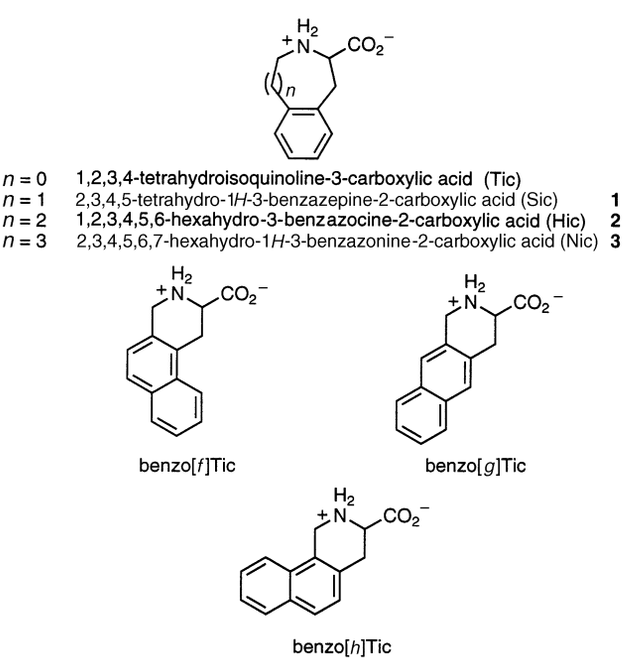
Synthesis of conformationally constrained phenylalanine analogues *via* 7-, 8- and 9-*endo* Heck cyclisations

Susan E. Gibson (née Thomas),*[a] Nathalie Guillo,[a] Richard J. Middleton,[a] Audrey Thuilliez[a] and Matthew J. Tozer[b]

[a] *Department of Chemistry, Imperial College of Science, Technology and Medicine, South Kensington, London SW7 2AY, UK*
[b] *James Black Foundation, 68 Half Moon Lane, Dulwich, London SE24 9JE, UK*

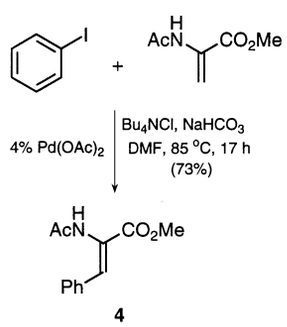
The novel conformationally constrained phenylalanine analogues 2,3,4,5-tetrahydro-1*H*-3-benzazepine-2-carboxylic acid (Sic) 1, 1,2,3,4,5,6-hexahydro-3-benzazocine-2-carboxylic acid (Hic) 2 and 2,3,4,5,6,7-hexahydro-1*H*-3-benzazonine-2-carboxylic acid (Nic) 3 have been synthesised from commercially available 2-iodobenzyl alcohol in 20, 18 and 22% overall yield respectively *via* 7-, 8- and 9-*endo* Heck cyclisations.

Restricting the conformational freedom of peptides often leads to a modification of their biological activity and may result in high potency/selectivity at biological receptors and increased stability with respect to enzymatic degradation.[1] 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (Tic) is a commonly used replacement for phenylalanine.[2] Incorporation of Tic into a peptide not only restricts the conformational freedom of the aromatic ring but also places constraints on the peptide backbone.[2a] These effects provide valuable insight into the bioactive conformation of a peptide ligand[2] and often lead to potent and selective compounds.[2a,c–e] For example, H-Tyr-Tic-Phe-OH is a highly potent and selective delta opioid antagonist.[2e] The value of Tic in studies of this type recently led to the synthesis of benzo[*f*]Tic, benzo[*g*]Tic and benzo[*h*]Tic, which were designed to probe in more detail the regions of receptors responsible for interacting with the Tic side chain.[3]



It is anticipated that 2,3,4,5-tetrahydro-1*H*-3-benzazepine-2-carboxylic acid (Sic) **1**, 1,2,3,4,5,6-hexahydro-3-benzazocine-2-carboxylic acid (Hic) **2** and 2,3,4,5,6,7-hexahydro-1*H*-3-benzazonine-2-carboxylic acid (Nic) **3**, together with Tic, will provide a useful series of compounds for probing bioactive conformations of peptide ligands. Although a few analogues of **1** have been synthesised and tested as antithrombotics,[4] and a small number of analogues of **1** have been formed by low-yielding ring-expansion methods with no regioselectivity,[5] to the best of our knowledge the classes of compounds to which **2** and **3** belong have not been synthesised to date.

The intermolecular Heck coupling of aryl halides and didehydroalanine derivatives to give (*Z*)-didehydrophenylalanine derivatives such as **4** is well established.[6] We thus postulated



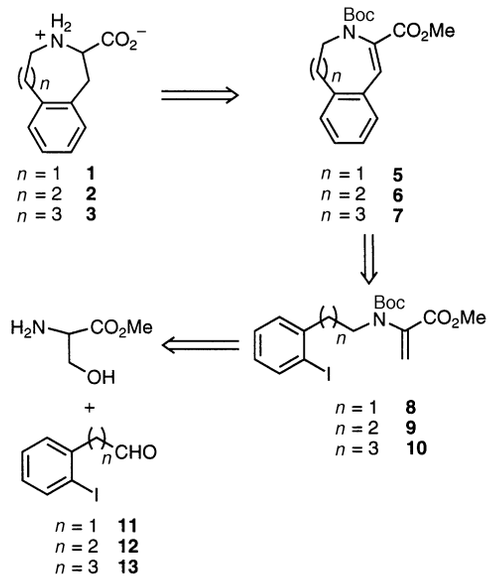
4

that it may be possible to use an intramolecular version of this reaction as the basis of a synthetic approach to the medium-sized rings **1**–**3**. The results of our studies, which led to the synthesis of the seven-, eight- and nine-membered ring amino acids **1**–**3**, are described herein. (Some preliminary results from this work have been published in communication form.[7])

