

Direct synthesis of Fmoc-protected amino acids using organozinc chemistry: application to polymethoxylated phenylalanines and 4-oxoamino acids †

Hervé J. C. Deboves,^a Christian A. G. N. Montalbetti^a and Richard F. W. Jackson^{*b}

^a Department of Chemistry, Bedson Building, The University of Newcastle, Newcastle upon Tyne, UK NE1 7RU

^b Department of Chemistry, Dainton Building, The University of Sheffield, Sheffield, UK S3 7HF

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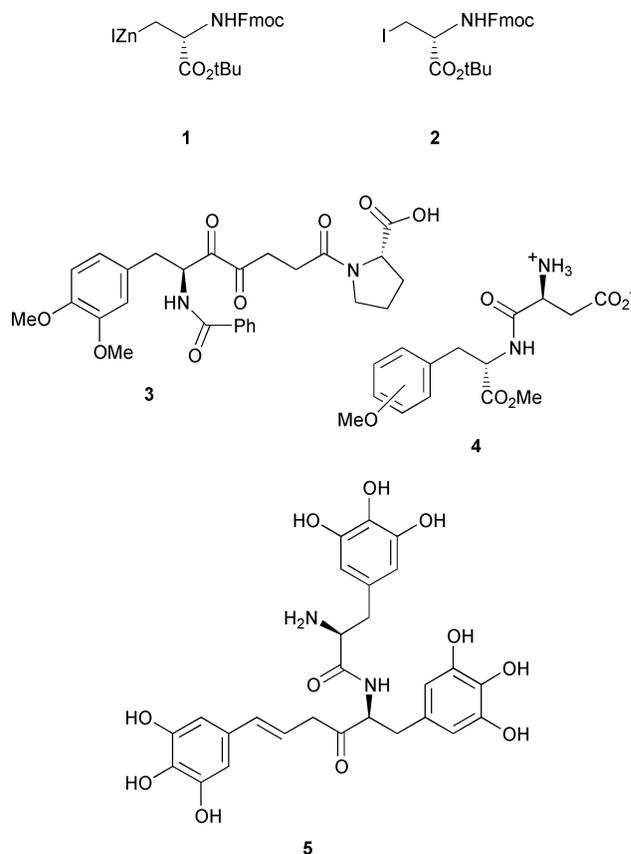
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The new *N*-Fmoc 3-iodoalanine *tert*-butyl ester derived organozinc reagent **1**, obtained in 7 steps from optically pure L-serine, was coupled to a range of electrophiles under palladium catalysis to give substituted phenylalanines and 4-oxoamino acids in variable yields (21–59%). Transformation into the organocopper reagent **13** allowed coupling with allyl chloride and ethyl oxalyl chloride. Removal of the *tert*-butyl group gives Fmoc-protected amino acids (63–95%), suitable for use in automated solid phase peptide synthesis.

The synthesis of nonproteinogenic amino acids continues to provide a challenge for organic chemists. We have developed effective methods for the conversion of readily available enantiomerically pure natural amino acids (serine, aspartic acid, glutamic acid) into unnatural amino acids using organometallic chemistry without loss of stereochemical integrity.^{1–5} Since *N*-Fmoc protected amino acids are routinely used in automated solid phase peptide synthesis (SPPS),^{6–8} it was of interest to establish whether these methods could be applied to *N*-Fmoc protected starting materials. One unoptimised example of the coupling of the corresponding Fmoc methyl ester iodoalanine-derived zinc reagent has been reported,⁹ and although conditions were reported for the selective hydrolysis of the methyl ester of the product in the presence of the Fmoc-protecting group, the use of a carboxylic acid protecting group more obviously orthogonal to the methyl ester was desirable. We have therefore synthesised the new *N*-Fmoc protected serine-derived organozinc reagent **1**, from the corresponding iodide precursor **2**, and studied the palladium catalysed coupling of **1** with aromatic iodides and acid chlorides, and the copper mediated coupling reactions of **1**. Furthermore, in the case of the phenylalanine derivatives, we have targeted polyoxygenated analogues as most of these derivatives, to our knowledge, have not been reported previously in the literature. Biologically active molecules containing polyoxygenated phenylalanine fragments include angiotensin-converting enzyme (ACE) inhibitors such as **3**,¹⁰ HIV-1 protease inhibitors,¹¹ the antibiotic puromycin, sweeteners **4**,¹² tunichromes **5**¹³ and 3,4-dihydroxyphenylalanine (DOPA), a prodrug for the neurotransmitter dopamine, which has been prescribed in the treatment of Parkinson's disease.

Results and discussion

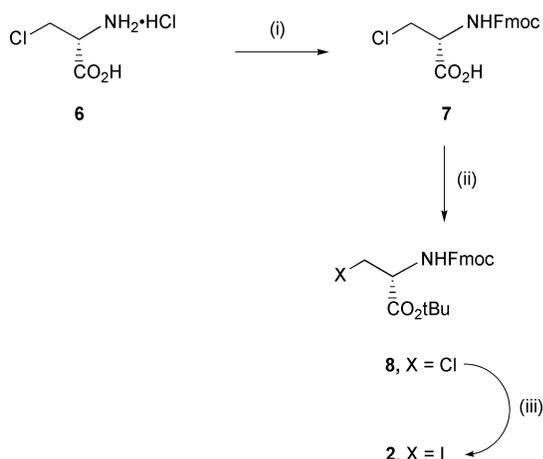
The iodide precursor **2** was synthesised from commercially available L-serine. The approach used previously for the syn-



thesis of protected 3-iodoalanines¹ proved unsuccessful in the case of intermediate **2** due to the instability of the latter during the final chromatographic purification. The following method starting from the known β-chloroalanine **6** hydrochloride was therefore developed (Scheme 1).

Treatment of **6** under Paquet's conditions¹⁴ gave the *N*-Fmoc protected derivative **7** in good yield (78%) which was used without further purification. For the esterification, the *tert*-butyl cation was generated using isobutene under acidic conditions (sulfuric acid), in dichloromethane as reported by Andreson.¹⁵

† Electronic supplementary information (ESI) available: details of the preparation and spectral properties of 3-iodobenzophenone, 2,3,4-trimethoxyiodobenzene, 2,4-dimethoxyiodobenzene, 3,4-dimethoxyiodobenzene, 3,4,5-trimethoxyiodobenzene and 3,5-dimethoxyiodobenzene. See <http://www.rsc.org/suppdata/p1/b1/b103832j/>

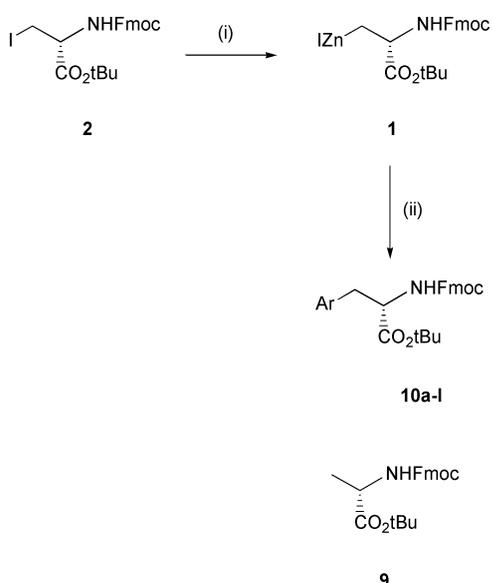


Scheme 1 Reagents and conditions: i, FmocOsuccinimide, NaHCO₃, H₂O–acetone mixture (1 : 1) (78%); ii, isobutene, H₂SO₄, CH₂Cl₂, –78 °C (84%); iii, NaI, acetone (99%).

This step gave the ester **8** in good yield (84%) as a nice crystalline material after purification. The iodide **2** was finally obtained in near-quantitative yield by Finkelstein reaction.

The *N*-Fmoc protected organozinc reagent **1** was formed by direct insertion of activated zinc powder into the carbon–iodine bond of iodide **2**, the zinc powder being previously activated by treatment with chlorotrimethylsilane in DMF at room temperature for 30 min. This activation method appears to be at least as reliable as the method for zinc activation¹⁶ which included a pre-treatment with 1,2-dibromoethane, but it has the advantage that the use of carcinogenic 1,2-dibromoethane is avoided. The organozinc reagent **1** was shown to be formed quantitatively by quenching the reaction either with water, giving *N*-Fmoc-protected alanine *tert*-butyl ester **9**, or with iodine regenerating the starting iodide **2**.

The optimisation of the conditions for the palladium catalysed coupling reaction between organozinc reagent **1** and aryl iodides was carried out using *p*-nitroiodobenzene. The optimum result was obtained at 50 °C, using Pd₂dba₃ (2.5 mol%) and P(*o*-tol)₃ (10 mol%) as the catalytic system (Scheme 2). The main difference between the behaviour of the



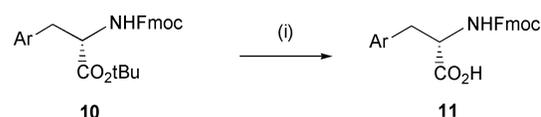
Scheme 2 Reagents and conditions: i, Zn* (prepared from zinc dust using Me₃SiCl, in DMF), DMF, rt, 1 h; ii, Pd₂dba₃ (2.5 mol%), P(*o*-tol)₃ (10 mol%), DMF, ArI, 50 °C, 4 h.

zinc reagent **1** and other analogous protected serine-derived zinc reagents is the higher temperature required for effective cross-coupling of reagent **1**.

Using the conditions developed for *p*-iodonitrobenzene, several phenylalanine analogues **10a–n** were synthesised with yields ranging from good to moderate (21–59%, Table 1). The yield obtained for the coupling of **1** with 4-iodonitrobenzene (59%) was almost identical to that obtained with the analogous *N*-Boc protected methyl ester zinc reagent³ so the Fmoc protection is not a limiting factor in the coupling process.

The yields of the coupling reaction with electron rich aromatic iodides (entries **10e–m**) were generally slightly lower than for the electron poor ones (entries **10a–e**) as expected, with the exception of entries **10c** (21%) and **10l** (59%). We were however surprised by the higher yields obtained for the tri-substituted derivatives (47 and 59%, entries **10k** and **10l**). While the yields are moderate (45% on average), these results nevertheless show the utility of organozinc reagents in the synthesis of various polyoxygenated phenylalanine derivatives.

Removal of the *tert*-butyl protecting group to give the Fmoc-protected amino acids **11** was efficiently achieved using trifluoroacetic acid in the presence of triethylsilane (Scheme 3), a



Scheme 3 Reagents and conditions: i, TFA, Et₃SiH (2.5 equiv.), CH₂Cl₂, 4 h.

scavenger of the *tert*-butyl cation, which has been described by Douglas and co-workers¹⁷ to limit side reactions in this process (Table 2).

The specific rotation of our sample of *N*-Fmoc-4-methoxyphenylalanine **11g** compared favourably with that reported by Motawia and co-workers¹⁸ for the same material prepared from 4-*O*-Me-*L*-tyrosine. We have previously established that the palladium catalysed coupling of organozinc reagents with aromatic iodides proceeds without affecting the chiral integrity of the α -carbon,⁴ and we are therefore confident that all the examples are enantiomerically pure.

Due to the success of the new *N*-Fmoc protected organozinc reagent **1** in the palladium catalysed coupling reaction with aromatic iodides, we decided to investigate the coupling procedure with acid chlorides.¹ The organozinc reagent **1** was prepared using zinc–copper couple in a mixture of toluene–DMA (93 : 7), which avoids the incompatibility of DMF and acid chlorides. While zinc insertion is very slow in this solvent below 40 °C, it takes less than 5 minutes at 70 °C but is accompanied by significant decomposition. At 50 °C, insertion is complete within 20 minutes with less than 5% decomposition being detected. The conditions for the coupling reaction were optimised using acetoxyacetyl chloride. The best yield (47%) was obtained when bis(triphenylphosphine)dichloropalladium was used as catalyst and the reaction carried out for 4 hours (Scheme 4). The coupling reaction was then carried out using these optimised conditions with a range of acid chlorides (Table 3) to give the corresponding 4-oxo derivatives **12** in moderate yields (42–52%).

