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Asymmetric Synthesis of β^2-Tryptophan Analogues via Friedel–Crafts Alkylation of Indoles with a Chiral Nitroacrylate

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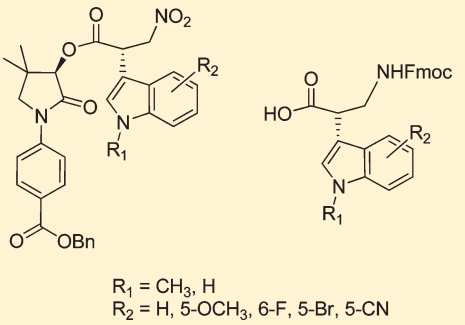
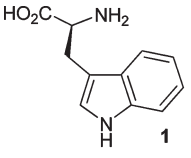
Supporting Information

ABSTRACT: The asymmetric Friedel–Crafts alkylation of various indoles with a chiral nitroacrylate provides optically active β-tryptophan analogues after reduction of the nitro group and removal of the chiral auxiliary. This reaction generally occurs in good yield and high diastereoselectivity (up to 90:10).



INTRODUCTION

Tryptophan **1**, an essential amino acid, both functions as a building block in protein biosynthesis and as a biochemical precursor. It is abundantly found in most biologically active peptides that exhibit various physiological properties, in particular hormonal and antimicrobial activities.[1] Some of its natural derivatives such as serotonin and tryptamine, and also unnatural derivatives such as sumatriptan, have neurophysiologic effects.[2] Tryptophan analogues are also important building blocks for the synthesis of peptidomimetics, natural products, and biologically active compounds.[3] Another important property of tryptophan and tryptophan analogues is related to the fluorescence of the indole ring that can be used to study conformational changes in protein and in protein–membrane interactions.[4]



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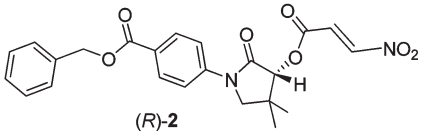
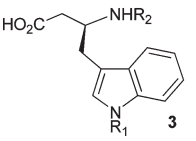


(*R*)-**2**

In view of the central role that tryptophan plays particularly in peptides and proteins, the preparation of new analogues in an enantiomerically pure form is particularly attractive. In connection with a project exploiting the use of the new chiral β-nitroacrylate (*R*)-**2**[5] in organic synthesis, we have focused our attention to the development of enantiopure β-amino acids synthesis. These derivatives incorporated into peptides and proteins will result in biologically active materials with enhanced resistance to enzymatic degradation[6] and relevant roles in medicinal chemistry.[7] Herein, we report the preparation of enantiopure β-tryptophan analogues **5**, for which only very few asymmetric synthesis have been reported.

The enantioselective preparation of the two β-homologues of tryptophan, i.e., *N*-Fmoc-(or *N*-Z)-3-amino-4-(*N*-Boc-1*H*-indol-3-yl)butanoic acid **3** (β^3-homotryptophan) and *N*-Boc-3-amino-2-(1*H*-indol-3-yl)methyl propionic acid **4** (β^2-homotryptophan) have been previously described via Curtius degradation of a succinic acid derivative and aminomethylation of chiral silyl enol ethers, respectively.[8]



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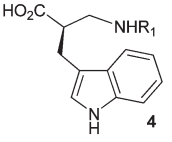

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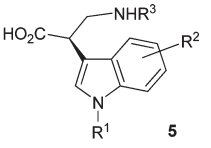

5

Concerning β-tryptophan analogues **5**, the racemic 5-methoxy analogue ($R^1 = R^3 = H$ and $R^2 = 5\text{-}OCH_3$) presents antihypertensive activity[9] and has previously been obtained from the corresponding 3-indolylacetonitrile. More recently, the Friedel–Crafts alkylation of various indoles with the (*E*)-methyl-3-nitroacrylate has been developed to provide racemic nitro precursors **6** of

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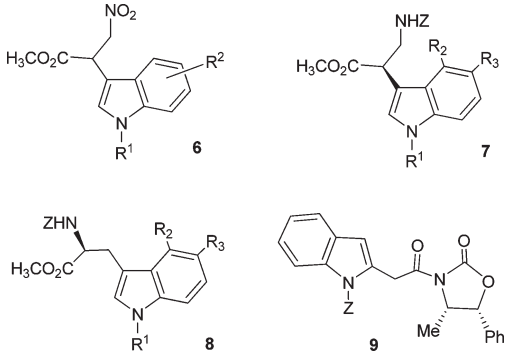
β-tryptophan derivatives **5**.[10] The preparation of optically active compounds via ring-opening of chiral methyl *N*-Z-2-aziridine carboxylate with indoles has been reported[11] to afford a mixture of optically active β-tryptophan methyl esters analogues **7** and the corresponding α-regioisomers **8**. These two series of compounds were separated by repeated column chromatography. Finally, the (*R*)-di-*N*-Z protected tryptophan analogue **5** (R^1 = R^3 = Z and R^2 = H) is also obtained, after removal of the chiral auxiliary, using an electrophilic attack of the aminomethyl cation $[H_2NCH_2]^+$ on the chiral enolate derived from the chiral 3-acyl-1,3-oxazolidin-2-one **9**.[12]



The Friedel−Crafts alkylation between an aromatic C-nucleophile and an electron-deficient olefin is a powerful method for carbon−carbon bond formation. The Friedel−Crafts reactivity of indoles, that are electron-rich heteroaromatic and efficient Michael acceptors, has been extensively studied under Lewis acid catalysis. In the case of tryptophan analogues, the asymmetric version of this reaction has only been developed using reaction of an indole with a glyoxylimine to yield optically active α-(3-indolyl)glycine.[13]

The Friedel−Crafts alkylation of indoles with a chiral β-nitroacrylate is an attractive reaction to provide optically active β-tryptophan analogues **5**, because the nitro functional group is a strongly electron-withdrawing group that can be readily transformed into an amino functional group. We present herein our results concerning the asymmetric Friedel−Crafts alkylation of substituted indoles with the β-nitroacrylate (*R*)-**2**, and the following transformations were performed to afford optically active β-tryptophan analogues **5**.

RESULTS AND DISCUSSION

The Friedel−Crafts alkylation of β-nitroacrylate (*R*)-**2** with *N*-methylindole **10a** (R_1 = CH_3 and R_2 = H), used as representative indole, was first carried out according to the protocol described by Chen et al.,[10] i.e., room temperature using copper(II) triflate, $Cu(OTf)_2$ (5 mol %) as Lewis acid (Scheme 1). We used dry dichloromethane as solvent because of the low solubility of the β-nitroacrylate (*R*)-**2** in diethyl ether. Under these conditions, a total conversion of the β-nitroacrylate (*R*)-**2** was observed within 16 h to yield the alkylated product **11a**. Analysis of the crude reaction by HPLC (achiral and chiral columns), LC/MS, and ^{1}H NMR showed the formation of a mixture of two diastereoisomers **11a**, one being predominant (88/12 ratio) (Table 1, entry 1).[14]

In an attempt to increase the stereoselectivity of the reaction, we investigated several reaction parameters including solvents, Lewis acid, temperatures, and concentration of reactants. Solvent and temperature effects are summarized in Table 1. Using $Cu(OTf)_2$ as additive and performing the reaction at room temperature, dichloromethane and toluene as solvents yielded similar results in both reaction rate and stereoselectivity (Table 1, entry 2). When the reaction was carried out in a more polar solvent such as tetrahydrofuran, a minor effect on diastereoselectivity was detected (Table 1, entry 3). However, HPLC analysis of the crude reaction revealed formation of side products, which is also the case when a mixture of diethyl ether and dichloromethane was used (Table 1, entry 4). We also observed that an increase of the concentration of the reaction mixture, i.e., 0.35 M instead of 0.15 M, had no beneficial effect on the diastereoselectivity of the Friedel−Crafts alkylation and was associated to the formation of side products.[15] In addition, when the reaction was carried out at lower temperature (−20 °C), we observed an enhanced selectivity of the Friedel−Crafts alkylation but a decrease of the reaction rate[15] (Table 1, entry 5). At −78 °C, only 11% of the nitroacrylate (*R*)-**2** was transformed after 24 h. On the other hand, increasing the temperature to −40 °C allowed a total conversion of β-nitroacrylate (*R*)-**2** within 96 h to yield a 91/9 mixture of the two diastereoisomers **11a**. This slight improvement to the stereoselectivity was not attractive enough, considering the increase in the reaction time. We chose to perform the alkylation reactions in dichloromethane, at room temperature for the following syntheses.

To select the Lewis acid, which is assumed to form a 1,3-metal bonding species with the nitro functional group during Friedel−Crafts alkylation of nitroalkenes,[10,16] we evaluated other metal and lanthanide triflates.

Scheme 1. Asymmetric Friedel−Crafts Alkylation of Indoles 10a−f with the β-Nitroacrylate (*R*)-2

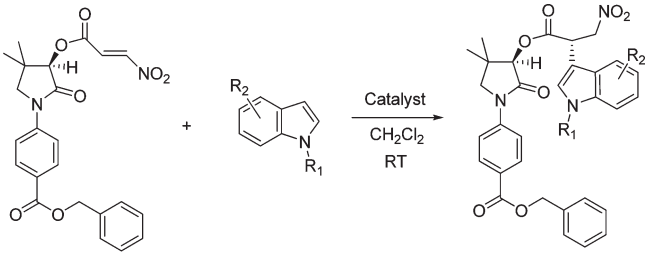


Table 1. Solvent and Temperature Effects on the Friedel−Crafts Reaction of *N*-Me Indole 10a with β-Nitroacrylate (*R*)-2

entry	solvent[a]	temp	time (h)	conversion (%)[b]	(3′*R*,2*S*)/(3′*R*,2*R*) **11a−f** (%)[d]
1	CH_2Cl_2	r.t.	16	>99	88/12
2	toluene	r.t.	16	>99	88/12
3	THF	r.t.	16	>99[c]	91/9
4	Et_2O/CH_2Cl_2[e]	r.t.	16	>99	/[c]
5	CH_2Cl_2	−20 °C	42	>99	90/10
6	CH_2Cl_2	−78 °C and −40 °C[f]	96	98	91/9

[a] 0.15 M nitroacrylate concentration. [b] Determined by HPLC analysis of the crude product and based on nitroacrylate disappearance. [c] Side products formed. [d] Determined by HPLC (achiral and chiral columns), LC/MS, and ^{1}H NMR analysis. [e] 10% of CH_2Cl_2 was added to solubilize totally the nitroacrylate. [f] After 24 h, the temperature was increased to −40 °C.

