Pergamon

Tetrahedron, Vol. 53, No. 14, pp. 5273-5290, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00192-0

Towards a Versatile Synthesis of Kainoids III : Efficient Methods for Control of C-4 Stereochemistry

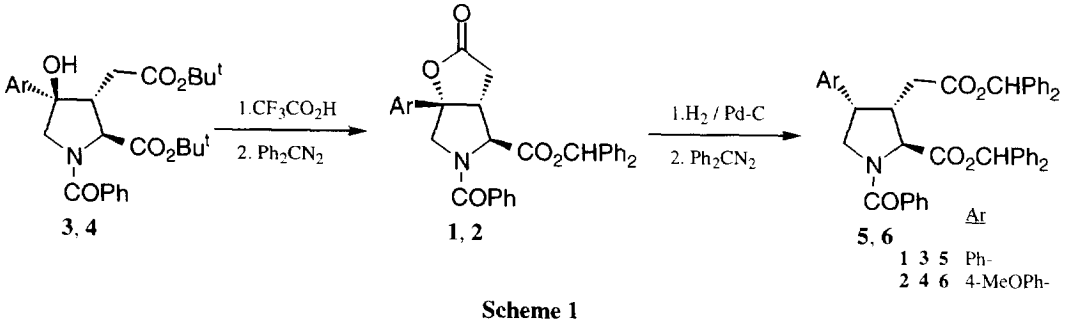
Jack E. Baldwin,*[a] Andrew M. Fryer,[a] Mark R. Spyvee,[a] Roger C. Whitehead[b] and Mark E. Wood[c]

[a]The Dyson Perrins Laboratory, South Parks Road, Oxford, OX1 3QY, U.K., [b]Department of Chemistry, University of Reading, Whiteknights, Reading, RG6 6AD, U.K. [c]Department of Chemistry, University of Exeter, Stocker Road, Exeter, EX4 4QD, U.K.

Abstract: Halo- and selenolactonisation methods were used to prepare benzylic lactones from enamide carboxylic acids. The lactones were subsequently cleaved with predominantly inversion of configuration at the benzylic centre to give protected acromelic analogues with the correct C-4 stereochemistry. Hydroxyl directed heterogeneous hydrogenation of related enamide carbinols gave total stereocontrol at C-4. © 1997 Elsevier Science Ltd.

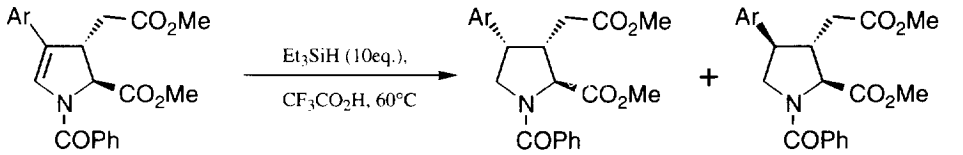
In the previous two papers[1] we described methods for the manipulation of *trans*-4-hydroxy-L-proline into compounds with suitable substitution patterns for conversion into acromelic acid analogues. After stereospecific introduction of the C-3 side-chain *via* an enamine alkylation, ketone functionality at C-4 was used to introduce various aryl substituents at this position in two different ways, appropriate methods being used in both cases to establish the required stereochemistry at this centre.

Firstly, lactones **1 / 2**, prepared by acid-mediated cyclisation of tertiary carbinols **3 / 4**, which were in turn, generated by Grignard addition to protected 4-ketoproline derivatives, were hydrogenolysed with inversion of configuration at the "benzylic" centre. Subsequent esterification with diphenyldiazomethane gave kainoid derivatives as their corresponding benzhydryl esters **5 / 6** (Scheme 1).



Scheme 1

Secondly, enamides **7** - **10**, formed by palladium (0) catalysed cross-coupling of arylboronic acids to a vinyl triflate, were reduced to protected kainoid derivatives **11** - **14** and their corresponding C-4 epimers **15** - **18** (Scheme 2).



7 - 10 **11 - 14** **15 - 18**

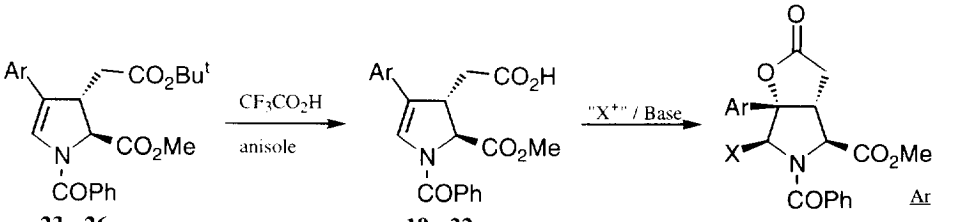
		Ar
7	**11** **15**	Ph-
8	**12** **16**	2-MeOPh-
9	**14** **17**	3-MeOPh-
10	**14** **18**	4-MeOPh-

Scheme 2

We report here, two further extensions of this methodology which increase the overall synthetic efficiency, particularly improving the efficiency of establishment of the required C-3 / C-4 *cis*- relative stereochemistry.

1. Halo- or Selenolactonisation / Hydrogenolysis

The efficiency of the palladium (0) catalysed cross-coupling reactions used to prepare enamides **7 - 10** and the apparent stereoselectivity of the lactone hydrogenolysis procedure described in the previous two papers[1] led us to attempt to combine these methodologies. The aim was to firstly lactonise in the presence of a suitable electrophile (X^+), enamide acids **19 - 22** (prepared from the corresponding *tert*-butyl esters **23 - 26** by acidolytic cleavage with trifluoroacetic acid as described previously[1]) with a view towards reducing the lactones produced using appropriate methods, depending on the nature of X (Scheme 3).

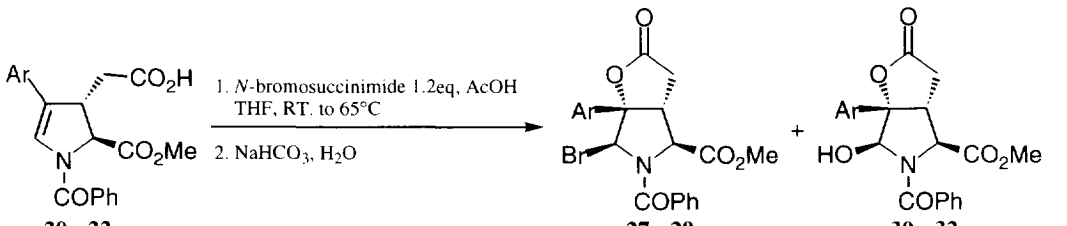


23 - 26 **19 - 22**

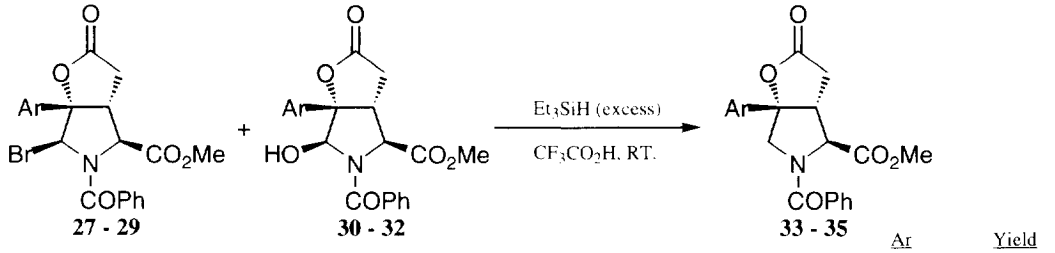
		Ar
19	**23**	Ph-
20	**24**	2-MeOPh-
21	**25**	3-MeOPh-
22	**26**	4-MeOPh-

Scheme 3

Attempts to use standard iodolactonisation[2] conditions gave rise to complex mixtures of apparently labile products so attention was turned to the use of bromolactonisation. The use of bromine as electrophile[3] gave inconsistent results but more success was encountered using *N*-bromosuccinimide.[4] Although reaction with the 4-phenyl enamide acid **19** appeared slow and very low yielding, some success was obtained for Ar = 3-MeOPh- **21** and more pleasing results with the Ar = 2-MeOPh- **20** and Ar = 4-MeOPh- **22** analogues. In all three cases, a mixture of two major products was obtained. These appeared relatively labile and were tentatively assigned (from crude ^{1}H NMR, IR and mass spectrometric data) as bromolactones **27 - 29** and the corresponding "hemiaminals" **30 - 32** (Scheme 4). These mixtures of products were reduced without further purification / characterisation using an excess of triethylsilane in trifluoroacetic acid to give the corresponding bicyclic lactones **33 - 35** (Scheme 5). (Yields are quoted over the two steps *ie.* lactonisation / reduction).



