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Synthesis of Some N-Aryl α-Amino Acids Using Diaryliodonium Salts

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Bis[(3'-methoxycarbonyl)phenyl]iodonium bromide (**4a**), *bis* (4'-methoxyphenyl)iodonium iodide (**4b**) and *bis* (4'-acetamidophenyl)iodonium iodide (**4c**) were employed for the first time in the arylation of α-amino acid methyl esters. Yields of the synthesised products **5**, **6** and **7** were good to high. These were then hydrolyzed to the corresponding N-aryl α-amino acids **8** and **9**. The chiral integrity of the amino acids was maintained throughout the reaction sequence as confirmed by the synthesis of chiral tripeptide **10** and dipeptides **11**. The structures of the new compounds were confirmed by IR, ^{1}H and ^{13}C NMR in addition to CHN microanalysis or high resolution mass spectrometry.

Key Words: N-Arylation, α-Amino acids, Diaryliodonium salts, Maintained chirality.

INTRODUCTION

In recent years the use of N-aryl amino acids as building blocks in the synthesis of a variety of biologically important products has gained significant momentum[1-9]. These N-aryl amino acids have been used in the synthesis of such molecules as protein kinase C activators[10], indolactam[10]-V10 and its analogue benzolactam[2]-V8. In the synthesis of these compounds, the maintenance of chirality is particularly important to the biological activity of the molecule.

Ma *et al.*[1,2], reported the synthesis of chiral N-phenyl amino acids through the direct reaction of the free amino acid with an aryl halide using a copper catalyzed Ullmann type reaction. While this is a very useful pathway, it is limited in the range of amino acids and aryl functions that can be employed.

Another approach to N-aryl amino acids reports the use of α-diazo-compounds in copper complexes of chiral spiro-bisoxazolines[11]. Again the reaction was limited in the number of chiral N-aryl α-amino acids that could be synthesized.

Diaryliodonium salts have long been used as arylating electrophiles to carbanions, alcohols, Grignard reagents, alkoxides and phenoxides[12]. We have previously reported the use of these reagents in the synthesis of N-aryl amino acid esters commencing from the parent α-amino acid with chirality being maintained[13].

Herein we report the synthesis of eleven N-[(3'-methoxy-carbonyl)phenyl]-L-amino acid methyl esters (**5**), nine of the corresponding N-(3'-carboxyphenyl)-L-amino acids (**8**), nine N-(4'-methoxyphenyl)-L-amino acid esters (**6**), three of the corresponding N-(4'-methoxyphenyl)-L-amino acids (**9**) and N-(4'-acetamidophenyl)-L-leucine methyl ester (**7d**).

EXPERIMENTAL

All solvents and reagents were purchased as analytical grade and used without further purification unless otherwise stated. Dichloromethane was distilled from CaH 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. Temperatures are expressed in degrees celsius (ºC) and are uncorrected. Optical rotation measurements were conducted on a Bellingham and Stanley polarimeter No. 582129 using a 10 cm cell. Infrared (IR) spectra were recorded on a Perkin-Elmer 1720-X FT-IR using sodium chloride plates or potassium bromide disc. NMR measurement was performed on a Bruker AC 200 spectrometer. Proton NMR (^{1}H NMR) spectra were acquired at 200 MHz. ^{13}C NMR were acquired at 50 MHz. Spectra were recorded using $CDCl_3$, CD_3COCD_3 and CD_3SOCD_3 with 0.05 % TMS as internal standard, or D_2O using acetone as the internal standard. Chemical shifts (δ) are expressed in ppm relative to the internal standard. Multiplicities are expressed as singlet (s), doublet (d), double doublet (dd), double doublet of doublets (ddd), triplet (t), quartet (q), pentet (pent) and multiplet (m). Each peak is presented in the order: chemical shift, multiplicity, integration, coupling constant and assignment.

GC-MS was performed on a Shimadzu GC-17A gas chromatograph coupled with a Shimadzu QP-5000 mass spectrometer with 70 eV EI ionization. The major ion peaks m/z values are stated with their relative intensities in parentheses. HRMS was conducted by Dr. Sally-Ann Poulsen and co-workers 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 co-workers from Chemical and MicroAnalytical Services Pty. Ltd. in Belmont, Victoria. Analytical thin layer chromatography (TLC) was carried out using Merck Silica Gel 60 F_{254} aluminium supported sheets viewing under UV at λ 254 and 366 nm. Flash column chromatography was performed using Sigma-Aldrich silica gel (200-400 mesh) using compressed air pressure.

Preparation of diaryliodonium salts

General procedure A (based on Berringer *et al.*[12]: Iodine (3.85 g), potassium iodate (10 g) and conc. H_2SO_4 (40 mL) were combined and the mixture stirred at room temp for 24 h. The yellow iodyl sulphate collected on sintered glass, washed thoroughly with acetic acid then resuspended in acetic acid (40 mL). A solution of the aromatic compound (156 mmol) in acetic anhydride (17 mL) was added drop wise over 1 h period to the suspension, stirring at 0 ºC. The reaction vessel was then sealed and stirred for a further 24 h. The mixture was poured onto ice (200 g), the solution then washed with ether (5 × 50 mL). To the aqueous layer (starch-iodide negative) a solution of potassium iodide or bromide (78 mmol) in water (40 mL) was added. The diaryliodonium salt was collected and washed with methanol, ethyl acetate and ether. The solid was then dried under vacuum, over phosphorus pentoxide.

***Bis*[(3-methoxycarbonyl) phenyl] iodonium bromide (4a):** Prepared from methyl benzoate (19.4 mL, 156 mmol) and potassium bromide (9.3 g, 78 mmol), *via* general procedure **A**. The product was collected as a light brown solid. This was washed with ethyl acetate and ether until the filtrate was colourless. The resulting white solid was dried under vacuum over phosphorus pentoxide and solid sodium hydroxide to yield a white powder (23.8 g, 64 %). m.p.: 200-202 ºC. ^{1}H NMR (200 MHz, CD_3SOCD_3, 25 ºC): δ 8.84 (s, 2H, ArH 2'); 8.54 (d, 2H, *J* = 8.0 Hz, ArH 4'); 8.16 (d, *J* = 8.0 Hz, 2H, ArH 6'); 7.67 (t, *J* = 8.0 Hz, 2H, ArH 5'); 3.91 (s, 6H, OCH_3 × 2). ^{13}C NMR (50 MHz, CD_3SOCD_3, 25 ºC): δ = 165.6 (C7'), 140.5 (C6'), 136.4 (C2'), 133.1 (C3'), 132.9 (C5'), 132.8 (C4'), 120.4 (C1'), 53.7 (OCH_3 × 2).

***Bis*(4'-methoxyphenyl)iodonium iodide (4b):** Prepared from methoxy benzene (156 mmol) and potassium bromide (9.30 g, 78 mmol) according to procedure **A**. The resulting precipitate was collected and washed with methanol, ethyl acetate and finally with ether. The solid was dried under vacuum, over phosphorous pentoxide to obtain the product as a white powder (15.0 g, 42 %). m.p.: 179-181 ºC. (Lit.[12] 179-182 ºC). ^{1}H NMR (200 MHz, CD_3SOCD_3, 25 ºC): δ 8.15 (d, *J* = 9.0 Hz, 4H, ArH 2',6'), 7.08 (d, *J* = 9.0 Hz, 4H, ArH 3',5'), 3.82 (s, 6H, OCH_3 × 2). ^{13}C NMR (50 MHz, CD_3SOCD_3, 25 ºC): δ 161.7 (C4'), 136.9 (C3',5'), 117.3 (C2',6'), 107.7 (C1'), 55.8 (C7').

***Bis*(4'-acetamidophenyl) Iodonium iodide (4c):** Prepared from acetanilide (156 mmol) and potassium bromide (9.3 g, 78 mmol) according to procedure **A**. The resulting precipitate was collected, washed with alcohol and ether until the washings were colourless, then dried *in vacuo* over phosphorus pentoxide and sodium hydroxide to obtain the product as a yellow powder (10.6 g, 66 %). m.p.: 174-176 ºC, (Lit.[12] 173 ºC). ^{1}H NMR (200 MHz, CD_3SOCD_3, 25 ºC): δ 10.33 (bs exchanges with D_2O, 2H, NH × 2), 8.13 (d, *J* = 8.5 Hz, 4H, ArH2,6,2',6'), 7.70 (d, *J* = 8.5 Hz, 4H, ArH3,5,3',5'), 2.09 (s, 6H, C8,8'H3). ^{13}C NMR (50 MHz, CD_3SOCD_3, 25 ºC): δ 170.0 (C7,7'), 143.2 (C4,4'), 136.8 (C2,6 and 2',6'), 122.2 (C3,5,3',5'), 109.9 (C1,1'), 25.0 (C8,8').

N-[(3'-Methoxycarbonyl)phenyl]amino acid methyl esters (5)

General procedure B: The (S)-amino acid methyl ester free amine **3** (10.0 mmol), silver nitrate (5.1 mmol), copper (I) bromide (0.1 mmol), *bis*[(3'-methoxycarbonyl)phenyl] iodonium bromide **4a** (5.0 mmol) and anhydrous acetonitrile (25 mL) were combined in a 100 mL round bottomed flask equipped with stirring bar, reflux condenser and suspended in an oil bath. The system was flushed with nitrogen, sealed with a latex balloon and refluxed at 90 ºC for 5 h in a dark room. On cooling to room temperature, sodium carbonate (1 g) was added, the mixture gravity filtered and the filtrate concentrated *in vacuo*. The resulting oil was loaded onto a silica flash column and eluted using hexane/dichloromethane/ethyl acetate. The collected fractions were run on analytical TLC plates, the product being observed as a fluorescent blue spot at 366 nm.

N-[(3'-Methoxycarbonyl)phenyl]glycine methyl ester (5a): Prepared from **3a** (0.92 g, 10 mmol), *via* general procedure **B**. The crude product was isolated as brown oil, this was re-run on a flash column eluting with hexane/ethyl acetate. The pure compound **5a** was obtained as a bright yellow oil (0.33 g, 30 %). ^{1}H NMR (200 MHz, $CDCl_3$, 25 ºC): δ 7.42 (dt, *J* = 1.0 Hz, 8.0 Hz, 1H, ArH4'), 7.26 (m, 1H, ArH2'), 7.24 (t, *J* = 8.0 Hz, 1H, ArH5'), 6.80 (ddd, *J* = 2.5 Hz, 1.0 Hz, 1H, 8.0 Hz, ArH6'), 4.46 (bs exchanges with D_2O, 1H, NH), 3.95 (s, 2H, C1H_2), 3.89 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 171.2 (C2), 167.2 (C7'), 146.9 (C1'), 131.0 (C3'), 129.1 (C5'), 119.2 (C6'), 117.5 (C4'), 113.2 (C2'), 52.2 (OCH_3), 51.9 (OCH_3), 45.4 (C1).

