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Towards a Versatile Synthesis of Kainoids II : Two Methods for Establishment of C-4 Stereochemistry

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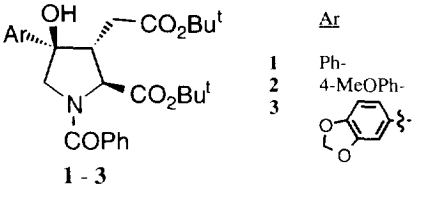
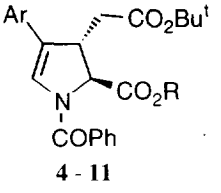
Abstract: Benzylic lactone hydrogenolysis and enamide reduction were used to generate protected C-4 aryl substituted kainoid analogues which were deprotected to their corresponding free amino acids. X-ray crystographic data were obtained for the C-4 2-MeOPh- analogue. © 1997 Elsevier Science Ltd.

In the previous paper,[1] we described methods for functionalising the pyrrolidine ring of *trans*-4-hydroxy-L-proline in order to establish the necessary substitution pattern for the preparation of C-4 aryl substituted kainoid analogues. The intermediates generated are illustrated in Figure 1.



1 - 3

	Ar
1	Ph-
2	4-MeOPh-
3	



4 - 11

	R	Ar
4	But	Ph-
5	But	2-MeOPh-
6	But	3-MeOPh-
7	But	4-MeOPh-
8	Me	Ph-
9	Me	2-MeOPh-
10	Me	3-MeOPh-
11	Me	4-MeOPh-

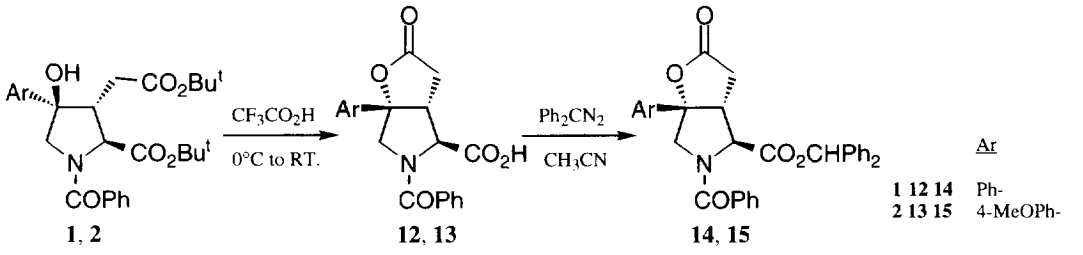
Figure 1

Here we describe methods for reduction of most of these derivatives to their corresponding protected kainoid analogues and a straightforward method for deprotection to the free amino acids.

1. Benzylic lactone hydrogenolysis[2]

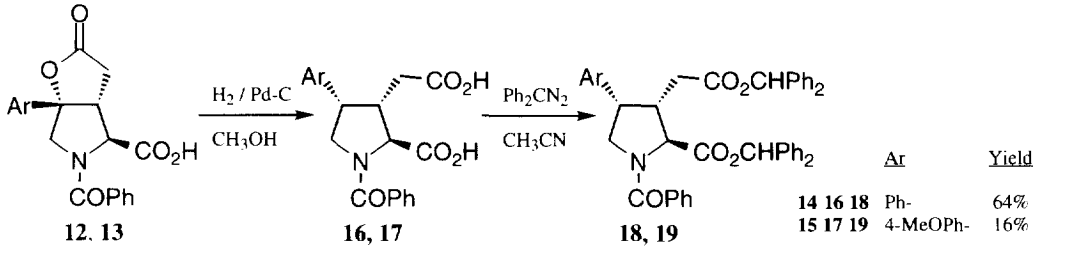
Benzylic hydrogenolysis using a variety of transition metal catalysts has been examined in detail and has been found to be a stereoselective process[3] with the reaction over palladium catalysts proceeding mainly with inversion of configuration at the original benzylic carbon.

With this in mind, benzylic lactones **12** and **13** were prepared from the respective carbinols by treatment with trifluoroacetic acid. Quantitative yields were obtained for the free acids **12** and **13** which were characterised as their corresponding benzhydryl esters **14** and **15** after reaction with diphenyldiazomethane (Scheme 1).



Scheme 1

Catalytic hydrogenolysis of lactones **12** and **13** over 10% palladium on activated charcoal gave acids **16** and **17** which were isolated as their corresponding di-benzhydryl esters **18** and **19**. Only the products derived from inversion at the "benzylic" centre could be isolated[4] (Scheme 2).



Scheme 2

An analogous lactone hydrogenolysis procedure was subsequently adopted by Shirahama[5] in a synthesis of the phenyl substituted kainoid **28** (see later).

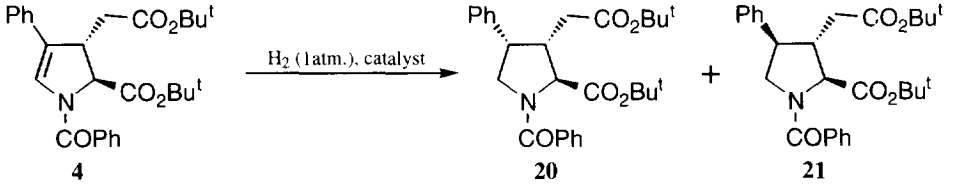
The apparently rather limited scope of the organometallic reagent addition needed to prepare carbinols such as **1** - **3** and disappointing yields in the hydrogenolysis procedure however, led us to an examination of the reduction of enamides **4** - **11**.

2. Enamide reduction[6]

The efficiency and apparent versatility of the palladium (0) catalysed cross-coupling reactions used to prepare enamides **4** - **11** made this the method of choice for introduction of the C-4 substituent.

Various methods for reduction of **4** - **11** were therefore examined with two processes proving useful in the long term. Using **4** as the substrate, heterogeneous catalytic hydrogenation was attempted using a variety of metal catalysts and solvents at atmospheric pressure (Scheme 3). Table 1 summarises the results thus obtained.

Unfortunately, it was clear that the reduction in all cases was being directed by the C-2 *tert*-butyl ester (a result consistent with that obtained for a related intermediate in a synthesis of allokainic acid[7]) resulting in the formation of the C-4 epimer of the required protected acromelic acid analogue. The highest yields were obtained using palladium black as catalyst, an 81% yield of **21** being obtained as a single diastereoisomer.



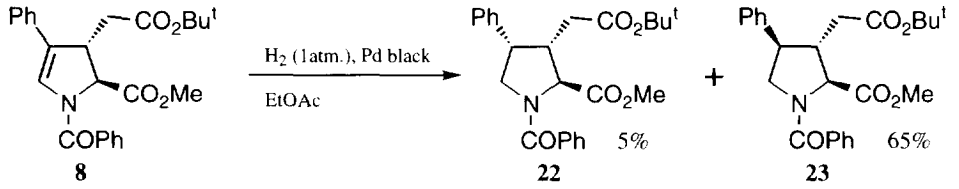
Scheme 3

Catalyst	Solvent	Reaction time	Ratio **20** : **21**
10% Pd-C	EtOAc	20h	1 : 12
Pd black	EtOAc	6h	0 : 1
Raney Ni	EtOH	6h	a
PtO_2	EtOH	6h	a
PtO_2	EtOH	1h	1 : 6
$Pd(OH)_2$-C	EtOH	6h	1 : 8
Rh-C	EtOAc	3days	b

a. reduction of the phenyl groups occurred
b. no reduction observed

Table 1

This conclusion was supported on reduction of enamide **8** where the less bulky methyl ester at C-2 allowed formation of **22** and **23** in approximately a 1 : 13 isolated ratio (overall 70% yield) (Scheme 4).



Scheme 4

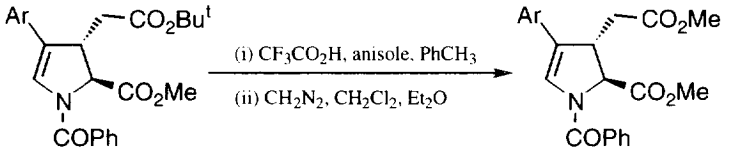
Attempts to use homogeneous catalysts such as Wilkinson's and Crabtree's over a range of temperatures and pressures resulted in no reduction of the enamide functionality in **4** presumably due to steric constraints imposed by the trisubstituted double bond.

This route does however represent a viable stereospecific synthesis of the C-4 epimers of acromelic acid analogues if required.

Reduction of the enamide functionality using excess triethylsilane / trifluoroacetic acid[8] did however yield more useful results.

Firstly, the *tert*-butyl esters at C-3 were exchanged for methyl in good yields by deprotection with trifluoroacetic acid followed by re-esterification with diazomethane (Scheme 5) giving di-methyl esters **24** - **27** (limited analytical data was obtained on the intermediate free acids). For all four enamides **24** - **27**, equal mole ratios of the required protected acromelic acid analogues **28** - **31** and their C-4 epimers **32** - **35** were

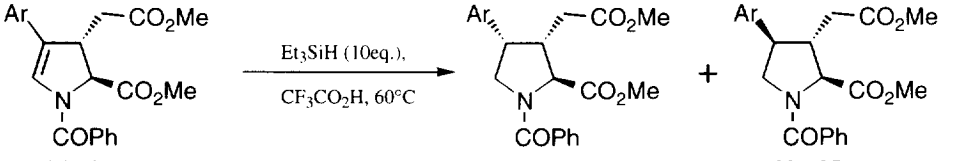
obtained on exposure to triethylsilane (10eq.) in trifluoroacetic acid at 60°C (Scheme 6). The results are summarised in Table 2.



8 - 11 **24 - 27**

Substrate	Product	Ar	Yield
8	**24**	Ph-	90%
9	**25**	2-MeOPh-	96%
10	**26**	3-MeOPh-	96%
11	**27**	4-MeOPh-	68%

Scheme 5



24 - 27 **28 - 31** **32 - 35**

Scheme 6

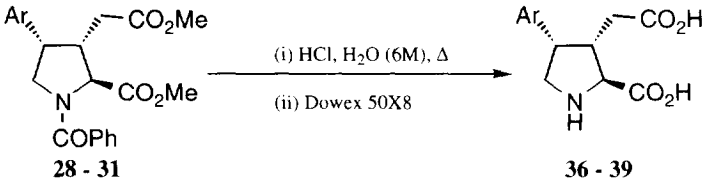
Substrate	Product	Ar	Yield
24	**28**	Ph-	28%
25	**29**	2-MeOPh-	38%
26	**30**	3-MeOPh-	37%
27	**31**	4-MeOPh-	38%
24	**32**	Ph-	28%
25	**33**	2-MeOPh-	38%
26	**34**	3-MeOPh-	35%
27	**35**	4-MeOPh-	34%

Table 2

All four epimer pairs proved readily separable by silica gel chromatography, isomers **28** - **31** proving less polar than their corresponding C-4 epimers **32** - **35**. Assignment of the C-3 / C-4 relative stereochemistry in the products **28** - **35** could be achieved by comparative nOe experiments.

