Synthesis of Novel Amino Acids and Dehydroamino Acids Containing the Benzo[*b*]thiophene Moiety

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Several novel amino acids and dehydroamino acids containing the benzo[*b*]thiophene moiety were prepared by Michael addition or sequential Michael addition and palladium-catalyzed C–C or C–N cross couplings. The substrates for Michael addition were the methyl esters of *N*,*N*-bis(*tert*-butyloxycarbonyl)dehydroalanine [Boc_2–ΔAla–OMe] and *N*-(4-toluenesulfonyl)-*N*-(*tert*-butyloxycarbonyl)dehydroalanine [Tos–ΔAla(*N*-Boc)–OMe], and the nucleophiles were aromatic thiols and 3-iodobenzylamine. The addition of mercaptobenzo[*b*]thiophenes directly to Tos–ΔAla(*N*-Boc)–OMe gave stereoselectively, in good yields, the *E*-isomer of the corresponding dehydrocysteine. When thiophenols and 3-iodobenzylamine were used as nucleophiles the presence of an additional function (halogen or amine) allowed a subsequent palladium-catalyzed cross-coupling reaction with functionalized benzo[*b*]thiophenes (boronic acids, a halogen or an amine). Using this strategy, several racemic amino acid and dehydroamino acid derivatives, which are linked to the benzo[*b*]thiophene moiety by an aromatic spacer, were obtained in good yields.

Introduction

Non-proteinogenic amino acids constitute an important group of compounds in the field of peptide chemistry. These compounds have several applications, either as biologically active substrates or as individual structural components. Among these amino acids are α,β-dehydroamino acids[1] and β-substituted alanines.[2] When inserted into peptides, α,β-dehydroamino acids confer conformational constraints that are important features for studies of structure−activity relationships.

We have developed a highly efficient method for the synthesis of *N*,*N*-diacyldehydroamino acid derivatives from the corresponding β-hydroxyamino acids.[3] These compounds are versatile substrates in Michael addition reactions and allow the preparation of several new β-substituted amino acids as well as β-substituted dehydroamino acids.[4]

The benzo[*b*]thiophenes are important heterocycles, either as biologically active molecules or as electronic or luminescent components used in organic materials.[5] Recently, we reported the synthesis of several sulfur analogues of dehydrotryptophan using Suzuki cross-coupling of β-bromodehydroamino acid derivatives with benzo[*b*]thiophene boronic acids.[6] Here we describe the synthesis of novel amino acids and dehydroamino acids containing the benzo[*b*]thiophene moiety by Michael addition or sequential Michael addition and palladium-catalyzed C−C or C−N cross couplings. The final compounds have the potential for biological activity and for the use as biomarkers because of their expected fluorescence.

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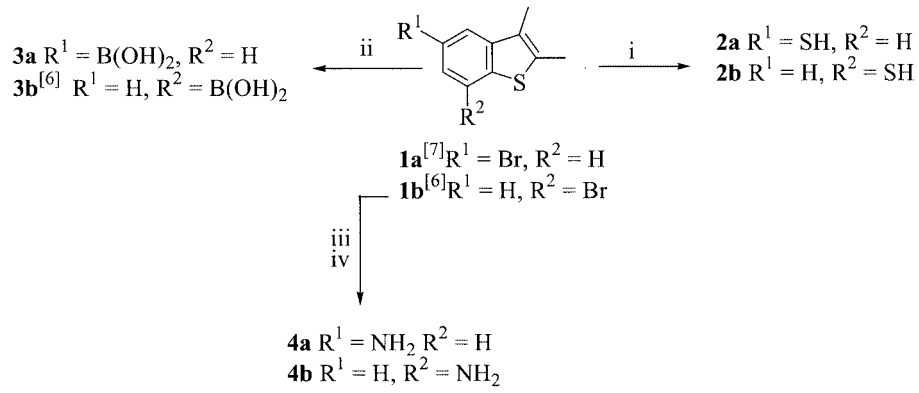
Results and Discussion

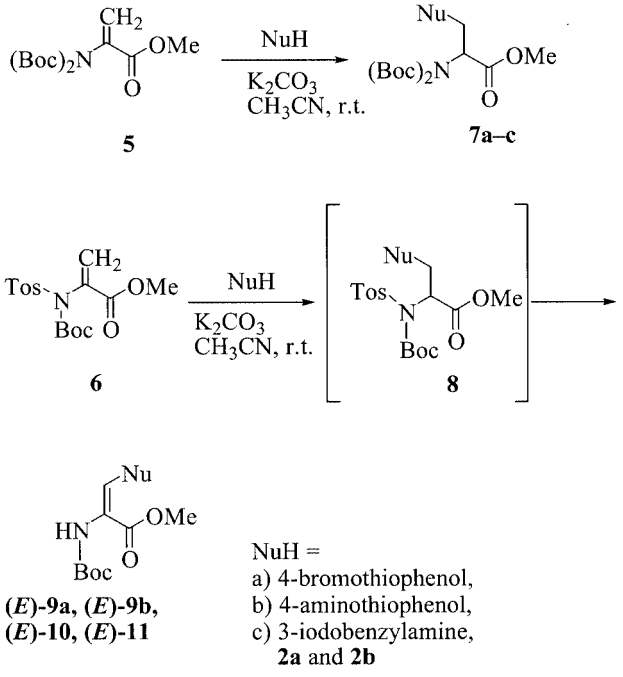
Several 5- and 7-functionalized 2,3-dimethylbenzo[*b*]thiophenes were prepared from the corresponding bromo compounds **1a**[7] and **1b**[6] (Scheme 1). The mercaptobenzo[*b*]-thiophenes **2a** and **2b** were synthesized by halogen−lithium exchange followed by reaction with sulfur, and were used as nucleophiles in Michael addition reactions (Scheme 2, Table 1). The benzo[*b*]thiophene boronic acids **3a** and **3b**[6] were obtained according to a procedure that we have already described.[6] The amines **4a** and **4b** were prepared by palladium-catalyzed C−N cross-coupling of compounds **1a** and **1b**, respectively, with benzophenone imine, followed by hydrolysis of the imino-coupled products.[8] It was possible to obtain the amine **4a** only by using the catalytic system $Pd_2(dba)_3$, BINAP, and CH_3ONa as base,[8a] while compound **4b** was obtained using the more general system, $Pd(OAc)_2$, BINAP, and Cs_2CO_3[8b] (Scheme 1). Both catalytic systems have been applied by us, with no significant differences, to the syntheses of methylated 6-aminobenzo-[*b*]thiophenes.[8c]

Michael addition reactions were performed using the substrates Boc_2−ΔAla-OMe[3] **5** and Tos−ΔAla(*N*-Boc)−OMe[3] **6** and the nucleophiles 4-bromothiophenol,



i. 1. *n*BuLi, ether, 0 °C, 2. 1/8 S_8, 3. H^+
ii. 1. *n*BuLi, ether, 0 °C, 2. $B(OBu)_3$, 3. H^+
iii. $HN{=}C(Ph)_2$, $Pd_2(dba)_3$, BINAP, CH_3ONa for **4a**; $HN{=}C(Ph)_2$, $Pd(OAc)_2$, BINAP, Cs_2CO_3, for **4b**, toluene, 100 °C, Ar
iv. HCl, THF/AcOEt

Scheme 1



NuH =
a) 4-bromothiophenol,
b) 4-aminothiophenol,
c) 3-iodobenzylamine,
2a and **2b**

Scheme 2

4-aminothiophenol, 3-iodobenzylamine, and 7- and 5-mercaptobenzo[*b*]thiophenes **2a** and **2b** (Scheme 2). The Michael adducts **7a** and **7c** were obtained in good to high yields as shown in Table 1. Boc−Ala(*N*-Boc)−β-(4-aminophenylsulfanyl)−OMe **7b** has been described by us previously.[4b]

When compound **6** was used as the substrate, the Michael adducts **8** eliminate the tosyl group spontaneously giving the *E*-isomers, stereoselectively, of the corresponding β-substituted α,β-dehydroamino acids **9a**, **9b**, **10** and **11** (Table 1). With 4-bromothiophenol, we could isolate the intermediate addition product **8a** in high yield (Table 1). Using nucleophiles **b**, **2a** and **2b**, the corresponding intermediates **8** were detected during the course of the reaction by NMR spectroscopy, but were not isolated. The stereochemistry of the products was determined by differential NOE enhancements between the βCH and the αNH protons.