N-[(3'-Methoxycarbonyl)phenyl]-L-alanine methyl ester (5b): Prepared from **3b** (0.46 g, 4.5 mmol), *via* general procedure **B**. The crude product was isolated as viscous yellow oil. This was re-run on a flash column to obtain the analytically pure **5b** as yellow oil (0.43 g, 83 %). $[\alpha]_D^{22}$ -31.3 (c 3.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, 25 ºC): δ 7.41 (dt, *J* = 1.0 Hz, 8.0 Hz, 1H, ArH4'), 7.27 (m, 1H, ArH2'), 7.23 (t, *J* = 8.0 Hz, 1H, ArH5'), 6.78 (ddd, *J* = 2.5 Hz, 1.0 Hz, 8.0 Hz, 1H, ArH6'), 4.70 (bs exchanges with D_2O, 1H, NH), 4.24 (q, *J* = 7.0 Hz, 1H, C1H), 3.89 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 1.49 (d, *J* = 7.0 Hz, 3H, C3H_3). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 174.7 (C2), 167.3 (C7'), 146.5 (C1'), 131.0 (C3'), 129.2 (C5'), 119.3 (C6'), 117.7(C4'), 113.8 (C2'), 52.2 (C1), 51.9 (OCH_3), 51.7 (OCH_3), 18.7 (C3). MS m/z: 237 (16), 178 (100), 146 (12), 118 (21), 104 (10), 59 (24). Found (%): C, 60.80; H, 6.45; N, 5.93. $C_{12}H_{15}NO_4$ requires: C, 60.75; H, 6.37; N, 5.90.

N-[(3'-Methoxycarbonyl)phenyl]-L-valine methyl ester (5c): Prepared from **3c** (1.80 g, 14 mmol), *via* general procedure

B. The crude product was initially isolated as yellow oil, this was re-run on a flash column and freeze dried under moderate vacuum to yield the pure compound **5c** as light yellow oil (1.33 g, 72 %). $[\alpha]_D^{20}$ -63.4 (c 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 ºC): δ 7.39 (dt, *J* = 1.0 Hz, 8.0 Hz, 1H, ArH4'), 7.30 (m, 1H, ArH2'), 7.22 (t, *J* = 8.0 Hz, 1H, ArH5'), 6.80 (ddd, *J* = 2.5 Hz, 1.0 Hz, 8.0 Hz, 1H, ArH6'), 4.27 (bs exchanges with D_2O, 1H, NH), 3.94 (d, *J* = 6.0 Hz, 1H, C1H), 3.88 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 2.14 (m, 1H, C3H), 1.04 (d, *J* = 7.0 Hz, 3H, C4/5H_3), 1.02 (d, *J* = 7.0 Hz, 3H, C4/5H3). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 174.1 (C2), 167.6 (C7'), 147.6 (C1'), 131.4 (C3'), 129.6 (C5'), 119.6 (C6'), 118.2 (C4'), 114.4 (C2'), 62.5 (C1), 52.3 (OCH_3), 52.2 (OCH_3), 31.8 (C3), 18.8, 18.4 (C4,5). MS m/z: 265 (13), 222 (27), 206 (100), 162 (42). Found (%): C, 63.19; H, 7.18; N, 5.27. $C_{12}H_{19}NO_4$ requires: C, 63.38; H, 7.22; N, 5.28.

N-[(3'-Methoxycarbonyl)phenyl]-DL-valine methyl ester (5c*): Prepared from **3c*** (0.64 g, 5 mmol), *via* general procedure **B**. The product **5c*** was isolated as a golden brown, viscous oil (0.50 g, 75 %). $[\alpha]_D^{22}$ 0.0 (c 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 ºC): δ 7.39 (dt, *J* = 1.0Hz, 8.0 Hz, 1H, ArH4'), 7.30 (dd, *J* = 2.5 Hz, 1.5 Hz, 1H, ArH2'), 7.21 (t, *J* = 8.0 Hz, 1H, ArH5'), 6.80 (ddd, *J* = 2.5 Hz, 1.0 Hz, 8.0 Hz, 1H, ArH6'), 4.28 (bs exchanges with D_2O, 1H, NH), 3.93 (d, *J* = 6.0 Hz, 1H, C1H), 3.88 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 2.13 (m, 1H, C3H), 1.03 (d, *J* = 7.0 Hz, 3H, C4/5H3), 0.99 (d, *J* = 7.0 Hz, 3H, C4/5H3). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 173.7 (C2), 167.1 (C7'), 147.2 (C1'), 130.9 (C3'), 129.1 (C5'), 119.1 (C6'), 117.7 (C4'), 114.0 (C2'), 62.0 (C1), 51.89 (OCH_3), 51.7 (OCH_3), 31.3 (C3), 18.8, 18.4 (C4,5).

N-[(3'-Methoxycarbonyl)phenyl]-L-leucine methyl ester (5d): Prepared from **3d** (3.10 g, 21.3 mmol), *via* general method **B**. The crude product was isolated as yellow oil which was distilled under vacuum to yield **5d** as a clear, viscous oil (2.32 g, 78 %). b.p.: 138 ºC @ 0.02 mmHg. $[\alpha]_D^{22}$ -72.5 (c 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 ºC): δ 7.40 (dt, *J* = 1.0 Hz, 8.0 Hz, 1H, ArH4'), 7.29 (dd, *J* = 2.5 Hz, 1.5 Hz, 1H, ArH2'), 7.21 (t, *J* = 8.0 Hz, 1H, ArH5'), 6.68 (ddd, *J* = 2.5 Hz, 1.0 Hz, 8.0 Hz, 1H, ArH6'), 4.14 (bs exchanges with D_2O, 1H, NH), 4.14 (t, *J* = 7.0 Hz, 1H, C1H), 3.88 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 1.81 (m, 1H, C4H), 1.66 (m, 2H, $C3H_2$), 1.01 (d, *J* = 6.0 Hz, 3H, C5/6H_3), 0.96 (d, *J* = 6.0 Hz, 3H, C5/6H_3). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 174.6 (C2), 167.0 (C7'), 146.8 (C1'), 130.9 (C3'), 129.0 (C5'), 119.1 (C6'), 117.4 (C4'), 113.8 (C2'), 54.7 (C1), 51.8 (OCH_3), 51.7 (OCH_3), 41.9 (C4), 24.6 (C3), 22.5, 21.9 (C5,6). MS m/z: 279 (67), 220 (100), 178 (74), 164 (77), 135 (28), 118 (40), 103 (17), 91 (20). Found (%): C, 64.39; H, 7.61; N, 4.97. $C_{15}H_{21}NO_4$ requires: C, 64.50; H, 7.58; N, 5.01.

N-[(3'-Methoxycarbonyl)phenyl]-L-isoleucine methyl ester (5e): Prepared from **3e** (0.85 g, 5.9 mmol), *via* general procedure **B**. The product **5e** was isolated as clear, light red, viscous oil (0.63 g, 77 %). $[\alpha]_D^{20}$ -41.0 (c 1.2, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 ºC): δ 7.39 (dt, *J* = 1.0 Hz, 8.0 Hz, 1H, ArH4'), 7.29 (dd, *J* = 2.5 Hz, 1.0 Hz, 1H, ArH2'), 7.22 (t, *J* = 8.0 Hz, 1H, ArH5'), 6.80 (ddd, *J* = 2.5Hz, 1.0 Hz, 8.0 Hz, 1H, ArH6'), 4.27 (bs exchanges with D_2O, 1H, NH), 4.01 (d, *J* = 6.0 Hz, 1H, C1H), 3.89 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 1.89 (m, 1H, C3H), 1.63 and 1.31 (m, 1H and m, 1H, $C4H_2$), 0.98 (d, *J* = 7.0 Hz, 3H, C6H_3), 0.97 (t, *J* = 7.0 Hz, 3H, C5H_3). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 173.6 (CO), 167.1 (C7'), 147.1 (C1'), 130.9 (C5'), 129.0 (C5'), 118.0 (C6'), 117.5 (C4'), 113.9 (C2'), 60.7 (C1), 51.7(OCH_3), 51.6 (OCH_3), 37.8 (C3), 25.4 (C6), 15.3 (C4), 11.2 (C5). MS m/z: 279 (18), 220 (100), 162 (58), 103 (11). Found (%): C, 64.57; H, 7.61; N, 5.01. $C_{15}H_{21}NO_4$ requires: C, 64.50; H, 7.58; N, 5.01.

N-[(3'-Methoxycarbonyl)phenyl]-L-phenylalanine methyl ester (5f): Prepared from **3f** (2.50 g, 14 mmol), *via* general procedure **B**. The product was isolated as a viscous yellow oil which was distilled under vacuum to yield **5f** as viscous, clear yellow oil (1.84 g, 84 %). b.p.: 169 ºC @ 0.02 mmHg. $[\alpha]_D^{20}$ +26.3 (c 4.2, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 ºC): δ 7.40 (dt, *J* = 1.0 Hz, *J* = 8.0 Hz, 1H, ArH4'), 7.26 (m, 6H, ArH5-9,2'), 7.17 (t, *J* = 8.0 Hz, 1H, ArH5'), 6.76 (ddd, *J* = 2.5 Hz, 1.0 Hz, 8.0 Hz, 1H, ArH6'), 4.43 (t, X part of ABX system, *J* = 6.0 Hz, 1H, C1H), 3.89 (bs exchanges with D_2O, 1H, NH), 3.87 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.15 (AB part of ABX system, *J* = 14.0 Hz, 2H, $C3H_2$). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 173.2 (C2), 167.2 (C7'), 146.3 (C1'), 136.0 (C4), 131.1 (C3'), 129.2 (C5,6,8,9), 128.5 (C5'), 127.0 (C7), 119.5 (C6'), 117.9 (C4'), 114.0 (C2'), 57.4 (C1), 52.1 (OCH_3), 52.0 (OCH_3), 38.4 (C3). MS m/z: 313 (50), 254 (67), 222 (100), 162 (82), 135 (54), 103 (38), 91 (45). Found (%): C, 69.02; H, 6.20; N, 4.39. $C_{18}H_{19}NO_4$ requires: C, 68.99; H, 6.11; N, 4.47.