Conversion of the organozinc reagent **1** into the more reactive zinc–copper reagent **13** was achieved by treatment with CuCN·2LiCl (Scheme 5). Treatment with allyl chloride gave the adduct **14a** (60%), a similar yield to that obtained with the *N*-Boc protection (52%)² which shows that the Fmoc group is not a limiting factor in such reactions. Treatment with ethyl oxalyl chloride gave the corresponding adduct **14b** (30%).

Conclusions

N-Fmoc 3-iodoalanine *tert*-butyl ester **2** is easily prepared in good overall yield *via* a six step sequence to give a crystalline compound which can be stored in the fridge without decomposition for months. It gives access to organozinc reagent **1**

Table 1 Preparation of phenylalanine derivatives **10a–l**

	Aryl iodide	Ar	Yield (%) ^a
10a	4-Nitroiodobenzene	4-Nitrophenyl	59
10b	2-Bromoiodobenzene	2-Bromophenyl	47
10c	2-Methoxycarbonyliodobenzene	2-Methoxycarbonylphenyl	21
10d	3-Iodobenzophenone	3-Benzoylphenyl	55
10e	2-Iodoanisole	2-Methoxyphenyl	31
10f	3-Iodoanisole	3-Methoxyphenyl	48
10g	4-Iodoanisole	4-Methoxyphenyl	34
10h	2,4-Dimethoxyiodobenzene	2,4-Dimethoxyphenyl	24
10i	3,4-Dimethoxyiodobenzene	3,4-Dimethoxyphenyl	41
10j	3,5-Dimethoxyiodobenzene	3,5-Dimethoxyphenyl	47
10k	2,3,4-Trimethoxyiodobenzene	2,3,4-Trimethoxyphenyl	47
10l	3,4,5-Trimethoxyiodobenzene	3,4,5-Trimethoxyphenyl	59

^a Based on *N*-Fmoc-3-iodoalanine *tert*-butyl ester **2**.

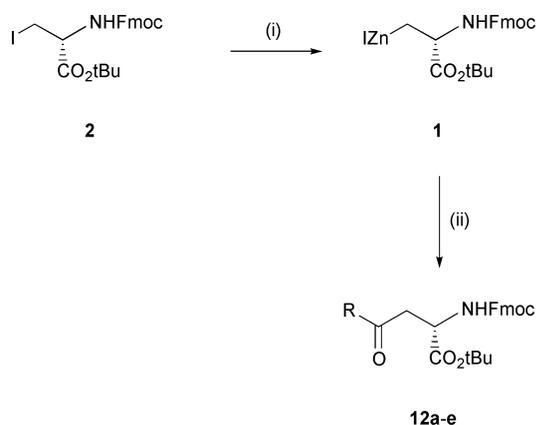
Table 2 Cleavage of the *tert*-butyl protecting group

	Ar	Yield (%)
11d	3-Benzophenyl	73
11g	4-Methoxyphenyl	64
11h	2,4-Dimethoxyphenyl	74
11j	3,5-Dimethoxyphenyl	63
11k	2,3,4-Trimethoxyphenyl	81
11l	3,4,5-Trimethoxyphenyl	95

Table 3 Preparation of 4-oxo derivatives **12a–e**

	R	Yield (%) ^a
12a	AcOCH ₂	47
12b	CH ₃ CH ₂	47
12c	(<i>S</i>)- <i>N</i> -Trifluoroacetylpyrrolidin-2-yl	46
12d	PhthNCH ₂ ^b	43
12e	CH ₂ =CH	42

^a Based on *N*-Fmoc-3-iodoalanine *tert*-butyl ester **2**. ^b Phth = 1,3-phthaloyl.

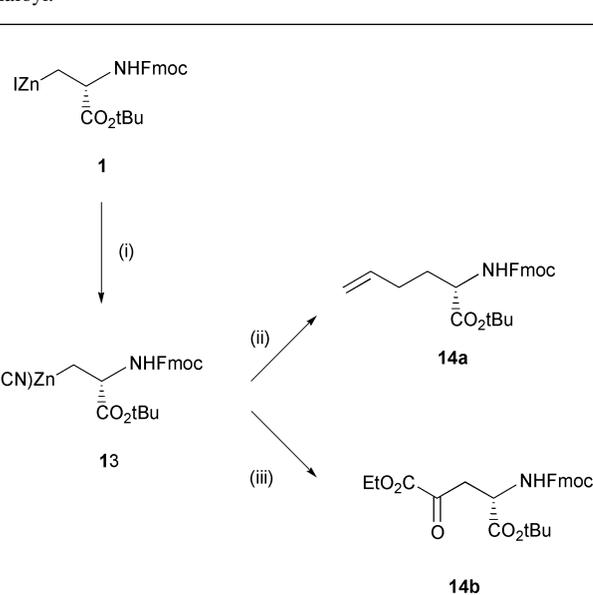


Scheme 4 Reagents and conditions: i, Zn–Cu couple, toluene–DMA (93 : 7), 50 °C, 20 min; ii, RCOCl, Pd(PPh₃)₂Cl₂, toluene–DMA (93 : 7), 50 °C, 4 h.

which can be converted into *N*-Fmoc *tert*-butyl protected phenylalanine derivatives **10a–l** in moderate yields (21–59%). The ester derivatives obtained can be easily converted into the corresponding acids **11** which are ready for use in solid phase peptide synthesis. Organozinc reagent **1** can also be used in the preparation of 4-oxoamino acids (**12a–e** and **14b**) as well as in the preparation of amino acids bearing an unsaturated side chain **14a**.

Experimental

For general experimental procedures, see our previous paper.¹⁹ Methyl (2*R*)-2-amino-3-chloropropionate hydrochloride was prepared from serine using the literature method.²⁰ 3-Iodobenzophenone was prepared from 3-iodobenzoic acid.²¹ Poly-oxygenated aromatic iodides containing *ortho*- and *para*-substituents with respect to the iodine were synthesised in good yields (79–83%) following a method described by Orito and co-workers.²² The *meta* substituted iodides were prepared in moderate yields (38–72%) *via* the corresponding diazonium salts following procedures described by Pavia²³ and Erdtman.²⁴ Procedures and full characterisation data for these aryl iodides are reported in the supplementary information.† The procedure for the preparation of **12c**, and the characterisation data, have



Scheme 5 Reagents and conditions: i, CuCN·2LiCl, THF, –10 °C; ii, allyl chloride, –25 °C, overnight; iii, ethyl oxalyl chloride, –25 °C, overnight.

been reported.²⁵ *J* Values are given in Hz and optical rotations in 10^{–1} deg cm² g^{–1}.

(2*R*)-Amino-3-chloropropionic acid hydrochloride (*t*-(β-Cl)-Ala)^{6,26,27}

Methyl (2*R*)-2-amino-3-chloropropionate hydrochloride (9.0 g, 51.7 mmol) was dissolved in aqueous HCl 20% solution (90 ml, 520 mmol, 10 equiv.). The solution was refluxed for 1.5 hours followed by overnight stirring at room temperature. The solvent was evaporated to yield a pale yellow powder which was dissolved in dry methanol (30 ml) and precipitated by the addition of diethyl ether (9 ml) to yield (2*R*)-2-amino-3-chloropropionic acid hydrochloride **6** (6.6 g, 80%) as white crystals. Mp 180–185 °C (Found *M*⁺ 124.0167; C₃H₇NO₂Cl requires 124.0165); [α]_D¹⁷ +1.0 (*c* 1.0 in H₂O) (Found: C, 22.6; H, 4.5; N, 8.8%. C₃H₇NO₂Cl requires C, 22.6; H, 4.4 and N, 8.8%); ν_{max} (KBr disc)/cm^{–1} 3200–2700 (s), 1984 (m), 1960 (m), 1744 (s), 1496 (s),

1230 (s), 1200 (s) and 794 (m); δ_{H} (CD₃OD) 4.25 (1H, dd, *J* 3.5, 12.5, C(3)*H*), 4.39 (1H, dd, *J* 4.5, 12.5, C(3)*H'*), 4.87 (1H, dd, *J* 3.5, 4.5, C(2)*H*); δ_{C} (CD₃OD) 44.36 (C(3)), 56.07 (C(2)), 169.61 (C(1)); *m/z* (EI) *M*⁺ 126 (0.42), 124 (0.3), 104 (0.2), 102 (0.1), 80 (33), 78 (100%).

(2*R*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-chloropropionic acid **7**

(2*R*)-2-Amino-3-chloropropionic acid hydrochloride (6.5 g, 40.6 mmol) was dissolved in a 1 : 1 water–acetone mixture (150 ml). NaHCO₃ (6.82 g, 81.2 mmol, 2 equiv.) was added in portions. When carbon dioxide evolution had stopped Fmoc succinimide (14.4 g, 42.7 mmol, 1.05 equiv.) was added. The “milky” solution was stirred at ambient temperature for the following two days. The acetone was evaporated and the resulting solution acidified to pH 1 with 5 M HCl. The acidic solution was extracted with ethyl acetate (3 × 50 ml) and the combined organic phases were washed with saturated NaHCO₃ (50 ml). The aqueous phase was collected and acidified to pH 1 with 5 M HCl and then extracted with ethyl acetate (3 × 50 ml). The combined organic phases were dried and evaporated to yield (2*R*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-chloropropionic acid **7** (11.0 g, 78%) as white crystals. Mp 155–157 °C (Found: *M*⁺ 345.0769; C₁₈H₁₆NO₄Cl requires 345.0768); [*a*]_D¹⁷ +28.2 (*c* 0.5 in CHCl₃) (Found: C, 62.5; H, 4.6; N, 4.1%. C₁₈H₁₆NO₄Cl requires C, 62.5; H, 4.65 and N, 4.05%); ν_{max} (KBr disc)/cm⁻¹ 3316 (s), 3039 (m), 2964 (m), 2926 (s), 1703 (s), 1537 (s) and 794 (s); δ_{H} (CD₃OD) 3.91 (2H, d, *J* 5.0, C(3)*H*₂), 4.22 (1H, t, *J* 7.0, *CH* Fmoc), 4.34 (1H, d, *J* 7.0, *CH*₂ Fmoc), 4.56 (1H, t, *J* 5.0, C(2)*H*), 7.30 (2H, dt, *J* 7.5, 1.0, *ArH* Fmoc), 7.37 (2H, t, *J* 7.5, *ArH* Fmoc), 7.64–7.68 (2H, m, *ArH* Fmoc), 7.78 (2H, d, *J* 7.5, *ArH* Fmoc); δ_{C} (CD₃OD) 45.53 (C(3)), 51.50 (*CH* Fmoc), 57.00 (C(2)), 68.40 (*CH*₂ Fmoc), 121.08 (*Ar* Fmoc), 126.44 (*Ar* Fmoc), 128.33 (*Ar* Fmoc), 128.96 (*Ar* Fmoc), 142.72 (*Ar* Fmoc), 145.30 (*Ar* Fmoc), 158.48 (C=O, Fmoc), 169.61 (C(1)); *m/z* (EI) *M*⁺ 345 (0.30), 309 (0.5), 265 (0.2), 178 (100), 165 (40%).

