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USE OF DIPHENYLIODONIUM BROMIDE IN THE SYNTHESIS OF SOME N-PHENYL α-AMINO ACIDS

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The N-phenyl methyl esters 4 of glycine, alanine, valine, leucine, isoleucine, phenylalanine, methionine, proline, serine, threonine, tyrosine, aspartic acid, and glutamic acid have been synthesized in good to excellent yields using diphenyliodonium bromide, $AgNO_3$, and a catalytic amount of CuBr starting from the relevant amino acid ester. The chiral integrity of the amino acids 5 was maintained during these reactions, which were confirmed by the synthesis of dipeptide for each N-phenyl amino acid. The structures of the new compounds were confirmed by the analysis of their IR, ^1H, and ^{13}C NMR spectra in addition to CHN microanalysis or high-resolution mass spectrometry for the new N-phenyl amino acids 5 and the esters 4.

Keywords: α-Amino acids; diphenyliodonium bromide; esters; N-phenylation

INTRODUCTION

The synthesis of N-aryl amino acids is an area of research that has gained momentum in recent times.[1] These compounds find application as structural components of antimicrobial, antiviral, and pharmacologically active molecules.[1a,b] They are also important core structures of synthetically challenging and medicinally important agents, such as protein kinase C activators,[2] indolactam-V10,[2] and its analog benzolactam-V8.[3]

Early work on the synthesis of these compounds used achiral starting materials, resulting in a racemic mixture that required several steps to isolate the enantiomerically pure form.[4] A method that allows for the direct synthesis of enantiomerically pure N-phenyl-α-amino acids is therefore of great interest. Ma and coworkers[1a,b] were able to use an Ullmann-type reaction to prepare N-phenyl amino acids directly from the amino acid and an aryl halide.

This method, while relatively simple, requires long reaction times (48 h) and was limited to only amino acids bearing nonpolar side chains. Recently, Rottger et al.[1g] developed a protocol for the N-arylation of free and protected amino acids in water

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using a microwave-enhanced copper-catalyzed method. However, the method was used only with phenylalanine, leucine, t-leucine, and proline. α-Diazo-compounds were used with copper complexes of chiral spirobisoxazolines to synthesize a limited number of chiral N-aryl α-amino acids esters.[1j,k] Diaryliodonium salts have long been used as arylating electrophiles[5] to carbanions, alcohols, amines, Grignard reagents, alkoxides, and phenoxides. The use of diaryliodonium salts in the synthesis of 11 N-phenyl amino acid esters commencing from the parent L-amino acid, with chirality being maintained, are reported for the first time.

RESULTS AND DISCUSSION

Because of the possibility of the acid group of the amino acid interfering in the reactions, the amino acids were first converted into the corresponding methyl ester HCl salt using thionyl chloride in anhydrous methanol. These were prepared in excellent yields (85–99% only, tyrosine was 61%).

Removal of HCl was via triethylamine in chloroform. Except for the serine methyl ester (ME) (41%), threonine ME (82%), and tyrosine ME (80%) derivatives, this was essentially a quantitative reaction. All amino acid ester free amines were characterized by infrared (IR), ^{1}H NMR, and ^{13}C NMR spectroscopy. Structural assignments were made by comparison of the spectroscopic data with the amino ester hydrochloride spectra.[6]

The amino ester was generally carried directly through to N-phenylation because prolonged standing of the amino esters can lead to polymerization.

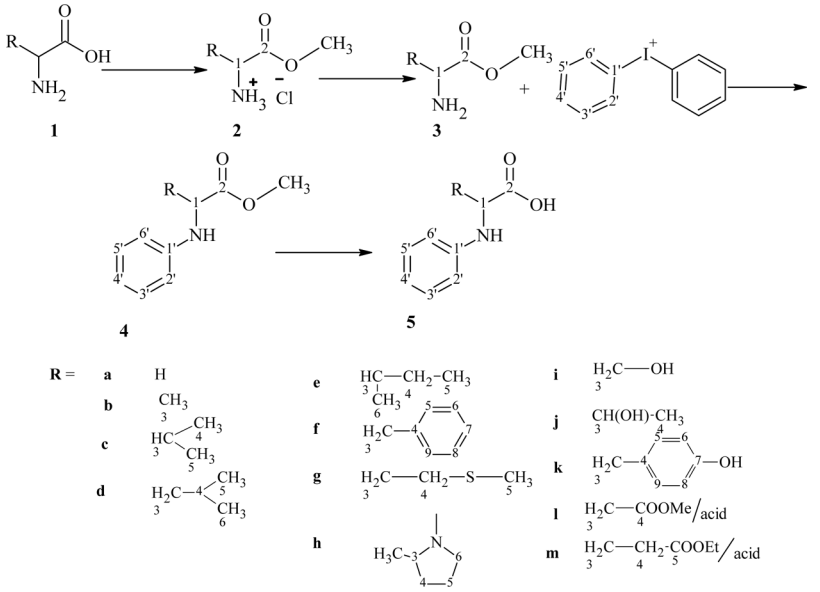
Optimum N-phenylation (Scheme 1) was achieved in refluxing acetonitrile using 2 equivalents of amino ester, 1 equivalent of diphenyliodonium bromide, 1 equivalent of silver nitrate, and a catalytic amount of cuprous bromide. The silver cation precipitates the bromide anion as AgBr, which otherwise competes as a nucleophile. The nitrate caused no side reactions. The second equivalence of amino ester acts as a mild base, absorbing the acid (H^{+}) released during the coupling of the amine and aryl group.

Triethylamine and pyridine were tested as alternate bases, but both resulted in considerably lower yields. Purification was via column chromatography, grading from hexane to ethyl acetate.

The optimum condition of N-phenylation of α-amino acid ester were used on α-amino acid (glycine and valine), which gave back the α-amino acid used, bromobenzene, and iodobenzene. However, no N-aryl α-amino acid was identified.

Poor N-phenylation yields were obtained for the glycine ester (7%), because of competing polymerization, and the proline ester (60%), because of the steric hindrance of the secondary amine. The remaining N-phenyl amino esters were obtained in good yields (see Experimental). All of the N-phenyl amino esters were light orange/brown color. The leucine, tyrosine, and valine derivatives were solids, whereas the remaining eight were oils. The structures of products **4** were confirmed using ^{1}H and ^{13}C NMR spectroscopy in addition to the CHN microanalysis or high-resolution mass spectrometry (HRMS).

The N-phenyl α-amino acid esters **4** were then hydrolyzed to the corresponding acids **5** using dilute NaOH solution under mild conditions to keep the chirality unchanged, and good to excellent yields (see Experimental) of the acids were obtained. The structures of products **5** were confirmed using P NMR, ^{13}C NMR,



Scheme 1. Synthesis of N-phenyl amino acid starting from amino acid **1**, converting to its methyl amino acid ester **2**, neutralization to **3**, N-phenyl substitution to **4**, and then hydrolysis to N-phenyl amino acid **5**.

and CHN microanalysis or HRMS. Physical and spectroscopy data agreed with previously reported data (for references, see Experimental).

Chirality and Anisochrony (Magnetic Nonequivalence)

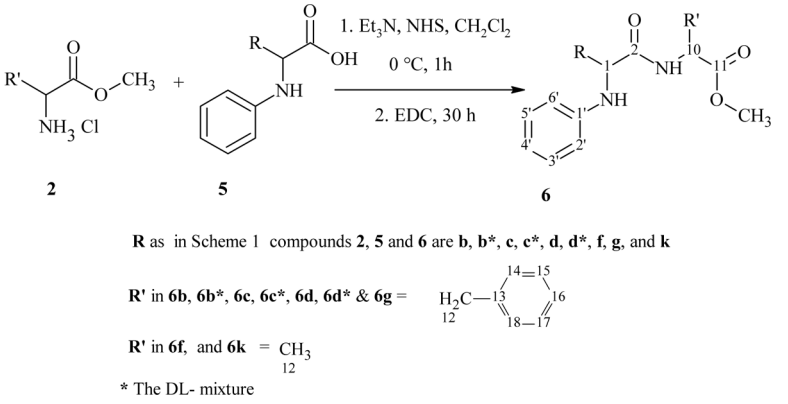
As a result of chirality, some of amino acid esters **3**, N-phenyl amino acid esters **4**, and the corresponding N-phenyl amino acids **5** showed magnetic nonequivalent protons and carbon-13 chemical shift for the chemically equivalent groups.[9]

L-Valine derivatives **3**, **4**, **5c**, and **5c*** (* indicates the DL mixture) showed two different proton and carbon-13 chemical shifts for the 4- and 5-methyl groups. Similarly, the methyl groups 5 and 6 in leucine derivatives **3**, **4**, **5d**, and **5d*** showed two different proton and carbon-13 chemical shifts.

However, the CH_2 protons of C4 in isoleucine derivatives **3e**, **4e**, **5e**, and **5e*** showed that the two protons of the CH_2 are nonequivalent. Similarly, the $C3H_2$ protons in phenylalanine derivatives **3f**, **4f**, **5f**, and **5f***, $C3H_2$ protons in methionine derivatives **3 g**, **4 g**, **5 g**, and **5g***, tyrosine derivatives **3k**, **4k**, **5k**, and **5k***, aspartic derivatives **3 l**, **4 l**, **5 l**, and **5l***, and glutamic derivatives **3 m**, **4 m**, and **5 m** showed that the two protons of the $C3H_2$ are nonequivalent.

Chiral Integrity and Structural Assignment of N-Aryl Amino Acid Dipeptide Methyl Esters 6

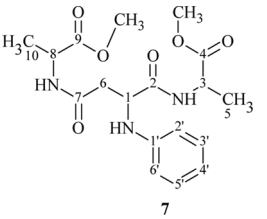
Chiral analysis was undertaken by preparing the chiral dipeptide derivative of each product to determine if single compounds or diastereoisomers existed.[7] The



Scheme 2. Dipeptide formation by coupling of N-phenyl α-amino acid with L-alanine or L-phenylalanine amino acid methyl ester. NHS, N-hydroxysuccinimide; EDC, N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide.

N-phenyl-L-amino acids **5** were coupled with L-phenylalanine methyl ester HCl (**2f**) or L-alanine methyl ester HCl (**2b**) to yield the respective chiral dipeptides **6** using N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide (EDC) as the coupling reagent (Scheme 2). The two carboxylic acid functions on N-phenyl-L-aspartic acid (**5l**) resulted in the formation of the chiral tripeptide **7** (Fig. 1).