N-[(3'-Methoxycarbonyl)phenyl]-L-methionine methyl ester (5g): Prepared from **3g** (1.60 g, 9.8 mmol), *via* general procedure **B**. The crude product was isolated as a brown oil, this was re-run on a flash column eluting with hexane/ethyl acetate. The pure compound **5g** was obtained as viscous, green/brown oil (0.95 g, 65 %). $[\alpha]_D^{20}$ -12.1 (c 3.3, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 ºC): δ 7.42 (dt, *J* = 1.0 Hz, 8.0 Hz, 1H, ArH4'), 7.32 (m, 1H, ArH2'), 7.24 (t, *J* = 8.0 Hz, 1H, ArH5'), 6.84 (ddd, *J* = 2.5 Hz, 1.0 Hz, 8.0 Hz, 1H, ArH6'), 4.33 (bs exchanges with D_2O, 1H, NH), 4.32 (dd, X part of ABM2X system, J_{AX} = 5.0 Hz, J_{BX} = 7.0 Hz, 1H, C1H), 3.89 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 2.63 (t, M_2 part of ABM_2X system, *J* = 7.0 Hz, 2H, $C4H_2$), 2.13 (unresolved AB part of ABM_2X system, 2H, $C3H_2$), 2.11 (s, 3H, SCH_3). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 173.8 (C2), 167.1 (C7'), 146.69 (C1'), 130.9 (C3'), 129.1 (C5'), 119.4 (C6'), 117.8 (C4'), 114.0 (C2'), 55.1 (C1), 52.2 (OCH_3), 51.9 (OCH_3), 31.9 (C4), 30.0 (C3), 15.2 (SCH_3). MS m/z: 297 (37), 238 (96), 190 (55), 162 (30), 61 (100). Found (%): C, 56.40; H, 6.50; N, 4.67; S, 10.60. $C_{14}H_{19}NO_4S$ requires: C, 56.55; H, 6.44; N, 4.71; S, 10.78.

N-[(3'-Methoxycarbonyl)phenyl]-L-proline methyl ester (5h): Prepared from **3h** (1.50 g, 12 mmol), *via* general procedure **B**. Reaction time was 5 h with the product isolated as a yellow oil. The oil was dissolved in dichloromethane and extracted into 20 % HCl. The aqueous layer was then neutralized with solid Na_2CO_3, extracted with hexane/chloroform (50/50), the organic layer dried over $MgSO_4$ and concentrated to afford the pure compound 5 h as a light yellow oil (1.12 g, 73 %).

$[\alpha]_D^{22}$ -87.2 (c 1.0, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 ºC): δ 7.38 (dt, *J* = 1.0 Hz, 8.0 Hz, 1H, ArH4'), 7.26 (t, *J* = 8.0 Hz, 1H, ArH5'), 7.22 (m, 1H, ArH2'), 6.70 (ddd, *J* = 2.5 Hz, 1.0 Hz, 8.0 Hz, 1H, ArH6'), 4.30 (dd, *J* = 8.0 Hz, 2.5 Hz, 1H, C1H), 3.89 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.61 and 3.41 (m, 1H and m, 1H, $C5H_2$), 2.35 - 2.05 (m, 4H, $C3H_2$ and $C4H_2$). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 174.5 (C2), 167 (C7'), 146.5 (C1'), 130.9 (C3'), 129.1 (C5'), 117.7 (C6'), 116.2 (C4'), 112.7 (C2'), 60.6 (C1), 52.2 (OCH_3), 52.0 (OCH_3), 48.3 (C5), 30.8 (C3), 23.7 (C4). MS m/z: 263 (14), 204 (100), 145 (11). HRMS: Found (%): M + H, 264.122031. $C_{14}H_{18}NO_4$ requires M + H, 264.123032.

N-[(3'-Methoxycarbonyl)phenyl]-L-threonine methyl ester (5i): Prepared from **3i** (1.04 g, 8.0 mmol), *via* general procedure **B**. The product **5i** was isolated as brown oil (0.47 g, 45 %). $[\alpha]_D^{22}$ -39.2 (c 1.2, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 ºC): δ 7.44 (dt, *J* = 1.0 Hz, 8.0 Hz, 1H, ArH4'), 7.34 (t, *J* = 2.5 Hz, 1H, ArH2'), 7.24 (t, *J* = 8.0 Hz, 1H, ArH5'), 6.86 (dd, *J* = 2.5 Hz, *J* = 8.0 Hz, 1H, ArH6'), 4.65 (bs exchanges with D_2O, 1H, OH), 4.23 (dd, *J* = 6.0 Hz, 4.0 Hz, 1H, C3H), 4.04 (bs exchanges with D_2O, 1H, NH), 3.89 (s, 3H, OCH_3), 3.78 (d, *J* = 6.0 Hz, 1H, C1H), 3.76 (s, 1H, OCH_3), 1.32 (d, *J* = 6.0 Hz, 3H, $C4H_3$). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 173.4 (C2), 167.6 (C7'), 147.5 (C1'), 131.5 (C3'), 129.6 (C5'), 120.3 (C6'), 118.8 (C4'), 114.7 (C2'), 68.6 (C3), 62.4 (C1), 52.8 (OCH_3), 52.4 (OCH_3), 20.1 (C4). MS m/z: 223 (17), 164 (100), 132 (10), 104 (14). HRMS: Found (%): M + H, 268.116663. $C_{13}H_{18}NO_5$ requires M + H, 268.117951.

N-[(3'-Methoxycarbonyl)phenyl]-L-tyrosine methyl ester (5j): Prepared from **3j** (2.73 g, 14 mmol), *via* general procedure **B**. The product was initially isolated as an orange oil. This was re-run on a silica flash column eluting with hexane/ethyl acetate to obtain the pure compound **5j** as a clear, light orange oil (1.73 g, 75 %). $[\alpha]_D^{20}$ +35.9 (c 1.3, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 ºC): δ 7.40 (dt, *J* = 1.0 Hz, 8.0 Hz, 1H, ArH4'), 7.25 (m, 1H, ArH2'), 7.22 (t, *J* = 8.0 Hz, 1H, ArH5'), 7.01 (d, *J* = 8.5 Hz, 2H, ArH5,9), 6.78 (m, 1H, ArH6'), 6.75 (d, *J* = 8.5 Hz, 2H, ArH6,8), 4.89 (bs exchanges with D_2O, 1H, OH), 4.36 (bs exchanges with D_2O, 1H, NH), 4.37 (dd, X part of ABX system, J_{AX} = 6.0 Hz, J_{BX} = 7.0 Hz, 1H, C1H), 3.89 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.08 (AB part of ABX system, *J* = 14.0 Hz, 2H, $C3H_2$). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 173.5 (C2), 167.5 (C7'), 155.2 (C7), 146.4 (C1'), 130.9 (C3'), 130.3 (C5,9), 129.3 (C5'), 127.4 (C4), 119.5 (C6'), 118.1 (C4'), 115.5 (C6,8), 114.0 (C2'), 57.5 (C1), 52.2 (OCH_3), 52.1 (OCH_3), 37.5 (C3). Found (%): C, 65.70; H, 5.87; N, 4.31. $C_{18}H_{19}NO_5$ requires: C, 65.64; H, 5.81; N, 4.25.

N-[(3'-Methoxycarbonyl)phenyl]-L-aspartic acid dimethyl ester (5k): Prepared from **3k** (2.26 g, 14 mmol), *via* general procedure **B**. The product was initially isolated as bright green oil, this was re-run on a silica flash column eluting with hexane/ethyl acetate to obtain the pure compound **5k** as a bright yellow oil (1.24 g, 60 %). $[\alpha]_D^{22}$ +24.7 (c 0.90, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 ºC): δ 7.44 (dt, *J* = 1.0 Hz, 8.0 Hz, 1H, ArH4'), 7.32 (dd, *J* = 2.5 Hz, 1.5 Hz, 1H, ArH2'), 7.24 (t, *J* = 8.0 Hz, 1H, ArH5'), 6.85 (dd, *J* = 2.5 Hz, 8.0 Hz, 1H, ArH6'), 4.62 (bd exchanges with D_2O, 1H, NH), 4.50 (t, *J* = 5.5 Hz, 1H, C1H), 3.89 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 2.92 (d, *J* = 5.5 Hz, 2H, $C3H_2$). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 172.8 (C2), 171.2 (C4), 167.5 (C7'), 146.6 (C1'), 131.5 (C3'), 129.6 (C5'), 120.2 (C6'), 118.6 (C4'), 114.4 (C2'), 53.4 (C1), 53.0 (OCH_3), 52.4 (OCH_3 × 2), 37.3 (C3). MS m/z: 295 (19), 236 (96), 204 (14), 162 (100), 135 (16). Found (%): C, 57.02; H, 5.83; N, 4.69. $C_{14}H_{17}NO_6$ requires: C, 56.94; H, 5.80; N, 4.74.

N-(4'-Methoxyphenyl)-L-amino acid methyl esters (6)

General procedure C: Amino acid ester free amine (10.0 mmol), *bis* (4'-methoxyphenyl) iodonium iodide (5.0 mmol), $AgNO_3$ (5.1 mmol), CuBr (0.1 mmol) and anhydrous acetonitrile (25 mL) were combined in an oven dried round bottom flask equipped with magnetic stirrer bar and fitted with a condenser. The system was thoroughly flushed with nitrogen, sealed with a latex balloon and heated in an oil bath at 90 ºC for 4 h. The crude reaction mixture was cooled, sodium carbonate (0.5 g) added and the mixture gravity filtered. The solvent was removed under water pump vacuum, the oil was then loaded onto a silica gel flash column and eluted with a solvent grading of hexane/dichloromethane/ethyl acetate. The fractions were analyzed by TLC in dichloromethane. The product was isolated as a clear oil which discoloured on exposure to air. The colour was removed by extraction into 1M HCl, neutralization with sodium carbonate and extraction back into hexane. The organic phase was collected, dried over anhydrous magnesium sulphate and concentrated under nitrogen to a viscous oil.