The products obtained from Michael addition reactions, **7a**, **7c**, **8a**, and **(*E*)-9a**, were coupled with several benzo[*b*]thiophene boronic acids under Suzuki cross-coupling conditions in good to high yields (Table 2). With benzo[*b*]thiophene 3-boronic acid as starting material, a 3,3′-benzo[*b*]thiophene dimer was also isolated. Using **3a** or **3b**[6] as coupling components, the corresponding deboronated benzo[*b*]thiophenes were obtained as byproducts and, in the latter case, a small amount of 2,3-dimethyl-7-hydroxybenzo[*b*]thiophene[6,9] was also isolated. After several trial experiments, we established these conditions to be the best for the Suzuki cross-couplings: DME/H_2O (10:1) as solvent and a 30% excess of the boronic acid. As an example, the yield in the synthesis of **(*E*)-15** from **(*E*)-9a** was improved from 34% to 52% by increasing the amount of the boronic acid (from 10% to 30% excess). The latter yield was improved again to 85% by changing the ratio of DME to H_2O from 6:1 to 10:1.

Using compound **8a** in the coupling reaction with benzo[*b*]thiophene 3-boronic acid, elimination of the Tos group occurred, with regeneration of the α,β double bond, giving a mixture of the stereoisomers **(*E*)-15** and **(*Z*)-15** (ratio 4:1), which were separated by column chromatography (Table 2). The stereochemistry of each was determined by NOE experiments in which we found, as we have observed in other cases,[6] that the chemical shift of the OMe signal is higher for the *Z*-isomer (δ = 3.94 vs. 3.82 ppm) than for the *E*-isomer.

On comparing the yields obtained in the syntheses of compounds **12**, **13**, and **14** from compound **7a**, we conclude that the benzo[*b*]thiophene 3-boronic acid is the most reac-

Table 1. Starting materials and yields of products in the Michael addition reactions

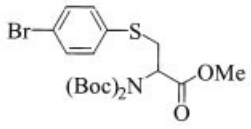
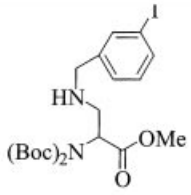
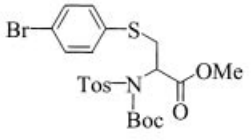
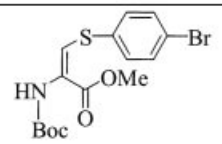
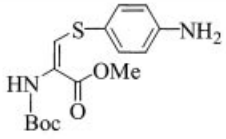
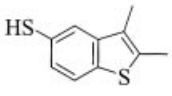
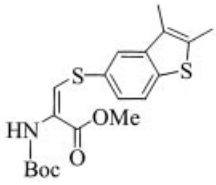
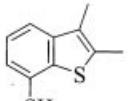
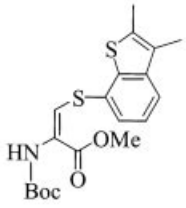
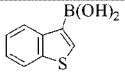
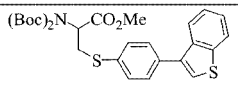
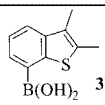
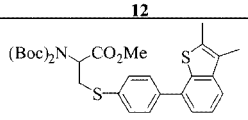
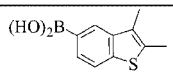
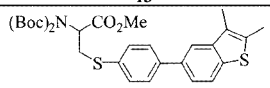
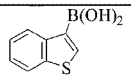
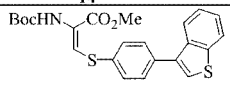
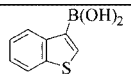
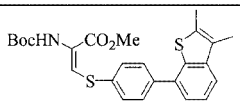
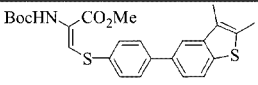
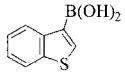
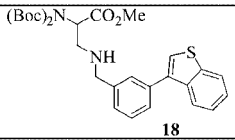
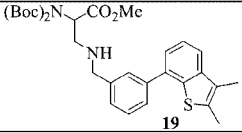
Substrate	NuH	Product	Yield (%)
5	**a**	 **7a**	72
5	**c**	 **7c**	90
6	**a**	 **8a**	85
6	**a**	 **(*E*)-9a**	75
6	**b**	 **(*E*)-9b**	95
6	 **2a**	 **(*E*)-10**	75
6	 **2b**	 **(*E*)-11**	65

Table 2. Starting materials and yields of products in the Suzuki cross-coupling reactions; reaction conditions: Boronic acid (1.3 equiv.), $Pd(PPh_3)_4$ (10 mol %), Na_2CO_3 (2 equiv.), DME/H_2O (10:1), 90 °C; a) boronic acid (1.1 equiv.), DME/H_2O (6:1)

Aa	Benzo[*b*]thiophene	Product	Yield %
7a		 **12**	95
7a	 **3b**	 **13**	72
7a	 **3a**	 **14**	50
(*E*)-9a		 **(*E*)-15**	85
8a		**(*Z*)-15** **(*E*)-15**	12[a] 48
(*E*)-9a	**3b**	 **(*E*)-16**	86
(*E*)-9a	**3a**	 **(*E*)-17**	55
7c		 **18**	71
7c	**3b**	 **19**	50

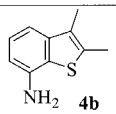
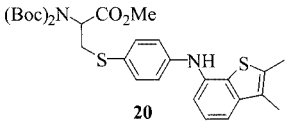
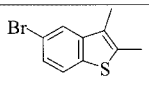
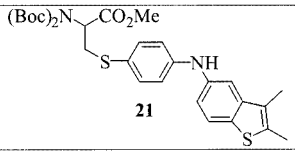
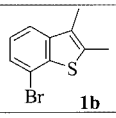
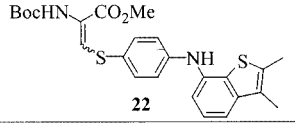
tive one. Some cleavage of the β-C−S bond was observed during the synthesis of **13** and **14** from compound **7a**, with Boc_2−ΔAla−OMe being isolated in 23 and 45%, respectively. In the latter case, the higher percentage of cleavage we observed could be due to the lower reactivity of compound **3a** in the Suzuki coupling.

Compound **3a** was also the least reactive boronic acid when **(*E*)-9a** was used as the starting material, but no difference was observed between the reactivities of **3b** and 3-boronic benzo[*b*]thiophene acid and their corresponding products were obtained in similar yields (Table 2).

Compound **4b** was coupled with the Michael adduct **7a**, which has a bromine atom as an additional function, using Buchwald's C−N cross-coupling conditions[10,11] to give the diarylamine **20** (Table 3). The amine **4a** did not react; instead, it decomposes under the reaction conditions.

The same C−N coupling reactions were performed using bromobenzo[*b*]thiophenes **1a** and **1b** with Michael adducts having a free amino function, **7b**[4b] and **(*E*)-9b**, giving the diarylamines **20**, **21**, and **22** (Table 3). In these cases, an

Table 3. Starting materials and product yields in the C−N cross couplings reactions; reaction conditions: $Pd(OAc)_2$ (10 mol %), BINAP (15 mol %), Cs_2CO_3 (1.4 equiv.), dry toluene, 100 °C under Ar, 5 h. **1a** or **1b** (1.5 equiv.)

Aa	Benzo[*b*]thiophene	Product	Yield %
7a	 **4b**	 **20**	60
7b	 **1a**	 **21**	55
7b	 **1b**	**20**	52
(*E*)-9b	**1b**	 **22**	**(*E*)-22** 35 **(*Z*)-22** 14

excess (1.5 equiv.) of the benzo[*b*]thiophene coupling component was needed to obtain the products in good yields. When compounds **7a** and **7b** were used as starting materials, cleavage of the β-C−S bond occurred to some extent, yielding Boc_2−ΔAla−OMe (≈ 30%).

The C−N coupling reaction of compound **(*E*)-9b** with **1b** gave a mixture (2.5:1) of stereoisomers **(*E*)-22** and **(*Z*)-22** (Table 3), which were separated by column chromatography. The stereochemistry was determined by NOE experiments, with which it was observed again that the chemical shift of the OMe group is higher for the *Z*-isomer (δ = 3.91 vs. 3.77 ppm) than for the *E*-isomer.