Analysis of the ^{1}H NMR of the crude and recrystallized coupling product using L-N-phenyl amino acids showed the presence of only one isomer, whereas analysis of the crude and recrystallized coupling product using racemic D, L-N-phenyl amino acids clearly showed two isomers to be present (see experimental). The individual ^{1}H NMR spectra of the components were relatively unchanged in product **6** compared with those of compound **5**, except that the chiral carbon (C10H) of L-alanine ME was shifted downfield as result of amide formation from δ 3.74 to δ 4.50. The system no longer showed as a first-order spectrum and became very complicated. The ^{1}H NMR of the N-phenyl-L-alanine-L-phenylalanine ME **6b** clearly showed the presence of a single isomer of the dipeptide (see Experimental). Only one signal was observed for the OCH_3 δ 3.63 ppm (s) and $C3H_3$ at δ 1.37 ppm (d), whereas for LL and DL-mixture **6b***, two signals equal integration for OCH_3 at δ 3.63 (LL-product) and 3.80 ppm (s) (DL-product) and $C3H_3$ at δ1.47 and 1.38 ppm (d). In the ^{13}C NMR of the LL-derivatives [δ: 174.1 (C11), 171.8 (C2), 146.8 (C1′), 136.3 (C16), 129.5 (C14,18), 129.4 (C3′,5′), 128.8 (C15,17), 127.3 (C16), 119.5



7

Figure 1. Structure of N-phenyl-L-aspartic acid di-(L-alanine methyl ester).

(C4′), 114.23 (C2′,6′), 55.6 (C3), 53.1 (C1), 52.5 (OCH_3), 38.0 (C5), 19.8 (C3)], only a single peak was observed for each carbon environment.

The ^{13}C NMR of the LL and LD derivatives showed two sets of signals, one for LL- and one for LD-N-phenyl-L-alanine-L-phenylalanine ME **6b*** [δ: 174.2, 174.0 (C11), 172.0, 171.8 (C2), 146.8, 146.7 (C1′), 136.3, 135.7 (C13), 129.7, 129.6 (C15,17), 129.5, 129.4 (C3′,5′), 128.9, 128.8 (C14, 18), 127.3, 127.2 (C16), 119.5, 119.4 (C4′), 114.23, 113.8 (C2′,6′), 55.6, 55.2 (C3), 53.1, 53.0 (C1), 52.5, 52.4 (OCH_3), 38.3, 38.0 (C12), 19.9, 19.8 (C3)]. The ^1H NMR of N-phenyl-L-valine-L-phenylalanine ME and DL are in good agreement with previously reported P NMR.[1a,b]

The same findings were observed in the ^1H NMR and ^{13}C NMR of the crude and recrystallized dipeptide **6c**, **d** compared with **6c***, **d***, which confirms the retention of amino acid chirality after N-phenylation using diphenyliodonium bromide.

EXPERIMENTAL

All solvents and reagents were purchased and used without further purification unless otherwise stated. Dichloromethane was distilled from CaH_2 and stored over type 3A molecular sieve. Acetonitrile was dried over type 4A molecular sieve; diethyl formamide and dimethyl formamide were both dried over type 3A molecular sieve and distilled under reduced pressure before use. Melting points (mp) were determined using a Stuart SMP3 melting-point apparatus. Optical rotation measurements were conducted on Bellingham and Stanley polarimeter no. 582129 using a 10-cm cell. IR spectra were recorded on a Perkin-Elmer 1720-X FT. NMR measurement was performed on a Bruker AC 200 spectrometer. Proton NMR (^1H NMR) spectra were acquired at 200 MHz. ^{13}C NMR were acquired at 50 MHz. Chemical shifts (δ) are expressed in parts per million (ppm) relative to the internal standard (tetramethylsilane in $CDCl_3$ and solvent peak of acetone d_6 and d_6 dimethylsulfoxide). GC-MS was performed on a Shimadzu GC-17A gas chromatograph coupled with a Shimadzu QP-5000 mass spectrometer with 70-eV electron impact (EI) ionization. HRMS was conducted by Dr. Sally-Ann Poulsen and coworkers at Griffith University on a Bruker Daltronics Apex III 4.7e Fourier transform mass spectrometer, fitted with an Apollo API source. Microanalysis was performed by E. Mocellin and coworkers from Chemical and MicroAnalytical Services Pty. Ltd. in Belmont, Victoria.

Preparation of Diaryliodonium Bromide[5]

Diaryliodonium bromide was prepared according to the published procedure.[5] The product was obtained as long white needles (60%), mp 208–210 °C (lit.[5] 208–209 °C). ^1H NMR (d_6-DMSO) δ: 8.22 (d, 4H, $J = 8.0$ Hz, ArH2,6,2′,6′), 7.64 (t, 2H, $J = 8.0$ Hz, ArH4,4′), 7.50 (t, 4H, $J = 8.0$ Hz, ArH3,5,3′,5′). ^{13}C NMR (d_6-DMSO) δ: 135.8 (C2′,6′), 132.3 (C3′,4′,5′), 120.3 (C1′).

Amino Acid Methyl Ester Hydrochloride Salts 2: General Method A

Amino acid salts were prepared following the procedure of Gmeiner and coworkers.[8] The products were recrystallized from an appropriate solvent (solvent/yield %): **1a** acetonitrile/89, **1b** acetonitrile/78, **1c** acetonitrile/85, **1d** ethyl acetate/99,

1d* ethyl acetate/99, **1e** methanol–ether/88, **1f** chloroform/89, **1 g** chloroform–ether/90, **1i** methanol–ether/88, **1k** acetonitril/61, **1 l** methanol–ether/90, and **1 m** ethyl acetate/98, whereas compounds **1 h** (99%) and **1j** (58%) gave clear oils that solidified on standing at room temperature. The purified products were characterized by melting point, IR, ^{1}H NMR, and ^{13}C NMR and compared with reported spectroscopy data.[6]

Amino Acid Methyl Ester Free Amine (3): General Method B

The amino acid ester hydrochloride salt **2** (14 mmol) was mixed with chloroform (10 mL) in a 50-mL, round-bottom flask. A solution of triethylamine (14 mmol) in chloroform (10 mL) was added dropwise to the stirred solution and the mixture then stirred for 4 h at room temperature. The mixture was heated at 70 °C for 1 h, then cooled to room temperature and concentrated in vacuo to a white solid. The solid was diluted with 50 ml ether, filtered, and washed with 10 mL of ether. Concentration of the ether filtrate in vacuo yielded the amino acid ester free amine **3**.

Glycine methyl ester 3a. The free amine **3a** was isolated as yellow oil (1.25 g, 100%). The IR, ^{1}H, and ^{13}C NMR data are in good agreement with the previously reported values.[8]

L-Alanine methyl ester 3b. The free amine **3b** was isolated as a light yellow oil (1.47 g, 100%). The IR, ^{1}H, and ^{13}C NMR data are in good agreement with the previously reported values.[9]

DL-Alanine methyl ester 3b*. The free amine **3b*** was isolated as a light yellow oil (1.47 g, 100%). The IR, ^{1}H, and ^{13}C NMR data are in good agreement with the previously reported values.[10]

L-Valine methyl ester 3c. The free amine **3c** was isolated as a light yellow oil (1.84 g, 100%). The IR, ^{1}H, and ^{13}C NMR data are in good agreement with the previously reported values.[10]

DL-Valine methyl ester 3c*. The free amine **3c*** was obtained as a light yellow oil (1.84 g, 100%). The IR, ^{1}H, and ^{13}C NMR data are in good agreement with the previously reported values.[10]

L-Leucine methyl ester 3d. The free amine **3d** was obtained as a clear yellow liquid (2.02 g, 100%). The IR, ^{1}H, and ^{13}C NMR data are in good agreement with the previously reported values.[10]

DL-Leucine methyl ester 3d*. The free amine **3d*** was isolated as a clear yellow liquid (2.03 g, 100%). The IR, ^{1}H, and ^{13}C NMR data are in good agreement with the previously reported values.[10]

L-Isoleucine methyl ester 3e. The free amine **3e** was isolated as a clear yellow oil (2.03 g, 100%). The IR, ^{1}H, and ^{13}C NMR data are in good agreement with the previously reported values.[11]

L-Phenylalanine methyl ester 3f. The free amine **3f** was isolated as a clear yellow oil (2.51 g, 100%). The IR, ^{1}H, and ^{13}C NMR data are in good agreement with the previously reported values.[12]

L-Methionine methyl ester 3g. The free amine **3g** was isolated as a clear yellow oil (2.20 g, 96%). The IR, ^{1}H, and ^{13}C NMR data are in good agreement with the previously reported values.[9]

L-Proline methyl ester 3h. The free amine **3h** was isolated as a clear oil (1.80 g, 100%). The IR, ^{1}H, and ^{13}C NMR data are in good agreement with the previously reported values.[11]

L-Serine methyl ester 3i. The free amine **3i** was isolated as a clear yellow oil (0.70 g, 41%). The IR, ^{1}H, and ^{13}C NMR data are in good agreement with the previously reported values.[9]

L-Threonine methyl ester 3j. Prepared from **2j** (4.13 g, 24 mmol) and Et_3N (3.4 mL, 24 mmol) in tetrahydrofuran (30 mL). The mixture was stirred for 1 h at 25 °C, the triethylamine hydrochloride was removed by filtration, and the filtrate was concentrated in vacuo. The free amine **3j** was isolated as a clear oil (2.66 g, 82%). The IR, ^{1}H, and ^{13}C NMR data are in good agreement with the previously reported values.[8]

L-Tyrosine methyl ester 3k. The light yellow solid was obtained, which was recrystallized from ethyl acetate to afford **3k** as clear yellow crystals (2.18 g, 80%). The IR, ^{1}H, and ^{13}C NMR data are in good agreement with the previously reported values.[13]

L-Aspartic acid dimethyl ester 3l. The free amine **3l** was isolated as a clear yellow oil (2.26 g, 100%). The IR, ^{1}H, and ^{13}C NMR data are in good agreement with the previously reported values.[9]

L-Glutamic acid diethyl ester 3m. Prepared via general procedure B using absolute ethanol instead methanol. The free amine **3m** was isolated as a clear yellow oil (2.82 g, 100%). ^{1}H NMR ($CDCl_3$) δ: 4.18 (q, 2H, $J = 7.0$ Hz, OCH_2), 4.14 (q, 2H, $J = 7.0$ Hz, OCH_2), 3.42 (dd, X part of ABM2X system, 1H, JAX = 5.0 Hz, JBX = 8.0 Hz, C1H), 2.40 (t, M2 part of ABM2X system, 2H, $J = 7.0$ Hz, $C4H_2$), 2.06 and 1.85 (m, 1H and m, 1H, unresolved AB part of ABM2X system, $C3H_2$), 1.61 (bs exchanges with D_2O, 2H, NH_2), 1.28 (t, 3H, $J = 7.0$ Hz, $CH_2\mathbf{CH_3}$), 1.26 (t, 3H, $J = 7.0$ Hz, CH_2CH_3). ^{13}C NMR ($CDCl_3$) δ: 175.8 (C2), 173.4 (C5), 61.2 (OCH_2), 60.6 (OCH_2), 54.0 (C1), 30.9 (C4), 30.0 (C3), 14.0 ($CH_2CH_3 \times 2$).