Results and discussion

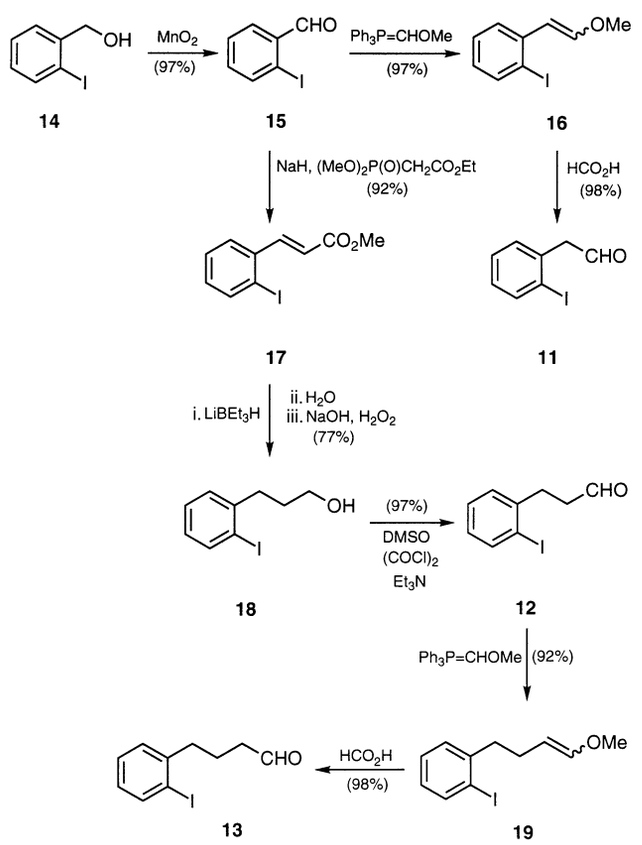
Our retrosynthetic analysis of the cyclic amino acids **1**–**3** is shown in Scheme 1. Thus, functional group protection and introduction of a double bond gave the unsaturated cyclic amino acids **5**–**7**, which it was anticipated could be obtained from the acyclic precursors **8**–**10** *via* Heck reactions, provided that these proceeded intramolecularly to give the required medium-sized rings rather than intermolecularly to give dimers and polymers, and that the cyclisations occurred *via endo* rather than *exo* pathways. Addition of water to the alkene of the Heck substrates **8**–**10**, *N*-deprotection and disconnection of a carbon–nitrogen bond revealed (±)-serine methyl ester and the iodo aldehydes **11**–**13**.

Our initial targets were thus the known iodo aldehydes **11**[8] and **12**[9] and the novel iodo aldehyde **13**. These were all readily synthesised from 2-iodobenzaldehyde **15**[10] which was generated



Scheme 1

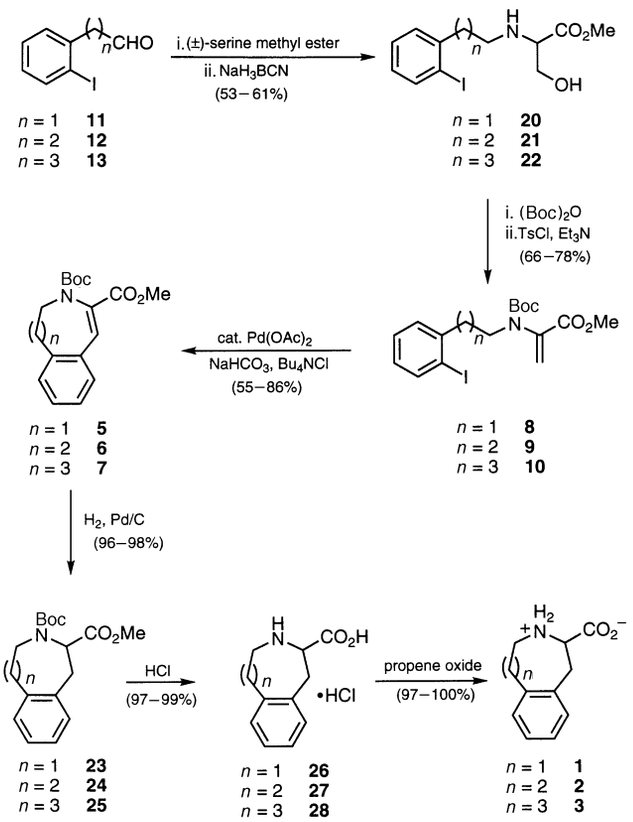
from commercially available 2-iodobenzyl alcohol **14** in high yield (97%) by oxidation with manganese dioxide (Scheme 2). One-carbon homologation of aldehyde **15** was achieved in



Scheme 2

excellent overall yield (95% from **15**) by reaction with (methoxymethyl)triphenylphosphonium chloride–potassium *tert*-butoxide to give the novel vinyl ether **16** followed by acid hydrolysis of **16** to give the desired aldehyde **11**, whilst two-carbon homologation of **15** was achieved in acceptable overall yield (69% from **15**) by reaction with trimethyl phosphonoacetate–sodium hydride to give the unsaturated ester **17** followed by lithium triethylborohydride reduction of **17**[11] to alcohol **18**[9,12] and Swern oxidation of the alcohol to the desired aldehyde **12**.[9] A subsequent one-carbon homologation of aldehyde **12** proceeded smoothly *via* the novel vinyl ether **19** to give the required aldehyde **13** in acceptable overall yield (62% from aldehyde **15**).

