOH). ^{1}H NMR (500 MHz): δ 1.63 (bs, 2H, NH_2), 2.93 (dd, J=7.3, 13.7 Hz, 1H, H-4a), 3.09 (dd, J=6.3, 13.7 Hz, 1H, H-4b), 3.23–3.29 (m, 1H, H-3), 3.60 (s, 3H, OCH_3), 3.61–3.67 (m, 3H, H-2 and NC*H*Ph), 3.70 (d, J=13.7 Hz, 2H, NC*H*Ph), 7.10–7.40 (m, 15H, H-Ar). ^{13}C NMR (100 MHz): δ 32.7, 52.2, 55.1, 55.6, 63.8, 126.5, 127.4, 128.5, 128.7, 129.4, 129.9, 139.9, 140.5, 175.9. IR (KBr, cm^{-1}): ν 3530–3210, 1712. Anal. Calcd for $C_{25}H_{28}N_2O_2$: C 77.29, H 7.26, N 7.21. Found: C 77.19, H 7.25, N 7.23.

Methyl (2S,3R)-2-amino-4-(benzyloxy)-3-(dibenzylamino)-butanoate (**9c**). Oil (65%). $[\alpha]_D^{20}$ +30.9 (*c* 1.0). ^{1}H NMR (500 MHz, C_6D_6): δ 1.48 (bs, 2H, NH_2), 3.22–3.28 (m, 1H, H-3), 3.29 (s, 3H, OCH_3), 3.58 (d, J=6.8 Hz, 1H, H-2), 3.60 (dd, J=5.8, 9.8 Hz, 1H, H-4a), 3.65 (d, 2H, J=13.7 Hz, NC*H*Ph), 3.72 (dd, 1H, J=4.9, 9.8 Hz, H-4b), 3.84 (d, 2H, J=13.7 Hz, NC*H*Ph), 7.05–7.40 (m, 15H, *H*-Ar). ^{13}C NMR (100 MHz): δ 52.1, 55.4, 55.6, 61.1, 67.2, 73.7, 127.3, 127.9, 128.0, 128.5, 128.8, 129.4, 138.7, 140.2, 175.7. IR (KBr, cm^{-1}): ν 3510–3200, 1716. Anal. Calcd for $C_{26}H_{30}N_2O_3$: C 74.61, H 7.22, N 6.69. Found: C 74.59, H 7.20, N 7.01.

4.1.4. Methyl (4*S*,5*S*)-4-methoxycarbonyl-5-phenyl-2-imidazolidinone (10). A magnetically stirred solution of **9a** (0.020 g; 0.053 mmol) in glacial AcOH (0.5 mL) was hydrogenolysed over 30% Pd/C catalyst (0.006 g) for 2 h at 50 °C, under a slightly positive pressure given by an inflated balloon (~3 bar). The mixture was then filtered through Celite® washing with MeOH (10 mL). Removal of the solvents under reduced pressure gave a residue that was redissolved in dry THF (1.1 mL). The solution was cooled to 0 °C. Et_3N (0.063 mL, 0.053 mmol) and 1,1′-carbonyldiimidazole (0.013 g; 0.079 mmol) were then added in sequence. After 30 min at 0 °C and 2 h at rt the solvents were evaporated under reduced pressure and the remaining crude residue was dissolved in EtOAc and filtered on a short silica gel plug (~3 cm^3) with the same solvent (3×10 mL). By partial evaporation of the solvent under reduced pressure, a semicrystalline residue could be collected whose recrystallization by the same solvent afforded the pure **10** (0.010 g; 0.045 mmol; 88%) as a white solid. Mp 202–203 °C dec. (lit.[27] 203–205 °C). ^{1}H, ^{13}C NMR and IR spectra were superimposable to those reported.

4.1.5. Methyl (2*S*,3*S*)-2-(*tert*-butoxycarbonylamino)-3-(dibenzylamino)-3-phenylpropanoate (11). To a solution of compound **9a** (0.67 g; 1.80 mmol) in dioxane (21 mL) at 0 °C, Et_3N (0.42 mL; 2.70 mmol) and Boc_2O (0.89 g; 3.60 mmol) were added in sequence. The reaction mixture, warmed up to room temperature and stirred for 1 h, was then diluted with EtOAc. The organic layer was washed with brine until neutral, dried (Na_2SO_4), and the solvents evaporated in vacuo to give an oil. Its chromatography on silica gel (hexane/EtOAc, 9:1) afforded the pure title compound **11** (oil; 0.78 g; 1.66 mmol; 92%). $[\alpha]_D^{20}$ +50.7 (*c* 1.5). ^{1}H NMR (400 MHz): δ 1.55 (s, 9H, Boc), 3.04 (d, J=13.5 Hz, 2H, NC*H*Ph), 3.86 (s, 3H, OCH_3), 3.97–4.02 (m, 3H, H-3, NC*H*Ph), 4.58 (bd, J=8.3 Hz, 1H, N*H*Boc), 5.14 (bt, J=9.7 Hz, 1H, H-2), 7.24–7.44 (m, 15H, *H*-Ar). ^{13}C NMR (125 MHz): δ 28.3, 52.3, 54.1, 54.7, 65.0, 80.2, 127.3, 128.3, 128.5, 129.2, 130.1, 132.6, 139.1, 146.9, 154.9, 172.3. IR (KBr, cm^{-1}): ν 1718, 1705. Anal. Calcd for $C_{29}H_{34}N_2O_4$: C 73.39, H 7.22, N 5.90. Found: C 73.25, H 7.20, N 5.92.