(2*R*)-2-(Fluoren-9-ylmethoxycarbonylamino)-3-chloropropionic acid *tert*-butyl ester **8**

(2*R*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-chloropropionic acid **7** (11.0 g, 31.8 mmol) was dissolved in CH₂Cl₂ (500 ml). The solution was cooled to –78 °C then 2-methylpropene (110 ml) was condensed into the solution. The mixture was allowed to warm to room temperature and H₂SO₄ (2.9 ml, 52.6 mmol, 1.7 equiv.) was added (solution became purple). The solution was stirred for 19 hours (checked regularly by TLC: EtOAc). The 2-methylpropene was removed under vacuum then the solution was washed with saturated NaHCO₃ (160 ml). The solution was neutralised (pH 6–7) by adding solid NaHCO₃ then was washed with brine (2 × 100 ml), dried and evaporated to yield a yellow oil. The oil was purified by flash chromatography (petroleum ether–ethyl acetate, 9 : 1) to give (2*R*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-chloropropionic acid *tert*-butyl ester **8** (10.7 g, 84%) as white crystals. Mp 89–91 °C (Found *M*⁺ 401.1393; C₂₂H₂₄NO₄Cl requires 401.1394); [*a*]_D²¹ +18.1 (*c* 1.05 in CHCl₃) (Found: C, 65.2; H, 6.2; N, 3.3%. C₂₂H₂₄NO₄Cl requires C, 65.7; H, 6.0 and N, 3.5%); ν_{max} (KBr disc)/cm⁻¹ 3347 (s), 3003 (m), 2969 (m), 1703 (s), 1694 (s) and 738 (s); δ_{H} (CDCl₃) 1.51 (9H, s, Bu^t), 3.89 (1H, dd, *J* 3.0, 11.5, C(3)*H*), 3.97 (1H, dd, *J* 3.0, 11.5, C(3)*H'*), 4.24 (1H, t, *J* 7.0, *CH* Fmoc), 4.36–4.42 (1H, m, *OCH* Fmoc), 4.63–4.66 (2H, m, C(2)*H* and *OCH'* Fmoc), 5.73 (1H, d, *J* 7.5, *NH*), 7.30–7.34 (2H, m, *ArH* Fmoc), 7.39–7.42 (2H, m, *ArH* Fmoc), 7.61 (2H, d, *J* 7.5, *ArH* Fmoc), 7.76 (2H, d, *J* 7.5, *ArH* Fmoc); δ_{C} (CDCl₃) 27.92 (C(CH₃)₃), 45.66 (C(3)), 47.05 (*CH* Fmoc), 55.08 (C(2)), 67.29 (*CH*₂ Fmoc), 83.49 (C(CH₃)₃), 119.99 (*Ar* Fmoc), 125.10 (*Ar* Fmoc), 127.07 (*Ar* Fmoc), 127.73 (*Ar* Fmoc), 141.27 (*Ar* Fmoc), 143.64 (*Ar* Fmoc),

155.57 (C=O, Fmoc), 167.64 (C(1)); *m/z* (EI) *M*⁺ 403 (0.07), 401 (0.2), 300 (5.5), 178 (100), 165 (13), 57 (17%).

(2*R*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-iodopropionic acid *tert*-butyl ester **2**

(2*R*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-chloropropionic acid *tert*-butyl ester **8** (7.84 g, 19.5 mmol) was dissolved in acetone (500 ml). NaI (11.8 g, 79.2 mmol, 4.0 equiv.) was added in a single portion. The yellow solution was refluxed for 3 days (the extent of reaction was checked by ¹H NMR). Acetone was removed under vacuum giving a yellow oil which was dissolved in CHCl₃ (500 ml). The solution was washed with water (500 ml), sodium thiosulfate (1 M, 250 ml), water (500 ml), dried and evaporated to give a pale yellow oil which was triturated with petrol (25 ml) to give (2*R*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-iodopropionic acid *tert*-butyl ester **2** (9.4 g, 99%) as a pale yellow powder. Mp 78–81 °C (Found *M*⁺ 493.0768; C₂₂H₂₄NO₄I requires 493.0750); [*a*]_D²³ +16.3 (*c* 1.05 in CHCl₃) (Found: C, 53.7; H, 4.9; N, 2.9%. C₂₂H₂₄NO₄I requires C, 53.6; H, 4.9 and N, 2.8%); ν_{max} (KBr disc)/cm⁻¹ 3387 (m), 3011 (m), 2968 (m), 1723 (s), 1720 (s), 1513 (s), 1242 (m) and 471 (w); δ_{H} (CDCl₃) 1.51 (9H, s, Bu^t), 3.58 (1H, dd, *J* 3.5, 10.5, C(3)*H*), 3.61 (1H, dd, *J* 3.5, 10.5, C(3)*H'*), 4.24 (1H, t, *J* 7.5, *CH* Fmoc), 4.32–4.43 (3H, m, C(2)*H* and *OCH*₂ Fmoc), 5.72 (1H, d, *J* 6.5, *NH*), 7.29–7.33 (2H, m, *ArH* Fmoc), 7.39 (2H, t, *J* 7.5, *ArH* Fmoc), 7.61 (2H, d, *J* 7.5, *ArH* Fmoc), 7.75 (2H, d, *J* 7.5, *ArH* Fmoc); δ_{C} (CDCl₃) 8.43 (C(3)), 27.97 (C(CH₃)₃), 47.05 (*CH* Fmoc), 55.04 (C(2)), 67.29 (*CH*₂ Fmoc), 83.60 (C(CH₃)₃), 119.99 (*Ar* Fmoc), 125.18 (*Ar* Fmoc), 127.07 (*Ar* Fmoc), 127.73 (*Ar* Fmoc), 141.27 (*Ar* Fmoc), 143.66 (*Ar* Fmoc), 155.37 (C=O, Fmoc), 168.16 (C(1)); *m/z* (EI) *M*⁺ 493 (0.1), 392 (0.7), 178 (100), 165 (17), 57 (17%).

General procedure for the coupling reaction between zinc reagent **1 and aromatic iodides**

Zinc dust (325 mesh, 0.150 g, 2.25 mmol, 3.0 equivalents) was weighed into a 50 ml round-bottomed flask with side arm which was repeatedly evacuated (with heating using a hot air gun) and flushed with nitrogen. Dry DMF (0.3 ml) and trimethylsilyl chloride (30 μ L, 0.375 mmol) were added, and the resultant mixture was allowed to stir for a further 30 min under nitrogen. *N*-(Fluoren-9-ylmethoxycarbonyl)-3-iodo-L-alanine *tert*-butyl ester **2** (0.370 g, 0.75 mmol) in dry DMF (0.5 ml under nitrogen) was added to the flask and stirred at room temperature until no starting material remained as judged by TLC (4 : 1, petroleum ether–ethyl acetate). The aromatic iodide (1.0 mmol, 1.3 equivalents), tri-*o*-tolylphosphine (31 mg, 0.1 mmol, 0.13 equivalents), and tris(dibenzylideneacetone)dipalladium (23 mg, 0.025 mmol, 6.6 mol%), were added sequentially to the reaction mixture. Stirring was continued for 4 h at 50 °C. The reaction mixture was diluted with ethyl acetate (50 ml), and the organic layer was washed with aq. sodium thiosulfate (1 M, 20 ml), water (2 × 20 ml), and brine (40 ml), dried and concentrated under reduced pressure to give the crude product as an oil. Purification by flash column chromatography over silica with a suitable petroleum ether–ethyl acetate gradient furnished the pure protected products. In each case, varying amounts of the protonated zinc reagent **9** were isolated.

(2*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)propionic acid *tert*-butyl ester **9.** The compound was isolated as white crystals, mp 78–80 °C (Found *M*⁺, 367.1798; C₂₂H₂₅NO₄ requires 367.1784); [*a*]_D²⁵ +0.3 (*c* 0.95 in CH₂Cl₂); ν_{max} (KBr disc)/cm⁻¹ 3336, 1724 and 1696; δ_{H} (CDCl₃) 1.37 (3H, d, *J* 7.0, CH₃), 1.46 (9H, s, C(CH₃)₃), 4.20 (1H, t, *J* 7.5, *CH* Fmoc), 4.26–4.31 (1H, m, C(2)*H*), 4.35–4.39 (2H, m, *OCH*₂ Fmoc), 5.48 (1H, d, *J* 7.5, *NH*), 7.29 (2H, t, *J* 7.5, *ArH* Fmoc), 7.36 (2H, t, *J* 7.5, *ArH* Fmoc), 7.59 (2H, d, *J* 7.5, *ArH* Fmoc), 7.73 (2H, d, *J* 7.5, *ArH* Fmoc); δ_{C} (CDCl₃) 18.85 (CH₃), 27.95

(CH₃), 47.17 (CH), 50.14 (CH), 66.88 (CH₂), 81.92 (quat.), 119.94 (Ar), 125.11 (Ar), 127.03 (Ar), 127.65 (Ar), 141.27 (Ar), 143.84 (Ar), 143.96 (Ar), 155.62 (CO), 172.30 (CO); *m/z* (EI) 367 (M⁺, 3), 266 (23), 178 (100), 165 (64), 57 (78%).

(2*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-(4-nitrophenyl)propionic acid *tert*-butyl ester 10a. Following the procedure described for the coupling reaction, treatment with 1-iodo-4-nitrobenzene (249 mg, 1.0 mmol) gave (2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-(4-nitrophenyl)propionic acid *tert*-butyl ester **10a** (216 mg, 59%) isolated as yellow needles, mp 122–123 °C (Found M⁺, 488.1943; C₂₈H₂₈N₂O₆ requires 488.1947); [α]_D²⁵ +31.4 (*c* 0.82 in CH₂Cl₂); ν_{max} (KBr disc)/cm⁻¹ 3500, 1721, 1521, 1346 and 739; δ_H (CDCl₃) 1.42 (9H, s, C(CH₃)₃), 3.13 (1H, dd, *J* 13.5, 5.5, C(3)*H*), 3.21 (1H, dd, *J* 13.5, 6.0, C(3)*H'*), 4.19 (1H, t, *J* 6.5, CH), 4.38 (1H, dd, *J* 10.5, 6.5, OCH Fmoc), 4.40 (1H, dd, *J* 10.5, 7.0, OCH' Fmoc), 4.56 (2H, m, C(2)*H*), 5.36 (1H, d, *J* 7.0, NH), 7.27 (2H, d, *J* 8.5, Ar*H*), 7.31 (2H, d, *J* 7.5, Ar*H* Fmoc), 7.40 (2H, d, *J* 7.5, Ar*H* Fmoc), 7.54–7.57 (2H, m, Ar*H* Fmoc), 7.77 (2H, d, *J* 7.5, Ar*H* Fmoc), 8.12 (2H, d, *J* 8.5, Ar*H*); δ_C (CDCl₃) 27.98 (CH₃), 38.20 (CH₂), 47.17 (CH), 54.77 (CH), 66.78 (CH₂), 83.10 (quat.), 120.02 (Ar), 120.04 (Ar), 123.50 (Ar), 124.90 (Ar), 124.98 (Ar), 127.06 (Ar), 127.78 (Ar), 130.39 (Ar), 141.32 (Ar), 141.37 (Ar), 143.60 (Ar), 143.77 (Ar), 144.10 (Ar), 147.04 (Ar), 155.47 (CO), 169.88 (CO); *m/z* (EI) 488 (M⁺, 0.1), 415 (6), 387 (7), 178 (95), 165 (100%).