Reductive amination of aldehydes **11**–**13** with (±)-serine methyl ester proved to be the most problematic step in the synthesis of amino acids **1**–**3**. After investigating several sets of



conditions, it was eventually found that premixing (±)-serine methyl ester hydrochloride and potassium acetate in isopropyl alcohol in the presence of 3 Å molecular sieves for 15 min at room temperature, followed by addition of the appropriate aldehyde and stirring for 40 min at room temperature, and finally the addition of sodium cyanoborohydride and stirring for 14–15 h at room temperature gave the best results. After work-up, the required novel secondary amines **20**–**22** were obtained in acceptable yield (53–61%). Nitrogen protection of amines **20**–**22** and introduction of the carbon–carbon double bond required for the Heck coupling were achieved in one pot by addition of di-*tert*-butyl dicarbonate to the appropriate amine followed by treatment of the reaction mixture with tosyl chloride–triethylamine. Work-up gave the novel Heck substrates **8**–**10** in good yield (66–78%).

The intramolecular version of the Heck reaction has attracted considerable attention over the last decade and there are now many elegant and impressive examples of its use in organic synthesis.[13] Examination of this literature reveals that (i) in the overwhelming majority of cases, products resulting from an *exo* cyclisation pathway are isolated in preference to products that would result from an *endo* cyclisation pathway, and (ii) attention has been focussed almost completely on the formation of five- and six-membered rings although interest in the formation of medium-sized rings *via* the Heck reaction is now increasing.[14] Preliminary studies on the Heck reactions required to synthesise the target amino acids **1**–**3**, using the *N*-acetyl analogues of substrates **8**–**10**, had led to conditions that produced the desired *endo* products in satisfactory yields (54, 60 and 58% for the seven-, eight- and nine-membered products

Table 1 Yields obtained (%) for the Heck cyclisation of substrate **8** to the seven-membered ring **5** using 15 mol% $Pd(OAc)_2$ at temperature T (°C) and concentration C (mol dm^{-3})

C/mol dm^{-3}	T/°C	Yield (%)
0.075	95	31
	105	46
0.050	95	43
	105	53–57
	110	59
	115	55
	120	55
0.025	105	56

Table 2 Yields obtained (%) for the Heck cyclisation of substrate **9** to the eight-membered ring **6** using 10 mol% $Pd(OAc)_2$ at temperature T (°C) and concentration C (mol dm^{-3})

C/mol dm^{-3}	T/°C	Yield (%)
0.075	100	59
	105	60
0.050	105	70
	110	65
0.025	105	71
	110	74

respectively) but required more of the expensive palladium acetate catalyst (20, 15 and 10 mol% respectively) than was desirable on a synthetic scale.[7] A series of optimisation studies for the cyclisations of substrates **8**–**10** were thus performed.

The optimisation studies (Tables 1–3) focussed on the effect of changing the temperature, substrate concentration and catalyst loading for the Heck reactions of substrates **8**–**10**. Initially, substrate **8** was reacted with 15 mol% $Pd(OAc)_2$ at two temperatures (95 and 105 °C) using two different substrate concentrations (0.075 and 0.050 M). The isolated yields of product **5** from these reactions (Table 1) indicated that the higher temperature and the lower concentration were more effective. Experiments which lowered the concentration and raised the temperature still further suggested that there was little to be gained by further dilution and that the 105–110 °C temperature range was probably optimum. The amount of $Pd(OAc)_2$ used was then varied whilst the substrate concentration and temperature were kept constant at 0.050 M and 110 °C respectively. From the results of this study, shown in Table 4, it was decided to use 10 mol% of $Pd(OAc)_2$ for the preparative scale cyclisation of **8** to **5**. Thus cyclisation of **8** using 10 mol% $Pd(OAc)_2$ at 110 °C and 0.05 M substrate concentration gave the novel seven-membered product **5** in 55% yield. The effect of temperature and substrate concentration on the cyclisation of substrate **9** was investigated using 10 mol% $Pd(OAc)_2$ over the ranges 100–110 °C and 0.075–0.025 M. From the results obtained from six experiments (Table 2), 105 °C and 0.050 M were selected for further experiments. Thus the effect of varying the amount of $Pd(OAc)_2$ used at 105 °C and 0.050 M substrate concentration over the range 10–1 mol% was investigated. On the basis of the yields of **6** obtained in these experiments (Table 4), the preparative scale cyclisation of substrate **9** was performed using 5 mol% $Pd(OAc)_2$ at 105 °C and 0.05 M substrate concentration. These conditions gave a 73% yield of the desired novel eight-membered product **6**. Finally, the initial temperature and concentration study for the cyclisation of substrate **10** was carried out using 2.5 mol% $Pd(OAc)_2$ over the ranges 105–115 °C and 0.075–0.025 M (Table 3). A temperature of 110 °C and a concentration of 0.050 M were selected for the catalyst loading study, which was carried out over the range 5–1 mol% and

Table 3 Yields obtained (%) for the Heck cyclisation of substrate **10** to the nine-membered ring **7** using 2.5 mol% $Pd(OAc)_2$ at temperature T (°C) and concentration C (mol dm^{-3})