It was possible with this strategy to obtain diarylamines, linked to amino acids and dehydroamino acids, that could have interesting applications as biomaterials with electronic properties. These diarylamines are also precursors of thienocarbazoles,[11] bioisosteres of the natural antitumor pyridocarbazoles (ellipticines and olivacines) that intercalate in DNA.

Conclusion

Saturated and unsaturated amino acids having a benzo[*b*]thiophene moiety were obtained in good to high yields either by Michael additions or by sequential Michael addition and palladium catalyzed C−C or C−N cross couplings. The starting materials were functionalized benzo[*b*]thiophenes (Br, $B(OH)_2$, SH, NH_2) and dehydroamino acids or Michael adducts having an additional functionality (Br or NH_2). The final compounds might have biological activity or, when inserted into peptides, might be useful for conformational studies. These compounds might also be used as biomarkers because of their expected fluorescence properties.

Experimental Section

General Remarks: Melting points were determined on a Gallenkamp apparatus and are uncorrected. The ^1H NMR spectra were measured on a Varian Unity Plus spectrometer at 300 MHz. Spin-spin decoupling techniques were used to assign the signals. NOE experiments were performed to determine the stereochemistry of the products. The ^{13}C NMR spectra were measured in the same instrument at 75.4 MHz (using DEPT θ 45°). Elemental analyses were determined on a LECO CHNS 932 elemental analyzer. Mass spectra (EI and FAB) and HRMS were obtained by the mass spectrometry service of University of Vigo, Spain.

Column chromatography was performed on Macherey−Nagel silica gel (230−400 mesh). Petroleum ether refers to that of the boiling range 40−60 °C. When a solvent gradient was used, the increase of polarity was made gradually from neat petroleum ether to mixtures of diethyl ether/petroleum ether, with sequential 10% increases of the proportion of diethyl ether, until the product was isolated.

The benzo[*b*]thiophenes **1a**,[7] **1b**,[6] **3a**, and **3b**[6] were prepared by methods already described by us.[6] Amino acids **5**,[3] **6**,[3] and **7b**[4b] were prepared also according to methods described by us.

General Procedure for the Synthesis of 2a and 2b: A solution of *n*BuLi in hexane (2.5 M, 1.24 mL, 3.10 mol) was added dropwise, under Ar, to a solution of **1a** or **1b** (0.500 g, 2.07 mmol) in dry diethyl ether (10 mL) at 0 °C. The mixture was stirred for 10 min at 0 °C, then sulfur (0.100 g, 3.11 mmol) was added under Ar and the mixture was stirred at room temperature for 2 h. Ice and conc. HCl (1 mL) were added and the mixture was stirred for 15 min. The phases were separated and the aqueous phase was extracted with diethyl ether (2 × 10 mL). The organic extracts were collected, dried ($MgSO_4$), and then the solvent was evaporated to give the products as oils, which were used directly in the Michael additions without further purification. The corresponding Michael adducts were characterized completely.

2,3-Dimethyl-5-mercaptobenzo[*b*]thiophene (2a): 0.350 g (≈ 87%); ^1H NMR ($CDCl_3$): δ = 2.26 (s, 3 H, $ArCH_3$), 2.48 (s, 3 H, $ArCH_3$), 3.60 (s, 1 H, SH), 7.20 (dd, *J* = 8.4, 1.8 Hz, 1 H, 6-H), 7.54 (d, *J* = 1.8 Hz, 1 H, 4-H), 7.61 (d, *J* = 8.4 Hz, 1 H, 7-H) ppm.

2,3-Dimethyl-7-mercaptobenzo[*b*]thiophene (2b): 0.300 g (≈ 72%); ^1H NMR ($CDCl_3$): δ = 2.30 (s, 3 H, $ArCH_3$), 2.52 (s, 3 H, $ArCH_3$), 3.60 (s, 1 H, SH), 7.27−7.30 (m, 2 H, 2 × ArH), 7.44−7.50 (m, 1 H, ArH) ppm.

2,3-Dimethylbenzo[*b*]thiophene 5-Boronic Acid (3a): From compound **1a** (1.50 g, 6.20 mmol), following the method described by us for the synthesis of **3b**,[6] compound **3a** was obtained as a white solid (0.650 g, 50%), m.p. 184.0−186.0 °C. ^1H NMR ([D$_6$]DMSO): δ = 2.28 (s, 3 H, $ArCH_3$), 2.45 (s, 3 H, $ArCH_3$), 7.67 (d, *J* = 8.0 Hz, 1 H, 6- or 7-H), 7.77 (d, *J* = 8.0 Hz, 1 H, 7- or 6-H), 8.05 (br s, 2 H, 2 × OH), 8.11 (s, 1 H, 4-H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 11.1 (CH_3), 13.5 (CH_3), 121.0 (CH), 127.1 (C), 127.5 (CH), 129.2 (CH), 132.7 (C), 139.32 (C), 140.1 (C) ppm.

5-Amino-2,3-dimethylbenzo[*b*]thiophene (4a): A dried Schlenk tube was charged under Ar with dry toluene (4 mL), compound **1a** (500 mg, 2.10 mmol), $Pd_2(dba)_3$ (9.60 mg, 0.011 mmol), BINAP

(13.0 mg, 0.021 mmol), CH_3ONa (170 mg, 3.15 mmol), and benzophenone imine (0.5 mL, 2.95 mmol), and then the mixture was stirred for 21 h at 100 °C. After cooling, diethyl ether (6 mL) was added and the mixture filtered. Removal of the solvents gave an oily yellow solid that after washing with MeOH gave a yellow solid, which corresponded to the imino-coupled product (560 mg), m.p. 158.5−160.2 °C. ^{1}H NMR ($CDCl_3$): δ = 2.14 (s, 3 H, $ArCH_3$), 2.44 (s, 3 H, $ArCH_3$), 6.63 (dd, *J* = 8.4, 2.1 Hz, 1 H, 6-H), 7.03 (d, *J* = 2.1 Hz, 1 H, 4-H), 7.14−7.26 (m, 4 H, ArH), 7.39−7.51 (m, 5 H, ArH), 7.84−7.89 (m, 2 H, ArH). THF (7 mL) and HCl (2 M, 1.5 mL) were added to this solid and the mixture was then stirred overnight. A mixture of EtOAc and hexane (1:2, 3 mL) and HCl (0.5 M, 5 mL) were added and the mixture was stirred for 1 h. The phases were separated and the aqueous phase was basified and then extracted with chloroform (2 × 20 mL). The organic phase was dried and the solvent evaporated to give the amine **4a** as an oil (130 mg, overall yield 35%). ^{1}H NMR ($CDCl_3$): δ = 2.22 (s, 3 H, $ArCH_3$), 2.45 (s, 3 H, $ArCH_3$), 3.65 (br s, 2 H, NH_2), 6.71 (dd, *J* = 8.4, 2.4 Hz, 1 H, 6-H), 6.89 (d, *J* = 2.4 Hz, 1 H, 4-H), 7.50 (d, *J* = 8.4 Hz, 1 H, 7-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.3 (CH_3), 13.8 (CH_3), 106.5 (CH), 113.6 (CH), 122.5 (CH), 126.3 (C), 128.5 (C), 134.6 (C), 142.2 (C), 143.3 (C) ppm. MS (EI): *m*/*z* (%) = 179 (15) [M^+ + 2], 178 (39) [M^+ + 1], 177 (100) [M^+], 176 [M^+ − 1], 162 (65) [M^+ − 15]. HRMS: found (calcd.) for $C_{10}H_{11}NS$ [M^+], 177.0614 (177.0612).