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No improvement was observed using lanthanide complexes $Yb(OTf)_3$ and $Er(OTf)_3$ (Table 2, entries 4 and 5). On the other hand, $Zn(OTf)_2$ gave fast reaction at room temperature, however, with lower selectivity (Table 2, entries 2 and 3). A better selectivity was obtained using $Zn(OTf)_2$ at lower temperature (−20 °C) but not higher than that obtained when using $Cu(OTf)_2$, $Yb(OTf)_3$, or $Er(OTf)_3$ at room temperature (Table 2, entries 3, 1, 4, and 5). In the absence of Lewis acid the reaction proceeded rapidly with a small decrease of the selectivity compared to reactions carry out with $Cu(OTf)_2$, $Yb(OTf)_3$, or $Er(OTf)_3$, (Table 2, entry 6).[17] However, in the absence of Lewis acid, the reaction became too slow when the reaction temperature was lowered to −40 °C (Table 2, entry 7) and showed a slight decrease of the reaction rate without increase of the selectivity from room temperature to 0 °C (Table 2, entry 8).

Encouraged by the results obtained with the *N*-methylindole, the Friedel−Crafts alkylation of a variety of indoles **10b**−**f** with the β-nitroacrylate (*R*)-**2** was investigated using the optimized conditions and results are summarized in Table 3.

All indole derivatives tested in these conditions, i.e., $Cu(OTf)_2$ as additive at room temperature and in dichloromethane, provided the corresponding alkylated products in moderate to good yields depending on the reaction time and on the nature of the substituent on the nitrogen or on the 5/6-position of the indole ring (Table 3). The *N*-methylindole **10a** and the unprotected indole **10b** gave total conversion of the nitroacrylate within 16 and 22 h, respectively (Table 3, entries 1 and 2). A similar result was obtained in the presence of the electron-donating group 5-OCH_3 (Table 3, entry 3). With fluoro and bromo functional groups that have opposite inductive (−I) and mesomeric (+M) effects, the mesomeric effect could be considered as the most significant because the corresponding expected products were obtained in fairly good yield by extending the reaction time (Table 3, entries 4 and 5). However, it should be underscored that in these last cases, byproduct formation (3−5%)[15] related to the loss of the nitro group appeared after 96 h reaction. On the other hand, neither electron-donating groups, nor electron-withdrawing groups, affected significantly the reaction diastereoselectivity. In the presence of the CN electron-withdrawing group, a significant increase in the reaction time was observed and only a modest conversion was obtained even after 170 h (Table 3, entry 4).

In all cases, the main alkylated products **11a**−**e** could be isolated in enantiopure form after column chromatography on silica gel.[18] The absolute configuration of the newly generated center was assigned by X-ray diffraction analysis of the main nitroester **11e**, after recrystallization from a mixture of diethyl ether/CH_2Cl_2/cyclohexane (see Supporting Information). From the known *R* configuration of the chiral auxiliary, it was ascertained that compound **11e** had the (3′*R*,2*S*) configuration. Absolute configurations (3′*R*,2*S*) of the other main nitroesters **11a**−**d** were assigned by analogy with **11e**.

On the basis of the diastereofacial selectivity observed in the presence or in absence of the Lewis acid, a plausible stereochemical model for this asymmetric Friedel−Crafts alkylation of indoles is represented in Figure 1. In this model, the nitroacrylate and the five-membered ring of the chiral auxiliary are in two perpendicular planes. The two carbonyl groups are also nearly perpendicular to each other,[19] and the geminal dimethyl groups of the auxiliary, situated on both sides of the five-membered ring, create minimal steric interactions while blocking the nitroacrylate re face. To avoid steric repulsion with the chiral auxiliary, indoles attack

Table 2. Lewis Acid Effects in the Friedel−Crafts Reaction of *N*-Me Indole 10a with β-Nitroacrylate (*R*)-2

entry	Lewis acid[a]	temp	time t (h)	conversion (%)[b]	(3′*R*,2*S*)/(3′*R*,2*R*) **11a**−**f** (%)[d]
1	$Cu(OTf)_2$	r.t.	16	>99	88/12
2	$Zn(OTf)_2$	r.t.	4	>99	73/27
3	$Zn(OTf)_2$	−20 °C	16	90	80/20[c]
4	$Yb(OTf)_3$	r.t.	16	>99	88/12
5	$Er(OTf)_3$	r.t.	16	>99	88/12
6	–	r.t.	5	>99	84/16
7	–	−40 °C	75 h	81	88/12
8	–	0 °C	12	>99	84/16

[a] Solvent = CH_2Cl_2, 0.15 M nitroacrylate concentration. [b] Determined by HPLC analysis of the crude product and based on nitroacrylate disappearance. [c] Side products formed. [d] Determined by HPLC (achiral and chiral columns), LC/MS, and ^1H NMR analysis.

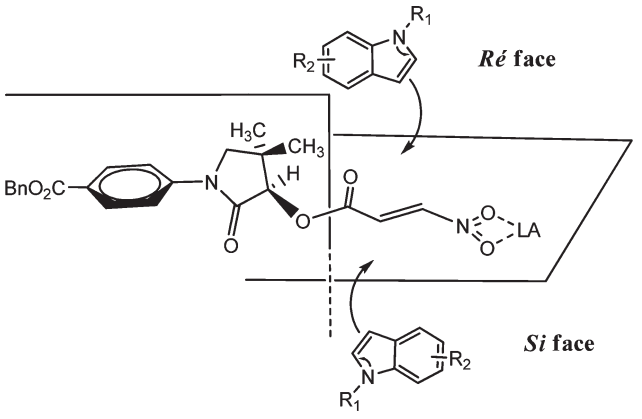

Figure 1. Model for stereocontrol.

Table 3. Friedel−Crafts Alkylation of Substituted Indoles 10a−f with β-Nitroacrylate (*R*)-2

entry	indoles	R_1	R_2	time (h)	conversion (%)[a]	(3′*R*,2*S*)/(3′*R*,2*R*) **11a**−**f** (%)[b]	(3′*R*,2*S*)-**11a**−**f** Yield[c]/ee[b] (%)
1	**6a**	CH_3	H	16	>99	88/12	36/>99
2	**6b**	H	H	22	>99	82/18	34/>99
3	**6c**	H	5-OCH_3	22	>99	86/14	35/>99
4	**6d**	H	6-F	96	92	89/11	30/>99
5	**6e**	H	5-Br	96	95	83/17	30/>99
6	**6f**	H	5-CN	170	62	–	–

[a] Determined by HPLC analysis of the crude product and based on nitroacrylate disappearance. [b] Determined by HPLC (achiral and chiral columns), LC/MS, and ^1H NMR analysis. [c] Isolated yield.

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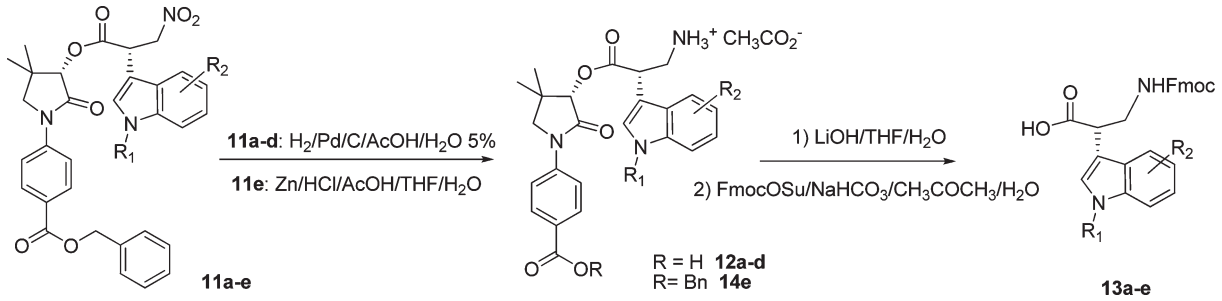
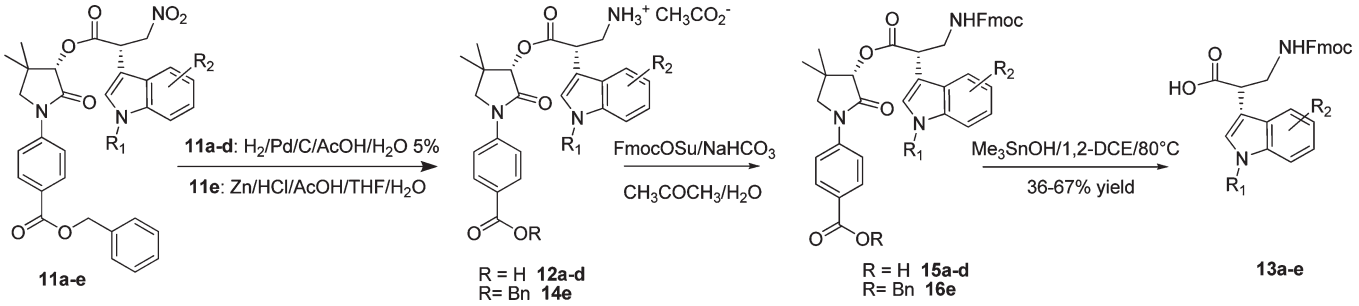
Scheme 2. Transformation of Enantiopure Alkylated Products 11a−d into *N*-Fmoc β-Tryptophan Analogues 13a−d



Scheme 3. Optimized Conditions to Transform Enantiopure Alkylated Products 11a−d into *N*-Fmoc β-Tryptophan Analogues 13a−d



preferentially from the sterically nonblocked bottom face (si face) of the double bond to give corresponding (3′*R*,2*S*) compounds.

