Pergamon

Tetrahedron, Vol. 53, No. 14, pp. 5233-5254, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00190-7

Towards a Versatile Synthesis of Kainoids I : Introduction of the C-3 and C-4 Substituents

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Abstract: The first stages in the synthesis of acromelic acid analogues from *trans*-4-hydroxy-L-proline are described. An enamine alkylation was used to stereospecifically introduce the C-3 substituent, Grignard addition to a ketone or Pd(0) catalysed cross-coupling procedures adding C-4 aryl substituents for further manipulation. A number of versatile intermediates were generated.

The kainoids are a well-known group of pyrrolidine dicarboxylic acids of general structure **1** (Figure 1), the interesting feature for synthetic chemists being the three contiguous chiral centres from C-2 to C-4.

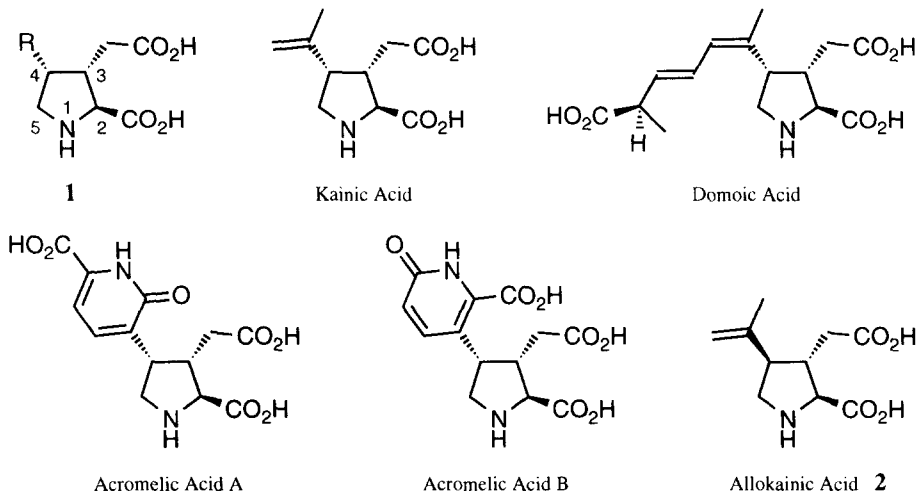
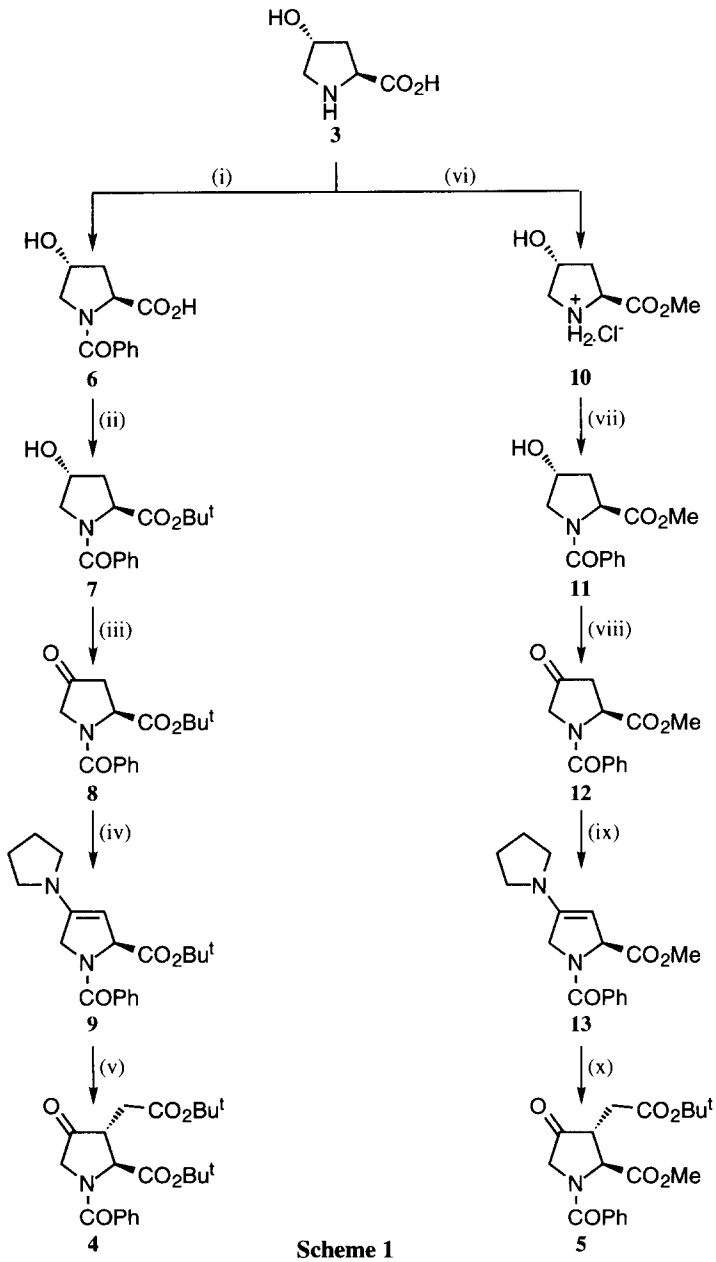


Figure 1

Common to all members of the kainoid family is the *S*-absolute stereochemistry at C-2 and a *trans*-stereochemical relationship to the adjacent substituent at C-3. With the exception of allokainic acid **2**, all of the kainoids isolated so far have possessed a *cis*- relative disposition of the C-3 and C-4 substituents.

The diverse biological properties of these amino acids are well-documented[1] but it is their importance in the study of neuronal function which is of particular interest.[2]



Scheme 1

Reagents and conditions: (i) PhCOCl, NaOH, H_2O, Et_2O, 0°C to RT., 65%[7]; (ii) DMF-dineopentylacetal (1.5eq.), Bu^tOH (1.5eq.), C_6H_6, Δ, 71% or BTEAC (1eq.), K_2CO_3 (26eq.), Bu^tBr (48eq.), CH_3CONMe_2, 55°C, 69%; (iii) $RuO_2.xH_2O$ (25mol. %), $NaIO_4$ (2eq.), CCl_4, $CHCl_3$, H_2O, RT., 76%; (iv) pyrrolidine (1.2eq.), 5Å mol. sieves, C_6H_6, RT., 99%; (v) $BrCH_2CO_2Bu^t$ (1eq.), K_2CO_3 (1.8eq.), CH_3CN, RT. then 10% v/v CH_3CO_2H (aq.), $CHCl_3$, 41%; (vi) CH_3OH, $SOCl_2$ (1.8eq.), 0°C to 50°C, 87%; (vii) PhCOCl (1.1eq.), $NaHCO_3$ (2.1eq.), H_2O, THF, 0°C to RT., 94%; (viii) $RuCl_3.3H_2O$ (5mol. %), $NaIO_4$ (4.1eq.), CH_3CN, CCl_4, H_2O, RT., 85%; (ix) pyrrolidine (1.2eq.), benzene, Δ (-H_2O), 100%; (x) $BrCH_2CO_2Bu^t$ (1.5eq.), K_2CO_3 (1.9eq.), CH_3CN, Δ then 10% v/v CH_3CO_2H (aq.), $CHCl_3$, 52%.

Several syntheses of these compounds have been reported[1] and it has become clear that a major obstacle to overcome is the establishment of the C-3 / C-4 *cis*-relative stereochemistry. Our recent work has been targetted towards the synthesis of naturally occurring kainoids and analogues with a long-term view of developing a general synthesis, allowing variation in the C-4 substituent, starting from cheap and readily available starting materials.

Our chosen starting material was *trans*-4-hydroxy-L-proline[3] **3** which is available in large quantities from the hydrolysate of collagen. It is therefore surprising that few syntheses of kainoids so far have started with this material.[4] To this end, we have reported in preliminary form, two routes[5,6] to unnatural acromelic acid analogues **1** (R = various aryl groups) which we begin to describe here in detail.

Both routes chosen were based on ketones **4** / **5** as common intermediates with manipulation of the keto group being used to introduce the C-4 substituent.

Trans-4-hydroxy-L-proline **3** was *N*-benzoylated under standard Schotten-Baumann conditions[7] in reasonable yield (65%), the product **6** being converted to its *tert*-butyl ester **7** by a modification of the procedure described by Widmer[8] using dimethylformamide-dineopentyl acetal and *tert*-butanol. This provided crystalline **7** in 71% yield from **6**. An alternative approach to **7** using a large excess of *tert*-butyl bromide, benzyltriethylammonium chloride and potassium carbonate[9] gave a comparable yield of 69% from **6**.

Oxidation of **7** to protected 4-ketoproline derivative **8** was achieved by a literature procedure employing ruthenium dioxide and sodium metaperiodate[10] giving **8** in 76% yield. Alkylation of **8** at C-3 was carried out *via* enamine **9**[11] using *tert*-butylbromoacetate, highly crystalline alkylated ketone **4** being obtained in adequate (41%) yield after acidic hydrolysis. There was no evidence for formation of the other possible regioisomeric enamine and the alkylated ketone **4** proved to be a single diastereoisomer with only C-2 / C-3 *trans*-relative stereochemistry.

A similar approach was adopted for the corresponding C-2 methyl ester **5**. *Trans*-4-hydroxy-L-proline methyl ester hydrochloride[12] **10** was *N*-benzoylated to give protected carbinol **11** in high yield (94%). It was found that use of the optimised ruthenium tetraoxide oxidation conditions of Sharpless[13] gave a significantly improved yield (85%) of the corresponding ketone **12**. Alkylation of enamine **13** was also improved in efficiency by moving to elevated temperatures with consistent yields of 52% of **5** being obtained on scales up to 20g.[14] Again, the product **5** was a single, highly crystalline diastereoisomer (Scheme 1).

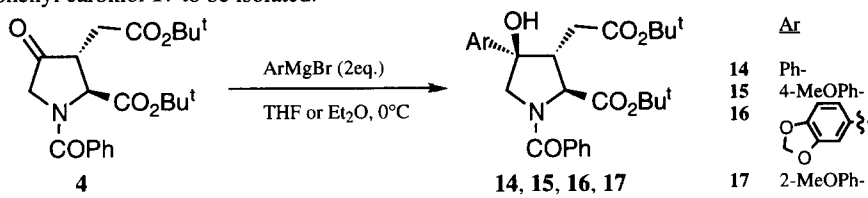
Two approaches to the introduction of C-4 aryl substituents were then explored.

1. Grignard addition[5]

Addition of aryl Grignard reagents to *N*-protected-4-oxoproline derivatives has been reported to give the corresponding *cis*-carbinols stereoselectively.[15] Such reactions were therefore attempted on alkylated ketone **4** (Scheme 2), the results being summarised in Table 1.

Adequate yields could be obtained of single diastereoisomers of the required carbinols (**14**, **15**, **16**) when using ether as solvent but disappointingly, no addition of 2-methoxyphenylmagnesium bromide could be achieved. This was required to access the highly neuroexcitatory 2-methoxyphenyl substituted kainoid[16] **1** (R = 2-MeOPh-). The relatively poor yields for Grignard addition were thought to be due to competing enolisation of ketone **4** towards C-3. Unfortunately, attempts to use less basic organocerium reagents[17] gave only comparable yields for addition with two epimeric (at C-4) carbinols being obtained accompanied also by

some loss of stereochemical integrity at C-3. This method did however allow very small quantities of the 2-methoxyphenyl carbinol **17** to be isolated.



Scheme 2

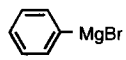
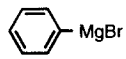
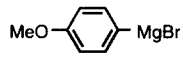
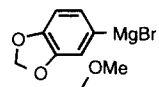
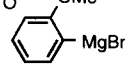
	Solvent	Product	Yield
	THF	**14**	30%
	Et_2O	**14**	50%
	Et_2O	**15**	46%
	Et_2O	**16**	41%
	Et_2O	**17**	0%

Table 1

In view of the apparently limited versatility of this procedure, we turned our attention to another method for introduction of the C-4 substituent.

2. Palladium (0) catalysed cross-coupling[6]

There has been much recent interest in palladium (0) catalysed cross-coupling reactions of vinyl triflates which can in turn, be prepared regioselectively from ketones.[18] With these processes in mind, we envisaged a possible method for the introduction of C-4 substituents using vinyl triflates **18** and **19** derived from ketones **4** and **5** respectively (Figure 2).