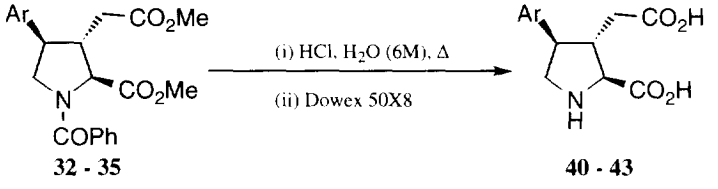
Deprotection to the corresponding free amino acids was achieved using standard amide / ester hydrolysis conditions with 6M hydrochloric acid under reflux. Final purification was achieved by ion-exchange chromatography (Dowex 50X8) (Scheme 7).

In all cases of the free amino acids, the *cis*- C-3 / C-4 relative stereochemistry was characterised by the proton at C-4 appearing at lower field than for the corresponding *trans*- case, a result reported by Shirahama.[9] X-ray crystallography gave final confirmation of the structure of **37**[10] (Figure 2).



28 - 31 36 - 39

Substrate	Product	Ar	Yield
28	36	Ph-	100%
29	37	2-MeOPh-	97%
30	38	3-MeOPh-	96%
31	39	4-MeOPh-	96%



32 - 35 40 - 43

Substrate	Product	Ar	Yield
32	40	Ph-	71%
33	41	2-MeOPh-	82%
34	42	3-MeOPh-	82%
35	43	4-MeOPh-	96%

Scheme 7

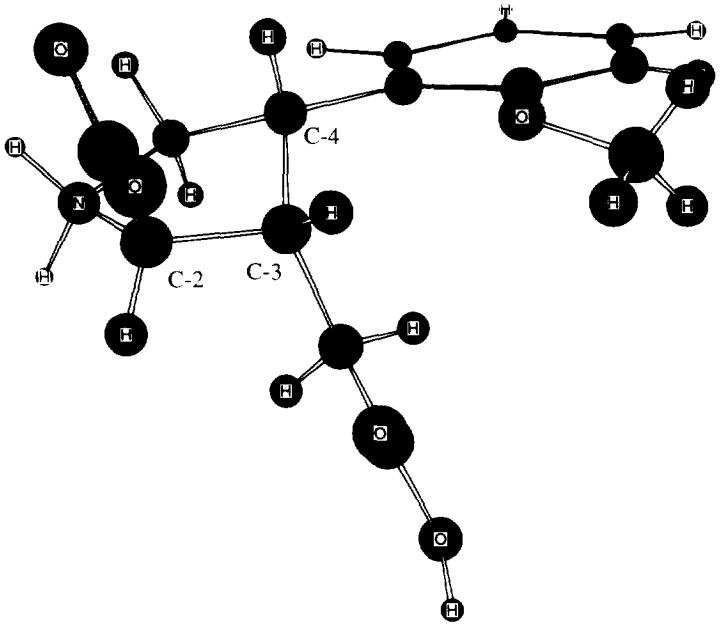


Figure 2

In summary, we have developed a short and versatile route to various acromelic acid analogues and their C-4 epimers. Such a synthetic route should prove useful where both C-4 epimers of natural and unnatural kainoids are required for biological testing.

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., Prof. C. K. Prout (Oxford) for X-ray

crystallographic work, 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[11] 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), V.G. Masslab 20-250 (CI / DCI) and V.G. Bio-Q (Electrospray) 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.

6-Benzoyl-2-oxo-8(*S*)-phenyl-6-aza-1-oxa-4(*R*)-bicyclo [3.3.0] octane-5(*S*)-carboxylic acid (12) and 6-Benzoyl-5(*S*)-diphenylmethoxycarbonyl-2-oxo-8(*S*)-phenyl-6-aza-1-oxa-4(*R*)-bicyclo [3.3.0] octane (14)

(2*S*,3*R*,4*R*)-*N*-Benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-hydroxy-4-phenylpyrrolidine (**1**) (20mg, 41μmol) was dissolved in trifluoroacetic acid (3ml) at 0°C and the reaction mixture was allowed to attain room temperature with stirring being continued for 12h. The trifluoroacetic acid was evaporated *in vacuo* and the residue was triturated with carbon tetrachloride to give 6-benzoyl-2-oxo-8(*S*)-phenyl-6-aza-1-oxa-4(*R*)-bicyclo [3.3.0] octane-5(*S*)-carboxylic acid (**12**) as a colourless amorphous solid (14.6mg, 100%); υ_{max}/cm^{-1} ($CHCl_3$) 3400-2600m, 1787s, 1725m, 1641m; δ_H (200MHz; $CDCl_3$) 2.82-3.95 (2H, m, C<u>H</u>$_2$CO$_2$H), 3.49-3.62 (1H, m, C<u>H</u>CH$_2$CO$_2$H), 4.12 and 4.23 (2 x 1H, ABq, *J* 13Hz, NC<u>H</u>$_2$),

4.97 (1H, d, *J* 5Hz, C<u>H</u>CO_2H), 7.29-7.66 (10H, complex, Ar-<u>H</u>), 10.80 (1H, brs, CO_2<u>H</u>). Further characterisation was obtained as the benzhydryl ester 6-benzoyl-5(*S*)-diphenylmethoxycarbonyl-2-oxo-8(*S*)-phenyl-6-aza-1-oxa-4(*R*)-bicyclo [3.3.0] octane (**14**) obtained as a colourless syrup after treatment of the free acid (**12**) with diphenyldiazomethane; υ_{max}/cm^{-1} ($CHCl_3$) 3150-2840m, 1789s, 1744s, 1646s; δ_H (500MHz; $CDCl_3$) 2.76-2.91 (2H, 6 line m, C<u>H</u>$_2CO_2$), 3.23-3.27 (1H, m, C<u>H</u>CH_2CO_2), 3.93 and 4.14 (2 x 1H, ABq, *J* 13Hz, NC<u>H</u>$_2$), 5.14 (1H, d, *J* 3.5Hz, C<u>H</u>CO_2CHPh_2), 7.04 (1H, brs, CO_2C<u>H</u>Ph_2), 7.14-7.54 (20H, complex, Ar-<u>H</u>); δ_C (125.8MHz; $CDCl_3$) 35.11 (<u>C</u>H$_2CO_2$), 49.46 (<u>C</u>HCH_2CO_2), 61.51 (N<u>C</u>H$_2$), 65.44 (<u>C</u>HCO_2CHPh_2), 78.76 (CO_2<u>C</u>HPh_2), 94.21 (NCH_2<u>C</u>), 124.65, 127.26, 127.40, 128.37, 128.54, 128.73, 128.95, 130.75, 139.25 (Ar-<u>C</u>), 169.65, 171.90, 173.81 (<u>C</u>=O); *m/z* (DCI, NH_3) 518 (MH^+, 7%), 306 (33), 167 (100), 105 (62).

<u>6-Benzoyl-2-oxo-8(*S*)-(4-methoxyphenyl)-6-aza-1-oxa-4(*R*)-bicyclo [3.3.0] octane-5(*S*)-carboxylic acid (13) and 6-Benzoyl-5(*S*)-diphenylmethoxycarbonyl-2-oxo-8(*S*)-(4-methoxyphenyl)-6-aza-1-oxa-4(*R*)-bicyclo [3.3.0] octane (15)</u>

Procedure as for (**12**) and (**14**) above using (2*S*, 3*R*, 4*R*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-hydroxy-4-(4-methoxyphenyl) pyrrolidine (**2**) (20mg, 39μmol) yielded 6-benzoyl-2-oxo-8(*S*)-(4-methoxyphenyl)-6-aza-1-oxa-4(*R*)-bicyclo [3.3.0] octane-5(*S*)-carboxylic acid (**13**) as a colourless, amorphous solid (14.9mg, 100%); υ_{max}/cm^{-1} ($CHCl_3$) 3400-2600br m, 1788br s; δ_H (200MHz; $CDCl_3$) 2.78-2.87 (2H, m, C<u>H</u>CO_2H), 3.50-3.62 (1H, m, C<u>H</u>CH_2CO_2H), 3.81 (3H, s, C<u>H</u>$_3$O-), 4.01 and 4.20 (2 x 1H, ABq, *J* 13Hz, NC<u>H</u>$_2$), 4.89 (1H, br d, *J* 4Hz, C<u>H</u>CO_2H), 6.92 and 7.33 (2 x 1H, ABq, *J* 9Hz, $CH_3OC_6H_4$-), 7.38-7.61 (5H, complex, Ar-<u>H</u>), 8.65 (1H, br s, CO_2<u>H</u>). Further characterisation was obtained as the benzhydryl ester 6-benzoyl-5(*S*)-diphenylmethoxycarbonyl-2-oxo-8(*S*)-(4-methoxyphenyl)-6-aza-1-oxa-4(*R*)-bicyclo [3.3.0] octane (**15**) obtained as a white solid after treatment of the free acid (**13**) with diphenyldiazomethane; m.p. 153°C; $[\alpha]_D^{20}$ -46.3 (c 0.8, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3150-2800m, 1788s, 1746s, 1646s; δ_H (500MHz; $CDCl_3$) 2.75-2.93 (2H, 6 line m, C<u>H</u>$_2CO_2$), 3.19-3.25 (1H, m, C<u>H</u>CH_2CO_2), 3.78 (3H, s, C<u>H</u>$_3$O-), 3.89 and 4.12 (2 x 1H, ABq, *J* 13Hz, NC<u>H</u>$_2$), 5.11 (1H, br d, *J* 3.5Hz, C<u>H</u>CO_2CHPh_2), 6.75-7.60 (20H, complex, CO_2C<u>H</u>Ph_2 and Ar-<u>H</u>); δ_C (50.3MHz; $CDCl_3$) 35.11 (<u>C</u>H$_2CO_2$), 49.16 (<u>C</u>HCH_2CO_2), 55.32 (<u>C</u>H$_3$O-), 61.32 (N<u>C</u>H$_2$), 65.28 (<u>C</u>HCO_2CHPh_2), 78.64 (CO_2<u>C</u>HPh_2), 94.14 (NCH_2<u>C</u>), 114.22, 125.93, 127.18, 127.34, 128.31, 128.48, 128.68, 130.69, 134.72, 139.13 (Ar-<u>C</u>), 159.79 (CH_3O<u>C</u>), 169.63, 169.94, 173.92 (<u>C</u>=O); *m/z* (DCI, NH_3) 548 (MH^+, 7%), 336 (35), 167 (100), 105 (65).