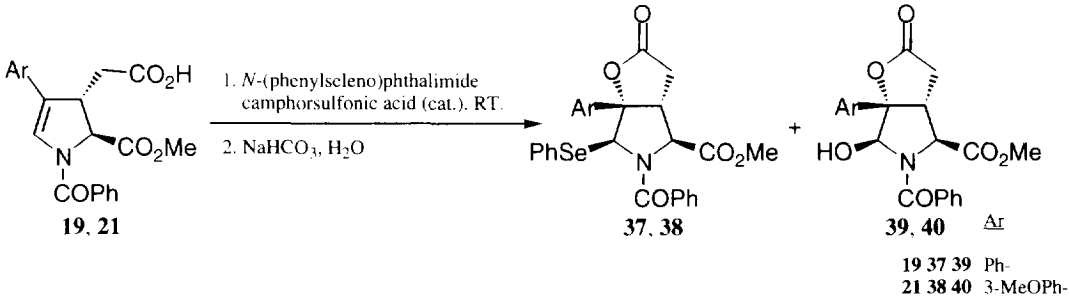
Scheme 4



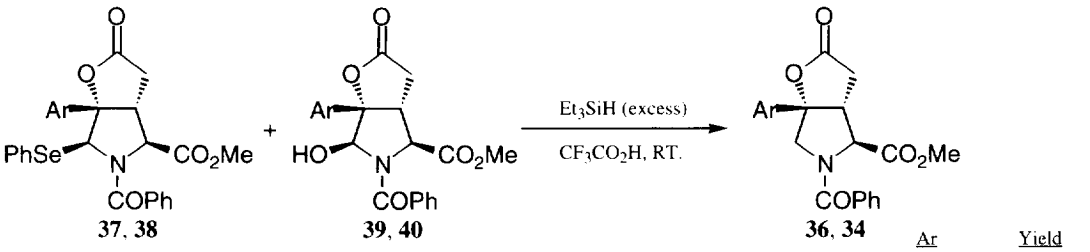
Scheme 5

The significantly lower yield obtained for the 3-MeOPh- analogue **34** and a failure to obtain significant conversion of the 4-Ph- enamide acid **19** when compared with the 2- and 4-MeOPh- derivatives (**20** and **22** respectively) can be explained by activation of the enamide double bond towards electrophilic attack in the latter two cases compared with the first two.

The use of a selenolactonisation[5] / reduction procedure however, gave much improved yields of the required lactones **34** and **36** as illustrated in Schemes 6 and 7. The products of the selenolactonisation step appeared to be the required selenolactones **37** and **38** and the corresponding "hemiaminals" **39** and **40** (Scheme 6). These were partially purified and then combined for reduction with triethylsilane in the presence of trifluoroacetic acid (Scheme 7).



Scheme 6

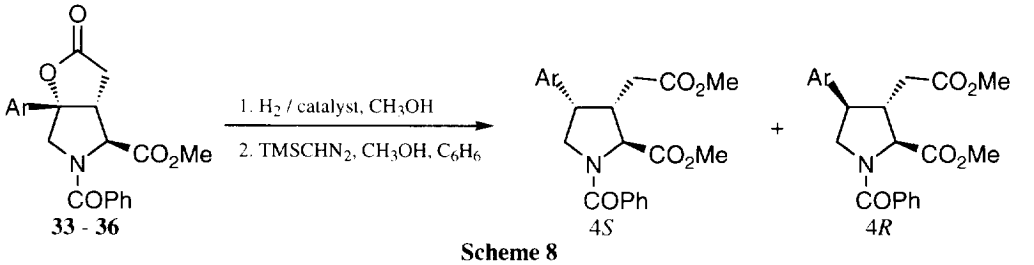


37, 38 **39, 40** **36, 34**

	Ar	Yield
37 39 36	Ph-	49%
38 40 34	3-MeOPh-	62%

Scheme 7

With the desired lactones **33** - **36** in hand, we attempted hydrogenolysis as reported earlier[1] under a variety of conditions. After hydrogenolysis, the free acids were esterified using trimethylsilyldiazomethane[6] and the ratio of C-4 epimers was determined by ^{1}H NMR. Yields in all cases were essentially quantitative (Scheme 8). The results are summarised in Table 1.



33 - 36 4*S* 4*R*

Scheme 8

Substrate	Ar	Catalyst	Pressure / atm.	4*S* : 4*R*
36	Ph-	20% Pd on C	1	10 : 1
		Pd black	1	5 : 1
33	2-MeOPh-	20% Pd on C	1	3 : 2
		Pd black	1	3 : 2
		$Pd(OH)_2$	2.25	1 : 1
		20% Pd on C	3.5	1 : 1
		20% Pd on C, $HClO_4$ (cat.)	1	2 : 3
34	3-MeOPh-	20% Pd on C	1	5 : 1
		Pd black	1	13 : 1
35	4-MeOPh-	20% Pd on C	1	4 : 1
		Pd black	1	12 : 1
		$Pd(OH)_2$	3.5	4 : 1
		Raney Ni	1	a
		20% Pd on C, $HClO_4$ (cat.)	1	3 : 1

[a] lactone hydrolysis occurred

Table 1

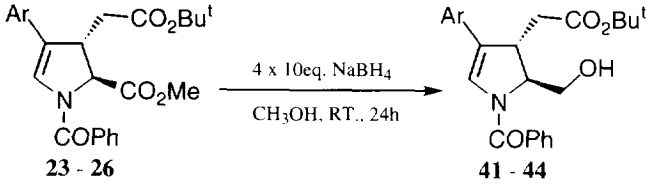
Firstly it was noted that the optimum ratio of 4*S* : 4*R* epimers was generally obtained at lower pressures of hydrogen. The choice of appropriate catalyst was found to depend on the nature of the aromatic

substituent at C-4 and in all cases studied for Ar = 2-MeOPh- **33**, the yield of the desired 4*S* epimer was disappointing. The reasons for these variations are as yet, unclear. The addition of catalytic quantities of perchloric acid caused a worsening of the 4*S* : 4*R* ratio and experiments carried out using Raney nickel (which would be expected to give predominantly, the 4*R* product[7]) resulted only in lactone hydrolysis despite exhaustive washing of the catalyst.

2. Hydroxyl Directed Enamide Hydrogenation

The benzylic lactone hydrogenolysis, although reasonably efficient for establishment of the required *S* stereochemistry at C-4 for some aryl substituents, did not satisfy the criterion of being applicable to a wide variety of systems. It was also felt that limiting the synthetic scheme to C-4 aryl substituents would also be too restrictive. We therefore turned our attention back to the reduction of enamides **23** - **26**.

Hydroxyl directed homogeneous hydrogenation is well known but the heterogeneous equivalent has also been reported.[8] To attempt such a process, the methyl esters of enamides **23** - **26** were firstly reduced chemoselectively using an excess of sodium borohydride in methanol (Scheme 9). The yields and selectivity obtained were good, the only disappointment being the large excess of sodium borohydride required to effect complete reduction. This is believed to be due to the reduction being relatively slow and hence competitive with destruction of the borohydride by methanol.



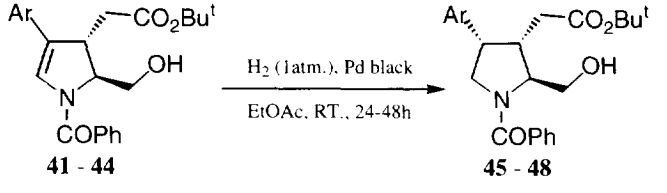
	Ar-	Yield
23 41	Ph-	91%
24 42	2-MeOPh-	80%
25 43	3-MeOPh-	80% [a]
26 44	4-MeOPh-	71%

[a] 94% based on recovered **25**

Scheme 9

Attempts to slow down the destruction of the borohydride using ethanol or *iso*-propanol as solvent unfortunately led to complex mixtures of products.

Heterogeneous catalytic hydrogenation of **41** - **44** using palladium black as catalyst gave excellent yields of carbinols **45** - **48** with only the required C-3 / C-4 *cis*- relative stereochemistry (Scheme 10).



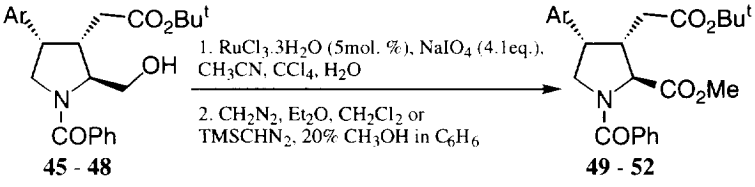
	Ar-	Yield
41 45	Ph-	91%
42 46	2-MeOPh-	89%
43 47	3-MeOPh-	89%
44 48	4-MeOPh-	85%

Scheme 10

This result is complementary to the reduction of enamide esters such as **23** which were found to be reduced almost exclusively from the face of the ring opposite the C-2 ester.

Primary carbinols **45** - **48** were subsequently re-oxidised using the ruthenium tetraoxide conditions reported by Sharpless.[9] The resulting carboxylic acids were esterified using either diazomethane or

trimethylsilyldiazomethane to give esters **49 - 52** which were unfortunately contaminated with small quantities of their corresponding 2*R* epimers (Scheme 11). Presumably, these epimers are the result of the C-2 proton being labile in the aldehyde intermediate formed during the oxidation. (Note: The aldehyde could be seen by thin layer chromatography during monitoring of the oxidation process).



45 - 48 49 - 52

	Ar-	Yield (2*S*)	2*S* : 2*R*
45 49	Ph-	47%	14 : 1
46 50	2-MeOPh-	53%	7 : 1
47 51	3-MeOPh-	62%	8 : 1
48 52	4-MeOPh-	71%	8 : 1

Scheme 11

Different oxidising methods were attempted, however it was found that the ruthenium tetraoxide method gave the most consistent results and most importantly, required the least chromatographic purification of the products. These results are summarised in Table 2. (Note: Yields are given for the mixture of 2*S* and 2*R* products after esterification of the acids with trimethylsilyldiazomethane as described earlier). Fortunately, the C-2 epimers obtained were easily separable by silica gel chromatography.