(2*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-(2'-bromophenyl)propionic acid *tert*-butyl ester 10b. Following the procedure described for the coupling reaction, treatment with 1-iodo-2-bromobenzene (283 mg, 1.0 mmol) gave (2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-(2'-bromophenyl)propionic acid *tert*-butyl ester **10b** (246 mg, 47%) as a colourless oil (Found M⁺ 521.1211; C₂₈H₂₈NO₄Br requires 521.1202); [α]_D²⁰ +18.4 (*c* 1.0 in CHCl₃) (Found: C, 64.4; H, 5.3; N, 2.6%; C₂₈H₂₈NO₄Br requires C, 64.4; H, 5.4 and N, 2.7%); ν_{max} (KBr disc)/cm⁻¹ 3420 (m), 3064 (m), 2976 (m), 1734 (s), 1717 (s), 1506 (m), 1154 (s), 1046 (m) and 759 (m); δ_H (CDCl₃) 1.41 (9H, s, Bu'), 3.14 (1H, dd, *J* 8.5, 14.0, C(3)*H*), 3.29 (1H, dd, *J* 6.5, 14.0, C(3)*H'*), 4.17 (1H, t, *J* 7.5, CH Fmoc), 4.20–4.29 (1H, m, CH₂ Fmoc), 4.31–4.38 (1H, m, CH'₂ Fmoc), 4.66 (1H, dt, *J* 6.5, 8.5, C(2)*H*), 5.39 (1H, d, *J* 8.5, NH), 7.09 (1H, t, *J* 8.0, Ar*H*), 7.21 (1H, t, *J* 7.5, Ar*H*), 7.25 (1H, d, *J* 7.0, Ar*H*), 7.28–7.32 (2H, m, Ar*H* Fmoc), 7.39 (2H, t, *J* 7.5, Ar*H* Fmoc), 7.56 (2H, t, *J* 7.5, Ar*H* Fmoc), 7.60 (1H, d, *J* 7.5, Ar*H* Fmoc), 7.75 (2H, d, *J* 7.5, Ar*H* Fmoc); δ_C (CDCl₃) 27.98 (C(CH₃)₃), 38.88 (C(3)), 47.19 (CH Fmoc), 54.45 (C(2)), 67.01 (CH₂ Fmoc), 82.40 (Ar), 119.95 (Ar Fmoc), 125.14 (Ar), 125.19 (Ar Fmoc), 127.04 (Ar Fmoc), 127.41 (Ar), 127.67 (Ar Fmoc), 128.61 (Ar), 131.40 (Ar), 132.95 (Ar), 136.27 (Ar), 141.27 (Ar Fmoc), 143.84 (Ar Fmoc), 155.58 (C(4)), 170.76 (C(1)); *m/z* (EI) M⁺ 521 (1.2), 466 (1.0), 420 (32), 368 (98), 313 (15), 198 (35), 178 (100), 165 (12), 57 (28%).

(2*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-(2'-methoxycarbonylphenyl)propionic acid *tert*-butyl ester 10c. Following the procedure described for the coupling reaction, treatment with 2-methoxycarbonyliodobenzene (263 mg, 1.0 mmol) gave (2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-(2'-methoxycarbonylphenyl)propionic acid *tert*-butyl ester **10c** (80 mg, 21%) as a yellow oil; [α]_D²¹ +19.0 (*c* 1.0 in CHCl₃); δ_H (200 MHz, CDCl₃) 1.44 (9H, s, Bu'), 3.37–3.39 (1H, m, C(3)*H*), 3.40–3.43 (1H, m, C(3)*H'*), 3.94 (3H, s, OMe), 4.10–4.25 (3H, m, CH₂ Fmoc and CH Fmoc), 4.48–4.59 (1H, m, C(2)*H*), 6.07 (1H, d, *J* 8.0, NH), 7.20–7.60 (9H, m, Ar*H*), 7.75 (2H, d, *J* 7.5, Ar Fmoc*H*), 7.92 (1H, d, *J* 7.5, Ar*H*); *m/z* (EI) (Found M⁺ 501.2152; C₃₀H₃₁NO₆ requires 501.2151) M⁺ – H 500 (1.5), 469 (0.5), 444 (1.6), 412 (1.1), 337 (3.1), 322 (2.7), 178 (100), 165 (37), 146 (73), 118 (10), 57 (30%).

(2*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-(3'-benzoylphenyl)propionic acid *tert*-butyl ester 10d. Following the procedure described for the coupling reaction, treatment with 3-iodobenzophenone (308 mg, 1.0 mmol) gave (2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-(3'-benzoylphenyl)propionic acid *tert*-butyl ester **10d** (226 mg, 55%) as colourless crystals. Mp 56–60 °C; [α]_D²⁵ +49.7 (*c* 1.0 in CHCl₃) (Found: C, 76.8; H, 6.0; N, 2.6%. C₃₅H₃₃NO₅ requires C, 76.8; H, 6.1 and N, 2.6%); ν_{max} (KBr disc)/cm⁻¹ 3425 (m), 1723 (s), 1657 (s), 1508 (s), 1250 (s) and 1153 (s); δ_H (CDCl₃) 1.40 (9H, s, Bu'), 3.15 (1H, dd, *J* 6.0, 14.0, C(3)*H*), 3.21 (1H, dd, *J* 6.0, 14.0, C(3)*H'*), 4.18 (1H, t, *J* 7.4, CH Fmoc), 4.33 (1H, dd, *J* 7.4, 10.6, CH₂ Fmoc), 4.40 (1H, dd, *J* 7.4, 10.6, CH'₂ Fmoc), 4.57 (1H, m, C(2)*H*), 5.34 (1H, d, *J* 8.0, NH), 7.27–7.78 (17H, m, Ar Fmoc and benzoylphenyl); δ_C (CDCl₃) 27.95 (C(CH₃)₃), 38.24 (C(3)), 47.16 (CH Fmoc), 55.03 (C(2)), 66.98 (CH₂ Fmoc), 82.81 (C(CH₃)₃), 119.99 (Ar Fmoc), 124.81 (Ar), 125.14 (Ar Fmoc), 127.08 (Ar Fmoc), 127.72 (Ar Fmoc), 128.32 (Ar), 128.89 (Ar), 130.00 (Ar), 131.04 (Ar), 132.44 (Ar), 133.69 (Ar), 136.59 (Ar), 137.53 (Ar), 137.70 (Ar), 141.30 (Ar Fmoc), 143.79 (Ar Fmoc), 155.53 (C=O, Fmoc), 170.29 (C(1)); *m/z* (EI) M⁺ – C₂₁H₁₅O 264 (0.18), 178 (100), 165 (23), 105 (14), 77 (8), 57 (14%).

(2*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-(2'-methoxyphenyl)propionic acid *tert*-butyl ester 10e. Following the procedure described for the coupling reaction, treatment with 2-iodoanisole (234 mg, 1.0 mmol) gave (2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-(2'-methoxyphenyl)propionic acid *tert*-butyl ester **10e** (110 mg, 31%) as a clear yellow oil (Found M⁺ – C₅H₉O₂ 372.1604; C₂₄H₂₂NO₃ requires 372.1600); [α]_D²³ +16.0 (*c* 1.0 in CH₂Cl₂) (Found: C, 73.7; H, 6.9; N, 3.0%. C₂₉H₃₁NO₅ requires C, 73.6; H, 6.6 and N, 3.0%); ν_{max} (KBr disc)/cm⁻¹ 3338 (m), 3065 (m), 2977 (m), 2837 (m), 1724 (s), 1516 (s), 1156 (s) and 740 (s); δ_H (CDCl₃) 1.40 (9H, s, Bu'), 3.03–3.12 (2H, m, C(3)*H*₂), 3.83 (3H, s, OCH₃), 4.18 (1H, t, *J* 7.0, CH Fmoc), 4.28–4.33 (2H, m, OCH₂ Fmoc), 4.48–4.54 (1H, m, C(2)*H*), 5.59 (1H, d, *J* 8.0, NH), 6.86 (1H, d, *J* 8.0, Ar*H*), 6.89 (1H, t, *J* 7.5, Ar*H*), 7.14 (1H, d, *J* 7.5, Ar*H*), 7.23 (1H, dd, *J* 7.5, 8.0, Ar*H*), 7.26–7.32 (2H, m, Ar*H* Fmoc), 7.39 (2H, t, *J* 7.5, Ar*H* Fmoc), 7.51–7.57 (2H, m, Ar*H* Fmoc), 7.75 (2H, d, *J* 7.5, Ar*H* Fmoc); δ_C (CDCl₃) 27.94 (C(CH₃)₃), 33.13 (C(3)), 47.15 (CH Fmoc), 55.04 (OCH₃), 55.28 (C(2)), 66.78 (CH₂ Fmoc), 81.74 (C(CH₃)₃), 110.40 (Ar), 119.92 (Ar Fmoc), 120.65 (Ar), 125.07 (Ar), 125.17 (Ar Fmoc), 127.00 (Ar Fmoc), 127.62 (Ar Fmoc), 128.41 (Ar), 131.28 (Ar), 141.27 (Ar Fmoc), 143.93 (Ar Fmoc), 155.70 (C=O, Fmoc), 157.68 (Ar), 171.33 (C(1)); *m/z* (EI) M⁺ – C₅H₉O₂ 372 (0.8), 328 (9.0), 267 (0.6), 178 (100), 165 (6), 121 (10), 57 (5.0%).

(2*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-(3'-methoxyphenyl)propionic acid *tert*-butyl ester 10f. Following the procedure described for the coupling reaction, treatment with 3-iodoanisole (234 mg, 1.0 mmol) gave (2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-(3'-methoxyphenyl)propionic acid *tert*-butyl ester **10f** (170 mg, 48%) as a clear yellow oil (Found M⁺ 473.2187; C₂₉H₃₁NO₅ requires 473.2202); [α]_D²³ +18.4 (*c* 1.05 in CH₂Cl₂) (Found: C, 73.7; H, 6.7; N, 2.8%. C₂₉H₃₁NO₅ requires C, 73.6; H, 6.6 and N, 3.0%); ν_{max} (KBr disc)/cm⁻¹ 3339 (m), 3065 (m), 2977 (m), 2835 (m), 1723 (s), 1511 (s), 1155 (s), 886 (w) and 760 (s); δ_H (CDCl₃) 1.43 (9H, s, Bu'), 3.04–3.11 (2H, m, C(3)*H*₂), 3.76 (3H, s, OCH₃), 4.21 (1H, t, *J* 7.0, CH Fmoc), 4.33 (1H, dd, *J* 7.0, 10.5, OCH Fmoc), 4.41 (1H, dd, *J* 7.0, 10.5, OCH' Fmoc), 4.52–4.58 (1H, m, C(2)*H*), 5.31 (1H, d, *J* 8.0, NH), 6.73 (1H, br s, Ar*H*), 6.76 (1H, d, *J* 8.0, Ar*H*), 6.79 (1H, dd, *J* 8.0, 2.5, Ar*H*), 7.20 (1H, t, *J* 8.0, Ar*H*), 7.28–7.34 (2H, m, Ar*H* Fmoc), 7.40 (2H, t, *J* 7.5, Ar*H* Fmoc), 7.57 (2H, t, *J* 8.5, Ar*H* Fmoc), 7.76 (2H, d, *J* 7.5, Ar*H* Fmoc); δ_C (CDCl₃) 27.99 (C(CH₃)₃), 38.43 (C(3)), 47.17 (CH Fmoc), 55.00 (OCH₃), 55.15 (C(2)), 67.00 (CH₂ Fmoc), 82.40

(C(CH₃)₃), 112.35 (Ar), 115.30 (Ar), 119.98 (Ar Fmoc), 121.91 (Ar), 125.18 (Ar Fmoc), 127.05 (Ar Fmoc), 127.69 (Ar Fmoc), 129.40 (Ar), 137.58 (Ar), 141.29 (Ar Fmoc), 143.90 (Ar Fmoc), 155.56 (C=O, Fmoc), 159.63 (Ar), 170.60 (C(1)); *m/z* (EI) M⁺ 473 (0.2), 372 (0.5), 295 (0.5), 267 (1.6), 235 (3.2), 178 (100), 165 (17), 121 (16), 57 (20%).