C/mol dm^{-3}	T/°C	Yield (%)
0.075	105	81
0.050	105	85
	110	89
	115	81
0.025	105	86
	110	85

Table 4 Yields obtained (%) for the cyclisation of substrates **8**–**10** ($C = 0.050$ mol dm^{-3}) to products **5**–**7** using varying amounts of $Pd(OAc)_2$ catalyst (mol%)

$Pd(OAc)_2$ (mol%)	Yield of **5**[a] (%)	Yield of **6**[b] (%)	Yield of **7**[c] (%)
20	55		
15	59		
10	54	70	
5	49	69	81
2.5	41	63	89
1	22	58	58

[a] $T = 110$ °C. [b] $T = 105$ °C. [c] $T = 110$ °C.

gave the yields of **7** indicated in Table 4. On the basis of the results obtained in this study the preparative scale cyclisation of substrate **10** to product **7** was carried out at 110 °C with a substrate concentration of 0.050 M using 2.5 mol% $Pd(OAc)_2$. This gave the desired novel nine-membered ring product **7** in 86% yield.

In summary, after optimisation, cyclisation of substrates **8**, **9** and **10** to give the seven-, eight and nine-membered cyclic products **5**, **6** and **7** proceeded in good to excellent yield (55, 73 and 86% respectively) using acceptable amounts of palladium catalyst (10, 5 and 2.5 mol% respectively). From these results and the results displayed in Table 4, it is clear that the palladium catalyst becomes dramatically more effective as the size of the ring formed increases from seven to nine. The relative difficulty in forming the seven-membered ring is tentatively attributed to a competing degradative 6-*exo* pathway that effectively removes significant quantities of the substrate and/or the palladium catalyst from the productive manifold.

Conversion of the Heck cyclisation products into the desired amino acids **1**–**3** proceeded smoothly. Hydrogenation of **5**–**7** gave the novel saturated systems **23**–**25** (96–98%), acid hydrolysis of **23**–**25** gave the deprotected salts **26**–**28** (97–99%), and finally, propene oxide mediated removal of hydrogen chloride gave the novel amino acids Sic **1**, Hic **2** and Nic **3** (97–100%). Thus, Sic, Hic and Nic were obtained in 20, 18 and 22% overall yield respectively from commercially available 2-iodobenzyl alcohol.

Experimental

N,*N*-Dimethylformamide (DMF) was stirred over barium oxide and then alumina, distilled under reduced pressure and stored over molecular sieves. Dichloromethane (DCM) was distilled from calcium hydride. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Isopropyl alcohol was stirred over calcium oxide, distilled from more calcium oxide and stored over molecular sieves. Diethyl ether was stored over sodium wire. Dry dimethyl sulfoxide was purchased from Aldrich Chemical Company. Oxalyl chloride was freshly distilled at atmospheric pressure under nitrogen. Sodium hydride was purchased as an oil dispersion (60% oil suspension), washed with hexane, decanted and filtered three times before

use. Triethylamine was distilled from and stored over potassium hydroxide pellets. Potassium *tert*-butoxide was sublimed under reduced pressure. Light petroleum refers to the fraction boiling at 40–60 °C. The hydrogen used in the hydrogenation was BOC Grade O.

Melting points, which are uncorrected, were determined using an Electrothermal IA9100 Digital or a Gallenkamp capillary melting point apparatus. Elemental analyses were performed by the Imperial College Microanalytical Service. IR Spectra were obtained on Perkin-Elmer 1710 and Mattson 5000 FTIR spectrometers. NMR Spectra were recorded in $CDCl_3$ at room temperature (unless noted otherwise) on JEOL GSX 270, Bruker DRX 300, Bruker DRX 400 and Bruker AM-500 spectrometers. Chemical shifts are given in ppm and *J* values in Hz. Mass spectra were recorded on VG Micromass 7070E and Kratos MS890MS instruments.

For the sake of clarity in the assignment of spectra, the carbon atoms in the aromatic rings of the iodinated compounds, the cyclised products and their derivatives have been numbered. The carbon atom bearing the iodine atom is 'C-1', the carbon atom bearing the methylene tether 'C-2' and so on round the ring. In the cyclised products of the intramolecular Heck reaction and their derivatives the carbon atom bearing the methylene tether remains as 'C-2' and the carbon atom which bore the iodine but is now part of the new carbon–carbon bond is 'C-1'. The numbering continues around the ring as before.

2-Iodobenzaldehyde 15[10]

2-Iodobenzyl alcohol **14** (50.0 g, 0.214 mol) and manganese(IV) oxide (500 g, 5.7 mmol) were heated to reflux in chloroform (2 dm^3) for 3 days. The reaction mixture was then filtered through Kieselguhr. The solvent was removed *in vacuo* to give a yellow oil which slowly solidified to give the title compound as a brown crystalline solid (48.2 g, 0.208 mol, 97%), mp 38–39 °C (lit.,[10] 37 °C); ν_{max}(Nujol)/cm^{-1} 1703s (C=O); δ_H(270 MHz) 7.29 (1 H, dd, *J* 8, 8, H-5), 7.47 (1 H, dd, *J* 8, 8, H-4), 7.88 (1 H, d, *J* 8, H-3), 7.96 (1 H, d, *J* 8, H-6) and 10.07 (1 H, s, CHO); $\delta_C\{^1H\}$ (125 MHz) 100.7 (C-1), 128.7, 130.3, 135.4 (C-3, 4, 5), 135.1 (C-2), 140.7 (C-6) and 197.7 (CHO); *m*/*z* (EI, 70 eV, 200 °C) 232 (M^+, 100%), 231 (M − H, 31), 203 (M − CHO, 19), 104 (M − H − I, 38) and 76 (M − I − CHO, 24).