N-(4'-Methoxyphenyl)-L-alanine methyl ester (6b): Prepared from **3b** (1.44 g, 14 mmol), *via* general procedure **C**. The product **6b** was initially isolated as viscous yellow oil which solidified to a light yellow powder (1.04 g, 71 %) on cooling at -20 ºC. m.p.: 32-34 ºC. $[\alpha]_D^{20}$ -66.7 (c 0.80, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 ºC): δ 6.77 (d, *J* = 9.0 Hz, 2H, ArH3',5'), 6.59 (d, *J* = 9.0 Hz, 2H, ArH2',6'), 4.07 (q, *J* = 7.0 Hz, 1H, C1H), 3.86 (bs exchanges with D_2O, 1H, NH), 3.74 (s, 3H, OCH_3), 3.72 (s, 3H, $C7'H_3$), 1.46 (d, *J* = 7.0 Hz, 3H, $C3H_3$). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 175.3 (C2), 152.6 (C4'), 140.6 (C1'), 114.9, 114.8 (C2',6',3',5'), 55.5 (C1), 52.9 (C7'), 52.0 (OCH_3), 18.9 (C3). MS m/z: 209 (20), 150 (100), 135 (14). Found (%): C, 63.14; H, 7.27; N, 6.75. $C_{11}H_{15}NO_3$ requires: C, 63.14; H, 7.23; N, 6.69.

N-(4'-Methoxyphenyl)-L-valine methyl ester (6c): Prepared from **3c** (0.78 g, 6 mmol), *via* general procedure **C**. The product 6c was isolated as viscous yellow oil (0.60 g, 85 %). $[\alpha]_D^{20}$ -90.8 (c, 0.98 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 ºC): δ 6.76 (d, *J* = 9.0 Hz, 2H, ArH3',5'), 6.60 (d, *J* = 9.0 Hz, 2H, ArH2',6'), 3.84 (bs exchanges with D_2O, 1H, NH), 3.77 (d, *J* = 7.0 Hz, 1H, C1H), 3.73 (s, 3H, OCH_3), 3.69 (s, 3H, C7'H3), 2.08 (m, 1H, C3H), 1.04 (d, *J* = 7.0 Hz, 3H, $C4/5H_3$), 1.01 (d, *J* = 7.0 Hz, 3H, $C4/5H_3$). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 174.8 (C2), 153.0 (C4'), 141.8 (C1'), 115.5, 115.2 (C2',6',3',5'), 64.1 (C1), 56.0 (C7'), 52.0 (OCH_3), 31.9 (C3), 19.4, 19.0 (C4,5). MS m/z: 237 (38), 178 (100), 134 (76), 122 (38), 77 (14). HRMS: Found (%): M + H, 238.142696. $C_{13}H_{20}NO_3$ requires M + H, 238.143772.

N-(4'-Methoxyphenyl)-L-leucine methyl ester (6d): Prepared from **3d** (2.03 g, 14 mmol), *via* general procedure **C**. The product was initially isolated as viscous, clear oil which crystallized to yield **6d** as long clear needle crystals (1.44 g, 82 %). m.p.: 38-40 ºC. $[\alpha]_D^{22}$ -47.3 (c, 1.8 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 ºC): δ 6.76 (d, *J* = 9.0 Hz, 2H, ArH3',5'), 6.59 (d, *J* = 9.0 Hz, 2H, ArH2',6'), 4.01 (t, *J* = 7.0 Hz, 1H, C1H), 3.73 (s, 3H, OCH_3), 3.70 (bs exchanges with D_2O, 1H, NH), 3.68 (s, 3H, C7'H_3), 1.89 (m, 1H, C4H), 1.62 (t, *J* = 7.0Hz, 2H, C3H_2), 0.98 (d, *J* = 8.0 Hz, 3H, C5/6H_3), 0.94 (d, *J* = 8.0 Hz, 3H, C5/6H_3). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 175.4 (C2), 152.7 (C4'), 140.9 (C1'), 115.1, 114.8 (C2',6',3',5'), 56.3 (C7'), 55.6 (C1), 51.8 (OCH_3), 42.4 (C4), 24.8 (C3), 22.7, 22.1 (C5,6). MS m/z: 251 (20), 192 (100), 150 (18), 134 (25). Found (%): C, 67.03; H, 8.37; N, 5.50. $C_{14}H_{21}NO_3$ requires: C, 66.91; H, 8.42; N, 5.57.

N-(4'-Methoxyphenyl)-L-isoleucine methyl ester (6e): Prepared from **3e** (2.03 g, 14 mmol), *via* general procedure **C**. The product **6e** was isolated as clear, colourless oil (1.55 g, 88 %). $[\alpha]_D^{20}$ -60.3 (c, 1.0 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 ºC): δ 6.76 (d, *J* = 9.0 Hz, 2H, ArH3',5'), 6.60 (d, *J* = 9.0 Hz, 2H, ArH2',6'), 3.86 (bs exchanges with D_2O, 1H, NH), 3.84 (d, *J* = 6.0 Hz, 1H, C1H), 3.73 (s, 3H, OCH_3), 3.69 (s, 3H, C7'H_3), 1.83 (m, 1H, C3H), 1.63 and 1.29 (m, 1H and m, 1H, C4H_2), 0.97 (d, *J* = 7.0 Hz, 3H, C6H_3), 0.95 (t, *J* = 7.0 Hz, 3H, C5H_3). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 172.6 (C2), 152.6 (C4'), 141.2 (C1'), 115.0, 114.8 (C2',6',3, 5'), 62.4 (C1), 55.6 (C7'), 51.5 (OCH_3), 38.0 (C3), 25.5 (C6), 15.4 (C4), 11.3 (C5). MS m/z: 251 (29), 192 (100), 162 (16), 134 (82), 122 (17). Found (%): C, 67.02; H, 8.50; N, 5.57. $C_{14}H_{21}NO_3$ requires: C, 66.91; H, 8.42; N, 5.57.

N-(4'-Methoxyphenyl)-L-phenylalanine methyl ester (6f): Prepared from **3f** (2.51 g, 14 mmol), *via* general procedure **C**. The product **6f** was isolated as viscous, yellow oil (1.51 g, 75 %). $[\alpha]_D^{20}$ +26.6 (c, 1.3 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 ºC): δ 7.30-7.15 (m, 5H, ArH5-9), 6.75 (d, *J* = 9.0 Hz, 2H, ArH3',5'), 6.56 (d, *J* = 9.0 Hz, 2H, ArH2',6'), 4.27 (t, *J* = 6.0 Hz, 1H, C1H), 3.87 (bs exchanges with D_2O, 1H, NH), 3.73 (s, 3H, OCH_3), 3.65 (s, 3H, C7'H_3), 3.10 (dd, *J* = 1.5 Hz, *J* = 6.0 Hz, 2H, C3H_2). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 173.3 (C2), 152.1 (C4'), 140.1 (C1'), 136.2 (C4), 128.7 (C5,9), 127.9 (C6,8), 126.3 (C7), 114.5, 114.3 (C2',6',3',5'), 58.3 (C1), 54.8 (C7'), 51.1 (OCH_3), 38.2 (C3). MS m/z: 285 (17), 226 (20), 194 (88), 162 (18), 134 (100), 91 (16), 77 (16). Found (%): C, 71.49; H, 6.68; N, 4.85. $C_{17}H_{19}NO_3$ requires: C, 71.56; H, 6.71; N, 4.91.

N-(4'-Methoxyphenyl)-L-methionine methyl ester (6g): Prepared from **3g** (1.15 g, 7.0 mmol), *via* general procedure **C**. The product **6g** was isolated as viscous, light brown oil (0.33 g, 35 %). $[\alpha]_D^{20}$ -38.5 (c, 1.8 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 ºC): δ 6.76 (d, *J* = 9.0 Hz, 2H, ArH3',5'), 6.62 (d, *J* = 9.0 Hz, 2H, ArH2',6'), 4.17 (dd, X part of ABM_2X system, J_{AX} = 5.0 Hz, J_{BX} = 7.0 Hz, 1H, C1H), 3.72 (s, 3H, OCH_3), 3.70 (s, 3H, C7'H_3), 2.64 (t, M_2 part of ABM_2X system, *J* = 7.0 Hz, 2H, C4H_2), 2.11 (bs exchanges with D_2O, 1H, NH), 2.09 (s, 3H, SCH_3), 2.18-1.86 (unresolved AB part of ABM_2X system, 2H, C3H_2). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 174.8 (C2), 153.1 (C4'), 141.1 (C1'), 115.5, 115.1 (C2',6',3',5'), 56.9 (C1), 55.8 (C7'), 52.4 (OCH_3), 32.6 (C4), 30.5 (C3), 15.6 (SCH_3). MS m/z: 269 (61), 210 (100), 162 (70), 134 (58), 61 (90). HRMS: Found (%): M + H, 270.114971. $C_{13}H_{20}NO_3S$ requires M + H, 270.115842.

N-(4'-Methoxyphenyl)-L-proline methyl ester (6h): Prepared from **3h** (1.80 g, 14 mmol), *via* general procedure **C**. The product **6h** was isolated as a viscous yellow oil (1.13 g, 69 %). $[\alpha]_D^{22}$ -82.4 (c, 1.6 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 ºC): δ 6.82 (d, *J* = 9.0 Hz, 2H, ArH3',5'), 6.50 (d, *J* = 9.0 Hz, 2H, ArH2',6'), 4.19 (dd, *J* = 8.0 Hz, 2.5 Hz, 1H, C1H), 3.74 (s, 3H, OCH_3), 3.70 (s, 3H, C7'H_3), 3.55 and 3.32 (m, 1H and m, 1H, C5H_2), 2.14 (m, 4H, C3H_2 and C4H_2). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 174.7 (C2), 151.0 (C4'), 141.0 (C1'), 114.4, 112.2 (C2',6',3',5'), 60.7 (C1), 55.1 (C7'), 51.4 (OCH_3), 48.2 (C5), 30.3 (C3), 23.4 (C4). MS m/z: 235 (14), 176 (100), 133 (10). Found (%): C, 65.84; H, 6.82; N, 5.78. $C_{13}H_{17}NO_3$ requires: C, 66.36; H, 7.28; N, 5.95.