(2S)-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-3-(4'-methoxyphenyl)propionic acid tert-butyl ester 10g. Following the procedure described for the coupling reaction, treatment with 4-iodoanisole (234 mg, 1.0 mmol) gave (2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-(4'-methoxyphenyl)propionic acid tert-butyl ester **10g** (120 mg, 34%) as an orange oil (Found M⁺ 473.2209; C₂₉H₃₁NO₅ requires 473.2202); [α]_D²³ +17.5 (*c* 0.99 in CH₂Cl₂) (Found: C, 73.6; H, 6.9; N, 2.9%. C₂₉H₃₁NO₅ requires C, 73.6; H, 6.6 and N, 3.0%); ν_{max} (KBr disc)/cm⁻¹ 3337 (m), 3065 (m), 2975 (m), 2934 (m), 2835 (m), 1723 (s), 1612 (s), 1511 (s), 1155 (s) and 845 (s); δ_H (CDCl₃) 1.43 (9H, s, Bu^t), 3.02 (1H, dd, *J* 6.0, 14.0, C(3)H), 3.06 (1H, dd, *J* 6.0, 14.0, C(3)H'), 3.77 (3H, s, OCH₃), 4.21 (1H, t, *J* 7.0, CH Fmoc), 4.32 (1H, dd, *J* 7.0, 10.5, OCH Fmoc), 4.44 (1H, dd, *J* 7.0, 10.5, OCH' Fmoc), 4.48–4.52 (1H, m, C(2)H), 5.26 (1H, d, *J* 8.0, NH), 6.81 (2H, d, *J* 8.0, ArH), 7.06 (1H, d, *J* 8.0, ArH), 7.31 (2H, dt, *J* 7.5, 2.5, ArH Fmoc), 7.31 (2H, t, *J* 7.0, ArH Fmoc), 7.56–7.59 (2H, m, ArH Fmoc), 7.76 (2H, d, *J* 7.5, ArH Fmoc); δ_C (CDCl₃) 28.01 (C(CH₃)₃), 37.46 (C(3)), 47.20 (CH Fmoc), 55.22 (C(2)), 56.63 (OCH₃), 66.86 (CH₂ Fmoc), 82.33 (C(CH₃)₃), 113.83 (Ar), 119.98 (Ar Fmoc), 125.18 (Ar Fmoc), 127.04 (Ar Fmoc), 127.69 (Ar Fmoc), 128.01 (Ar), 130.55 (Ar), 141.31 (Ar Fmoc), 143.91 (Ar Fmoc), 155.52 (C=O, Fmoc), 158.63 (Ar), 170.66 (C(1)); *m/z* (EI) M⁺ 473 (0.1), 372 (1.0), 328 (0.3), 178 (100), 165 (10), 121 (49), 57 (70%).

(2S)-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-3-(2',4'-dimethoxyphenyl)propionic acid tert-butyl ester 10h. Following the procedure described for the coupling reaction, treatment with 2,4-dimethoxyiodobenzene (264 mg, 1.0 mmol) gave (2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-(2',4'-dimethoxyphenyl)propionic acid tert-butyl ester **10h** (91 mg, 24%) as a clear oil. [α]_D¹⁶ +8.2 (*c* 1.01 in CHCl₃) (Found: C, 71.2; H, 6.4; N, 2.6%. C₃₀H₃₃NO₆ requires C, 71.5; H, 6.6 and N, 2.8%); ν_{max} (KBr disc)/cm⁻¹ 3342 (s), 3065 (s), 2976 (s), 2836 (m), 1724 (vs), 1508 (s), 1157 (vs), 877 (m), 837 (m) and 740 (s); δ_H (CDCl₃) 1.41 (9H, s, Bu^t), 2.90–3.10 (2H, m, C(3)H), 3.76 (3H, s, OCH₃), 3.78 (3H, s, OCH₃), 4.15–4.20 (1H, m, CH Fmoc), 4.27–4.33 (2H, m, OCH Fmoc), 4.42–4.48 (1H, m, C(2)H), 5.59 (1H, d, *J* 7.5, NH), 6.40 (1H, d, *J* 7.5, ArH), 6.44 (1H, s, ArH), 6.53 (1H, d, *J* 7.5, ArH), 7.29 (2H, d, *J* 7.5, ArH Fmoc), 7.38 (2H, t, *J* 7.5, ArH Fmoc), 7.50–7.60 (2H, m, ArH Fmoc), 7.74 (2H, d, *J* 7.5, ArH Fmoc); δ_C (CDCl₃) 28.02 (C(CH₃)₃), 32.38 (C(3)), 47.15 (CH Fmoc), 55.22 (C(2)), 55.33 (OCH₃), 55.65 (OCH₃), 66.76 (CH₂ Fmoc), 81.65 (C(CH₃)₃), 98.55 (Ar), 104.14 (Ar), 117.31 (Ar), 119.90 (Ar Fmoc), 125.17 (Ar Fmoc), 127.07 (Ar Fmoc), 127.69 (Ar Fmoc), 131.56 (Ar), 141.26 (Ar Fmoc), 143.92 (Ar Fmoc), 155.77 (C=O, Fmoc), 158.56 (Ar), 160.08 (Ar), 171.34 (C(1)); *m/z* (EI) M⁺ 503 (4.5), 325 (42), 178 (100), 165 (19), 151 (46), 121 (11), 57 (3%).

(2S)-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-3-(3',4'-dimethoxyphenyl)propionic acid tert-butyl ester 10i. Following the procedure described for the coupling reaction, treatment with 3,4-dimethoxyiodobenzene (264 mg, 1.0 mmol) gave (2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-(3',4'-dimethoxyphenyl)propionic acid tert-butyl ester **10i** (155 mg, 41%) as a white powder. Mp 98–100 °C (Found M⁺ 503.2318; C₃₀H₃₃NO₆ requires 503.2308); [α]_D¹⁶ +25.1 (*c* 1.0 in CHCl₃) (Found: C, 71.0; H, 6.9; N, 2.8%. C₃₀H₃₃NO₆ requires C, 71.5; H, 6.6 and N, 2.8%); ν_{max} (KBr disc)/cm⁻¹ 3344 (m), 3065 (m), 2973 (m), 2833 (m), 1723 (s), 1700 (s), 1541 (s), 1154 (s), 815 (m) and 736 (s); δ_H (CDCl₃) 1.44 (9H, s, Bu^t), 3.01–3.09 (2H, m, C(3)H₂), 3.82

(3H, s, OCH₃), 3.85 (3H, s, OCH₃), 4.21 (1H, t, *J* 7.0, CH Fmoc), 4.35 (1H, dd, *J* 7.0, 11.0, OCH Fmoc), 4.39 (1H, dd, *J* 7.0, 11.0, OCH' Fmoc), 4.51–4.80 (1H, m, C(2)H), 5.29 (1H, d, *J* 8.0, NH), 6.68–6.71 (2H, m, 2 × ArH), 6.77 (1H, d, *J* 7.0, ArH), 7.30 (2H, d, *J* 7.5, ArH Fmoc), 7.40 (2H, t, *J* 7.5, ArH Fmoc), 7.54–7.59 (2H, m, ArH Fmoc), 7.76 (2H, d, *J* 7.5, ArH Fmoc); δ_C (CDCl₃) 28.02 (C(CH₃)₃), 37.98 (C(3)), 47.15 (CH Fmoc), 55.11 (C(2)), 55.83 (OCH₃), 55.88 (OCH₃), 66.96 (CH₂ Fmoc), 82.30 (C(CH₃)₃), 111.12 (Ar), 112.58 (Ar), 119.99 (Ar Fmoc), 121.71 (Ar), 125.09 (Ar Fmoc), 127.04 (Ar Fmoc), 127.70 (Ar Fmoc), 128.49 (Ar), 141.29 (Ar Fmoc), 143.78 (Ar Fmoc), 148.08 (Ar), 148.81 (Ar), 155.59 (C=O, Fmoc), 170.76 (C(1)); *m/z* (EI) M⁺ 503 (4.8), 325 (4), 178 (35), 165 (16), 151 (100), 57 (9%).

(2S)-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-3-(3',5'-dimethoxyphenyl)propionic acid tert-butyl ester 10j. Following the procedure described for the coupling reaction, treatment with 3,5-dimethoxyiodobenzene (264 mg, 1.0 mmol) gave (2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-(3',5'-dimethoxyphenyl)propionic acid tert-butyl ester **10j** (177 mg, 47%) as a white powder. Mp 48–50 °C (Found M⁺ 503.2325; C₃₀H₃₃NO₆ requires 503.2308); [α]_D¹⁷ +7.5 (*c* 0.99 in CHCl₃) (Found: C, 71.1; H, 6.6; N, 3.0%. C₃₀H₃₃NO₆ requires C, 71.5; H, 6.6 and N, 2.8%); ν_{max} (KBr disc)/cm⁻¹ 3340 (m), 3065 (m), 2975 (m), 2837 (m), 1724 (s), 1511 (s), 1152 (s), 843 (m) and 741 (s); δ_H (CDCl₃) 1.44 (9H, s, Bu^t), 3.04–3.09 (2H, m, C(3)H₂), 3.74 (6H, s, OCH₃), 4.18–4.24 (1H, m, CH Fmoc), 4.33 (1H, dd, *J* 7.5, 10.5, OCH Fmoc), 4.38 (1H, dd, *J* 7.5, 10.5, OCH' Fmoc), 4.52–4.58 (1H, m, C(2)H), 5.30 (1H, d, *J* 8.0, NH), 6.32–6.36 (3H, m, ArH), 7.28–7.33 (2H, m, ArH Fmoc), 7.36–7.42 (2H, m, ArH Fmoc), 7.54–7.60 (2H, m, ArH Fmoc), 7.76 (2H, d, *J* 7.5, ArH Fmoc); δ_C (CDCl₃) 28.01 (C(CH₃)₃), 38.63 (C(3)), 47.14 (CH Fmoc), 54.90 (C(2)), 55.28 (OCH₃), 67.06 (CH₂ Fmoc), 82.38 (C(CH₃)₃), 98.95 (Ar), 107.59 (Ar), 119.98 (Ar Fmoc), 125.18 (Ar Fmoc), 127.07 (Ar Fmoc), 127.69 (Ar Fmoc), 138.25 (Ar), 141.27 (Ar Fmoc), 143.82 (Ar Fmoc), 155.59 (C=O, Fmoc), 160.79 (Ar), 170.61 (C(1)); *m/z* (EI) M⁺ 503 (1.2), 325 (27), 269 (32), 178 (100), 165 (23), 151 (25), 57 (25%).