<u>(2*S*,3*S*,4*S*)-*N*-Benzoyl-2-diphenylmethoxycarbonyl-3-diphenylmethoxycarbonylmethyl-4-phenylpyrrolidine (18)</u>

A solution of 6-benzoyl-2-oxo-8(*S*)-phenyl-6-aza-1-oxa-4(*R*)-bicyclo [3.3.0] octane-5(*S*)-carboxylic acid (**12**) (20mg, 57μmol) in methanol (3ml) containing 10% palladium on activated charcoal (30mg) was stirred under an atmosphere of hydrogen from a balloon for 16h. The reaction mixture was filtered through a syringe filter (Whatman "Anatop®", pore size 0.02μm), the filter being washed with methanol before evaporation of the filtrate *in vacuo*. The crude product was dissolved in acetonitrile (2ml) and diphenyldiazomethane was added to the stirred solution at 50°C until the pink colour persisted. The solvent was evaporated *in vacuo* and the residue was purified by radial chromatography on silica gel (eluting with

1:48v/v chloroform : acetonotrile) to give (2*S*,3*S*,4*S*)-*N*-benzoyl-2-diphenylmethoxycarbonyl-3-diphenylmethoxycarbonylmethyl-4-phenylpyrrolidine (**18**) as colourless needles (25mg, 64%); m.p. 206°C; R_f 0.45 (1:48v/v $CHCl_3$: CH_3CN); $[\alpha]_D^{20}$ -10.4 (c 0.27, $CHCl_3$); υ_{max}/cm^{-1} (KBr disc) 1740s, 1632s; δ_H (500MHz; $CDCl_3$) 2.02 (1H, dd, *J* 18 and 11Hz, C<u>H</u>$_2CO_2CHPh_2$), 2.60 (1H, dd, *J* 18 and 4Hz, C<u>H</u>$_2CO_2CHPh_2$), 3.04 (1H, dddd, *J* 11, 9.5, 6.5 and 4Hz, C<u>H</u>$CH_2CO_2CHPh_2$), 3.60 (1H, ddd, *J* 6.5, 6.5 and 2Hz, NC<u>H</u>$_2$), 4.51 (1H, d, *J* 9.5Hz, C<u>H</u>CO_2CHPh_2), 6.76-7.62 (32H, complex, 2 x C<u>H</u>Ph_2 and Ar-<u>H</u>); δ_C (125.8MHz; $CDCl_3$) 33.1 (<u>C</u>$H_2CO_2CHPh_2$), 43.0 (<u>C</u>$HCH_2CO_2CHPh_2$), 45.8 (<u>C</u>HPh), 55.3 (N<u>C</u>H_2), 62.5 (<u>C</u>HCO_2CHPh_2), 78.0 (<u>C</u>HPh_2), 126.5, 126.9, 127.0, 127.1, 127.3, 127.4, 127.9, 128.4, 128.9, 130.5, 135.8, 138.6, 139.4, 139.7 (Ar-<u>C</u>), 169.9, 170.4 (<u>C</u>=O); *m/z* (CI, NH_3) 686 (MH^+, 11%), 308 (7), 167 (100), 105 (25).

(2*S*,3*S*,4*S*)-*N*-Benzoyl-2-diphenylmethoxycarbonyl-3-diphenylmethoxycarbonylmethyl-4-(4-methoxyphenyl)pyrrolidine (19)

Procedure as for (2*S*,3*S*,4*S*)-*N*-benzoyl-2-diphenylmethoxycarbonyl-3-diphenylmethoxycarbonylmethyl-4-phenylpyrrolidine (**18**) above using 6-benzoyl-2-oxo-8(*S*)-(4-methoxyphenyl)-6-aza-1-oxa-4(*R*)-bicyclo [3.3.0] octane-5(*S*)-carboxylic acid (**13**) in methanol (3ml) containing 10% palladium on activated charcoal (30mg). After esterification with diphenyldiazomethane, purification of the crude product by radial chromatography on silica gel (eluting with 1:48v/v chloroform : acetonitrile) gave (2*S*,3*S*,4*S*)-*N*-benzoyl-2-diphenylmethoxycarbonyl-3-diphenylmethoxycarbonylmethyl-4-(4-methoxyphenyl)pyrrolidine (**19**) as a colourless solid (6mg, 16%); m.p. 168°C; R_f 0.30 (1 : 48v/v $CHCl_3$: CH_3CN); $[\alpha]_D^{20}$ -16.8 (c 0.25, $CHCl_3$); υ_{max}/cm^{-1} (KBr disc) 1741s, 1631s; δ_H (500MHz; $CDCl_3$) 2.04 (1H, dd, *J* 17.5 and 11Hz, C<u>H</u>$_2CO_2CHPh_2$), 2.60 (1H, dd, *J* 17.5 and 4Hz, C<u>H</u>$_2CO_2CHPh_2$), 3.00 (1H, dddd, *J* 11, 8.5, 6.5 and 4Hz, C<u>H</u>$CH_2CO_2CHPh_2$), 3.56 (1H, ddd, *J* 6.5, 6.5 and 2Hz, C<u>H</u>Ar), 3.70 (1H, dd, *J* 11 and 2Hz, NC<u>H</u>$_2$), 3.73 (3H, s, C<u>H</u>$_3$O), 4.11 (1H, dd, *J* 11, 6.5Hz, NC<u>H</u>$_2$), 4.50 (1H, d, *J* 8.5Hz, C<u>H</u>CO_2CHPh_2), 6.64-6.70 (4H, complex, Ar-<u>H</u>), 6.83 (1H, s, C<u>H</u>Ph_2), 6.97 (1H, s, C<u>H</u>Ph_2), 7.21-7.43 (23H, complex (Ar-<u>H</u>), 7.60-7.62 (2H, complex, Ar-<u>H</u>); δ_C (125.8MHz; $CDCl_3$) 33.1 (<u>C</u>$H_2CO_2CHPh_2$), 43.1 (<u>C</u>$HCH_2CO_2CHPh_2$), 45.1 (<u>C</u>HAr) 55.2 (O<u>C</u>H_3), 55.6 (N<u>C</u>H_2), 62.5 (<u>C</u>HCO_2CHPh_2), 76.2 and 78.0 (2 x <u>C</u>HPh_2), 114.3, 126.5, 126.9, 127.1, 127.2, 127.3, 127.4, 127.9, 128.0, 128.5, 130.5, 135.5, 139.5, 139.7, 139.9, 158.5 (Ar-<u>C</u>), 169.8, 170.4, 170.5 (<u>C</u>=O).

(2*S*,3*S*,4*R*)-*N*-Benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenylpyrrolidine (21)

A solution of (2*S*,3*S*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenyl-[4,5]-dehydropyrrolidine (**4**) (50mg, 0.11mmol) in ethyl acetate (3ml) containing palladium black (3mg, 28μmol) was vigorously stirred under an atmosphere of hydrogen from a balloon for 6h. The reaction mixture was filtered through a Celite® plug and evaporated *in vacuo* to give a colourless syrup which was purified by flash chromatography on silica gel (eluting with 1:1v/v 40-60 petroleum ether : diethyl ether) to give (2*S*,3*S*,4*R*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenylpyrrolidine (**21**) as a colourless syrup (41mg, 81%); R_f 0.20 (1:1v/v 40-60 PE : Et_2O); $[\alpha]_D^{25}$ -0.25 (c 2.0, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3020s, 1732m, 1628m; δ_H (500MHz; $CDCl_3$) 1.29 (9H, s, C(C<u>H</u>$_3$)$_3$), 1.55 (9H, s, C(C<u>H</u>$_3$)$_3$), 2.42 (1H, dd, *J* 16 and 6Hz, C<u>H</u>$_2CO_2Bu^t$), 2.58 (1H, dd, *J* 16 and 5Hz, C<u>H</u>$_2CO_2Bu^t$), 2.85-2.92 (1H, m, C<u>H</u>$CH_2CO_2Bu^t$), 3.15-3.21

(1H, *ca.* q, C<u>H</u>Ph), 3.81 (2H, d, *J* 9Hz, NC<u>H</u>$_2$), 4.42 (1H, d, *J* 9.5Hz, C<u>H</u>CO$_2$Bu^t), 7.35-7.40 and 7.57-7.62 (10H, complex, Ar-<u>H</u>); δ_C (125.8MHz; $CDCl_3$) 27.90 and 28.05 (2 x C(<u>C</u>H$_3$)$_3$), 36.28 (<u>C</u>H$_2$CO$_2$Bu^t), 45.62 (<u>C</u>HCH$_2$CO$_2$Bu^t), 50.50 (<u>C</u>HPh), 57.20 (NC<u>H</u>$_2$), 64.67 (<u>C</u>HCO$_2$Bu^t), 80.79, 81.77 (<u>C</u>(CH$_3$)$_3$), 127.48, 127.68, 127.97, 128.23, 128.82, 130.37 (Ar-<u>C</u>), 135.65, 137.37 (Ar-<u>C</u>$_{ipso}$), 169.05, 170.04, 170.60 (<u>C</u>=O); *m/z* (Probe CI, NH_3) 466 (MH^+, 24%), 410 (50), 354 (100), 105 (35).

