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An Efficient and Enantioselective Synthesis of Suitably Protected β-[1-(4-Malonyl)naphthyl]-L-alanine and β-[1-(4-Malonylmethyl)naphthyl]-L-alanine: Novel Fluorescent and Non-Hydrolysable Phosphotyrosine Mimetics

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Molecular dynamics simulations based on the structure of the Grb7 SH2 domain in complex with the ErbB2 phosphorylated peptide pTyr1139 have suggested that β-[1-(4-malonyl)naphthyl]-L-alanine (L-mNal) may be accommodated in the pTyr binding pocket and offer additional beneficial interactions. Therefore, this compound and its analog β-[1-(4-malonylmethyl)naphthyl]-L-alanine (L-mmNal), which are new non-hydrolysable phosphotyrosine mimetics, have been prepared by the catalytic asymmetric hydrogenation of the corresponding prochiral enamides with excellent enantioselectivities. These compounds and their dehydro derivatives show interesting fluorescent properties.

Introduction

Src homology-2 (SH2) domains and phosphotyrosine binding (PTB) domains are the most prevalent phosphotyrosine-binding modules and have been shown to bind to phosphorylated protein tyrosine kinases or other phosphorylated proteins in response to external stimuli, such as the binding of growth factors. These modules, which are a promising therapeutic target, play an important role in signal transduction and have been the focus of drug discovery efforts to develop novel inhibitors over recent years.[1]

A major challenge of SH2 domain inhibitors has been the design of phosphotyrosine (pTyr) bioisosters that mimic the complex hydrogen-binding network within the highly positively charged pTyr-binding pocket. One of the approaches for developing metabolically stable pTyr mimetics is the modification of the charged nature of a phosphate group by replacement with a carboxylate, as exemplified by *para*-malonylphenylalanine (Pmf), which has been reported as being approximately equivalent to the phosphonate-based pTyr mimetics in binding with the growth factor receptor-bound protein 2 (Grb2) SH2 domain.[2] Although the structure of malonate as a phosphate bioisoster is chemically distinct, molecular dynamics simulations based on the NMR solution structure of the SH2 domain of growth factor receptor-bound protein 7 (Grb7), another adaptor protein, in a complex with the ErbB2 (epidermal growth factor receptor family protein-2) phosphorylated peptide pTyr1139[3] reveals that the malonate group occupies about 13% more volume than the phosphate, although their interaction with the SH2 domain looks very similar and both structures possess similar SH2 domain geometries. This study has provided an impetus to further investigate the effect of modifying Pmf by β-[1-(4-malonyl)naphthyl]-L-alanine (L-mNal), in which the phenyl ring is replaced by a naphthyl structure.

Molecular dynamic simulations performed in our laboratory indicate that this new pTyr mimetic can dock favorably in the pTyr pocket of the Grb7 SH2 domain, with the onset of an additional beneficial cation–π interaction between the electron-rich naphthyl ring and the electron-deficient guanidinium moiety of an Arg residue. This type of interaction has often been reported in proteins and protein complexes.[4] Moreover, it has been observed in the crystal structure of Grb2 SH2 complexed with the 2-Abz-EpYINQ-NH_2 ligand, which has an anthranyl group attached to the N-terminal end and is found stacked over an Arg residue. Such a stacking interaction could account for the enhancement of affinities of anthranyl-capped phosphopeptides for different SH2 domains, such as Grb2, T-cell tyrosine kinase (Lck), phospholipase Cγ (PLC-γ), and the p85 subunit of phosphatidylinositol-3 (PI-3) kinase (p85).[5] In addition, some compounds containing a naphthalene nucleus have been reported to be attractive photoluminescent materials due to their high efficiency and good thermal stability.[6,7] The use of an amino acid as a fluorescent chromophore[7–9] offers at least two advantages: first, peptides containing this amino acid can be synthesized by solid-phase peptide synthesis (SPPS), and second, since both ends of these peptides are free, residues may be attached to improve solubility or lability.[10] Thus, in this paper, we report the synthesis of L-mNal, L-mmNal, and their dehydro derivatives, in which the amino group is protected with widely used protecting

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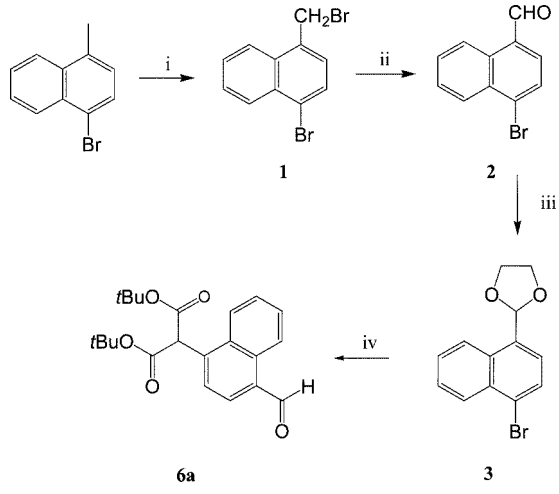
groups such as Fmoc, Cbz, or Boc. These compounds could be incorporated into peptides and may afford pharmacologically interesting alternatives to phosphonate-based pTyr mimetics and also serve as a fluorescent probe for visualizing and studying biological processes or molecular interactions.