Oxidation method	Substrate	Ar	Yield	4*S*:4*R*
$RuCl_3.3H_2O$ (40mol.%) / $NaIO_4$	**46**	2-MeOPh-	57%	9 : 1
PDC (5eq.) / DMF (45°C)	**45**	Ph-	41%	1 : 0
PDC (5eq.) / DMF (45°C)	**46**	2-MeOPh-	24%	1 : 0
Jones[10] (CrO_3, c.H_2SO_4, H_2O, acetone)	**45**	Ph-	76%	8 : 1
Jones[10] (CrO_3, c.H_2SO_4, H_2O, acetone)	**46**	2-MeOPh-	83%	15 : 1
O_2 (1atm.) / PtO_2[11]	**46**	2-MeOPh-	0%	
O_2 (2atm.) / PtO_2[11]	**46**	2-MeOPh-	32%[a]	6 : 1

[a] 67% based on recovered starting material

Table 2

Deprotection to the corresponding amino acids was efficiently accomplished using 6M hydrochloric acid under reflux as reported previously with separation from the benzoic acid by-product being achieved by ion-exchange chromatography on Dowex resin (50X8).

To conclude, we have developed a short and potentially, highly versatile synthesis of acromelic acid analogues starting from relatively cheap and readily available *trans*-4-hydroxy-L-proline. The procedures are applicable to relatively large-scale work and should be suitable for the preparation of other kainoid derivatives.

Acknowledgements

We thank the EPSRC for a studentship to A.M.F., the EPSRC (formerly SERC) for a studentship to M.R.S. (and Zeneca for further support), 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[12] 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-5(*S*)-methoxycarbonyl-2-oxo-8(*S*)-(2-methoxyphenyl)-6-aza-1-oxa-4(*R*)-bicyclo [3.3.0] octane (33)

To a stirred solution of (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methylenecarboxy-4-(2-methoxyphenyl)-[4,5]-dehydropyrrolidine (**20**) (100mg, 0.25mmol) in tetrahydrofuran (3.5ml) at room temperature was added *N*-bromosuccinimide (65mg, 0.30mmol) and acetic acid (2 drops). After stirring at this temperature for 3.5h and at 50°C for 1h, the reaction mixture was evaporated to dryness *in vacuo* and the residue was taken up in ethyl acetate (10ml). The resulting solution was washed with saturated sodium bicarbonate solution (10ml), water (10ml) and brine (10ml) and was dried ($MgSO_4$), filtered and evaporated *in vacuo*. The crude product was dissolved in a mixture of trifluoroacetic acid (2ml) and triethylsilane (100μl, 0.63mmol) and after stirring at room temperature for 35min, the mixture was concentrated *in vacuo* and the

excess trifluoroacetic acid was removed by azeotropic distillation with toluene. The residue was purified by flash chromatography on silica gel (eluting with 9:1v/v dichloromethane : ethyl acetate) to give 6-benzoyl-5(*S*)-methoxycarbonyl-2-oxo-8(*S*)-(2-methoxyphenyl)-6-aza-1-oxa-4(*R*)-bicyclo [3.3.0] octane (**33**) as a pale yellow syrup (77mg, 77%); R_f 0.20 (9:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{21}$ -53.7 (c 0.68, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1787s, 1755s, 1641s, 1604m, 1418s; δ_H (300MHz; $CDCl_3$) 2.72-2.92 (2H, complex, $CHC\underline{H}_2CO_2$), 3.71-3.75 (1H, m, $C\underline{H}CH_2CO_2$), 3.85, 3.89 (2 x 3H, 2 x s, $C\underline{H}_3OAr$, $CHCO_2C\underline{H}_3$), 3.90 (1H, d, *J* 12Hz, $NC\underline{H}_2$), 4.32 (1H, d, *J* 12Hz, $NC\underline{H}_2$), 5.04 (1H, d, *J* 4Hz, $C\underline{H}CO_2CH_3$), 6.91-7.57 (9H, complex, Ar-H); δ_C (50.3MHz; $CDCl_3$) 35.36 ($CH\underline{C}H_2CO_2$), 46.36 ($\underline{C}HCH_2CO_2$), 52.67 ($CO_2\underline{C}H_3$), 55.12 ($\underline{C}H_3OAr$), 57.91 ($N\underline{C}H_2$), 65.36 ($\underline{C}HCO_2CH_3$), 93.73 ($NCH_2\underline{C}$), 111.47, 121.28, 124.44, 126.60, 127.61, 128.59, 130.72, 135.33 (Ar-C), 155.35 (Ar-$\underline{C}OCH_3$), 170.27, 170.81, 174.96 (3 x C=O); *m/z* (Probe CI, NH_3) 397 (20%), 396 (MH^+, 100), 336 (10), 105 (45); (Found MH^+ 396.1447, $C_{22}H_{22}NO_6$ requires 396.1447).

6-Benzoyl-5(*S*)-methoxycarbonyl-2-oxo-8(*S*)-(3-methoxyphenyl)-6-aza-1-oxa-4(*R*)-bicyclo [3.3.0] octane (34) Method 1 - Bromolactonisation

Procedure as for 6-benzoyl-5(*S*)-methoxycarbonyl-2-oxo-8(*S*)-(2-methoxyphenyl)-6-aza-1-oxa-4(*R*)-bicyclo [3.3.0] octane (**33**) above using (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methylenecarboxy-4-(3-methoxyphenyl)-[4,5]-dehydropyrrolidine (**21**) (100mg, 0.29mmol), *N*-bromosuccinimide (65mg, 0.30mmol) and acetic acid (2 drops) in tetrahydrofuran (3.5ml). Work-up was followed by reduction using triethylsilane (300µl, 1.86mmol) in trifluoroacetic acid (2ml) for 3h to give the crude product which was purified by flash chromatography on silica gel (eluting with 14:1v/v dichloromethane: ethyl acetate) to give 6-benzoyl-5(*S*)-methoxycarbonyl-2-oxo-8(*S*)-(3-methoxyphenyl)-6-aza-1-oxa-4(*R*)-bicyclo [3.3.0] octane (**34**) as a colourless oil (33mg, 33%); R_f 0.25 (9:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{23}$ -53.3 (c 1.16, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1790s, 1750s, 1647s, 1421s, 930s; δ_H (300MHz; $CDCl_3$) 2.72-2.92 (2H, complex, $CHC\underline{H}_2CO_2$), 3.31-3.37 (1H, m, $C\underline{H}CH_2CO_2$), 3.82, 3.90 (2 x 3H, 2 x s, $C\underline{H}_3OAr$, $CHCO_2C\underline{H}_3$), 4.08, 4.19 (2H, ABq, *J* 12Hz, $NC\underline{H}_2$), 4.93 (1H, d, *J* 2Hz, $C\underline{H}CO_2CH_3$), 6.73-7.80 (9H, complex, Ar-H); δ_C (125.8MHz; $CDCl_3$) 35.01 ($CH\underline{C}H_2CO_2$), 49.65 ($\underline{C}HCH_2CO_2$), 52.92 ($CO_2\underline{C}H_3$), 55.34 ($\underline{C}H_3OAr$), 61.28 ($N\underline{C}H_2$), 65.11 ($\underline{C}HCO_2CH_3$), 94.02 ($NCH_2\underline{C}$), 111.01, 112.91, 113.97, 114.38, 116.81, 127.40, 127.86, 128.46, 129.61, 130.18, 130.73, 138.29 (Ar-C), 160.03 (Ar-$\underline{C}OCH_3$), 169.89, 171.23, 173.79 (3 x C=O); *m/z* (Probe CI, NH_3) 396 (MH^+, 30%), 122 (28), 105 (100); (Found MH^+ 396.1447, $C_{22}H_{22}NO_6$ requires 396.1447).

6-Benzoyl-5(*S*)-methoxycarbonyl-2-oxo-8(*S*)-(4-methoxyphenyl)-6-aza-1-oxa-4(*R*)-bicyclo [3.3.0] octane (35)

Procedure as for 6-benzoyl-5(*S*)-methoxycarbonyl-2-oxo-8(*S*)-(2-methoxyphenyl)-6-aza-1-oxa-4(*R*)-bicyclo [3.3.0] octane (**33**) above using (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methylenecarboxy-4-(4-methoxyphenyl)-[4,5]-dehydropyrrolidine (**22**) (115mg, 0.29mmol), *N*-bromosuccinimide (62mg, 0.35mmol) and acetic acid (2 drops) in tetrahydrofuran (3.5ml). Work-up was followed by reduction using triethylsilane (115µl, 0.72mmol) in trifluoroacetic acid (2.5ml) for 3h to give the crude product which was purified by flash

chromatography on silica gel (eluting with 1:1v/v 40-60 petroleum ether : ethyl acetate) to give 6-benzoyl-5(*S*)-methoxycarbonyl-2-oxo-8(*S*)-(4-methoxyphenyl)-6-aza-1-oxa-4(*R*)-bicyclo [3.3.0] octane (**35**) as a colourless foam (92mg, 80%); R_f 0.20 (9:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{21}$ -48.3 (c 1.625, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1789s, 1750s, 1645s, 1418s; δ_H (300MHz; $CDCl_3$) 2.72-2.92 (2H, complex, $CHC\underline{H}_2CO_2$), 3.26-3.33 (1H, m, $C\underline{H}CH_2CO_2$), 3.79, 3.87 (2 x 3H, 2 x s, $C\underline{H}_3OAr$, $CHCO_2C\underline{H}_3$), 4.05, 4.16 (2H, ABq, *J* 13Hz, $NC\underline{H}_2$), 4.90 (1H, d, *J* 5Hz, $C\underline{H}CO_2CH_3$), 6.90, 7.29 (4H, ABq, *J* 9Hz, Ar-H), 7.30-7.55 (5H, complex, Ar-H); δ_C (50.3MHz; $CDCl_3$) 35.03 ($CH\underline{C}H_2CO_2$), 49.36 ($\underline{C}HCH_2CO_2$), 52.96 ($CO_2\underline{C}H_3$), 55.37 ($\underline{C}H_3OAr$), 61.16 ($N\underline{C}H_2$), 65.05 ($\underline{C}HCO_2CH_3$), 94.27 ($NCH_2\underline{C}$), 114.51, 126.31, 127.65, 128.52, 128.70, 130.98, 134.92 (Ar-C), 160.27 (Ar-$\underline{C}OCH_3$), 170.19, 171.67, 174.42 (3 x C=O); *m/z* (Probe CI, NH_3) 397 (20%), 396 (MH^+, 100), 105 (53); (Found MH^+ 396.1447, $C_{22}H_{22}NO_6$ requires 396.1447).