(2*S*,3*S*,4*S*)-*N*-Benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenylpyrrolidine (20) and (2*S*,3*S*,4*R*)-*N*-Benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenylpyrrolidine (21)

To a solution of (2*S*,3*S*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenyl-[4,5]-dehydropyrrolidine (**4**) (40mg, 90μmol) in ethanol (3ml) was added palladium hydroxide on moist carbon (5mg, 9μmol) and the mixture was stirred under an atmosphere of hydrogen from a balloon for 6h. The reaction mixture was filtered through a Celite® plug and evaporated *in vacuo* to give a colourless syrup which was purified by flash chromatography on silica gel (eluting with 1:1v/v 40-60 petroleum ether : diethyl ether) to give 2 close running fractions. Fraction 1 contained (2*S*,3*S*,4*S*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenylpyrrolidine (**20**) as a colourless syrup (3mg, 8%); R_f 0.20 (1:1 v/v 40-60 PE : Et_2O); δ_H (500MHz; $CDCl_3$) 1.44 (9H, s, C(C<u>H</u>$_3$)$_3$), 1.53 (9H, s, C(C<u>H</u>$_3$)$_3$), 1.88 (1H, dd, *J* 17.5 and 10.5Hz, C<u>H</u>$_2$CO$_2$Bu^t), 2.47 (1H, dd, *J* 17.5 and 4.5Hz, C<u>H</u>$_2$CO$_2$Bu^t), 3.00-3.08 (1H, m, C<u>H</u>CH$_2$CO$_2$Bu^t), 3.71-3.74, 3.79-3.82 and 4.12-4.17 (3 x 1H, 3 x m, NC<u>H</u>$_2$, C<u>H</u>Ph), 4.26 (1H, d, *J* 9.5Hz, C<u>H</u>CO$_2$Bu^t), 6.98-7.65 (10H, complex, Ar-<u>H</u>); *m/z* (DCI, NH_3) 466 (MH^+, 40%), 410 (79), 354 (33), 105 (100). Fraction 2 contained (2*S*,3*S*,4*R*)-*N*-benzoyl-2-*tert*-butoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenylpyrrolidine (**21**) as a colourless syrup (33mg, 83%). Physical data as reported above.

(2*S*, 3*S*)-*N*-Benzoyl-2-methoxycarbonyl-3-methylenecarboxy-4-phenyl-[4,5]-dehydropyrrolidine and (2*S*, 3*S*)-*N*-Benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-phenyl-[4,5]-dehydropyrrolidine (24)

To a solution of (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenyl-[4,5]-dehydropyrrolidine (**8**) (33mg, 78μmol) in toluene (1ml), was added anisole (1 drop) and trifluoroacetic acid (1ml) and the mixture was stirred overnight at room temperature. After concentration *in vacuo*, azeotropic removal of residual trifluoroacetic acid with toluene yielded (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methylenecarboxy-4-phenyl-[4,5]-dehydropyrrolidine which was used in the next reaction without any further purification or characterisation, assuming a quantitative yield; δ_H (200MHz; $CDCl_3$) 2.60 (1H, *ca.* dd, *J* 16 and 9Hz, C<u>H</u>$_2$CO$_2$H), 2.90 (1H, *ca.* dd, *J* 16 and 3Hz, C<u>H</u>$_2$CO$_2$H), 3.88 (3H, s, CO$_2$C<u>H</u>$_3$), 3.88-3.99 (1H, m, NCHC<u>H</u>), 5.12 (1H, d, *J* 3Hz, C<u>H</u>CO$_2$CH$_3$), 6.95 (1H, s, C<u>H</u>=C), 6.90-7.75 (10H, complex, Ar-<u>H</u>). To a solution of the (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methylenecarboxy-4-phenyl-[4,5]-dehydropyrrolidine (104mg, 0.28mmol) in dichloromethane (15ml) was added an ethereal solution of diazomethane (50ml from Diazald® (excess)) and the mixture was stirred at room temperature for 2h. After quenching with acetic acid, the solution was evaporated to dryness *in vacuo* and the residue was purified by flash chromatography on silica gel (eluting with 9:1v/v dichloromethane : ethyl acetate) yielding (2*S*, 3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-phenyl-[4,5]-dehydropyrrolidine (**24**) as a colourless syrup (97mg, 90%); R_f 0.25 (9:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{25}$ -22.3 (c 1.075, $CHCl_3$); υ_{max}/cm^{-1}

($CHCl_3$) 1738s, 1657m, 1624s, 1417s; δ_H (200MHz; $CDCl_3$) 2.53 (1H, *ca.* dd, *J* 10 and 15Hz, $C\underline{H}_2CO_2CH_3$), 2.83 (1H, *ca.* dd, *J* 3 and 15Hz, $C\underline{H}_2CO_2CH_3$), 3.72 (3H, s, $CH_2CO_2C\underline{H}_3$), 3.80-3.95 (1H, m, NCHC<u>H</u>), 3.85 (3H, s, $CHCO_2C\underline{H}_3$), 5.02 (1H, d, *J* 3Hz, $C\underline{H}CO_2CH_3$), 6.96 (1H, s, NC<u>H</u>=C), 7.15-7.7 (10H, complex, Ar-<u>H</u>); δ_C (50.3MHz; $CDCl_3$) 37.8 ($\underline{C}H_2CO_2CH_3$), 43.22 (NCH<u>C</u>H), 51.93, 52.75 ($CH_2CO_2\underline{C}H_3$, $CO_2\underline{C}H_3$), 64.41 ($\underline{C}HCO_2CH_3$), 125.08, 125.26, 125.76, 126.21, 127.29, 127.6, 128.13, 128.78, 129.01, 131.215, 132.07, 134.64 (Ar-<u>C</u>H, N<u>C</u>=C, NC=<u>C</u>), 167.46, 170.64, 171.62 ($CH_2\underline{C}O_2CH_3$, $\underline{C}O_2CH_3$, N<u>C</u>=O); *m/z* (CI, NH_3) 381 (20%), 380 (MH^+, 100), 105 (30); (Found MH^+ 380.1498, $C_{22}H_{22}NO_5$ requires 380.1498).

(2*S*,3*S*)-*N*-Benzoyl-2-methoxycarbonyl-3-methylenecarboxy-4-(2-methoxyphenyl)-[4,5]-dehydropyrrolidine and (2*S*,3*S*)-*N*-Benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(2-methoxyphenyl)-[4,5]-dehydropyrrolidine (25).

To a solution of (2*S*,3*S*)-N-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2-methoxyphenyl)-[4,5]-dehydropyrrolidine (**9**) (126mg, 0.28mmol) in toluene (5ml), was added anisole (4 drops) and trifluoroacetic acid (4ml) and the mixture was stirred overnight at room temperature. After concentration *in vacuo*, azeotropic removal of residual trifluoroacetic acid with toluene yielded (2*S*, 3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methylenecarboxy-4-(2-methoxyphenyl)-[4,5]-dehydropyrrolidine which was used in the next reaction without any further purification or characterisation, assuming a quantitative yield; δ_H (200MHz; $CDCl_3$) 2.58 (1H, *ca.* dd, *J* 15 and 9Hz, $C\underline{H}_2CO_2H$), 2.88 (1H, *ca.* dd, *J* 15 and 3Hz, $C\underline{H}_2CO_2H$), 3.79, 3.86 (2 x 3H, 2 x s, $CO_2C\underline{H}_3$, Ar-$OC\underline{H}_3$), 4.00-4.10 (1H, m, NCHC<u>H</u>), 5.09 (1H, d, *J* 2Hz, $C\underline{H}CO_2CH_3$), 6.80-7.80 (10H, complex, Ar-<u>H</u>, C<u>H</u>=C). To a solution of (2*S*, 3*S*)-N-benzoyl-2-methoxycarbonyl-3-methylenecarboxy-4-(2-methoxyphenyl)-[4,5]-dehydropyrrolidine (110mg, 0.28mmol) in dichloromethane (15ml) was added an ethereal solution of diazomethane (45ml from Diazald® (excess)) and the mixture was stirred at room temperature for 2h. After quenching with acetic acid, the solution was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (eluting with 9:1v/v dichloromethane : ethyl acetate) yielding (2*S*, 3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(2-methoxyphenyl)-[4,5]-dehydropyrrolidine (**25**) as a colourless syrup (110mg, 96%); R_f 0.30 (9:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{22}$ -16.9 (c 0.87, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1738s, 1642m, 1613s, 1412s; δ_H (200MHz; $CDCl_3$) 2.49 (1H, *ca.* dd, *J* 15 and 9Hz, $C\underline{H}_2CO_2CH_3$), 2.79 (1H, *ca.* dd, *J* 15 and 3Hz, $C\underline{H}_2CO_2CH_3$), 3.73, 3.76, 3.83 (3 x 3H, 3 x s, Ar-$OC\underline{H}_3$, $CH_2CO_2C\underline{H}_3$, $CO_2C\underline{H}_3$), 3.80-4.02 (1H, m, NCHC<u>H</u>), 4.95 (1H, d, *J* 2Hz, $C\underline{H}CO_2CH_3$), 6.80-7.80 (10H, complex, C<u>H</u>=C, Ar-<u>H</u>); δ_C (50.3MHz; $CDCl_3$) 37.89 ($\underline{C}H_2CO_2CH_3$), 44.08 (NCH<u>C</u>H), 51.87, 52.67, 55.15 (Ar-$O\underline{C}H_3$, $CH_2CO_2\underline{C}H_3$, $CO_2\underline{C}H_3$), 63.46 ($\underline{C}HCO_2CH_3$), 110.96, 120.91, 121.21, 127.47, 128.16, 128.35, 128.48, 129.74, 131.13, 134.78 (Ar-<u>C</u>H, N<u>C</u>=C, NC=<u>C</u>), 157.30 (Ar-<u>C</u>-OCH_3), 167.46 (N<u>C</u>=O), 170.79, 171.87 ($CH_2\underline{C}O_2CH_3$, $\underline{C}O_2CH_3$); *m/z* (Probe CI, NH_3) 411 (18%), 410 (MH^+, 100), 105 (33); (Found MH^+ 410.1604, $C_{23}H_{24}NO_6$ requires 410.1604).

(2*S*,3*S*)-*N*-Benzoyl-2-methoxycarbonyl-3-methylenecarboxy-4-(3-methoxyphenyl)-[4,5]-dehydropyrrolidine and (2*S*,3*S*)-*N*-Benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(3-methoxyphenyl)-[4,5]-dehydropyrrolidine (26).