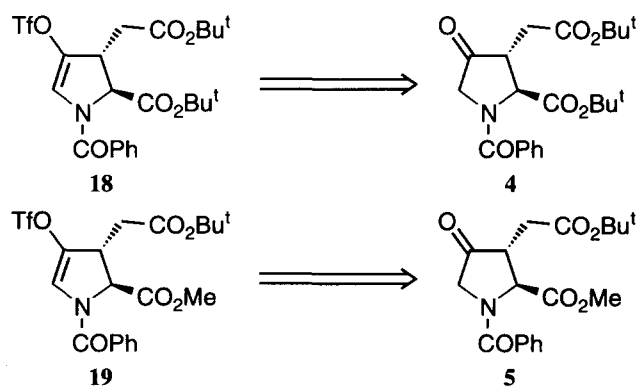
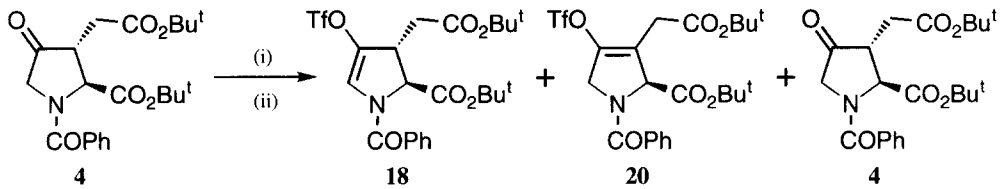


Figure 2

Reasoning that we required enolisation of **4** and **5** *via* removal of the sterically more accessible protons at C-5, we chose to use "kinetic" deprotonation conditions (strong, non-nucleophilic base, low temperature) and also chose *N*-phenyltriflimide[19] as triflating agent owing to relative ease of handling compared with triflic anhydride. Experiments were firstly carried out using di-*tert*-butyl ester **4** and enolate triflations were performed with and without DMPU present as a cosolvent. Both LDA and LHMDS were examined as bases, LHMDS finally being chosen again for ease of handling of reliable, commercially available solutions (Scheme 3). The results obtained are summarised in Table 2.



4 **18** **20** **4**

Scheme 3

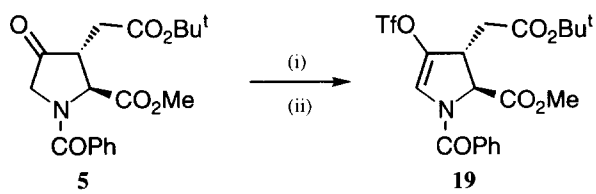
Reagents and conditions: (i) LDA (1.0M solution in THF, 1.5eq.) or LHMDS (1.0M solution in THF, 1.5eq.), THF, -78°C; (ii) *N*-phenyltriflimide, THF, with or without DMPU, -78°C to RT.

Base	DMPU (eq.)	Yield / **18**	Yield / **20**	Yield / **4**
LHMDS	0	16%	16%	40%
LDA	0	14%	14%	34%
LHMDS	23[a]	29%	35%	0%
LHMDS	4[a]	40%	0%	0%
LHMDS	3[b]	53%	0%	0%

a. DMPU added to generated enolate before *N*-phenyltriflimide solution
b. DMPU added with *N*-phenyltriflimide

Table 2

Firstly, it was found that the addition of DMPU as cosolvent resulted in complete consumption of ketone **4**. The optimal yield of 53% of triflate **18** was also obtained on addition of the DMPU in the *N*-phenyltriflimide solution on enolate quenching. Repeating this procedure with methyl ester **5** gave vinyl triflate **19** exclusively in excellent (93%) yield, a procedure which can be performed readily on a gram scale with high consistency, vinyl triflate **19** being reasonably stable to silica gel chromatography (Scheme 4).

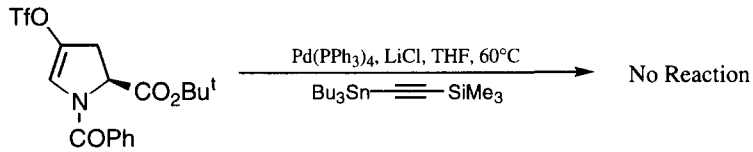


5 **19**

Scheme 4

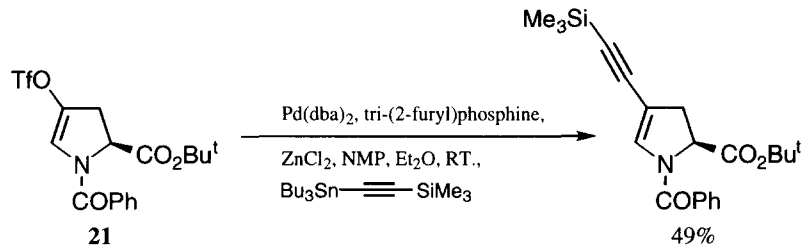
Reagents and conditions: (i) LHMDS (1.0M solution in THF, 1.5eq.), THF, -78°C; (ii) *N*-phenyltriflimide (1.2eq.), DMPU (3eq.), THF, -78°C to RT., 93%.

Initial palladium (0) cross-coupling experiments were carried out using Stille methodology with transmetallation from organostannanes[20]. Experiments to determine the reactivity of vinyl triflates **18** and **19** in such reactions were carried out using model vinyl triflate **21**, derived from ketone **8**. As alkynyl stannanes are known to transfer most rapidly to palladium (II) in the rate limiting transmetallation step, initial experiments were carried out using trimethylsilylethynyltributyltin. Under standard Stille conditions,[21] however, no coupling was observed (Scheme 5).



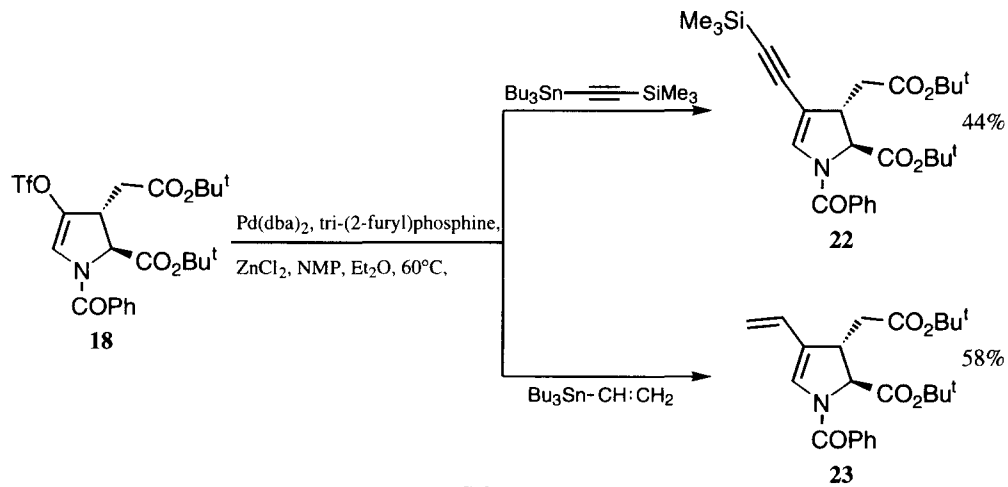
Scheme 5

Using the more "forcing" conditions of Farina,[22] coupling was achieved in moderate yield (Scheme 6).



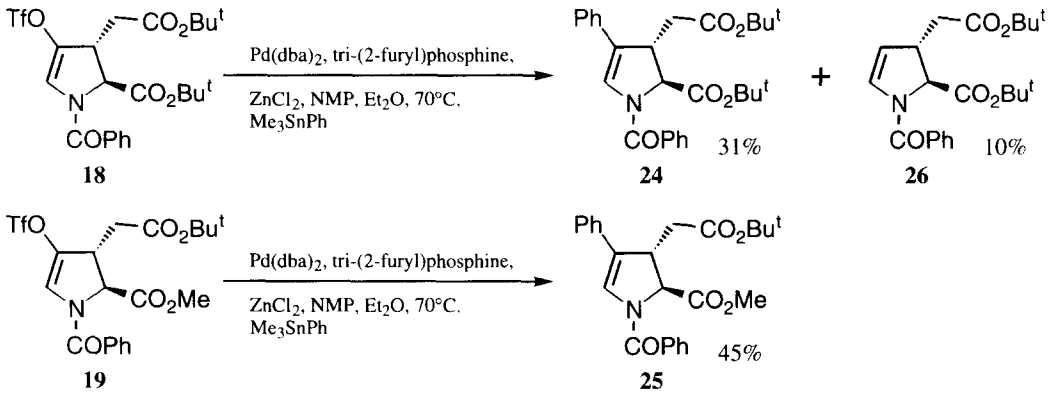
Scheme 6

With vinyl triflate **18**, a comparable yield of coupled product **22** was obtained at higher temperature (60°C) and vinyltributyltin also gave the expected product **23** under the same conditions (Scheme 7).



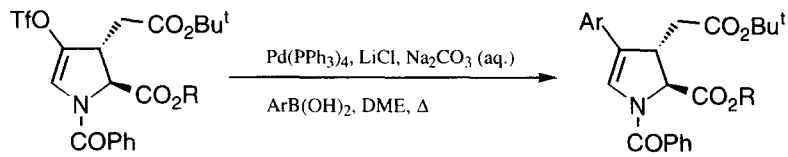
Scheme 7

Unfortunately however, phenyltributyltin, tetraphenyltin, (2-methoxyphenyl)tributyltin and (4-methoxyphenyl)tributyltin all failed to cross-couple to **18** under these conditions. The use of phenyltrimethyltin did however give rise to the expected products **24** and **25** from triflates **18** and **19** respectively (Scheme 8). The product of the reaction with triflate **18** was also accompanied by enamide **26**, resulting from reduction of the vinyl triflate. Similar reduction products have also been reported in analogous coupling reactions of vinyl iodides.[23]



Scheme 8

The necessity to prepare and use highly toxic trimethyltin derivatives led us to examine the use of Suzuki methodology with transmetallation from arylboronic acids. The conditions employed were those reported by Wustrow[24] (Scheme 9) with the required boronic acids being prepared by a standard method.[25] The results of these experiments are summarised in Table 3.



R = Bu^t, **18**; R = Me, **19**

Scheme 9

Product	R	Ar	Yield
24	Bu^t	Ph-	78%
27	Bu^t	2-MeOPh-	52%
28	Bu^t	3-MeOPh-	53%
29	Bu^t	4-MeOPh-	62%
25	Me	Ph-	73%
30	Me	2-MeOPh-	89%
31	Me	3-MeOPh-	68%
32	Me	4-MeOPh-	72%

Table 3

The improved efficiency of the cross-coupling reactions along with the relative ease of reaction work-up made this the method of choice for introduction of the C-4 substituent in the preparation of acromelic acid analogues **1** (R = various aryl groups).

Methods for reduction of the carbinols from the Grignard additions and the enamides generated in the palladium (0) cross-coupling reactions are described in the following papers.[26] These methods address the problem of establishment of the C-3 / C-4 *cis*- relative stereochemistry.

Acknowledgements

We thank the EPSRC for a studentship to A.M.F., the Commission of the E.C. for a postdoctoral bursary to M.P.W.R., Glaxo-Wellcome for a fellowship to M.E.W., the EPSRC mass spectrometry service (Swansea) for high resolution mass spectra and various colleagues for useful discussions.

Experimental

Melting points were obtained using a Büchi 510 capillary apparatus and are uncorrected.

Specific optical rotations were determined with a Perkin-Elmer 241 automatic polarimeter with a cell of path length 1dm. Concentrations are given in g/100ml.

Infrared spectra were recorded using a Perkin-Elmer 1750 Fourier transform spectrometer with major absorbances only being quoted. The following abbreviations are used: w, weak; m, medium; s, strong; br, broad.

^{1}H NMR spectra were recorded at 200, 300 and 500MHz using Varian Gemini 200, Brüker AC200, Brüker WH300, Brüker AM500 and Brüker AMX500 instruments. For ^{1}H spectra recorded in $CDCl_3$ or D_2O, chemical shifs are quoted in parts per million and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Coupling constants are quoted to the nearest 0.5Hz.