(*E*)- and (*Z*)-1-(2-Iodophenyl)-2-methoxyethene 16

Potassium *tert*-butoxide (27.2 g, 0.24 mmol) was added portionwise to a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (93.8 g, 0.27 mol) in THF (200 cm^3) under nitrogen in an ice bath. After stirring the red solution at room temperature for 30 min, 2-iodobenzaldehyde **15** (28.2 g, 0.121 mol) in THF (150 cm^3) was added *via* a cannula. The reaction mixture was stirred at room temperature for 12 h and its colour was seen to change from dark red to an opaque yellow–brown. Saturated aqueous ammonium chloride (200 cm^3) was added with stirring. The organic layer was decanted and the aqueous layer was extracted with diethyl ether (3 × 100 cm^3). The combined organic layers were washed with water (200 cm^3), dried ($MgSO_4$) and evaporated *in vacuo* to give a viscous brown oil. Upon addition of light petroleum, triphenylphosphine oxide precipitated. It was removed by vacuum filtration on Kieselguhr and the filtrate concentrated under vacuum. The precipitation, filtration and evaporation procedure was repeated until no further precipitation of triphenylphosphine oxide occurred. The oil was then subjected to vacuum distillation which yielded the *title compound* as a pale yellow oil [30.4 g, 0.117 mmol, 97%, (*E*):(*Z*) = 1.2:1], bp 106–120 °C (at ~1 mmHg) [Found: *m*/*z* (MH^+) 260.9777. $C_9H_{10}IO$ requires *M*, 260.9776]; ν_{max}(neat)/cm^{-1} 1636s (C=C), 1237m (C–O–C) and 1094m (C–O); δ_H(270 MHz) 3.74 [3 H, s, (*E*)- or (*Z*)-CH_3], 3.78 [3 H, s, (*E*)- or (*Z*)-CH_3], 5.46 [1 H, d, *J* 7, (*Z*)-C*H*OCH_3], 5.98 [1 H, d, *J* 13, (*E*)-C*H*OCH_3], 6.24 [1 H, d, *J* 7, (*Z*)-C*H*=CHOCH_3], 6.82–6.88 [2 H, m, (*E*)- and (*Z*)-H-4], 6.92 [1 H, d, *J* 13, (*E*)-C*H*=CHOCH_3], 7.24–7.33 [2 H, m, (*E*)- and (*Z*)-H-5], 7.82 [2 H, ddd, *J* 7.9, 1.5, 1.7, (*E*)- and (*Z*)-H-3] and 7.98 [2 H, dd, *J* 7.9, 1.7, (*E*)- and (*Z*)-H-6]; $\delta_C\{^1H\}$ (67.9 MHz) 56.5 [(*E*)-OCH_3], 60.7 [(*Z*)-OCH_3], 99.4 [(*Z*)-C-1], 99.7 [(*E*)-C-1], 109.0 [(*Z*)-*C*HOCH_3], 109.4 [(*E*)-*C*HOCH_3], 125.1, 127.3 × 2, 127.9, 128.3, 129.5 [(*E*)- and (*Z*)-C-3, 4, 5], 138.2 [(*Z*)-C-2], 139.1 [(*Z*)-C-6], 139.3 [(*E*)-C-2], 139.5 [(*E*)-C-6] 149.0 [(*Z*)-CH=*C*HOCH_3] and 150.5 [(*E*)-CH=*C*HOCH_3]; *m*/*z* (CI, NH_3) 279 (MNH_4^+, 34%), 261 (MH, 100) and 246 (MH − CH_3, 61).

(2-Iodophenyl)ethanal 11[8]

Formic acid (115 cm^3) was added to a pale yellow solution of (*E*)- and (*Z*)-1-(2-iodophenyl)-2-methoxyethene **16** (31.5 g, 0.121 mol) in DCM (230 cm^3). Upon addition, the solution immediately deepened to a bright yellow colour. The reaction was stirred at room temperature in a foil-covered vessel for 64 h. Water (125 cm^3) was then added to the reaction mixture and the two layers mixed and allowed to separate. The organic layer was removed and the aqueous layer extracted with DCM (2 × 50 cm^3). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (2 × 150 cm^3) and brine (150 cm^3), dried (Na_2SO_4) and evaporated *in vacuo* to give the title compound as a brown oil (29.0 g, 0.118 mol, 98%) which needed no further purification [Found: *m*/*z* (M^+) 245.9542. C_8H_7IO requires *M*, 245.9542]; ν_{max}(neat)/cm^{-1} 1723vs (C=O); δ_H(270 MHz) 3.89 (2 H, d, *J* 1.7, CH_2), 7.01 (1 H, ddd, *J* 8, 8, 1.7, H-5), 7.23 (1 H, dd, *J* 8, 1.7, H-3), 7.35 (1 H, ddd, *J* 8, 8, 1.2, H-4), 7.90 (1 H, dd, *J* 8, 1.2, H-6) and 9.78 (1 H, t, *J* 1.7, CHO); $\delta_C\{^1H\}$ (67.9 MHz) 54.6 (CH_2), 101.0 (C-1), 128.7, 129.2 and 130.9 (C-3, 4, 5), 136.1 (C-2), 139.6 (C-6) and 198.3 (CHO); *m*/*z* (EI, 70 eV, 160 °C) 246 (M^+, 2.4%), 217 (M − CHO, 68), 119 (M − I, 100) and 90 (M − I − CHO, 82).