7-Amino-2,3-dimethylbenzo[*b*]thiophene (4b): A dried Schlenk tube was charged under Ar with dry toluene (4 mL), compound **1b** (500 mg, 2.10 mmol), $Pd(OAc)_2$ (19.0 mg, 0.0840 mmol), BINAP (65.0 mg, 0.105 mmol), Cs_2CO_3 (960 mg, 2.94 mmol), and benzophenone imine (0.5 mL, 2.95 mmol), and then the mixture was stirred for 21 h at 100 °C. After cooling, diethyl ether (6 mL) was added and the mixture filtered. Evaporation of the solvents gave an oily yellow solid that after washing with MeOH gave a yellow solid, which corresponded to the imino-coupled product (650 mg), m.p. 109.3−111.6 °C. ^{1}H NMR ($CDCl_3$): δ = 2.28 (s, 3 H, $ArCH_3$), 2.48 (s, 3 H, $ArCH_3$), 6.32 (dd, *J* = 7.5, 0.9 Hz, 1 H, 6-H), 7.05 (t, *J* = 7.5 Hz, 1 H, 4-H), 7.14−7.26 (m, 5 H, ArH), 7.40−7.52 (m, 4 H, ArH), 7.84−7.89 (m, 2 H, Ar-H) ppm. THF (7 mL) and HCl (2 M, 1.5 mL) were added to this solid and the mixture was stirred overnight. A mixture of EtOAc and hexane (1:2, 3 mL) and HCl (0.5 M, 5 mL) were added and the mixture was stirred for 1 h. The phases were separated and the aqueous phase was basified and then extracted with chloroform (2 × 20 mL). The organic phase was dried and the solvent evaporated to give the amine **4b** as a white solid (234 mg, overall yield 63%). Recrystallization from diethyl ether/petroleum ether gave colorless crystals, m.p. 94.0−95.0 °C. ^{1}H NMR ($CDCl_3$): δ = 2.29 (s, 3 H, $ArCH_3$), 2.50 (s, 3 H, $ArCH_3$), 3.80 (br s, 2 H, NH_2), 6.64 (dd, *J* = 7.5, 0.9 Hz, 1 H, 6-H), 7.11 (dd, *J* = 7.5, 0.9 Hz, 1 H, 4-H), 7.22 (t, *J* = 7.5 Hz, 1 H, 5-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.7 (CH_3), 13.9 (CH_3), 109.2 (CH), 112.5 (CH), 124.5 (C), 125.3 (CH), 128.3 (C), 132.6 (C), 140.3 (C), 142.4 (C) ppm. $C_{10}H_{11}NS$ (177.28): calcd. C 67.76, H 6.25, N 7.90, S 18.09; found C 67.56, H 6.30, N 7.94, S 18.05.

General Procedure for Michael Addition of Nucleophiles to Dehydro-Amino Acid Derivatives: As described elsewhere,[4a,4b] K_2CO_3 (6 equiv.) was added to a solution of (unless stated otherwise) the methyl esters of compounds **5**[3] or **6**[3] (3 mmol) in acetonitrile (20 mL), and then the nucleophile (1 equiv.) was added with rapid stirring at room temperature. The reaction was monitored by ^{1}H NMR spectroscopy and then, when no starting material was detected, the solution was filtered and the solvents evaporated under reduced pressure. The residue was chromatographed with a solvent gradient, from petroleum ether to 30% diethyl ether/petroleum ether (unless stated otherwise).

Boc-Ala[*N*-Boc-β-(4-bromophenylsulfanyl)]-OMe (7a): Column chromatography gave product **7a** (1.06 g, 72%) as a white solid. Recrystallization from diethyl ether/*n*-hexane gave colorless crystals, m.p. 64.7−65.4 °C. ^{1}H NMR ($CDCl_3$): δ = 1.47 (s, 18 H, Boc CH_3), 3.46 (dd, *J* = 14.7, 9.9 Hz, 1 H, βCH_2), 3.71 (dd, *J* = 14.7, 4.5 Hz, 1 H, βCH_2), 3.73 (s, 3 H, OCH_3), 5.08 (dd, *J* = 9.9, 4.5 Hz, 1 H, αCH), 7.25 (d, *J* = 8.4 Hz, 2 H, 2 × ArH), 7.40 (d, *J* = 8.4 Hz, 2 H, 2 × ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 27.9 [C(*C*H_3)$_3$], 34.9 (βCH_2), 52.5 (OCH_3), 57.7 (αCH), 83.4 [O*C*(CH_3)$_3$], 120.40 (C), 131.4 (CH), 132.0 (CH), 134.8 (C), 151.8 (C=O), 170.1 (C=O) ppm. $C_{20}H_{28}BrNO_6S$ (490.41): calcd. C 48.98, H 5.75, N 2.86, S 6.54; found C 49.26, H 6.06, N 2.93, S 6.41.

Boc-Ala[*N*-Boc-β-(3-iodobenzylamino)]-OMe (7c): Column chromatography gave product **7c** (1.44 g, 90%) as an oil that failed all attempts to crystallize it. ^{1}H NMR ($CDCl_3$): δ = 1.45 (s, 18 H, CH_3 Boc), 3.40−3.50 (m, 2 H, βCH_2), 3.75 (s, 3 H, OCH_3), 4.27−4.49 (m, 3 H, αCH and CH_2 Bn), 5.54 (d, *J* = 6.3 Hz, 1 H, NH), 7.07 (t, *J* = 7.5 Hz, 1 H, 5-H), 7.18−7.21 (m, 1 H, ArH), 7.59−7.62 (m, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.2 [C(*C*H_3)$_3$], 47.8 (CH_2), 50.5 (CH_2), 52.4 (OCH_3), 52.7 (αCH), 79.7 [O*C*(CH_3)$_3$], 80.7 [O*C*(CH_3)$_3$], 126.2 (CH), 126.8 (CH), 130.2 (CH), 136.1 (C), 136.2 (CH), 140.2 (C), 155.2 (C=O), 156.0 (C=O), 171.0 (C=O) ppm. HMRS: $C_{21}H_{31}IN_2O_6$ [M + H]$^+$, found (calcd.) 535.1329 (535.1305).

Tos-Ala[*N*-Boc-β-(4-bromophenylsulfanyl)]-OMe (8a): The procedure described above was followed using compound **6** (1.50 mmol). Column chromatography gave product **8a** (0.690 g, 85%) as a white solid. Recrystallization from petroleum ether gave colorless crystals, m.p. 70.8−72.6 °C. ^{1}H NMR ($CDCl_3$): δ = 1.28 (s, 9 H, Boc CH_3), 2.45 (s, 3 H, Tos CH_3), 3.48 (dd, *J* = 14.7, 9.3 Hz, 1 H, βCH_2), 3.75 (s, 3 H, OCH_3), 3.83 (dd, *J* = 14.7, 4.5 Hz, 1 H, βCH_2), 5.22 (dd, *J* = 9.3, 4.5 Hz, 1 H, αCH), 7.26−7.45 (m, 6 H, ArH) 7.93 (d, *J* = 8.4 Hz, 2 H, 2 × ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.4 (CH_3), 27.5 [C(*C*H_3)$_3$], 35.0 (βCH_2), 52.6 (OCH_3), 58.5 (αCH), 85.2 [O*C*(CH_3)$_3$], 120.5 (C), 128.6 (CH), 128.8 (CH), 131.8 (CH), 131.8 (CH), 134.3 (C), 136.2 (C), 144.3 (C), 149.7 (C=O), 169.1 (C=O) ppm. $C_{22}H_{26}BrNO_6S_2$ (544.49): calcd. C 48.53, H 4.81, N 2.57, S 11.78; found C 48.86, H 4.69, N 2.65, S 11.48.

Boc-(*E*)-ΔAla[β-(4-bromophenylsulfanyl)]-OMe [(*E*)-9a]: The procedure described above was followed using compound **6** (2.58 mmol, 0.920 g). Column chromatography gave product **(*E*)-9a** (0.750 g, 75%) as a white solid. Recrystallization from diethyl ether/petroleum ether gave colorless crystals, m.p. 115.7−116.7 °C. ^{1}H NMR ($CDCl_3$): δ = 1.51 (s, 9 H, Boc CH_3), 3.80 (s, 3 H, OCH_3), 6.35 (br s, 1 H, αNH), 7.33 (d, *J* = 8.4 Hz, 2 H, 2 × ArH), 7.34 (s, 1 H, βCH), 7.49 (d, *J* = 8.4 Hz, 2 H, 2 × ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.1 [C(*C*H_3)$_3$], 52.6 (OCH_3), 81.2 [O*C*(CH_3)$_3$], 122.3 (C), 122.9 (C), 128.3 (CH), 132.4 (CH), 133.7 (C), 152.4 (C=O), 163.5 (C=O) ppm. $C_{15}H_{18}BrNSO_4$ (388.28): calcd. C 46.40, H 4.67, N 3.61, S 8.26; found C 46.28, H 4.77, N 3.62, S 8.28.