6-Benzoyl-5(*S*)-methoxycarbonyl-2-oxo-8(*S*)-phenyl-6-aza-1-oxa-4(*R*)-bicyclo [3.3.0] octane (36)

To a stirred solution of (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methylenecarboxy-4-phenyl-[4,5]-dehydropyrrolidine (**19**) (41mg, 0.11mmol) in dichloromethane (2ml) at room temperature was added *N*-(phenylseleno)phthalimide (41mg, 0.13mmol) and camphorsulfonic acid (2.5mg, 11μmol). After stirring at this temperature for 48h, a further portion of *N*-(phenylseleno)phthalimide (28mg, 88μmol) was added and stirring was continued at room temperature for a further 24h. The solvent was removed *in vacuo* and the residue was taken up in ethyl acetate (10ml), the resulting solution being washed with saturated aqueous sodium bicarbonate solution (10ml), water (10ml) and brine (10ml) and dried ($MgSO_4$), filtered and evaporated to dryness *in vacuo*. The residue was partially purified by flash chromatography on silica gel (eluting with 9:1v/v dichloromethane : ethyl acetate) to give two fractions (R_f 0.40 and R_f 0.35 (9:1v/v CH_2Cl_2 : EtOAc)) which were combined. This mixture of products was dissolved in a mixture of trifluoroacetic acid (2ml) and triethylsilane (42μl, 0.26mmol) and after stirring at room temperature for 1h, the mixture was concentrated *in vacuo* and the excess trifluoroacetic acid was removed by azeotropic distillation with toluene. The residue was purified by flash chromatography on silica gel (eluting with 9:1v/v dichloromethane : ethyl acetate) to give 6-benzoyl-5(*S*)-methoxycarbonyl-2-oxo-8(*S*)-phenyl-6-aza-1-oxa-4(*R*)-bicyclo [3.3.0] octane (**36**) as a white, crystalline solid (20mg, 49%); m.p. 124-125°C; R_f 0.25 (9:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{21}$ -68.4 (c 0.43, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1789s, 1747s, 1646s, 1603s, 1412s; δ_H (300MHz; $CDCl_3$) 2.74-2.95 (2H, complex, $CHC\underline{H}_2CO_2$), 3.31-3.39 (1H, m, $C\underline{H}CH_2CO_2$), 3.90 (3H, s, $CO_2C\underline{H}_3$), 4.10 (1H, *ca* d, *J* 13Hz, $NC\underline{H}_2$), 4.21 (1H, *ca* d, *J* 13Hz, $NC\underline{H}_2$), 4.95 (1H, d, *J* 4Hz, $C\underline{H}CO_2CH_3$), 7.36-7.57 (10H, complex, Ar-H); δ_C (125.8MHz; $CDCl_3$) 35.03 ($CH\underline{C}H_2CO_2$), 49.74 ($\underline{C}HCH_2CO_2$), 52.99 ($CO_3\underline{C}H_3$), 61.32 ($N\underline{C}H_2$), 65.13 ($\underline{C}HCO_2CH_3$), 94.19 ($NCH_2\underline{C}$), 124.75, 127.44, 128.48, 129.03, 130.78, 134.63, 136.57 (Ar-C), 169.92, 171.36, 173.91 (3 x C=O); *m/z* (Probe CI, NH_3) 367 (23%), 366 (MH^+, 100), 306 (12), 105 (64); (Found MH^+ 366.1341, $C_{21}H_{20}NO_5$ requires 366.1341).

6-Benzoyl-5(*S*)-methoxycarbonyl-2-oxo-8(*S*)-(3-methoxyphenyl)-6-aza-1-oxa-4(*R*)-bicyclo [3.3.0] octane (34) Method 2 - Selenolactonisation

Procedure as for 6-benzoyl-5(*S*)-methoxycarbonyl-2-oxo-8(*S*)-phenyl-6-aza-1-oxa-4(*R*)-bicyclo [3.3.0] octane (**36**) above using (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-methylenecarboxy-4-(3-methoxyphenyl)-[4,5]-dehydropyrrolidine (**21**) (71mg, 0.18mmol), a single portion of *N*-(phenylseleno)phthalimide (109mg, 0.36mmol) and camphorsulfonic acid (4.5mg, 18μmol) in dichloromethane (3ml). Work-up gave the crude product which was partially purified by flash chromatography on silica gel (eluting with 9:1v/v dichloromethane : ethyl acetate) to give two fractions (R_f 0.55 and 0.40 (9:1v/v CH_2Cl_2 : EtOAc)) which were combined. This mixture of products was dissolved in a mixture of trifluoroacetic acid (1ml) and triethylsilane (200μl, 1.25mmol) and after stiring at room temperature for 1h, the mixture was concentrated *in vacuo* and the excess trifluoroacetic acid was removed by azeotropic distillation with toluene. The residue was purified by flash chromatography on silica gel (eluting with 12:1v/v dichloromethane : ethyl acetate) to give 6-benzoyl-5(*S*)-methoxycarbonyl-2-oxo-8(*S*)-(3-methoxyphenyl)-6-aza-1-oxa-4(*R*)-bicyclo [3.3.0] octane (**34**) as a colourless oil (44mg, 62%). Physical data as reported in Method 1 above.

General procedure for benzylic lactone hydrogenolysis

A solution of the appropriate lactone (60μmol) in methanol (2ml) containing the required catalyst (*ca.* 50mol%) was vigorously stirred under an atmosphere of hydrogen from a balloon (or in a Fisher-Porter apparatus for higher pressures) until all of the starting material had been consumed (as assayed by thin layer chromatography). Reaction times were generally *ca.* 12-36h. The catalyst was removed on a Celite® pad and the methanol was removed *in vacuo*. The crude product was taken up into a mixture of methanol and benzene (20%v/v methanol, 2.5ml) and the resulting stirred solution was treated with a solution of trimethylsilyldiazomethane in hexanes (2.0M, 45μl, 90μmol). After stirring at room temperature for 1h, the reaction was quenched by the addition of glacial acetic acid (3 drops) and the mixture was concentrated *in vacuo*. Yields were essentially quantitative, the ratios of C-4 epimers being estimated by comparing integrals for the C-2 protons in the ^1H NMR spectrum of the crude product. Separation of the epimers could be achieved by flash chromatography on silica gel, physical data for the products being identical to that reported in the previous paper in this issue[1].

(2*S*,3*S*)-*N*-Benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-phenyl-[4,5]-dehydropyrrolidine (41)

To a stirred solution of (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenyl-[4,5]-dehydropyrrolidine (**23**) (100mg, 0.24mmol) in methanol (2.5ml) at room temperature was added sodium borohydride (360mg, 9.6mmol) in 4 equal portions over 24h. (Note: A further portion of methanol (2ml) was added after 12h). The reaction mixture was poured into saturated aqueous ammonium chloride solution (55ml) and the resulting mixture was extracted with ethyl acetate (5 x 40ml), the combined extracts being washed with 0.1M aqueous hydrochloric acid (55ml), saturated aqueous sodium bicarbonate solution

(55ml) and brine (55ml). The separated organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo* and the residue was purified by flash chromatography on silica gel (eluting with 3:2v/v dichloromethane : ethyl acetate) to give (2*S*,3*S*)-*N*-benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-phenyl-[4,5]-dehydropyrrolidine (**41**) as a white, crystalline solid (85mg, 91%); m.p. 156°C; R_f 0.50 (2:3v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{23}$ -117.5 (c 1.15, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3376 brw, 1720s, 1612s, 1600s, 1449m, 1423s, 1152s; δ_H (300MHz; $CDCl_3$) 1.49 (9H, s, $CO_2C(CH_3)_3$), 2.39 (1H, *ca* dd, *J* 16, 11Hz, $CH_2CO_2Bu^t$), 2.68 (1H, *ca* dd, *J* 16, 3Hz, $CH_2CO_2Bu^t$), 3.43-3.47 (1H, m, $CHCH_2CO_2Bu^t$), 4.88-4.03 (2H, 8 line m, CH_2OH), 4.30 (1H, brs, OH), 4.68-4.72 (1H, m, $CHCH_2OH$), 6.81 (1H, s, CH=C), 7.23-7.63 (10H, complex, Ar-H); δ_C (50.3MHz; $CDCl_3$) 28.03 ($CO_2C(CH_3)_3$), 38.47 ($CH_2CO_2Bu^t$), 41.65 ($CHCH_2CO_2Bu^t$), 65.80 (CH_2OH), 67.38 ($CHCH_2OH$), 81.65 ($CO_2C(CH_3)_3$), 125.32, 125.44, 127.72, 128.34, 128.86, 129.08, 131.34 (CH=C, CH=C, Ar-C), 169.22, 171.36 (2 x C=O); *m/z* (Probe CI, NH_3) 395 (20%), 394 (MH^+, 100), 338 (27), 105 (47); (Found MH^+ 394.2018, $C_{24}H_{28}NO_4$ requires 394.2018).