N-Phenylation: General Procedure C

The amino acid ester free amine **3** (10 mmol) was combined with diphenyliodonium bromide (5 mmol), $AgNO_3$(5.1 mmol), CuBr (0.1 mmol), and anhydrous acetonitrile (25 mL) in a 100-mL, round-bottom flask equipped with stirrer bar and fitted with a condenser. The system was flushed with N_2, sealed with a latex balloon, heated at 90 °C for 3 h, and protected from light. The reaction was cooled to room temperature, Na_2CO_3(0.5 g) was added, the mixture was gravity filtered, and the

filtrate was concentrated to an oil. Purification of the product was achieved by flash chromatography on a silica-gel column using hexane/ethyl acetate.

N-Phenyl glycine methyl ester 4a. Prepared from **3a** (1.25 g, 14 mmol) via general procedure **C**. The product **4a** was isolated as a viscous yellow oil (0.32 g, 28%). ^{1}H NMR ($CDCl_3$) δ: 7.18 (t, 2H, $J = 8.0$ Hz, ArH3′), 6.74 (t, 1H, $J = 8.0$ Hz, ArH4′), 6.61 (d, 2H, $J = 8.0$ Hz, ArH2′), 4.32 (bs, exchanges with D_2O, 1H, NH), 3.97 (s, 2H, C1H_2), 3.73 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$) δ: 173.1 (C2), 147.3 (C1′), 129.5 (C3′), 118.6 (C4′), 113.5 (C2′), 52.1 (OCH_3), 46.0 (C1). Data are consistant with literature values.[1k] MS m/z: 165 (24), 106 (100), 91 (49), 77 (32).

N-Phenyl-L-alanine methyl ester 4b. Prepared from **3b** (1.44 g, 14 mmol) via general procedure C to yield a viscous yellow oil, which was distilled under vacuum to afford **4b** as a light yellow oil (1.01 g, 80%). Bp 72 °C at 0.02 mmHg. $[\alpha]_D^{22}$ −57.8 (c 1.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 7.18 (t, 2H, $J = 8.0$ Hz, ArH3′), 6.74 (t, 1H, $J = 8.0$ Hz, ArH4′), 6.61 (d, 2H, $J = 8.0$ Hz, ArH2′), 4.15 (q, 1H, $J = 7.0$ Hz, C1H), 4.14 (bs, exchanges with D_2O, 1H, NH), 3.73 (s, 3H, OCH_3), 1.47 (d, 3H, $J = 7.0$ Hz, C3H_3). ^{13}C NMR ($CDCl_3$,) δ: 175.0 (C2), 146.5 (C1′), 129.2 (C3′), 118.2 (C4′), 113.3 (C2′), 52.1 (OCH_3), 51.8 (C1), 18.8 (C3). MS m/z: 179 (68), 120 (100), 104 (26), 91 (17), 77 (44). Data are consistant with literature values.[1k] Found: C, 66.97; H 7.40; N, 7.88. $C_{10}H_{13}NO_2$ requires C, 67.02; H, 7.31; N, 7.82.

N-Phenyl-DL-alanine methyl ester 4b*. Prepared from **3b*** (2.75 g, 27 mmol) via general procedure C. The product **4b*** was isolated as a viscous yellow oil (1.81 g, 76%). ^{1}H NMR ($CDCl_3$) δ: 7.17 (t, 2H, $J = 8.0$ Hz, ArH3′), 6.74 (t, 1H, $J = 8.0$ Hz, ArH4′), 6.60 (d, 2H, $J = 8.0$ Hz, ArH2′), 4.14 (bs exchanges with D_2O, 1H, NH), 4.12 (q, 1H, $J = 7.0$ Hz, C1H), 3.73 (s, 3H, OCH_3), 1.47 (d, 3H, $J = 7.0$ Hz, C3H_3). ^{13}C NMR ($CDCl_3$) δ: 175.0 (C2), 146.5 (C1′), 129.2 (C3′), 118.2 (C4′), 113.3 (C2′), 52.1 (OCH_3), 51.8 (C1), 18.8 (C3). MS m/z: 179 (68), 120 (100), 104 (26), 91 (17), 77 (44). Data are consistant with literature values.[11]

N-Phenyl-L-valine methyl ester 4c. Prepared from **3c** (2.49 g, 19 mmol) via general procedure C. The product **4c** was isolated as a bright yellow oil (1.54 g, 80%), which solidified to a light yellow solid on cooling at 0 °C. Mp 26–27 °C. $[\alpha]_D^{22}$ −75.8 (c 1.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 7.16 (dd, 2H, $J = 7.0$ Hz, $J = 8.0$ Hz, ArH3′), 6.72 (t, 1H, $J = 7.0$ Hz, ArH4′), 6.62 (d, 2H, $J = 8.0$ Hz, ArH2′), 4.11 (bs exchanges with D_2O, 1H, NH), 3.86 (d, 1H, $J = 6.0$ Hz, C1H), 3.69 (s, 3H, OCH_3), 2.11 (m, 1H, C3H), 1.04 (d, 3H, $J = 7.0$ Hz, C4/5H_3), 1.00 (d, 3H, $J = 7.0$ Hz, C4/5H_3). ^{13}C NMR ($CDCl_3$) δ: 174.1 (C2), 147.3 (C1′), 129.3 (C3′), 118.2 (C4′), 113.5 (C2′), 62.4 (C1), 51.7 (OCH_3), 31.6 (C3), 19.0, 18.6 (C4, 5). MS m/z: 207 (19), 164 (34), 148 (100), 104 (45), 77 (28). Data are consistant with literature values.[14] Found: C, 69.61; H, 8.31; N, 6.71. $C_{12}H_{17}NO_2$ requires: C, 69.54; H, 8.27; N, 6.76.

N-Phenyl-DL-valine methyl ester 4c*. Prepared from **3c*** (1.83 g, 14 mmol) via general procedure C. The product was isolated as a yellow solid which was recrystallised from hexane/ethyl acetate to afford **4c*** as light yellow crystals (1.17 g, 81%). Mp 52–53 °C. $[\alpha]_D^{22}$ 0.0 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 7.17 (dd, 2H, $J = 7.0$ Hz, $J = 8.0$ Hz, ArH3′), 6.73 (t, 1H, $J = 7.0$ Hz, ArH4′), 6.63 (d, 2H, $J = 8.0$ Hz, ArH2′), 4.09 (bs exchanges with D_2O, 1H, NH), 3.87 (d, 1H, $J = 6.0$ Hz,

C1H), 3.71 (s, 3H, OCH_3), 2.11 (m, 1H, C3H), 1.05 (d, 3H, $J = 7.0$ Hz, C4/5H_3), 1.01 (d, 3H, $J = 7.0$ Hz, C4/5H_3). ^{13}C NMR ($CDCl_3$) δ: 174.5 (C2), 147.6 (C1′), 129.6 (C3′), 118.5 (C4′), 113.8 (C2′), 62.7 (C1H), 52.1 (OCH_3), 31.9 (C3), 19.4, 19.0 (C4,5). Data are consistant with literature values.[15] MS m/z: 207 (74), 164 (74), 148 (100), 104 (74), 77 (50).

N-Phenyl-L-leucine methyl ester 4d. Prepared from **3d** (2.03 g, 14 mmol) via general procedure C. The product was initially isolated as a viscous oil, which slowly formed opaque crystals on standing at 0 °C. The solid was dissolved in hexane and slowly evaporated to yield **4d** as needle crystals (1.26 g, 81%). Mp 50–51 °C. $[\alpha]_D^{22}$ −62.0 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 7.17 (dd, 2H, $J = 7.0$ Hz, $J = 8.0$ Hz, ArH3′), 6.73 (t, 1H, $J = 7.0$ Hz, ArH4′), 6.61 (d, 2H, $J = 8.0$ Hz, ArH2′), 4.09 (t, 1H, $J = 7.0$ Hz, C1H), 3.97 (bs exchanges with D_2O, 1H, NH), 3.70 (s, 3H, OCH_3), 1.77 (m, 1H, C4H), 1.65 (m, 2H, C3H_2), 0.99 (d, 3H, $J = 6.0$ Hz, C5/6H_3), 0.94 (d, 3H, $J = 6.0$ Hz, C5/6H_3). ^{13}C NMR ($CDCl_3$) δ: 175.5 (C2), 147.3 (C1′), 129.6 (C3′), 118.6 (C4′), 113.7 (C2′), 55.4 (C1), 52.3 (OCH_3), 42.7 (C4), 25.2 (C3), 23.0, 22.5 (C5, 6). MS m/z: 221 (78), 162 (100), 120 (77), 104 (49), 91 (14), 77 (49). Found: C, 70.54; H, 8.60; N, 6.28. $C_{13}H_{19}NO_2$ requires C, 70.56; H, 8.65; N, 6.33.