The first step to transform the enantiopure alkylated products **11a−d** into the *N*-Fmoc β-tryptophan analogues **13a−d** was the hydrogenation of the nitro group concomitant with hydrogenolysis of the benzyl ester, in acetic acid and in the presence of 5% of water, using palladium on charcoal as catalyst. In the absence of water and/or using a different solvent, no reduction of the nitro group occurred. The resulting amino esters **12a−d** were used without further purification[20] and engaged in the LiOH hydrolysis.[21] Then Fmoc protection of the amino group using Fmoc-OSu yielded the corresponding *N*-Fmoc-(*S*)-β-tryptophan analogue (*S*)-**13a−d** (Scheme 2).

In the case of compound **11e**, reduction of the nitro group was performed using Zn/HCl to avoid debromination of the indole ring observed when using Pd/C as catalyst during the hydrogenation reaction. Under this condition, the benzyl ester of the chiral auxiliary was preserved and the compound **14e** was obtained. LiOH cleavage and Fmoc protection provided the *N*-Fmoc-(*S*)-β-tryptophan analogue (*S*)-**13e**.

To control the optical purity of compounds **13a−e** and/or to detect the possible epimerization that could have occurred during the removal of the chiral auxiliary, we performed Friedel−Crafts reactions with racemic nitroacrylate (*RS*)-**2**. These experiments led to the corresponding racemic *N*-Fmoc-β-tryptophan analogues *rac*-**13a−e**, after transformation of the different racemic esters *rac*-**11a−e**. The HPLC profile of each racemic mixture *rac*-**13a−e** was then compared to the compounds obtained from the chiral experiments. We found that transformation of enantiopure alkylated products **11a−e** took place with a low but significant degree of epimerization (10−12%) that may occur during basic hydrolysis due to the acidity of the proton α to the amino acid's ester group of the intermediates **12a−d** and **14e**.

To avoid or to minimize the epimerization, we decided to use trimethyltin hydroxide reported to suppress undesired epimerization during the hydrolysis of an ester bond.[22] Furthermore, as the Fmoc protecting group should remain intact throughout this hydrolysis, we applied the Me_3SnOH conditions to the *N*-Fmoc protected substrates **15a−d**. Application of this new procedure (Scheme 3) yielded the desired *N*-(*S*)-Fmoc-β-tryptophan analogues (*S*)-**13a−d** in good yields without undesired epimerization.

CONCLUSION

We have established a new route to prepare enantiopure β-tryptophan analogues ((*S*)-2-indolyl-β-alanines). We showed that β-nitroacrylate (*R*)-**2** is a good chiral auxiliary for asymmetric Friedel−Crafts alkylation of indoles. (*R*)-2-Indolyl-β-alanines were obtained by the same synthetic route by using the chiral compound (*S*)-**2**. β-Tryptophan analogues are delivered in their *N*-Fmoc-protected form, ready to use for instance in solid-phase peptide synthesis, which is one of the most popular methods for peptide synthesis. This study provides a new example of asymmetric β^2-tryptophan analogues preparation, and further studies concerning their applications in medicinal chemistry and in organic synthesis are now in progress.

EXPERIMENTAL SECTION

General Remarks. All reagents were used as purchased from commercial suppliers without further purification. Solvents were dried and purified by conventional methods prior to use. ^1H or ^{13}C NMR spectra (DEPT, $^1H/^{13}C$ 2D-correlations) were recorded using the

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solvent as internal reference. Data are reported as follows: chemical shifts (δ) in parts per million, coupling constants (J) in hertz (Hz). The ESI mass spectra were recorded with a platform II quadrupole mass spectrometer fitted with an electrospray source. HPLC analyses were performed with variable detector using: column A: SymmetryShield RP-18, 3.5 μm, (50 × 4.6 mm), flow: 1 mL/min, H_2O (0.1% TFA)/CH_3CN (0.1% TFA), gradient 0→100% (15 min) and 100% (4 min); column B: Chromolith SpeedROD RP-18e, 2 μm, (50 × 4.6 mm), flow: 3 mL/min, H_2O (0.1% TFA)/CH_3CN (0.1% TFA), eluent I: gradient 0→100% (4 min) and 100% (1 min), eluent II: gradient 0→100% (10 min) and 100% (1 min); column C: Chiracel OD-R, flow: 1 mL/min, H_2O (0.1% TFA)/CH_3CN (0.1% TFA), eluent I: 20/80; eluent II: 40/60; eluent III: 30/70, eluent IV: 0/100; column D: Chiracel OJ-R, flow: 1 mL/min, H_2O (0.1% TFA)/CH_3CN (0.1% TFA); eluent I: 40/60; HRMS were recorded in positive mode using NBA (3-nitrobenzyl alcohol or GT (glycerol/thioglycerol) as matrix. An automated flash purification system was often used for the flash chromatography on silica gel.[23]

(*R*)-Benzyl 4-(3-(3-Nitroacryloyloxy)-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoate (*R*)-2. The enantiopure nitroacrylate (*R*)-**2** was prepared as previously described[5] except for the last step that has been optimized. Mesyl chloride (1.04 mL, 13.15 mmol, 3 equiv) was added dropwise at −78 °C and under argon to a stirred solution of compound (3*S*,2′*RS*)-benzyl 4-(3-(2-hydroxy-3-nitropropionyloxy)-4,4-dimethyl-2-oxopyrrolidin-1-yl)benzoate (2.00 g, 4.38 mmol, 1 equiv) in dry CH_2Cl_2 (25 mL). Then NEt_3 (2.44 mL, 17.52 mmol, 4 equiv) was added under stirring, and the reaction mixture was immediately diluted with dichloromethane (80 mL). This organic layer was successively washed with a 0.1 N HCl solution (40 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude nitroacrylate (*R*)-**2** (quantitative yield) was used without further purification in the following step. HPLC, MS, and ^{1}H and ^{13}C NMR data are identical to those previously described.[5]

General Procedure for Asymmetric Friedel−Crafts Alkylations of Indoles with *β*-Nitroacrylate (*R*)-2. To a solution of β-nitroacrylate (*R*)-**2** (1.0 g, 2.28 mmol, 1 equiv) in dry CH_2Cl_2 (16 mL) under argon atmosphere was added $Cu(OTf)_2$ (40 mg, 0.16 mmol, 0.05 equiv). The solution was stirred at room temperature for 5 min, and indole **10** (1.2 equiv) was added. After 16−96 h stirring at the same temperature, the nitroacrylate **2** was consumed (monitored by HPLC column B). The solvent was removed under reduced pressure, and the residue was purified by automated flash chromatography on silica gel.[23]

(3′*R*,2*S*)-[*N*-(4-Benzyloxycarbonylphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl] 2-(1-Methyl-1*H*-indol-3-yl)-3-nitropropionate (3′*R*,2*S*)-11a. Synthesized according to the general procedure from *N*-methylindole **10a** (358 mg, 2.74 mmol, 1.2 equiv) at room temperature for 16 h. The crude expected product **11a** (>99% yield) was obtained as a brown oil. The expected pure nitro ester (3′*R*,2*S*)-**11a** (467 mg, 0.82 mmol, 36% yield, 99% ee) was obtained as an off-white solid after automated flash column chromatography on silica gel (cartridge 100 g) using a 40/60 isocratic elution of a binary system of cyclohexane and dichloromethane−diethyl ether (2/3). Mp 67−68 °C; $[\alpha]_D^{20}$ −47 (*c* 1.0, CH_2Cl_2); t_R (HPLC, column A) 12.3 min; t_R (HPLC, column C, eluent I) 22.9 min; [t_R diastereoisomer (3′*R*,2*R*) (HPLC, column C, eluent I) 9.2 min]; MS (ESI) *m*/*z*: 570.0 [(M + H)$^+$], 592.0 [(M + Na)$^+$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.20 (s, 3H, C*H*$_3$), 1.37 (s, 3H, C*H*$_3$), 3.57 (d, *J* = 9.6 Hz, 1H, 5′-*H*), 3.64 (d, *J* = 9.6 Hz, 1H, 5′-*H*), 3.79 (s, 3H, N-C*H*$_3$), 4.76 (dd, *J* = 3.9 and 14.8 Hz, 1H, *H*CH-NO$_2$), 4.90 (dd, *J* = 3.9 and 10.5 Hz, 1H, *H*CCO-O), 5.17 (dd, *J* = 10.5 and 14.8 Hz, 1H, *H*CH-NO$_2$), 5.37 (s, 2H, OC*H*$_2$C$_6$H$_5$), 5.52 (s, 1H, 3′-*H*), 7.17 (t and s, *J* = 7.0 Hz, 2H, *H*-indole), 7.25−7.48 (m, 7H, *H*-arom and *H*-indole), 7.65 (d, *J* = 8.0 Hz 1H, *H*-indole), 7.70 (d, *J* = 7.0 Hz, 2H, *H*-arom), 8.08 (d, *J* = 7.0 Hz, 2H, *H*-arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.1 (*C*H$_3$), 24.7 (*C*H$_3$), 33.0 (N-*C*H$_3$), 37.4 (*C*-4′), 41.0 (*C*HCO-O), 57.4 (*C*-5′), 66.7 (O*C*H$_2$C$_6$H$_5$), 75.4 (*C*H$_2$NO$_2$), 79.1 (*C*-3′), 105.0 (*C*-indole), 109.9 (*C*H-indole), 118.3, 118.7, 119.1, 120.0, 122.4, 126.2, 128.2, 128.3, 128.6, 130.8 (*C*H-arom and *C*H-indole), 136.0, 137.1, 142.9 (*C*-arom), 165.8, 168.7, 171.0 (*C*═O); HRMS (ESI) Calcd for $C_{32}H_{32}N_3O_7$ (MH$^+$) 570.2240, found 570.2250.