Boc-(*E*)-ΔAla[β-(4-aminophenylsulfanyl)]-OMe [(*E*)-9b]: Column chromatography using diethyl ether gave product **(*E*)-9b** (0.924 g, 95%) as a light-yellow solid. Recrystallization from diethyl ether/petroleum ether gave light-yellow crystals, m.p. 123.4−125.1 °C. ^{1}H NMR ($CDCl_3$) : δ = 1.51 (s, 9 H, CH_3 Boc), 3.75 (s, 3 H, OCH_3), 3.83 (br s, 2 H, NH_2), 6.16 (br s, 1 H, αNH), 6.65 (d, *J* = 8.7 Hz,

2 H, 2 × ArH), 7.29 (d, J = 8.7 Hz, 2 H, 2 × ArH), 7.36 (s, 1 H, βCH) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.2 [C(CH_3)$_3$], 52.3 (OCH_3), 80.9 [OC(CH_3)$_3$], 115.6 (CH), 120.68 (C), 121.2 (C), 133.9 (CH), 138.0 (CH), 147.2 (C), 152.5 (C=O), 163.5 (C=O) ppm. $C_{15}H_{20}N_2O_4S$ (324.40): calcd. C 55.54, H 6.21, N 8.64, S 9.88; found C 55.55, H 6.36, N 8.47, S 9.71.

Boc-ΔAla[β-(2,3-dimethylbenzo[*b*]thienyl-5-sulfanyl)]-OMe [(*E*)-10]: The procedure described above was followed using compound **6** (0.500 mmol, 0.180 g). Column chromatography gave product **(*E*)-10** (0.140 g, 65%) as a white solid. Recrystallization from diethyl ether/*n*-hexane gave colorless crystals, m.p. 120.9−122.5 °C. ^{1}H NMR ($CDCl_3$): δ = 1.53 (s, 9 H, Boc CH_3), 2.29 (s, 3 H, $ArCH_3$), 2.50 (s, 3 H, $ArCH_3$), 3.77 (s, 3 H, OCH_3), 6.27 (br s, 1 H, αNH), 7.37 (dd, J = 6.9, 1.5 Hz, 1 H, 6-H), 7.47 (s, 1 H, βCH), 7.71−7.74 (m, 2 H, 4-H and 7-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.3 (CH_3), 13.9 (CH_3), 28.2 [C(CH_3)$_3$], 52.4 (OCH_3), 81.0 [OC(CH_3)$_3$], 121.5 (C), 122.8 (CH), 124.7 (CH), 126.7 (CH), 126.9 (C), 129.2 (C), 135.7 (C), 136.1 (CH), 138.3 (C), 141.7 (C), 152.5 (C=O), 163.6 (C=O) ppm. $C_{19}H_{23}NO_4S_2$ (393.52): calcd. C 57.99, H 5.88, N 3.56, S 16.30; found C 58.17, H 5.97, N 3.59, S 15.90.

Boc-ΔAla[β-(2,3-dimethylbenzo[*b*]thienyl-7-sulfanyl)]-OMe [(*E*)-11]: The procedure described above was followed using compound **6** (1.20 mmol, 0.430 g). Column chromatography gave product **(*E*)-11** (0.360 g, 75%) as a white solid. Recrystallization from diethyl ether/*n*-hexane gave colorless crystals, m.p. 103.4−104.9 °C. ^{1}H NMR ($CDCl_3$): δ = 1.54 (s, 9 H, Boc CH_3), 2.31 (s, 3 H, $ArCH_3$), 2.50 (s, 3 H, $ArCH_3$), 3.74 (s, 3 H, OCH_3), 6.28 (br s, 1 H, αNH), 7.36 (s, 1 H, βCH), 7.38 (t, J = 7.5 Hz, 1 H, 5-H), 7.46 (dd, J = 7.5, 1.2 Hz, 1 H, 4-H or 6-H), 7.60 (dd, J = 7.5, 1.2 Hz, 1 H, 4-H or 6-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.6 (CH_3), 13.8 (CH_3), 28.2 [C(CH_3)$_3$], 52.4 (OCH_3), 81.1 [OC(CH_3)$_3$], 121.8 (CH), 122.8 (C), 124.8 (CH), 126.1 (C), 127.9 (C), 128.0 (CH), 133.9 (CH), 135.4 (C), 141.7 (C), 142.0 (C), 152.5 (C=O), 163.5 (C=O) ppm. $C_{19}H_{23}NS_2O_4$ (393.52): calcd. C 57.99, H 5.88, N 3.56, S 16.30; found C 57.97, H 6.04, N 3.58, S 15.95.

General Procedure for the Suzuki Reaction: Compounds **7a**, **7c**, **8a**, and **(*E*)-9a** were coupled with several boronic acids (Table 2) (1.3 equiv.) using $Pd(PPh_3)_4$ (10 mol %) and Na_2CO_3 (2 equiv.) in DME/water (10:1) at 90 °C. The reactions were monitored by TLC, which determined the different reaction times. After cooling, water and ethyl acetate were added and then the phases were separated. The organic phase was washed with brine, dried ($MgSO_4$), filtered, and the solvent was evaporated to give a brown oil that was subjected to column chromatography.

Boc-Ala{*N*-Boc-β-[4-(benzo[*b*]thien-3-yl)phenylsulfanyl]}-OMe (12): The procedure described above was followed using compound **7a** (0.500 mmol, 0.250 g) and heating for 2 h 30 min. Column chromatography using a solvent gradient, from neat petroleum ether to 20% diethyl ether/petroleum ether, gave product **12** as a white solid (0.260 g, 95%). Recrystallization from diethyl ether/*n*-hexane gave colorless crystals, m.p. 110.0−110.8 °C. ^{1}H NMR ($CDCl_3$): δ = 1.48 (s, 18 H, Boc CH_3), 3.54 (dd, J = 14.4, 9.9 Hz, 1 H, βCH$_2$), 3.76 (s, 3 H, OCH_3), 3.82 (dd, J = 14.4, 4.5 Hz, 1 H, βCH$_2$), 5.18 (dd, J = 9.9, 4.5 Hz, 1 H, αCH), 7.38−7.42 (m, 3 H, ArH), 7.48−7.55 (m, 4 H, ArH), 7.87−7.95 (m, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 27.9 [C(CH_3)$_3$], 34.8 (βCH$_2$), 52.5 (OCH_3), 57.8 (αCH), 83.4 [OC(CH_3)$_3$], 122.8 (CH), 122.9 (CH), 123.4 (CH), 124.4 (CH), 124.4 (CH), 129.2 (CH), 130.0 (CH), 134.2 (C), 135.0 (C), 137.3 (C), 137.7 (C), 140.6 (C), 151.8 (C=O), 170.2 (C=O) ppm. $C_{28}H_{33}NO_6S_2$ (543.71): calcd. C 61.83, H 6.12, N 2.58, S 11.79; found C 62.11, H 6.27, N 2.57, S 11.72.

Boc-Ala{*N*-Boc-β-[4-(2,3-dimethylbenzo[*b*]thien-7-yl)-phenylsulfanyl]}-OMe (13): The procedure described above was followed using compound **7a** (0.500 mmol, 0.250 g), with heating for 5 h. Column chromatography using a solvent gradient, from neat petroleum ether to 20% diethyl ether/petroleum ether, gave product **13** as a white solid (0.210 g, 72%). Recrystallization from petroleum ether gave colorless crystals, m.p. 79.5−80.7 °C. ^{1}H NMR ($CDCl_3$): δ = 1.48 (s, 18 H, Boc CH_3), 2.34 (s, 3 H, $ArCH_3$), 2.49 (s, 3 H, $ArCH_3$), 3.54 (dd, J = 14.6, 9.9 Hz, 1 H, βCH$_2$), 3.76 (s, 3 H, OCH_3), 3.82 (dd, J = 14.6, 4.5 Hz, 1 H, βCH$_2$), 5.19 (dd, J = 9.9, 4.5 Hz, 1 H, αCH), 7.27 (dd, J = 7.4, 1.2 Hz, 1 H, 4′ or 6′-H), 7.41−7.49 (m, 3 H, 2 × ArH and 5′-H), 7.58 (dd, J = 8.0, 1.2 Hz, 1 H, 6′ or 4′-H), 7.64 (d, J = 8.4 Hz, 2 H, 2 × ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.5 (CH_3), 13.6 (CH_3), 27.9 [C(CH_3)$_3$], 34.6 (βCH$_2$), 52.4 (OCH_3), 57.8 (αCH), 83.4 [OC(CH_3)$_3$], 120.2 (CH), 123.5 (CH), 124.6 (CH), 127.4 (C), 128.8 (CH), 129.5 (CH), 134.2 (C), 135.3 (C), 135.3 (C), 136.8 (C), 138.9 (C), 141.7 (C), 151.8 (C=O), 170.2 (C=O) ppm. $C_{30}H_{37}NO_6S_2$ (571.76): calcd. C 63.02, H 6.52, N 2.45, S 11.21; found C 63.23, H 6.66, N 2.49, S 10.98.