N-Phenyl-DL-leucine methyl ester 4d*. Prepared from **3d*** (2.03 g, 14 mmol) via general procedure C. The product **4d*** was initially isolated as a viscous orange oil (1.30 g, 84%), which solidified on prolonged cooling at 0 °C. Mp 46–47 °C. ^{1}H NMR ($CDCl_3$) δ: 7.17 (dd, 2H, $J = 7.0$ Hz, $J = 8.0$ Hz, ArH3′), 6.73 (t, 1H, $J = 7.0$ Hz, ArH4′), 6.61 (d, 2H, $J = 8.0$ Hz, ArH2′), 4.09 (t, 1H, $J = 7.0$ Hz, C1H), 3.95 (bs exchanges with D_2O, 1H, NH), 3.69 (s, 3H, OCH_3), 1.79 (m, 1H, C4H), 1.64 (m, 2H, C3H_2), 0.99 (d, 3H, $J = 6.0$ Hz, C5/6H_3), 0.94 (d, 3H, $J = 6.0$ Hz, C5/6H_3). ^{13}C NMR ($CDCl_3$) δ: 175.5 (C2), 147.3 (C1′), 129.6 (C3′), 118.6 (C4′), 113.7 (C2′), 55.4 (C1), 53.3 (OCH_3), 42.7 (C4), 25.2 (C3), 23.0, 22.5 (C5,6).

N-Phenyl-L-isoleucine methyl ester 4e. Prepared from **3e** (1.45 g, 10 mmol) via general procedure C. The product **4e** was isolated as clear colorless oil (0.84 g, 76%). $[\alpha]_D^{22}$ −47.4 (c 0.61, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 7.17 (t, 2H, $J = 8.0$ Hz, ArH3′), 6.72 (t, 1H, $J = 8.0$ Hz, ArH4′), 6.62 (d, 2H, $J = 8.0$ Hz, ArH2′), 4.13 (bs exchanges with D_2O, 1H, NH), 3.95 (d, 1H, $J = 6.0$ Hz, C1H), 3.70 (s, 3H, OCH_3), 1.85 (m, 1H, C3H), 1.63 and 1.29 (m, 1H and m, 1H, C4H_2), 0.97 (d, 3H, $J = 6.0$ Hz, C6H_3), 0.95 (t, 3H, $J = 7.0$ Hz, C5H_3). ^{13}C NMR ($CDCl_3$) δ: 174.4 (C2), 147.4 (C1′), 129.6 (C3′), 118.4 (C4′), 113.7 (C2′), 61.4 (C1), 52.1 (OCH_3), 38.3 (C3), 25.9 (C6), 15.8 (C4), 11.8 (C5). MS m/z: 221 (19), 162 (100), 132 (12), 104 (52), 77 (30). Found: C, 70.43; H, 8.61; N, 6.43. $C_{13}H_{19}NO_2$ requires C, 70.56; H, 8.65; N, 6.33.

N-Phenyl-L-phenylalanine methyl ester 4f. Prepared from **3f** (2.30 g, 13 mmol) via general method C. The product was isolated as dark orange oil, which was distilled under vacuum to isolate **4f** as light orange oil (1.30 g, 80%). Bp 130 °C at 0.024 mmHg. $[\alpha]_D^{22}$ +44.7 (c 1.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$,) δ: 7.30–7.10 (m, 7H, ArH5–9,3′), 6.72 (t, 1H, $J = 8.0$ Hz, ArH4′), 6.58 (d, 2H, $J = 8.0$ Hz, ArH2′), 4.36 (t, X part of ABX system, 1H, $J = 6.0$ Hz, C1H), 4.13 (bs exchanges with D_2O, 1H, NH), 3.67 (s, 3H, OCH_3), 3.11 (AB part of ABX system, 2H, $J = 13.5$ Hz,

$C3H_2$). ^{13}C NMR ($CDCl_3$) δ: 173.5 (C2), 146.2 (C1′), 136.2 (C4), 129.2 (C6, 8), 129.1 (C3′), 128.4 (C7), 126.9 (C5, 9), 118.3 (C4′), 113.4 (C2′), 57.6 (C1), 51.9 (OCH_3), 38.5 (C3). MS m/z: 255 (12), 196 (20), 164 (100), 104 (56), 77 (30). Data are consistant with literature values.[16] Found: C, 75.38; H, 6.75; N, 5.58. $C_{16}H_{17}NO_2$ requires C, 75.27; H, 6.71; N, 5.49.

N-Phenyl-L-methionine methyl ester 4g. Prepared from **3g** (1.96 g, 12 mmol) via general procedure C. The product **4g** was isolated as clear light brown oil (0.98 g, 68%). Bp 122 °C at 0.02 mmHg. $[\alpha]_D^{22}$ −50.8 (c 0.80, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 7.18 (t, 2H, $J = 8.0$ Hz, ArH3′), 6.75 (t, 1H, $J = 8.0$ Hz, ArH4′), 6.65 (d, 2H, $J = 8.0$ Hz, ArH2′), 4.26 (dd, X part of ABM_2X system, 1H, $J_{AX} = 5.0$ Hz, $J_{BX} = 7.0$ Hz, C1H), 4.17 (bs exchanges with D_2O, 1H, NH), 3.73 (s, 3H, OCH_3), 2.63 (t, M_2 part of ABM_2X system, 2H, $J = 7.0$ Hz, $C4H_2$), 2.20–1.90 (unresolved AB part of ABM_2X system, 2H, $C3H_2$), 2.10 (s, 3H, SCH_3). ^{13}C NMR ($CDCl_3$) δ: 174.1 (C2), 146.7 (C1′), 129.3 (C3′), 118.5 (C4′), 113.6 (C2′), 55.5 (C1), 52.2 (OCH_3), 32.3 (C4), 30.2 (C3), 15.4 (SCH_3). MS m/z: 239 (23), 180 (62), 132 (52), 104 (19), 77 (24), 61 (100). Found: C, 60.06; H, 7.21; N, 5.90; S, 13.35. $C_{12}H_{17}NO_2S$ requires C, 60.22; H, 7.16; N, 5.85; S, 13.40.

N-Phenyl-L-proline methyl ester 4h. Prepared from **3h** (1.80 g, 14 mmol) via general procedure C. The product **4h** was isolated as a viscous yellow oil (0.83 g, 60%). $[\alpha]_D^{22}$ −110.6 (c 2.2, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 7.21 (dd, 2H, $J = 7.0$ Hz, 8.0 Hz, ArH3′), 6.70 (t, 1H, $J = 7.0$ Hz, ArH4′), 6.54 (dd, 2H, $J = 1.0$ Hz, 8.0 Hz, ArH2′), 4.24 (dd, 1H, $J = 2.0$ Hz, 8.0 Hz, C1H), 3.70 (s, 3H, OCH_3), 3.56 and 3.34 (m, 1H and m, 1H, $C5H_2$), 2.15 (m, 4H, $C3H_2$ and $C4H_2$). ^{13}C NMR ($CDCl_3$) δ: 174.9 (C2), 146.6 (C1′), 129.1 (C3′), 116.6 (C4′), 111.9 (C2′), 60.7 (C1), 52.0 (OCH_3), 48.2 (C5), 30.8 (C3), 23.8 (C4). Data are consistant with literature values.[12] MS m/z: 205 (12), 146 (100), 104 (18), 77 (23). Found: C, 70.20; H, 7.40; N, 6.78. $C_{12}H_{15}NO_2$ requires C, 70.22; H, 7.37; N, 6.82.

N-Phenyl-L-serine methyl ester 4i. Prepared from **3i** (0.70 g, 6 mmol) via general procedure C. The product **4i** was isolated as clear yellow oil (0.30 g, 51%). $[\alpha]_D^{22}$ −22.5 (c 1.3, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ: 7.20 (dd, 2H, $J = 7.0$ Hz, 8.0 Hz, ArH3′), 6.79 (t, 1H, $J = 7.0$ Hz, ArH4′), 6.69 (d, 2H, $J = 8.0$ Hz, ArH2′), 4.21 (t, 1H, $J = 4.0$ Hz, C1H), 3.96 (AB part of ABX system, 2H, $J = 11.0$ Hz, $C3H_2$), 3.79 (s, 3H, OCH_3), 2.25 (bs exchanges with D_2O, 2H, OH and NH). ^{13}C NMR ($CDCl_3$) δ: 172.9 (C2), 146.8 (C1′), 129.7 (C3′, 5′), 119.3 (C4′), 114.2 (C2′, 6′), 63.2 (C3), 58.8 (C1), 52.9 (OCH_3).

N-Phenyl-L-threonine methyl ester 4j. Prepared from **3j** (2.66 g, 20 mmol) via general procedure C. The product **4j** was isolated as a thin, clear yellow oil (0.98 g, 47%). $[\alpha]_D^{22}$ −56.3 (c 4.1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 7.19 (dd, 2H, $J = 7.0$ Hz, 8.0 Hz, ArH3′), 6.78 (t, 1H, $J = 7.0$ Hz, ArH4′), 6.69 (d, 2H, $J = 8.0$ Hz, ArH2′), 4.44 (bs exchanges with D_2O, 1H, OH), 4.13 (m, 1H, C3H), 3.96 (bs exchanges with D_2O, 1H, NH), 3.78 (m, 1H, C1H), 3.74 (s, 3H, OCH_3), 1.32 (d, 3H, $J = 6.0$ Hz, $C4H_3$). ^{13}C NMR ($CDCl_3$) δ: 173.6 (C2), 147.4 (C1′), 129.6 (C3′), 119.3 (C4′), 114.4 (C2′), 68.7 (C3), 62.9 (C1), 52.6 (OCH_3), 20.0 (C4). MS m/z: 165 (36), 106 (100), 77 (56). HRMS: Found: M +H, 210.112005. $C_{11}H_{16}NO_3$ requires M + H, 210.11247.

N-Phenyl-L-tyrosine methyl ester 4k. Prepared from **3k** (2.73 g, 14 mmol) via general procedure C. The product was isolated as a brown solid. This was recrystallized from ether/hexane to yield **4k** as long, straw-colored, needle crystals (1.60 g, 85%). Mp 125–126 °C. $[\alpha]_D^{22}$ +46.0 (c 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 7.17 (t, 2H, $J = 8.0$ Hz, ArH3′), 7.02 (d, 2H, $J = 8.0$ Hz, ArH5,9), 6.74 (t, 1H, $J = 8.0$ Hz, ArH4′), 6.73 (d, 2H, $J = 8.0$ Hz, ArH6,8), 6.59 (d, 2H, $J = 8.0$ Hz, ArH2′), 4.84 (bs exchanges with D_2O, 1H, OH), 4.32 (t, X part of ABX system, 1H, $J = 6.0$ Hz, C1H), 4.13 (bs exchanges with D_2O, 1H, NH), 3.67 (s, 3H, OCH_3), 3.06 (AB part of ABX system, 2H, J = 14.0 Hz, $C3H_2$). ^{13}C NMR ($CDCl_3$) δ: 174.1 (C2), 154.9 (C7), 146.6 (C1′), 130.8 (C5, 9), 129.7 (C3′), 128.6 (C4), 118.8 (C4′), 115.7 (C6, 8), 113.9 (C2′), 58.1 (C1), 52.4 (OCH_3), 38.1 (C3). MS m/z: 271 (53), 212 (37), 164 (100), 132 (23), 104 (80), 77 (52). Found: C, 70.98; H, 6.22; N, 5.09. $C_{16}H_{17}NO_3$ requires C, 70.83; H, 6.32; N, 5.16.