(2S)-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-3-(2',3',4'-trimethoxyphenyl)propionic acid tert-butyl ester 10k. Following the procedure described for the coupling reaction, treatment with 2,3,4-trimethoxyiodobenzene (294 mg, 1.0 mmol) gave (2S)-2-(9H-fluoren-9-ylmethoxycarbonylamino)-3-(2',3',4'-trimethoxyphenyl)propionic acid tert-butyl ester **10k** (188 mg, 47%) as a clear oil (Found M⁺ 533.2395; C₃₁H₃₅NO₇ requires 533.2414); [α]_D²³ +5.0 (*c* 1.0 in CH₂Cl₂) (Found: C, 69.8; H, 6.7; N, 2.6%. C₃₁H₃₅NO₇ requires C, 69.8; H, 6.6 and N, 2.6%); ν_{max} (KBr disc)/cm⁻¹ 3064 (m), 2835 (m), 1724 (s), 1495 (s), 1100 (s) and 741 (s); δ_H (CDCl₃) 1.43 (9H, s, Bu^t), 2.98 (1H, dd, *J* 6.0, 14.0, C(3)H), 3.20 (1H, dd, *J* 6.0, 14.0, C(3)H'), 3.82 (3H, s, OCH₃), 3.86 (3H, s, OCH₃), 3.92 (3H, s, OCH₃), 4.19 (1H, t, *J* 6.5, CH Fmoc), 4.29 (1H, dd, *J* 6.5, 10.0, OCH Fmoc), 4.31 (1H, dd, *J* 6.5, 10.0, OCH' Fmoc), 4.39–4.46 (1H, m, C(2)H), 5.67 (1H, d, *J* 8.0, NH), 6.58 (1H, d, *J* 6.0, ArH), 6.84 (1H, d, *J* 6.0, ArH), 7.28–7.31 (2H, m, ArH Fmoc), 7.39 (2H, t, *J* 7.5, ArH Fmoc), 7.57 (2H, t, *J* 7.5, ArH Fmoc), 7.75 (2H, d, *J* 7.5, ArH Fmoc); δ_C (CDCl₃) 27.98 (C(CH₃)₃), 32.75 (C(3)), 47.18 (CH Fmoc), 55.56 (C(2)), 56.00 (OCH₃), 60.74 (OCH₃), 60.89 (OCH₃), 66.90 (CH₂ Fmoc), 81.83 (C(CH₃)₃), 107.20 (Ar), 119.92 (Ar Fmoc), 122.38 (Ar), 125.15 (Ar), 125.19 (Ar Fmoc), 127.03 (Ar Fmoc), 127.64 (Ar Fmoc), 141.27 (Ar Fmoc), 142.10 (Ar), 143.92 (Ar Fmoc), 144.04 (Ar), 153.01 (Ar), 155.82 (C=O, Fmoc), 171.21 (C(1)); *m/z* (EI) M⁺ 533 (1.4), 355 (3.1), 181 (100), 178 (46), 166 (62), 57 (12%).

(2S)-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-3-(3',4',5'-trimethoxyphenyl)propionic acid tert-butyl ester 10l. Following the procedure described for the coupling reaction, treatment

with 3,4,5-trimethoxyiodobenzene (294 mg, 1.0 mmol) gave (2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-(3',4',5'-trimethoxyphenyl)propionic acid *tert*-butyl ester **10l** (235 mg, 59%) as colourless needles. Mp 84–86 °C (Found M^+ 533.2436; $C_{31}H_{35}NO_7$ requires 533.2414); $[\alpha]_D^{23} +6.2$ (c 0.99 in CH_2Cl_2) (Found: C, 69.6; H, 6.3; N, 2.4%. $C_{31}H_{35}NO_7$ requires C, 69.8; H, 6.6 and N, 2.6%); ν_{max} (KBr disc)/ cm^{-1} 3351 (m), 3065 (m), 2934 (m), 2835 (m), 1724 (s), 1691 (s), 1508 (s), 1128 (s), 846 (w) and 737 (s); δ_H ($CDCl_3$) 1.41 (9H, s, Bu'), 3.02 (1H, dd, J 6.5, 14.0, C(3)*H*), 3.07 (1H, dd, J 6.0, 14.0, C(3)*H'*), 3.80 (6H, s, OCH₃), 3.81 (3H, s, OCH₃), 4.21 (1H, t, J 7.0, CH Fmoc), 4.30–4.50 (2H, m, OCH₂ Fmoc), 4.52–4.58 (1H, m, C(2)*H*), 5.30 (1H, d, J 6.0, NH), 6.39 (2H, s, Ar*H*), 7.29 (2H, dt, J 1.0, 7.5, Ar*H* Fmoc), 7.39 (2H, t, J 7.5, Ar*H* Fmoc), 7.52–7.59 (2H, m, Ar*H* Fmoc), 7.76 (2H, d, J 7.5, Ar*H* Fmoc); δ_C ($CDCl_3$) 28.08 (C(CH₃)₃), 38.80 (C(3)), 47.13 (CH Fmoc), 54.98 (C(2)), 56.90 (OCH₃), 60.85 (OCH₃), 67.05 (CH₂ Fmoc), 82.33 (C(CH₃)₃), 106.46 (Ar), 120.01 (Ar Fmoc), 125.01 (Ar Fmoc), 127.05 (Ar Fmoc), 127.74 (Ar Fmoc), 131.71 (Ar), 137.04 (Ar), 141.29 (Ar Fmoc), 143.71 (Ar Fmoc), 153.14 (Ar), 155.62 (C=O, Fmoc), 170.74 (C(1)); m/z (EI) M^+ 533 (32), 355 (11), 182 (41), 178 (100), 165 (21), 57 (23%).

General method for the removal of the *tert*-butyl protective group of *N*-Fmoc protected substituted phenylalanines

The *N*-Fmoc protected *tert*-butyl ester (0.5 mmol) and Et₃SiH (0.2 ml, 1.25 mmol, 2.5 equiv.) were dissolved in dichloromethane (5 ml) under nitrogen. TFA (2 ml) was added slowly. The reaction mixture was stirred at room temperature for 4 hours then solvent and TFA were evaporated. The residue was dissolved in diethyl ether, and the product was precipitated by the addition of petroleum ether. The resulting powder was then triturated with petrol to yield the *N*-Fmoc protected substituted phenylalanine derivative, usually as an amorphous powder.

(2*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-(3'-benzoylphenyl)propionic acid **11d.** Following the general method for the removal of the *tert*-butyl protecting group, treatment of (2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-(3'-benzoylphenyl)propionic acid *tert*-butyl ester **10d** (200 mg, 0.36 mmol) gave (2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-(3'-benzoylphenyl)propionic acid **11d** (131 mg, 73%) as a white amorphous powder. Mp 122–123 °C; $[\alpha]_D^{18} +11.2$ (c 1.0 in $CHCl_3$) (Found: C, 75.4; H, 4.9; N, 2.6%. $C_{31}H_{25}NO_5$ requires C, 75.8; H, 5.1 and N, 2.6%); ν_{max} (KBr disc)/ cm^{-1} 3421 (m), 2854 (s), 1654 (s), 1598 (s), 1507 (m), 1207 (m), 840 (w) and 720 (m); δ_H ($CDCl_3$) 3.15 (1H, dd, J 6.0, 14.0, C(3)*H*), 3.21 (1H, dd, J 6.0, 14.0, C(3)*H'*), 4.18 (1H, t, J 6.5, CH Fmoc), 4.33 (1H, dd, J 6.5, 10.5, OCH Fmoc), 4.40 (1H, dd, J 6.5, 10.5, OCH' Fmoc), 4.47–4.62 (1H, m, C(2)*H*), 5.34 (1H, d, J 8.0, NH), 7.22–8.10 (17H, m, Ar*H* Fmoc); δ_C ($CDCl_3$) 37.68 (C(3)), 47.09 (CH Fmoc), 54.53 (C(2)), 67.20 (CH₂ Fmoc), 119.99 (Ar Fmoc), 125.02 (Ar), 125.07 (Ar Fmoc), 127.10 (Ar Fmoc), 127.76 (Ar Fmoc), 128.34 (Ar), 129.49 (Ar), 130.16 (Ar), 131.52 (Ar), 132.67 (Ar), 133.55 (Ar), 136.22 (Ar), 137.26 (Ar), 137.84 (Ar), 141.30 (Ar Fmoc), 143.63 (Ar Fmoc), 155.85 (C=O, Fmoc), 174.61 (C(1)), 196.93 (C=O); m/z (EI) M^+ – C₆H₄ 415 (0.11), 295 (0.21), 196 (0.07), 178 (100), 165 (25), 76 (8%).

(2*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-(4'-methoxyphenyl)propionic acid **11g.** Following the general method for the removal of the *tert*-butyl protecting group, treatment of (2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-(4'-methoxyphenyl)propionic acid *tert*-butyl ester **10g** (75 mg, 0.16 mmol) gave (2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-(4'-methoxyphenyl)propionic acid **11g** (43 mg, 64%) as a beige amorphous powder. Mp 154–156 °C (lit.¹⁸ 158–158.3 °C) (Found M^+ 402.1342; $C_{24}H_{20}NO_5$ requires 402.1341); $[\alpha]_D^{21} -3.5$ (c 1.0 in H₂O) (lit.¹⁸ $[\alpha]_D^{20} -2.94$ (c 1.0 in H₂O)) (Found: C,

72.0; H, 5.3; N, 3.2%. $C_{27}H_{27}NO_7$ requires C, 71.9; H, 5.6 and N, 3.4%); δ_H (CD_3OD) 2.87 (1H, dd, J 9.5, 14.0, C(3)*H*), 3.13 (1H, dd, J 4.5, 14.0, C(3)*H'*), 3.70 (3H, s, OCH₃), 4.13 (1H, t, J 7.0, OCH Fmoc), 4.19 (1H, dd, J 7.0, 10.5, OCH Fmoc), 4.29 (1H, dd, J 7.0, 10.5, OCH' Fmoc), 4.37 (1H, dd, J 5.0, 9.5, C(2)*H*), 6.79 (2H, d, J 8.5, Ar*H*), 7.13 (2H, d, J 8.5, Ar*H*), 7.27 (2H, dt, J 3.5, 7.5, Ar*H* Fmoc), 7.37 (2H, t, J 7.5, Ar*H* Fmoc), 7.58 (2H, dd, J 3.5, 7.5, Ar*H* Fmoc), 7.77 (2H, d, J 7.5, Ar*H* Fmoc); δ_C (CD_3OD) 37.84 (C(3)), 48.34 (CH Fmoc), 55.69 (C(2)), 57.07 (OCH₃), 67.96 (CH₂ Fmoc), 114.85 (Ar), 120.87 (Ar Fmoc), 126.34 (Ar Fmoc), 128.14 (Ar Fmoc), 128.74 (Ar Fmoc), 130.58 (Ar), 131.31 (Ar), 142.53 (Ar Fmoc), 145.22 (Ar Fmoc), 158.33 (C=O, Fmoc), 159.98 (Ar), 175.40 (C(1)); m/z (EI) M^+ 417 (0.2), 402 (1.5), 373 (1.3), 357 (0.8), 178 (100), 165 (30), 121 (96%).

(2*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-(2',4'-dimethoxyphenyl)propionic acid **11h.** Following the general method for the removal of the *tert*-butyl protecting group, treatment of (2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-(2',4'-dimethoxyphenyl)propionic acid *tert*-butyl ester **10h** (251 mg, 0.5 mmol) gave (2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-(2',4'-dimethoxyphenyl)propionic acid **11h** (165 mg, 74%) as a white amorphous powder. Mp 163–164 °C (Found M^+ 447.1674; $C_{26}H_{25}NO_6$ requires 447.1682); $[\alpha]_D^{16} +28.1$ (c 1.0 in $CHCl_3$); ν_{max} (KBr disc)/ cm^{-1} 3500–2700 (m), 3417 (m), 3182 (m), 2956 (m), 2841 (m), 1714 (s), 1691 (s), 1509 (s), 1158 (s), 831 (s), 739 (s); δ_H ($CDCl_3$) 3.08 (1H, dd, J 8.0, 14.0, C(3)*H*), 3.14 (1H, dd, J 4.5, 14.0, C(3)*H'*), 3.76 (3H, s, OCH₃), 3.77 (3H, s, OCH₃), 4.16–4.20 (1H, m, OCH Fmoc), 4.30–4.40 (2H, m, CH₂ Fmoc), 4.49–4.57 (1H, m, C(2)*H*), 5.70 (1H, d, J 7.0, NH), 6.42 (1H, d, J 8.0, Ar*H*), 6.45 (1H, s, Ar*H*), 7.03 (1H, d, J 8.0, Ar*H*), 7.29 (2H, t, J 7.5, Ar*H* Fmoc), 7.40 (2H, t, J 7.0, Ar*H* Fmoc), 7.47–7.58 (2H, m, Ar*H* Fmoc), 7.75 (2H, d, J 7.0, Ar*H* Fmoc); δ_C ($CDCl_3$) 32.32 (C(3)), 47.09 (CH Fmoc), 54.90 (C(2)), 55.22 (OCH₃), 55.36 (OCH₃), 67.36 (CH₂ Fmoc), 98.71 (Ar), 104.57 (Ar), 116.56 (Ar), 119.97 (Ar Fmoc), 125.09 (Ar Fmoc), 127.05 (Ar Fmoc), 127.72 (Ar Fmoc), 131.70 (Ar), 141.30 (Ar Fmoc), 143.72 (Ar Fmoc), 156.27 (C=O, Fmoc), 158.42 (Ar), 160.31 (Ar), 176.64 (C(1)); m/z (EI) M^+ 447 (0.44), 178 (43), 165 (37), 151 (100%).