(3′*R*,2*S*)-[*N*-(4-Benzyloxycarbonylphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl] 2-(1*H*-Indol-3-yl)-3-nitropropionate (3′*R*,2*S*)-11b. Synthesized according to the general procedure from indole **10b** (320 mg, 2.74 mmol, 1.2 equiv) at room temperature for 22 h. The crude expected product **11b** (>99% yield) was obtained as a brown oil. The expected pure nitro ester (3′*R*,2*S*)-**11b** (430 mg, 0.77 mmol, 34% yield, 98% ee) was obtained as an off-white solid after automated flash column chromatography on silica gel (cartridge 100 g) using a 10−40% linear gradient elution (12 CV)[23] followed by a 40/60 isocratic elution (8 CV)[23] of a binary system of cyclohexane and dichloromethane−diethyl ether (1.5/2.5). Mp 74−75 °C; $[\alpha]_D^{20}$ −56 (*c* 1.0, CH_2Cl_2); t_R (HPLC, column B, eluent I) 2.8 min; t_R (HPLC, column C, eluent I) 11.0 min; [t_R diastereoisomer (3′*R*,2*R*) (HPLC, column C, eluent I) 9.9 min]; MS (ESI) *m*/*z*: 556.2 [(M + H)$^+$], 578.0 [(M + Na)$^+$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.11 (s, 3H, C*H*$_3$), 1.27 (s, 3H, C*H*$_3$), 3.47 (d, *J* = 9.5 Hz, 1H, 5′-*H*), 3.55 (d, *J* = 9.5 Hz, 1H, 5′-*H*), 4.63 (dd, *J* = 3.7 and 14.9 Hz, 1H, *H*CHNO$_2$), 4.80 (dd, *J* = 3.7 and 10.6 Hz, 1H, *H*CCO-O), 5.09 (dd, *J* = 10.6 and 14.9 Hz, 1H, *H*CHNO$_2$), 5.26 (s, 2H, OC*H*$_2$C$_6$H$_5$), 5.45 (s, 1H, 3′-H), 7.10 (m, 3H, *H*-arom and *H*-indole), 7.23−7.37 (m, 6H, *H*-arom and *H*-indole), 7.56 (br t, 3H, *H*-arom and *H*-indole), 7.96 (d, 2H, *H*-arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 20.1 (*C*H$_3$), 23.6 (*C*H$_3$), 36.4 (*C*-4′), 39.7 (*C*HCO-O), 56.5 (*C*-5′), 65.7 (O*C*H$_2$C$_6$H$_5$), 74.2 (*C*H$_2$NO$_2$), 78.0 (*C*-3′), 105.4 (*C*-indole), 110.8 (*C*H-indole), 117.0, 117.5, 119.2, 121.7, 122.6 (*C*H-arom and *C*H-indole), 124.6, 125.2 (*C*-arom), 127.1, 127.2, 127.3, 129.7, (*C*H-arom and *C*H-indole), 135.0, 135.2, 141.8 (*C*-arom), 164.7, 167.8, 170.0 (*C*═O); HRMS (ESI) Calcd for $C_{31}H_{30}N_3O_7$ (MH$^+$) 556.2084, found 556.2089.

(3′*R*,2*S*)-[*N*-(4-Benzyloxycarbonylphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl] 2-(5-Methoxy-1*H*-indol-3-yl)-3-nitropropionate (3′*R*,2*S*)-11c. Synthesized according to the general procedure from 5-methoxyindole **10c** (403 mg, 2.74 mmol, 1.2 equiv) at room temperature for 22 h. The crude expected product **11c** (>99% yield) was obtained as a brown oil. The expected pure nitro ester (3′*R*,2*S*)-**11c** (467 mg, 0.79 mmol, 35% yield, 98% ee) was obtained as an off-white solid after automated flash column chromatography on silica gel (cartridge 100 g) using a 10−40% linear gradient elution (12 CV)[23] followed by a 40/60 isocratic elution (12 CV)[23] of a binary system of cyclohexane and dichloromethane−diethyl ether (1.5/2.5). Mp 66−67 °C; $[\alpha]_D^{20}$ −68 (*c* 1.0, CH_2Cl_2); t_R (HPLC, column B, eluent I) 2.7 min; t_R (HPLC, column C, eluent II) 36.9 min; [t_R diastereoisomer (3′*R*,2*R*) (HPLC, column C, eluent II) 34.5 min]; MS (ESI) *m*/*z*: 586.2 [(M + H)$^+$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.12 (s, 3H, C*H*$_3$), 1.28 (s, 3H, C*H*$_3$), 3.48 (d, *J* = 9.6 Hz, 1H, 5′-*H*), 3.55 (d, *J* = 9.6 Hz, 1H, 5′-*H*), 4.62 (dd, *J* = 3.9 and 14.9 Hz, 1H, *H*CHNO$_2$), 4.75 (dd, *J* = 3.9 and 10.6 Hz, 1H, *H*CCO-O), 5.08 (dd, *J* = 10.6 and 14.9 Hz, 1H, *H*CHNO$_2$), 5.27 (s, 2H, OC*H*$_2$C$_6$H$_5$), 5.45 (s, 1H, 3′-*H*), 6.78 (dd, *J* = 2.3 and 8.8 Hz, 1H, *H*-indole), 6.96 (d, *J* = 2.3 Hz, 1H, *H*-indole), 7.07 (br s, 1H, *H*-indole), 7.14 (d, *J* = 8.8 Hz, 1H, *H*-indole), 7.26−7.36 (m, 5H, *H*-arom), 7.56 (d, *J* = 7.0 Hz, 2H, *H*-arom), 7.97 (d, *J* = 7.0 Hz, 2H, *H*-arom), 8.32 (br s, 1H, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.1 (*C*H$_3$), 24.6 (*C*H$_3$), 37.4 (*C*-4′), 40.7 (*C*HCO-O), 55.9 (O*C*H$_3$), 57.5 (*C*-5′), 66.7 (O*C*H$_2$C$_6$H$_5$), 75.2 (*C*H$_2$NO$_2$), 79.0 (*C*-3′), 99.9 (*C*H-indole), 106.0 (*C*-indole), 112.6, 112.9 (*C*H-indole), 118.7 *C*H-arom), 124.0 (*C*H-indole), 126.1, 126.2 (*C*-arom), 128.2, 128.3, 128.6, 130.8 (*C*H-arom), 132.4, 136.0, 142.8, 154.5 (*C*-arom), 165.8, 168.9, 171.0 (*C*═O); HRMS (ESI) Calcd for $C_{32}H_{32}N_3O_8$ (MH$^+$) 586.2189, found 586.2194.

(3′*R*,2*S*)-[*N*-(4-Benzyloxycarbonylphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl] 2-(6-Fluoro-1*H*-indol-3-yl)-3-nitropropionate (3′*R*,2*S*)-11d. Synthesized according to the general procedure

from 6-fluoroindole **10d** (370 mg, 2.74 mmol, 1.2 equiv) at room temperature for 96 h. The crude expected product **11d** (>99% yield) was obtained as a brown oil. The pure nitro ester (3′*R*,2*S*)-**11d** (392 mg, 0.68 mmol, 30% yield, 96% ee) was obtained as an off-white solid after automated flash column chromatography on silica gel (cartridge 100 g) using a 12−50% linear gradient elution (11 CV)[23] followed by a 50/50 isocratic elution (6 CV)[23] of a binary system of cyclohexane and dichloromethane−diethyl ether (2/3). Mp 79−80 °C; $[\alpha]_D^{20}$ −48 (*c* 1.0, CH_2Cl_2); t_R (HPLC, column B, eluent I) 2.8 min; t_R (HPLC, column D, eluent I) 14.8 min; [t_R diastereoisomer (3′*R*,2*R*) (HPLC, column D, eluent I) 24.6 min]; MS (ESI) *m*/*z*: 574.2 [$(M + H)^+$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.14 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 3.48 (d, *J* = 9.6 Hz, 1H, 5′-*H*), 3.56 (d, *J* = 9.6 Hz, 1H, 5′-*H*), 4.58 (dd, *J* = 3.9 and 14.9 Hz, 1H, *H*CHNO$_2$), 4.73 (dd, *J* = 3.9 and 10.6 Hz, 1H, *H*CCO-O), 5.08 (dd, *J* = 10.6 and 14.9 Hz, 1H, *H*CHNO$_2$), 5.25 (s, 2H, OC$H_2C_6H_5$), 5.45 (s, 1H, 3′-*H*), 6.80 (m, 2H, *H*-indole), 6.95 (br s, 1H, *H*-indole), 7.23−7.37 (m, 5H, C_6H_5), 7.43 (dd, *J* = 8.8 Hz, 1H, *H*-indole), 7.54 (d, *J* = 8.6 Hz, 2H, C_6H_4), 7.97 (d, *J* = 8.6 Hz, 2H, C_6H_4), 8.63 (br s, 1H, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.1 (CH_3), 24.6 (CH_3), 37.5 (*C*-4′), 40.6(*C*HCO-O), 57.6 (*C*-5′), 66.8 (O*C*$H_2C_6H_5$), 75.2 (CH_2NO_2), 79.1 (*C*-3′), 97.9 and 98.2 (*C*H-indole), 106.3 (*C*-indole), 108.9 and 109.1 (*C*H-indole), 118.6 (*C*H-arom), 118.8 and 118.9 (*C*H-indole), 124.0 (*C*H-indole), 126.4 (*C*-arom or *C*-indole), 128.2, 128.3, 128.6, 130.8 (*C*H-arom), 135.9, 136.2, 136.4, 142.7, 158.9, 161.26 (*C*-arom and *C*-indole), 165.7, 169.0, 171.0 (*C*═O); HRMS (ESI) Calcd for $C_{31}H_{29}N_3O_7$ F (MH^+) 574.1990, found 574.1991.