^{13}C NMR spectra were recorded at 50.3 and 125.8MHz using Varian Gemini 200 and Brüker AM500 or AMX500 instruments using DEPT[27] editing to assist assignment. Chemical shifts are quoted in parts per million and are referenced to $CDCl_3$.

Low resolution mass spectra were recorded on V.G. Micromass ZAB 1F (FAB / CI / DCI) and V.G. Masslab 20-250 (CI / DCI) instruments as appropriate with only molecular ions, fragments from molecular ions and other major peaks being reported.

Flash chromatography was carried out using Sorbsil™ C60 (40-63mm, 230-40 mesh) silica gel as stationary phase. Thin layer chromatography was carried out on aluminium and glass backed plates pre-coated with Merck silica gel 60 F_{254} which were visualised by quenching of u.v. fluorescence or by staining with iodine vapour or 10% w/v ammonium molybdate in 2M sulfuric acid (followed by heat) as appropriate.

All solvents and reagents were purified by standard techniques reported in Perrin, D. D.; Armarego, W. L. F., *Purification of Laboratory Chemicals*, 3rd edition, Pergamon Press, Oxford, 1988 or used as supplied from commercial sources as appropriate. 40-60 Petroleum ether (40-60 PE) refers to the fraction of light petroleum ether boiling between 40-60°C. Solvents were removed under reduced pressure using a Büchi R110 or R114 Rotavapor fitted with a water or dry ice condenser as necessary.

trans-N-Benzoyl-4-hydroxy-L-proline _tert_-butyl ester (7) - Method 1

To a suspension of *trans-N*-benzoyl-4-hydroxy-L-proline[7] (**6**) (11.54g, 98mmol) in benzene (60ml) and *tert*-butanol (13.80ml, 147mmol) under reflux was added dimethylformamide-dineopentylacetal (41.00ml, 147mmol) dropwise over 6h. The yellow solution was concentrated *in vacuo* and the residue was taken up in ethyl acetate (80ml), the resulting solution being washed with saturated aqueous sodium bicarbonate (80ml), 0.5M hydrochloric acid (80ml) and brine (80ml). After drying ($MgSO_4$) and filtration, removal of the solvent *in vacuo* gave a colourless oil which crystallised on trituration with diethyl ether. Recrystallisation from diethyl ether afforded *trans-N*-benzoyl-4-hydroxy-L-proline *tert*-butyl ester (**7**) (10.20g, 71%) as a white crystalline solid; m.p. 90°C (from Et_2O); $[\alpha]_D^{21}$ -137.2 (c 1, $CHCl_3$); (Found: C, 66.22; H, 7.62; N, 4.79. $C_{16}H_{21}NO_4$ requires C, 65.96; H, 7.27; N, 4.81%); υ_{max}/cm^{-1} (KBr disc) 3456s, 3404s, 2930m, 1737s, 1633s; δ_H (300MHz; $CDCl_3$) 2 rotamers, 1.22 (3H, s, C$\underline{H}_3$), 1.50 (6H, s, C$\underline{H}_3$), 2.12 (1H, ddd, *J* 13, 8.5 and 4.5Hz, NCHC$\underline{H}_2$), 2.33-2.40 (1H, m, NCHC$\underline{H}_2$), 3.50 (1H, br d, *J* 11Hz, NC$\underline{H}_2$), 3.81 (1H, dd, *J* 11 and 4Hz, NC$\underline{H}_2$), 4.49 (1H, br m, C$\underline{H}$OH), 4.73 (1H, dd, *J* 8.5 and 8.5Hz, C$\underline{H}CO_2Bu^t$), 7.39-7.57 (5H, complex, Ar-H); δ_C (50.3Hz; $CDCl_3$) 2 rotamers 27.44, 27.85 (C$\underline{H}_3$), 37.62, 39.86 (NCH$\underline{C}H_2$), 55.30, 57.88 (N$\underline{C}H_2$), 57.89, 60.58 ($\underline{C}HCO_2Bu^t$), 68.31, 69.98 ($\underline{C}$HOH), 81.58, 81.80 ($\underline{C}(CH_3)_3$), 127.28, 127.48, 128.43, 130.18, 130.48 (Ar-$\underline{C}$), 136.00 (Ar$\underline{C}_{ipso}$), 170.47, 171.54, 171.91 ($\underline{C}$=O); *m/z* (DCI, NH_3) 292 (MH^+, 27%), 236 (100), 190 (55), 105 (69).

trans-N-Benzoyl-4-hydroxy-L-proline _tert_-butyl ester (7) - Method 2

To a solution of *trans-N*-benzoyl-4-hydroxy-L-proline[7] (**6**) (510mg, 2.12mmol) and benzyltriethylammonium chloride (482mg, 2.12mmol) in dimethylacetamide (20ml) was added potassium carbonate (7.62g, 55.12mmol) followed by *tert*-butyl bromide (11.72ml, 101.76mmol) and the mixture was stirred at 55°C for 24h. After cooling to room temperature, water (200ml) was added to the reaction mixture and the resulting solution was extracted with ethyl acetate (50ml). The organic phase was separated, washed with water (2 x 20ml), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a yellow oil which crystallised on trituration with diethyl ether. Recrystallisation from diethyl ether yielded *trans-N*-benzoyl-4-hydroxy-L-proline *tert*-butyl ester (**7**) (436mg, 69%) as a white crystalline solid. Physical data as reported in Method 1 above.

_N_-Benzoyl-4-oxo-L-proline _tert_-butyl ester (8)

To a suspension of ruthenium (IV) oxide hydrate (730mg, 5.50mmol) in carbon tetrachloride (44ml) at 0°C was added sodium metaperiodate (9.42mg, 44.00mmol) in water (110ml). The two-phase system was stirred vigorously until the organic layer became orange-yellow coloured when a solution of *trans-N*-benzoyl-4-hydroxy-L-proline *tert*-butyl ester (**7**) (6.50g, 22.31mmol) in ethanol free chloroform (50ml) was added and the mixture was stirred at room temperature for 6h. The layers were separated and the aqueous phase was washed with chloroform (2 x 100ml). To the pooled organic fractions was added *iso*-propanol (5 drops), followed by drying ($MgSO_4$), filtration through a Celite® plug and removal of the solvent *in vacuo*. Recrystallisation of the residue from diethyl ether afforded *N*-benzoyl-4-oxo-L-proline *tert*-butyl ester (**8**) (4.87g, 76%) as a white crystalline solid; m.p. 112.5°C (from Et_2O); $[\alpha]_D^{22}$ +11.3 (c 1, $CHCl_3$); (Found: C, 66.66; H, 6.89; N, 4.80. $C_{16}H_{19}NO_4$ requires C, 66.42; H, 6.62; N, 4.84%); υ_{max}/cm^{-1} (KBr disc) 2980m,

1762s, 1740s, 1623s; δ_H (200MHz; $CDCl_3$) 1.47 (9H, br s, C<u>H</u>$_3$), 2.62 (1H, br d, *J* 18.5Hz, NCHC<u>H</u>$_2$), 2.96 (1H, dd, *J* 18.5 and 10Hz, NCHC<u>H</u>$_2$), 3.77-4.09 (2H, br m, NC<u>H</u>$_2$), 4.20-4.30 (1H, m, C<u>H</u>CO$_2$Bu^t), 7.38-7.48 (5H, complex, Ar-<u>H</u>); δ_C (50.3MHz; $CDCl_3$) 27.73 (<u>C</u>H$_3$), 40.16 (br, NCH<u>C</u>H$_2$), 55.30, 56.28 (br, N<u>C</u>H$_2$, <u>C</u>HCO$_2$Bu^t), 82.95 (br, <u>C</u>(CH$_3$)$_3$), 127.18, 128.78, 130.85 (Ar-<u>C</u>), 135.34 (Ar-<u>C</u>$_{ipso}$), 170.49 (<u>C</u>O$_2$Bu^t), 208.04 (ketone <u>C</u>=O); *m/z* (Probe CI, NH_3) 290 (MH^+, 7%), 234 (70), 105(100).

<u>2*S*-*N*-Benzoyl-2-*tert*-butoxycarbonyl-4-(1-pyrrolidin)yl-[3,4]-dehydropyrrolidine (9)</u>

To a solution of *N*-benzoyl-4-oxo-L-proline *tert*-butyl ester (**8**) (2.00g, 6.91mmol) in benzene (26ml) was added dry pyrrolidine (690µl, 8.28mmol) and powdered 5Å molecular sieves (3.49g) and the mixture was stirred at room temperature for 16h. Removal of the solvent *in vacuo* afforded 2*S*-*N*-benzoyl-2-*tert*-butoxycarbonyl-4-(1-pyrrolidin)yl-[3,4]-dehydropyrrolidine (**9**) (2.36g, 99%) as a pale green solid; m.p. 154°C; $[\alpha]_D^{22}$ -232.8 (c 1, $CHCl_3$); (Found:C, 70.32; H, 7.85; N, 8.05. $C_{20}H_{26}N_2O_3$ requires C, 70.15; H, 7.65; N, 8.18%); υ_{max}/cm^{-1} (KBr disc) 2972m, 2836m, 1724s, 1642s; δ_H (300MHz; $CDCl_3$) mixture of rotamers, 1.24 (5H, s, C<u>H</u>$_3$), 1.51 (3H, s, C<u>H</u>$_3$), 1.52 (1H, s, C<u>H</u>$_3$) 1.84-1.88, 1.90-1.94 (4H, 2 x m, pyrrolidine NCH$_2$C<u>H</u>$_2$), 2.96-3.00, 3.03-3.07, 3.15-3.20 (4H, 3 x m, pyrrolidine NC<u>H</u>$_2$CH$_2$), 3.91-5.47 (4H, complex, NC<u>H</u>$_2$, C<u>H</u>CO$_2$Bu^t, NCHC<u>H</u>), 7.35-7.56 (5H, m, Ar-<u>H</u>); δ_H (50.3MHz; $CDCl_3$) mixture of rotamers, 25.02, 25.20 (pyrrolidine NCH$_2$<u>C</u>H$_2$), 27.55, 27.90, 30.76 (<u>C</u>H$_3$), 48.09, 48.63 (pyrrolidine N<u>C</u>H$_2$CH$_2$), 52.38, 54.26 (N<u>C</u>H$_2$), 65.85, 67.79 (NCH<u>C</u>H), 80.95, 81.17 (<u>C</u>(CH$_3$)$_3$), 83.64, 84.40 (<u>C</u>HCO$_2$Bu^t), 126.90, 127.14, 128.38, 128.58, 129.80, 130.12 (Ar-<u>C</u>), 136.46, 136.65 (Ar-<u>C</u>$_{ipso}$), 144.94, 145.23 (C=<u>C</u>N), 169.20, 170.51, 171.74 (<u>C</u>=O); *m/z* (DCI, NH_3) 343 (MH^+, 93%), 287 (40), 241 (100), 105 (47).