N-Phenyl-L-aspartic acid dimethyl ester 4l. Prepared from **3l** (1.13 g, 7 mmol) via general procedure C. The product **4l** was isolated as a viscous, bright yellow oil (0.60 g, 72%). $[\alpha]_D^{22}$ +7.0 (c 2.6, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ: 7.19 (dd, 2H, $J = 7.0$ Hz, $J = 8.0$ Hz, ArH3′), 6.77 (t, 1H, $J = 7.0$ Hz, ArH4′), 6.66 (dd, 2H, $J = 1.0$ Hz, $J = 8.0$ Hz, ArH2′), 4.46 (t, 1H, $J = 6.0$ Hz, C1H), 4.45 (bs exchanges with D_2O, 1H, NH), 3.75 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 2.88 (d, 2H, $J = 6.0$ Hz, $C3H_2$). ^{13}C NMR ($CDCl_3$) δ: 173.0 (C2), 171.2 (C4), 146.4 (C1′), 129.6 (C3′), 119.0 (C4′), 114.0 (C2′), 53.6 (C1), 52.8 (OCH_3), 52.2 (OCH_3), 37.4 (C3). MS m/z: 237 (19), 178 (90), 146 (24), 104 (100), 77 (29), 59 (20). Found: C, 60.81; H, 6.42; N, 5.87. $C_{12}H_{15}NO_4$ requires C, 60.75; H, 6.37; N, 5.90.

N-Phenyl-L-glutamic acid diethyl ester 4m. Prepared from **3m** (1.42 g, 7 mmol) via general procedure C. The product **4m** was isolated as a brown oil (0.65 g, 67%). $[\alpha]_D^{22}$ −21.6 (c 2.8, CHCl). ^1H NMR ($CDCl_3$) δ: 7.16 (dd, 2H, $J = 7.0$ Hz, $J = 8.0$ Hz, ArH3′), 6.74 (t, 1H, $J = 7.0$ Hz, ArH4′), 6.62 (d, 2H, $J = 8.0$ Hz, ArH2′), 4.71 (dd, X part of ABM_2X system, 1H, $J = 3.0$ Hz, $J = 8.0$ Hz, C1H), 4.19 (q, 2H, $J = 7.0$ Hz, OCH_2), 4.13 (q, 2H, $J = 7.0$ Hz, OCH_2), 2.50 (bs exchanges with D_2O, 1H, NH), 2.47 (t, M_2 part of ABM_2X system, 2H, $J = 7.0$ Hz, $C4H_2$), 2.30–2.13 (unresolved AB part of ABM_2X system, 2H, $C3H_2$), 1.25 (t, 3H, $J = 7.0$ Hz, CH_2CH_3), 1.24 (t, 3H, $J = 7.0$ Hz, CH_2CH_3). ^{13}C NMR ($CDCl_3$,) δ: 173.8 (C2), 173.2 (C5), 147.0 (C1′), 129.6 (C3′), 118.7 (C4′), 113.8 (C2′), 61.6 (OCH_2), 60.9 (OCH_2), 56.3 (C1), 30.7 (C4), 28.2 (C3), 14.5 ($CH_2CH_3 \times 2$). MS m/z: 279 (10), 234 (8), 206 (76), 160 (100), 132 (48), 104 (34), 77 (37).

Hydrolysis of N-Phenyl Amino Acid Esters 4 and Preparation of N-Phenyl Amino Acids 5: General Procedure D

The N-phenyl amino acid ester **4** (1 mmol) was dissolved in anhydrous methanol (5 mL/mmol of ester), and 1 M NaOH (1.1 mmol) was added dropwise to this solution. The hydrolysis was monitored by thin-layer chromatography (TLC). When the hydrolysis was deemed complete, the solution was concentrated to 5 mL; the resulting mixture was then extracted between 10% Na_2CO_3 and dichloromethane. The aqueous layer was acidified with 1 M HCl; the precipitate was collected and

washed with a 50/50 mixture of hexane/dichloromethane. The collected solid was then recrystallized from a suitable solvent.

N-Phenyl-L-alanine 5b. Prepared from **4b** (0.63 g, 3.5 mmol) via general procedure D. Hydrolysis was complete in 12 h. The product was initially collected as a bright orange solid and recrystallized from toluene to yield **5b** as small off-white crystals (0.47 g, 81%). Mp 138–139 °C. $[\alpha]_D^{22}$ −52.0 (c 1.0, CH_3COCH_3 [lit.[1b] $[\alpha]_D^{25}$ −44.8 (c 0.84, CH_3COCH_3]. ^{1}H NMR ($CDCl_3$) δ: 7.20 (t, 2H, $J = 8.0$ Hz, ArH3′), 6.79 (t, 1H, $J = 8.0$ Hz, ArH4′), 6.63 (d, 2H, $J = 8.0$ Hz, ArH2′), 4.20 (bs exchanges with D_2O, 2H, OH and NH), 4.13 (q, 1H, $J = 7.0$ Hz, $CHCH_3$), 1.54 (d, 3H, $J = 7.0$ Hz, $CHCH_3$) C5H_3. ^{13}C NMR (CD_3COCD_3) δ: 176.5 (C2), 149.3 (C1′), 130.5 (C3′), 118.7 (C4′), 114.5 (C2′), 53.0 (C1), 19.6 (C3). Data are consistant with literature values.[1b] Found: C, 65.38; H, 6.67; N, 8.51. $C_9H_{11}NO_2$ requires C, 65.44; H, 6.71; N, 8.48.

N-Phenyl-DL-alanine 5b*. Prepared from **4b*** (1.50 g, 8.4 mmol) via general procedure D. Hydrolysis was complete in 12 h. The product was initially collected as a light brown powder and recrystallized from toluene to yield **5b*** as small white crystals (1.10 g, 80%). Mp 157–159 °C. $[\alpha]_D^{22}$ 0.0 (c 1.0, CH_3COCH_3) ^{1}H NMR (CD_3COCD_3) δ: 7.12 (t, 2H, $J = 8.0$ Hz, ArH3′), 6.65 (t, 1H, $J = 8.0$ Hz, ArH4′), 6.60 (d, 2H, $J = 8.0$ Hz, ArH2′), 4.03 (q, 1H, $J = 7.0$ Hz, C1H), 3.70 (bs exchanges with D_2O, 2H, NH and OH), 1.48 (d, 3H, $J = 7.0$ Hz, C3H_3). ^{13}C NMR (CD_3COCD_3) δ: 176.5 (C2), 149.3 (C1′), 130.5 (C3′), 118.7 (C4′), 114.5 (C2′), 53.0 (C1), 19.6 (C3) data is consistant with literature values.[12]

N-Phenyl-L-valine 5c. Prepared from **4c** (1.34 g, 6.5 mmol) via general procedure D. Hydrolysis was complete in 15 h. The product was initially collected as an orange solid and recrystallized from hexane to yield **5c** as short white needles (1.06 g, 85%). Mp 108–109 °C. $[\alpha]_D^{22}$ −47.0 (c 1.0, $CHCl_3$) [lit.[1b]$[\alpha]_D^{25}$ −49.5 (c 0.84, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 7.19 (t, 2H, $J = 8.0$ Hz, ArH3′), 6.78 (t, 1H, $J = 8.0$ Hz, ArH4′), 6.65 (d, 2H, $J = 8.0$ Hz, ArH2′), 3.86 (d, 1H, $J = 5.0$ Hz, C1H), 2.90 (bs exchanges with D_2O, 2H, OH and NH), 2.22 (m, 1H, C3H), 1.06 (d, 6H, $J = 7.0$ Hz, C4H_3 and C5H_3. ^{13}C NMR ($CDCl_3$) δ: 177.4 (C2), 147.0 (C1′), 129.4 (C3′), 118.8 (C4′), 113.7 (C2′), 62.6 (C1), 31.3 (C3), 19.1, 18.3 (C4,5). Data are consistant with literature values.[1b] Found: C, 68.32; H, 7.78; N, 7.30. $C_{11}H_{15}NO_2$ requires C, 68.37; H, 7.82; N, 7.25.

N-Phenyl-DL-valine 5c*. Prepared from **4c*** (1.12 g, 5.4 mmol) via general procedure **D**. Hydrolysis was complete in 16 h. The product was initially collected as a brown solid and recrystallized from hexane to yield **5c*** as flat white crystals (0.94 g, 90%). Mp 125–127 °C. $[\alpha]_D^{22}$ 0.0 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$,) δ: 7.36 (bs exchanges with D_2O, 2H, OH and NH), 7.18 (t, 2H, $J = 8.0$ Hz, ArH3′), 6.76 (t, 1H, $J = 8.0$ Hz, ArH4′), 6.64 (d, 2H, $J = 8.0$ Hz, ArH2′), 3.87 (d, 1H, $J = 5.0$ Hz, C1H), 2.18 (m, 1H, C3H), 1.06 (d, 6H, $J = 7.0$ Hz, C4H_3 and C5H_3). ^{13}C NMR ($CDCl_3$,) δ: 179.1 (C2), 147.3 (C1′), 129.7 (C3′), 119.1 (C4′), 114.0 (C2′), 62.8 (C1), 31.7 (C3), 19.4, 18.6 (C4, 5). Data are consistant with literature values.[1b]

N-Phenyl-L-leucine 5d. Prepared from **4d** (0.73 g, 3.3 mmol) via general procedure D. Hydrolysis was complete in 20 h. The product was initially collected as

a white solid and recrystallized from toluene to yield **5d** as flat white crystals (0.59 g, 86%). Mp 156–157 °C. $[\alpha]_D^{22}$ −63.9 (c 0.54, $CHCl_3$), lit. [1g]$[\alpha]_D^{20}$ −45.0 (c 1.08, acetone). ^{1}H NMR (CD_3COCD_3) δ: 7.10 (t, 2H, $J = 8.0$ Hz, ArH3′), 6.67 (d, 2H, $J = 8.0$ Hz, ArH2′), 6.61 (t, 1H, $J = 8.0$ Hz, ArH4′), 4.04 (t, 1H, $J = 7.0$ Hz, C1H), 2.87 (bs exchanges with D_2O, 2H, OH and NH), 1.95–1.80 (m, 1H, (C4H), 1.69 (t, 2H, $J = 7.0$ Hz, $C3H_2$), 0.98 (d, 3H, $J = 7.0$ Hz, $C5/6H_3$), 0.94 (d, 3H, J = 7.0 Hz, $C5/6H_3$). ^{13}C NMR ($CDCl_3$,) δ: 179.3 (C2), 146.5 (C1′), 129.4 (C3′), 118.9 (C4′), 113.6 (C2′), 55.4 (C1), 42.1 (C4), 24.9 (C3), 22.7, 21.9 (C5,6). Data are consistant with literature values.[12] Found: C, 69.58; H, 8.24; N, 6.80. $C_{12}H_{17}NO_2$ requires C, 69.54; H, 8.27; N, 6.76.