(2*S*,3*S*)-*N*-Benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(2-methoxyphenyl)-[4,5]-dehydropyrrolidine (42)

To a stirred solution of (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2-methoxyphenyl)-[4,5]-dehydropyrrolidine (**24**) (600mg, 1.33mmol) in methanol (15ml) at room temperature was added sodium borohydride (2.012g, 53.2mmol) in 4 equal portions over 24h. (Note: A further portion of methanol (15ml) was added after 12h). The reaction mixture was poured into saturated aqueous ammonium chloride solution (180ml) and the resulting mixture was extracted with ethyl acetate (4 x 100ml), the combined extracts being washed with 0.1M aqueous hydrochloric acid (180ml), saturated aqueous sodium bicarbonate solution (180ml) and brine (180ml). The separated organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo* and the residue was purified by flash chromatography on silica gel (eluting with 4:1v/v dichloromethane : ethyl acetate) to give (2*S*,3*S*)-*N*-benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(2-methoxyphenyl)-[4,5]-dehydropyrrolidine (**42**) as a colourless oil (449mg, 80%); R_f 0.51 (1:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{21}$ -73.7 (c 2.115, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3619w, 3362brw, 1720s, 1602s, 1575s, 1436s, 1423s, 1152s, 1029m; δ_H(300MHz; $CDCl_3$) 1.49 (9H, s, $CO_2C(CH_3)_3$), 2.36 (1H, *ca* dd, *J* 17, 11Hz, $CHCH_2CO_2Bu^t$), 2.66 (1H, *ca* dd, *J* 17, 3Hz, $CHCH_2CO_2Bu^t$), 3.47-3.50 (1H, m, $CHCH_2CO_2Bu^t$), 3.76 (3H, s, CH_3OAr), 3.88-4.08 (3H, complex, CH_2OH, CH_2OH), 4.59-4.65 (1H, m, $CHCH_2OH$), 6.86-7.69 (10H, complex, CH=C, Ar-H); δ_C (50.3MHz; $CDCl_3$) 27.99 ($CO_2C(CH_3)_3$), 38.55 ($CH_2CO_2Bu^t$), 42.54 ($CHCH_2CO_2Bu^t$), 55.15 (CH_3OAr), 66.15 ($CHCH_2OH$), 66.38 (CH_2OH), 81.42 ($CO_2C(CH_3)_3$), 110.98, 120.95, 121.21, 122.56, 127.64, 128.04, 128.20, 128.44, 128.59, 129.05, 131.25, 135.00 (CH=C, CH=C, Ar-C) 157.42 (Ar-$COCH_3$), 169.22, 171.45 (2 x C=O); *m/z* (APCI+) 424 (MH^+, 3%), 406 (4), 369 (20), 368 (100), 350 (28), 202 (10), 105 (7); (Found MH^+ 424.2124, $C_{25}H_{30}NO_5$ requires 424.2124).

(2*S*,3*S*)-*N*-Benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(3-methoxyphenyl)-[4,5]-dehydropyrrolidine (43)

To a stirred solution of (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(3-methoxyphenyl)-[4,5]-dehydropyrrolidine (**25**) (164mg, 0.36mmol) in methanol (4ml) at room temperature was added sodium borohydride (552mg, 14.6mmol) in 4 equal portions over 24h. (Note: A further portion of methanol (2ml) was added after 12h). The reaction mixture was poured into saturated aqueous ammonium chloride solution (60ml) and the resulting mixture was extracted with ethyl acetate (4 x 40ml), the combined extracts being washed with 0.1M aqueous hydrochloric acid (100ml), saturated aqueous sodium bicarbonate solution (100ml) and brine (100ml). The separated organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo* and the residue was purified by flash chromatography on silica gel (eluting with 8:5v/v dichloromethane : ethyl acetate) to give (2*S*,3*S*)-*N*-benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(3-methoxyphenyl)-[4,5]-dehydropyrrolidine (**43**) as a colourless oil (123mg, 80%) (Note: (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(3-methoxyphenyl)-[4,5]-dehydropyrrolidine (**25**) (16mg, 35μmol, 10%) was also recovered); R_f 0.50 (1:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{21}$ -96.7 (c 1.09, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3363brw, 1723s, 1600s, 1577s, 1452m, 1423s, 1154s; δ_H (300MHz; $CDCl_3$) 1.48 (9H, s, $CO_2C(C\underline{H}_3)_3$), 2.39 (1H, *ca* dd, *J* 16, 11Hz, $CHC\underline{H}_2CO_2Bu^t$), 2.71 (1H, *ca* dd, *J* 16, 3Hz, $CHC\underline{H}_2CO_2Bu^t$), 3.40-3.44 (1H, m, $C\underline{H}CH_2CO_2Bu^t$), 3.79 (3H, s, $C\underline{H}_3OAr$), 3.83-4.01 (2H, m, $C\underline{H}_2OH$), 4.26-4.30 (1H, m, $CH_2O\underline{H}$), 4.65-4.70 (1H, m, $C\underline{H}CH_2OH$), 6.76-7.61 (10H, complex, C<u>H</u>=C, Ar-<u>H</u>); δ_C (50.3MHz; $CDCl_3$) 28.04 ($CO_2C(\underline{C}H_3)_3$), 38.52 ($\underline{C}H_2CO_2Bu^t$), 41.73 ($\underline{C}HCH_2CO_2Bu^t$), 55.29 ($\underline{C}H_3OAr$), 65.82 ($\underline{C}H_2OH$), 67.42 ($\underline{C}HCH_2OH$), 81.65 ($CO_2\underline{C}(CH_3)_3$), 111.68, 112.40, 118.01, 125.69, 128.34, 128.87, 130.13, 131.36, 133.91, 135.01 (<u>C</u>H=C, CH=<u>C</u>, Ar-<u>C</u>), 160.19 (Ar-<u>C</u>OCH$_3$), 169.26, 171.35 (2 x <u>C</u>=O); *m/z* (APCI+) 406 (MH^+-H_2O, 5%), 369 (22), 368 (100), 350 (23), 246 (7), 186 (8), 105 (7); (Found MH^+-H_2O 406.2020, $C_{25}H_{28}NO_4$ requires 406.2020).

(2*S*,3*S*)-*N*-Benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(4-methoxyphenyl)-[4,5]-dehydropyrrolidine (44)

To a stirred solution of (2*S*,3*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(4-methoxyphenyl)-[4,5]-dehydropyrrolidine (**26**) (309mg, 0.685mmol) in methanol (8ml) at room temperature was added sodium borohydride (777mg, 20.6mmol) in 4 equal portions over 24h. (Note: A further portion of methanol (4ml) was added after 12h). The reaction mixture was poured into saturated aqueous ammonium chloride solution (100ml) and the resulting mixture was extracted with ethyl acetate (4 x 60ml), the combined extracts being washed with 0.1M aqueous hydrochloric acid (100ml), saturated aqueous sodium bicarbonate solution (100ml) and brine (100ml). The separated organic phase was dried ($MgSO_4$), filtered and evaporated *in vacuo* and the residue was purified by flash chromatography on silica gel (eluting with 3:2v/v dichloromethane : ethyl acetate) to give (2*S*,3*S*)-*N*-benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(4-methoxyphenyl)-[4,5]-dehydropyrrolidine (**44**) as a pale yellow foam (205mg, 71%); R_f 0.45 (1:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{21}$ -83.5 (c 1.57, $CHCl_3$); υ_{max}/cm^{-1} 3691w, 3360brw, 1723s, 1607s, 1424s, 1152s; δ_H (300MHz; $CDCl_3$) 1.48 (9H, s, $CO_2C(C\underline{H}_3)_3$), 2.37 (1H, *ca* dd, *J* 17, 11Hz, $CHC\underline{H}_2CO_2Bu^t$), 2.67 (1H, *ca* dd,

J 17, 3Hz, $CHCH_2CO_2Bu^t$), 3.38-3.41 (1H, m, $CHCH_2CO_2Bu^t$), 3.78 (3H, s, CH_3OAr), 3.86-4.00 (3H, complex, CH_2OH, CH_2OH), 4.62-4.68 (1H, m, $CHCH_2OH$), 6.67-7.61 (10H, complex, CH=C, Ar-H); δ_C (50.3MHz; $CDCl_3$) 28.03 ($CO_2C(CH_3)_3$), 38.50 ($CHCH_2CO_2Bu^t$), 41.86 ($CHCH_2CO_2Bu^t$), 55.28 (CH_3OAr), 65.77 (CH_2OH), 67.25 ($CHCH_2OH$), 81.57 ($CO_2C(CH_3)_3$), 114.47 (CH=C), 123.64, 124.91, 126.75, 128.31, 128.81, 131.21, 135.19 (Ar-C), 159.36 (Ar-$COCH_3$); 168.97, 174.10 (2 x C=O); *m/z* (APCI+) 424 (MH^+, 9%), 406 (22), 369 (19), 368 (100), 350 (22), 105 (7); (Found, MH^+ 424.2124 $C_{25}H_{30}NO_5$ requires 424.2124).