Methyl 3-(2-iodophenyl)prop-2-enoate 17[11]

Trimethyl phosphonoacetate (43.3 g, 0.238 mol) was added to a stirred suspension of sodium hydride (5.2 g, 0.22 mol) in THF (400 cm^3) at 0 °C to give a white foam. The mixture was allowed to warm to room temperature and after 30 min was recooled in an ice bath and 2-iodobenzaldehyde **15** (46.0 g, 0.198 mol) added as a solution in THF (140 cm^3). After 20 min the reaction mixture was allowed to warm to room temperature and stirred for a further 19 h. Saturated aqueous ammonium chloride (250 cm^3) was then added to the pale green opaque mixture. Diethyl ether (100 cm^3) was added and the layers separated. The aqueous layer was extracted again with diethyl ether (2 × 150 cm^3) and then the organic layers were combined and washed with water (3 × 250 cm^3), dried ($MgSO_4$) and the solvent removed *in vacuo* to give a yellow oil. Distillation (136–138 °C, ~1 mmHg) gave the title compound as a pale yellow oil (52.6 g, 0.183 mol, 92%) (Found: C, 41.5; H, 3.1. $C_{10}H_9IO_2$ requires C, 41.69; H, 3.15%); ν_{max}(neat)/cm^{-1} 1723vs (C=O) and 1633m (C=C); δ_H(270 MHz) 3.83 (3 H, s, CH_3), 6.32 (1 H, d, *J* 16, C*H*CO_2CH_3), 7.05 (1 H, dd, *J* 8, 8, H-5), 7.36 (1 H, dd, *J* 8, 8, H-4), 7.56 (1 H, d, *J* 8, H-3), 7.90 (1 H, d, *J* 8, H-6) and 7.90 (1 H, d, *J* 16, ArCH); $\delta_C\{^1H\}$ (67.9 MHz) 51.8 (CO_2CH_3), 101.1 (C-1), 120.8 (*C*HCO_2CH_3), 127.3, 128.5, 131.2 (C-3, 4, 5), 137.8 (C-2), 140.0 (C-6), 147.9 (ArCH) and 166.6 (CO_2CH_3); *m*/*z* (CI, NH_3) 306 (MNH_4^+, 100%), 289 (MH, 18), 180 (MNH_4 − I + H, 68) and 163 (MH − I + H, 40).

3-(2-Iodophenyl)propanol 18[9,12]

To a stirred solution of methyl 3-(2-iodophenyl)prop-2-enoate **17** (45.8 g, 0.159 mol) in THF (220 cm^3) at −78 °C under nitrogen was added Super-Hydride® (lithium triethylborohydride) (635 cm^3 of a 1 M solution in THF, 0.635 mol) dropwise over 1 h. The reaction mixture was then stirred for a further hour at −78 °C and then allowed to warm to room temperature. After stirring for 18 h, water (176 cm^3) was added carefully and the reaction mixture was refluxed for 2 h. After cooling to room temperature, 3 M aqueous sodium hydroxide (423 cm^3, 1.27 mol)

was added. Finally, after cooling at 0 °C, 27% aqueous hydrogen peroxide (480 cm^3, 3.81 mol) was added dropwise. When the reaction was less vigorous the ice bath was removed and the reaction allowed to warm to room temperature. After complete addition, the reaction mixture was stirred for a further hour and then diluted with water (200 cm^3). It was then split into two batches which were worked up independently due to the scale of the reaction; thus the following is the work-up procedure for one half of the mixture. After extraction with diethyl ether (3 × 300 cm^3), the organic layers were combined, washed with water (3 × 400 cm^3), dried (Na_2SO_4) and evaporated *in vacuo* to give a pale yellow oil. The two portions of crude oily product were then combined and distilled (bp 162 °C at ~1 mmHg) to give the title compound as a colourless oil (32.1 g, 0.123 mol, 77%) [Found: *m*/*z* (MNH_4^+) 280.0201. $C_9H_{15}INO$ requires *M*, 280.0198]; ν_{max}(neat)/cm^{-1} 3100–3400br s (OH); δ_H(270 MHz) 1.81–1.92 (3 H, m, CH_2CH_2OH), 2.81 (2 H, t, *J* 8, ArCH_2), 3.71 (2 H, t, *J* 6, CH_2OH), 6.85–6.91 (1 H, m, H-5), 7.21–7.30 (2 H, m, H-3, 4) and 7.81 (1 H, dd, *J* 8, 1, H-6); $\delta_C\{^1H\}$ (100 MHz) 32.8 (*C*H_2CH_2OH), 36.9 (ArCH_2), 61.7 (CH_2OH), 100.5 (C-1), 127.6, 128.2, 129.3 (C-3, 4, 5), 139.3 (C-6) and 144.2 (C-2); *m*/*z* (CI, NH_3) 280 (MNH_4^+, 100%), 260 (M − 2 H, 36), 244 (MH − H_2O, 14) and 152 (MNH_4 − I + H, 18).