(3′*R*,2*S*)-[*N*-(4-Benzyloxycarbonylphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl] 2-(5-Bromo-1*H*-indol-3-yl)-3-nitropropionate (3′*R*,2*S*)-11e. Synthesized according to the general procedure from 5-bromoindole **10e** (537 mg, 2.74 mmol, 1.2 equiv) at room temperature for 96 h. The crude expected product **11e** (>99% yield) was obtained as a brown oil. The expected pure nitro ester (3′*R*,2*S*)-**11e** (434 mg, 0.68 mmol, 30% yield, 99% ee) was obtained as an off-white solid after automated flash column chromatography on silica gel (cartridge 100 g) using a 12−50% linear gradient elution (8.5 CV)[23] followed by a 50/50 isocratic elution (7 CV)[23] of a binary system of cyclohexane and dichloromethane−diethyl ether (2/3). Mp 85−86 °C; $[\alpha]_D^{20}$ −89 (*c* 1.0, CH_2Cl_2); t_R (HPLC, column B, eluent I) 2.9 min; t_R (HPLC, column C, eluent II) 51.3 min; [t_R diastereoisomer (3′*R*,2*R*) (HPLC, column C, eluent II) 54.8 min]; MS (ESI) *m*/*z*: 633.9 and 636.1[$(M + H)^+$], 656.1 and 658.0 [$(M + Na)^+$]; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.15 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 3.50 (d, *J* = 9.6 Hz, 1H, 5′-*H*), 3.58 (d, *J* = 9.6 Hz, 1H, 5′-*H*), 4.57 (dd, *J* = 3.9 and 14.9 Hz, 1H, *H*CHNO$_2$), 4.70 (dd, *J* = 3.9 and 10.6 Hz, 1H, *H*CCO-O), 5.08 (dd, *J* = 10.6 and 14.9 Hz, 1H, *H*CHNO$_2$), 5.26 (s, 2H, OC$H_2C_6H_5$), 5.46 (s, 1H, 3′-H), 6.94 (s, 1H, *H*-indole), 7.00 (d, *J* = 8.6 Hz, 1H, *H*-indole), 7.13 (d, *J* = 8.6 Hz, 1H, *H*-indole), 7.23−7.35 (m, 5H, *H*-arom), 7.54 (d, *J* = 8.6 Hz, 2H, *H*-arom), 7.66 (s, 1H, *H*-indole), 7.95 (d, *J* = 8.6 Hz, 2H, *H*-arom), 8.74 (br s, 1H, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.2 (CH_3), 24.6 (CH_3), 37.5 (*C*-4′), 40.4 (*C*HCO-O), 57.6 (*C*-5′), 66.7 ($OCH_2C_6H_5$), 75.0 (CH_2NO_2), 79.1 (*C*-3′), 105.6 (*C*-indole), 113.3 (*C*H-indole), 118.7 (*C*H-arom), 122.7, 124.6, 125.5 (*C*H-indole), 126.4, 127.2 (*C*-arom), *H*-indole), HRMS (ESI) Calcd for $C_{31}H_{29}BrN_3O_7$ (MH^+) 634.1189, found 634.1199.

General Procedure To Transform Compounds 11a−d into *N*-Fmoc-(*S*)-β-Tryptophan Analogues 13a−d. A mixture of compound **11** (0.3 mmol) and 10% Pd/C (320 mg) in acetic acid (8 mL) and water (400 μL, 5%) was stirred vigorously under 1 atm of H_2 for 16 h at room temperature (monitored by HPLC, column B). The suspension was filtered through Celite, and the filtrate was concentrated in vacuo to yield quantitatively the acetic acid salt of the expected compound **12** (>99% yield) that was used without further purification.[20]

Procedure A (Scheme 2). To compound **12** dissolved in a mixture of THF/H_2O (1/1) (12 mL) was added a solution of LiOH·H_2O (47 mg, 0.9 mmol, 3 equiv)[21] in water (1 mL) dropwise. The mixture was stirred at room temperature until completion of the hydrolysis (∼2 h) (monitored by HPLC, column B). The organic solvent was removed in vacuo. The aqueous phase was acidified (pH 2), washed with ethyl acetate (3 × 10 mL), and concentrated in vacuo. To the residue dissolved in a mixture of water and acetone (1/1) (20 mL) was added 50 mg (0.6 mmol, 2 equiv) of sodium bicarbonate followed by 101 mg (0.3 mmol, 1 equiv) of 9-fluorenylmethyloxycarbonyl-*N*-hydroxysuccinimide (Fmoc-OSu). After 2 h of stirring at room temperature, the organic solvent was removed in vacuo and the aqueous phase was acidified to pH 2−3 with 1 N HCl. The aqueous phase was extracted with ethyl acetate (3 × 10 mL), and the combined organic extracts were concentrated in vacuo. The residue was purified by automated flash column chromatography on silica gel to yield the expected compound N-Fmoc-(*S*)-β-tryptophan analogue **13**.

Procedure B (Scheme 3). To compound **12** dissolved in a mixture of water and acetone (1/1) (30 mL) was added sodium bicarbonate (101 mg, 1.2 mmol, 4 equiv) followed by 9-fluorenylmethyloxycarbonyl-*N*-hydroxysuccinimide (Fmoc-OSu) (189 mg, 0.3 mmol, 1 equiv). After 2 h of stirring at room temperature (monitored by HPLC, column B), the organic solvent was removed in vacuo and the aqueous phase was acidified to pH 2−3 with 1 N HCl. The aqueous phase was extracted with ethyl acetate (3 × 10 mL), and the combined organic extracts were concentrated in vacuo to yield the crude *N*-Fmoc-β-tryptophan ester **15**, which was subjected to automated flash column chromatography on silica gel. A mixture of the purified compound **15** dissolved in 1,2-dichloroethane and trimethyltin hydroxide (10 equiv) in a thick-glass tube with a septum was heated at 80−85 °C (bath temperature 90−95 °C), until completion of the reaction (monitored by HPLC, column B). Then, the organic solvent was removed in vacuo, and the residue was dissolved in ethyl acetate. The organic layer was washed with 5% HCl, brine, and dried over sodium sulfate. The oily product obtained after removal of the solvent in vacuo was purified by automated flash column chromatography on silica gel to yield the expected pure *N*-Fmoc-(*S*)-β-tryptophan analogue **13**.

(*S*)-3-(9-Fluorenylmethoxycarbonylamino)-2-(1-methyl-1*H*-indol-3-yl)propionic Acid (*S*)-13a. Synthesized according to procedure B from compound **11a** (170 mg, 0.30 mmol). The crude expected intermediate acetic acid salt of [*N*-(4-carboxyphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl] 2-(1-methyl-1*H*-indol-3-yl)-3-aminopropionate (3′*R*,2*S*)-**12a** was first obtained as a brown solid (>99% yield); t_R (HPLC, column B, eluent I) 1.74 min; MS (ESI) *m*/*z*: 450.2 [$(M + H)^+$]. After *N*-Fmoc protection, the pure *N*-Fmoc-β-tryptophan ester (3′*R*,2*S*)-**15a** (94 mg, 0.14 mmol, 45% yield) was isolated as a white solid after automated flash column chromatography on silica gel (cartridge 25 g) using a 11−45% linear gradient elution (10 CV)[23] followed by a 55/45 isocratic elution (8 CV)[23] of a binary system of cyclohexane and ethylacetate. Mp 121−122 °C; $[\alpha]_D^{20}$ +71 (*c* 1.5, CH_2Cl_2); t_R (HPLC, column B, eluent I) 2.8 min; 99% ee: t_R (HPLC, column C, eluent I) 26.9 min; [t_R enantiomer (3′*R*,2*R*) (HPLC, column C) 39.3 min]; MS (ESI) *m*/*z*: 672.2 [$(M + H)^+$], 694.0 [$(M + Na)^+$]; ^{1}H NMR (400 MHz, CD_3COCD_3) δ (ppm): 1.16 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 3.72−3.89 (m+s, 7H, 5′-CH_2, N-CH_3 and CH_2NH), 4.26 (m, 1H, OCH$_2$C*H*), 4.35 (m, 2H, OCH_2), 4.47 (m, 1H, C*H*COO), 5.69 (s, 1H, 3′-*H*), 7.09 (m, 2H, N*H* and *H*C-indole), 7.22 (m, 1H, *H*C-indole), 7.31−7.44 (2 m, 6H, *H*C-Fmoc and *H*C-indole), 7.75 (d, *J* = 8.8 Hz, 2H, *H*-arom), 7.80−7.91 (3 m, 5H, *H*C-Fmoc and *H*C-indole), 8.08 (d, *J* = 8.8 Hz, 2H, *H*-arom); ^{13}C NMR (100 MHz, CD_3COCD_3) δ (ppm): 20.1 (CH_3), 23.1 (CH_3), 31.5 (N-CH_3), 36.5 (C-4′), 43.0 (CH_2NH), 43.5 (*C*HCOO), 46.7 (OCH$_2$*C*H), 56.4 (*C*-5′), 65.8 (OCH_2), 77.9 (*C*-3′), 108.4 (*C*-indole or *C*-Fmoc), 109.0 (*C*H-indole), 117.9, 118.5, 118.6, 119.4, 121.2, 124.9 (*C*H-arom, *C*H-Fmoc and *C*H-indole), 125.6 (*C*-indole or *C*-Fmoc), 126.6, 126.7, 126.8, 127.1, 129.9 (*C*H-arom, *C*H-Fmoc and *C*H-indole), 136.6, 140.7, 142,9, 143.7 (*C*-arom, *C*-indole and

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C-Fmoc), 155.9, 165.6, 169.4, 171.2 (*C*═O); HRMS (ESI) Calcd for $C_{40}H_{38}N_3O_7$ (MH^+) 672.2710, found 672.2715.