(2*S*,3*S*,4*S*)-*N*-Benzoyl-2-hydroxymethyl-3-methoxycarbonylmethyl-4-phenylpyrrolidine (45)

A solution of (2*S*,3*S*)-*N*-benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-phenyl-[4,5]-dehydropyrrolidine (**41**) (85mg, 0.22mmol) in ethyl acetate (4ml) containing palladium black (31mg, 0.29mmol) was stirred under an atmosphere of hydrogen from a balloon for 20h. The reaction mixture was filtered through a Celite® plug and evaporated to dryness *in vacuo*, the residue being purified by flash chromatography on silica gel (eluting with 3:2v/v dichloromethane : ethyl acetate) to give (2*S*,3*S*,4*S*)-*N*-benzoyl-2-hydroxymethyl-3-methoxycarbonylmethyl-4-phenylpyrrolidine (**45**) as a colourless oil (78mg, 91%); R_f 0.35 (2:3v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{23}$ -77.1 (c 1.59, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3360brw, 1721s, 1612s, 1602s, 1424s, 1370m, 1154s; δ_H (300MHz; $CDCl_3$) 1.41 (9H, s, $CO_2C(CH_3)_3$), 1.85 (1H, *ca* dd, *J* 18, 10Hz, $CHCH_2CO_2Bu^t$), 2.30 (1H, *ca* dd, *J* 18, 5Hz, $CHCH_2CO_2Bu^t$), 2.68-2.80 (1H, m, $CHCH_2CO_2Bu^t$), 3.53-3.59 (1H, m, CHPh), 3.70 (1H, *ca* dd, *J* 12, 2Hz, CH_2OH), 3.86 (1H, *ca* dd, *J* 12, 6Hz, NCH_2), 3.95 (1H, *ca* dd, *J* 12, 2Hz, CH_2OH), 4.01 (1H, *ca* dd, *J* 12, 6Hz, NCH_2), 4.09-4.15 (1H, m, $CHCH_2OH$), 4.18 (1H, brs, OH), 6.94-7.58 (10H, complex, Ar-H); δ_C (50.3MHz; $CDCl_3$) 27.93 ($CO_2C(CH_3)_3$), 34.59 ($CHCHCO_2Bu^t$), 41.39 ($CHCH_2CO_2Bu^t$), 45.25 (CHPh), 56.43 (NCH_2), 64.58 ($CHCH_2OH$), 65.40 (CH_2OH), 80.92 ($CO_2C(CH_3)_3$), 127.32, 127.46, 127.81, 128.53, 128.71, 129.07, 130.69, 136.38, 139.96 (Ar-C), 171.73, 172.47 (2 x C=O); *m/z* (Probe CI, NH_3) 397 (16%), 396 (MH^+, 72), 322 (17), 105 (100); (Found MH^+ 396.2175, $C_{24}H_{30}NO_4$ requires 396.2175).

(2*S*,3*S*,4*S*)-*N*-Benzoyl-2-hydroxymethyl-3-methoxycarbonylmethyl-4-(2-methoxyphenyl)pyrrolidine (46)

A solution of (2*S*,3*S*)-*N*-benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(2-methoxyphenyl)-[4,5]-dehydropyrrolidine (**42**) (482mg, 1.14mmol) in ethyl acetate (15ml) containing palladium black (177mg, 1.66mmol) was stirred under an atmosphere of hydrogen from a balloon for 48h. The reaction mixture was filtered through a Celite® plug and evaporated to dryness *in vacuo*, the residue being purified by flash chromatography on silica gel (eluting with 1:1v/v dichloromethane : ethyl acetate) to give (2*S*,3*S*,4*S*)-*N*-benzoyl-2-hydroxymethyl-3-methoxycarbonylmethyl-4-(2-methoxyphenyl)pyrrolidine (**46**) as a colourless oil (432mg, 89%); R_f 0.20 (2:3v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{21}$ -97.5 (c 1.00, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3345brw, 1723s, 1611s, 1601s, 1424s, 930s; δ_H (300MHz; $CDCl_3$) 1.40 (9H, s, $CO_2C(CH_3)_3$), 1.98-2.19 (2H, 8 line m, $CHCH_2CO_2Bu^t$), 2.82-2.91 (1H, m, $CHCH_2CO_2Bu^t$), 3.62-3.71 (1H, m, CHAr), 3.77 (3H, s, CH_3OAr), 3.88-3.98 (4H, complex, CH_2OH, NCH_2), 4.14-4.22 (1H, m, $CHCH_2OH$), 4.75 (1H, brs, OH),

6.82-7.56 (9H, complex, Ar-H); δ_C (50.3MHz; $CDCl_3$) 27.93 ($CO_2C(CH_3)_3$), 34.84 ($CHCH_2CO_2Bu^t$), 39.02 ($CHCH_2CO_2Bu^t$), 40.28 (CHAr), 55.37 (CH_3OAr, NCH_2), 65.87 (CH_2OH, $CHCH_2OH$), 80.79 ($CO_2C(CH_3)_3$), 110.59, 120.95, 127.22, 127.46, 127.69, 128.11, 128.48, 128.63, 130.43, 136.74 (Ar-C), 157.46 (Ar-$COCH_3$), 171.86, 172.54 (2 x C=O); *m/z* (APCI+) 427 (9%), 426 (MH^+, 32), 408 (7), 371 (20), 370 (100), 353 (22), 352 (98), 248 (19); (Found MH^+ 426.2280, $C_{25}H_{32}NO_5$ requires 426.2280).

(2*S*,3*S*,4*S*)-*N*-Benzoyl-2-hydroxymethyl-3-methoxycarbonylmethyl-4-(3-methoxyphenyl)pyrrolidine (47)

A solution of (2*S*,3*S*) -*N*-benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(3-methoxyphenyl)-[4,5]-dehydropyrrolidine (**43**) (115mg, 0.27mmol) in ethyl acetate (4ml) containing palladium black (43mg, 0.40mmol) was stirred under an atmosphere of hydrogen from a balloon for 48h (Note: More palladium black (20mg, 0.19mmol) was added after 24h). The reaction mixture was filtered through a Celite® plug and evaporated to dryness *in vacuo*, the residue being purified by flash chromatography on silica gel (eluting with 4:3v/v dichloromethane : ethyl acetate) to give (2*S*,3*S*,4*S*)-*N*-benzoyl-2-hydroxymethyl-3-methoxycarbonylmethyl-4-(3-methoxyphenyl)pyrrolidine (**47**) as a white, crystalline solid (103mg, 89%); m.p. 113°C; R_f 0.35 (1:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{21}$ -86.0 (c 1.375, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 3693w, 3631w, 3379brw, 1721s, 1602s, 1425s, 1154s; δ_H (300MHz; $CDCl_3$) 1.43 (9H, s, $CO_2C(CH_3)_3$), 1.90 (1H, *ca* dd, *J* 17, 10Hz, $CHCH_2CO_2Bu^t$), 2.30 (1H, *ca* dd, *J* 17, 5Hz, $CHCH_2CO_2Bu^t$), 2.65-2.78 (1H, m, $CHCH_2CO_2Bu^t$), 3.33-3.54 (2H, complex, CHAr, CH_2OH), 3.70-4.03 (4H, complex, NCH_2, CH_2OH), 4.07-4.15 (1H, m, $CHCH_2OH$), 6.50-7.58 (9H, complex, Ar-H); δ_C (50.3MHz; $CDCl_3$) 27.92 ($CO_2C(CH_3)_3$), 34.54 ($CHCH_2CO_2Bu^t$), 41.32 ($CHCH_2CO_2Bu^t$), 45.25 (CHAr), 55.08 (CH_3OAr), 56.36 (NCH_2), 64.60 ($CHCH_2OH$), 65.41 (CH_2OH), 80.96 ($CO_2C(CH_3)_3$), 112.67, 113.53, 120.00, 127.36, 128.71, 130.06, 130.74, 136.30, 141.48 (Ar-C), 160.15 (Ar-$COCH_3$), 171.77, 172.46 (2 x C=O); *m/z* (APCI+) 426 (MH^+, 15%), 371 (19) 370 (100), 353 (10), 352 (46), 248 (13); (Found MH^+ 426.2280, $C_{25}H_{32}NO_5$ requires 426.2280).