<u>(2*S*, 3*R*)-*N*-Benzoyl-3-*tert*-butoxycarbonylmethyl-4-oxo proline *tert*-butyl ester (4)</u>

To a stirred solution of 2*S* - *N*-benzoyl-2-*tert*-butoxycarbonyl-4-(1-pyrrolidin)yl-[3,4]-dehydropyrrolidine (**9**) (1.00g, 2.92mmol) in anhydrous acetonitrile (40ml) was added *tert*-butyl bromoacetate (470µl, 2.90mmol) and finely powdered, anhydrous potassium carbonate (720mg, 5.21mmol). After 60h, another portion of *tert*-butyl bromoacetate (470µl, 2.90mmol) was added and the mixture was stirred for a further 60h. The solvent was removed *in vacuo* and the residue was taken up in chloroform (14ml). To this solution was added a 10% aqueous solution of acetic acid (14ml) and the 2-phase system was stirred for 26h at room temperature. The separated aqueous phase was further extracted with chloroform (2 x 14ml) and the combined organic fractions were washed with aqueous sodium bicarbonate (14ml) and water (14ml) and dried ($MgSO_4$), filtered and evaporated to dryness *in vacuo*. Flash chromatography on silica gel (eluting with 3:2 v/v diethyl ether : 40-60 petroleum ether) yielded a white solid which was recrystallised from diethyl ether to give (2*S*, 3*R*)-*N*-benzoyl-3-*tert*-butoxycarbonylmethyl-4-oxo proline *tert*-butyl ester (**4**) as a white crystalline solid (521mg, 41%); m.p. 96°C (from Et_2O); R_f 0.30 (3:2 v/v Et_2O : 40-60 PE); $[\alpha]_D^{23}$ +10.1 (c 1, $CHCl_3$); (Found: C, 65.61; H, 7.48; N, 3.40. $C_{22}H_{29}NO_6$ requires C, 65.49; H, 7.24; N, 3.47%); υ_{max}/cm^{-1} (KBr disc) 2987m, 1760s, 1727s, 1629s; δ_H (500MHz; toluene-d_8, 90°C) 1.29 (9H, s, C(C<u>H</u>$_3$)$_3$), 2.48-2.57 (2H, 8 line m, C<u>H</u>$_2$CO$_2$Bu^t), 2.69-2.72 (1H, 4 line m, C<u>H</u>CH$_2$CO$_2$Bu^t), 3.79-3.89 (2H, m, NC<u>H</u>$_2$), 4.71 (1H, d, *J* 5.5Hz, C<u>H</u>CO$_2$Bu^t), 7.04-7.08, 7.40 (5H, m, Ar-<u>H</u>); δ_H (50.3MHz; $CDCl_3$) mixture of rotamers 27.76, 27.86 (<u>C</u>H$_3$), 30.72, 35.53 (CH<u>C</u>H$_2$CO$_2$Bu^t), 46.69, 48.27 (<u>C</u>HCH$_2$CO$_2$Bu^t), 51.84, 54.93 (N<u>C</u>H$_2$), 59.84, 62.93 (<u>C</u>HCO$_2$Bu^t), 81.61, 82.23 (<u>C</u>(CH$_3$)$_3$), 127.26, 127.62, 128.74, 130.77, 130.94 (Ar-<u>C</u>), 135.44 (Ar-<u>C</u>$_{ipso}$),

169.73, 169.95, 170.30, 170.96 (C=O), 207.59, 208.68 (ketone C=O); *m/z* (DCI, NH_3) 404 (MH^+, 12%), 348 (80), 292 (77), 246 (80), 105 (100).

trans-N-Benzoyl-4-hydroxy-L-proline methyl ester (11)

To a solution of *trans*-4-hydroxy-L-proline methyl ester hydrochloride[12] (**10**) (10.00g, 55.1mmol) in water and tetrahydrofuran (1:1v/v, 40ml) was slowly added sodium bicarbonate (9.72g, 115.7mmol) and the mixture was stirred and cooled to 0°C. A solution of benzoyl chloride (7.04ml, 60.6mmol) in tetrahydrofuran (16ml) was added dropwise and the mixture was stirred at room temperature for 1.5h. The solution was concentrated *in vacuo* and the residue was taken up in chloroform (100ml). The aqueous layer was washed with chloroform (4 x 50ml) and the combined organic extracts were washed with brine (100ml). After drying ($MgSO_4$) and evaporation to dryness *in vacuo*, the white solid was recrystallized from ethyl acetate to yield *trans*-N-benzoyl-4-hydroxy-L-proline methyl ester (**11**) (12.89g, 94%) as a white crystalline solid; m.p. 141°C (from EtOAc) [lit.[7] m.p. 145-146°C (from EtOAc)]; R_f 0.20 (1:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{25}$ -142.4 (c 1.6, $CHCl_3$) [lit.[7] $[\alpha]_D^{26}$ -139.2 (c 1.15, EtOH)]; (Found: C, 62.87; H, 6.05; N, 5.40%. $C_{13}H_{15}NO_4$ requires C, 62.64; H, 6.07; N, 5.62%); υ_{max}/cm^{-1} ($CHCl_3$) 3612s, 2955w, 1746s, 1631s, 1423s; δ_H (200MHz; $CDCl_3$) 2.01-2.14 (1H, m, NCHC$\underline{H}_2$), 2.28-2.41 (1H, m, NCHC$\underline{H}_2$), 3.08 (1H, br s, O$\underline{H}$), 3.40-3.50 (1H, m, NC$\underline{H}_2$), 3.72-3.80 (1H, m, NC$\underline{H}_2$), 3.75 (3H, s, $CO_2C\underline{H}_3$), 4.43 (1H, br s, C$\underline{H}$OH), 4.81 (1H, t, *J* 8Hz, C$\underline{H}CO_2CH_3$), 7.27-7.54 (5H, complex, Ar-$\underline{H}$); δ_C (50.3MHz; $CDCl_3$) 37.46 (NCH$\underline{C}H_2$), 52.12, 52.27 ($CO_2\underline{C}H_3$, NC$\underline{H}_2$), 57.97 ($\underline{C}$HOH), 69.84 ($\underline{C}HCO_2CH_3$), 126.83, 127.50, 128.40, 130.62 (Ar-$\underline{C}$H), 135.51 (Ar-$\underline{C}_{ipso}$), 170.60 (N$\underline{C}$=O), 173.19 ($\underline{C}O_2CH_3$); *m/z* (Probe CI, NH_3) 251 (16%), 250 (MH^+, 100), 190 (13), 105 (19).

N-Benzoyl-4-oxo-proline methyl ester (12)

To a solution of *trans*-*N*-benzoyl-4-hydroxy-L-proline methyl ester (**11**) (4.00g, 16mmol) in a mixture of acetonitrile (32ml), carbon tetrachloride (32ml) and water (48ml) was added sodium metaperiodate (14.00g, 65mmol). Ruthenium trichloride hydrate (160mg, 0.8mmol) was added to this biphasic mixture which was vigorously stirred for 3.5h at room temperature. Dichloromethane (160ml) was added and the aqueous phase was further extracted with dichloromethane (3 x 20ml). The combined organic extracts were dried ($MgSO_4$) and evaporated to dryness *in vacuo*. Flash chromatography on silica gel (eluting with 1:1v/v dichloromethane : ethyl acetate) afforded *N*-benzoyl-4-oxo-L-proline methyl ester (**12**) (3.37g, 85%) as a light brown syrup; R_f 0.54 (1:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{25}$ +9.0 (c 1.23, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3063m, 1765s, 1745s, 1651s, 1422s; δ_H (200MHz; $CDCl_3$) 2.59-2.69 (1H, br m, NCHC$\underline{H}_2$), 2.90-3.03 (1H, 4 line m, NCHC$\underline{H}_2$), 3.76 (3H, br s, $CO_2C\underline{H}_3$), 3.90-4.12 (2H, m, NC$\underline{H}_2$), 5.30 (1H, m, C$\underline{H}CO_2CH_3$), 7.30-7.70 (5H, complex, Ar-$\underline{H}$); δ_C (50.3MHz; $CDCl_3$) 39.83 (NCH$\underline{C}H_2$), 52.84 ($CO_2\underline{C}H_3$), 55.26 (N$\underline{C}H_2$), 77.43 ($\underline{C}HCO_2CH_3$), 127.26, 128.85, 131.04, (Ar-$\underline{C}$H), 135.03 (Ar-$\underline{C}_{ipso}$), 170.89, 171.92 (N$\underline{C}$=O, $\underline{C}O_2CH_3$); *m/z* (Probe CI, NH_3) 249 (13%), 248 (MH^+, 100), 105 (72); (Found MH^+ 248.0923, $C_{13}H_{14}NO_4$ requires 248.0923).

2S-N-Benzoyl-2-methoxycarbonyl-4-(1-pyrrolidin)yl-[3,4]-dehydropyrrolidine (13)

To a solution of *N*-benzoyl-4-oxo-L-proline methyl ester (**12**) (3.235g, 13.1mmol) in benzene (50ml) was added pyrrolidine (1.33ml, 15.7mmol). The reaction flask was fitted with Dean and Stark apparatus and

the stirred reaction mixture was heated under reflux for 20min. Concentration of the resulting solution *in vacuo* yielded 2*S*-*N*-benzoyl-2-methoxycarbonyl-4-(1-pyrrolidin)yl-[3,4]-dehydropyrrolidine (**13**) (3.816g, 100%) as a yellow / green syrup. This was used without further purification. $[\alpha]_D^{25}$ -1.3 (c 1, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 2949m, 1737s, 1611s; δ_H (200MHz; $CDCl_3$) mixture of rotamers, 1.84-1.94 (4H, complex, $NCH_2\underline{CH_2}$), 2.91-3.23 (4H, complex, $NC\underline{H_2}CH_2$), 3.49 (1.5H, s, $CO_2C\underline{H_3}$), 3.77 (1.5H, s, $CO_2C\underline{H_3}$), 3.81-5.50 (4H, complex, $C\underline{H}$=C, $NC\underline{H_2}$, $C\underline{H}CO_2CH_3$), 7.36-8.05 (5H, complex, Ar-$\underline{H}$); δ_C (50.3MHz; $CDCl_3$) mixture of rotamers, major peaks only assigned, 24.93, 25.13, 25.30 (pyrrolidine $NCH_2\underline{C}H_2$), 37.59 (pyrrolidine $N\underline{C}H_2CH_2$), 52.25 ($CO_2\underline{C}H_3$), 57.82, 58.01 ($N\underline{C}H_2$), 69.72 ($\underline{C}HCO_2CH_3$), 126.63, 127.34, 128.19, 130.37 (Ar-$\underline{C}$), 135.45 (Ar-$\underline{C}_{ipso}$), 170.22, 172.54, 172.91 ($\underline{C}$=O); *m/z* (Probe CI, NH_3) 301 (MH^+, 9%), 250 (100), 190 (14), 105 (22).

(2*S*,3*R*)-*N*-Benzoyl-3-*tert*-butoxycarbonylmethyl-4-oxo-proline methyl ester (5)

To a solution of 2*S*-*N*-benzoyl-2-methoxycarbonyl-4-(1-pyrrolidin)yl-[3,4]-dehydropyrrolidine (**13**) (940mg, 3.13mmol) in acetonitrile (40ml) was added powdered anhydrous potassium carbonate (821mg, 5.9mmol) and *tert*-butylbromoacetate (760µl, 4.7mmol). The mixture was stirred and heated under reflux for 18h. The solution was then evaporated to dryness *in vacuo* and the residue was taken up in chloroform (13ml). A solution of 9:1v/v water / acetic acid (13ml) was then added and the biphasic mixture was stirred at room temperature for 5.5h. The separated aqueous phase was further extracted with chloroform (3 x 12ml) and the combined organic fractions were washed with aqueous sodium bicarbonate (14ml), water (14ml), then dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography on silica gel (eluting with 9:1v/v dichloromethane : ethyl acetate) afforded a white crystalline solid. Recrystallisation from diethyl ether yielded (2*S*, 3*R*)-*N*-benzoyl-3-*tert*-butoxycarbonylmethyl-4-oxo-proline methyl ester (**5**) as a white crystalline solid (582mg, 52%); m.p. 125-127°C (from Et_2O); R_f 0.25 (19:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{25}$ -35.9 (c 0.93, $CHCl_3$); (Found: C, 63.33; H, 6.48; N, 3.57. $C_{19}H_{23}NO_6$ requires C, 63.15; H, 6.41; N, 3.88%); υ_{max}/cm^{-1} ($CHCl_3$) 1767s, 1750s, 1723s, 1646s, 1412s, 1369s, 1154s; δ_H (200MHz; $CDCl_3$) 2 rotamers, 1.44, 1.59 (7.7H + 1.3H, 2 x s, $C(C\underline{H_3})_3$), 2.68-3.06 (3H, complex, $C\underline{H_2}CO_2Bu^t$, NCHC$\underline{H}$), 3.81 (3H, br s, $CO_2C\underline{H_3}$), 3.99-4.33 (2H, complex, $NC\underline{H_2}$), 4.80 (1H, brs, $C\underline{H}CO_2CH_3$), 7.39-7.70 (5H, complex, Ar-$\underline{H}$); δ_C (50.3MHz; $CDCl_3$) 27.86 ($C(\underline{C}H_3)_3$), 35.26 ($\underline{C}H_2CO_2Bu^t$), 46.73 (NCH$\underline{C}$H), 52.75 ($CO_2\underline{C}H_3$), 55.72 ($N\underline{C}H_2$), 61.52 ($\underline{C}HCO_2CH_3$), 82.34 ($\underline{C}(CH_3)_3$), 127.34, 128.78, 130.94 (Ar-$\underline{C}$H), 135.17 (Ar-$\underline{C}_{ipso}$), 169.82 ($N\underline{C}$=O), 170.88, 171.82 ($\underline{C}O_2CH_3$, $\underline{C}O_2Bu^t$); *m/z* (Probe CI, NH_3) 362 (MH^+, 57%), 306 (93), 305 (22), 105 (100), 77 (9).