After trimethyltin hydroxide hydrolysis of the purified compound (3′*R*,2*S*)-**15a**, the *N*-Fmoc-*β*-tryptophan analogue (*S*)-**13a** (41 mg, 0.094 mmol, 67% yield) was isolated as a white solid after column chromatography on silica gel with cyclohexane/ethyl acetate/CH_2Cl_2/AcOH (5.5/4/0.5/0.1%). Mp 118−119 °C; $[\alpha]_D^{20}$ −46 (*c* 1.0, CH_2Cl_2); t_R (HPLC, column B, eluent I) 2.5 min; 99% ee: t_R (HPLC, column C, eluent I) 11.1 min; [t_R enantiomer (*R*) (HPLC, column C) 17.4 min]; MS (ESI) *m*/*z*: 441.3 [$(M + H)^+$]; ^{1}H NMR (400 MHz, CD_3COCD_3) *δ* (ppm): 3.49 (m, 1H, *H*CHNH), 3.64 (s and m, 4H, *H*CHNH and N-C*H*$_3$), 4.10 (m, 2H, C*H*CO$_2$H and OCH$_2$C*H*), 4.19 (m, 2H, OC*H*$_2$), 6.52 (br t, 1H, N*H*), 6.92 (t, *J* = 7.5 Hz, 1H, *H*C-indole), 7.03 (t, *J* = 7.5 Hz, 1H, *H*C-indole), 7.12−7.27 (2 m, 6H, *H*C-Fmoc and *H*C-indole), 7.52 (d, *J* = 7.5 Hz, 2H, *H*C-Fmoc), 7.58 (d, *J* = 7.9 Hz, 1H, *H*C-indole), 7.70 (d, *J* = 7.5 Hz, 2H, *H*C-Fmoc); ^{13}C NMR (100 MHz, CD_3COCD_3) *δ* (ppm): 31.9 (N-CH_3), 42.8 (*C*HCO$_2$H), 42.4 (*C*H$_2$NH), 47.2 (OCH$_2$*C*H), 66.1 (O*C*H$_2$), 109.5 (*C*H-indole), 109.8 (*C*-indole or *C*-Fmoc), 118.9, 119.0, 119.9, 121.5, 125.3, 127.0, 127.3, 127.6 (*C*H-Fmoc and *C*H-indole), 137.2, 141.2, 144.2, 144.3 (*C*-indole and *C*-Fmoc), 156.4, 173.6 (*C*═O); HRMS (ESI) Calcd for $C_{27}H_{25}N_2O_4$ (MH^+) 441.1814, found 441.1796.

(*S*)-3-(9-Fluorenylmethoxycarbonylamino)-2-(1*H*-indol-3-yl)-propionic Acid (*S*)-13b. Synthesized according to procedure B from compound **11b** (167 mg, 0.3 mmol). The crude expected intermediate acetic acid salt of [*N*-(4-carboxyphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl] 2-(1*H*-indol-3-yl)-3-aminopropionate (3′*R*,2*S*)-**12b** was first obtained as a brown solid (>99% yield); t_R (HPLC, column B, eluent I) 1.64 min; MS (ESI) *m*/*z*: 436.3 [$(M + H)^+$]. Then, after *N*-Fmoc protection, the *N*-Fmoc-*β*-tryptophan ester (3′*R*,2*S*)-**15b** (118 mg, 0.18 mmol, 60% yield) was isolated as a white solid after automated flash column chromatography on silica gel (cartridge 25 g) using a 12−50% linear gradient elution (10 CV)[23] followed by a 50/50 isocratic elution (10 CV)[23] of a binary system of cyclohexane and ethyl acetate. Mp 142−143 °C; $[\alpha]_D^{20}$ +20 (*c* 1.5, CH_2Cl_2); t_R (HPLC, column B, eluent I) 2.6 min; 99% ee: t_R (HPLC, column C, eluent I) 13.5 min; MS (ESI) *m*/*z*: 658.2 [$(M + H)^+$] 680.1 [$(M + Na)^+$]; ^{1}H NMR (400 MHz, CD_3COCD_3) *δ* (ppm): 1.15 (s, 3H, C*H*$_3$), 1.30 (s, 3H, C*H*$_3$), 3.73 (d, *J* = 9.6 Hz, 1H, 5′-*H*), 3.88 (m, 3H, 5′-C*H*$_2$ and C*H*$_2$NH), 4.27 (m, 1H, OCH$_2$C*H*), 4.36 (m, 2H, OC*H*$_2$), 4.49 (m, 1H, C*H*COO), 5.70 (s, 1H, 3′-*H*), 7.08−7.18 (m, 3H, N*H* and *H*C-indole), 7.33 and 7.44 (2 m, 6H, *H*C-Fmoc and *H*C-indole), 7.75 (d, *J* = 8.8 Hz, 2H, *H*-arom), 7.82−7.91 (m, 5H, *H*C-Fmoc and *H*C-indole), 8.07 (d, *J* = 8.8 Hz, 2H, *H*-arom), 10.28 (s, 1H, N*H*-indole); ^{13}C NMR (100 MHz, CD_3COCD_3) *δ* (ppm): 20.1 (*C*H$_3$), 23.1 (*C*H$_3$), 36.5 (*C*-4′), 43.0 (*C*H$_2$NH), 43.7 (*C*HCOO), 46.7 (OCH$_2$*C*H), 56.4 (*C*-5′), 65.8 (O*C*H$_2$), 77.8 (*C*-3′), 109.3 (*C*-indole or *C*-Fmoc), 111.0 (*C*H-indole), 117.9, 118.3, 118.6, 119.4, 121.2, 122.5, 124.9, 125.6, 126.3 (*C*H-arom, *C*H-Fmoc and *C*H-indole), 125.5, 126.6 (*C*-indole or *C*-Fmoc), 127.1, 130.0 (*C*H-arom, *C*H-Fmoc and *C*H-indole), 140.7, 142,9, 143.7 (*C*-arom, *C*-indole and *C*-Fmoc), 155.9, 165.7, 169.5, 171.2 (*C*═O); HRMS (ESI) Calcd for $C_{39}H_{36}N_3O_7$ (MH^+) 658.2553, found 658.2554.

After trimethyltin hydroxide hydrolysis of the purified compound (3′*R*,2*S*)-**15b**, the *N*-Fmoc-*β*-tryptophan analogue (*S*)-**13b** (51 mg, 0.119 mmol, 66% yield) was isolated as a white solid after column chromatography on silica gel with cyclohexane/ethyl acetate/CH_2Cl_2/AcOH (3/5/2/0.1%). Mp 129−130 °C; $[\alpha]_D^{20}$ −60 (*c* 1.0, CH_2Cl_2); t_R (HPLC, column B) (eluent I) 2.3 min, (eluent II) 4.6 min; 98% ee: t_R (HPLC, column C, eluent III) 11.3 min; [t_R enantiomer (*R*) (HPLC, column C) 16.6 min]; MS (ESI) *m*/*z*: 427.2 [$(M + H)^+$]; ^{1}H NMR (400 MHz, CD_3COCD_3) *δ* (ppm): 2.75 (br s, 1H, O*H*), 3.51 (m, 1H, *H*CHNH), 3.66 (m, 1H, *H*CHNH), 4.08−4.19 (m, 4H, C*H*CO$_2$H, OCH$_2$C*H* and OC*H*$_2$), 6.54 (br t, 1H, N*H*-Fmoc), 6.90 (t, *J* = 7.4 Hz, 1H *H*C-indole), 7.00 (t, *J* = 7.1 Hz, 1H *H*C-indole), 7.14 (m, 3H, *H*C-Fmoc and *H*C-indole), 7.26 (t, *J* = 7.9 Hz, 3H, *H*C-Fmoc and *H*C-indole), 7.53 (d, *J* = 7.5 Hz, 2H, *H*C-Fmoc), 7.60 (d, *J* = 7.9 Hz, 1H, *H*C-indole), 7.71 (d, *J* = 7.5 Hz, 2H, *H*C-Fmoc), 10.07 (br s, 1H, N*H*-indole); ^{13}C NMR (100 MHz, CD_3COCD_3) *δ* (ppm): 42.9 (*C*HCO$_2$H), 43.3 (*C*H$_2$NH), 47.2 (OCH$_2$*C*H), 66.1 (O*C*H$_2$), 110.8 (*C*-indole or *C*-Fmoc), 111.4, 118.9, 119.0, 119.9, 121.5, 123.0, 125.3, 127.0, 127.6 (*C*H-Fmoc and *C*H-indole), 136.7, 141.2, 144.2, 144.3 (*C*-indole and *C*-Fmoc), 156.4, 173.7 (*C*═O); HRMS (ESI) Calcd for $C_{26}H_{23}N_2O_4$ (MH^+) 427.1658, found 427.1651.