3-(2-Iodophenyl)propanal 12[9]

Dimethyl sulfoxide (18.8 cm^3, 0.266 mol) was added to a solution of oxalyl chloride (11.6 cm^3, 0.133 mol) in DCM (250 cm^3) and was stirred under nitrogen at −60 °C during which time gas was seen to evolve. After 3 min, a solution of 3-(2-iodophenyl)propanol **18** (31.7 g, 0.121 mol) in DCM (90 cm^3) was added to the reaction mixture over 10 min *via* a cannula under nitrogen. After stirring at −60 °C for a further 20 min, triethylamine (84.2 cm^3, 0.61 mol) was added and the reaction mixture was seen to change from cloudy to clear after the first equivalent had been added and then back to cloudy. After stirring for 10 min, the reaction mixture was allowed to warm to room temperature and water (250 cm^3) was added. The layers were separated and the aqueous layer was extracted with DCM (3 × 150 cm^3). The combined organic layers were washed with 5% aqueous HCl (2 × 250 cm^3), saturated aqueous sodium hydrogen carbonate (350 cm^3) and water (400 cm^3), dried (Na_2SO_4) and evaporated *in vacuo* to give the title compound as a yellow oil (30.5 g, 0.117 mol, 97%) which needed no further purification [Found: *m*/*z* (MNH_4^+) 278.0043. $C_9H_{13}INO$ requires *M*, 278.0042]; ν_{max}(neat)/cm^{-1} 1711s (C=O); δ_H(270 MHz) 2.78 (2 H, t, *J* 8, CH_2CHO), 3.07 (2 H, t, *J* 8, ArCH_2), 6.90–6.95 (1 H, ddd, *J* 8, 8, 2, H-5), 7.24–7.33 (2 H, m, H-3, 4), 7.83 (1 H, d, *J* 8, H-6) and 9.93 (1 H, s, CHO); $\delta_C\{^1H\}$ (75 MHz) 32.9 (Ar*C*H_2CH_2), 43.6 (ArCH_2*C*H_2), 100.1 (C-1), 128.0, 128.3, 128.8 (C-3, 4, 5), 139.3 (C-6), 142.7 (C-2) and 200.4 (C=O); *m*/*z* (CI, NH_3) 278 (MNH_4^+, 100%) and 133 (M − I, 35).

(*E*)- and (*Z*)-4-(2-Iodophenyl)-1-methoxybut-1-ene 19

Potassium *tert*-butoxide (5.04 g, 45 mmol) was added portionwise to a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (16.9 g, 49.3 mmol) in dry THF (55 cm^3) in an ice bath. Upon addition a wine-red solution was formed and heat was evolved. The reaction vessel was degassed and filled with nitrogen, the water bath removed and the reaction stirred at room temperature for 30 min. A solution of 3-(2-iodophenyl)propanal **12** (5.9 g, 22.7 mmol) in THF (45 cm^3) was added to the reaction mixture *via* a cannula under nitrogen. After stirring at room temperature for 12 h, the reaction mixture had become an opaque brown–red colour. Saturated aqueous ammonium chloride (120 cm^3) was then added. The organic layer was separated and the aqueous layer extracted with diethyl ether (3 × 120 cm^3). The organic layers were combined and extracted with brine (3 × 100 cm^3), dried ($MgSO_4$) and evaporated to give a thick dark brown oil. Upon addition of light petroleum, triphenylphosphine oxide precipitated. It was removed by filtration on Kieselguhr and the filtrate concentrated under vacuum. The precipitation, filtration and evaporation procedure was repeated until no further precipitation of triphenylphosphine oxide occurred. Distillation using a Kügelrohr apparatus (200 °C at ~1 mmHg) gave the *title compound* as a colourless oil [6.04 g, 21.0 mmol, 93%, (*E*):(*Z*) = 1.7:1] [Found: *m*/*z* (MH^+) 289.0083. $C_{11}H_{14}IO$ requires *M*, 289.0089]; ν_{max}(neat)/cm^{-1} 1655s (C=C), 1208s (C–O–C) and 1108s (C–O); δ_H(270 MHz) 2.23 [2 H, dt, *J* 7, 7, (*E*)-CH_2CH=CH], 2.38 [2 H, dt, *J* 7, 7, (*Z*)-CH_2CH=CH], 2.76 [4 H, t, *J* 8, (*E*)- and (*Z*)-ArCH_2], 3.51 [3 H, s, (*E*)-CH_3], 3.57 [3 H, s, (*Z*)-CH_3], 4.40 [1 H, dt, *J* 8, 8, (*Z*)-C*H*=CHOCH_3], 4.79 [1 H, dt, *J* 8, 12, (*E*)-C*H*=CHOCH_3], 5.90 [1 H, d, *J* 8, (*Z*)-C*H*OCH_3], 6.33 [1 H, d, *J* 12, (*E*)-C*H*OCH_3], 6.83–6.91 [2 H, m, (*E*)- and (*Z*)-H-5], 7.18–7.30 [4 H, m, (*E*)- and (*Z*)-H-3, 4] and 7.81 [2 H, dd, *J* 8, 1, (*E*)- and (*Z*)-H-6]; $\delta_C\{^1H\}$ (125 MHz) 24.3 [(*Z*)-ArCH_2*C*H_2], 28.5 [(*E*)-ArCH_2*C*H_2], 40.7 [(*Z*)-ArCH_2], 42.1 [(*E*)-ArCH_2], 55.9 [(*E*)-OCH_3], 59.5 [(*Z*)-OCH_3], 100.6 [(*E*)-C-1], 100.8 [(*Z*)-C-1], 101.6 [(*E*)-*C*H=CHOCH_3], 105.3 [(*Z*)-*C*H=CHOCH_3], 127.6, 127.7, 128.1, 128.2, 129.4, 129.5 [(*E*)- and (*Z*)-C-3, 4, 5], 139.3 [(*Z*)-C-6], 139.4 [(*E*)-C-6], 144.4 [(*E*)-C-2], 144.6 [(*Z*)-C-2], 146.8 [(*Z*)-*C*HOCH_3] and 147.7 [(*E*)-*C*HOCH_3]; *m*/*z* (CI, NH_3) 289 (MH^+, 67%) and 274 (MH − CH_3, 100).