(2*S*,3*S*,4*S*)-*N*-Benzoyl-2-hydroxymethyl-3-methoxycarbonylmethyl-4-(4-methoxyphenyl)pyrrolidine (48)

A solution of (2*S*,3*S*) -*N*-benzoyl-2-hydroxymethyl-3-*tert*-butoxycarbonylmethyl-4-(4-methoxyphenyl)-[4,5]-dehydropyrrolidine (**44**) (202mg, 0.48mmol) in ethyl acetate (7ml) containing palladium black (74mg, 0.70mmol) was stirred under an atmosphere of hydrogen from a balloon for 48h (Note: More palladium black (20mg, 0.19mmol) was added after 24h). The reaction mixture was filtered through a Celite® plug and evaporated to dryness *in vacuo*, the residue being purified by flash chromatography on silica gel (eluting with 1:1v/v dichloromethane : ethyl acetate) to give (2*S*,3*S*,4*S*)-*N*-benzoyl-2-hydroxymethyl-3-methoxycarbonylmethyl-4-(4-methoxyphenyl)pyrrolidine (**48**) as a white, crystalline solid (172mg, 85%); m.p. 142°C R_f 0.35 (1:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{21}$ -111.3 (c 1.045, $CHCl_3$); υ_{max}/cm^{-1} 3695w, 3363brw, 1721s, 1612s, 1427s, 1154s, 929s; δ_H (300MHz; $CDCl_3$) 1.41 (9H, s, $CO_2C(CH_3)_3$), 1.86 (1H, *ca* dd, *J* 17, 10Hz, $CHCH_2CO_2Bu^t$), 2.29 (1H, *ca* dd, *J* 17, 5Hz, $CHCH_2CO_2Bu^t$), 2.64-2.76 (1H, m, $CHCH_2CO_2Bu^t$), 3.48-3.52 (1H, m, CHAr), 3.63-4.10 (6H, complex, CH_2OH, CH_2OH,

NCH_2, $CHCH_2OH$), 3.76 (3H, s, CH_3OAr), 6.77-7.57 (9H, complex, Ar-H); δ_C (50.3MHz; $CDCl_3$) 27.87 ($CO_2C(CH_3)_3$), 34.56 ($CHCH_2CO_2Bu^t$), 41.28 ($CHCH_2CO_2Bu^t$), 44.48 (CHAr), 55.11 (CH_3OAr), 56.60 (NCH_2), 64.27 ($CHCH_2OH$), 64.80 (CH_2OH), 80.75 ($CO_2C(CH_3)_3$), 114.23, 127.28, 128.59, 128.73, 130.56, 131.87, 136.35 (Ar-C), 158.79 (Ar-$COCH_3$), 171.72, 172.19 (2 x C=O); *m/z* (APCI+) 426 (MH^+, 4%), 408 (4), 371 (17), 370 (83), 353 (21), 352 (100), 248 (18), 105 (5); (Found MH^+ 426.2280, $C_{25}H_{32}NO_5$ requires 426.2280).

(2*S*,3*S*,4*S*)-*N*-Benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenylpyrrolidine (49)

To a solution of (2*S*,3*S*,4*S*)-*N*-benzoyl-2-hydroxymethyl-3-methoxycarbonylmethyl-4-phenylpyrrolidine (**45**) (54mg, 0.14mmol) in a mixture of acetonitrile (300µl), carbon tetrachloride (300µl) and water (450µl) was added sodium metaperiodate (120mg, 0.56mmol) and ruthenium trichloride hydrate (2mg, 7.6µmol). The biphasic mixture was stirred vigorously for 18h after which time, the separated aqueous phase was extracted with dichloromethane (4 x 5ml) and the combined organic phases were dried ($MgSO_4$), filtered and evaporated to dryness *in vacuo*. Trimethylsilyldiazomethane (2M solution in hexanes, 105µl, 0.21mmol) was added to a solution of the crude product in a mixture of benzene / methanol (4:1v/v, 2.5ml) and after stirring the mixture at room temperature for 40min, the reaction was quenched by the addition of glacial acetic acid (3 drops). The crude product was found to contain a mixture of (2*S*,3*S*,4*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenylpyrrolidine (**49**) and (2*R*,3*S*,4*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenylpyrrolidine in a ratio of 14:1 (as determined by 300MHz ^1H NMR). Purification by flash chromatography on silica gel (eluting with 13:1v/v dichloromethane : ethyl acetate) gave (2*S*,3*S*,4*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-phenylpyrrolidine (**49**) as a white, crystalline solid (27mg, 47%); m.p. 108°C; R_f 0.35 (9:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{23}$ -42.4 (c 1.40, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1741s, 1723s, 1632s, 1422s, 1370s, 1153s; δ_H (300MHz; $CDCl_3$) 1.43 (9H, s, $CO_2C(CH_3)_3$), 1.92 (1H, *ca* dd, *J* 17, 9Hz, $CHCH_2CO_2Bu^t$), 2.42 (1H, *ca* dd, *J* 17, 6Hz, $CHCH_2CO_2Bu^t$), 3.00-3.08 (1H, m, $CHCH_2CO_2Bu^t$), 3.70-3.83 (2H, complex, CHPh, NCH_2), 3.82 (3H, s, CO_2CH_3), 4.18 (1H, *ca* dd, *J* 11, 6Hz, NCH_2), 4.40 (1H, d, *J* 9Hz, $CHCO_2CH_3$), 6.96-7.67 (10H, complex, Ar-H); δ_C (125.8MHz; $CDCl_3$), 27.95 ($CO_2C(CH_3)_3$), 34.34 ($CHCH_2CO_2Bu^t$), 42.91 ($CHCH_2CO_2Bu^t$), 46.01 (CHPh), 52.46 (CO_2CH_3), 54.93 (NCH_2), 62.94 ($CHCO_2CH_3$), 80.87 ($CO_2C(CH_3)_3$), 127.35, 127.56, 128.32, 128.83, 130.49, 135.43, 138.75 (Ar-C), 169.60, 170.80, 171.91 (3 x C=O); *m/z* (Probe CI, NH_3) 424 (MH^+, 27%), 368 (26), 105 (100); (Found MH^+ 424.2124, $C_{25}H_{30}NO_5$ requires 424.2124).

(2*S*,3*S*,4*S*)-*N*-Benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2-methoxyphenyl)pyrrolidine (50)

To a solution of (2*S*,3*S*,4*S*)-*N*-benzoyl-2-hydroxymethyl-3-methoxycarbonylmethyl-4-(2-methoxyphenyl)pyrrolidine (**46**) (300mg, 0.71mmol) in a mixture of acetonitrile (1.4ml), carbon tetrachloride (1.4ml) and water (2.3ml) was added sodium metaperiodate (598mg, 2.79mmol) and ruthenium trichloride hydrate (9mg, 34.4µmol). The biphasic mixture was stirred vigorously for 24h after which time, the separated

aqueous phase was extracted with dichloromethane (4 x 20ml) and the combined organic phases were dried ($MgSO_4$), filtered and evaporated to dryness *in vacuo*. A solution of diazomethane in diethyl ether (20ml, excess, from Diazald®) was added to a solution of the crude product in dichloromethane (10ml) and after stirring the mixture at room temperature for 30min, the reaction was quenched by the addition of glacial acetic acid (10 drops). The crude product was found to contain a mixture of (2*S*,3*S*,4*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2-methoxyphenyl)pyrrolidine (**50**) and (2*R*,3*S*,4*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2-methoxyphenyl)pyrrolidine in a ratio of 7:1 (as determined by 300MHz ^1H NMR). Purification by flash chromatography on silica gel (eluting with 9:1v/v dichloromethane : ethyl acetate) gave (2*S*,3*S*,4*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(2-methoxyphenyl)pyrrolidine (**50**) as a white, crystalline solid (169mg, 53%); R_f 0.20 (9:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{21}$ -69.5 (c 0.975, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1742s, 1724s, 1631s, 1422s, 1152s, 929m; δ_H (300MHz; $CDCl_3$) mixture of rotamers - major resonances only quoted, 1.39 (9H, s, $CO_2C(C\underline{H}_3)_3$), 2.07 (1H, *ca* dd, *J* 17, 7Hz, $CHC\underline{H}_2CO_2Bu^t$), 2.23 (1H, *ca* dd, *J* 17, 8Hz, $CHC\underline{H}_2CO_2Bu^t$), 3.13-3.24 (1H, m, $C\underline{H}CO_2Bu^t$), 3.72-4.13 (3H, complex, $NC\underline{H}_2$, $C\underline{H}Ar$), 3.76, 3.81 (2 x 3H, 2 x s, $CO_2C\underline{H}_3$, $C\underline{H}_3OAr$), 4.45 (1H, d, *J* 7Hz, $C\underline{H}CO_2CH_3$), 6.82-7.65 (9H, complex, Ar-H); δ_C (50.3MHz; $CDCl_3$) 27.93 ($CO_2C(\underline{C}H_3)_3$), 34.56 ($CH\underline{C}H_2CO_2Bu^t$), 39.97 ($\underline{C}HCH_2CO_2Bu^t$), 41.77 ($\underline{C}HAr$), 52.39 ($CO_2\underline{C}H_3$), 53.79 ($N\underline{C}H_2$), 55.38 ($\underline{C}H_3OAr$), 64.01 ($\underline{C}HCO_2CH_3$), 80.81 ($CO_2\underline{C}(CH_3)_3$), 110.65, 120.93, 126.70, 127.53, 127.71, 128.05, 128.53, 128.64, 130.56, 136.06 (Ar-$\underline{C}$), 157.53 (Ar-$\underline{C}OCH_3$), 170.13, 171.19, 172.53 (3 x C=O); *m/z* (APCI+) 455 (13%), 454 (MH^+, 44), 399 (25), 398 (98), 339 (22), 338 (100), 104 (14); (Found MH^+ 454.2230, $C_{26}H_{32}NO_6$ requires 454.2230).