Results and Discussion

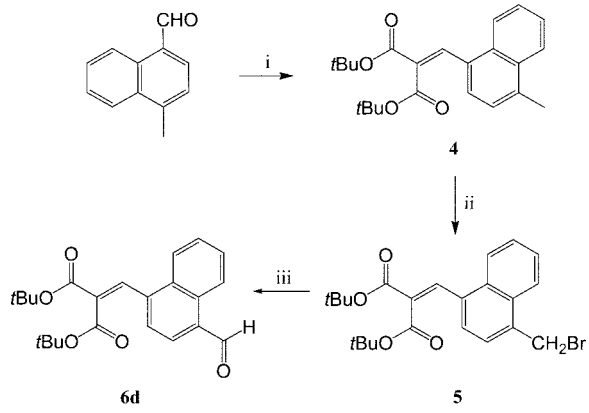
Synthesis

The synthesis of unusual α-amino acids is of considerable interest as they not only serve as building blocks for bioactive peptides or peptidomimetics but also as starting points for the preparation of drugs and natural products.[11,12] The recent development in this field is linked to advances in several synthetic methodologies, including the building-block approach,[13] and in the discovery of numerous chiral auxiliaries or ligands for the asymmetric synthesis. In particular, asymmetric hydrogenation of the prochiral enamides using the chiral complex Rh^{I}-(*S*,*S*)-Me-DuPHOS provides an efficient and attractive approach for the construction of α-amino acids with high enantiomeric excesses.[14,15] Recently, it has been reported that the preparation of 2-naphthylalanine from this type of precursors using a rhodium–methyl BioPhoz-catalyzed asymmetric hydrogenation also shows exceedingly high enantioselectivities.[16,17] The enhanced reactivity of the enamide double bond has been attributed to the ability of this group to chelate to the catalyst metal center. This property is believed to be important for achieving high enantioselectivity in rhodium-catalyzed hydrogenations. Therefore, we have developed a procedure that takes advantage of this feature to synthesize new L-mNal and L-mmNal derivatives for use as phosphotyrosine mimetics.



Scheme 1. i) NBS/dibenzoyl peroxide; ii) DMSO/$NaHCO_3$; iii) ethylene glycol/TosOH; iv) di-*tert*-butyl malonate/$[Pd_2(dba)_3]$/P(*t*Bu)$_3$/KO*t*Bu; TosOH/THF.

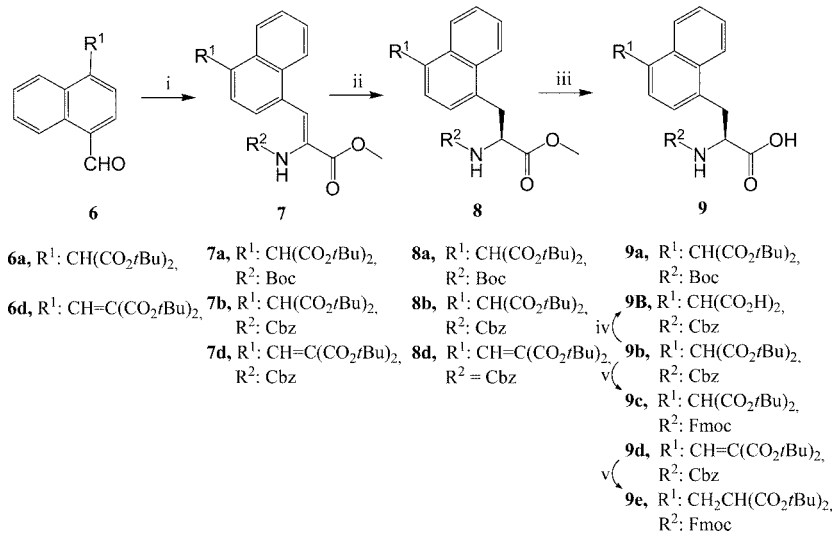
Towards this end, it was first necessary to prepare the key aldehyde intermediates **6a** and **6d**, as outlined in Schemes 1 and 2, respectively.



Scheme 2. i) Di-*tert*-butyl malonate/$TiCl_4$/pyridine; ii) NBS/dibenzoyl peroxide; iii) DMSO/$NaHCO_3$.

The synthesis of intermediate **6a** starts by the simple preparation of aldehyde **2** from commercially available 1-bromo-4-methylnaphthalene. As illustrated in Scheme 1, the *para*-methyl group of 1-bromo-4-methylnaphthalene was brominated with *N*-bromosuccinimide to provide 1-bromo-4-(bromomethyl)naphthalene (**1**), which was then subjected to a Kornblum reaction.[18] This DMSO-based oxidation led to 4-bromonaphthaldehyde (**2**) in excellent yield. The aldehyde group of **2** was protected by treatment with ethylene glycol in the presence of a catalytic amount of *p*-toluenesulfonic acid (TosOH) to afford the (4-bromonaphthyl)dioxolane **3**, which was used subsequently in further transformation without purification. The palladium-catalyzed arylation[19] of di-*tert*-butyl malonate with **3** was successfully achieved in anhydrous dioxane at 70 °C overnight, using *t*Bu_3P as ligand and *t*BuOK as base, to give a malonyl intermediate, which immediately underwent acidic hydrolysis to afford di-*tert*-butyl 2-(4-formylnaphthyl)-malonate (**6a**). *t*BuOK was the most effective base for the arylation as it gave significantly higher yields than reactions run with K_3PO_4 or NaH. Use of these latter bases resulted in very slow conversion or high levels of undesired side products.