(2*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-(3',5'-dimethoxyphenyl)propionic acid **11j.** Following the general method for the removal of the *tert*-butyl protecting group, treatment of (2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-(3',5'-dimethoxyphenyl)propionic acid *tert*-butyl ester **10j** (251 mg, 0.5 mmol) gave (2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-(3',5'-dimethoxyphenyl)propionic acid **11j** (140 mg, 63%) as a white amorphous powder. Mp 145–146 °C (Found M^+ 447.1677; $C_{26}H_{25}NO_6$ requires 447.1682); $[\alpha]_D^{16} +39.5$ (c 1.0 in $CHCl_3$); ν_{max} (KBr disc)/ cm^{-1} 3600–3200 (m), 3333 (m), 3064 (m), 2925 (m), 2856 (m), 1717 (s), 1684 (s), 1533 (s), 1157 (s), 845 (m) and 737 (s); δ_H ($CDCl_3$) 3.06 (1H, dd, J 6.0, 13.0, C(3)*H*), 3.14 (1H, dd, J 6.0, 13.0, C(3)*H'*), 3.72 (6H, s, 2 × OCH₃), 4.16–4.24 (1H, m, OCH Fmoc), 4.32–4.48 (2H, m, CH₂ Fmoc), 4.65–4.75 (1H, m, C(2)*H*), 5.35 (1H, d, J 7.5, NH), 6.35 (3H, br s, Ar*H*), 7.25–7.34 (2H, m, Ar*H* Fmoc), 7.35–7.42 (2H, m, Ar*H* Fmoc), 7.47–7.58 (2H, m, Ar*H* Fmoc), 7.75 (2H, d, J 7.0, Ar*H* Fmoc); δ_C ($CDCl_3$) 37.98 (C(3)), 47.07 (CH Fmoc), 54.47 (C(2)), 55.28 (OCH₃), 67.33 (CH₂ Fmoc), 99.17 (Ar), 107.41 (Ar), 120.01 (Ar Fmoc), 125.11 (Ar Fmoc), 127.11 (Ar Fmoc), 127.75 (Ar Fmoc), 137.81 (Ar), 141.29 (Ar Fmoc), 143.66 (Ar Fmoc), 155.98 (C=O, Fmoc), 160.94 (Ar), 175.74 (C(1)); m/z (EI) M^+ 447 (0.74), 269 (28), 178 (100), 165 (75), 151 (60%).

(2*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-(2',3',4'-trimethoxyphenyl)propionic acid **11k.** Following the general method for the removal of the *tert*-butyl protecting group,

treatment of (2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-(2',3',4'-trimethoxyphenyl)propionic acid *tert*-butyl ester **10k** (266 mg, 0.5 mmol) gave (2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-(2',3',4'-trimethoxyphenyl)propionic acid **11k** (193 mg, 81%) as a white amorphous powder. Mp 69–71 °C (Found M^+ 477.1772; $C_{27}H_{27}NO_7$ requires 477.1788); $[a]_D^{25} +47.1$ (c 1.0 in $CHCl_3$) (Found: C, 68.3; H, 5.7; N, 2.8%. $C_{27}H_{27}NO_7$ requires C, 67.9; H, 5.7 and N, 2.9%); ν_{max} (KBr disc)/ cm^{-1} 3450–3250 (m), 3065 (m), 2835 (m), 1723 (s), 1496 (s), 1099 (s) and 740 (s); δ_H ($CDCl_3$) 3.05 (1H, dd, J 4.0, 13.5, C(3)*H*), 3.14 (1H, dd, J 4.0, 13.5, C(3)*H'*), 3.81 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 4.18 (1H, t, J 7.0, OCH_2 Fmoc), 4.28–4.38 (2H, m, CH_2 Fmoc), 4.45–4.55 (1H, m, C(2)*H*), 5.86 (1H, d, J 7.0, NH), 6.59 (1H, d, J 8.5, ArH), 6.85 (1H, d, J 8.5, ArH), 7.25–7.32 (2H, m, ArH Fmoc), 7.38 (2H, t, J 7.5, ArH Fmoc), 7.54 (2H, t, J 7.0, ArH Fmoc), 7.74 (2H, d, J 7.5, ArH Fmoc); δ_C ($CDCl_3$) 32.00 (C(3)), 47.11 (CH Fmoc), 55.28 (C(2)), 55.97 (OCH_3), 60.77 (OCH_3), 60.98 (OCH_3), 67.17 (CH_2 Fmoc), 107.54 (Ar), 119.96 (Ar Fmoc), 121.70 (Ar), 125.18 (Ar Fmoc), 127.05 (Ar Fmoc), 127.71 (Ar Fmoc), 132.20 (Ar), 141.29 (Ar Fmoc), 142.06 (Ar), 143.76 (Ar Fmoc), 143.89 (Ar), 153.22 (Ar), 156.28 (C=O, Fmoc), 176.18 (C(1)); m/z (EI) M^+ 477 (0.94), 299 (4), 181 (100), 178 (30), 166 (4%).

(2*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-(3',4',5'-trimethoxyphenyl)propionic acid **11l.** Following the general method for the removal of the *tert*-butyl protecting group, treatment of (2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-(3',4',5'-trimethoxyphenyl)propionic acid *tert*-butyl ester **10l** (266 mg, 0.5 mmol) gave (2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-(3',4',5'-trimethoxyphenyl)propionic acid **11l** (226 mg, 95%) as a white amorphous powder. Mp 142–143 °C (Found M^+ 477.1801; $C_{27}H_{27}NO_7$ requires 477.1788); $[a]_D^{25} +38.5$ (c 1.0 in $CHCl_3$); ν_{max} (KBr disc)/ cm^{-1} 3500–3400 (m), 3065 (m), 2936 (m), 2837 (m), 1717 (s), 1689 (s), 1509 (s), 1129 (s), 823 (w) and 738 (s); δ_H ($CDCl_3$) 3.04 (1H, dd, J 6.5, 13.5, C(3)*H*), 3.16 (1H, dd, J 6.5, 13.5, C(3)*H'*), 3.77 (6H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.19 (1H, t, J 6.5, OCH_2 Fmoc), 4.32–4.46 (2H, m, CH_2 Fmoc), 4.70–4.80 (1H, m, C(2)*H*), 5.45 (1H, d, J 8.0, NH), 6.41 (2H, s, ArH), 7.27 (2H, t, J 7.5, ArH Fmoc), 7.38 (2H, t, J 7.5, ArH Fmoc), 7.48–7.57 (2H, m, ArH Fmoc), 7.75 (2H, d, J 7.5, ArH Fmoc), 9.11 (1H, br s, CO_2H); δ_C ($CDCl_3$) 38.10 (C(3)), 47.04 (CH Fmoc), 54.67 (C(2)), 56.10 (OCH_3), 60.85 (OCH_3), 67.33 (CH_2 Fmoc), 106.33 (Ar), 120.07 (Ar Fmoc), 124.98 (Ar Fmoc), 127.11 (Ar Fmoc), 127.83 (Ar Fmoc), 131.46 (Ar), 137.06 (Ar), 141.31 (Ar Fmoc), 143.54 (Ar Fmoc), 153.26 (Ar), 156.07 (C=O, Fmoc), 175.67 (C(1)); m/z (EI) M^+ 477 (1), 299 (0.5), 252 (5), 181 (100), 178 (23), 165 (32%).

General procedure for the coupling reaction of zinc reagent **1** with acid chlorides

Zinc–copper couple (0.294 g, 4.5 mmol, 6.0 equiv.) was placed in a 50 ml round-bottomed flask with side arm which was repeatedly evacuated (with heating using a hot air gun) and flushed with nitrogen. Toluene–DMA (93 : 7, 0.3 ml) was added, and the resultant mixture was allowed to stir for a further 30 min under nitrogen. *N*-(9-*H*-Fluorenylmethoxycarbonyl)-3-iodo-L-alanine-*tert*-butyl ester **2** (0.370 g, 0.75 mmol) in toluene–DMA (93 : 7, 0.5 ml under nitrogen) was added to the flask and stirred at 50 °C until no starting material remained as judged by TLC (4 : 1, petroleum ether–ethyl acetate). The supernatant was carefully removed *via* a syringe (care to be taken to avoid transferring too much zinc powder) and added dropwise to a solution of the acid chloride (1.0 mmol) in toluene–DMA (93 : 7, 1 ml) and $Pd(PPh_3)_2Cl_2$ (53 mg, 10 mol%) in a dried round-bottomed flask under nitrogen, and the mixture was heated at 50 °C for 4 hours. The solution was allowed to cool to room temperature and ethyl acetate (20 ml)

was added and stirring was continued for a further 10 min. The reaction mixture was transferred to a separating funnel and a further aliquot of ethyl acetate (30 ml) was added. The organic phase was washed successively with 1 M $Na_2S_2O_3$ (20 ml), water (2 × 20 ml) and brine (40 ml), dried and evaporated. The residue was then purified by flash chromatography on silica gel using a suitable ethyl acetate–petroleum ether gradient.

(2*S*)-5-Acetoxy-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-4-oxopentanoic acid *tert*-butyl ester **12a.** Following the general procedure for coupling with acid chlorides using acetoxyacetyl chloride (0.137 g, 0.108 ml, 1 mmol), (2*S*)-5-acetoxy-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-4-oxopentanoic acid *tert*-butyl ester **12a** was isolated as a yellow oil (0.165 g, 47%) (Found M^+ , 467.1980; $C_{26}H_{29}NO_7$ requires 467.1944); $[a]_D^{25} +8.9$ (c 1.09 in CH_2Cl_2); ν_{max} (KBr disc)/ cm^{-1} 3354, 1733 and 1510; δ_H ($CDCl_3$) 1.46 (9H, s, C(CH_3)₃), 2.18 (3H, s, $OCOCH_3$), 2.99 (1H, dd, J 18.0, 4.5, C(3)*H*), 3.13 (1H, dd, J 18.0, 4.5, C(3)*H'*), 4.22–4.40 (3H, m, OCH_2 Fmoc, CH Fmoc), 4.49–4.55 (1H, m, C(2)*H*), AB system (δ_A 4.62, δ_B 4.65, J_{AB} 7.0, CH_2OAc), 5.75 (1H, d, J 7.5, NH), 7.31 (2H, t, J 6.5, ArH Fmoc), 7.35 (2H, t, J 6.5, ArH Fmoc), 7.59 (2H, d, J 8.0, ArH Fmoc), 7.77 (2H, d, J 7.0, ArH Fmoc); δ_C ($CDCl_3$) 20.37 (CH_3), 27.81 (CH_3), 41.00 (CH_2), 47.12 (CH), 50.20 (CH), 67.22 (CH_2), 67.82 (CH_2), 82.89 (quat.), 119.97 (Ar), 125.17 (Ar), 127.67 (Ar), 127.72 (Ar), 141.20 (Ar), 147.75 (Ar), 147.87 (Ar), 156.02 (CO), 169.43 (CO), 170.18 (CO), 202.11 (CO); m/z (EI) 467 (M^+ , 0.1), 366 (1.5), 178 (100), 165 (26), 57 (24), 43 (8%).