N-(4'-Methoxyphenyl)-L-tyrosine methyl ester (6j): Prepared from **3j** (1.00 g, 5.1 mmol), *via* general procedure **C**. The product **6j** was isolated as powdery, yellow solid (1.17 g, 76 %). m.p.: 85-87 ºC. $[\alpha]_D^{20}$ +40.7 (c, 0.87 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 ºC): δ 7.02 (d, *J* = 8.0 Hz, 2H, ArH5,9), 6.76 (d, *J* = 9.0 Hz, 2H, ArH3',5'), 6.72 (d, *J* = 8.0 Hz, 2H, ArH6,8), 6.57 (d, *J* = 9.0 Hz, 2H, ArH2',6'), 5.11 (bs exchanges with D_2O, 1H, OH), 4.23 (t, *J* = 6.0 Hz, 1H, C1H), 3.86 (bs exchanges with D_2O, 1H, NH), 3.73 (s, 3H, OCH_3), 3.65 (s, 3H, C7'H_3), 3.03 (d, *J* = 6.0 Hz, 2H, C3H_2). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 174.4 (C2), 154.9 (C7), 152.7 (C4'), 140.3 (C1'), 130.2 (C5,9), 127.7 (C4), 115.4, 115.3 (C2',6',3',5'), 114.9 (C6,8), 59.1 (C1), 55.6 (C7'), 52.0 (OCH_3), 37.8 (C3). MS m/z: 301 (19), 242 (11), 194 (83), 162 (23), 134 (100), 107 (24). Found (%): C, 67.75; H, 6.45; N, 4.85. $C_{17}H_{19}NO_4$ requires: C, 67.76; H, 6.36; N, 4.65.

N-(4'-Methoxyphenyl)-L-aspartic acid dimethyl ester (6k): Prepared from **3k** (2.25 g, 14 mmol), *via* general procedure **C**. The product was initially isolated as viscous orange oil which solidified on cooling at -20 ºC to yield **6k** as large orange crystals (1.60 g, 86 %). m.p.: 24-25 ºC. $[\alpha]_D^{20}$ +4.2 (c, 1.2 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 ºC): δ 6.78 (d, *J* = 9.0 Hz, 2H, ArH3',5'), 6.66 (d, *J* = 9.0 Hz, 2H, ArH2',6'), 4.37 (t, *J* = 6.0 Hz, 1H, C1H), 3.74 (s, 6H, OCH_3 × 2), 3.71 (s, 3H, C7'H_3), 2.85 (d, *J* = 6.0 Hz, 2H, C3H_2). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 173.0 (C2), 170.9 (C4), 153.1 (C4'), 140.2 (C1), 115.7, 114.8 (C2',6',3'5'), 55.6 (C1), 54.8 (C7'), 52.4 (OCH_3), 51.9 (OCH_3), 37.3 (C3). MS m/z: 267 (32), 208 (100), 148 (60), 134 (87), 107 (13). Found (%): C, 58.50; H, 6.46; N, 5.23. $C_{13}H_{17}NO_5$ requires: C, 58.42; H, 6.41; 5.24.

N-(4'-Acetamidophenyl)-(S)-amino acid methyl esters (7)

N-(4'-Acetamidophenyl)-L-leucine methyl ester (7d): Prepared from **3d** (2.03 g, 14 mmol) and *bis*(4'-acetamidophenyl) iodonium iodide (3.65 g, 7 mmol), *via* general procedure **C**. The crude product was isolated as a pale purple

solid. This was recrystallized from hexane/CH_2Cl_2 to yield **7d** as fine white needles (1.38 g, 71 %). m.p.: 121-122 ºC. $[\alpha]_D^{22}$ -69.7 (c 0.90, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, 25 ºC): δ 7.25 (d, *J* = 9.0 Hz, 2H, ArH3',5'), 7.10 (bs, 1H, NH), 6.57 (d, *J* = 9.0 Hz, 2H, ArH2',6'), 4.05 (m, 1H, C1H), 3.94 (bs exchanges with D_2O, 2H, NH), 3.69 (s, 3H, OH_3), 2.12 (s, 3H, C8'H_3), 1.79 (m, 1H, C4H), 1.63 (m, 2H, C3H_2), 0.99 (d, *J* = 7.0 Hz, 3H, C5H_3), 0.94 (d, *J* = 7.0 Hz, 3H, C6H_3). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 175.5 (C2), 168.4 (C7'), 144.4 (C1'), 129.4 (C4'), 122.6 (C3',5'), 114.1 (C2',6'), 55.8 (C1), 52.3 (OCH_3), 42.7 (C4), 25.2 (C3), 24.6 (C8'), 23.0, 22.5 (C5,6). MS m/z: 278 (18), 219 (100), 177 (20), 163 (24), 106 (10). Found (%): C, 64.80; H, 8.03; N, 10.11. $C_{15}H_{22}N_2O_3$ requires: C, 64.73; H, 7.97; N, 10.06.

N-(3'-Carboxyphenyl)amino acids (8)

General procedure D: The N-aryl amino acid ester (1 mmol) was dissolved in anhydrous methanol (5 mL/mmol of ester), to this solution was added drop-wise 1M NaOH (1.1 mmol). The hydrolysis was monitored by TLC. When the hydrolysis was deemed complete, the solution was concentrated to 5 mL, the resulting mixture then extracted between 10 % Na_2CO_3 and dichloromethane, the aqueous layer then acidified with 1M HCl, the precipitate collected, washing with a 50/50 mixture of hexane/dichloromethane. The collected solid was then recrystallized from suitable solvent.

N-(3'-Carboxyphenyl)-L-alanine (8b): Prepared from **5b** (0.60 g, 2.5 mmol), *via* general procedure **D**, with hydrolysis taking 22 h. The product was isolated as a brown powder which was purified *via* column chromatography to yield **8b** as a light brown powder (0.47 g, 90 %). m.p.: 199-201 ºC. $[\alpha]_D^{22}$ -54.8 (c 1.0, CH_3COCH_3). ^{1}H NMR (200 MHz, CD_3COCD_3, 25 ºC): δ 7.33 (m, 2H, ArH2' and 4'), 7.23 (t, *J* = 8.0 Hz, 1H, ArH5'), 6.90 (m, 1H, ArH6'), 5.57 (bs exchanges with D_2O, 3H, OH, NH), 4.18 (q, *J* = 7.0 Hz, 1H, C1H), 1.50 (d, *J* = 7.0 Hz, 3H, C3H_3). ^{13}C NMR (50 MHz, CD_3COCD_3, 25 ºC): δ 176.3 (C2), 168.7 (C7'), 149.5 (C1'), 132.9 (C3'), 130.6 (C5'), 119.9 (C6'), 118.8 (C4'), 115.3 (C2'), 52.9 (C1), 19.5 (C3). HRMS: Found (%): M + H, 210.075035. $C_{10}H_{12}NO_4$ requires M + H, 210.076085.

N-(3'-Carboxyphenyl)-L-valine (8c): Prepared from **5c** (0.84 g, 3.1 mmol), *via* general procedure **D**, with hydrolysis taking 20 h. The crude product was isolated as a brown powder, which was recrystallized from ethyl acetate/hexane to yield **8c** as a white solid (0.65 g, 87 %). m.p.: 131-132 ºC. $[\alpha]_D^{22}$ -91.1 (c 1.0, CH_3COCH_3). ^{1}H NMR (200 MHz, CD_3COCD_3, 25 ºC): δ 9.65 (bs exchanges with D_2O, 2H, OH), 7.41 (m, 1H, ArH2'), 7.33 (dt, *J* = 2.0 Hz, 8.0 Hz, 1H, ArH4'), 7.23 (t, *J* = 8.0 Hz, 1H, ArH5'), 6.96 (ddd, *J* = 2.0 Hz, 1.0 Hz, 8.0 Hz, 1H, ArH6'), 5.39 (bs exchanges with D_2O, 1H, NH), 3.90 (d, *J* = 6.0 Hz, 1H, C1H), 2.20 (m, 1H, C3H), 1.10 (d, *J* = 5.0 Hz, 3H, C4/5H_3), 1.08 (d, *J* = 5.0 Hz, 3H, C4/5H_3). ^{13}C NMR (50 MHz, CD_3COCD_3, 25 ºC): δ 175.4 (C2), 168.9 (C7'), 150.0 (C1'), 132.8 (C3'), 130.6 (C5'), 119.9 (C6'), 119.0 (C4'), 115.5 (C2'), 63.6 (C1), 32.5 (C3), 20.2, 19.7 (C4,5). Found (%): C, 60.71; H, 6.40; N, 6.01. $C_{12}H_{15}NO_4$ requires: C, 60.75; H, 6.37; N, 5.90.

N-(3'-Carboxyphenyl)-L-leucine (8d): Prepared from **5d** (0.81 g, 2.8 mmol), *via* general procedure H, with hydrolysis taking 23 h. The crude product was obtained as a light brown powder which was recrystallized from acetonitrile to yield **8d** as small white crystals (0.66 g, 91 %). m.p.: 171-173 ºC. $[\alpha]_D^{20}$ -44.5 (c 1.0, CH_3COCH_3). ^{1}H NMR (200 MHz, CD_3COCD_3, 25 ºC): δ 7.38 (bs exchanges with D_2O, 2H, OH), 7.37 (s, 1H, ArH2'), 7.31 (d, *J* = 2.0 Hz, 1H, ArH4'), 7.23 (t, *J* = 8.0 Hz, 1H, ArH5'), 6.92 (d, *J* = 8.0 Hz, 1H, ArH6'), 5.52 (bs exchanges wih D_2O, 1H, NH), 4.12 (t, *J* = 7.0 Hz, 1H, C1H); 1.91 (m, 1H, C4H), 1.73 (m, 2H, C3H_2), 1.00 (d, *J* = 7.0 Hz, 3H, C5/6H_3), 0.96 (d, *J* = 7.0 Hz, 3H, C5/6H_3). ^{13}C NMR (50 MHz, CD_3COCD_3, 25 ºC): δ 175.5 (C2), 167.7 (C7'), 148.1 (C1'), 131.3 (C3'), 128.9 (C5'), 117.0 (C6'), 116.4 (C4'), 112.5 (C2'), 54.0 (C1), 40.9 (C4), 24.3 (C3), 22.7, 21.6 (C5,6). Found (%): C, 62.17; H, 6.79; N, 5.60. $C_{13}H_{17}NO_4$ requires: C, 62.14; H, 6.82; N, 5.57.