For the preparation of the vinylogue **6d**, we synthesized 1-[2′,2′-bis(*tert*-butoxycarbonyl)vinyl]-4-methylnaphthalene (**4**) from 4-methylnaphthaldehyde by a mild Knoevenagel condensation,[20] as shown in Scheme 2. Thus, equal molar equivalents of 4-methylnaphthaldehyde and di-*tert*-butyl malonate were condensed in the presence of titanium tetrachloride and pyridine at 0 °C, followed by warming the reaction mixture to room temperature for 3 h, to provide the desired product **4** in quantitative yield. Then, we again chose bromination of the *para*-methyl group of compound **4** followed by a Kornblum reaction to convert the methyl



Scheme 3. Asymmetric synthesis of *N*-protected β-[1-(4-malonyl)naphthyl]-L-alanine and β-[1-(4-malonylmethyl)naphthyl]-L-alanine and their dehydroamino acid derivatives: i) 2-(Boc-amino)-2-dimethylphosphonylacetate or 2-(Cbz-amino)-2-dimethylphosphonyl-acetate/TMG; ii) H_2, 10 atm/[Rh(COD)$_2$OTf]/(*S*,*S*)Me-DuPHOS; iii) Na_2CO_3/MeOH; iv) TFA/CH_2Cl_2; v) a, H_2/Pd-C; b, FmocOSu/$NaHCO_3$.

group into the aldehyde function. In this manner, **6d** was obtained in good yield after purification by column chromatography on silica gel.

Next, we performed the synthesis of differently protected L-mNal, L-mmNal, and their dehydroamino acids, as illustrated in Scheme 3. A Horner–Emmons-type olefination[21] of the compounds **6a** and **6d** proceeded smoothly with methyl 2-(Boc-amino)-2-dimethylphosphonylacetate or methyl 2-(Cbz-amino)-2-dimethylphosphonylacetate using tetramethylguanidine (TMG) as base at –78 °C, followed by allowing the solution to warm to room temperature, to afford the (*Z*)-enamido esters **7a**–**b** and **7d** in good yields.

The configurational assignment of the dehydroamino acids was based on the NOE difference technique. These derivatives with an (*E*) configuration have been reported to display strong NOE crosspeaks between the olefinic CH and NH protons;[22] in the case of **7a**–**b** and **7d** no such effects were observed.

Asymmetric hydrogenation of **7a**–**b** and **7d** using Burk's catalytic Rh^{I}-(*S*,*S*)-Me-DuPHOS system[23] at 10 atm of H_2 and 25 °C afforded the fully protected 4-substituted naphthyl-L-alaninate derivatives **8a**–**b** and **8d** in excellent yields. The absolute configurations were assigned as (*S*) based on the selectivity of the (*S*,*S*)-Me-DuPHOS ligand.[23]

In order to avoid partial hydrolysis of the di-*tert*-butyl malonate, compounds **8a**–**b** and **8d** were treated under mild conditions with Na_2CO_3 as base at room temperature overnight to provide the desired acids **9a**–**b** and **9d**. Conversion of **9b** to **9B** was achieved by TFA-mediated removal of the di-*tert*-butyl malonate protection. Finally, Pd-catalyzed hydrogenolytic removal of the Cbz group from **9b** and the Cbz and vinyl moieties from **9d**, followed by treatment with *N*-Fmoc-succinimide in the presence of sodium hydrogencarbonate in aqueous dioxane, afforded the *N*-Fmoc-4-substituted naphthyl-L-alanines **9c** and **9e** in good yield over the two steps.

Optical and Fluorescence Spectroscopy

Absorption and fluorescence emission, extinction coefficients, and fluorescence quantum yields (QY) were measured for some of the 4-substituted naphthyl-L-alanines and their dehydro derivatives (Figure 1, Table 1). The optical properties of the natural fluorescent amino acids Tyr and Trp are also included in the table for comparison. As observed in Table 1, the novel 4-substituted naphthyl-L-alanines and their dehydro compounds have higher maximum wavelength values of absorption and emission and display higher quantum yields than Trp or Tyr, especially in the case of dehydro compounds **7b** and **7d**, with values ranging from 0.43 to 0.44 vs. 0.13 and 0.12 for Tyr and Trp, respectively. As demonstrated in Figure 1, the emission spectra were obtained in ethanol with excitation close to λ_{max} (abs.) for each compound. As expected, the emission band of **7b**

Table 1. Spectral data for the 4-substituted naphthyl-L-alanines and their dehydro derivatives.

Compd.	λ_{max} (abs) [nm][a]	λ_{max} (em) [nm][a]	ε [cm^{-1} M^{-1}]	QY[b]
Tyr	274[24]	303[24]	1400[24]	0.13[25]
Trp	278[24]	352[24]	5300[24]	0.12[25]
7b	383	434	15900	0.44
7d	408	431	12900	0.43
9b	314	344	2600	0.16
9B	313	346	2900	0.17
9e	266	304	4107	0.39

[a] Determined in ethanol. [b] Determined by using the comparative method[26] and quinine sulfate in sulfuric acid (0.1 M) as a standard reference (QY_S = 0.577).[27]