(2*S*,3*R*,4*R*)-*N*-Benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-hydroxy-4-phenylpyrrolidine (14)

To a stirred solution of (2*S*,3*R*)-*N*-benzoyl-3-*tert*-butoxycarbonylmethyl-4-oxoproline-*tert*-butyl ester (**4**) (101mg, 0.25mmol) in diethyl ether (6ml) was added a solution of phenylmagnesium bromide in diethyl ether (1M, 500µl, 0.5mmol). After stirring for 2h at -78°C and 4h at 0°C, saturated ammonium chloride solution (1ml) and acetic acid (250µl) were added, followed by diethyl ether (10ml) after a further 20min of stirring. The separated aqueous phase was further extracted with diethyl ether (3 x 10ml) and the combined extracts were dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was purified by radial chromatography on silica gel (eluting with 97:3v/v dichloromethane : acetonitrile) yielding (2*S*,3*R*,4*R*)-*N*-

benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-hydroxy-4-phenylpyrrolidine (**14**) as a white, crystalline solid (60mg, 50%); m.p. 173-174°C (from Et_2O); R_f 0.20 (97:3v/v CH_2Cl_2 : CH_3CN); $[\alpha]_D^{20}$ -19.4 (c 0.16, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3416br w, 1719m, 1700m, 1630s, 1603s; δ_H (500MHz; $CDCl_3$) 1.54, 1.55 (2 x 9H, 2 x s, 2 x $C(C\underline{H}_3)_3$), 1.94 (1H, dd, *J* 10.5 and 18Hz, $C\underline{H}_2CO_2Bu^t$), 2.57 (1H, dd, *J* 4.5 and 18Hz, $C\underline{H}_2CO_2Bu^t$), 2.98 (1H, m, $C\underline{H}CH_2CO_2Bu^t$), 3.97, 4.17 (2 x 1H, ABq, *J* 11Hz, $NC\underline{H}_2$), 4.21 (1H, d, *J* 9Hz, $C\underline{H}CO_2Bu^t$), 5.89 (1H, s, O<u>H</u>), 7.20-7.62 (10H, complex, Ar-<u>H</u>); δ_C (50.3MHz; $CDCl_3$) 27.84, 27.95 (2 x $C(\underline{C}H_3)_3$), 35.63 ($\underline{C}H_2CO_2Bu^t$), 49.16 ($\underline{C}HCH_2CO_2Bu^t$), 62.02 ($N\underline{C}H_2$), 64.37 ($\underline{C}HCO_2Bu^t$), 79.94 (<u>C</u>OH), 82.22, 82.50 (2 x $\underline{C}(CH_3)_3$), 124.83, 127.29, 127.77, 128.39, 128.60, 130.62, 135.08, 141.57 (Ar-<u>C</u>), 169.40, 170.40, 173.18 (<u>C</u>=O); *m/z* (DCI, NH_3) 482 (MH^+, 23%), 426 (100), 470 (50), 105 (85).

(2*S*,3*R*,4*R*)-*N*-Benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-hydroxy-4-(4-methoxyphenyl)pyrrolidine (15)

Procedure as for (2*S*,3*R*,4*R*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-hydroxy-4-phenylpyrrolidine (**14**) above. To a stirred solution of (2*S*,3*R*)-*N*-benzoyl-3-*tert*-butoxycarbonylmethyl-4-oxoproline-*tert*-butyl ester (**4**) (101mg, 0.25mmol) in diethyl ether (6ml) was added a solution of 4-methoxyphenylmagnesium bromide in diethyl ether (1M, 500µl, 0.5mmol). The residue obtained after stirring and work-up was purified by radial chromatography on silica gel (eluting with 97:3v/v dichloromethane : acetonitrile) yielding (2*S*,3*R*,4*R*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-hydroxy-4-(4-methoxyphenyl)pyrrolidine (**15**) as colourless needles (59mg, 46%); m.p. 185°C; R_f 0.10 (97:3v/v CH_2Cl_2 : CH_3CN); $[\alpha]_D^{20}$ -32.8 (c 0.25, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3406br w, 3050-2850br m, 1740s, 1720s, 1700s, 1632s; δ_H (500MHz; $CDCl_3$) 1.41, 1.56 (2 x 9H, 2 x s, $C(C\underline{H}_3)_3$), 1.94 (1H, dd, *J* 10.5, 18Hz, $C\underline{H}_2CO_2Bu^t$), 2.57 (1H, dd, *J* 4.5, 18Hz, $C\underline{H}_2CO_2Bu^t$), 2.98 (1H, m, $C\underline{H}CH_2CO_2Bu^t$), 3.78 (1H, s, $OC\underline{H}_3$), 3.94, 4.13 (2 x 1H, ABq, *J* 11Hz, $NC\underline{H}_2$), 4.18 (1H, d, *J* 9Hz, $C\underline{H}CO_2Bu^t$), 6.84, 7.13 (2 x 1H, ABq, *J* 9Hz $CH_3OC_6\underline{H}_4$), 7.38-7.65 (5H, complex, Ar-<u>H</u>); δ_C (50.3MHz; $CDCl_3$) 27.87, 27.96 (2 x $C(\underline{C}H_3)_3$), 35.73 ($\underline{C}H_2CO_2Bu^t$), 49.19 ($\underline{C}HCH_2CO_2Bu^t$), 55.20 ($O\underline{C}H_3$), 63.03 ($N\underline{C}H_2$), 64.36 ($\underline{C}HCO_2Bu^t$), 79.77 (<u>C</u>OH), 82.17, 82.44 (2 x $\underline{C}(CH_3)_3$), 113.88, 126.12, 127.30, 128.37, 130.57, 133.58, 135.19 (Ar-<u>C</u>), 158.97 ($\underline{C}OCH_3$), 169.32, 170.51, 173.20 (<u>C</u>=O); *m/z* (DCI, NH_3) 512 (MH^+, 18%), 456 (25), 438 (65), 399 (50), 382 (100), 354 (25), 336 (46), 150 (40), 135 (48), 105 (100).

(2*S*,3*R*,4*R*)-*N*-Benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-hydroxy-4-(3,4-methylenedioxyphenyl)pyrrolidine (16)

Procedure as for (2*S*,3*R*,4*R*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-hydroxy-4-phenylpyrrolidine (**14**) above. To a stirred solution of (2*S*,3*R*)-*N*-benzoyl-3-*tert*-butoxycarbonylmethyl-4-oxoproline-*tert*-butyl ester (**4**) (101mg, 0.25mmol) in diethyl ether (6ml) was added a solution of 3,4-methylenedioxyphenylmagnesium bromide in diethyl ether (1M, 500µl, 0.5mmol). The residue obtained after stirring and work-up was purified by radial chromatography on silica gel (eluting with 9:1v/v chloroform : acetonitrile) yielding (2*S*,3*R*,4*R*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-hydroxy-4-(3,4-methylenedioxyphenyl)pyrrolidine (**16**) as a white solid (54mg, 41%); m.p. 194°C; R_f 0.30 (9:1v/v $CHCl_3$: CH_3CN); $[\alpha]_D^{20}$ -32.0 (c 0.5, $CHCl_3$); υ_{max}/cm^{-1} 3405br w, 3100-2830br m, 1723br s, 1635s; δ_H (500MHz; $CDCl_3$) 1.42, 1.53 (2 x 9H, 2 x s, 2 x $C(C\underline{H}_3)_3$, 2.01 (1H, dd, *J* 9.5,

17.5Hz, $C\underline{H}_2CO_2Bu^t$), 2.54 (1H, dd, *J* 5, 17.5Hz, $C\underline{H}_2CO_2Bu^t$), 2.93 (1H, m, $C\underline{H}CH_2CO_2Bu^t$), 3.92, 4.12 (2 x 1H, ABq, *J* 11Hz, $NC\underline{H}_2$), 4.18 (1H, d, *J* 8.5Hz, $C\underline{H}CO_2Bu^t$), 5.80 (1H, s, O<u>H</u>), 5.93 (2H, s, $OC\underline{H}_2O$), 6.62-7.60 (8H, complex Ar-<u>H</u>); δ_C (50.3MHz; $CDCl_3$) 27.89, 27.95 (2 x $C(\underline{C}H_3)_3$), 35.81 ($\underline{C}H_2CO_2Bu^t$), 49.19 ($\underline{C}HCH_2CO_2Bu^t$), 61.94 ($N\underline{C}H_2$), 64.32 ($\underline{C}HCO_2Bu^t$), 80.02 (<u>C</u>OH), 82.27, 82.51 (2 x $\underline{C}(CH_3)_3$), 101.12 ($O\underline{C}H_2O$), 105.95, 108.10, 118.05, 127.28, 128.39, 135.52 (Ar-<u>C</u>), 147.00, 148.05 (2 x Ar<u>C</u>-O), 169.26, 170.53, 173.14 (<u>C</u>=O); *m/z* (DCI, NH_3) 526 (MH^+, 0.5%), 396 (100), 164 (27), 105 (95).

(2*S*,3*R*)-*N*-Benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-trifluoromethanesulfonyloxy-[4,5]-dehydropyrrolidine (18)

A cold (-78°C) solution of (2*S*, 3*R*)-*N*-benzoyl-3-*tert*-butoxycarbonylmethyl-4-oxo proline *tert*-butyl ester (**4**) (1.00g, 2.48mmol) in tetrahydrofuran (15ml) was added dropwise to a solution of lithium hexamethyldisilylamide (1M solution in tetrahydrofuran, 3.72ml, 3.72mmol) at -78°C under an argon atmosphere and the mixture was stirred at this temperature for 40 min. A cold solution (-78°C) of phenyl triflimide (1.09g, 2.97mmol) and *N, N'*-dimethyl-*N, N'*-propylene urea (890µl, 7.44mmol) in tetrahydrofuran (15ml) was added dropwise and the mixture was allowed to warm to room temperature, with stirring being continued for 16h. The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (30ml). This solution was washed with aqueous sodium bicarbonate (30ml), water (30ml) and brine (30ml) and was dried ($MgSO_4$), filtered and evaporated *in vacuo*. Flash chromatography on silica gel (eluting with 1:1 v/v diethyl ether : 40-60 petroleum ether) yielded (2*S*, 3*R*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-trifluoromethanesulfonyloxy-[4,5]-dehydropyrrolidine (**18**) (702mg, 53%) as a colourless syrup; R_f 0.40 (1:1 v/v Et_2O : 40-60 PE); $[\alpha]_D^{25}$ -10.8 (c 0.5, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3025s, 3016s, 1732m, 1650m, 1427s, 1410s; δ_H (200MHz; $CDCl_3$) appears as 1 rotamer, 1.46 (18H, s, $C\underline{H}_3$), 2.44-2.75 (2H, 8 line m, $C\underline{H}_2CO_2Bu^t$), 3.49-3.57 (1H, m, $C\underline{H}CH_2$), 4.74 (1H, d, *J* 3.5Hz, $C\underline{H}CO_2Bu^t$), 6.76 (1H, s, $NC\underline{H}$=C), 7.40-7.53 (5H, m, Ar-<u>H</u>); δ_C (50.3MHz; $CDCl_3$) 2 rotamers, 27.61, 27.87 ($\underline{C}H_3$), 37.67 ($\underline{C}H_2CO_2Bu^t$), 42.90 ($\underline{C}HCH_2$), 63.72 ($\underline{C}HCO_2Bu^t$), 82.12, 83.14 ($\underline{C}(CH_3)_3$), 123.02, 123.29 ($N\underline{C}H$=C, N<u>C</u>HCOTf), 126.96, 127.91, 129.00, 129.54, 131.69, 133.59 (Ar-<u>C</u>), 136.95 (Ar-$\underline{C}_{ipso}$), 167.83, 169.14 (<u>C</u>=O); *m/z* (Probe CI, NH_3), 536 (MH^+, 3%), 335 (43), 105 (100); (Found MH^+ 536.157000, $C_{23}H_{29}F_3NO_8S$ requires 536.156599).