(*S*)-3-(9-Fluorenylmethoxycarbonylamino)-2-(5-methoxy-1*H*-indol-3-yl)propionic Acid (*S*)-13c. Synthesized according to procedure B from compound **11c** (176 mg, 0.3 mmol). The crude expected intermediate acetic acid salt of [*N*-(4-carboxyphenyl)-4,4-dimethyl-2-oxopyrrolidin-3-yl] 2-(5-methoxy-1*H*-indol-3-yl)-3-amino-propionate (3′*R*,2*S*)-**12c** was obtained as a brown solid (>99% yield); t_R (HPLC, column B, eluent I) 1.62 min; MS (ESI) *m*/*z*: 466.3 [$(M + H)^+$]. After *N*-Fmoc protection, the *N*-Fmoc-*β*-tryptophan ester (3′*R*,2*S*)-**15c** (96 mg, 0.14 mmol, 48% yield) was isolated as a white solid after automated flash column chromatography on silica gel (cartridge 25 g) using a 12−50% linear gradient elution (10 CV)[23] followed by a 50/50 isocratic elution (12 CV)[23] of a binary system of cyclohexane and ethyl-acetate. Mp 139−140 °C; $[\alpha]_D^{20}$ −43 (*c* 1.4, CH_2Cl_2); t_R (HPLC, column B, eluent I) 2.6 min; 99% ee: t_R (HPLC, column C, eluent I) 10.9 min; MS (ESI) *m*/*z*: 688.1 [$(M + H)^+$] 710.2 [$(M + Na)^+$]; ^{1}H NMR (400 MHz, CD_3COCD_3) *δ* (ppm): 1.05 (s, 3H, C*H*$_3$), 1.15 (s, 3H, C*H*$_3$), 3.58 (d, *J* = 9.6 Hz, 1H, 5′-*H*), 3.72 (m, 6H, 5′-C*H*$_2$, C*H*$_2$NH and OC*H*$_3$), 4.11 (m, 1H, OCH$_2$C*H*), 4.20 (m, 2H, OC*H*$_2$), 4.29 (m, 1H, C*H*COO), 5.54 (s, 1H, 3′-*H*), 6.66 (dd, *J* = 8.8 and 2.0 Hz, 1H, *H*C-indole), 6.90 (br t, 1H, N*H*), 7.16−7.28 (2 m, 7 H, *H*C-Fmoc and *H*C-indole), 7.60 (d, *J* = 8.8 Hz, 2H, *H*-arom), 7.29 (m, 4H, *H*C-Fmoc and *H*C-indole), 7.92 (d, *J* = 8.8 Hz, 2H, *H*-arom), 9.99 (s, 1H, N*H*-indole); ^{13}C NMR (100 MHz, CD_3COCD_3) *δ* (ppm): 20.1 (*C*H$_3$), 23.1 (*C*H$_3$), 36.5 (*C*-4′), 42.8 (*C*H$_2$NH), 43.6 (*C*HCOO), 46.7 (OCH$_2$*C*H), 54.5 (OC*H*$_3$), 56.4 (*C*-5′), 65.8 (O*C*H$_2$), 77.8 (*C*-3′), 99.92 (*C*H-indole), 109.0 (*C*-indole or *C*-Fmoc), 111.6, 117.9, 119.4, 123.2, 124.9 (*C*H-arom, *C*H-Fmoc and *C*H-indole), 125.6, 126.6 (*C*-indole or *C*-Fmoc), 126.7, 127.1, 129.9 (*C*H-arom, *C*H-Fmoc and *C*H-indole), 131.2, 140.7, 142,9, 143.7, 153.7 (*C*-arom, *C*-indole and *C*-Fmoc), 155.9, 165.8, 169.6, 171.3 (*C*═O); HRMS (ESI) Calcd for $C_{40}H_{38}N_3O_8$ (MH^+) 688.2659, found 688.2661.

After trimethyltin hydroxide hydrolysis of the purified compound (3′*R*,2*S*)-**15c**, the *N*-Fmoc-*β*-tryptophan analogue (*S*)-**13c** (30 mg, 0.066 mmol, 47% yield) was isolated as a white solid after column chromatography on silica gel with cyclohexane/ethyl acetate/CH_2Cl_2/AcOH (3/5/2/0.1%). Mp 110−111 °C; $[\alpha]_D^{20}$ −7 (*c* 0.4, CH_2Cl_2); t_R (HPLC, column B) (eluant I) 2.3 min, (eluant II) 4.5 min; 99% ee: t_R (HPLC, column C, eluent III) 8.2 min; [t_R enantiomer *R* (HPLC, column C, eluant III) 10.3 min]; MS (ESI) *m*/*z*: 457.3 [$(M + H)^+$]; ^{1}H NMR (400 MHz, CD_3COCD_3) *δ* (ppm): 2.90 (br s, 1H, O*H*), 3.67 (m, 1H, *H*CHNH), 3.81 (s and m, 4H, OC*H*$_3$ and *H*CHNH), 4.24 (m, 2H, C*H*CO$_2$H and OCH$_2$C*H*), 4.34 (d, *J* = 6.9 Hz, 2H, OC*H*$_2$), 6.68 (br s, 1H, N*H*-Fmoc), 6.80 (dd, *J* = 2.4 and 8.8 Hz, 1H, C*H*-indole), 7.28−7.34 (m, 5H, (C*H*-Fmoc and C*H*-indole),), 7.41 (t, *J* = 7.4 Hz, 2H, C*H*-Fmoc), 7.68 (d, *J* = 7.5 Hz, 2H, *H*C-Fmoc), 7.86 (d, *J* = 7.5 Hz, 2H, *H*C-Fmoc), 10.08 (br s, 1H, N*H*-indole); ^{13}C NMR (100 MHz, CD_3COCD_3) *δ* (ppm): 42.9 (*C*HCO$_2$H), 43.2 (*C*H$_2$NH), 47.2 (OCH$_2$*C*H), 54.9 (*C*H$_3$), 66.1 (O*C*H$_2$), 100.7 (*C*H-indole), 110.5 (*C*-indole or *C*-Fmoc), 111.8, 112.1, 119.9, 123.4, 123.6, 125.3, 127.0, 127.3, 127.6 (*C*H-Fmoc and *C*H-indole), 131.8, 141.2, 144.3, 154.0 (*C*-indole or *C*-Fmoc), 156.4, 173.7 (*C*═O); HRMS (ESI) Calcd for $C_{27}H_{25}N_2O_5$ (MH^+) 457.1763, found 457.1774.

(*S*)-3-(9-Fluorenylmethoxycarbonylamino)-2-(6-fluoro-1*H*-indol-3-yl)propionic Acid (*S*)-13d. Synthesized according to the procedure B from compound **11d** (172 mg, 0.3 mmol). The crude expected intermediate acetic acid salt of [*N*-(4-carboxyphenyl)-4,

4-dimethyl-2-oxopyrrolidin-3-yl] 2-(6-fluoro-1*H*-indol-3-yl)-3-aminopropionate (3′*R*,2*S*)-**12d** was obtained as a brown solid (>99% yield); t_R (HPLC, column B, eluent I) 1.71 min; MS (ESI) *m*/*z*: 454.2 [(M + H)$^+$]. Then, after *N*-Fmoc protection, the *N*-Fmoc-*β*-tryptophan ester (3′*R*,2*S*)-**15d** (140 mg, 0.21 mmol, 69% yield) was isolated as a white solid after automated flash column chromatography on silica gel (cartridge 25 g) using a 12−50% linear gradient elution (10 CV)[23] followed by a 50/50 isocratic elution (9 CV)[23] of a binary system of cyclohexane and ethyl acetate. Mp 177 °C; $[\alpha]_D^{20}$ +33 (*c* 1.5, CH_2Cl_2); t_R (HPLC, column B, eluent I) 2.7 min; 99% ee: t_R (HPLC, column C, eluent I) 11.1 min; MS (ESI) *m*/*z*: 676.2 [(M + H)$^+$]; ^{1}H NMR (400 MHz, CD_3COCD_3) *δ* (ppm): 1.15 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 3.73 (d, *J* = 9.6 Hz, 1H, 5′-*H*), 3.86 (m, 3H, 5′-CH_2 and CH_2NH), 4.26 (m, 1H, OCH_2CH), 4.37 (m, 2H, OCH_2), 4.47 (m, 1H, *CH*COO), 5.69 (s, 1H, 3′-*H*), 6.92 (dt, *J* = 9.6 and 2.2 Hz, 1H, *HC*-indole), 7.06 (br t, 1H, N*H*), 7.18 (dd, *J* = 9.9 and 2.2 Hz, 1H, *HC*-indole), 7.31−7.47 (2 m, 5H, *HC*-Fmoc and *HC*-indole), 7.74−7.90 (m, 6H, *H*-arom, *HC*-Fmoc and *HC*-indole), 8.07 (d, *J* = 8.8 Hz, 2H, *H*-arom), 10.38 (s, 1H, N*H*-indole); ^{13}C NMR (100 MHz, CD_3COCD_3) *δ* (ppm): 20.4 (CH_3), 24.4 (CH_3), 37.9 (*C*-4′), 44.2 (CH_2NH), 47.9 (CHCOO), 48.0 (OCH_2CH), 57.8 (*C*-5′), 67.2 (OCH_2), 79.2 (*C*-3′), 98.3 and 98.5 (*C*-indole), 108.6 and 108.4 (*C*H-indole), 111.2 (*C*-indole or *C*-Fmoc), 119.3, 120.8, (*C*H-Fmoc and *C*H-indole), 124.5, 127.0 (*C*-indole or *C*-Fmoc), 126.2, 127.9, 128.5, 131.6 (*C*H-arom, *C*H-Fmoc and *C*H-indole), 137.3, 137.6, 142.1, 144.3, 145.1, 157.3, 159.5, 161.9, 167.1, 170.8, 172.5 (*C*-arom, *C*-indole and *C*-Fmoc, *C*═O); HRMS (ESI) Calcd for $C_{39}H_{35}N_3O_7$ F(MH$^+$) 676.2459, found 676.2453.