To a solution of (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(3-methoxyphenyl)-[4,5]-dehydropyrrolidine (**10**) (72mg, 0.16mmol) in toluene (4ml), was added anisole (3

drops) and trifluoroacetic acid (3ml) and the mixture was stirred overnight at room temperature. After concentration *in vacuo*, azeotropic removal of residual trifluoroacetic acid with toluene yielded (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methylenecarboxy-4-(3-methoxyphenyl)-[4,5]-dehydropyrrolidine which was used in the next reaction without any further purification or characterisation, assuming a quantitative yield; δ_H (200MHz; $CDCl_3$) 2.58 (1H, *ca.* dd, *J* 15 and 9Hz, $C\underline{H}_2CO_2H$), 2.89 (1H, *ca.* dd, *J* 15 and 3Hz, $C\underline{H}_2CO_2H$), 3.75-3.95 (1H, m, NCHC<u>H</u>), 3.80, 3.85 (2 x 3H, 2 x s, $CO_2C\underline{H}_3$, Ar-$OC\underline{H}_3$), 5.07 (1H, d, *J* 3Hz, $C\underline{H}CO_2CH_3$), 6.75-7.75 (10H, complex, Ar-<u>H</u>, C<u>H</u>=C), 8.65 (1H, br s, $CO_2\underline{H}$). To a solution of (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methylenecarboxy-4-(3-methoxyphenyl)-[4,5]-dehydropyrrolidine (61mg, 0.15mmol) in dichloromethane (15ml) was added an ethereal solution of diazomethane (30ml from Diazald® (excess)) and the mixture was stirred at room temperature for 2h. After quenching with acetic acid, the solution was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (eluting with 7:1v/v dichloromethane : ethyl acetate yielding (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(3-methoxyphenyl)-[4,5]-dehydropyrrolidine (**26**) as a colourless syrup (63mg, 96%); R_f 0.35 (7:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{22}$ -7.2 (c 1.09, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1738s, 1645m, 1624s, 1600m, 1412s; δ_H (200MHz; $CDCl_3$) 2.52 (1H, *ca.* dd, *J* 15 and 9Hz, $C\underline{H}_2CO_2CH_3$), 2.83 (1H, *ca.* dd, *J* 15 and 3Hz, $C\underline{H}_2CO_2CH_3$), 3.60-3.95 (1H, m, NCHC<u>H</u>), 3.72, 3.78, 3.84 (3 x 3H, 3 x s, Ar-$OC\underline{H}_3$, $CH_2CO_2C\underline{H}_3$, $CO_2C\underline{H}_3$), 5.01 (1H, d, *J* 3Hz, $C\underline{H}CO_2CH_3$), 6.70-7.70 (10H, complex, C<u>H</u>=C, Ar-<u>H</u>); δ_C (50.3MHz; $CDCl_3$) 37.85 ($\underline{C}H_2CO_2CH_3$), 43.29 (NCH<u>C</u>H), 51.98, 52.82 ($CH_2CO_2\underline{C}H_3$, $CO_2\underline{C}H_3$), 55.26 (Ar-$O\underline{C}H_3$), 64.46 ($\underline{C}HCO_2CH_3$), 111.41, 112.47, 117.86, 126.63, 128.20, 128.86, 130.13, 131.31, 133.58, 134.65 (Ar-<u>C</u>H, N<u>C</u>=C, NC=<u>C</u>), 160.19 (Ar-<u>C</u>-OCH_3), 167.54 (N<u>C</u>=O), 170.68, 171.70 ($CH_2\underline{C}O_2CH_3$, $\underline{C}O_2CH_3$); *m/z* (Probe CI, NH_3) 411 (27%), 410 (MH^+, 100), 105 (57); (Found MH^+ 410.1604. $C_{23}H_{24}NO_6$ requires 410.1604).

(2*S*,3*S*)-*N*-Benzoyl-2-methoxycarbonyl-3-methylenecarboxy-4-(4-methoxyphenyl)-[4,5]-dehydropyrrolidine and (2*S*,3*S*)-*N*-Benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(4-methoxyphenyl)-[4,5]-dehydropyrrolidine (27)

To a solution of (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(4-methoxyphenyl)-[4,5]-dehydropyrrolidine (**11**) (43mg, 0.1mmol) in toluene (3ml), was added anisole (2 drops) and trifluoroacetic acid (2ml) and the mixture was stirred overnight at room temperature. After concentration *in vacuo*, azeotropic removal of residual trifluoroacetic acid with toluene yielded (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methylenecarboxy-4-(4-methoxyphenyl)-[4,5]-dehydropyrrolidine which was used in the next reaction without any further purification or characterisation, assuming a quantitative yield; δ_H (200MHz; $CDCl_3$) 2.56 (1H, *ca.* dd, *J* 15 and 8Hz, $C\underline{H}_2CO_2H$), 2.86 (1H, *ca.* dd, *J* 15 and 4Hz, $C\underline{H}_2CO_2H$), 3.66-3.96 (1H, m, NCHC<u>H</u>), 3.80, 3.83 (2 x 3H, 2 x s, $CO_2C\underline{H}_3$, Ar-$OC\underline{H}_3$), 5.09 (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). To a solution of (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methylenecarboxy-4-(4-methoxyphenyl)-[4,5]-dehydropyrrolidine (38mg, 95μmol) in dichloromethane (10ml) was added an ethereal solution of diazomethane (20ml from Diazald® (excess)) and the mixture was stirred at room temperature for 2h. After quenching with acetic acid, the solution was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (eluting with 9:1v/v dichloromethane : ethyl acetate) yielding (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-

4-(4-methoxyphenyl)-[4,5]-dehydropyrrolidine (**27**) as a colourless syrup (27mg, 68%); R_f 0.39 (9:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{22}$ -1.7 (c 1.5, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1738s, 1646m, 1625s, 1417s; δ_H (200MHz; $CDCl_3$) 2.50 (1H, *ca.* dd, *J* 15 and 10Hz, C<u>H</u>$_2$CO$_2$CH$_3$), 2.79 (1H, *ca.* dd, *J* 15 and 3Hz, C<u>H</u>$_2$CO$_2$CH$_3$), 3.70-3.98 (1H, complex, NCHC<u>H</u>), 3.73, 3.80, 3.84 (3 x 3H, 3 x s, Ar-OC<u>H</u>$_3$, CH$_2$CO$_2$C<u>H</u>$_3$, CO$_2$C<u>H</u>$_3$), 5.01 (1H, d, *J* 2Hz, C<u>H</u>CO$_2$CH$_3$, 6.80-7.70 (10H, complex, C<u>H</u>=C, Ar-<u>H</u>); δ_C (50.3MHz; $CDCl_3$) 37.93 (<u>C</u>H$_2$CO$_2$CH$_3$), 43.55 (NCH<u>C</u>H), 51.93, 52.73 (CH$_2$C O$_2$<u>C</u>H$_3$, CO$_2$<u>C</u>H$_3$), 55.27 (Ar-O<u>C</u>H$_3$), 64.36 (<u>C</u>HCO$_2$CH$_3$), 114.28, 124.41, 124.81, 126.46, 126.90, 127.93, 128.55, 130.89 (Ar-<u>C</u>H, N<u>C</u>=C, NC=<u>C</u>), 159.02 (Ar-<u>C</u>-OCH$_3$), 167.0 (N<u>C</u>=O), 170.42, 171.38 (CH$_2$<u>C</u>O$_2$CH$_3$, <u>C</u>O$_2$CH$_3$); *m/z* (Probe CI, NH_3) 411 (27%), 410 (MH^+, 100), 135 (29), 122 (24), 105 (100); (Found MH^+ 410.1604, $C_{23}H_{24}NO_6$ requires 410.1604).

(2*S*,3*S*,4*S*)-*N*-Benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-phenylpyrrolidine (28) and (2*S*,3*S*,4*R*)-*N*-Benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-phenylpyrrolidine (32)

To a solution of (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-phenyl-[4,5]-dehydropyrrolidine (**24**) (97mg, 0.26mmol) in trifluoroacetic acid (4.5ml), was added triethylsilane (320µl, 2.6mmol) and the reaction mixture was heated at 60-65°C for 18h. After cooling to room temperature, the mixture was concentrated *in vacuo* and then azeotropic removal of residual trifluoroacetic acid with toluene yielded a pale brown syrup. Flash chromatography on silica gel (eluting with 9:1v/v dichloromethane : ethyl acetate) yielded 2 fractions. One fraction afforded the (2*S*,3*S*,4*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-phenylpyrrolidine (**28**) (26mg, 28%) as a colourless syrup; R_f 0.35 (4:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{25}$ -39.3 (c 1.35, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1738s, 1632s, 1417s; δ_H (300MHz; $CDCl_3$) 2.05 (1H, *ca.* dd, *J* 17 and 9Hz, C<u>H</u>$_2$CO$_2$CH$_3$), 2.48 (1H, *ca.* dd, *J* 17 and 6Hz, C<u>H</u>$_2$CO$_2$CH$_3$), 3.07-3.17 (1H, m, NCHC<u>H</u>), 3.65, 3.82 (2 x 3H, 2 x s, CH$_2$CO$_2$C<u>H</u>$_3$, CO$_2$C<u>H</u>$_3$), 3.68-3.82 (2H, complex, NCH$_2$C<u>H</u>, NC<u>H</u>$_2$), 4.19 (1H, *ca.* dd, *J* 12 and 6Hz, NC<u>H</u>$_2$), 4.44 (1H, d, *J* 9Hz, C<u>H</u>CO$_2$CH$_3$), 6.96-7.67 (10H, complex, Ar-<u>H</u>); δ_C (125.8MHz; $CDCl_3$) 33.16 (<u>C</u>H$_2$CO$_2$CH$_3$), 42.90 (NCH<u>C</u>H), 46.17 (NCH$_2$<u>C</u>H), 51.71, 52.5 (CO$_2$<u>C</u>H$_3$, CH$_2$CO$_2$<u>C</u>H$_3$), 54.82 (N<u>C</u>H$_2$), 63.07 (<u>C</u>HCO$_2$CH$_3$), 126.64, 127.37, 127.46, 127.53, 128.38, 128.93, 130.54 (Ar-<u>C</u>H), 135.46, 138.53 (Ar-<u>C</u>$_{ipso}$), 169.69, (N<u>C</u>=O), 171.81, 171.98 (CH$_2$<u>C</u>O$_2$CH$_3$, <u>C</u>O$_2$CH$_3$; *m/z* (DCI, NH_3) 383 (23%), 382 (MH^+, 100), 105 (63); (Found MH^+ 382.1654, $C_{22}H_{24}NO_5$ requires 382.1654). The second fraction afforded (2*S*,3*S*,4*R*)-*N*-benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-phenylpyrrolidine (**32**) (26mg, 28%) as a colourless syrup; R_f 0.25 (4:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{25}$ -27.9 (c 1.45, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1741s, 1632s, 1423s; δ_H (300MHz; $CDCl_3$) 2.47-2.64 (2H, 8 line m, C<u>H</u>$_2$CO$_2$CH$_3$), 2.92-3.03 (1H, m, NCHC<u>H</u>), 3.07-3.22 (1H, m, NCH$_2$C<u>H</u>), 3.47, 3.82 (2 x 3H, 2 x s, CH$_2$CO$_2$C<u>H</u>$_3$, CO$_2$C<u>H</u>$_3$), 3.82-3.91 (2H, complex, NC<u>H</u>$_2$), 4.51 (1H, d, *J* 9Hz, C<u>H</u>CO$_2$CH$_3$), 7.24-7.64 (10H, complex, Ar-<u>H</u>); δ_C (125.8MHz; $CDCl_3$) 35.31 (<u>C</u>H$_2$CO$_2$CH$_3$), 45.59 (NCH<u>C</u>H), 50.62 (NCH$_2$<u>C</u>H), 51.53, 52.40 (CO$_2$<u>C</u>H$_3$, CH$_2$CO$_2$<u>C</u>H$_3$), 56.93 (N<u>C</u>H$_2$), 64.34 (<u>C</u>HCO$_2$CH$_3$), 127.57, 127.85, 128.22, 128.33, 128.85, 130.55, (Ar-<u>C</u>H), 135.18, 136.52 (Ar-<u>C</u>$_{ipso}$), 169.19, (N<u>C</u>=O), 171.20, 171.83 (CH$_2$<u>C</u>O$_2$CH$_3$, <u>C</u>O$_2$CH$_3$); *m/z* (Probe CI, NH_3) 383 (22%), 382 (MH^+, 100), 105 (60); (Found MH^+ 382.1654, $C_{22}H_{24}NO_5$ requires 382.1654).