N-(3'-Carboxyphenyl)-L-isoleucine (8e): Prepared from **5e** (0.57 g, 2.0 mmol), *via* general procedure **D**, with hydrolysis taking 22 h. The crude product was obtained as a brown solid, this was recrystallized from ether/hexane to yield **8e** as light brown crystals (0.42 g, 82 %). m.p.: 173-174 ºC. $[\alpha]_D^{20}$ -58.7 (c 1.0, CH_3COCH_3). ^{1}H NMR (200 MHz, CD_3COCD_3, 25 ºC): δ 9.53 (bs exchanges with D_2O, 2H, OH), 7.41 (m, 1H, ArH2'), 7.33 (dt, *J* = 2.0 Hz, 8.0 Hz, 1H, ArH4'), 7.23 (t, *J* = 8.0 Hz, 1H, ArH5'), 6.96 (ddd, *J* = 2.0 Hz, 1.0 Hz, 8.0 Hz, 1H, ArH6'), 5.61 (bs exchanges with D_2O, 1H, NH), 3.98 (d, *J* = 6.0 Hz, 1H, C1H), 1.97 (m, 1H, C3H), 1.73 and 1.41 (m, 1H and m, 1H, C4H_2), 1.04 (d, *J* = 7.0 Hz, 3H, C6H_3), 0.97 (t, *J* = 7.0 Hz, 3H, C5H_3). ^{13}C NMR (50 MHz, CD_3COCD_3, 25 ºC): δ 175.2 (C2), 168.8 (C7'), 149.9 (C1'), 132.8 (C3'), 130.6 (C5'), 119.9 (C6'), 118.9 (C4'), 115.4 (C2'), 62.3 (C1), 39.0 (C3), 26.9 (C6), 16.7 (C4), 12.4 (C5). HRMS: Found (%): M + H, 252.121996. $C_{13}H_{18}NO_4$ requires: 252.123038.

N-(3'-Carboxyphenyl)-L-phenylalanine (8f): Prepared from **5f** (1.96g, 6.3 mmol), *via* general procedure **D**, with hydrolysis taking 26 h. The crude product was isolated as a brown solid which was recrystallized from toluene to yield **8f** as light yellow crystals (1.57 g, 88 %). m.p.: 178-180 ºC. +7.9 (c 1.0, CH_3COCH_3). ^{1}H NMR (200 MHz, CD_3COCD_3, 25 ºC): δ 7.40-7.15 (m, 8H, ArH5-9,2',4',5'), 6.91 (ddd, *J* = 2.5 Hz, 1.0 Hz, 8.0 Hz, 1H, ArH6'), 5.50 (bs exchanges with D_2O, 2H, OH, NH), 4.41 (dd, X part of ABX system, J_{AX} = 6.0 Hz, J_{BX} = 8.0 Hz, 1H, C1H), 3.19 (AB part of ABX system, *J* = 14.0 Hz, 2H, C3H_2). ^{13}C NMR (50 MHz, CD_3COCD_3, 25 ºC): δ 175.0 (C2), 168.7 (C7'), 149.4 (C1'), 139.1 (C4), 132.9 (C3'), 130.9 (C6,8), 130.6 (C5'), 129.8 (C5,9), 128.1 (C7), 120.1 (C6'), 119.0 (C4'), 115.5 (C2'), 59.1 (C1), 39.8 (C3). Found (%): C, 67.40; H, 5.24; N, 5.03. $C_{16}H_{15}NO_4$ requires: C, 67.36; H, 5.30; N, 4.91.

N-(3'-Carboxyphenyl)-L-methionine 8g: Prepared from **5g** (0.73 g, 2.5 mmol), *via* general procedure **D**, with hydrolysis complete in 21 h. The product **8g** was obtained as a light yellow solid (0.50 g, 76 %) which rapidly decomposed to a red solid. m.p.: 156-157 ºC. $[\alpha]_D^{22}$ -54.0 (c 1.0, CH_3COCH_3). ^{1}H NMR (200 MHz, CD_3COCD_3, 25 ºC): δ 7.37 (m, 1H, ArH4'), 7.34

(dt, *J* = 2.0 Hz, 8.0 Hz, 1H, ArH6'), 7.24 (t, *J* = 8.0 Hz, 1H, ArH5'), 6.94 (ddd, *J* = 2.0 Hz, 1.0 Hz, 8.0 Hz, 1H, ArH2'), 5.53 (bs exchanges with D_2O, 3H, OH,NH), 4.31 (dd, X part of ABM_2X system, J_{AX} = 5.0 Hz, J_{BX} = 8.0 Hz, 1H, C1H), 2.71 (t, M2 part of ABM_2X system, *J* = 7.0 Hz, 2H, $C4H_2$), 2.13 (unresolved AB part of ABM_2X system, 2H, $C3H_2$), 2.10 (s, 3H, SCH_3). ^{13}C NMR (50 MHz, CD_3COCD_3, 25 ºC): δ 175.6 (C2), 168.7 (C7'), 149.7 (C1'), 132.9 (C3'), 130.6 (C5'), 120.1 (C6'), 119.0 (C4'), 115.4 (C2'), 56.5 (C1), 33.6 (C4), 31.7 (C3), 15.9 (SCH_3). HRMS: Found (%): M + H, 270.078755. $C_{12}H_{16}NO_4S$ requires M + H, 270.079455.

N-(3'-Carboxyphenyl)-L-proline (8h): Prepared from **5h** (1.00 g, 3.8 mmol), *via* general procedure **D**, with hydrolysis taking 20 h. The product **8h** was obtained as a light yellow oil (0.56 g, 63 %) which rapidly decomposed to a dark red powder. ^1H NMR (200 MHz, $CDCl_3$, 25 ºC): δ 10.4 (bs exchanges with D_2O, 2H, OH), 7.43 (d, 7.7 Hz, 1H, ArH4'), 7.31 (s, 1H, ArH6'), 7.27 (t, *J* = 7.7 Hz, 1H, ArH5'), 6.78 (ddd, *J* = 2.5 Hz, 1.3 Hz, 8.0 Hz, 1H, ArH2'), 4.39 (dd, *J* = 7.0 Hz, *J* = 4.0 Hz, 1H, C1H), 3.62 and 3.42 (m, 1H and m, 1H, $C5H_2$), 2.28 (m, 4H, $C3H_2$, $C4H_2$). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 177.2 (C2), 170.9 (C7'), 146.9 (C1'), 130.9 (C3'), 129.2 (C5'), 118.3 (C6'), 116.8 (C4'), 113.4 (C2'), 60.9 (C1), 48.6 (C5), 31.1 (C3), 23.9 (C4).

N-(3'-Carboxyphenyl)-L-Tyrosine (8j): Prepared from **5j** (0.98 g, 3.0 mmol), *via* general procedure **D**, with hydrolysis taking 30 h. The crude product was obtained as a light green solid which was recrystallized from toluene to yield **8j** as an off white solid (0.71 g, 79 %). m.p.: 176-178 ºC. $[\alpha]_D^{22}$ +9.9 (c 1.0, CH_3COCH_3). ^1H NMR (200 MHz, CD_3COCD_3, 25 ºC): δ 8.33 (bs exchanges with D_2O, 3H, OH), 7.37 (m, 1H, ArH2'), 7.32 (dt, *J* = 2.0 Hz, 8.0 Hz, 1H, ArH4'), 7.22 (t, *J* = 8.0 Hz, 1H, ArH5'), 7.16 (d, *J* = 8.5 Hz, 2H, ArH5,9), 6.92 (ddd, *J* = 2.0 Hz, 1.0 Hz, 8.0 Hz, 1H, ArH6'), 6.75 (d, *J* = 8.5 Hz, 2H, ArH6,8), 5.57 (bs exchanges with D_2O, 1H, NH), 4.34 (dd, X part of ABX system, J_{AX} = 6.0 Hz, J_{BX} = 7.0 Hz, 1H, C1H), 3.09 (AB part of ABX system, *J* = 14.0 Hz, 2H, $C3H_2$). ^{13}C NMR (50 MHz, CD_3COCD_3, 25 ºC): δ 175.2 (C2), 168.8 (C7'), 157.7 (C7), 149.3 (C1'), 132.9 (C3'), 131.9 (C5,9), 130.6 (C5'), 129.6 (C4), 120.0 (C6'), 119.0 (C4'), 116.7 (C6,8), 115.4 (C2'), 59.4 (C1), 38.9 (C3).

N-(3'-Carboxyphenyl)-L-aspartic acid 8k: Prepared from **5k** (1.00 g, 3.4 mmol), *via* general procedure **D**, with hydrolysis taking 46 h. The product **8k** was obtained as a bright orange solid (0.58 g, 69 %). m.p.: 111-113 ºC. $[\alpha]_D^{22}$ -21.8 (c 0.80, CH_3COCH_3). ^1H NMR (200 MHz, CD_3COCD_3, 25 ºC): δ 8.39 (bs, 3H, OH x 3), 7.40 (dt, *J* = 1.0 Hz, 8.0 Hz, 1H, ArH4'), 7.36 (m, 1H, ArH2'), 7.23 (t, *J* = 8.0 Hz, 1H, ArH5'), 6.91 (ddd, *J* = 2.5 Hz, 1.0 Hz, 8.0 Hz, 1H, ArH6'), 4.53 (t, *J* = 6.0 Hz, 1H, C1H), 2.98 (d, *J* = 6.0 Hz, 2H, $C3H_2$). ^{13}C NMR (50 MHz, CD_3COCD_3, 25 ºC): δ 174.5 (C2), 172.9 (C4), 168.9 (C7'), 149.2 (C1'), 132.5 (C3'), 130.7 (C5'), 120.3 (C6'), 119.3 (C4'), 115.3 (C2'), 54.3 (C1), 38.1 (C3).

N-(4'-Methoxyphenyl)-L-amino acids (9)

N-(4'-Methoxyphenyl)-L-valine (9c): Prepared from **6c** (0.68 g, 3.0 mmol), *via* general procedure **D**, with hydrolysis complete in 20 h. The product **9c** was isolated as a white solid (0.57 g, 89 %), which when recrystallized from chloroform yielded thin plate crystals which rapidly decomposed. m.p. 123-125 ºC. $[\alpha]_D^{22}$ -82.2 (c 0.82, CH_3COCH_3). ^1H NMR (200 MHz, CD_3COCD_3, 25 ºC): δ 6.75 (d, *J* = 9.0 Hz, 2H, ArH3',5'), 6.64 (d, *J* = 9.0 Hz, 2H, ArH2',6'), 3.77 (d, *J* = 6.0 z, 1H, C1H), 3.72 (s, 3H, $C7'H_3$), 2.15 (m, 1H, C3H), 2.13 (bs exchanges with D_2O, 2H, OH, NH), 1.10 (d, *J* = 7.0 Hz, 3H, $C4/5H_3$), 1.08 (d, *J* = 7.0 Hz, 3H, $C4/5H_3$). ^{13}C NMR (50 MHz, CD_3COCD_3, 25 ºC): δ 174.9 (C2), 152.5 (C4'), 141.6 (C1'), 115.1, 114.7 (C2',6',3',5'), 63.3 (C1), 55.4 (C7'), 31.1 (C3), 19.0, 18.3 (C4,5). HRMS: $C_{12}H_{18}NO_3$ (M + 1) requires: 224.128124. Found (%): 224.127087.