Boc-Ala{*N*-Boc-β-[4-(2,3-dimethylbenzo[*b*]thien-5-yl)-phenylsulfanyl]}-OMe (14): The procedure described above was followed using compound **7a** (0.39 mmol, 0.190 g) with heating for 5 h. Column chromatography using a solvent gradient, from neat petroleum ether to 20% diethyl ether/petroleum ether, gave product **14** as a white solid (0.110 g, 50%). Recrystallization from diethyl ether gave colorless crystals, m.p. 175.2−177.2 °C. ^{1}H NMR ($CDCl_3$): δ = 1.48 (s, 18 H, Boc CH_3), 2.35 (s, 3 H, $ArCH_3$), 2.52 (s, 3 H, $ArCH_3$), 3.48−3.53 (m, 1 H, βCH$_2$), 3.75−3.82 (m, 4 H, βCH$_2$ and OCH_3), 5.16 (dd, J = 9.8, 4.2 Hz, 1 H, αCH), 7.45−7.50 (m, 3 H, 2 × ArH and 6′-H), 7.59 (d, J = 8.4 Hz, 2 H 2 × ArH), 7.73 (d, J = 1.5 Hz, 1 H, 4′-H), 7.79 (d, J = 8.4 Hz, 1 H, 7′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.4 (CH_3), 13.9 (CH_3), 27.9 [C(CH_3)$_3$], 35.2 (βCH$_2$), 52.5 (OCH_3), 57.9 (αCH), 83.3 [OC(CH_3)$_3$], 119.4 (CH), 122.3 (CH), 122.7 (CH), 127.2 (C), 127.9 (CH), 130.4 (CH), 134.3 (C), 134.7 (C), 136.5 (C), 137.3 (C), 140.1 (C), 141.6 (C), 151.9 (C=O), 170.3 (C=O) ppm. $C_{30}H_{37}NO_6S_2$ (571.76): calcd. C 63.02, H 6.52, N 2.45, S 11.21; found C 62.71, H 6.55, N 2.50, S 11.15.

Boc-(*E*)-ΔAla{β-[4-(benzo[*b*]thien-3-yl)phenylsulfanyl]}-OMe [(*E*)-15]: The procedure described above was followed using compound **(*E*)-9a** (0.390 mmol, 0.150 g) with heating for 4 h. Column chromatography using a solvent gradient, from neat petroleum ether to 20% diethyl ether/petroleum ether, gave product **(*E*)-15** (0.150 g, 85%) as a white solid. Recrystallization from diethyl ether/*n*-hexane gave colorless crystals, m.p. 98.9−100.0 °C. ^{1}H NMR ($CDCl_3$): δ = 1.54 (s, 9 H, Boc CH_3), 3.82 (s, 3 H, OCH_3), 6.36 (br s, 1 H, αNH), 7.40−7.44 (m, 3 H, ArH), 7.51 (s, 1 H, βCH), 7.60 (br s, 4 H, ArH) 7.89−7.96 (m, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.2 [C(CH_3)$_3$], 52.5 (OCH_3), 81.1 [OC(CH_3)$_3$], 122.6 (CH), 123.0 (CH), 124.0 (CH), 124.5 (CH), 124.5 (CH), 129.4 (CH), 131.2 (CH), 133.6 (C), 135.8 (C), 136.8 (C), 137.5 (C), 140.7 (C), 152.4 (C=O), 163.6 (C=O) ppm. $C_{23}H_{23}NO_4S_2$ (441.58): calcd. C 62.56, H 5.25, N 3.17, S 14.52; found C 62.20, H 5.35, N 3.07, S 14.57.

Boc-(*E*)-ΔAla{β-[4-(benzo[*b*]thien-3-yl)phenylsulfanyl]}-OMe [(*E*)-15] and Boc-(*Z*)-ΔAla{β-[4-(benzo[*b*]thien-3-yl)phenylsulfanyl]}-OMe [(*Z*)-15]: The procedure described above was followed using compound **8a** (0.500 mmol, 0.270 g) and benzo[*b*]thiophene 3-boronic acid (1.1 equiv.) in DME/H_2O (6:1), with heating for 5 h. Column chromatography using a solvent gradient, from neat petroleum ether to 10% diethyl ether/petroleum ether, gave compound **(*Z*)-15** (0.0260 g, 12%), as an oil, as the less-polar product {^{1}H NMR ($CDCl_3$): δ = 1.49 (s, 9 H, Boc CH_3), 3.94 (s, 3 H, OCH_3),

6.80 (br s, 1 H, αNH), 7.40−7.43 (m, 3 H, ArH), 7.59 (d, J = 8.7 Hz, 2 H, 2 × ArH), 7.64 (d, J = 8.7 Hz, 2 H, 2 × ArH), 7.90−7.97 (m, 2 H, ArH), 8.07 (br s, 1 H, βCH) ppm} followed by **(*E*)-15** as a white solid (0.110 g, 48%) with spectroscopic data identical to those described above.

Boc-(*E*)-ΔAla{β-[4-(2,3-dimethylbenzo[*b*]thien-7-yl)phenylsulfanyl]}-OMe [(*E*)-16]: The procedure described above was followed using compound **(*E*)-9a** (0.390 mmol, 0.150 g) with heating for 4 h. Column chromatography using a solvent gradient, from neat petroleum ether to 30% diethyl ether/petroleum ether, gave product **(*E*)-16** as a white solid (0.160 g, 86%). Recrystallization from diethyl ether/petroleum ether gave colorless crystals, m.p. 133.7−134.4 °C. ^{1}H NMR ($CDCl_3$): δ = 1.54 (s, 9 H, Boc CH_3), 2.35 (s, 3 H, $ArCH_3$), 2.50 (s, 3 H, $ArCH_3$), 3.82 (s, 3 H, OCH_3), 6.31 (br s, 1 H, αNH), 7.30 (dd, J = 7.5, 0.9 Hz, 1 H, 4′-H or 6′-H), 7.46 (t, J = 7.5 Hz, 1 H, 5′-H), 7.53 (s, 1 H, βCH), 7.57−7.62 (m, 3 H, 2 × ArH and 6′-H or 4′-H), 7.72 (d, J = 8.1 Hz, 2 H, 2 × ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.5 (CH_3), 13.7 (CH_3), 28.2 [C(CH_3)$_3$], 52.5 (OCH_3), 81.1 [OC(CH_3)$_3$], 120.5 (CH), 123.6 (CH), 124.7 (CH), 127.5 (C), 129.0 (CH), 131.1 (CH), 133.7 (CH), 134.3 (C), 134.9 (C), 136.7 (C), 140.7 (C), 141.8 (C), 152.5 (C=O), 163.6 (C=O) ppm. $C_{25}H_{27}NO_4S_2$ (469.63): calcd. C 63.94, H 5.79, N 2.98, S 13.65; found C 63.78, H 5.87, N 3.06, S 13.45.