(2*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-4-oxohexanoic acid *tert*-butyl ester **12b.** Following the general procedure for coupling with acid chlorides using propanoyl chloride (0.093 g, 0.087 ml, 1 mmol) gave (2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-4-oxohexanoic acid *tert*-butyl ester **12b** isolated as a brown oil (0.149 g, 47%) (Found M^+ 423.2053; $C_{25}H_{29}NO_5$ requires 423.2046); ν_{max} (KBr disc)/ cm^{-1} 3339 and 1720; δ_H ($CDCl_3$) 1.06 (3H, t, J 7.0, C(5)*H*), 1.45 (9H, s, C(CH_3)₃), 2.36–2.49 (2H, m, CH_2), 2.92 (1H, dd, J 4.5, 18.0, C(3)*H*), 3.13 (1H, dd, J 4.5, 18.0, C(3)*H'*), 4.21 (1H, t, J 7.0, CH Fmoc), 4.31 (1H, dd, J 7.5, 10.5, OCH' Fmoc), 4.40 (1H, dd, J 7.5, 10.5, OCH'' Fmoc), 4.45–4.48 (1H, m, C(2)*H*), 5.41 (1H, br s, NH), 7.20 (2H, t, J 7.5, ArH Fmoc), 7.39 (2H, t, J 7.5, ArH Fmoc), 7.58–7.60 (2H, m, ArH Fmoc), 7.75 (2H, d, J 7.0, ArH Fmoc); δ_C ($CDCl_3$) 27.85 (CH_3), 35.95 (CH_2), 44.04 (CH_2), 47.12 (CH), 50.59 (CH), 67.09 (CH_2), 82.29 (quat.), 119.96 (Ar), 125.14 (Ar), 127.04 (Ar), 127.69 (Ar), 141.28 (Ar), 143.72 (Ar), 143.92 (Ar), 156.08 (CO), 169.98 (CO), 209.26 (CO); m/z (EI) 423 (M^+ , 0.1), 322 (7), 178 (100), 165 (11), 57 (12%).

(2*S*)-5-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-4-oxopentanoic acid *tert*-butyl ester **12d.** Following the general procedure for coupling with acid chlorides using phthalimidoglycine chloride (0.224 g, 1 mmol), (2*S*)-5-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-4-oxopentanoic acid *tert*-butyl ester **12d** was isolated as light yellow crystals (0.179 g, 43%), mp 115–116 °C (Found ($M - CO_2Bu^+$) 453.1431; $C_{32}H_{30}N_2O_7$ requires 453.1451); $[a]_D^{25} +36.1$ (c 1.02 in CH_2Cl_2); ν_{max} (KBr disc)/ cm^{-1} 3360 and 1720; δ_H ($CDCl_3$) 1.45 (9H, s, C(CH_3)₃), 3.10 (1H, dd, J 4.0, 18.0, C(3)*H*), 3.25 (1H, dd, J 4.0, 18.0, C(3)*H'*), 4.22 (1H, t, J 7.0, CH Fmoc), 4.36 (2H, d, J 7.0, OCH_2 Fmoc), 4.49 (2H, s, C(16)*H*), 4.52–4.55 (1H, m, C(2)*H*), 5.81 (1H, d, J 7.9, NH), 7.29–7.32 (2H, m, ArH Fmoc), 7.38 (2H, t, ArH Fmoc), 7.60 (2H, d, J 7.3, ArH Fmoc), 7.69–7.75 (4H, m, ArH Fmoc, ArH), 7.84–7.87 (2H, m, ArH); δ_C ($CDCl_3$) 27.84 (CH_3), 41.93 (CH_2), 46.97 (CH_2), 47.08 (CH), 50.23 (CH), 67.29 (CH_2), 82.96 (quat.), 119.93 (Ar), 123.58 (Ar), 125.21 (Ar), 127.10 (Ar), 127.68 (Ar), 131.97 (Ar), 134.23 (Ar), 141.25 (Ar), 143.80 (Ar), 156.08 (CO), 167.45 (CO), 169.26 (CO), 200.57 (CO); m/z (EI) 453 ($M - COOBu^+$, 0.3), 178 (100), 165 (10), 160 (15%).

(2*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-4-oxohex-5-enoic acid *tert*-butyl ester **12e.** Following the general procedure for coupling with acid chlorides using acryloyl chloride (0.091 g, 0.081 ml, 1 mmol), (2*S*)-2-(9*H*-fluoren-9-ylmethoxycarbonylamino)-4-oxohex-5-enoic acid *tert*-butyl ester **12e** was isolated as a colourless oil (0.133 g, 42%) (Found M^+ 421.1886; $C_{25}H_{27}NO_5$ requires 421.1889); $[a]_D^{25} +13.6$ (c 1.195 in CH_2Cl_2); ν_{max} (KBr disc)/ cm^{-1} 3334, 1723 and 1508; δ_H ($CDCl_3$) 1.45 (9H, s, $C(CH_3)_3$), 3.14 (1H, dd, J 4.5, 18.0, $C(3)H$), 3.33 (1H, dd, J 4.5, 18.0, $C(3)H'$), 4.12 (1H, t, J 7.0, CH Fmoc), 4.30–4.34 (1H, m, $C(5)H$), 4.37–4.41 (1H, m, $C(5)H'$), 4.51–4.56 (1H, m, $C(2)H$), 5.81 (1H, d, J 8.0, NH), 5.92 (1H, d, J 10.5, $C(6)H_{cis}$), 6.26 (1H, d, J 18.0, $C(6)H_{trans}$), 6.35 (1H, dd, J 10.4, 18.0, $C(5)H$), 7.30 (2H, t, J 7.5, ArH), 7.39 (2H, t, J 7.5, ArH), 7.59 (2H, d, J 7.0, ArH), 7.75 (2H, d, J 7.0, ArH); δ_C ($CDCl_3$) 27.85 (CH_3), 41.42 (CH_2), 47.15 (CH), 50.53 (CH), 67.15 (CH_2), 82.43 (quat.), 119.96 (Ar), 125.17 (Ar), 127.06 (Ar), 127.68 (Ar), 129.50 (CH_2), 136.18 (CH), 141.27 (Ar), 143.76 (Ar), 143.92 (Ar), 156.08 (CO), 169.85 (CO), 198.16 (CO); m/z (EI) 421 (M^+ , 0.4), 320 (1), 196 (3), 178 (100), 165 (15), 57 (10%).

(2*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)hex-5-enoic acid *tert*-butyl ester **14a**

N-(9*H*-Fluoren-9-ylmethoxycarbonyl)-3-iodo-L-alanine *tert*-butyl ester **2** (370 mg, 0.75 mmol) dissolved in dry THF (0.5 ml) was added dropwise, *via* a syringe, to a slurry of activated zinc (150 mg in 0.3 ml of THF, prepared as described previously) previously cooled at 0 °C. The reaction mixture was then allowed to warm up to room temperature and stirred for one hour to give a solution of the organozinc reagent **1**. Stirring of the organozinc reagent solution was stopped to allow the zinc powder to settle. The supernatant was carefully removed *via* a syringe (care to be taken to avoid transferring too much zinc powder) and added dropwise to a solution of $CuCN \cdot 2LiCl$ (0.75 mmol, 1 equiv.) in THF (1 ml) at –10 °C. The solution was stirred for 15 min, and allyl chloride (0.077 g, 0.083 ml, 1 mmol) was added dropwise. The cooling bath was removed and the solution was stirred at room temperature overnight. Ethyl acetate (20 ml) was added and stirring was continued for a further 10 min. The reaction mixture was transferred to a separating funnel and a further aliquot of ethyl acetate (30 ml) was added. The organic phase was washed successively with 1 M $Na_2S_2O_3$ (20 ml), water (2 × 20 ml) and brine (40 ml), dried and evaporated. The residue was then purified by flash chromatography on silica gel using a suitable ethyl acetate–petroleum ether gradient. (2*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)hex-5-enoic acid *tert*-butyl ester was isolated as a colourless oil (0.183 g, 60%) (Found M^+ , 407.2067; $C_{25}H_{29}NO_4$ requires 407.2096); ν_{max} (KBr disc)/ cm^{-1} 3338, 1722 and 1520; δ_H ($CDCl_3$) 1.48 (9H, s, $C(CH_3)_3$), 1.73–1.78 (1H, m, $C(3)H$), 1.91–1.97 (1H, m, $C(3)H'$), 2.04–2.15 (2H, m, $C(4)H_2$), 4.23 (1H, t, J 7.0, CH Fmoc), 4.28–4.31 (1H, m, $C(2)H$), 4.38–4.40 (2H, m, OCH_2 Fmoc), 5.01 (1H, d, J 17.0, $C(6)H_{trans}$), 5.06 (1H, d, J 10.0, $C(6)H_{cis}$), 5.32 (1H, d, J 8.0, NH), 5.77–5.85 (1H, m, $C(5)H$), 7.31 (2H, t, J 7.5, ArH Fmoc), 7.39 (2H, t, J 7.5, ArH Fmoc), 7.60 (2H, d, J 7.5, ArH Fmoc), 7.76 (2H, d, J 7.5, ArH Fmoc); δ_C ($CDCl_3$) 28.04 (CH_3), 29.36 (CH_2), 32.18 (CH_2), 47.26 (CH), 53.99 (CH), 66.92 (CH_2), 82.19 (quat.), 115.59 (CH_2), 119.99 (Ar), 125.11 (Ar), 127.06 (Ar), 127.70 (Ar), 137.21 (CH), 141.33 (Ar), 143.85 (Ar), 143.99 (Ar), 155.83 (CO), 171.59 (CO); m/z (EI) 407 (M^+ , 1.5), 306 (11), 179 (100), 165 (50), 57 (63), 41 (10%).

(2*S*)-2-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-4-oxopentane-1,5-dioic acid 1-*tert*-butyl ester 5-ethyl ester **14b**

Following the procedure described for **14a**, but using ethyl oxalyl chloride (0.137 g, 0.112 ml, 1 mmol), (2*S*)-2-(9*H*-fluoren-9-

ylmethoxycarbonylamino)-4-oxopentane-1,5-dioic acid 1-*tert*-butyl ester 5-ethyl ester **14b** was isolated as a colourless oil (0.105 g, 30%) (Found M^+ , 467.1923; $C_{26}H_{29}NO_7$ requires 467.1944); ν_{max} (KBr disc)/ cm^{-1} 3372 and 1729; δ_H ($CDCl_3$) 1.38 (3H, t, J 7, OCH_2CH_3), 1.46 (9H, s, $C(CH_3)_3$), 3.40–3.45 (2H, m, $C(3)H_2$), 4.20–4.42 (5H, m, CH Fmoc, OCH_2 Fmoc, OCH_2CH_3), 4.60–4.65 (1H, m, $C(2)H$), 5.68 (1H, d, J 8, NH), 7.31 (2H, t, J 7.5, ArH Fmoc), 7.40 (2H, m, ArH Fmoc), 7.58 (2H, d, J 7.5, ArH Fmoc), 7.76 (2H, d, J 7.5, ArH Fmoc); δ_C ($CDCl_3$) 13.97 (CH_3), 27.84 (CH_3), 42.03 (CH_2), 50.37 (CH), 59.95 (CH), 62.80 (CH_2), 67.25 (CH_2), 83.20 (quat.), 120.00 (Ar), 125.12 (Ar), 127.08 (Ar), 127.73 (Ar), 141.31 (Ar), 143.72 (Ar), 155.89 (CO), 160.11 (CO), 169.25 (CO), 191.70 (CO); m/z (EI) 467 (M^+ , 0.1), 368 (1), 178 (100), 165 (8), 57 (15%).

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