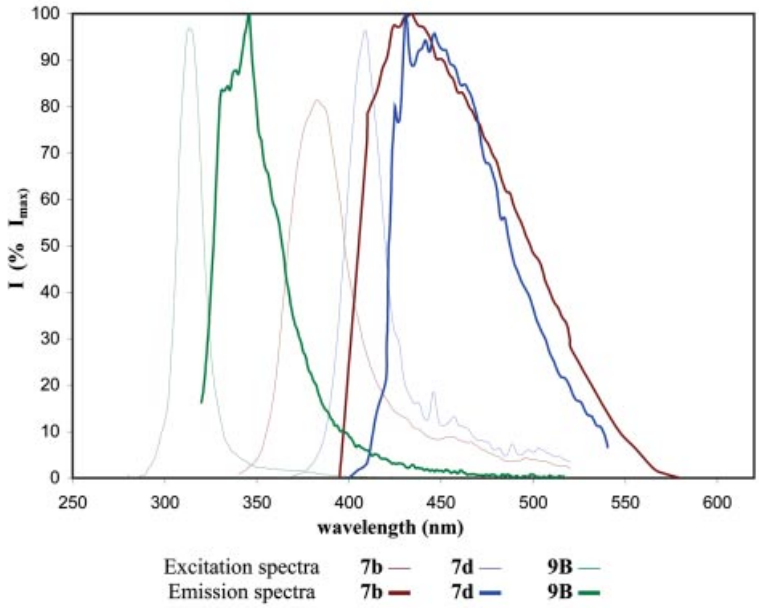


Figure 1. Excitation and emission spectra of *N*-(benzyloxycarbonyl)-β-{1-[4-bis(*tert*-butoxycarbonyl)methyl]naphthyl}-L-alanine (**9B**) and dehydroamino acids **7b** and **7d**.

and **7d** is shifted to longer wavelength. The maximum of emission is at 431–434 nm. These characteristics make these compounds potential new fluorophores for biological studies as they allow a good distinction from those of the natural fluorescent amino acids such as Tyr and Trp.

Conclusion

We have developed a practical and efficient procedure for the preparation of optically active and suitably protected L-mNal and L-mmNal in high enantiomeric purity from commercially available 1-bromo-4-methylnaphthalene and 4-methylnaphthaldehyde. These compounds, and their dehydro derivatives, show a promising fluorescence profile. Further investigation of the Grb7 SH2 binding affinity of these compounds as novel non-hydrolysable phosphotyrosine mimetics is in progress in our laboratory.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded with a Bruker WMFT-250 MHz spectrometer. Chemical shifts are expressed in parts per million (ppm) using TMS as internal standard. Mass spectra were recorded with a Q-Tof1 spectrometer with Z-spray source. Elemental analyses (C, H, N), performed at the Service de Microanalyse, Pierre et Marie Curie Université, Paris, France, were within ±0.4% of the theoretical values. Optical rotations were measured with a Perkin–Elmer Model 141 polarimeter. Absorption and emission spectra were measured with a Perkin–Elmer LB 50 Luminescence Spectrometer. Extinction coefficients and quantum yields were determined with a Beckman DU640 spectrophotometer. Melting points were determined with a Kofler apparatus and are uncorrected. The purity of the compounds and reaction progress were monitored by TLC on silica gel plates ($60F_{254}$, 0.2 mm thick, Merk). Spots were visualized under UV light (254 nm). Flash chromatography was performed with silica gel 60 (0.04–0.063 mm) purchased from Carlo Erba-SDS. All chemicals were purchased from Acros or Aldrich and used without further purification.

1-[2′,2′-Bis(*tert*-butoxycarbonyl)vinyl]-4-methylnaphthalene (4): Titanium tetrachloride (0.7 mL, 6.3 mmol) in dry carbon tetrachloride (1.5 mL) was added dropwise to dry THF (12 mL) at 0 °C to give a yellow precipitate. 4-Methylnaphthaldehyde (0.51 g, 3 mmol) and di-*tert*-butyl malonate (0.65 g, 3 mmol) in dry THF (1.5 mL) were added slowly, followed by pyridine (3.2 mL, 50 mmol) in dry THF (1.5 mL). The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 3 h. Water (10 mL) and ethyl acetate (20 mL) were added and stirring was continued until the solid material had dissolved. The organic layer was separated and washed with brine and saturated $NaHCO_3$, dried, and the solvents were evaporated. The residue was then chromatographed on silica gel (hexane/EtOAc = 4:1) to provide 1.1 g of the title compound in 100% yield as a white solid. M.p. 124–125 °C. ^{1}H NMR ($CDCl_3$): δ = 1.39 (s, 9 H, *t*Bu), 1.58 (s, 9 H, *t*Bu), 2.74 (s, 3 H, CH_3), 7.32–8.08 (m, 6 H, aromatic), 8.29 (s, 1 H, CH=) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.11, 28.22, 82.41, 125.06, 125.23, 126.33, 126.49, 126.73, 129.87, 131.92, 132.95, 137.22, 139.33, 163.87, 165.99 ppm. HRMS (ESI): calcd. for $C_{23}H_{28}NaO_4$ 391.1885 $[M + Na]^+$; found 391.1870.

General Procedure for Bromination: A solution of the 1-substituted 4-methylnaphthalene (5.6 mmol), *N*-bromosuccinimide (6.1 mmol), and benzoyl peroxide (0.2 mmol) in dry CCl_4 (20 mL) was refluxed under argon overnight, then cooled to room temperature, filtered, and the filtrate concentrated to dryness. The residue was purified by chromatography on silica gel (hexane/EtOAc = 9:1) to afford the desired compound.

1-Bromo-4-(bromomethyl)naphthalene (1): Orange solid. Yield: 94%. M.p. 102–103 °C. ^{1}H NMR ($CDCl_3$): δ = 4.94 (s, 2 H, CH_2), 7.39 (d, *J* = 8 Hz, 1 H, aromatic), 7.66 (d, *J* = 8 Hz, 1 H, aromatic), 7.70 (m, 2 H, aromatic), 8.15–8.32 (m, 2 H, aromatic) ppm. The spectroscopic data were in accordance with the literature.[28]

1-[2′,2′-Bis(*tert*-butoxycarbonyl)vinyl]-4-(bromomethyl)naphthalene (5): Orange solid. Yield: 95%. M.p. 142–144 °C. ^{1}H NMR ($CDCl_3$): δ = 1.3 (s, 9 H, *t*Bu), 1.5 (s, 9 H, *t*Bu), 4.98 (s, 2 H, CH_2), 7.38–8.22 (m, 6 H, aromatic), 8.23 (s, 1 H, CH=) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.56, 30.93, 82.45, 123.97, 124.93, 125.63, 126.13, 127.35, 127.65, 129.77, 131.82, 132.85, 132.31, 137.02, 159.87, 165.89 ppm. HRMS (ESI): calcd. for $C_{23}H_{27}BrNaO_4$ 469.0990 $[M + Na]^+$; found 469.0976.