N-Phenyl-DL-leucine 5d*. Prepared from **4d*** (0.92 g, 4.1 mmol) via general procedure D, Hydrolysis was complete in 20 h. The product was initially collected as a white solid and recrystallized from toluene to yield **5d*** as fine white crystals (0.70 g, 81%). Mp 163–165 °C. ^{1}H NMR (CD_3COCD_3) δ: 7.10 (t, 2H, $J = 8.0$ Hz, ArH3′), 6.67 (d, 2H, $J = 8.0$ Hz, ArH2′), 6.61 (t, 1H, $J = 8.0$ Hz, ArH4′), 4.04 (t, 1H, $J = 7.0$ Hz, C1H), 2.23 (bs exchanges with D_2O, 2H, OH and NH), 1.95–1.80 (m, 1H, C4H), 1.69 (t, 2H, $J = 7.0$ Hz, $C3H_2$), 0.98 (d, 3H, $J = 7.0$ Hz, $C5/6H_3$), 0.94 (d, 3H, $J = 7.0$ Hz, $C5/6H_3$). ^{13}C NMR (CD_3COCD_3) δ: 176.6 (C2), 149.7 (C1′), 130.5 (C3′), 118.7 (C4′), 114.5 (C2′), 56.2 (C1), 43.4 (C4), 26.3 (C3), 23.9, 23.0 (C5,6). Data are consistant with literature values.[12]

N-Phenyl-L-isoleucine 5e. Prepared from **4e** (1.11 g, 5.0 mmol) via general procedure D. Hydrolysis was complete in 21 h. The product was initially collected as a light brown solid and recrystallized from hexane to yield **5e** as fine white needles (0.80 g, 77%). Mp 115–116 °C. $[\alpha]_D^{22}$ −43.2 (c 1.0, $CDCl_3$). ^{1}H NMR ($CDCl_3$,) δ: 7.82 (bs exchanges with D_2O, 2H, OH and NH), 7.17 (t, 2H, $J = 8.0$ Hz, ArH3′), 6.75 (t, 1H, $J = 7.0$ Hz, ArH4′), 6.63 (d, 2H, $J = 8.0$ Hz, ArH2′), 3.94 (d, 1H, $J = 5.0$ Hz, C1H), 1.90 (m, 1H, C3H), 1.63 and 1.31 (m, 1H and m, 1H, $C4H_2$), 1.01 (d, 3H, $J = 7.0$ Hz, $C6H_3$), 0.95 (t, 3H, $J = 7.0$ Hz, $C5H_3$). ^{13}C NMR ($CDCl_3$) δ: 179.2 (C2), 146.8 (C1′), 129.4 (C3′), 118.6 (C4′), 113.6 (C2′), 61.2 (C1), 37.8 (C3), 25.4 (C6), 15.5 (C4), 11.4 (C5). Found: C, 69.60; H, 8.24; N, 6.80. $C_{12}H1_7NO_2$ requires C, 69.54; H, 8.27; N, 6.76.

N-Phenyl-L-phenylalanine 5f. Prepared from **4f** (1.14 g, 4.5 mmol) via general procedure D. Hydrolysis was complete in 16 h. The product was initially collected as a white solid and recrystallized from toluene to yield **5f** as small white crystals (0.89 g, 89%). Mp 176–177 °C. $[\alpha]_D^{22}$ +3.0 (c 1.0, CH_3COCH_3) [lit.[1g] $[\alpha]_D^{20}$ +2.1 (c 1.0, CH_3COCH_3)]. ^{1}H NMR (CD_3SOCD_3) δ: 7.42–7.13 (m, 5H,ArH5–9), 7.04 (t, 2H, $J = 8.0$ Hz, ArH3′), 6.56 (d, 2H, $J = 8.0$ Hz, ArH2′), 6.54 (t, 1H, $J = 8.0$ Hz, ArH4′), 4.10 (t, X part of ABX system, 1H, $J = 6.0$ Hz, C1H), 3.27–3.00 (AB part of ABX system, 2H, $J = 14.0$ Hz, $C3H_2$), 2.90 (bs exchanges with D_2O, 2H, OH and NH). ^{13}C NMR (CD_3SOCD_3) δ: 174.9 (C2), 147.8 (C1′), 138.3 (C4), 129.1 (C3′), 128.7 (C6,8), 127.9 (C5,9), 126.0 (C7), 115.9 (C4′), 112.4 (C2′), 57.8 (C1), 37.7 (C3). Data are consistant with literature values.[1b] HRMS: found M + H, 242.116893. $C_{15}H_{16}NO_2$ requires M + H, 242.117555.

N-Phenyl-L-methionine 5g. Prepared from **4 g** (0.77 g, 3.2 mmol) via general procedure D. Hydrolysis was complete in 20 h. The product was initially collected as

a brown solid, which was recrystallized from hexane to yield **5 g** as small white crystals (0.43 g, 60%). Mp: 141–143 °C. $[\alpha]_D^{22}$ −46.3 (c 1.0, CH_3COCH_3). ^1H NMR ($CDCl_3$) δ: 7.17 (t, 2H, $J = 8.0$ Hz, ArH3′), 6.74 (t, 1H, $J = 8.0$ Hz, ArH4′), 6.68 (d, 2H, $J = 8.0$ Hz, ArH2′), 6.15 (bs exchanges with D_2O, 2H, OH and NH), 4.26 (dd, X part of ABM2X system, 1H, JAX = 5.0 Hz, JBX = 7.0 Hz, C1H), 2.68 (t, M2 part of ABM2X system, 2H, $J = 7.0$ Hz, C4H2), 2.30–2.00 (unresolved AB part of ABM2X system, 2H, $C3H_2$), 2.11 (s, 3H, SCH_3). ^{13}C NMR ($CDCl_3$) δ: 179.3 (C2), 146.7 (C1′), 129.8 (C3′), 119.4 (C4′), 114.1 (C2′), 56.0 (C1), 32.4 (C4), 30.6 (C3), 15.7 (SCH_3). Data are consistant with literature values.[1b] HRMS: found M + H, 226.088805. $C_{11}H_{16}NO_2S$ requires M + H, 226.089628.

N-Phenyl-L-proline 5h. Prepared from **4 h** (1.02 g, 5.0 mmol) via general procedure **D**. Hydrolysis was complete after 20 h. The product was initially obtained as yellow oil, which was diluted with hexane and cooled at −20 °C. After 2 days, clusters of large clear plate crystals of **5 h** were collected (0.81 g, 85%). Mp: 90–91 °C. $[\alpha]_D^{22}$ −47.1 (c 1.0, $CHCl_3$) [lit.[1b] $[\alpha]_D^{22}$ −46.8 (c 1.1, $CHCl_3$)]. ^1H NMR ($CDCl_3$) δ: 10.68 (bs exchanges with D_2O, 1H, OH), 7.24 (dd, 2H, $J = 8.0$, 7.0 Hz, ArH3′), 6.76 (t, 1H, $J = 8.0$ Hz, ArH4′), 6.58 (d, 2H, $J = 8.0$ Hz, ArH2′), 4.21 (dd, 1H, $J = 8.0$, 3.0 Hz, C1H), 3.59 and 3.33 (m, 1H and m, 1H, $C5H_2$), 2.26 (m, 2H, $C3H_2$), 2.07 (m, 2H, $C4H_2$). ^{13}C NMR ($CDCl_3$) δ: 180.3 (C2), 146.9 (C1′), 129.6 (C3′), 117.7 (C4′), 112.67 (C2′), 61.3 (C1), 48.9 (C5), 31.3 (C3), 24.2 (C4) (compared well with the reported spectra[17] of N-phenyl-L-proline**)**. Found: C, 68.41; H, 6.50; N, 7.19. $C_{11}H_{13}NO_2$ requires C, 69.09; H, 6.85; N, 7.32.

N-Phenyl-L-tyrosine 5k. Prepared from **4k** (1.00 g, 3.7 mmol) via general procedure **D**. Hydrolysis was complete after 25 h. The product was initially obtained as a green solid, which was dissolved in acetone and decolorized with activated charcoal. The off-white powder was then dissolved in hot ether and allowed to slowly evaporate to yield **5k** as a white powder, mp 167–168 °C. $[\alpha]_D^{22}$ +21.7 (c, 1.0 CH_3OH) [lit.[1b] $[\alpha]_D^{25}$ +23.9 (c, 1.0 CH_3OH)]. ^1H NMR (CD_3COCD_3) δ: 7.13 (d, 2H, $J = 8.5$ Hz, ArH5,9), 7.09 (dd, 2H, $J = 8.0$ Hz, 7.0 Hz, ArH3′), 6.75 (d, 2H, $J = 8.5$ Hz, ArH6,8), 6.67 (d, 2H, $J = 8.0$ Hz, ArH2′), 6.61 (t, 1H, $J = 7.0$ Hz, ArH4′), 4.27 (dd, X part of ABX system, 1H, JAX = 6.0 Hz, JBX = 7.0 Hz, C1H), 3.05 (AB part of ABX system, 2H, $J = 14.0$ Hz, $C3H_2$), 2.12 (bs exchanges with D_2O, 2H, OH and NH). ^{13}C NMR (CD_3COCD_3) δ: 175.3 (C2), 157.7 (C7), 149.2 (C1′), 131.9 (C5,9), 130.5 (C3′), 129.7 (C4), 118.8 (C4′), 116.6 (C6,8), 114.7 (C2′), 59.3 (C1), 39.0 (C3). Data are consistant with literature values.[1b] HRMS: found M + H, 258.11171. $C_{15}H_{16}NO_3$ requires M + H, 258.112472.