4.1.6. Methyl (2*S*,3*S*)-2-(*tert*-butoxycarbonylamino)-3-amino-3-phenylpropanoate (12). A magnetically stirred solution of **11** (0.78 g; 1.66 mmol) in glacial AcOH (7.4 mL) was hydrogenolysed over 30% Pd/C catalyst (0.23 g) for 2 h at 50 °C, under a slightly positive pressure given by an inflated balloon (~3 bar). The mixture was then filtered trough Celite® and washed with MeOH (100 mL). The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (2×100 mL). The organic layer was washed with 10% aq Na_2CO_3 (300 mL), dried (Na_2SO_4), and the solvents evaporated in vacuo to give compound **12** as a white crystalline solid, after recrystallization from hexane/acetone 9:1 (0.44 g; 1.49 mmol; 90%). Mp 110.3–112.3 °C. $[\alpha]_D^{20}$ +29.0 (*c* 0.9). ^{1}H NMR (400 MHz, C_5D_5N): δ 1.35 (s, 9H, Boc), 3.62 (s, 3H, OCH_3), 5.34 (d, J=7.1 Hz, 1H, H-3), 5.77 (bt, J=8.0 Hz, 1H, H-2), 7.21–7.35 (m, 3H, *H*-Ar), 7.89 (d, J=7.3 Hz, 2H, Ar-H), 8.80 (bd, J=8.6 Hz, 1H, N*H*Boc). ^{13}C NMR (100 MHz, C_5D_5N): δ 28.3, 52.4, 57.1, 59.4, 79.3, 128.6, 128.9, 138.0, 140.2, 156.8, 172.0. IR (KBr, cm^{-1}): ν 3350, 3200, 1765, 1715. Anal. Calcd for $C_{15}H_{22}N_2O_4$: C 61.21, H 7.53, N 9.52. Found: C 61.32, H 7.57, N 9.58.

4.1.7. Methyl (2*S*,3*S*)-2-(*tert*-butoxycarbonylamino)-3-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-phenylpropanoate (13). To a stirred solution of **12** (0.44 g; 1.48 mmol) in dioxane (5.8 mL) and 10% aq Na_2CO_3 (0.31 g; 2.96 mmol) at 0 °C, Fmoc–OSu (0.41 g; 1.18 mmol) dissolved in DMF (1.5 mL) was added slowly. The reaction mixture, after 30 min at 0 °C and 2 h at rt, was extracted with CH_2Cl_2. The organic layer was washed with brine until neutral, dried (Na_2SO_4), and the solvents evaporated under reduced pressure to give an oil. The chromatography on silica gel ($CHCl_3$) afforded the pure compound **13**, white solid after recrystallization from hexane/acetone 9:1 (0.50 g; 0.96 mmol; 65%). Mp 166.6–168.1 °C. $[\alpha]_D^{20}$ +38.7 (*c* 0.3). ^{1}H NMR (500 MHz, C_5D_5N): δ 1.20 (s, 9H, Boc), 3.42 (s, 3H, OC*H*$_3$), 4.14 (t, *J*=6.8 Hz, 1H, Fmoc), 4.30 (dd, *J*=6.8, 10.3 Hz, 1H, C*H*Fmoc), 4.45 (dd, *J*=6.8, 10.3 Hz, 1H, C*H*Fmoc), 5.31 (t, *J*=9.3 Hz, 1H, H-2), 5.69 (t, *J*=9.3 Hz, 1H, H-3), 7.05–7.70 (m, 14H, *H*-Ar and N*H*Boc), 9.17 (d, *J*=9.3 Hz, 1H, N*H*Fmoc). ^{13}C NMR (125 MHz): δ 28.5, 47.5, 52.9, 57.7, 58.0, 67.3, 120.2, 125.4, 126.8, 127.3, 128.4, 128.9, 141.5, 144.1, 155.9, 156.5, 170.4. IR (KBr, cm^{-1}): ν 3395 (br), 1705. Anal. Calcd for $C_{30}H_{32}N_2O_6$: C 69.75, H 6.24, N 5.42. Found: C 69.82, H 6.27, N 5.43.

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