(2*S*,3*R*)-*N*-Benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-trifluoromethanesulfonyloxy-[4,5]-dehydropyrrolidine (19)

A cold (-78°C) solution of (2*S*, 3*R*)-*N*-benzoyl-3-*tert*-butoxycarbonylmethyl-4-oxo-proline methyl ester (**5**) (1.000g, 2.77mmol) in tetrahydrofuran (15ml) was added dropwise to a solution of lithium hexamethyldisilylamide (1M solution in tetrahydrofuran, 4.12ml, 4.12mmol) at -78°C under an argon atmosphere and the mixture was stirred at this temperature for 40min. A cold (-78°C) solution of phenyl triflimide (1.222g, 3.30mmol) and *N, N'*-dimethyl-*N, N'*-propylene urea (990µl, 2.33mmol) in tetrahydrofuran (15ml) was added dropwise and the mixture was allowed to warm to room temperature with stirring being continued for 16h. The solvent was removed *in vacuo* and the residue was taken up into ethyl acetate (30ml). This solution was washed with aqueous sodium bicarbonate (30ml), water (30ml) and brine (30ml) and was dried ($MgSO_4$), filtered and evaporated *in vacuo*. Flash chromatography on silica gel (eluting with 10:1v/v

dichloromethane : ethyl acetate) yielded (2*S*,3*R*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-trifluoromethanesulfonyloxy-[4,5]-dehydropyrrolidine (**19**) as a pale yellow syrup (1.272g, 93%). (Note:Yield=59% based on recovered ketone); R_f 0.40 (19:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{25}$ +10.5 (c 0.75, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1754s, 1728s, 1651s, 1430s, 1407s; δ_H (200MHz; $CDCl_3$) 1.49 (9H, s, $C(C\underline{H}_3)_3$), 2.5-2.8 (2H, m, $C\underline{H}_2CO_2Bu^t$), 3.58 (1H, m, NCHC<u>H</u>), 3.83 (3H, s, $CO_2C\underline{H}_3$), 4.9 (1H, d, *J* 4Hz, $C\underline{H}CO_2CH_3$), 6.82 (1H, s, C<u>H</u>=C), 7.2-7.6 (5H, complex, Ar-<u>H</u>); δ_C (50.3MHz; $CDCl_3$) 27.83 ($C(\underline{C}H_3)_3$), 37.38 ($\underline{C}H_2$), 42.75 (NCH<u>C</u>H), 52.96 ($CO_2\underline{C}H_3$), 62.85 ($\underline{C}HCO_2CH_3$), 82.20 ($\underline{C}(CH_3)_3$), 122.89 (<u>C</u>H=C), 128.04, 129.01, 131.84, (Ar-<u>C</u>H), 167.97, 169.10, 169.40 (N<u>C</u>=O, $\underline{C}O_2CH_3$, $\underline{C}O_2Bu^t$); *m/z* (DCI, NH_3) 452 (9%), 438 (17), 304 (24), 122 (27), 109 (36), 92 (22), 65 (17).

(2*S*,3*S*)-*N*-Benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-trimethylsilylethynyl-[4,5]-dehydropyrrolidine (22)

To a stirred solution of (2*S*,3*R*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-trifluoromethanesulfonyloxy-[4,5]-dehydropyrrolidine (**18**) (160mg, 0.30mmol) in degassed *N*-methylpyrrolidinone (6ml) under an argon atmosphere was added a solution of zinc chloride in ether (1M, 584µl, 0.58mmol), bis-(dibenzylideneacetone palladium (0) (9.6mg, 16.7µmol) and tri-2-furylphosphine (8.2mg, 35.2µmol). After stirring at room temperature for 10min, trimethylsilylethynyltri-*n*-butyltin (125mg, 0.32mmol) was added and the mixture was stirred at 60°C for 18h. The reaction mixture was diluted with ethyl acetate (45ml) and the resulting solution was washed with water (2 x 45ml). The separated organic phase was washed with brine (60ml), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a brown oil which was dissolved in acetonitrile (40ml). This solution was washed with 40-60 petroleum ether (2 x 40ml) and the separated acetonitrile layer was evaporated *in vacuo* to give a brown syrup which was purified by flash chromatography on silica gel (eluting with 49:1 v/v dichloromethane : ethyl acetate) to give (2*S*,3*S*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-trimethylsilylethynyl-[4,5]-dehydropyrrolidine (**22**) (63mg, 44%) as a yellow syrup; R_f 0.30 (49:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{25}$ -9.25 (c 0.40, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3019s, 2401w, 1730m, 1617m; δ_H (200MHz; $CDCl_3$) 0.17 (9H, s, $Si(C\underline{H}_3)_3$), 1.49 (18H, s, 2 x $C(C\underline{H}_3)_3$), 2.46 (1H, dd, *J* 16 and 9Hz, $C\underline{H}_2CO_2Bu^t$), 2.72 (1H, dd, *J* 16 and 6Hz, $C\underline{H}_2CO_2Bu^t$), 3.31-3.43 (1H, m, $C\underline{H}CH_2CO_2Bu^t$), 4.75 (1H, d, *J* 5Hz, $C\underline{H}CO_2Bu^t$), 6.79 (1H, brs, C<u>H</u>=C), 7.41-7.57 (5H, complex, Ar-<u>H</u>); δ_C (125.8MHz, $CDCl_3$) -0.14 ($Si(\underline{C}H_3)_3$), 27.89, 28.11 ($C(\underline{C}H_3)_3$), 39.01 ($\underline{C}H_2CO_2Bu^t$), 45.49 ($\underline{C}HCH_2CO_2Bu^t$), 64.57 ($\underline{C}HCO_2Bu^t$), 81.22 , 82.27 (2 x $\underline{C}(CH_3)_3$), 97.67, 99.54 ($\underline{C}CSi(CH_3)_3$, $C\underline{C}(CH_3)_3$), 106.84, (CH=<u>C</u>), 127.85, 128.56, 131.00 (Ar-<u>C</u>), 134.27, 135.81 (Ar-$\underline{C}_{ipso}$, <u>C</u>H=C), 166.96, 168.64, 169.71 (<u>C</u>=O); *m/z* (Probe CI, NH_3) 484 (MH^+, 13%), 428 (58), 372 (100), 105 (50).

(2*S*,3*S*)-*N*-Benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-vinyl-[4,5]-dehydropyrrolidine (23)

Coupling procedure as for (2*S*,3*S*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-trimethylsilylethynyl-[4,5]-dehydropyrrolidine (**22**) above. To a stirred solution of (2*S*,3*R*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-trifluoromethanesulfonyloxy-[4,5]-dehydropyrrolidine (**18**) (67mg, 0.13mmol) in degassed *N*-methylpyrrolidinone (3ml) under an argon atmosphere was added a solution of zinc chloride in ether (1M, 245µl, 0.25mmol), bis-(dibenzylideneacetone palladium (0) (4.0mg, 7µmol) and

tri-2-furylphosphine (3.4mg, 14.8μmol). After stirring at room temperature for 10min, vinyltri-*n*-butyltin (42.8mg, 0.14mmol) was added and the mixture was stirred at 60°C for 18h. After work-up, the crude product was purified by flash chromatography on silica gel (eluting with 99:1 v/v dichloromethane : ethyl acetate) to give (2*S*,3*S*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-vinyl-[4,5]-dehydropyrrolidine (**23**) (31mg, 58%) as a pale yellow syrup; R_f 0.20 (99:1v/v CH_2Cl_2 : EtOAc); δ_H (200MHz; $CDCl_3$) 1.50 (18H, s, 2 x (CH_3)$_3$C), 2.38 (1H, dd, *J* 15, 3Hz, $CH_2CO_2Bu^t$), 2.73 (1H, dd, *J* 15, 3Hz, $CH_2CO_2Bu^t$), 3.46-3.57 (1H, m, $CHCH_2CO_2Bu^t$), 4.76-4.82 (1H, m, $CHCO_2Bu^t$), 5.06 (1H, d, *J* 10Hz, CH=CH_2 *cis*-), 5.12 (1H, d, *J* 18Hz, CH=CH_2 *trans*-), 6.25 (1H, dd, *J* 18, 10Hz, CH=CH_2), 6.54 (1H, brs, N-CH=C), 7.39-7.66 (5H, complex, Ar-H); *m/z* (Probe CI, NH_3) 414 (MH^+, 4%), 358 (45), 302 (100), 256 (15), 105 (92).

(2*S*,3*S*)-*N*-Benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenyl-[4,5]-dehydropyrrolidine (24) "Stille" Methodology

To a stirred solution of (2*S*,3*R*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-trifluoromethanesulfonyloxy-[4,5]-dehydropyrrolidine (**18**) (260mg, 0.49mmol) in degassed *N*-methylpyrrolidinone (9ml) under an argon atmosphere was added a solution of zinc chloride in ether (1M, 950μl, 0.95mmol), bis-(dibenzylideneacetone palladium (0) (15.6mg, 27.2μmol) and tri-2-furylphosphine (13.4mg, 57.5μmol). After stirring at room temperature for 10min, phenyltrimethyltin (139mg, 0.59mmol) was added and the mixture was stirred at 50°C for 12h. The reaction mixture was diluted with ethyl acetate (60ml) and the resulting solution was washed with water (2 x 60ml). The separated organic phase was washed with brine (60ml), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a brown oil which was dissolved in acetonitrile (50ml). This solution was washed with 40-60 petroleum ether (2 x 50ml) and the separated acetonitrile layer was evaporated *in vacuo* to give a brown syrup which was purified by flash chromatography on silica gel (eluting with 49:1 v/v dichloromethane : ethyl acetate). Two close running fractions were isolated. One fraction gave (2*S*, 3*S*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenyl-[4,5]-dehydropyrrolidine (**24**) (70mg, 31%) as a yellow syrup; R_f 0.20 (49:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{24}$ -15.1 (c 0.4, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 2978s, 1729s, 1652s, 1601s; δ_H (200MHz; $CDCl_3$) 2 rotamers, 1.27, 1.29 (2H, 2 x br s, CH_3), 1.44, 1.49, 1.53 (16H, 3 x br s, CH_3), 2.41 (1H, dd, *J* 15 and 9Hz, $CH_2CO_2Bu^t$), 2.67 (1H, dd, *J* 15 and 3Hz, $CH_2CO_2Bu^t$), 3.71-3.89 (1H, m, $CHCH_2$), 4.82 (0.2H, br s, $CHCO_2Bu^t$), 4.90 (0.8H, d, *J* 3Hz, $CHCO_2Bu^t$), 6.89 (1H, s, CH=C), 7.18-7.65 (5H, complex, Ar-H); δ_C (50.3MHz; $CDCl_3$) 2 rotamers 27.94, 28.07, 29.64 (CH_3), 38.90, 39.41 ($CH_2CO_2Bu^t$), 43.59, 45.84 ($CHCH_2$), 65.24, 66.24 ($CHCO_2Bu^t$), 81.23, 82.13 ($C(CH_3)_3$), 125.18, 125.88, 127.20, 127.88, 128.55, 128.76, 129.23, 130.79, 132.30, 134.86 (CH=C, CH=C, Ar-C), 167.09, 169.03, 169.53, 170.08, 170.29 (C=O); *m/z* (Probe CI, NH_3) 464 (MH^+, 10%), 408 (84), 352 (100), 105 (71); (Found MH^+ 464.243700, $C_{28}H_{43}NO_5$ requires 464.243698); The second fraction gave (2*S*,3*S*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-[4,5]-dehydropyrrolidine (**26**) (18mg, 10%); R_f 0.20 (49:1 v/v CH_2Cl_2 : EtOAc); υ_{max}/ cm^{-1} ($CHCl_3$) 3020m, 1724s, 1642m, 1616m; δ_H (200MHz; $CDCl_3$) 1.49 (9H, s, $C(CH_3)_3$), 1.50 (9H, s, $C(CH_3)_3$), 2.44 (1H, dd, *J* 14 and 8Hz, $CH_2CO_2Bu^t$), 2.60 (1H, dd, *J* 14 and 6.5Hz, $CH_2CO_2Bu^t$), 3.35-3.38 (1H, br m, $CHCH_2$), 4.60-4.63 (1H, m, $CHCO_2Bu^t$), 5.16-5.19 (1H, m, NCH=CH), 6.54-6.56 (1H, br m, NCH=CH), 7.42-7.61 (5H, complex, Ar-H); δ_C (125.8MHz; $CDCl_3$) 27.94, 28.10 ($C(CH_3)_3$), 41.29 ($CH_2CO_2Bu^t$), 43.63 ($CHCH_2$), 64.29 ($CHCO_2Bu^t$), 81.14, 82.04 (CMe_3), 112.22 (NCH=CH), 127.82, 128.45, 130.70, 130.89 (NCH=CH,

Ar-C), 134.88 (Ar-C_{ipso}), 167.40, 169.24, 170.17 (C=O); *m/z* (DCI, NH_3) 388 (MH^+, 2%), 332 (52), 276 (100), 105 (33).