General Procedure for the Kornblum Reaction: $NaHCO_3$ (10.5 mmol) was added to a stirred solution of the 1-substituted 4-(bromomethyl)naphthalene (5.27 mmol) in DMSO (15 mL) and the reaction mixture was stirred at 95 °C for 3 h. Subsequently, the reaction mixture was cooled to room temperature, diluted with water (45 mL), and extracted twice with ethyl acetate (50 mL). The organic layer was dried with Na_2SO_4 and concentrated in vacuo.

4-Bromonaphthaldehyde (2): Isolated as a white solid after purification by flash chromatography on silica gel (hexane/EtOAc = 8:1). Yield: 91.3%. M.p. 120–122 °C. ^{1}H NMR ($CDCl_3$): δ = 7.68–7.88 (m, 2 H, aromatic), 7.81 (d, J = 8 Hz, 1 H, aromatic), 7.98 (d, J = 8 Hz, 1 H, aromatic), 8.37 (d, J = 8 Hz, 1 H, aromatic), 10.41 (s, 1 H, CHO) ppm. The spectroscopic data are in accordance with those in the literature.[29]

4-[2′,2′-Bis(*tert*-butoxycarbonyl)vinyl]naphthaldehyde (6d): Isolated as a white solid after flash chromatography (hexane/EtOAc = 4:1). Yield: 85%. M.p. 124–125 °C. ^{1}H NMR ($CDCl_3$): δ = 1.31 (s, 9 H, *t*Bu), 1.58 (s, 9 H, *t*Bu), 7.44–9.3 (m, 6 H, aromatic), 8.22 (s, 1 H, CH=), 10.44 (s, 1 H, CHO) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.41, 83.36, 122.95, 125.13, 126.12, 127.43, 127.65, 127.89, 129.18, 130.31, 133.60, 135.98, 139.31, 157.87, 164.98, 193.27 ppm. HRMS (ESI): calcd. for $C_{23}H_{26}NaO_5$ 405.1678 $[M + Na]^+$; found 405.1657.

(4-Bromonaphthyl)dioxolane 3: *p*-Toluenesulfonic acid (4 mg, 0.02 mmol) and ethylene glycol (0.36 g, 5.8 mmol) were added to a stirred solution of **2** (0.47 g, 2 mmol) in dry toluene (6 mL) under argon and the reaction mixture was refluxed in a Dean–Stark apparatus for 16 h. The reaction mixture was cooled to room temperature and extracted with saturated $NaHCO_3$ (3 mL) and then brine (3 mL). The organic layer was dried with Na_2SO_4 and concentrated in vacuo to give **3** (0.59 g) in 100% yield as a viscous, oil which was used without further purification. R_f = 0.3 (hexane/EtOAc = 8:1). ^{1}H NMR ($CDCl_3$): δ = 4.20 (s, 4 H, CH_2-CH_2), 6.48 (s, 1 H, CH), 7.29–8.35 (m, 6 H, aromatic) ppm. ^{13}C NMR ($CDCl_3$): δ = 65.75, 102.12, 124.30, 124.86, 127.32, 127.52, 128.2, 129.64, 132.48, 132.60, 133.72 ppm. HRMS (ESI): calcd. for $C_{13}H_{11}BrNaO_2$ 300.9840 $[M + Na]^+$; found 300.9840.

Di-*tert*-butyl 2-(4-Formylnaphthyl)malonate (6a): KO*t*Bu (255 mg, 2.1 mmol), $[Pd_2(dba)_3]$ (22.6 mg, 0.024 mmol), and P(*t*Bu)$_3$ (15.3 mg, 0.076 mmol) were added to a solution of di-*tert*-butyl malonate (590 mg, 2 mmol) and the (4-bromonaphthyl)dioxolane **3** (449 mg, 2.1 mmol) in dioxane (6 mL) and the heterogeneous reaction mixture was stirred at 70 °C overnight. The mixture was filtered through a plug of Celite and concentrated in vacuo to furnish the corresponding {4-[2′,2′-bis(*tert*-butoxycarbonyl)methyl]-naphthyl}dioxolane, which was used without further purification. *p*-Toluenesulfonic acid (12 mg, 0.06 mmol) was added to a solution of the above product in THF (11 mL) and water (1.2 mL) under argon. The reaction mixture was stirred at 36 °C for 12 h, cooled to room temperature, diluted with water (20 mL), and extracted twice with ethyl acetate (30 mL). The organic layer was dried with Na_2SO_4 and concentrated in vacuo. The residue was then chromatographed on silica gel to provide 0.75 g of the title compound in 75% yield as a viscous oil. R_f = 0.38 (hexane/EtOAc = 5:1). ^{1}H NMR ($CDCl_3$): δ = 4.20 (s, 4 H, CH_2-CH_2), 5.33 (s, 1 H, CH), 7.64–9.38 (m, 6 H, aromatic), 10.41 (s, 1 H, CHO) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.31, 57.22, 83.16, 123.77, 125.50, 126.02, 126.44, 128.63, 129.08, 130.11, 131.60, 136.40, 138.21, 167.37, 193.57 ppm. HRMS (ESI): calcd. for $C_{22}H_{26}NaO_5$ 393.1678 $[M + Na]^+$; found 393.1667.