After trimethyltin hydroxide hydrolysis of the purified compound (3′*R*,2*S*)-**15d**, the *N*-Fmoc-*β*-tryptophan analogue (*S*)-**13d** (33 mg, 0.075 mmol, 36% yield) was isolated as a white solid after column chromatography on silica gel with cyclohexane/ethyl acetate/CH_2Cl_2/AcOH (3/5/2/0.1%). Mp 90−91 °C; $[\alpha]_D^{20}$ −45 (*c* 1.0, CH_2Cl_2); t_R (HPLC, column B, eluent II) 4.7 min; 99% ee: t_R (HPLC, column C, eluent III) 7.6 min; [t_R enantiomer X (HPLC, column C, eluant III) 11.3 min]; MS (ESI) *m*/*z*: 445.1 [(M + H)$^+$]; ^{1}H NMR (400 MHz, CD_3COCD_3) *δ* (ppm): 2.74 (br s, 1H, O*H*), 3.50 (m, 1H, *H*CHNH), 3.67 (m, 1H, *H*CHNH), 4.06 (m, 2H, $CHCO_2H$ and OCH_2CH), 4.19 (d, *J* = 7.2 Hz, 2H, OCH_2), 6.56 (br s, 1H, N*H*-Fmoc), 6.73 (td, *J* = 2.3 and 8.7 Hz, 1H, *H*-indole), 7.01 (dd, *J* = 2.3 and 10.0 Hz, 1H, *H*-indole), 7.14−7.19 (m, 3H, *H*-Fmoc and *H*-indole),), 7.30 (t, *J* = 7.4 Hz, 2H, *H*-Fmoc), 7.53 (d, *J* = 7.5 Hz, 2H, *H*-Fmoc), 7.57 (dd, *J* = 5.4 and 8.7 Hz, 1H, *H*-indole), 7.71 (d, *J* = 7.5 Hz, 2H, *H*-Fmoc), 10.17 (br s, 1H, N*H*-indole); ^{13}C NMR (100 MHz, CD_3COCD_3) *δ* (ppm): 42.9 ($CHCO_2H$), 43.2 (CH_2NH), 47.2 (OCH_2CH), 66.1 (OCH_2), 97.3 and 97.54 (*C*H-indole), 107.3 and 107.6 (*C*H-indole), 111.1, 117.9 (*C*-indole and *C*-Fmoc), 119.9, 123.6, 125.2, 127.0, 127.6 (*C*H-Fmoc and *C*H-indole), 141.2, 144.3 (*C*-indole and *C*-Fmoc), 156.4, 158.6, 160.9 (*C*═O); HRMS (ESI) Calcd for $C_{26}H_{22}N_2O_4F$ (MH$^+$) 445.1564, found 445.1567.

Transformation of Compound 7e into the (*S*)-3-(9-Fluorenylmethoxycarbonylamino)-2-(5-bromo-1*H*-indol-3-yl)-propionic Acid (*S*)-13e. To a solution of compound **11e** (190 mg, 0.3 mmol) in acetic acid (5 mL) were added at room temperature THF (10 mL), water (2 mL), concentrated HCl (0.8 mL), and portionwise Zn dust (250 mg, 3.8 mmol). The reaction mixture was vigorously stirred for 1.5−2 h at the same temperature (monitored by HPLC, column B). The suspension was filtered, and the filtrate was concentrated in vacuo. The residue was diluted with CH_2Cl_2 and washed successively with water and with saturated aqueous $NaHCO_3$. The organic layer was then dried over Na_2SO_4, and after removal of the solvent, the crude acetic acid salt of the expected compound **14e** (>99% yield) was obtained and used without further purification;[20] t_R (HPLC, column B, eluent I) 2.38 min; MS (ESI) *m*/*z*: 604.3 and 606.3 [(M + H)$^+$].

After *N*-Fmoc protection, the *N*-Fmoc-*β*-tryptophan ester (3′*R*,2*S*)-**16e** (115 mg, 0.14 mmol, 48% yield) was isolated as a white solid after automated flash column chromatography on silica gel (cartridge 25 g) using a 10−40% linear gradient elution (10 CV)[23] followed by a 60/40 isocratic elution (8 CV)[23] of a binary system of cyclohexane and ethyl acetate. Mp 112 °C; $[\alpha]_D^{20}$ −21 (*c* 1.0, CH_2Cl_2); t_R (HPLC, column B, eluent I) 3.2 min; 98% ee: t_R (HPLC, column C, eluent IV) 12.5 min; MS (ESI) *m*/*z*: 826.1 and 826.0 [(M + H)$^+$], 848.1 and 850.0 [(M + Na)$^+$]; ^{1}H NMR (400 MHz, CD_3COCD_3) *δ* (ppm): 1.15 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 3.72 (d, *J* = 9.6 Hz, 1H, 5′-*H*), 3.86 (m, 3H, 5′-*H* and CH_2NH), 4.25 (br t, *J* = 7.2 Hz, 1H, OCH_2CH), 4.34 (m, 2H, OCH_2), 4.45 (dd, *J* = 6.4 and 8.8 Hz, 1H, *CH*COO), 5.37 (s, 2H, $CH_2C_6H_5$), 5.68 (s, 1H, 3′-H), 7.04 (br t, 1H, N*H*), 7.25−7.44 (m, 10H, *HC*-Fmoc, *H*-arom, and *HC*-indole), 7.51 (br d, *J* = 7.6 Hz, 2H, *HC*-Fmoc and/or *HC*-indole), 7.73 (d, *J* = 8.6 Hz, 2H, *H*-arom), 7.88 (m, 4H, *HC*-Fmoc and/or *HC*-indole), 7.99 (br s, 1H, *HC*-Fmoc and/or *HC*-indole), 8.07 (d, *J* = 8.6 Hz, 2H, *H*-arom), 10.50 (s, 1H, N*H*-indole); ^{13}C NMR (100 MHz, CD_3COCD_3) *δ* (ppm): 21.5 (CH_3), 24.4 (CH_3), 37.9 (*C*-4′), 44.3 (CH_2NH), 44.8 (CHCOO), 48.1 (OCH_2CH), 57.7 (*C*-5′), 67.0 (OCH_2), 67.2 ($OCH_2C_6H_5$), 79.3 (*C*-3′), 110.5, 112.9, 113.0 (*C*-arom, *C*-indole, and/or *C*-Fmoc), 114.3, 119.3, 120.8, 122.3, 125.8, 126.2, 127.9, 128.5, 128.9, 129.4, 131.2 (*C*H-arom, *C*H-Fmoc and *C*H-indole), 136.28, 137.5, 142.1, 144.5, 145.1 (*C*-arom, *C*-indole, and *C*-Fmoc), 157.3, 166.1, 170.7, 172.4 (*C*═O); HRMS (ESI) Calcd for $C_{46}H_{41}BrN_3O_7$ (MH$^+$) 826.2128, found 826.2114.

After trimethyltin hydroxide hydrolysis of the purified compound (3′*R*,2*S*)-**16e**, the *N*-Fmoc-*β*-tryptophan analogue (*S*)-**13e** (44 mg, 0.088 mmol, 63% yield) was isolated as a white solid after column chromatography on silica gel with cyclohexane/ethyl acetate/CH_2Cl_2/AcOH (3/5/2/0.1%). Mp 107−108 °C; $[\alpha]_D^{20}$ −13 (*c* 0.4, CH_2Cl_2); t_R (HPLC, column B) (eluant II) 4.8 min; 98% ee: t_R (HPLC, column C, eluent III) 10.9 min; [t_R enantiomer *R* (HPLC, column C, eluant III) 12.6 min]; MS (ESI) *m*/*z*: 504.9 and 506.9 [(M + H)$^+$], 526.9 and 528.9 [(M + Na)$^+$]; ^{1}H NMR (400 MHz, CD_3COCD_3) *δ* (ppm): 3.64 (m, 1H, *H*CHNH), 3.81 (m, 1H, *H*CHNH), 4.08−4.19 (m, 4H, $CHCO_2H$, OCH_2CH and OCH_2), 6.73 (br t, 1H, N*H*-Fmoc), 7.23 (dd, *J* = 2.0 and 8.8 Hz, 1H, *CH*-indole), 7.29 (br t, *J* = 7.6 Hz, 1H, *CH*-indole), 7.36−7.43 (br s, 1H, (*CH*-indole), 7.66 (d, *J* = 7.6 Hz, 2H, *HC*-Fmoc), 7.85 (d, *J* = 7.6 Hz, 2H, *HC*-Fmoc), 7.92 (br t, *J* = 7.6 Hz, 1H, *CH*-indole), 10.48 (br s, 1H, N*H*-indole); ^{13}C NMR (100 MHz, CD_3COCD_3) *δ* (ppm): 43.7 ($CHCO_2H$), 44.1 (CH_2NH), 48.1 (OCH_2CH), 67.0(OCH_2), 112.8 (*C*-indole or *C*-Fmoc), 114.2, 120.8, 122.3, 125.7, 126.1, 127.9 (*C*H-Fmoc and *C*H-indole), 128.8, 136.2, 142.1, 145.2 (*C*-indole or *C*-Fmoc), 157.3, 174.2 (*C*═O); HRMS (ESI) Calcd for $C_{26}H_{22}N_2O_4Br$ (MH$^+$) 505.0763, found 505.0764.

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H and ^{13}C NMR spectra of compounds **11a**−**e** and **13a**−**e**; HPLC chromatograms of compounds **11a**−**e** and **13a**−**e**; HRMS spectra for compounds **11a**−**e**, **13a**−**e**, **15a**−**d**, and **16e**; ORTEP drawing and crystal data for compound **7e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The diastereoisomeric ratio was determined by ^{1}H NMR and HPLC (column B: Chiralcel OD-RH).

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(18) Although conversions of the nitroacrylate occurred with good yields, enantiopure compounds **11a**−**e** (ee >99%) were obtained in moderate yields due in particular to the delicate separation of the mixture of the main and minor diastereoisomers (3′*R*,2*S*) and (3′*R*,2*R*).

(19) This preferential conformation has been previously proposed and should correspond to the nonchelated form of the two carbonyl groups of pantolactone derivatives (Camps, P.; Munoz-Torrero, D. *Curr. Org. Chem.* **2004**, *8*, 1339–1380); this arrangement is also found in the various X-ray crystallography data of compounds previously prepared by us using the same chiral auxiliary (see, for example: (a) Calmès, M.; Didierjean., C.; Didierjean, C.; Martinez, J. *Tetrahedron: Asymmetry* **2005**, *16*, 2173–2178. (b) Songis, O.; Didierjean, C.; Martinez, J.; Calmès, M. *Eur. J. Org. Chem.* **2007**, 3166–3172 and ref 5a).

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