(2*S*,3*S*)-*N*-Benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenyl-[4,5]-dehydropyrrolidine (25) "Stille" Methodology

To a stirred solution of (2*S*,3*R*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-trifluoromethanesulfonyloxy-[4,5]-dehydropyrrolidine (**19**) (65mg, 0.13mmol) in degassed *N*-methylpyrrolidinone (3ml) was added a solution of zinc chloride in diethyl ether (1M, 253µl, 0.25mmol) and bis-(dibenzylideneacetone) palladium (0) (4.1mg, 7.2µmol) and tri-2-furylphosphine (3.5mg, 15.2µmol). After stirring at room temperature for 10 min, phenyltrimethyltin (34mg, 0.14mmol) was added and the mixture was stirred at 55°C for 2h. The reaction mixture was diluted with ethyl acetate (15ml) and the resulting solution was washed with water (2 x 15ml). The separated organic phase was washed with brine (15ml), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give a brown oil which was dissolved in acetonitrile (15ml). This solution was washed with 40-60 petroleum ether (2 x 15ml) and the separated acetonitrile layer was evaporated *in vacuo* to give a brown syrup which was purified by flash chromatography on silica gel (eluting with 19:1v/v dichloromethane : ethyl acetate) to give (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenyl-[4,5]-dehydropyrrolidine (**25**) as a colourless syrup (25mg, 45%); R_f 0.25 (19:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{25}$ -12.5 (c 1.1, $CHCl_3$), υ_{max}/cm^{-1} ($CHCl_3$) 1752s, 1723s, 1652s, 1623s; δ_H (200MHz; $CDCl_3$) 1.48 (9H, s, $C(CH_3)_3$), 2.41 (1H, *ca.* dd, *J* 9 and 14Hz, $CH_2CO_2Bu^t$), 2.72 (1H, *ca.* dd, *J* 3 and 14Hz, $CH_2CO_2Bu^t$), 3.70-3.90 (1H, m, $CHCH_2CO_2Bu^t$), 3.82 (3H, s, CO_2CH_3), 5.03 (1H, d, *J* 3Hz, $CHCO_2CH_3$), 6.92 (1H, s, CH=C), 7.15-7.7 (10H, complex, Ar-H); δ_C (50.3MHz; $CDCl_3$) 27.92 ($C(CH_3)_3$), 39.20 ($CH_2CO_2Bu^t$), 43.49 (NCHCH), 52.64 (CO_2CH_3), 64.38 ($CHCO_2CH_3$), 81.53 ($C(CH_3)_3$), 125.29, 125.51, 125.97, 127.54, 128.15, 128.78, 129.00, 129.19, 131.21, 132.13, 134.66 (Ar-CH, NC=C, NC=C), 167.54, 170.43, 170.74 (CO_2CH_3, CO_2Bu^t, NC=O); *m/z* (Probe CI, NH_3) 423 (20%), 422 (MH^+, 100), 366 (44), 105 (55); (Found MH^+ 422.1967, $C_{25}H_{28}NO_5$ requires 422.1967).

(2*S*,3*S*)-*N*-Benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenyl-[4,5]-dehydropyrrolidine (24) "Suzuki" Methodology

To a vigorously stirred solution of (2*S*, 3*R*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-trifluoromethanesulfonyloxy-[4,5]-dehydropyrrolidine (**18**) (145mg, 0.29mmol) in degassed 1,2-dimethoxyethane (3.5ml), a solution of phenylboronic acid (50mg, 0.43mmol) in 1,2-dimethoxyethane (1.5ml), 2M aqueous sodium carbonate (2ml), lithium chloride (37mg, 0.86mmol) and tetrakis(triphenylphosphine) palladium (0) (17mg, 14.4µmol) were added sequentially. The stirred 2-phase system was heated under reflux under an argon atmosphere for 16h. After cooling to room temperature, the solvents were removed *in vacuo* and the residue was partitioned between dichloromethane (15ml) and a mixture of 2M aqueous sodium carbonate (15ml) and concentrated ammonium hydroxide (700µl). The separated aqueous layer was extracted with dichloromethane (2 x 15ml) and the combined organic extracts were dried ($MgSO_4$) and evaporated to dryness *in vacuo*. Flash chromatography on silica gel yielded (2*S*, 3*S*)-

N-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenyl-[4,5]-dehydropyrrolidine (**24**) as a colourless syrup (97mg, 78%). Physical data as reported above.

(2*S*,3*S*)-*N*-Benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2-methoxyphenyl)-[4,5]-dehydropyrrolidine (27)

Coupling procedure as for (2*S*, 3*S*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenyl-[4,5]-dehydropyrrolidine (**24**) above. To a solution of (2*S*, 3*R*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-trifluoromethanesulfonyloxy-[4,5]-dehydropyrrolidine (**18**) (54mg, 0.10mmol) in 1,2-dimethoxyethane (2ml) was added 2-methoxyphenylboronic acid (23mg, 0.15mmol) in 1,2-dimethoxyethane (500μl), 2M aqueous sodium carbonate (800μl), lithium chloride (12.8mg, 0.30mmol) and tetrakis(triphenylphosphine) palladium (0) (5.9mg, 5μmol). After stirring under reflux under an argon atmosphere for 16h, work-up as described previously yielded (2*S*,3*S*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2-methoxyphenyl)-[4,5]-dehydropyrrolidine (**27**) as a colourless syrup (26mg, 52%); R_f 0.30 (19:1 v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{25}$ -10.0 (c 0.85, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 2979s, 2934s, 1732s, 1651s, 1651s, 1618s; δ_H (200MHz; $CDCl_3$) 1.48 (9H, s, C$\underline{H}_3$), 1.52 (9H, s, C$\underline{H}_3$), 2.35 (1H, dd, *J* 15 and 10 Hz, C$\underline{H}_2CO_2Bu^t$), 2.62 (1H, dd, *J* 15 and 3Hz, C$\underline{H}_2CO_2Bu^t$), 3.75 (3H, s, OC$\underline{H}_3$), 3.87-3.91 (1H, m, C$\underline{H}CH_2$), 4.83 (1H, d, *J* 3Hz, C$\underline{H}CO_2Bu^t$), 6.84-7.69 (10H, complex, C$\underline{H}$=C, Ar-$\underline{H}$); δ_C (125.8MHz; $CDCl_3$) 27.97, 28.11 (C$\underline{H}_3$), 39.62 (C$\underline{H}_2CO_2Bu^t$), 44.54 (C$\underline{H}CH_2$), 55.15 (OC$\underline{H}_3$), 64.22 (C$\underline{H}CO_2Bu^t$), 81.08, 81.92 (C$\underline{(CH_3)_3}$), 110.83, 120.77, 121.36, 121.46, 127.53, 127.77, 128.12, 128.27, 129.42, 130.70, 135.10 (Ar-$\underline{C}$, $\underline{C}$H=C, CH=$\underline{C}$), 157.16 ($\underline{C}OCH_3$), 167.40, 169.19, 170.35 ($\underline{C}$=O); *m/z* (DCI, NH_3) 494 (MH^+, 35%), 438 (100), 382 (30), 105 (37); (Found MH^+ 494.254300, $C_{29}H_{36}NO_6$ requires 494.254263).

(2*S*,3*S*)-*N*-Benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(3-methoxyphenyl)-[4,5]-dehydropyrrolidine (28)

Coupling procedure as for (2*S*, 3*S*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenyl-[4,5]-dehydropyrrolidine (**24**) above. To a solution of (2*S*, 3*R*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-trifluoromethanesulfonyloxy-[4,5]-dehydropyrrolidine (**18**) (80mg, 0.15mmol) in 1,2-dimethoxyethane 3.6ml) was added 3-methoxyphenylboronic acid (34mg, 0.22mmol) in 1,2-dimethoxyethane (800μl), 2M aqueous sodium carbonate (1.4ml), lithium chloride (20.0mg, 0.47mmol) and tetrakis(triphenylphosphine) palladium (0) (8.6mg, 7.4μmol). After stirring under reflux under an argon atmosphere for 16h, work-up as described previously yielded (2*S*,3*S*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(3-methoxyphenyl)-[4,5]-dehydropyrrolidine (**28**) as a colourless syrup (39mg, 53%); R_f 0.40 (19:1 v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{25}$ -13.9 (c 1, $CHCl_3$); υ_{max}/cm^{-1} 2979s, 2930m, 1730s, 1652s, 1624s, 1602s; δ_H (200MHz; $CDCl_3$) 1.48 (9H, s, C($C\underline{H}_3$)$_3$), 1.53 (9H, s, C($C\underline{H}_3$)$_3$), 2.41 (1H, dd, *J* 15 and 9Hz, C$\underline{H}_2CO_2Bu^t$), 2.68 (1H, dd, *J* 15, 3Hz, C$\underline{H}_2CO_2Bu^t$), 3.80 (4H, br s, OC$\underline{H}_3$, C$\underline{H}CH_2$), 4.90 (1H, d, *J* 3Hz, C$\underline{H}CO_2Bu^t$), 6.76-7.65 (10H, complex, C$\underline{H}$=C, Ar-$\underline{H}$); δ_C (125.8MHz; $CDCl_3$) 27.95, 28.08 (C($\underline{C}H_3$)$_3$), 39.47 (C$\underline{H}_2CO_2Bu^t$), 43.64 (C$\underline{H}CH_2$), 55.23 (OC$\underline{H}_3$), 65.27 (C$\underline{H}CO_2Bu^t$), 81.19, 82.12 (C$\underline{(CH_3)_3}$), 111.35, 112.08, 117.80, 125.04, 126.25, 127.88, 128.56, 129.78, 130.79, 133.79, 134.86 (Ar-$\underline{C}$, $\underline{C}$H=C, CH=$\underline{C}$), 159.84 ($\underline{C}OCH_3$), 167.08, 169.02, 170.02 ($\underline{C}$=O); *m/z* (Probe CI, NH_3) 494 (MH^+, 28%), 438 (100), 382 (25), 105 (41); (Found MH^+ 494.254300, $C_{29}H_{36}NO_6$ requires 494.254263).

(2*S*,3*S*)-*N*-Benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(4-methoxyphenyl)-[4,5]-dehydropyrrolidine (29)

Coupling procedure as for (2*S*, 3*S*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenyl-[4,5]-dehydropyrrolidine (**24**) above. To a solution of (2*S*, 3*R*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-trifluoromethanesulfonyloxy-[4,5]-dehydropyrrolidine (**18**) (40mg, 0.08mmol) in 1,2-dimethoxyethane 1.8ml) was added 4-methoxyphenylboronic acid (17mg, 0.11mmol) in 1,2-dimethoxyethane (400μl), 2M aqueous sodium carbonate (700μl), lithium chloride (10.0mg, 0.24mmol) and tetrakis(triphenylphosphine) palladium (0) (4.3mg, 3.7μmol). After stirring under reflux under an argon atmosphere for 16h, work-up as described previously yielded (2*S*,3*S*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(4-methoxyphenyl)-[4,5]-dehydropyrrolidine (**29**) as a colourless syrup (23mg, 62%); R_f 0.30 (19:1 v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{25}$ -3.7 (c 1, $CHCl_3$); υ_{max}/cm^{-1} 3023s, 1733s, 1623s, 1604s; δ_H (200MHz; $CDCl_3$) 2 rotamers, 1.27, 1.28 (2H, 2 x br s, $C(C\underline{H}_3)_3$), 1.43, 1.48, 1.52 (16H, 3 x br s, $C(C\underline{H}_3)_3$), 2.39 (1H, dd, *J* 15 and 9Hz, $C\underline{H}_2CO_2Bu^t$), 2.65 (1H, dd, *J* 15, 3Hz, $C\underline{H}_2CO_2Bu^t$), 3.75 (1H, m, $C\underline{H}CH_2$), 3.79 (3H, s, $OC\underline{H}_3$), 4.77 (0.2H, br s, $C\underline{H}CO_2Bu^t$), 4.89 (0.8H, d, *J* 3Hz, $C\underline{H}CO_2Bu^t$), 6.77-7.64 (10H, complex, C<u>H</u>=C, Ar-H); δ_C (125.8MHz; $CDCl_3$) 2 rotamers, 27.69, 27.96, 28.11 ($C(\underline{C}H_3)_3$), 39.03, 39.47 ($\underline{C}H_2CO_2Bu^t$), 43.84, 46.29 ($\underline{C}HCH_2$), 55.29, 55.76 ($O\underline{C}H_3$), 65.20, 66.06 ($\underline{C}HCO_2Bu^t$), 81.26, 82.15 ($\underline{C}(CH_3)_3$), 114.24, 114.71, 116.00, 124.27, 124.85, 125.18, 126,53, 127.45, 127.88, 128.54, 130.72, 134.98 (Ar-<u>C</u>, <u>C</u>H=C, CH=<u>C</u>), 158.91 ($\underline{C}OCH_3$), 166.99, 169.15, 170.20 (<u>C</u>=O); *m/z* (DCI, NH_3) 494 (MH^+, 48%), 438 (100), 382 (94), 105 (68); (Found MH^+ 494.254300, $C_{29}H_{36}NO_6$ requires 494.254263).