General Procedure for Horner–Emmons-Type Olefination: TMG (0.16 mL, 1.3 mmol) was added to a solution of methyl 2-(Boc-amino)-2-dimethylphosphonylacetate or methyl 2-(Cbz-amino)-2-dimethylphosphonylacetate (1 mmol) in anhydrous THF (3 mL) at –78 °C, and the mixture was stirred for 30 min. A solution of the substituted naphthaldehyde derivative (1 mmol) in THF (1 mL) was added, and the mixture was stirred at –78 °C for 1 h and at room temperature for 6 h. The mixture was diluted with ethyl acetate, washed with 10% citric acid and water, dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/EtOAc = 4:1) to afford the desired compound.

Methyl (*Z*)-2-(*tert*-Butoxycarbonylamino)-3-[4-bis(*tert*-butoxycarbonyl)methyl]naphthylacrylate (7a): Isolated as a white solidified foam from **4** and methyl 2-(Boc-amino)-2-dimethylphosphonylacetate. Yield: 90%. R_f = 0.19 (hexane/EtOAc = 4:1). ^{1}H NMR ($CDCl_3$): δ = 1.45 (s, 27 H, *t*Bu), 3.95 (s, 3 H, CH_3), 5.29 (s, 1 H, CH), 6.14 (s, 1 H, CH=), 7.55–8.05 (m, 7 H, NH, aromatic) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.19, 28.35, 52.20, 57.65, 78.38, 82.81, 122.72, 122.98, 124.48, 124.84, 125.71, 125.87, 126.42, 126.64, 130.89, 132.60, 133.98, 134.20, 154.38, 161.84, 172.09 ppm. HRMS (ESI): calcd. for $C_{30}H_{39}NNaO_8$ 564.2573 $[M + Na]^+$; found 564.2592.

Methyl (*Z*)-2-(Benzyloxycarbonylamino)-3-[4-bis(*tert*-butoxycarbonyl)methyl]naphthylacrylate (7b): Isolated as a white solidified foam from **4** and methyl 2-(Cbz-amino)-2-dimethylphosphonylacetate. Yield: 85%. R_f = 0.2 (hexane/EtOAc = 4:1). ^{1}H NMR ($CDCl_3$): δ = 1.45 (s, 18 H, *t*Bu), 3.91 (s, 3 H, CH_3), 5.03 (s, 2 H, CH_2), 5.28 (s, 1 H, CH), 6.31 (s, 1 H, CH=), 7.28–8.02 (m, 12 H, NH, aromatic) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.30, 51.21, 57.52, 65.98, 82.82, 122.70, 122.94, 124.41, 124.82, 125.67, 125.78, 126.40, 126.62, 127.41, 127.87, 129.45, 130.86, 132.57, 133.95, 134.30, 141.42, 154.58, 161.74, 172.01 ppm. HRMS (ESI): calcd. for $C_{33}H_{37}KNO_8$ 614.2156 $[M + K]^+$; found 614.2159.

Methyl (*Z*)-2-(Benzyloxycarbonylamino)-3-{4-[2′,2′-bis(*tert*-butoxycarbonyl)vinyl]}naphthylacrylate (7d): Isolated as a white solidified foam from **10** and methyl 2-(Cbz-amino)-2-dimethylphosphonylacetate. Yield: 81%. R_f = 0.24 (hexane/EtOAc = 4:1). ^{1}H NMR ($CDCl_3$): δ = 1.34 (s, 9 H, *t*Bu), 1.58 (s, 9 H, *t*Bu), 3.92 (s, 3 H, CH_3), 4.99 (s, 2 H, CH_2), 5.28 (s, 1 H, CH), 6.38 (s, 1 H, CH=), 7.21–8.07 (m, 12 H, NH, aromatic), 8.25 (s, 1 H, CH=) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.31, 52.42, 66.06, 82.68, 122.74, 124.41, 125.98, 126.44, 126.60, 127.21, 127.67, 129.25, 129.96, 131.81, 134.95, 141.32, 152.48, 155.78, 161.70, 172.05 ppm. HRMS (ESI): calcd. for $C_{34}H_{37}NNaO_8$ 610.2417 $[M + Na]^+$; found 610.2408.

General Procedure for Asymmetric Hydrogenation: A reaction vessel for a Parr hydrogenation apparatus was charged with the substituted naphthylacrylate derivative (1 mmol) and bis(1,5-cyclooctadiene)rhodium trifluoromethanesulfonate (8.5 mg). The vessel was evacuated and filled with argon three times before degassed methanol (20–25 mL) and a solution of (*S*,*S*)-Me-DuPHOS (1 mg) in degassed methanol were added. The vessel was connected to the Parr apparatus and shaken under hydrogen (10 atm) for 1 d. The reaction mixture was concentrated in vacuo and the residue purified by flash chromatography on silica gel (hexane/EtOAc = 3:1) to provide the desired compound.

Methyl *N*-(*tert*-Butoxycarbonyl)-β-{1-[4-bis(*tert*-butoxycarbonyl)-methyl]naphthyl}-L-alaninate (8a): Isolated as a white solidified foam (94%). R_f = 0.19 (hexane/EtOAc = 4:1). ^{1}H NMR ($CDCl_3$): δ = 1.45 (s, 27 H, *t*Bu), 3.51–3.62 (m, 2 H, $CH_2\beta$), 3.63 (s, 3 H, CH_3), 4.60–4.80 (m, 1 H, CHα), 5.05 (d, J = 8 Hz, 1 H, NH), 5.28 (s, 1 H, CH), 7.29–8.17 (m, 6 H, aromatic) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.19, 28.30, 35.12, 52.40, 55.71, 57.64, 78.28, 82.83, 120.97, 124.38, 125.54, 130.29, 132.62, 133.52, 156.28, 168.54, 172.19 ppm. HRMS (ESI): calcd. for $C_{30}H_{41}NaNO_8$ 566.2730 [M + Na]$^+$; found 566.2692.