(2*S*,3*S*,4*S*)-*N*-Benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(2-methoxyphenyl)pyrrolidine (29) and

(2*S*,3*S*,4*R*)-*N*-Benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(2-methoxyphenyl)pyrrolidine (33)

To a solution of (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(2-methoxyphenyl)-[4,5]-dehydropyrrolidine (**25**) (102mg, 0.25mmol) in trifluoroacetic acid (7ml), was added triethylsilane (340µl, 2.5mmol) and the reaction mixture was heated at 60-65°C for 24h. After cooling to room temperature, the mixture was concentrated *in vacuo* and then azeotropic removal of residual trifluoroacetic acid with toluene yielded a pale brown syrup. Flash chromatography on silica gel (eluting with 9:1v/v dichloromethane : ethyl acetate) yielded 2 fractions. One fraction afforded (2*S*,3*S*,4*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(2-methoxyphenyl)pyrrolidine (**29**) (39mg, 38%) as a colourless syrup; R_f 0.25 (9:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{22}$ -66.9 (c 1.22, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1738s, 1631s, 1603, 1423s; δ_H (300MHz; $CDCl_3$) 2.13 (1H, *ca.* dd, *J* 17 and 8Hz, C<u>H</u>$_2$CO$_2$CH$_3$), 2.35 (1H, *ca.* dd, *J* 17 and 6Hz, C<u>H</u>$_2$CO$_2$CH$_3$), 3.21-3.31 (1H, m, NCHC<u>H</u>), 3.64, 3.75, 3.81 (3 x 3H, 3 x s, Ar-OC<u>H</u>$_3$, CH$_2$CO$_2$C<u>H</u>$_3$, CO$_2$C<u>H</u>$_3$), 3.75-3.81 (1H, complex, NC<u>H</u>$_2$), 4.04-4.19 (1H, complex, NC<u>H</u>$_2$, NCH$_2$C<u>H</u>), 4.38 (1H, d, *J* 8Hz, C<u>H</u>CO$_2$CH$_3$), 6.80-7.70 (9H, complex, Ar-<u>H</u>); δ_C (125.8MHz; $CDCl_3$) 32.94 (<u>C</u>H$_2$CO$_2$CH$_3$), 39.35 (NCH<u>C</u>H), 41.94 (NCH$_2$<u>C</u>H), 51.56, 52.38 (CO$_2$<u>C</u>H$_3$, CH$_2$CO$_2$<u>C</u>H$_3$), 54.14 (N<u>C</u>H$_2$), 55.06 (Ar-O<u>C</u>H$_3$), 63.32 (<u>C</u>HCO$_2$CH$_3$), 110.15, 120.87, 126.29, 126.55, 127.17, 127.31, 128.31, 128.48, 130.42 (Ar-<u>C</u>H), 135.56 (Ar-<u>C</u>$_{ipso}$), 157.00 (Ar-<u>C</u>-OCH$_3$), 169.64 (N<u>C</u>=O), 171.90, 171.93 (CH$_2$<u>C</u>O$_2$CH$_3$, <u>C</u>O$_2$CH$_3$); *m/z* (Probe CI, NH_3) 413 (23%), 412 (MH^+, 100), 105 (30); (Found MH^+ 412.1760, $C_{23}H_{26}NO_6$ requires 412.1760). The second fraction afforded (2*S*,3*S*,4*R*)-*N*-benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(2-methoxyphenyl)pyrrolidine (**33**) (39mg, 38%) as a colourless syrup; R_f 0.20 (9:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{22}$ -38.2 (c 1.02, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1741s, 1631s, 1423s; δ_H (300MHz; $CDCl_3$) 2.48 (1H, *ca.* dd, *J* 16 and 6Hz, C<u>H</u>$_2$CO$_2$CH$_3$), 2.59 (1H, *ca.* dd, *J* 16 and 7Hz, C<u>H</u>$_2$CO$_2$CH$_3$), 3.08-3.18 (1H, m, NCHC<u>H</u>), 3.46, 3.78, 3.80 (3 x 3H, 3 x s, CHCO$_2$C<u>H</u>$_3$, Ar-OC<u>H</u>$_3$, CH$_2$CO$_2$C<u>H</u>$_3$), 3.50-3.63 (1H, m, NCH$_2$C<u>H</u>), 3.73-3.90 (2H, complex, NC<u>H</u>$_2$), 4.48 (1H, d, *J* 10Hz, C<u>H</u>CO$_2$CH$_3$), 6.83-7.65 (9H, complex, Ar-<u>H</u>); δ_C (125.8MHz; $CDCl_3$) 35.72 (<u>C</u>H$_2$CO$_2$CH$_3$), 43.72, 43.86 (NCH$_2$<u>C</u>H, NCH<u>C</u>H), 51.46, 52.32 (CH$_2$CO$_2$<u>C</u>H$_3$, CO$_2$<u>C</u>H$_3$), 55.14 (N<u>C</u>H$_2$), 55.30 (ArO<u>C</u>H$_3$), 64.46 (<u>C</u>HCO$_2$CH$_3$), 110.70, 120.83, 124.47, 127.85, 128.14, 128.62, 130.45 (Ar-<u>C</u>H), 135.32 (Ar-<u>C</u>$_{ipso}$), 157.84 (Ar-<u>C</u>-OCH$_3$), 169.21 (N<u>C</u>=O), 171.49, 171.95 (CH$_2$<u>C</u>O$_2$CH$_3$, <u>C</u>O$_2$CH$_3$); *m/z* (Probe CI, NH_3) 413 (13%), 412 (MH^+, 100), 105 (47); (Found MH^+ 412.1760, $C_{23}H_{26}NO_6$ requires 412.1760).

(2*S*,3*S*,4*S*)-*N*-Benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(3-methoxyphenyl)pyrrolidine (30) and

(2*S*,3*S*,4*R*)-*N*-Benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(3-methoxyphenyl)pyrrolidine (34)

To a solution of (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(3-methoxyphenyl)-[4,5]-dehydropyrrolidine (**26**) (63mg, 0.15mmol) in trifluoroacetic acid (4ml), was added triethylsilane (210µl, 1.5mmol) and the reaction mixture was heated at 60-65°C for 24h. After cooling to room temperature, the mixture was concentrated *in vacuo* and then azeotropic removal of residual trifluoroacetic

acid with toluene yielded a pale brown syrup. Flash chromatography on silica gel (eluting with 8:1v/v dichloromethane : ethyl acetate) yielded 2 fractions. One fraction afforded (2*S*,3*S*,4*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(3-methoxyphenyl)pyrrolidine (**30**) (21mg, 37%) as a colourless syrup; R_f 0.25 (8:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{22}$ -41.9 (c 1.09, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1738s, 1633s, 1600m, 1417s; δ_H (300MHz; $CDCl_3$) 2.08 (1H, *ca.* dd, *J* 18 and 9Hz, C$\underline{H}_2CO_2CH_3$), 2.49 (1H, *ca.* dd, *J* 18 and 6Hz, C$\underline{H}_2CO_2CH_3$), 3.04-3.17 (1H, m, NCHC$\underline{H}$), 3.62-3.73 (1H, m, NCH$_2$C$\underline{H}$), 3.66, 3.76, 3.82 (3 x 3H, 3 x s, Ar-OC$\underline{H}_3$, $CH_2CO_2C\underline{H}_3$, $CO_2C\underline{H}_3$), 3.72-3.83 (1H, m, NC$\underline{H}_2$), 4.18 (1H, *ca.* dd, *J* 12 and 6Hz, NC$\underline{H}_2$), 4.43 (1H, d, *J* 9Hz, C$\underline{H}CO_2CH_3$), 7.15-7.70 (9H, complex, Ar-$\underline{H}$); δ_C (125.8MHz; $CDCl_3$) 33.14 (C$\underline{H}_2CO_2CH_3$), 42.86 (NCH$\underline{C}$H), 46.15 (NCH$_2\underline{C}$H), 51.70, 52.50 ($CO_2\underline{C}H_3$, $CH_2CO_2\underline{C}H_3$), 54.79 (N$\underline{C}H_2$), 55.09 (Ar-O$\underline{C}H_3$), 63.03 ($\underline{C}HCO_2CH_3$), 112.83, 113.28, 119.65, 127.38, 128.38, 129.95, 130.57 (Ar-$\underline{C}$H), 135.43, 140.08 (Ar-$\underline{C}_{ipso}$), 159.94 (Ar-$\underline{C}$-OCH$_3$), 169.66 (N$\underline{C}$=O), 171.82, 172.05 ($CH_2\underline{C}O_2CH_3$, $\underline{C}O_2CH_3$); *m/z* (Probe CI, NH_3) 413 (22%), 412 (MH^+, 100), 105 (65); (Found MH^+ 412.1760, $C_{23}H_{26}NO_6$ requires 412.1760). The second fraction afforded the (2*S*,3*S*,4*R*)-*N*-benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(3-methoxyphenyl)pyrrolidine (**34**) (20mg, 35%) as a colourless syrup; R_f 0.20 (8:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{22}$ -24.9 (c 1.06, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1741s, 1632s, 1423s; δ_H (300MHz; $CDCl_3$) 2.47-2.63 (2H, m, C$\underline{H}_2CO_2CH_3$), 2.89-3.02 (1H, m, NCHC$\underline{H}$), 3.04-3.17 (1H, m, NCH$_2$C$\underline{H}$), 3.51, 3.80, 3.82 (3 x 3H, 3 x s, $CHCO_2C\underline{H}_3$, Ar-OC$\underline{H}_3$, $CH_2CO_2C\underline{H}_3$), 3.79-3.89 (2H, m, NC$\underline{H}_2$), 4.50 (1H, d, *J* 9Hz, C$\underline{H}CO_2CH_3$), 6.76-7.70 (9H, complex, Ar-$\underline{H}$); δ_C (125.8MHz; $CDCl_3$) 35.21 (C$\underline{H}_2CO_2CH_3$), 45.47 (NCH$\underline{C}$H), 50.54 (NCH$_2\underline{C}$H), 51.60, 52.45 ($CH_2CO_2\underline{C}H_3$, $CO_2\underline{C}H_3$), 55.26 (ArO$\underline{C}H_3$), 56.80 (N$\underline{C}H_2$), 64.34 ($\underline{C}HCO_2CH_3$), 113.01, 113.73, 120.09, 127.62, 128.24, 129.91, 130.60 (Ar-$\underline{C}$H), 135.14, 138.12 (Ar-$\underline{C}_{ipso}$), 159.95 (Ar-$\underline{C}$-OCH$_3$), 169.21 (N$\underline{C}$=O), 171.27, 171.84 ($CH_2\underline{C}O_2CH_3$, $\underline{C}O_2CH_3$; *m/z* (Probe CI, NH_3) 413 (25%), 412 (MH^+, 100), 105 (67); (Found MH^+ 412.1760, $C_{23}H_{26}NO_6$ requires 412.1760).