(2*S*,3*S*)-*N*-Benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenyl-[4,5]-dehydropyrrolidine (25) "Suzuki" Methodology

To a vigorously stirred solution of (2*S*,3*R*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-trifluoromethanesulfonyloxy-[4,5]-dehydropyrrolidine (**19**) (154mg, 0.31mmol) in degassed 1,2-dimethoxyethane (4ml) a solution of phenylboronic acid (54mg, 0.44mmol) in 1,2-dimethoxyethane (1.5ml), 2M aqueous sodium carbonate (2.2ml), lithium chloride (39.5mg, 0.93mmol) and tetrakis(triphenylphosphine) palladium (0) (18.1mg, 15.7μmol) were added sequentially. The stirred 2-phase system was heated under reflux under an argon atmosphere for 16h. After cooling to room temperature, the solvents were removed *in vacuo* and the residue was partitioned between dichloromethane (13ml) and a mixture of 2M aqueous sodium carbonate (13ml) and concentrated ammonium hydroxide (650μl). The separated aqueous layer was extracted with dichloromethane (3 x 13ml) and the combined extracts were dried ($MgSO_4$), filtered and evaporated to dryness *in vacuo*. Flash chromatography on silica gel yielded (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenyl-[4,5]-dehydropyrrolidine (**25**) (96mg, 73%) as a colourless syrup. Physical data as reported above.

(2*S*,3*S*)-*N*-Benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2-methoxyphenyl)-[4,5]-dehydropyrrolidine (30)

Coupling procedure as for (2*S*, 3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenyl-[4,5]-dehydropyrrolidine (**25**) above. To a solution of (2*S*, 3*R*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-

butoxycarbonylmethyl-4-trifluoromethanesulfonyloxy-[4,5]-dehydropyrrolidine (**19**) (154mg, 0.31mmol) in 1,2-dimethoxyethane (4ml) was added 2-methoxyphenylboronic acid (71.3mg, 0.47mmol) in 1,2-dimethoxyethane (1.5ml), 2M aqueous sodium carbonate (2.2ml), lithium chloride (39.5mg, 0.93mmol) and tetrakis(triphenylphosphine) palladium (0) (18.1mg, 15.7μmol). After stirring under reflux under an argon atmosphere for 16h, work-up as described previously yielded (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2-methoxyphenyl)-[4,5]-dehydropyrrolidine (**30**) as a colourless syrup (126mg, 89%); R_f 0.35 (9:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{22}$ -26.0 (c 1.2, $CHCl_3$), υ_{max}/cm^{-1} ($CHCl_3$) 1745s, 1723s, 1640s, 1612s; δ_H (200MHz; $CDCl_3$) 1.50 (9H, s, $C(C\underline{H}_3)_3$), 2.38 (1H, *ca.* dd, *J* 10 and 15Hz, $C\underline{H}_2CO_2Bu^t$), 2.69 (1H, *ca.* dd, *J* 3 and 15Hz, $C\underline{H}_2CO_2Bu^t$), 3.76, 3.82 (2 x 3H, 2 x s, $CO_2C\underline{H}_3$, Ar-O-$C\underline{H}_3$), 3.80-3.95 (1H, m, NCHC$\underline{H}$), 4.99 (1H, d, *J* 3Hz, $C\underline{H}CO_2CH_3$), 6.80-7.75 (10H, complex, Ar-$\underline{H}$, C$\underline{H}$=C); δ_C (50.3MHz; $CDCl_3$) 27.96 ($C(\underline{C}H_3)_3$), 39.39 ($\underline{C}H_2CO_2Bu^t$), 44.41 (NCH$\underline{C}$H), 52.58, 55.16 ($CO_2\underline{C}H_3$, Ar-O$\underline{C}H_3$), 63.40 ($\underline{C}HCO_2CH_3$), 81.39 ($\underline{C}(CH_3)_3$), 110.98, 120.96 121.13, 121.47, 127.36, 127.54, 128.12, 128.44, 128.53, 128.89, 129.72, 131.16, 134.93 (Ar-$\underline{C}$H, N$\underline{C}$=C, NC=$\underline{C}$), 157.39 (Ar-$\underline{C}$-OCH_3), 167.50 (N$\underline{C}$=O), 170.74, 170.96 ($\underline{C}O_2Me$, $\underline{C}O_2Bu^t$); *m/z* (Probe CI, NH_3) 453 (33%), 452 (MH^+, 100), 451 (31), 396 (70), 105 (91); (Found MH^+ 452.2073, $C_{26}H_{30}NO_6$ requires 452.2073).

(2*S*,3*S*)-*N*-Benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(3-methoxyphenyl)-[4,5]-dehydropyrrolidine (31)

Coupling procedure as for (2*S*, 3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenyl-[4,5]-dehydropyrrolidine (**25**) above. To a solution of (2*S*, 3*R*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-trifluoromethanesulfonyloxy-[4,5]-dehydropyrrolidine (**19**) (131mg, 0.27mmol) in 1,2-dimethoxyethane (4ml) was added 3-methoxyphenylboronic acid (60.7mg, 0.40mmol) in 1,2-dimethoxyethane (1.5ml), 2M aqueous sodium carbonate (1.9ml), lithium chloride (33.9mg, 0.80mmol) and tetrakis(triphenylphosphine) palladium (0) (15.4mg, 13.1μmol). After stirring under reflux under an argon atmosphere for 16h, work-up as described previously yielded (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(3-methoxyphenyl)-[4,5]-dehydropyrrolidine (**31**) as a colourless syrup (81mg, 68%); (R_f 0.40 19:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{22}$ -7.1 (c 1.24, $CHCl_3$), υ_{max}/cm^{-1} ($CHCl_3$) 1749s, 1723s, 1651s, 1624s; δ_H (200MHz; $CDCl_3$) 1.49 (9H, s, $C(C\underline{H}_3)_3$), 2.41 (1H, *ca.* dd, *J* 10 and 14Hz, $C\underline{H}_2CO_2Bu^t$), 2.72 (1H, *ca.* dd, *J* 4 and 14Hz, $C\underline{H}_2CO_2Bu^t$), 3.70-3.90 (1H, m, NCHC$\underline{H}$), 3.79, 3.84 (2 x 3H, 2 x s, $CO_2C\underline{H}_3$, Ar-O-$C\underline{H}_3$), 5.02 (1H, d, *J* 3Hz, $C\underline{H}CO_2CH_3$), 6.70-7.70 (10H, complex, Ar-$\underline{H}$, C$\underline{H}$=C); δ_C (50.3MHz; $CDCl_3$) 27.96 ($C(\underline{C}H_3)_3$), 39.31 ($\underline{C}H_2CO_2Bu^t$), 43.58 (NCH$\underline{C}$H), 52.67 ($CO_2\underline{C}H_3$), 55.26 (Ar-O$\underline{C}H_3$), 64.43 ($\underline{C}HCO_2CH_3$), 81.57 ($\underline{C}(CH_3)_3$), 111.41, 112.44, 117.93, 125.35, 126.41, 128.20, 128.84, 130.09, 131.26, 133.66, 134.75, 135.29 (Ar-$\underline{C}$H, N$\underline{C}$=C, NC=$\underline{C}$), 160.15 (Ar-$\underline{C}$-OCH_3), 167.57 (N$\underline{C}$=O), 170.46, 170.78 ($\underline{C}O_2Me$, $\underline{C}O_2Bu^t$); *m/z* (Probe CI, NH_3) 453 (25%), 452 (MH^+, 100), 396 (30), 105 (62); (Found MH^+ 452.2073, $C_{26}H_{30}NO_6$ requires 452.2073).

(2*S*,3*S*)-*N*-Benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(4-methoxyphenyl)-[4,5]-dehydropyrrolidine (32)

Coupling procedure as for (2*S*, 3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenyl-[4,5]-dehydropyrrolidine (**25**) above. To a solution of (2*S*, 3*R*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-

butoxycarbonylmethyl-4-trifluoromethanesulfonyloxy-[4,5]-dehydropyrrolidine (**19**) (67mg, 0.14mmol) in 1,2-dimethoxyethane (2ml) was added 4-methoxyphenylboronic acid (31mg, 0.20mmol) in 1,2-dimethoxyethane (1ml), 2M aqueous sodium carbonate (1ml), lithium chloride (16.9mg, 0.40mmol) and tetrakis(triphenylphosphine) palladium (0) (7.8mg, 6.64μmol). After stirring under reflux under an argon atmosphere for 16h, work-up as described previously yielded (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(4-methoxyphenyl)-[4,5]-dehydropyrrolidine (**32**) as a colourless syrup (44mg, 72%); R_f 0.20 (19:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{22}$ -2.0 (c 1.21, $CHCl_3$), υ_{max}/cm^{-1} ($CHCl_3$) 1748s, 1723s, 1644s, 1625s, 1515s, 1422s; δ_H (200MHz; $CDCl_3$) 1.49 (9H, s, $C(C\underline{H}_3)_3$), 2.39 (1H, *ca.* dd, *J* 9 and 14Hz, $C\underline{H}_2CO_2Bu^t$), 2.68 (1H, *ca.* dd, *J* 3 and 14Hz, $C\underline{H}_2CO_2Bu^t$), 3.72-3.88 (1H, complex, NCHC<u>H</u>), 3.80, 3.83 (2 x 3H, 2 x s, $CO_2C\underline{H}_3$, Ar-O-$C\underline{H}_3$), 5.02 (1H, d, *J* 3Hz, $C\underline{H}CO_2CH_3$), 6.80-7.70 (10H, complex, Ar-<u>H</u>, C<u>H</u>=C); δ_C (50.3MHz; $CDCl_3$) 27.96 ($C(\underline{C}H_3)_3$), 39.29 ($\underline{C}H_2CO_2Bu^t$), 43.76 (NCH<u>C</u>H), 52.64 ($CO_2\underline{C}H_3$), 55.29 (Ar-O<u>C</u>H_3), 64.33 ($\underline{C}HCO_2CH_3$), 81.53 ($\underline{C}(CH_3)_3$), 114.43, 124.41, 124.74, 125.31, 126.68, 127.22, 128.18, 128.78, 131.109 (Ar-<u>C</u>H, N<u>C</u>=C, NC=<u>C</u>), 134.96 (Ar<u>C</u>$_{ipso}$), 159.27 (Ar-<u>C</u>-OCH_3), 167.30 (N<u>C</u>=O), 170.56, 170.89 ($\underline{C}O_2CH_3$, $\underline{C}O_2Bu^t$); *m/z* (Probe CI, NH_3) 453 (27%), 452 (MH^+, 100), 396 (33), 105 (47); (Found MH^+ 452.2073, $C_{26}H_{30}NO_6$ requires 452.2073).

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(*Received in UK* 14 *January* 1997; *revised* 19 *February* 1997; *accepted* 20 *February* 1997)