(2*S*,3*S*,4*S*)-*N*-Benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(3-methoxyphenyl)pyrrolidine (51)

To a solution of (2*S*,3*S*,4*S*)-*N*-benzoyl-2-hydroxymethyl-3-methoxycarbonylmethyl-4-(3-methoxyphenyl)pyrrolidine (**47**) (146mg, 0.34mmol) in a mixture of acetonitrile (700µl), carbon tetrachloride (700µl) and water (1ml) was added sodium metaperiodate (294mg, 1.37mmol) and ruthenium trichloride hydrate (3.5mg, 13.4µmol). The biphasic mixture was stirred vigorously for 20h after which time, the separated aqueous phase was extracted with dichloromethane (4 x 10ml) and the combined organic phases were dried ($MgSO_4$), filtered and evaporated to dryness *in vacuo*. A solution of diazomethane in diethyl ether (8ml, excess, from Diazald®) was added to a solution of the crude product in dichloromethane (8ml) and after stirring the mixture at room temperature for 1h, the reaction was quenched by the addition of glacial acetic acid (5 drops). The crude product was found to contain a mixture of (2*S*,3*S*,4*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(3-methoxyphenyl)pyrrolidine (**51**) and (2*R*,3*S*,4*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(3-methoxyphenyl)pyrrolidine in a ratio of 8:1 (as determined by 300MHz ^1H NMR). Purification by flash chromatography on silica gel (eluting with 13:1v/v dichloromethane : ethyl acetate) gave (2*S*,3*S*,4*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(3-methoxyphenyl)pyrrolidine (**51**) as a white, crystalline solid (97mg, 62%); m.p. 125°C; R_f 0.25 (9:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{21}$ -40.3 (c 1.525, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1738s, 1723s,

1632s, 1418s, 1155s, 930m; δ_H (300MHz; $CDCl_3$) mixture of rotamers - major resonances only quoted, 1.43 (9H, s, $CO_2C(C\underline{H}_3)_3$), 1.96 (1H, *ca* dd, *J* 18, 9Hz, $CHC\underline{H}_2CO_2Bu^t$), 2.42 (1H, *ca* dd, *J* 18, 6Hz, $CHC\underline{H}_2CO_2Bu^t$), 2.95-3.09 (1H, m, $C\underline{H}CH_2CO_2Bu^t$), 3.65-4.19 (3H, complex, $C\underline{H}Ar$, $NC\underline{H}_2$), 3.75, 3.82 (2 x 3H, 2 x s, $C\underline{H}_3OAr$, $CO_2C\underline{H}_3$), 4.39 (1H, d, *J* 9Hz, $C\underline{H}CO_2CH_3$), 6.51-7.66 (9H, complex, Ar-H); δ_C (50.3MHz; $CDCl_3$) 27.87 ($CO_2\underline{C}(CH_3)_3$, 34.25 ($CH\underline{C}H_2CO_2Bu^t$), 42.81 ($\underline{C}HCH_2CO_2Bu^t$), 45.94 ($\underline{C}HAr$), 52.45 ($CO_2\underline{C}H_3$), 54.86 ($N\underline{C}H_2$), 55.03 ($\underline{C}H_3OAr$), 62.94 ($\underline{C}HCO_2CH_3$), 80.97 ($CO_2\underline{C}(CH_3)_3$), 112.67, 113.53, 119.91, 126.74, 127.55, 128.53, 130.03, 130.17, 130.74, 135.58, 140.49 (Ar-C), 160.12 (Ar-$\underline{C}OCH_3$). 169.89, 171.15, 172.25 (3 x C=O); *m/z* (APCI+) 455 (10%), 454 (MH^+, 34), 399 (20), 398 (100), 339 (14), 338 (72), 105 (19); (Found MH^+ 454.2230, $C_{26}H_{32}NO_6$ requires 454.2230).

(2*S*,3*S*,4*S*)-*N*-Benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(4-methoxyphenyl)pyrrolidine (52)

To a solution of (2*S*,3*S*,4*S*)-*N*-benzoyl-2-hydroxymethyl-3-methoxycarbonylmethyl-4-(4-methoxyphenyl)pyrrolidine (**48**) (168mg, 0.40mmol) in a mixture of acetonitrile (800µl), carbon tetrachloride (800µl) and water (1.3ml) was added sodium metaperiodate (339mg, 1.58mmol) and ruthenium trichloride hydrate (5mg, 19.1µmol). The biphasic mixture was stirred vigorously for 20h after which time, the separated aqueous phase was extracted with dichloromethane (4 x 10ml) and the combined organic phases were dried ($MgSO_4$), filtered and evaporated to dryness *in vacuo*. A solution of diazomethane in diethyl ether (8ml, excess, from Diazald®) was added to a solution of the crude product in dichloromethane (8ml) and after stirring the mixture at room temperature for 1h, the reaction was quenched by the addition of glacial acetic acid (5 drops). The crude product was found to contain a mixture of (2*S*,3*S*,4*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(4-methoxyphenyl)pyrrolidine (**52**) and (2*R*,3*S*,4*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(4-methoxyphenyl)pyrrolidine in a ratio of 8:1 (as determined by 300MHz ^1H NMR). Purification by flash chromatography on silica gel (eluting with 13:1v/v dichloromethane : ethyl acetate) gave (2*S*,3*S*,4*S*)-*N*-benzoyl-2-methoxycarbonyl-3-*tert*-butoxycarbonylmethyl-4-(3-methoxyphenyl)pyrrolidine (**52**) as a colourless oil (128mg, 71%); R_f 0.25 (9:1v/v CH_2Cl_2 : EtOAc); $[\alpha]_D^{21}$ -46.0 (c 1.465, $CHCl_3$); υ_{max}/cm^{-1} ($CHCl_3$) 1742s, 1724s, 1631s, 1422s, 1369m, 1153s; δ_H (300MHz; $CDCl_3$) mixture of rotamers - major resonances only quoted, 1.43 (9H, s, $CO_2C(C\underline{H}_3)_3$), 1.93 (1H, *ca* dd, *J* 17, 9Hz, $CHC\underline{H}_2CO_2Bu^t$), 2.41 (1H, *ca* dd, *J* 17, 6Hz, $CHC\underline{H}_2CO_2Bu^t$), 2.92-3.04 (1H, m, $C\underline{H}CH_2CO_2Bu^t$), 3.63-4.18 (3H, complex, $NC\underline{H}_2$, $C\underline{H}Ar$), 3.77, 3.81 (2 x 3H, 2 x s, $C\underline{H}_3OAr$, $CO_2C\underline{H}_3$), 4.37 (1H, d, *J* 9Hz, $C\underline{H}CO_2CH_3$), 6.79-7.66 (9H, complex, Ar-H); δ_C (50.3MHz; $CDCl_3$) 27.92 ($CO_2C(\underline{C}H_3)_3$), 34.30 ($CH\underline{C}H_2CO_2Bu^t$), 42.99 ($\underline{C}HCH_2CO_2Bu^t$), 45.28 ($\underline{C}HAr$), 52.48 ($CO_2\underline{C}H_3$), 55.19 ($\underline{C}H_2N$, $\underline{C}H_3OAr$), 62.94 ($\underline{C}HCO_2CH_3$), 80.95 ($\underline{C}(CH_3)_3$), 114.36, 126.79, 127.61, 128.57, 128.82, 129.02, 130.75, 130.93, 135.70 (Ar-C), 159.02 (Ar-$\underline{C}OCH_3$), 169.97, 171.25, 172.34 (3 x C=O); *m/z* (APCI+) 455 (18%), 454 (MH^+, 62), 399 (22), 398 (100), 339 (10), 338 (53), 105 (14); (Found MH^+ 454.2230, $C_{26}H_{32}NO_6$ requires 454.2230).

References

1. See previous two papers in this issue.
2. Gonzalez, F. B.; Bartlett, P. A. *Org. Synth., Coll. Vol. VII*, **1990**, 164-167.
3. Conditions employed were identical to those used for iodolactonisation.[2]
4. Jew, S.-S.; Terashima, S.; Koga, K. *Tetrahedron*, **1979**, *35*, 2337-2343.
5. Nicolaou, K.C. *Tetrahedron*, **1981**, *37*, 4097-4109.
6. Shioiri, T.; Aoyama, T. *Chem. Pharm. Bull.*, **1991**, *29*, 3249-3255.
7. Khan, A. M.; McQuillin, F. J.; Jardine, I. *J. Chem. Soc. (C)*, **1967**, 136-139.
8. For example, see: Kunzer, H.; Sauer, G.; Wiechert, R. *Tetrahedron Lett.*, **1991**, *32*, 743-746.
9. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.*, **1981**, *46*, 3936-3938.
10. Jones oxidation method used was identical to that used in a synthesis of (-)-α-kainic acid except for an extended reaction time (18h); Cooper, J.; Knight, D. W.; Gallagher, P. T. *J. Chem. Soc., Perkin Trans. 1*, **1992**, 553-559.
11. Marino, J. P.; de la Pradilla, R. F.; Laborde, E. *J. Org. Chem.*, **1987**, *52*, 4898-4913.
12. Derome, A. E., *Modern NMR Techniques for Chemistry Research*, Pergamon Press, Oxford, 1987.

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