N-(4'-Methoxyphenyl)-L-leucine (9d): Prepared from **6d** (0.14 g, 0.6 mmol), *via* general procedure **D**, with hydrolysis complete in 24 h. The product **9d** was isolated as a white powder (0.12 g, 91 %), which slowly discoloured on prolonged standing. m.p.: 160-162 ºC. $[\alpha]_D^{22}$ -46.3 (c 1.0, CH_3COCH_3). ^1H NMR (200 MHz, CD_3COCD_3, 25 ºC): δ 6.74 (d, *J* = 9.0 Hz, 2H, ArH3',5'), 6.64 (d, *J* = 9.0 Hz, 2H, ArH2',6'), 3.97 (dd, *J* = 7.0 Hz, 7.0 Hz, 1H, C1H), 3.68 (s, 3H, C7'H3), 2.00 (bs exchanges with D_2O, 2H, OH, NH), 1.90 (m, 1H, C4H), 1.66 (t, *J* = 7.0 Hz, 2H, $C3H_2$), 0.98 (d, *J* = 8.5 Hz, 3H, $C5H_3$), 0.95 (d, *J* = 8.5 Hz, 3H, $C6H_3$). ^{13}C NMR (50 MHz, CD_3COCD_3, 25 ºC): δ 174.2 (C2), 152.2 (C4'), 141.4 (C1'), 116.1, 116.0 (C2',6',3',5'), 56.5 (C1), 56.4 (C7'), 43.6 (C4), 26.3 (C3), 23.9, 23.1 (C5,6). HRMS: $C_{13}H_{20}NO_3$ (M + 1) requires: 238.143765. Found (%): 238.143076.

N-(4'-Methoxyphenyl)-L-Aspartic acid (9k): Prepared from **6k** (0.96 g, 3.8 mmol), *via* general procedure H. The product **9k** was isolated as a light yellow powder (0.80 g, 93 %), which rapidly decomposed to a black solid. Recrystallization from acetonitrile afforded clear crystals which decomposed immediately on collection. ^1H NMR (200 MHz, CD_3SOCD_3, 25 ºC): δ 7.00 (d, *J* = 9.0 Hz, 2H, ArH3' and 5'), 6.90 (d, *J* = 9.1 Hz, 2H, ArH2' and 6'), 4.38 (t, *J* = 5.9 Hz, 1H, C1H), 4.00 (bs exchanges with D_2O, 1H, NH), 3.73 (s, 3H, $C7'H_3$), 2.77 (d, *J* = 6.0 Hz, 2H, $C3H_2$), 2.54 (bs exchanges with D_2O, 2H, OH). ^{13}C NMR (50 MHz, CD_3SOCD_3, 25 ºC): δ 173.0 (C2), 172.3 (C4), 155.6 (C4'), 136.7 (C1'), 119.6 and 115.7 (C2' and 6', 3' and 5'), 56.8 (C1), 56.4 (C7'), 36.5 (C3).

Synthesis of chiral peptides

N-{[3'-(L-Phenylalanine methyl ester) carboxy] phenyl}-L-leucine-L-phenylalanine methyl ester (10): Prepared from **8d** (0.13 g, 0.6 mmol), **2f** (0.26 g, 1.2 mmol), triethylamine (0.20 mL, 1.2 mmol), EDC (0.22 mL, 1.2 mmol), N-hydroxy-succinimide (0.14 g, 1.22 mmol) *via* the previously reported procedure[16]. The product was isolated as an off white solid which was recrystallized from CH_2Cl_2/hexane to yield **10** as white crystals (0.20 g, 58 %). m.p.: 113-115 ºC. ^1H NMR (200 MHz, $CDCl_3$, 25 ºC): δ 7.30-6.60 (m, 14H, ArH), 5.07 (m, 1H, C3H), 4.79 (m, 1H, C8'H), 3.74 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.30-2.90 (m, 4H, CH_2Ph × 2), 1.70 (m, 3H, CH_2CH), 0.95 (d, *J* = 6.0 Hz, 3H, $CHCH_3$), 0.86 (d, *J* = 6.0 Hz, 3H, $CHCH_3$). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 173.7 (C4), 172.5, 172.2 (C2,9'), 167.6 (C7'), 147.1 (C1'), 136.5

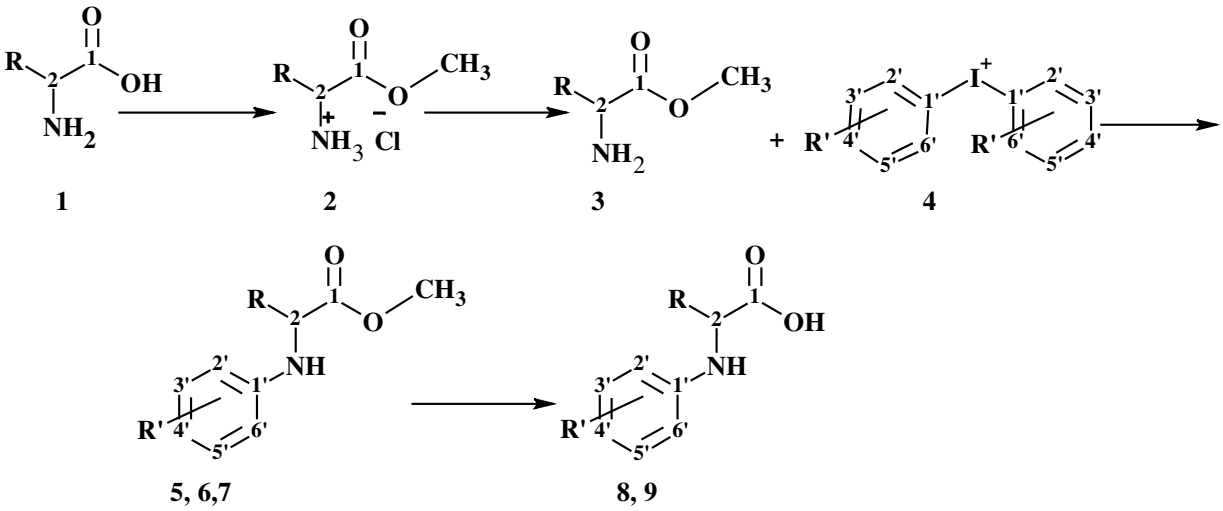
(C3'), 136.0, 135.6 (C6,11'), 129.7, 129.2, 129.0, 128.9 (C7,11,8,10,12',16',13',15',5'), 127.4, 127.3 (C9,14'), 118.3 (C6'), 117.2 (C4'), 112.4 (C2'), 58.4 (C3), 54.6, 54.2 (C3,8'), 53.0 (OCH_3), 52.6 (OCH_3), 42.7 (C13), 38.3, 37.6 (C5,10'), 25.4 (C12), 23.4, 21.9 (C14,15).

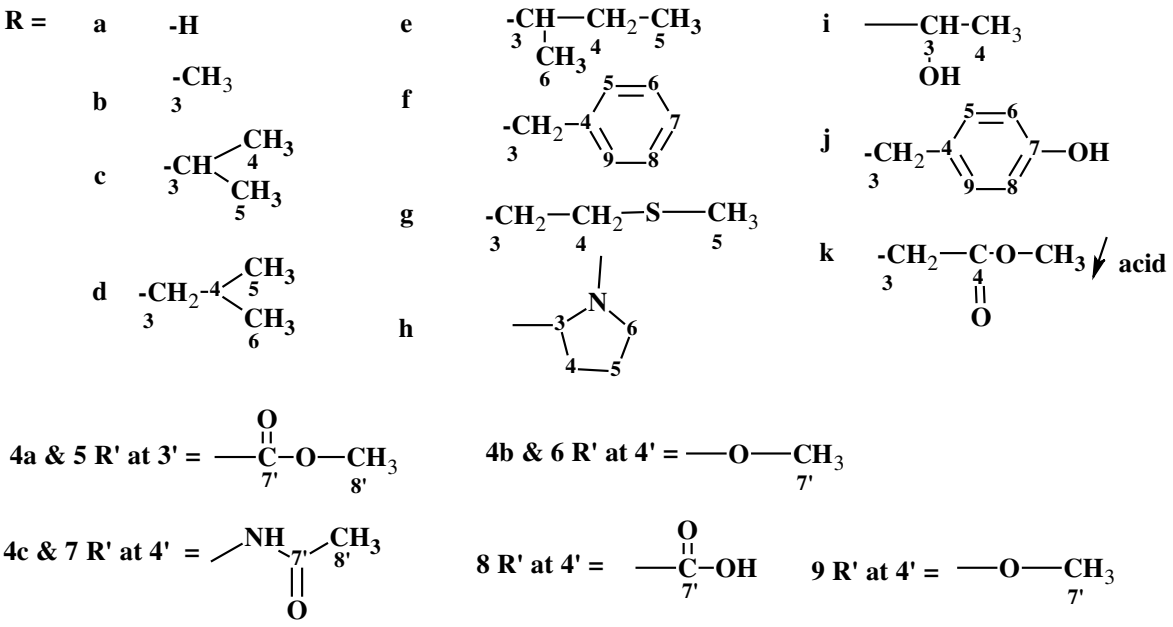
N-(4'-MeOPh)-L-valine-L-phenylalanine methyl ester (11): Prepared from **9c** (0.13 g, 0.6 mmol) and **2f** (0.26 g, 1.2 mmol), *via* the previously reported procedure[16]. The product was isolated as an off white solid which was recrystallized from CH_2Cl_2/hexane to yield **11** as white crystals (0.16 g, 69 %). ^{1}H NMR (200 MHz, $CDCl_3$, 25 ºC): δ 7.27-7.04 (m, 5H, ArH7-11), 6.75 (d, *J* = 9.0 Hz, 2H, ArH3',5'), 6.64 (d, *J* = 9.0 Hz, 2H, ArH2',6'), 4.87 (m, 1H, C3H), 3.80 (d, *J* = 4.0 Hz, 1H, C1H), 3.74 (s, 3H, OCH_3), 3.64 (s, 3H, C7'H3), 3.09 (AB part of ABX system, *J* = 14.0 Hz, 2H, $C5H_2$), 2.11 (m, 1H, C12H), 0.92 (d, *J* = 7.0 Hz, 3H, $C13/14H_3$), 0.79 (d, *J* = 7.0 Hz, 3H, $C13/14H_3$). ^{13}C NMR (50 MHz, $CDCl_3$, 25 ºC): δ 173.3 (C4), 172.0 (C2), 153.5 (C4'), 141.8 (C1'), 136.4 (C6), 129.3 (C8,10), 128.8 (C7,11), 127.3 (C9), 115.8, 115.1(C2',6',3',5'), 66.6 (C3), 56.0 (C7'), 53.2 (C1), 52.5 (OCH3), 38.2 (C5), 31.4 (C12), 19.8, 17.7 (C13,14).