Boc-(*E*)-ΔAla{β-[4-(2,3-dimethylbenzo[*b*]thien-5-yl)phenylsulfanyl]}-OMe [(*E*)-17]: The procedure described above was followed using compound **(*E*)-9a** (0.390 mmol, 0.150 g), with heating for 7 h. Column chromatography using a solvent gradient, from neat petroleum ether to 30% diethyl ether/petroleum ether, gave product **(*E*)-17** (0.100 g, 55%) as a white solid. Recrystallization from diethyl ether/petroleum ether gave colorless crystals, m.p. 75.0−76.2 °C. ^{1}H NMR ($CDCl_3$): δ = 1.53 (s, 9 H, Boc CH_3), 2.35 (s, 3 H, $ArCH_3$), 2.52 (s, 3 H, $ArCH_3$), 3.81 (s, 3 H, OCH_3), 6.32 (br s, 1 H, αNH), 7.49 (dd, J = 8.1, 1.2 Hz, 1 H, 6′-H), 7.50 (s, 1 H, βCH), 7.57 (d, J = 8.4 Hz, 2 H, 2 × ArH), 7.67 (d, J = 8.4 Hz, 2 H, 2 × ArH), 7.76 (d, J = 1.2 Hz, 1 H, 4′-H), 7.81 (dd, J = 8.1, 1.2 Hz, 1 H, 7′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.4 (CH_3), 13.9 (CH_3), 28.2 [C(CH_3)$_3$], 52.5 (OCH_3), 81.1 [OC(CH_3)$_3$], 119.5 (CH), 122.3 (CH), 122.7 (CH), 127.2 (C), 128.2 (CH), 131.4 (CH), 132.9 (C), 134.2 (CH), 134.8 (C), 136.0 (C), 137.6 (C), 141.5 (C), 141.6 (C), 152.5 (C=O), 163.6 (C=O) ppm. $C_{25}H_{27}NO_4S_2$ (469.63): calcd. C 63.94, H 5.79, N 2.98, S 13.65; found C 63.56, H 5.90, N 3.04, S 13.68.

Boc-Ala{*N*-Boc-β-[3-(benzo[*b*]thien-3-yl)benzylamino]}-OMe (18): The procedure described above was followed using compound **7c** (0.280 mmol, 0.150 g) with heating for 7 h. Column chromatography using a solvent gradient, from neat petroleum ether to 30% diethyl ether/petroleum ether, gave product **18** (0.110 g, 71%) as an oil, which failed all attempts to crystallize it. ^{1}H NMR ($CDCl_3$): δ = 1.44 (s, 18 H, Boc CH_3), 3.42−3.56 (m, 2 H, βCH$_2$), 3.73 (s, 3 H, OCH_3), 4.40−4.72 (m, 3 H, αCH and CH_2), 5.61 (br s, 1 H, NH), 7.36−7.54 (m, 7 H, ArH), 7.86−7.97 (m, 2 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.2 [C(CH_3)$_3$], 47.5 (CH_2), 51.0 (CH_2), 52.4 (OCH_3), 52.8 (αCH), 80.6 [OC(CH_3)$_3$], 122.7 (CH), 122.8 (CH), 123.5 (CH), 124.3 (CH), 124.4 (CH), 126.3 (CH), 127.7 (CH), 129.0 (CH), 136.2 (C), 137.6 (C), 138.0 (C), 138.4 (C), 140.6 (C), 155.3 (C=O), 171.4 (C=O) ppm. $C_{29}H_{36}N_2O_6S$ HMRS (FAB) [M + H]$^+$ found (calcd.) 541.2386 (541.2372).

Boc-Ala{*N*-Boc-β-[3-(2,3-dimethylbenzo[*b*]thien-7-yl)benzylamino]}-OMe (19): The procedure described above was followed using compound **7c** (0.300 mmol, 0.160 g) with heating for 7 h. Column chromatography using a solvent gradient, from neat petroleum ether to 30% diethyl ether/petroleum ether, gave product **19** (0.090 g, 50%) as a light-yellow oil, which failed all attempts to crystallize it. ^{1}H NMR ($CDCl_3$): δ = 1.44 (s, 18 H, $ArCH_3$, Boc), 2.34 (s, 3 H, $ArCH_3$), 2.48 (s, 3 H, $ArCH_3$), 3.40−3.58 (m, 2 H, βCH$_2$), 3.73 (s, 3 H, OCH_3), 4.38−4.76 (m, 3 H, αCH and CH_2), 5.64 (br d, 1 H, J = 6.6 Hz, NH), 7.22−7.34 (m, 2 H, ArH), 7.41−7.49 (m, 2 H, ArH), 7.55−7.65 (m, 3 H, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.5 (CH_3), 13.6 (CH_3), 28.3 [C(CH_3)$_3$], 47.5 (CH_2), 51.0 (CH_2), 52.5 (OCH_3), 52.9 (αCH), 80.6 [OC(CH_3)$_3$], 120.2 (CH), 123.6 (CH), 124.6 (CH), 126.6 (CH), 126.9 (CH), 127.2 (CH), 128.9 (CH), 134.1 (C), 135.1 (C), 135.7 (C), 136.8 (C), 138.3 (C), 141.2 (C), 141.7 (C), 155.4 (C=O), 171.5 (C=O) ppm. $C_{31}H_{40}N_2O_6S$ HMRS (FAB) [M + H]$^+$ found (calcd.) 569.2677 (569.2685).

General Procedure for C−N Coupling: A dried Schlenk tube was charged under Ar with dry toluene (2 mL), the bromo compound was added and the mixture heated for 10 min at 80 °C. $Pd(OAc)_2$ (10 mol %), BINAP (15 mol %), and Cs_2CO_3 (1.4 equiv.) were added and the mixture was heated for another 10 min at 80 °C. The amine was added in dry toluene (2 mL) and the mixture was heated with stirring at 100 °C under Ar for ca. 5 h (Table 3). The reactions were monitored by TLC and stopped when no amino acid seemed to be present. Water and diethyl ether were added, the phases were separated, and then the aqueous phase was washed with diethyl ether (3 × 10 mL). The organic phase was collected, dried ($MgSO_4$), filtered, and then the solvent was evaporated to give a brown oil, which was subjected to column chromatography after traces of toluene were evaporated using MeOH. Solvent gradient was used from neat petroleum to 30% diethyl ether/petroleum ether.

Boc-Ala{*N*-Boc-β-[4-amino-(2,3-dimethylbenzo[*b*]thien-7-yl)-phenylsulfanyl]}-OMe (20): The procedure described above was followed using compound **7a** (0.400 mmol, 0.200 g) and amine **4b** (1 equiv.). Column chromatography gave product **20** as a light-yellow solid (0.140 g, 60%). Recrystallization from diethyl ether/petroleum ether gave light-yellow crystals, m.p. 97.8−99.7 °C. ^{1}H NMR ($CDCl_3$): δ = 1.49 (s, 18 H, Boc CH_3), 2.31 (s, 3 H, $ArCH_3$), 2.49 (s, 3 H, $ArCH_3$), 3.38 (dd, J = 14.4, 9.9 Hz, 1 H, βCH$_2$), 3.63 (dd, J = 14.4, 4.5 Hz, 1 H, βCH$_2$), 3.72 (s, 3 H, OCH_3), 5.09 (dd, J = 9.9, 4.5 Hz, 1 H, αCH), 5.61 (br s, 1 H, NH), 6.95 (d, J = 8.7 Hz, 2 H, 2 × ArH), 7.14−7.18 (m, 1 H, 6′-H), 7.29−7.32 (m, 2 H, 4′ and 5′-H), 7.36 (d, J = 8.7 Hz, 2 H, 2 × ArH) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.6 (CH_3), 13.8 (CH_3), 27.9 [C(CH_3)$_3$], 37.1 (βCH$_2$), 52.3 (OCH_3), 57.9 (αCH), 83.2 [OC(CH_3)$_3$], 113.5 (CH), 115.9 (CH), 117.8 (CH), 124.9 (CH), 125.4 (C), 128.1 (C), 130.2 (C), 133.1 (C), 133.5 (CH), 136.4 (C), 142.7 (C), 142.9 (C), 151.9 (C=O), 170.3 (C=O) ppm. $C_{30}H_{38}N_2O_6S_2$ (586.78): calcd. C 61.41, H 6.53, N 4.77, S 10.93; found C 61.35, H 6.51, N 4.72, S 10.40.

Compound **20** was also obtained following the same procedure by using compound **7b** (0.380 mmol, 0.160 g) and **1b** (1.5 equiv.). Column chromatography gave product **20** as a light-yellow solid (0.120 g, 52%) which displayed identical spectroscopic data to those described above.