Methyl *N*-(Benzyloxycarbonyl)-β-{1-[4-bis(*tert*-butoxycarbonyl)-methyl]naphthyl}-L-alaninate (8b): Isolated as a white solidified foam (93%). R_f = 0.2 (hexane/EtOAc = 4:1). ^{1}H NMR ($CDCl_3$): δ = 1.49 (s, 9 H, *t*Bu), 1.59 (s, 9 H, *t*Bu), 3.40–3.70 (m, 4 H, CH_3, $CH_2\beta$), 4.70–4.82 (m, 1 H, CHα), 5.11 (s, 2 H, CH_2), 5.28 (s, 1 H, CH), 5.33 (d, J = 8 Hz, 1 H, NH), 7.29–8.13 (m, 11 H, aromatic) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.35, 35.12, 51.24, 56.85, 57.54, 65.94, 82.87, 120.63, 124.19, 125.51, 127.28, 127.89, 129.17, 130.28, 132.56, 133.48, 141.50, 156.27, 168.84, 172.16 ppm. HRMS (ESI): calcd. for $C_{33}H_{39}NaNO_8$ 600.2573 [M + Na]$^+$; found 600.2491.

Methyl *N*-(Benzyloxycarbonyl)-β-(1-{4-[2′,2′-bis(*tert*-butoxycarbonyl)]vinyl}naphthyl)-L-alaninate (8d): Isolated as a white solidified foam (90%). R_f = 0.21 (hexane/EtOAc = 4:1). ^{1}H NMR ($CDCl_3$): δ = 1.34 (s, 9 H, *t*Bu), 1.59 (s, 9 H, *t*Bu), 3.52–3.62 (m, 2 H, $CH_2\beta$), 3.62 (s, 3 H, CH_3), 4.79–4.82 (m, 1 H, CHα), 5.11 (s, 2 H, CH_2), 5.30 (d, J = 8 Hz, 1 H, NH), 7.17–8.14 (m, 11 H, aromatic), 8.25 (s, 1 H, CH=) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.36, 35.38, 52.49, 55.32, 66.08, 82.71, 125.01, 125.14, 125.33, 126.13, 126.26, 126.41, 127.20, 127.74, 129.03, 129.98, 131.86, 132.97, 137.12, 139.68, 141.40, 155.78, 156.61, 166.82, 177.34 ppm. HRMS (ESI): calcd. for $C_{34}H_{39}NaNO_8$ 612.2573 [M + Na]$^+$, found 612.2496.

General Procedure for Saponification: A solution of the 4-substituted naphthyl-L-alaninate (1 mmol) in methanol (64 mL) at 0 °C was treated with a 1 M Na_2CO_3 aqueous solution (16 mL). The reaction was complete after 16 h at room temperature (TLC monitoring) and the reaction mixture was neutralized with 1 N HCl. The mixture obtained after solvent removal was extracted with dichloromethane. The organic layer was dried with Na_2SO_4 and concentrated in vacuo and the residue purified by flash chromatography on silica gel (CH_2Cl_2/MeOH = 9:1) to give the desired compound.

***N*-(*tert*-Butoxycarbonyl)-β-{1-[4-bis(*tert*-butoxycarbonyl)methyl]-naphthyl}-L-alanine (9a):** Isolated as a white solid (87.8%). M.p. 90–92 °C. $[\alpha]_D^{20}$ = –8.5 (c = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.50 (s, 27 H, *t*Bu), 3.30–3.90 (m, 2 H, $CH_2\beta$), 4.67–4.75 (m, 1 H, CHα), 5.03 (d, J = 8 Hz, 1 H, NH), 5.27 (s, 1 H, CH), 7.37–8.32 (m, 6 H, aromatic) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.21, 28.32, 35.16, 56.95, 57.62, 78.24, 82.85, 120.77, 124.34, 125.52, 130.27, 132.58, 133.42, 156.23, 168.34, 176.16 ppm. HRMS (ESI): calcd. for $C_{29}H_{39}NNaO_8$ 552.2573 [M + Na]$^+$; found 552.2489.

***N*-(Benzyloxycarbonyl)-β-{1-[4-bis(*tert*-butoxycarbonyl)methyl]-naphthyl}-L-alanine (9b):** Isolated as a white solid (85%). M.p. 94–96 °C. $[\alpha]_D^{20}$ = –10.5 (c = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.50 (s, 18 H, *t*Bu), 3.37–3.78 (m, 2 H, $CH_2\beta$), 4.70–4.90 (m, 1 H, CHα), 5.10 (s, 2 H, CH_2), 5.26 (s, 1 H, CH), 5.30 (d, J = 8 Hz, 1 H, NH), 7.29–8.15 (m, 11 H, aromatic) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.32, 35.18, 56.85, 57.58, 65.98, 82.83, 120.57, 124.14, 125.56, 127.32, 127.87, 129.14, 130.25, 132.59, 133.46, 141.52, 156.34, 168.54, 176.36 ppm. HRMS (ESI): calcd. for $C_{32}H_{37}NaNO_8$ 586.2417 [M + Na]$^+$; found 586.2325.