N-Phenyl-L-aspartic acid 5l. Prepared from **4l** (0.67 g, 2.8 mmol) and 1 M NaOH (6 mL, 6 mmol) via general procedure D. Hydrolysis was complete after 20 h. The product was initially collected as an orange solid and recrystallized from ether/hexane to yield **5l** as clear flat crystals (0.50 g, 85%). Mp 146–147 °C. $[\alpha]_D^{22}$ −17.5 (c 1.0, CH_3COCH_3). ^1H NMR (CD_3COCD_3) δ: 7.13 (t, 2H, $J = 8.0$ Hz, ArH3′), 6.74 (d, 2H, $J = 8.0$ Hz, ArH2′), 6.65 (t, 1H, $J = 8.0$ Hz, ArH4′), 4.49 (dd, X part of ABX system, 1H, JAX = 6.0 Hz, JBX = 7.0 Hz, C1H), 2.88 (AB part of ABX system, 2H, $J = 16.0$ Hz, $C3H_2$).^{13}C NMR (CD_3COCD_3) δ: 174.6 (C2), 172.8

(C4), 149.0 (C1′), 130.6 (C3′), 119.2 (C4′), 115.0 (C2′), 54.5 (C1), 38.2 (C3). HRMS: found: M + H, 210.075763. $C_{10}H_{12}NO_4$ requires M + H, 210.076085.

Synthesis of Chiral Dipeptides 6: General Procedure E

N-Phenyl amino acid **5** (1 mmol), L-alanine, or L-phenylalanine amino acid methyl ester hydrochloride **2b** or **2f** (1 mmol), triethylamine (1 mmol), N-hydroxysuccinimide (1 mmol), and CH_2Cl_2 (20 mL) were mixed in a 50-mL, round-bottom flask and stirred at 0 °C for 1 h. EDC (1 mmol) was added to the stirred mixture, which was allowed to slowly warm to room temperature, and stirring continued for 30 h. The clear solution was concentrated to dryness in vacuo, dissolved in ethyl acetate, and washed with 10% Na_2CO_3 and water before drying over $MgSO_4$ and evaporated to dryness. The residue was dissolved in minimal CH_2Cl_2, diluted with hexane, and slowly evaporated. The product was obtained as a white precipitate, which was recrystallized from a suitable solvent.

N-Phenyl-L-alanine-L-phenylalanine methyl ester 6b. Prepared from **5b** (0.10 g, 0.6 mmol) and **2f** (0.13 g, 0.6 mmol) via general procedure E. The product was collected as a white solid and recrystallized from CH_2Cl_2/hexane to yield **6b** as small white crystals (0.14 g, 71%). Mp 131–133 °C. ^{1}H NMR ($CDCl_3$,) δ: 7.32–7.02 (m, 7H, ArH14–18, 3′,5′), 6.79 (t, 1H, $J = 7.5$ Hz, ArH4′), 6.57 (d, 2H, $J = 8.0$ Hz, ArH2′,6′), 4.84 (m, X part of ABX system,1H, C3H), 3.76 (bs exchanges with D_2O, 2H, NH), 3.75 (m, 1H, C1H), 3.63 (s, 3H, OCH_3), 3.27–2.94 (AB part of ABX system, 2H, $J = 14.0$ Hz, C12H_2), 1.37 (d, 3H, $J = 7.0$ Hz, C3H_3). ^{13}C NMR ($CDCl_3$) δ: 174.1 (C11), 171.8 (C2), 146.8 (C1′), 136.3 (C16), 129.5 (C14,18), 129.4 (C3′,5′), 128.8 (C15,17), 127.3 (C16), 119.5 (C4′), 114.23 (C2′,6′), 55.6 (C3), 53.1 (C1), 52.5 (OCH_3), 38.0 (C5), 19.8 (C3).

N-Phenyl-DL-alanine-L-phenylalanine methyl ester 6b*. Prepared from **5b*** (0.10 g, 0.6 mmol) and **2f** (0.13 g, 0.6 mmol) via general procedure E. The product was collected as an off white-solid and recrystallized from CH_2Cl_2/hexane to yield **6b*** as a white crystalline solid (0.12 g, 62%). Mp: 116–118 °C. ^{1}H NMR ($CDCl_3$) δ: 7.33–7.02 (m, 14H, ArH15–17,3′,5′), 6.79 (t, 2H, $J = 7.5$ Hz, ArH4′), 6.58 (d, 2H, $J = 7.5$ Hz, ArH2′, 6′, DL), 6.57 (d, 2H, $J = 7.5$ Hz, ArH2′ LL), 4.84 (m, 2H, C12H), 3.75 (bs exchanges with D_2O, 4H, NH), 3.74 (m, 2H, C1H), 3.63 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.27–2.93 (m, 4H, C12H_2), 1.47 (d, 3H, $J = 7.0$ Hz, C3H_3, DL), 1.38 (d, 3H, $J = 7.0$ Hz, C3H_3, LL). ^{13}C NMR ($CDCl_3$) δ: 174.2, 174.0 (C11), 172.0, 171.8 (C2), 146.8, 146.7 (C1′), 136.3, 135.7 (C13), 129.7, 129.6 (C15,17), 129.5, 129.4 (C3′,5′), 128.9, 128.8 (C14, 18), 127.3, 127.2 (C16), 119.5, 119.4 (C4′), 114.23, 113.8 (C2′,6′), 55.6, 55.2 (C3), 53.1, 53.0 (C1), 52.5, 52.4 (OCH_3), 38.3, 38.0 (C12), 19.9, 19.8 (C3).

N-Phenyl-L-valine-L-phenylalanine methyl ester 6c. Prepared from **5c** (0.12 g, 0.6 mmol) and **2f** (0.13 g, 0.6 mmol) via general procedure E. The crude product was collected as an off-white solid and recrystallized from CH_2Cl_2/hexane to yield **6c** as small white crystals (0.18 g, 84%). Mp 107–109 °C. ^{1}H NMR ($CDCl_3$,) δ: 7.30–6.97 (m, 7H, ArH14–18, 3′,5′), 6.79 (t, 1H, $J = 8.0$ Hz, ArH4′), 6.61 (d, 2H, $J = 8.0$ Hz, ArH2′,6′), 4.88 (dt, X part of ABX system, 1H, JAX = 6.0 Hz,

JBX = 8.0 Hz, C10H), 3.78 (bs exchanges with D_2O, 1H, NH), 3.62 (s, 3H, OCH_3), 3.52 (d, 1H, $J = 5.0$ Hz, C1H), 3.22–2.92 (AB part of ABX system, 2H, $J = 14.0$ Hz, $C12H_2$), 2.23 (m, 1H, C3H), 1.91 (bs exchanges with D_2O, 1H, NH), 0.93 (d, 3H, $J = 7.0$ Hz, $C4/5H_3$), 0.80 (d, 3H, $J = 7.0$ Hz, $C4/5H_3$) (in good agreement with the reported spectra[1b] of N-phenyl-L-valine-L-phenylalanine methyl ester). ^{13}C NMR ($CDCl_3$) δ: 173.0 (C11), 171.9 (C2), 147.7 (C1′), 136.4 (C13), 129.6 (C15,17), 129.4 (C3′), 128.8 (C14,18), 127.3 (C116), 119.4 (C4′), 114.4 (C2), 65.5 (C10), 53.2 (C1), 52.5 (OCH_3), 38.2 (C12), 31.4 (C3), 19.8, 17.8 (C4,5).

N-Phenyl-DL-valine-L-phenylalanine methyl ester 6c*. Prepared from **5c*** (0.12 g, 0.6 mmol) and **2f** (0.13 g, 0.6 mmol) via general procedure E. The crude product was collected as an off-white solid and recrystallized from CH_2Cl_2/hexane to yield **6c*** as small white crystals (0.18 g, 84%). Mp 95–97 °C. ^1H NMR ($CDCl_3$,) δ: 7.32–6.97 (m, 14H, ArH14–18, 3′, 5′), 6.78 (m, 2H, ArH4′), 6.49 (m, 4H, ArH2′,6′), 4.90 (m, 2H, C10H), 4.02 (bs exchanges with D_2O, 4H, NH), 3.70 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 3.57 (d, 1H, $J = 5.0$ Hz, C1H, DL), 3.52 (d, 1H, $J = 5.0$ Hz, C1H,LL), 3.23–2.87 (m, 4H, C12H2), 2.41–2.12 (m, 2H, C3H), 1.02 (d, 3H, $J = 7.0$ Hz, $C4/5H_3$, DL), 0.97 (d, 3H, $J = 7.0$ Hz, $C4/5H_3$, DL), 0.92 (d, 3H, $J = 7.0$ Hz, $C4/5H_3$, LL), 0.80 (d, 3H, J = 7.0 Hz, $C4/5H_3$, LL) (in good agreement with the reported spectra[1b] of N-phenyl-DL-valine-L-phenylalanine methyl ester). ^{13}C NMR ($CDCl_3$) δ: 173.1, 172.9 (C11), 172.1, 171.9 (C2), 147.7, 147.4 (C1′), 136.3, 135.6 (C13), 129.7, 129.5 (C15, 17), 129.4, 129.3 (C3′,5′), 128.9, 128.8 (C14,18), 127.3, 127.2 (C16), 119.4, 119.3 (C4′), 114.4, 114.0 (C2′,6′), 65.5, 64.8 (C10), 53.2, 53.2 (C1), 52.5, 52.5 (OCH_3), 38.2, 38.1 (C112), 31.4, 31.3 (C12), 20.0, 19.8, 17.8, 17.6 (C13,14).