(2*S*,3*S*,4*S*)-*N*-Benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(4-methoxyphenyl)pyrrolidine (31) and (2*S*,3*S*,4*R*)-*N*-Benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(4-methoxyphenyl)pyrrolidine (35)

To a solution of (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(4-methoxyphenyl)-[4,5]-dehydropyrrolidine (**27**) (29mg, 71μmol) in trifluoroacetic acid (2.5ml), was added triethylsilane (110μl, 0.71mmol) and the reaction mixture was heated at 60-65°C for 24h. After cooling to room temperature, the mixture was concentrated *in vacuo* and then azeotropic removal of residual trifluoroacetic acid with toluene yielded a pale brown syrup. Flash chromatography on silica gel (eluting with 9:1v/v dichloromethane : ethyl acetate) yielded 2 fractions. One fraction afforded (2*S*,3*S*,4*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(4-methoxyphenyl)pyrrolidine (**31**) (11mg, 38%) as a colourless syrup; R_f 0.30 (9:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{22}$ -48.1 (c 0.515, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1738s, 1632s, 1515s, 1417s; δ_H (300MHz; $CDCl_3$) 2.07 (1H, *ca.* dd, *J* 18 and 9Hz, C$\underline{H}_2CO_2CH_3$), 2.48 (1H, *ca.* dd, *J* 18 and 4Hz, C$\underline{H}_2CO_2CH_3$), 3.02-3.12 (1H, m, NCHC$\underline{H}$), 3.57-3.88 (2H, complex, NC$\underline{H}_2$, NCH$_2$C$\underline{H}$), 3.65, 3.78, 3.82 (3 x 3H, 3 x s, Ar-OC$\underline{H}_3$, $CH_2CO_2C\underline{H}_3$, $CO_2C\underline{H}_3$), 4.16 (1H, *ca.* dd, *J* 11 and 7Hz, NC$\underline{H}_2$), 4.41 (1H, d, *J* 9Hz, C$\underline{H}CO_2CH_3$), 6.79-7.66 (9H, complex, Ar-$\underline{H}$); δ_C (125.8MHz; $CDCl_3$) 33.19 (C$\underline{H}_2CO_2CH_3$),

43.04 (NCHCH), 45.50 (NCH_2CH), 51.74, 52.53 (CO_2CH_3, $CH_2CO_2CH_3$), 55.13 (NCH_2), 55.24 (Ar-OCH_3), 63.04 ($CHCO_2CH_3$), 114.31, 126.66, 127.22, 127.41, 128.40, 128.60, 130.06, 130.56 (Ar-CH), 135.50 (Ar-C_{ipso}), 158.84 (Ar-C-OCH_3), 169.71 (NC=O), 171.89, 172.09 ($CH_2CO_2CH_3$, CO_2CH_3); *m/z* (Probe CI, NH_3) 413 (22%), 412 (MH^+, 100), 105 (72); (Found MH^+ 412.1760, $C_{23}H_{26}NO_6$ requires 412.1760). The second fraction afforded the (2*S*,3*S*,4*R*)-*N*-benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(4-methoxyphenyl)pyrrolidine (**35**) (20mg, 34%) as a colourless syrup; R_f 0.20 (4:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{22}$ -20.4 (c 0.49, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1741s, 1632s, 1516s, 1417s; δ_H (300MHz; $CDCl_3$) 2.46-2.61 (2H, 8 line m, $CH_2CO_2CH_3$), 2.86-2.97 (1H, m, NCHCH), 3.01-3.11 (1H, m, NCH_2CH), 3.49, 3.78, 3.82 (3 x 3H, 3 x s, $CHCO_2CH_3$, Ar-OCH_3, $CH_2CO_2CH_3$), 3.78-3.88 (2H, complex, NCH_2), 4.48 (1H, d, *J* 9Hz, $CHCO_2Me$), 6.82-7.66 (9H, complex, Ar-H); δ_C (125.8MHz; $CDCl_3$) 35.30 ($CH_2CO_2CH_3$), 45.68 (NCHCH), 49.94 (NCH_2CH), 51.60, 52.42 ($CH_2CO_2CH_3$, CO_2CH_3), 55.29 ($ArOCH_3$), 57.03 (NCH_2), 64.36 ($CHCO_2CH_3$), 114.28, 127.62, 128.23, 128.36, 128.89, 130.56 (Ar-CH), 135.24, (Ar-C_{ipso}), 159.22 (Ar-C-OCH_3), 169.20 (NC=O), 171.33, 171.90 ($CH_2CO_2CH_3$, CO_2CH_3); *m/z* (Probe CI, NH_3) 413 (11%), 412 (MH^+, 47), 105 (100); (Found MH^+ 412.1760, $C_{23}H_{26}NO_6$ requires 412.1760).

(2*S*,3*S*,4*S*)-3-Methylenecarboxy-4-phenylpyrrolidine-2-carboxylic acid (36)

To (2*S*,3*S*,4*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-phenylpyrrolidine (**28**) (14.7mg, 39μmol) was added 6M hydrochloric acid (2ml) and the mixture was heated under reflux for 16h. The solution was cooled to room temperature, concentrated *in vacuo* and the solid residue was dissolved in water (10ml) and loaded onto a pre-activated column of ion-exchange resin (Dowex 50W-X8 (H^+ form)). After flushing the column with water (40ml) the compound was eluted with 2M ammonia solution (50ml) and the resulting solution was evaporated *in vacuo*. The white solid was redissolved in water (12ml) and the solution was freeze-dried to yield (2*S*,3*S*,4*S*)-3-methylenecarboxy-4-phenylpyrrolidine-2-carboxylic acid (**36**) (9.6mg, 100%) as a white solid. Free amino acid; $[\alpha]_D^{22}$ +27.8 (c 0.27, H_2O); υ_{max}/cm^{-1} (KBr disc) 3410w, 3033br, 1714s, 1622s, 1401s; δ_H (300MHz; D_2O) 1.78 (1H, *ca.* dd, *J* 16 and 9Hz, CH_2CO_2H), 2.15 (1H, *ca.* dd, *J* 16 and 6Hz, CH_2CO_2H), 2.84-2.96 (1H, m, NCHCH), 3.47 (1H, *ca.* dd, *J* 11 and 7Hz, NCH_2), 3.58-3.73 (2H, complex, NCH_2, NCH_2CH), 3.80 (1H, d, *J* 7Hz, $CHCO_2H$), 7.00-7.40 (5H, complex, Ar-H); *m/z* (Electrospray) 251 (14%), 250 (MH^+, 100), 205 (17), 204 (33).

(2*S*,3*S*, 4*S*)-3-Methylenecarboxy-4-(2-methoxyphenyl)pyrrolidine-2-carboxylic acid (37)

Procedure as for (2*S*,3*S*,4*S*)-3-methylenecarboxy-4-phenylpyrrolidine-2-carboxylic acid (**36**). A stirred mixture of (2*S*,3*S*,4*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(2-methoxyphenyl)-pyrrolidine (**29**) (38mg, 92μmol) and 6M hydrochloric acid (2ml) was heated under reflux for 16h. After purification by ion-exchange chromatography (Dowex 50W-X8 (H^+ form)) the solution was freeze-dried yielding (2*S*,3*S*, 4*S*)-3-methylenecarboxy-4-(2-methoxyphenyl)pyrrolidine-2-carboxylic acid (**37**) (25mg, 97%) as a white solid. Free amino acid; m.p. >230°C (from H_2O); $[\alpha]_D^{22}$ +2.5 (c 1.1, H_2O); υ_{max}/cm^{-1} (KBr disc) 3437s, 3064br, 1729s, 1621s, 1384s; δ_H (300MHz; D_2O) 1.77 (1H, *ca.* dd, *J* 16 and 10Hz, CH_2CO_2H), 2.23 (1H, *ca.* dd, *J* 16 and 5Hz, CH_2CO_2H), 2.89-2.99 (1H, m, NCHCH), 3.47-3.66 (2H, complex, NCH_2, NCH_2CH), 3.63 (3H, s, Ar-OCH_3), 3.69-3.80 (1H, 4 line m, NCH_2), 3.84 (1H, d, *J* 8Hz, $CHCO_2H$), 6.70-7.70 (4H, complex, Ar-H); *m/z* (Electrospray) 281 (16%), 280 (MH^+, 100).