RESULTS AND DISCUSSION

Diaryliodonium approach: Reaction (**Scheme-I**) outlines the approach taken to the target N-aryl amino acids. To prevent the possibility of competing O-arylation of the amino acid carboxyl function, the amino acids **1** were first converted to the corresponding methyl ester HCl salt **2** using thionyl chloride in anhydrous methanol. These were prepared in high yields (85-99 %) with the exception of tyrosine (61 %). The removal of the HCl salt using triethylamine in chloroform to give the methyl amino ester **3** was essentially quantitative with the exception of serine (41 %), threonine (82 %) and tyrosine (80 %).

This is the first reported synthesis of *bis*[3'-(methoxycarbonyl)phenyl]iodonium bromide (**4a**), while *bis*(4'-methoxyphenyl)iodonium iodide (**4b)** and *bis*(4'-acetamidophenyl) iodonium iodide (**4c)** were prepared by the reported methods[12].





Scheme-I: N-Arylation using diaryliodonium salts

N-Arylation reaction was undertaken by heating a mixture of the amino ester (2 equiv), diaryliodonium salt (1 equiv), $AgNO_3$ (1.02 equiv), CuBr (2 % mol equiv) in anhydrous acetonitrile at 90 ºC for 3-5 h in dark conditions, as previously reported[13]. The protecting ester was then hydrolyzed to the corresponding acid using dilute NaOH solution under mild conditions to maintain the chirality of the amino acid.

Scope and limitations of amino acids: In general the range of amino acids applicable to this method was limited by the preparation of the amino acid methyl esters. As such, reactions were only conducted on amino acids bearing non-polar, polar (only -OH) and charged (acidic only) side chains. The side chain -OH containing amino acids were not further protected. The acidic side chain of L-aspartic acid **3k** was esterified simultaneously with the backbone carboxyl group. The amino acids with polar or charged side chains containing amine or sulphur functions were not easily esterified and required more complex side-chain protection and were not studied further. This represents a limitation of the diaryliodonium salt pathway to N-aryl derivatives of amino acids bearing these functionalized side chains.

Assessment of N-arylation of amino esters by diaryliodonium salts: The analysis of the crude reaction mixtures of products **5** by GC-MS showed the expected by-products methyl 3-bromobenzoate and methyl 3-iodobenzoate which arise from the transfer of only one of the aryl groups from [3'-(methoxycarbonyl)phenyl] iodonium bromide. Methyl 3-hydroxybenzoate was also found to be present in small amounts which indicated that some moisture must have been present in the reaction mixture. Amino acid methyl esters bearing non-polar side chains (with the exception of glycine **4a**, L-methionine and L-proline) undergo N-arylation in good to excellent yields.

The N-[(3'-methoxycarbonyl)phenyl] glycine methyl ester (**5a**) was obtained in low yield (30 %), resulting from extensive polymerization of glycine methyl ester **3a** during the reaction.

Side reactions were also identified for the L-methionine methyl ester (**3g)** in which cleavage off the methylthiol and gave methyl 2-aminobut-3-enoate which then underwent N-arylation.

The lower yield for the N-arylation of **3h** is attributed to the lower reactivity of the secondary amine.

The hydroxy group in the side chain of L-threonine methyl ester (**3i)** was observed to undergo competing O-arylation, thus affording a mixture of N-aryl, O-aryl and N,O-diaryl amino esters. This indicated the requirement for further protection of the amino acid to exclude the side O-arylation. In contrast to this, L-tyrosine methyl ester (**3j)** was less susceptible to O-arylation, probably due to the lower nucleophilicity of the phenolic functional group.

Acidic side chains **3k** which could be co-protected with the backbone carboxyl function were N-arylated in good to excellent yields (Table-1).

A trend was observed in that higher yields (product **5** Table-1) were observed for electron rich diaryliodonium salts than for electron deficient diaryliodonium salts. Further work is being conducted to conclusively state whether this observation is general.

Chiral integrity of N-aryl amino acid dipeptide (10) and tripeptide (11) methyl esters: We previously reported the use of chiral dipeptide derivatives of N-phenyl amino acids prepared using diphenyliodonium bromide[13] to determine if the chiral integrity of the amino acid had been maintained. Similarly in this work we used L-phenylalanine and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDC) to prepare the dipeptide derivatives of the N-(4'-methoxyphenyl) amino acids (**10**) and tripeptide derivatives of N-(3'-carboxyphenyl) amino acids (**11**). Analysis of the ^1H and ^{13}C NMR spectra of these compounds showed the presence of only a single diastereoisomer (in each case of **10**) or triastereoisomer (in each case of **11**).

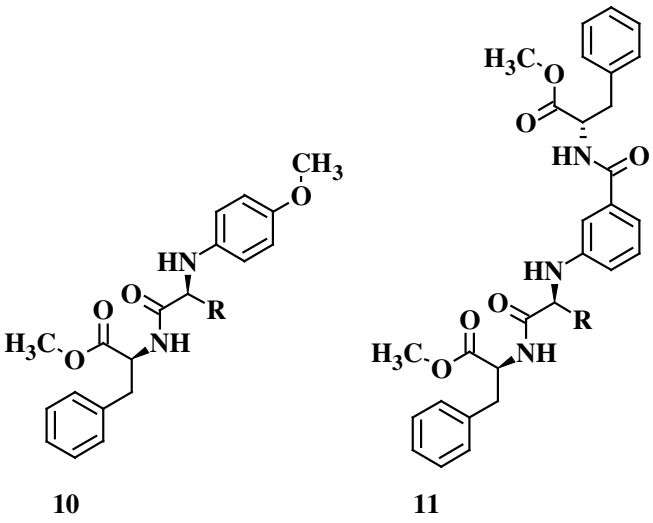
TABLE-1
N-ARYL AMINO ACIDS PREPARED USING DIARYLIODONIUM SALTS

	Diaryliodonium salt	Amino ester	Ester yield (%)		Acid yield (%)
5a	**4a**	Glycine	30	–	–
5b	**4a**	L-Alanine	83	**8b**	90
5c	**4a**	L-Valine	72	**8c**	87
5c*	**4a**	DL-Valine	75	–	–
5d	**4a**	L-Leucine	78	**8d**	91
5e	**4a**	L-Isoleucine	77	**8e**	82
5f	**4a**	L-Phenylalanine	84	**8f**	88
5g	**4a**	L-Methionine	65	**8g**	76
5h	**4a**	L-Proline	73	**8h**	63
5i	**4a**	L-Threonine	45	–	–
5j	**4a**	L-Tyrosine	75	**8j**	79
5k	**4a**	L-Aspartic acid	60	**8k**	69
6b	**4b**	L-Alanine	71	–	–
6c	**4b**	L-Valine	85	**9c**	89
6d	**4b**	L-Leucine	82	**9d**	91
6e	**4b**	L-Isoleucine	88	–	–
6f	**4b**	L-Phenylalanine	75	–	–
6g	**4b**	L-Methionine	35	–	–
6h	**4b**	L-Proline	69	–	–
6j	**4b**	L-Tyrosine	76	–	–
6k	**4b**	L-Aspartic acid	86	**9k**	93
7d	**4c**	L-Leucine	71	–	-

TABLE-2
N-ARYL AMINO ACIDS PREPARED *VIA* ULLMANN TYPE, COPPER-CATALYZED COUPLING

	Aryl halide	Amino acid	Yield (%)	m.p. (ºC)
8b	3-$BrC_6H_4CO_2H$	L-Alanine	51	199-201
8c	3-$BrC_6H_4CO_2H$	L-Valine	69	131-132
8d	3-$BrC_6H_4CO_2H$	L-Leucine	66	171-173
8e	3-$BrC_6H_4CO_2H$	L-Isoleucine	54	173-174
8f	3-$BrC_6H_4CO_2H$	L-Phenylalanine	70	178-180
8g	3-$BrC_6H_4CO_2H$	L-Methionine	43	156-157
8h	3-$BrC_6H_4CO_2H$	L-Proline	0	–
8i	3-$BrC_6H_4CO_2H$	L-Serine	0	–
8j	3-$BrC_6H_4CO_2H$	L-Threonine	0	–
8k	3-$BrC_6H_4CO_2H$	L-Tyrosine	44	176-178
8l	3-$BrC_6H_4CO_2H$	L-Aspartic acid	0	–
8b	3-$BrC_6H_4CO_2H$	L-Alanine	51	199-201

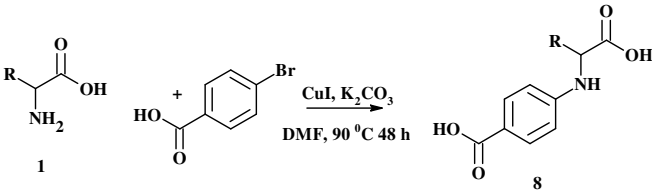
Further evidence for the chiral analysis of the N-arylation product become clear from the comparison of the optical activity of N-[(3'-methoxycarbonyl)phenyl]-L-valine methyl ester **5c** $[\alpha]_D^{22}$ -63.4 (c 1.0, $CHCl_3$) and that for-[(3'-methoxycarbonyl)phenyl]-DL-valine methyl ester **5c*** $[\alpha]_D^{22}$ 0.0 (c 1.0, $CHCl_3$).



10 **11**

Structure of chiral dipeptide (**10**) and tripeptide (**11**) structures

Ullmann copper-catalyzed method: The reported procedure[1,2] was used in the preparation of N-aryl amino acids in a moderate to high yield (**Scheme-II** and Table-2). Chiral analysis of the products also showed that in most cases chiral integrity was maintained throughout the reaction. Physical and spectral data of these compounds was identical to corresponding compounds prepared *via* the diaryliodonium approach.



Scheme-II: N-Arylation *via* Ullmann type copper catalyzed reaction

The advantage of this approach is that it is a single step reaction for the direct synthesis of N-aryl amino acids in moderate to high yields. The disadvantages include the long reaction time, purification of products can be tedious, limited to amino acids bearing non-polar and hydrophobic side chains, slight racemization of some amino acids is observed and it is not applicable to the preparation of N-(4'-methoxyphenyl) **9** and N-(4'-acetamidophenyl) derivatives of amino acids **7**.

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