***N*-(Benzyloxycarbonyl)-β-(1-{4-[2′,2′-bis(*tert*-butoxycarbonyl)-vinyl]}naphthyl)-L-alanine (9d):** Isolated as a white solid (90%). M.p. 93–94 °C. $[\alpha]_D^{20}$ = –10.1 (c = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.34 (s, 9 H, *t*Bu), 1.60 (s, 9 H, *t*Bu), 3.47–3.79 (m, 2 H, $CH_2\beta$), 4.79–4.82 (m, 1 H, CHα), 5.09 (s, 2 H, CH_2), 5.27 (d, J = 8 Hz, 1 H, NH), 7.27–8.06 (m, 11 H, aromatic), 8.24 (s, 1 H, CH) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.40, 35.28, 56.92, 66.12, 82.81, 125.06, 125.25, 125.43, 126.33, 126.46, 126.71, 127.22, 127.84, 129.13, 129.88, 131.82, 132.93, 137.22, 139.68, 141.42, 155.98, 156.31, 165.89, 176.14 ppm. HRMS (ESI): calcd. for $C_{33}H_{37}NNaO_8$ 598.2417 [M + Na]$^+$; found 598.2321.

***N*-(Benzyloxycarbonyl)-β-[1-(4-malonyl)naphthyl]-L-alanine (9B):** Compound **9b** (56.3 mg, 0.1 mmol) was dissolved in dichloromethane (1 mL), TFA (1 mL) was added at 0 °C, and the mixture stirred at the same temperature for 30 min and then at room temperature for 2 h. After solvent removal, the residue was precipitated by addition of diethyl ether to give 42.9 mg of the title compound in 95% yield as a white solid. M.p. 97–99 °C. $[\alpha]_D^{20}$ = –10.8 (c = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 3.37–3.79 (m, 2 H, $CH_2\beta$), 4.70–4.90 (m, 1 H, CHα), 5.10 (s, 2 H, CH_2), 5.28 (s, 1 H, CH), 5.30 (d, J = 8 Hz, 1 H, NH), 7.29–8.15 (m, 11 H, aromatic) ppm. ^{13}C NMR ($CDCl_3$): δ = 35.16, 56.95, 61.12, 65.96, 120.51, 124.18, 125.49, 127.35, 127.89, 129.12, 130.27, 132.53, 133.45, 141.50, 156.31, 171.34, 176.32 ppm. HRMS (ESI): calcd. for $C_{24}H_{21}NNaO_8$ 474.1165 [M + Na]$^+$; found 474.1278.

General Procedure for Hydrogenation and Fmoc Protection: A solution of the *N*-(benzyloxycarbonyl)-4-substituted naphthylalanine (1 mmol) in methanol (10 mL) was hydrogenated in the presence of 10% Pd black (10%) under 1 atm of H_2 at room temperature for 4 h. The catalyst was removed by filtration and the combined organic layers were concentrated to give a white powder sufficiently pure for further use. A mixture of the above product, Fmoc-OSu (1.02 mmol), and $NaHCO_3$ (3 mmol) in dioxane/water (1:1; 16 mL) was stirred at room temperature overnight, then cooled, acidified with 1 N HCl, and extracted twice with ethyl acetate (2×20 mL). The combined extracts were washed with brine, dried with Na_2SO_4, concentrated, and purified by silica gel chromatography (CH_2Cl_2/MeOH = 10:1) to provide the desired compound.

***N*-Fmoc-β-{1-[4-bis(*tert*-butoxycarbonyl)methyl]naphthyl}-L-alanine (9c):** Isolated as a white solid (92%). M.p. 125–128 °C. $[\alpha]_D^{20}$ = –15.2 (c = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.49 (s, 18 H, 2×*t*Bu), 3.51–3.76 (m, 2 H, $CH_2\beta$), 4.21–4.40 (m, 3 H, CH_2-CH), 4.80–4.83 (m, 1 H, CHα), 5.27 (s, 1 H, CH), 5.39 (d, J = 8 Hz, 1 H, NH), 7.31–8.19 (s, 14 H, aromatic) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.30, 35.08, 47.10, 56.82, 57.56, 67.48, 82.87, 120.31, 124.12, 125.58, 126.65, 127.49, 128.07, 128.70, 130.23, 132.56, 133.44, 141.65, 144.21, 156.41, 168.26, 176.16 ppm. HRMS (ESI): calcd. for $C_{39}H_{41}NNaO_8$ 674.2730 [M + Na]$^+$; found 674.2836.

***N*-Fmoc-β-(1-{4-[2′,2′-bis(*tert*-butoxycarbonyl)]ethyl}naphthyl)-L-alanine (9e):** Isolated as a white solid (90%). M.p. 126–128 °C. $[\alpha]_D^{20}$ = –11.3 (c = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.42 (s, 18 H, 2×*t*Bu), 3.30–3.39 [m, 5 H, $CH_2\beta$, CH_2, $CH(CO_2tBu)_2$], 4.10–4.50 (m, 3 H, CH_2-CH), 4.70–4.80 (m, 1 H, CHα), 5.30 (d, J = 8 Hz, 1 H, NH), 7.34–8.24 (m, 14 H, aromatic) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.42, 31.10, 35.05, 47.08, 53.25, 56.80, 67.48, 82.85, 120.51, 124.22, 125.68, 126.63, 127.59, 128.17, 128.75, 132.68, 133.55, 141.68, 144.31, 156.45, 166.64, 176.05 ppm. HRMS (ESI): calcd. for $C_{40}H_{43}NNaO_8$ 688.2886 [M + Na]$^+$; found 688.2929.

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