N-Phenyl-L-leucine-L-phenylalanine methyl ester 6d. Prepared from **5d** (0.13 g, 0.6 mmol) and **2f** (0.13 g, 0.6 mmol) via general procedure E. The crude product was collected as a white solid and recrystallized from CH_2Cl_2/hexane to yield **6d** as a white crystalline solid (0.18 g, 81%). Mp 120–122 °C. ^1H NMR ($CDCl_3$) δ: 7.30–7.00 (m, 7H, ArH14–18, 3′, 5′), 6.78 (t, 1H, $J = 7.0$ Hz, ArH4′), 6.58 (d, 2H, $J = 7.0$ Hz, ArH2′,6′), exchanges with D_2O, 2H, NH), 3.68 (m, 1H, C1H), 3.62 (s, 3H, OCH_3), 3.10 (AB part of ABX system, 2H, $J = 14.0$ Hz, $C12H_2$), 1.70 (m, 2H, $C3H_2$), 1.40 (m, 1H, C4H), 0.95 (d, 3H, $J = 6.0$ Hz, $C5/6H_3$), 0.86 (d, 3H, $J = 6.0$ Hz, C5/6H3). ^{13}C NMR ($CDCl_3$) δ: 174.2 (C11), 171.8 (C2), 147.1 (C1′), 136.3 (C3), 129.6 (C15,17), 129.5 (C3′,5′), 128.8 (C14,18), 127.3 (C16), 119.4 (C4′), 114.1 (C2′,6′), 58.6 (C10), 53.1 (C1), 52.5 (OCH_3), 43.0 (C4), 38.0 (C12), 25.4 (C3), 23.4, 22.0 (C5,6).

N-Phenyl-DL-leucine-L-phenylalanine methyl ester 6d*. Prepared from **5d*** (0.13 g, 0.6 mmol) and **2f** (0.13 g, 0.6 mmol) via general procedure E. The crude product was collected as an off-white solid and recrystallised from CH_2Cl_2/hexane to yield **6d*** as small white crystals (0.15 g, 68%). Mp 133–134 °C. ^1H NMR ($CDCl_3$) δ: 7.30–6.98 (m, 14H, ArH14–18,3′,5′), 6.77 (m, 2H, ArH4′), 6.56 (m, 4H, ArH2′,6′), 4.85 (m, 2H, C10H), 3.93 (bs exchanges with D_2O, 4H, NH), 3.71 (m, 2H, C1H), 3.68 (s, 3H, OCH_3, DL), 3.60 (s, 3H, OCH_3, LL), 3.25–2.86 (m, 4H, $C12H_2$), 1.70 (m, 4H, $C3H_2$), 1.41 (m, 2H, C13H), 0.95 (d, 3H, $J = 6.0$ Hz,$C5/6H_3$,), 0.94 (d, 3H, $J = 6.0$ Hz, $C5/6H_3$,), 0.87 (d, 3H, $J = 6.0$ Hz, $C5/6H_3$,), 0.85 (d, 3H, $J = 6.0$ Hz, $C5/6H_3$). ^{13}C NMR ($CDCl_3$) δ: 174.2, 174.1 (C11), 172.0, 171.9 (C2), 147.1, 147.0

(C1′), 136.3, 135.7 (C14), 129.6, 129.5 (C15,117), 129.4, 129.3 (C3′,5′), 128.8, 128.7 (C14,18), 127.2, 127.1 (C16), 119.4, 119.3 (C4′), 114.1, 113.7 (C2′,6′), 58.5, 58.1 (C10), 53.1, 52.5 (C1), 52.5, 52.4 (OCH_3), 43.0, 42.8 (C4), 38.3, 38.0 (C12), 25.5, 25.4 (C3), 23.4, 23.3, 22.0, 21.8 (C5,6).

N-Phenyl-L-phenylalanine-L-alanine methyl ester 6f. Prepared from **5f** (0.15 g, 0.6 mmol) and **2b** (0.09 recrystallized from CH_2Cl_2/hexane to yield **6f** as fine white crystals (0.16 g, 80%). Mp 95–97 °C. ^{1}H NMR ($CDCl_3$) δ: 7.40–7.05 (m, 7H, ArH7–12,3′,5′), 6.79 (t, 1H, $J = 7.0$ Hz, ArH4′), 6.58 (d, 2H, $J = 8.0$ Hz, ArH2′,6′), 4.59 (m, 1H, C3H), 4.00 (dd, X part of ABX system, 1H, JAX = 5.0 Hz, JBX = 8.0 Hz, C1H), 3.87 (bs exchanges with D_2O, 1H, NH), 3.65 (s, 3H, OCH_3), 3.19 (AB part of ABX system, 2H, J = 14.0 Hz, $C6H_2$), 1.36 (d, 3H, J = 7.0 Hz, $C5H_3$). ^{13}C NMR ($CDCl_3$) δ: 173.0 (C4), 172.8 (C2), 146.8 (C1′), 136.7 (C7), 129.6 (C8,10), 129.5 (C3′,5′), 129.2 (C7,11), 127.5 (C9), 119.7 (C4′), 114.6 (C2′,6′), 60.5 (C3), 52.5 (OCH_3), 48.2 (C1), 38.9 (C6), 18.4 (C5).

N-Phenyl-L-methionine-L-phenylalanine methyl ester 6g. Prepared from **5g** (0.14 g, 0.6 mmol) and **2f** (0.13 g, 0.6 mmol) via general procedure E. The crude product was collected as an off-white solid and recrystallized from CH_2Cl_2/hexane to yield **6g** as off-white crystals (0.21 g, 89%). Mp: 97–99 °C. ^{1}H NMR ($CDCl_3$) δ: 7.24 (m, 3H, ArH15,17), 7.18 (t, 2H, $J = 8.0$ Hz, ArH3′,5′), 7.07 (m, 2H, ArH14,18), 6.79 (t, 1H, $J = 7.0$ Hz, ArH4′), 6.60 (d, 2H, $J = 8.0$ Hz, ArH2′,6′), 4.86 (dt, X part of ABX system, 1H, JAX = 6.0 Hz, JBX = 8.0 Hz, C10H), 4.17 (bs exchanges with D_2O, 1H, NH), 3.86 (bs exchanges with D_2O, 1H, NH), 3.86 (dd, X part of ABM2X system, 1H, JAX = 5.0 Hz, JBX = 8.0 Hz, C1H), 3.65 (s, 3H, OCH_3), 3.10 (AB part of ABX system, 2H, $J = 14.0$ Hz, $C12H_2$), 2.51 (t, 2H, $J = 7.0$ Hz, $C5H_2$), 2.10 and 1.90 (m, 1H and m, 1H, AB part of ABM2X system, $C3H_2$), 2.06 (s, 3H, SCH_3). ^{13}C NMR ($CDCl_3$) δ: 173.0 (C11), 171.8 (C2), 146.8 (C1′), 136.2 (13), 129.6 (C3′,5′), 129.4 (C15,17), 128.9 (C14,18), 127.4 (C16), 119.6 (C4′), 114.3 (C2′,6′), 59.2 (C10), 53.2 (C1), 52.6 (OCH_3), 38.1 (C12), 32.2 (C4), 31.0 (C12), 15.7 (SCH_3).

N-Phenyl-L-tyrosine-L-alanine methyl ester 6k. Prepared from **5k** (0.27 g, 1.0 mmol) and **2b** (0.14 g, 1.0 mmol) via general procedure E. The crude product was collected as a yellow solid and recrystallized from ether/hexane to yield **6k** as a white solid (0.21 g, 61%). ^{1}H NMR ($CDCl_3$) δ: 7.16 (t, 2H, $J = 8.0$ Hz, ArH3′,5′), 7.06 (d, 2H, $J = 8.5$ Hz, ArH5,9), 6.80 (t, 1H, $J = 7.0$ Hz, ArH4′), 6.78 (d, 2H, $J = 8.5$ Hz, ArH6,8), 6.57 (d, 2H, $J = 8.0$ Hz, ArH2′,6′), 4.59 (d, 1H, $J = 7.0$ Hz, C10H), 3.92 (dd, X part of ABX system, 1H, JAX = 5.0 Hz, JBX = 8.0 Hz, C1H), 3.87 (bs exchanges with D_2O, 1H, OH/NH), 3.65 (s, 3H, OCH_3), 3.10 (AB part of ABX system, 2H, $J = 14.0$ Hz, $C3H_2$), 1.68 (bs exchanges with D2O, 2H, OH/NH), 1.36 (d, 3H, $J = 7.0$ Hz, $C12H_3$). ^{13}C NMR ($CDCl_3$) δ: 173.3 (C11), 173.0 (C2), 155.4 (C7), 146.9 (C1′), 130.7 (C5,9), 129.6 (C3′,5′), 128.3 (C4), 119.8 (C4′), 116.1 (C6,8), 114.7 (C2′,6′), 60.7 (C1), 52.6 (OCH_3), 48.2 (C10), 38.1 (C6), 18.4 (C12).

N-Phenyl-L-aspartic acid di-(L-alanine methyl ester) 7. Prepared from **5l** (0.13 g, 0.6 mmol) **2b** (0.17 g, 1.2 mmol), triethylamine (0.20 mL, 1.2 mmol), EDC (0.22 mL, 1.2 mmol), and N-hydroxysuccinimide (0.14 g, 1.2 mmol) via general procedure E. The crude product was collected as an off-white solid and recrystallized

from ether/hexane to yield **7** as a white solid (0.20 g, 88%). Mp 146–148 °C. ^{1}H NMR ($CDCl_3$) δ: 7.20 (t, 2H, $J = 8.0$ Hz, ArH3′,5′), 6.79 (t, 1H, $J = 8.0$ Hz, ArH4′), 6.71 (d, 2H, $J = 8.0$ Hz, ArH2′,6′), 4.56 (m, 2H, C3H,C8H), 3.73 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 2.75 (AB part of ABX system, 2H, $J = 14.0$ Hz, $C6H_2$), 1.41 (d, 3H, $J = 7.0$ Hz, $C5/10H_3$), 1.39 (d, 3H, $C5/10H_3$). ^{13}C NMR ($CDCl_3$) δ: 173.9, 173.6, 172.3, 170.9 (C2,4,7, 9), 146.3 (C1′), 129.7 (C3′,5′), 119.3 (C4′), 114.5 (C2′,6′), 56.1 (C1), 52.9, 52.7 (OCH_3), 48.6, 48.5 (C3,8), 38.2 (C6), 18.1, 17.9 (C5,10).

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