(2*S*,3*S*, 4*S*)-3-Methylenecarboxy-4-(3-methoxyphenyl)pyrrolidine-2-carboxylic acid (38)

Procedure as for (2*S*,3*S*,4*S*)-3-methylenecarboxy-4-phenylpyrrolidine-2-carboxylic acid (**36**). A stirred mixture of (2*S*,3*S*,4*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(3-methoxyphenyl)-pyrrolidine (**30**) (20mg, 49μmol) and 6M hydrochloric acid (2ml) was heated under reflux for 16h. After purification by ion-exchange chromatography (Dowex 50W-X8 (H^+ form)) the solution was freeze-dried yielding (2*S*,3*S*, 4*S*)-3-methylenecarboxy-4-(3-methoxyphenyl)pyrrolidine-2-carboxylic acid (**38**) (13mg, 96%) as a white solid. Free amino acid; $[\alpha]_D^{22}$ -56.7 (c 0.25, H_2O); υ_{max}/cm^{-1} (KBr disc) 3410m, 2968br, 1715s, 1608s, 1397s; δ_H (300MHz; D_2O) 1.81 (1H, *ca.* dd, *J* 16 and 9Hz, C$\underline{H}_2CO_2H$), 2.18 (1H, *ca.* dd, *J* 16 and 6Hz, C$\underline{H}_2CO_2H$), 2.86-2.97 (1H, m, NCHC$\underline{H}$), 3.48 (1H, *ca.* dd, *J* 11 and 8Hz, NC$\underline{H}_2$), 3.57-3.74 (2H, complex, NC$\underline{H}_2$, NCH$_2$C$\underline{H}$), 3.63 (3H, s, Ar-OC$\underline{H}_3$), 3.81 (1H, d, *J* 7Hz, C$\underline{H}CO_2H$), 6.60-7.70 (4H, complex Ar-$\underline{H}$); *m/z* (Electrospray) 281 (18%), 280 (MH^+, 100).

(2*S*,3*S*, 4*S*)-3-Methylenecarboxy-4-(4-methoxyphenyl)pyrrolidine-2-carboxylic acid (39)

Procedure as for (2*S*,3*S*,4*S*)-3-methylenecarboxy-4-phenylpyrrolidine-2-carboxylic acid (**36**). A stirred mixture of (2*S*,3*S*,4*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(4-methoxyphenyl)-pyrrolidine (**31**) (10mg, 24μmol) and 6M hydrochloric acid (2ml) was heated under reflux for 16h. After purification by ion-exchange chromatography (Dowex 50W-X8 (H^+ form)) the solution was freeze-dried yielding (2*S*,3*S*, 4*S*)-3-methylenecarboxy-4-(4-methoxyphenyl)pyrrolidine-2-carboxylic acid (**39**) (6.5mg, 96%) as a white solid. Free amino acid; $[\alpha]_D^{22}$ +13.1 (c, 0.18, H_2O); υ_{max}/cm^{-1} (KBr disc) 3424w, 2970br, 1708s, 1614s, 1517s, 1253s; δ_H (300MHz; D_2O) 1.76 (1H, *ca.* dd, *J* 16 and 9Hz, C$\underline{H}_2CO_2H$), 2.11 (1H, *ca.* dd, *J* 16 and 6Hz, C$\underline{H}_2CO_2H$), 2.83-2.92 (1H, m, NCHC$\underline{H}$), 3.46 (1H, *ca.* dd, *J* 11 and 8 Hz, NC$\underline{H}_2$), 3.57-3.74 (2H, complex, NC$\underline{H}_2$, NCH$_2$C$\underline{H}$), 3.66 (3H, s, Ar-OC$\underline{H}_3$), 3.82 (1H, d, *J* 6Hz, C$\underline{H}CO_2H$), 6.70-7.15 (4H, complex, Ar-$\underline{H}$); *m/z* (Electrospray) 281 (15%), 280 (MH^+, 100), 234 (19).

(2*S*,3*S*,4*R*)-3-Methylenecarboxy-4-phenylpyrrolidine-2-carboxylic acid (40)

Procedure as for (2*S*,3*S*,4*S*)-3-methylenecarboxy-4-phenylpyrrolidine-2-carboxylic acid (**36**). A stirred mixture of (2*S*,3*S*,4*R*)-*N*-benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-phenylpyrrolidine (**32**) (26mg, 68μmol) and 6M hydrochloric acid (2ml) was heated under reflux for 16h. After purification by ion-exchange chromatography (Dowex 50W-X8 (H^+ form)) the solution was freeze-dried yielding (2*S*,3*S*,4*R*)-3-methylenecarboxy-4-phenylpyrrolidine-2-carboxylic acid (**40**) (12mg, 71%) as a white solid. Free amino acid; $[\alpha]_D^{22}$ -28.3 (c 0.29, H_2O); υ_{max}/cm^{-1} (KBr disc) 3030br, 1718s, 1610s; δ_H (300MHz; D_2O) 2.29 (1H, *ca.* dd, *J* 15 and 7Hz, C$\underline{H}_2CO_2H$), 2.47 (1H, *ca.* dd, *J* 15 and 5Hz, C$\underline{H}_2CO_2H$), 2.53-2.62 (1H, m, NCHC$\underline{H}$), 3.02-3.32 (2H, complex, NC$\underline{H}_2$, NCH$_2$CH), 3.54 (1H, *ca.* dd, *J* 11 and 7Hz, NC$\underline{H}_2$), 3.84 (1H, d, *J* 9Hz, C$\underline{H}CO_2H$), 7.05-7.35 (5H, complex, Ar-$\underline{H}$); *m/z* (Electrospray) 251 (14%), 250 (MH^+, 100), 205 (8), 204 (19).

(2*S*,3*S*, 4*R*)-3-Methylenecarboxy-4-(2-methoxyphenyl)pyrrolidine-2-carboxylic acid (41)

Procedure as for (2*S*,3*S*,4*S*)-3-methylenecarboxy-4-phenylpyrrolidine-2-carboxylic acid (**36**). A stirred mixture of (2*S*,3*S*,4*R*)-*N*-benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(2-methoxyphenyl)-

pyrrolidine (**33**) (34mg, 80μmol) and 6M hydrochloric acid (2ml) was heated under reflux for 16h. After purification by ion-exchange chromatography (Dowex 50W-X8 (H^+ form)) the solution was freeze-dried yielding (2*S*,3*S*, 4*R*)-3-methylenecarboxy-4-(2-methoxyphenyl)pyrrolidine-2-carboxylic acid (**41**) (19mg, 82%) as a white solid. Free amino acid; $[\alpha]_D^{22}$ -4.4 (c 0.45, H_2O); υ_{max}/cm^{-1} (KBr disc) 3436m, 3245m, 2975br, 1714s, 1601s; δ_H (300MHz; D_2O) 2.33 (1H, *ca.* dd, *J* 15 and 8Hz, $C\underline{H}_2CO_2H$), 2.53 (1H, *ca.* dd, *J* 15 and 4Hz, $C\underline{H}_2CO_2H$), 2.74-2.87 (1H, m, NCHC$\underline{H}$), 3.35-3.55 (3H, complex, $NC\underline{H}_2$, $NCH_2C\underline{H}$), 3.67 (3H, s, Ar-$OC\underline{H}_3$), 3.85 (1H, d, *J* 9Hz, $C\underline{H}CO_2H$), 6.79-7.74 (4H, complex, Ar-$\underline{H}$); *m/z* (Electrospray) 281 (14%), 280 (MH^+, 100), 279 (10).

(2*S*,3*S*, 4*R*)-3-Methylenecarboxy-4-(3-methoxyphenyl)pyrrolidine-2-carboxylic acid (42)

Procedure as for (2*S*,3*S*,4*S*)-3-methylenecarboxy-4-phenylpyrrolidine-2-carboxylic acid (**36**). A stirred mixture of (2*S*,3*S*,4*R*)-*N*-benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(3-methoxyphenyl)-pyrrolidine (**34**) (18mg, 44μmol) and 6M hydrochloric acid (2ml) was heated under reflux for 16h. After purification by ion-exchange chromatography (Dowex 50W-X8 (H^+ form)) the solution was freeze-dried yielding (2*S*,3*S*, 4*R*)-3-methylenecarboxy-4-(3-methoxyphenyl)prrrolidine-2-carboxylic acid (**42**) (10mg, 82%) as a white solid. Free amino acid; $[\alpha]_D^{22}$ -16.6 (c 0.18, H_2O); υ_{max}/cm^{-1} (KBr disc) 3419w, 2926br, 1714s, 1630s; δ_H (300MHz; D_2O) 2.25 (1H, *ca.* dd, *J* 15 and 8Hz, $C\underline{H}_2CO_2H$), 2.42 (1H, *ca.* dd, *J* 15 and 4Hz, $C\underline{H}_2CO_2H$), 2.53-2.65 (1H, m, NCHC$\underline{H}$), 3.12-3.33 (2H, complex, $NC\underline{H}_2$, $NCH_2C\underline{H}$), 3.56 (1H, *ca.* dd, *J* 12 and 7Hz, $NC\underline{H}_2$), 3.64 (3H, s, Ar-$OC\underline{H}_3$), 3.89 (1H, d, *J* 9Hz, $C\underline{H}CO_2H$), 6.60-7.70 (4H, complex, Ar-$\underline{H}$); *m/z* (Electrospray) 281 (16%), 280 (MH^+, 100).

(2*S*,3*S*,4*R*)-3-Methylenecarboxy-4-(4-methoxyphenyl)pyrrolidine-2-carboxylic acid (43)

Procedure as for (2*S*,3*S*,4*S*)-3-methylenecarboxy-4-phenylpyrrolidine-2-carboxylic acid (**36**). A stirred mixture of (2*S*,3*S*,4*R*)-*N*-benzoyl-2-methoxycarbonyl-3-methoxycarbonylmethyl-4-(4-methoxyphenyl)-pyrrolidine (**35**) (9mg, 22μmol) and 6M hydrochloric acid (2ml) was heated under reflux for 16h. After purification by ion-exchange chromatography (Dowex 50W-X8 (H^+ form)) the solution was freeze-dried yielding (2*S*,3*S*, 4*R*)-3-methylenecarboxy-4-(4-methoxyphenyl)prrrolidine-2-carboxylic acid (**43**) (6mg, 96%) as a white solid. Free amino acid; $[\alpha]_D^{22}$ -13.2 (c 0.21, H_2O); υ_{max}/cm^{-1} (KBr disc) 3439w, 3144br, 1729s, 1614s, 1409s; δ_H (300MHz; D_2O) 2.31 (1H, *ca.* dd, *J* 15 and 7Hz, $C\underline{H}_2\ CO_2H$), 2.51 (1H, *ca.* dd, *J* 15 and 4Hz, $C\underline{H}_2CO_2H$), 2.51-2.63 (1H, m, NCHC$\underline{H}$), 3.10-3.31 (2H, complex, $NC\underline{H}_2$, $NCH_2C\underline{H}$), 3.53 (1H, *ca.* dd, *J* 10 and 7Hz, $NC\underline{H}_2$), 3.65 (3H, s, Ar-$OC\underline{H}_3$), 3.87 (1H, d, *J* 9Hz, $C\underline{H}CO_2H$), 6.82, 7.14 (2 x 2H, *ca.* ABq, *J* 12Hz, Ar-$\underline{H}$); *m/z* (Electrospray) 281 (18%), 280 (MH^+, 100), 234 (27).

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