Boc-Ala{*N*-Boc-β-[4-amino-(2,3-dimethylbenzo[*b*]thien-5-yl)-phenylsulfanyl]}-OMe (21): The procedure described above was followed using compound **7b** (0.500 mmol, 0.210 g) and **1a** (1.5 equiv.). Column chromatography gave product **21** as a light-brown solid (0.160 g, 55%). Recrystallization from diethyl ether/petroleum ether gave beige crystals, m.p. 98.8−100.5 °C. ^{1}H NMR ($CDCl_3$): δ = 1.50 (s, 18 H, Boc CH_3), 2.24 (s, 3 H, $ArCH_3$), 2.48 (s, 3 H, $ArCH_3$), 3.37 (dd, J = 14.4, 9.9 Hz, 1 H, βCH$_2$), 3.61 (dd, J = 14.4, 4.5 Hz, 1 H, βCH$_2$), 3.71 (s, 3 H, OCH_3), 5.08 (dd, J = 9.9, 4.5 Hz, 1 H, αCH), 5.78 (br s, 1 H, NH), 6.96 (d, J = 8.7 Hz, 2 H, 2 × ArH), 7.05 (dd, J = 8.4, 1.8 Hz, 1 H, 6′-H), 7.32 (d, J =

1.8 Hz, 1 H, 4′-H), 7.35 (d, J = 8.7 Hz, 2 H, 2 × ArH), 7.63 (d, J = 8.4 Hz, 1 H, 7′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.4 (CH_3), 13.9 (CH_3), 27.9 [C(CH_3)$_3$], 37.3 (βCH_2), 52.4 (OCH_3), 57.9 (αCH), 83.2 [OC(CH_3)$_3$], 111.8 (CH), 116.6 (CH), 117.5 (CH), 122.6 (CH), 124.4 (C), 126.7 (C), 132.0 (C), 133.9 (CH), 135.0 (C), 138.7 (C), 142.1 (C), 144.2 (C), 152.0 (C=O), 170.4 (C=O) ppm. $C_{30}H_{38}N_2O_6S_2$ (586.78): calcd. C 61.41, H 6.53, N 4.77, S 10.93; found C 61.57, H 6.69, N 4.84, S 10.58.

Boc-(*E*)-ΔAla{β-[4-amino(2,3-dimethylbenzo[*b*]thien-7-yl)-phenylsulfanyl]}-OMe [(*E*)-22] and Boc-(*Z*)-ΔAla{β[-4-amino(2,3-dimethylbenzo[*b*]thien-7-yl)phenylsulfanyl]}-OMe [(*Z*)-22]: The procedure described above was followed using compound **(*E*)-9b** (0.310 mmol, 0.100 g) and **1b** (1.5 equiv.). Column chromatography gave **(*Z*)-22** as a light-yellow solid (0.200 g, 14%) as the less-polar product. Recrystallization from diethyl ether/petroleum ether gave light-yellow crystals, m.p. 133.4−134.4 °C. ^{1}H NMR ($CDCl_3$): δ = 1.47 (s, 9 H, Boc CH_3), 2.32 (s, 3 H, ArCH_3), 2.50 (s, 3 H, ArCH_3), 3.91 (s, 3 H, OCH_3), 5.71 (br s, 1 H, NH), 6.68 (br s, 1 H, αNH), 6.98 (d, J = 8.7 Hz, 2 H, 2 × ArH), 7.19−7.23 (m, 1 H, 6′-H), 7.30−7.38 (m, 2 H, 5′ and 4′-H), 6.98 (d, J = 8.7 Hz, 2 H, 2 × ArH), 7.41 (d, J = 8.7 Hz, 2 H, 2 × ArH), 7.87 (br s, 1 H, βCH) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.7 (CH_3), 13.9 (CH_3), 28.3 [C(CH_3)$_3$], 52.4 (OCH_3), 80.5 [OC(CH_3)$_3$], 114.3 (CH), 116.3 (CH), 117.6 (CH), 118.6 (C), 125.0 (CH), 126.4 (C), 128.2 (C), 132.9 (CH), 133.3 (C), 136.1 (C), 142.8 (C), 143.7 (C), 152.9 (C=O), 163.6 (C=O) ppm. $C_{25}H_{28}N_2O_4S_2$ (484.65): calcd. C 61.96, H 5.82, N 5.78, S 13.23; found C 61.90, H 6.12, N 5.64, S 12.81. Product **(*E*)-22** eluted next and was isolated as a white solid (0.500 g, 35%). Recrystallization from ethyl acetate/diethyl ether gave colorless crystals, m.p. 192.8−194.3 °C. ^{1}H NMR ($CDCl_3$): δ = 1.52 (s, 9 H, Boc CH_3), 2.32 (s, 3 H, ArCH_3), 2.50 (s, 3 H, ArCH_3), 3.77 (s, 3 H, OCH_3), 5.71 (br s, 1 H, NH), 6.20 (br s, 1 H, αNH), 6.96 (d, J = 8.7 Hz, 2 H, 2 × ArH), 7.20 (dd, J = 6.9, 1.8 Hz, 1 H, 6′-H), 7.30−7.40 (m, 5 H, βCH, 2 × ArH, 4′ and 5′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 11.6 (CH_3), 13.8 (CH_3), 28.1 [C(CH_3)$_3$], 52.3 (OCH_3), 80.9 [OC(CH_3)$_3$], 114.8 (CH), 116.6 (CH), 117.2 (CH), 121.0 (C), 123.6 (C), 124.9 (CH), 128.1 (C), 131.1 (C), 133.4 (CH), 135.7 (C), 137.2 (CH), 142.8 (C), 144.2 (C), 152.5 (C=O), 163.6 (C=O) ppm. $C_{25}H_{28}N_2O_4S_2$ (484.65): calcd. C 61.96, H 5.82, N 5.78, S 13.23; found C 61.70, H 5.81, N 5.71, S 12.76.

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[1] [1a] U. Schmidt, A. Lieberknecht, J. Wild, *Synthesis* **1988**, 159−171. [1b] G. Jung, *Angew. Chem.* **1991**, *103*, 1067−1084; G. Jung, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1051−1058. [1c] A. Giannis, T. Kolter, *Angew. Chem.* **1993**, *105*, 1303−1326; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1244−1267.
[2] F. Ikegami, Y. Komada, M. Korobi, D. R. Hawkins, I. Murakoshi, *Phytochemistry* **1990**, *29*, 2507−2508.
[3] P. M. T. Ferreira, H. Maia, L. S. Monteiro, J. Sacramento, *J. Chem. Soc., Perkin Trans. 1* **1999**, 3697−3703.
[4] [4a] P. M. T. Ferreira, H. Maia, L. S. Monteiro, J. Sacramento, J. Sebastião, *J. Chem. Soc., Perkin Trans. 1* **2000**, 3317−3324. [4b] P. M. T. Ferreira, H. Maia, L. S. Monteiro, J. Sacramento, *J. Chem. Soc., Perkin Trans. 1* **2001**, 3167−3172.
[5] [5a] E. Campaigne, in *Comprehensive Heterocyclic Chemistry* (Eds.: A. R. Katritzky, C. W. Rees), Pergamon Press, Oxford, **1984**; Vol. 4, 863−934. [5b] K. R. Ronald, B. P. Jefery, in *Comprehensive Heterocyclic Chemistry II* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon Press, Oxford, **1996**; Vol. 2, 679−729.
[6] N. O. Silva, A. S. Abreu, P. M. T. Ferreira, L. S. Monteiro, M.-J. R. P. Queiroz, *Eur. J. Org. Chem.* **2002**, 2524−2528.
[7] P. Cagniant, P. Faller, D. Cagniant, *Bull. Soc. Chim. Fr.* **1966**, 3055−3065.
[8] [8a] M. Prashad, B. Hu, Y. Lu, R. Draper, D. Har, O. Repic, T. J. Blacklock, *J. Org. Chem.* **2000**, *65*, 2612−2614. [8b] J. P. Wolfe, J. Ahman, J. P. Sadighi, R. A. Singer, S. L. Buchwald, *Tetrahedron Lett.* **1997**, *38*, 6367−6370. [8c] I. C. F. R. Ferreira, M.-J. R. P. Queiroz, G. Kirsch, *Tetrahedron* **2003**, *59*, 975−981.
[9] M.-J. R. P. Queiroz, R. Dubest, J. Aubard, R. Faure, R. Guglielmetti, *Dyes and Pigments* **2000**, *47*, 219−229.
[10] [10a] J. P. Wolfe, S. L. Buchwald, *Tetrahedron Lett.* **1997**, *38*, 6359−6362. [10b] J. P. Wolfe, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 1144−1157.
[11] I. C. F. R. Ferreira, M.-J. R. P. Queiroz, G. Kirsch, *Tetrahedron* **2002**, *58*, 7943−7947.

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