4-(2-Iodophenyl)butanal 13

To a solution of (*E*)- and (*Z*)-4-(2-iodophenyl)-1-methoxybut-1-ene **19** (9.04 g, 31.4 mmol) in DCM (30 cm^3) was added formic acid (30 cm^3) and upon addition the colour of the solution changed from pale to deep yellow. After stirring at room temperature for 30 h the reaction mixture was washed with water (3 × 50 cm^3) and saturated aqueous sodium hydrogen carbonate (2 × 50 cm^3), dried ($MgSO_4$) and evaporated *in vacuo* to give the *title compound* as a brown oil (8.4 g, 30.7 mmol, 98%) [Found: *m*/*z* (MNH_4^+) 292.0191. $C_{10}H_{15}INO$ requires *M*, 292.0198]; ν_{max}(neat)/cm^{-1} 1730s (C=O); δ_H(270 MHz) 1.94 (2 H, tt, *J* 8, 7, ArCH_2CH_2), 2.50 (2 H, dt, *J* 7, 2, CH_2CHO), 2.76 (2 H, t, *J* 8, ArCH_2), 6.89 (1 H, ddd, *J* 8, 8, 2, H-5), 7.17–7.30 (2 H, m, H-3, 4), 7.80 (1 H, d, *J* 8, H-6) and 9.79 (1 H, t, *J* 2, CHO); $\delta_C\{^1H\}$ (67.5 MHz) 22.5 (ArCH_2*C*H_2), 39.7 (ArCH_2), 43.0 (*C*H_2CHO), 100.4 (C-1), 127.9, 128.4, 129.4 (C-3, 4, 5), 139.5 (C-6), 143.8 (C-2) and 202 (CHO); *m*/*z* (CI, NH_3) 292 (MNH_4^+, 79%) and 247 (MH − CHO + H, 100).

N-[2-(2-Iodophenyl)ethyl]serine methyl ester 20

(±)-Serine methyl ester hydrochloride (0.95 g, 6.1 mmol), potassium acetate (0.80 g, 8.1 mmol) and activated 3 Å molecular sieves (4 g) were successively introduced into a reaction vessel which was then evacuated and filled with nitrogen. Dry isopropyl alcohol (15 cm^3) was added *via* syringe and, after stirring for 15 min, a solution of (2-iodophenyl)ethanal **11** (1.0 g, 4.1 mmol) in dry isopropyl alcohol (5 cm^3) was transferred into the reaction vessel *via* a cannula. The mixture was stirred for 40 min at room temperature and sodium cyanoborohydride (0.51 g, 8.14 mmol) was then added. At this point, evolution of gas was observed together with a small exotherm. The reaction mixture was then stirred at room temperature for 15 h. Excess sodium cyanoborohydride was hydrolysed by rendering the mixture acidic (pH 2) by the addition of 6 M hydrochloric acid (10 cm^3). The gas evolved was passed through a 5 M sodium hydroxide solution. When no more gas was seen to evolve, the mixture was rendered alkaline (pH 10) by careful addition of saturated aqueous potassium carbonate. The mixture was filtered through a sintered funnel (isopropyl alcohol) and the paste obtained was thoroughly washed with isopropyl alcohol. Isopropyl alcohol was evaporated *in vacuo*, the resulting slurry was extracted with ethyl acetate (3 × 50 cm^3) and the combined organic layers were treated with dilute HCl (pH 1) (3 × 50 cm^3). Potassium carbonate was added to the combined aqueous layers until pH 10 was reached and the basic solution was extracted with ethyl acetate (3 × 50 cm^3). The combined organic

extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give the *title compound* as a colourless oil (753 mg, 2.16 mmol, 53%) (Found: C, 41.1; H, 4.4; N, 4.0. $C_{12}H_{16}INO_3$ requires C, 41.28; H, 4.62; N, 4.01%); ν_{max}(neat)/cm^{-1} 3387 br and 3316 br (OH and NH) and 1737vs (C=O); δ_H(270 MHz) 2.29 (2 H, br s, NH and OH), 2.70–2.80 (1 H, m, C*H*HCH$_2$N), 2.80–3.05 (3 H, m, C*H*HC*H*$_2$N), 3.43 (1 H, dd, *J* 6.4, 4.5, C*H*CO$_2$CH$_3$), 3.59 (1 H, dd, *J* 10.6, 6.4, C*H*HOH), 3.74 (3 H, s, CO$_2$CH$_3$), 3.78 (1 H, dd, *J* 10.6, 4.5, CH*H*OH), 6.87–6.93 (1 H, m, H-5), 7.21–7.28 (2 H, m, H-3, 4) and 7.80 (1 H, dd, *J* 7.9, 1.2, H-6); $\delta_C\{^1H\}$ (67.9 MHz) 41.3 (*C*H$_2$CH$_2$N), 48.0 (CH$_2$N), 52.2 (CO$_2$*C*H$_3$), 62.2 (CH$_2$OH), 62.5 (*C*HCO$_2$CH$_3$), 100.6 (C-1), 128.2, 128.3, 129.7 (C-3, 4, 5), 139.6 (C-6), 142.0 (C-2) and 173.4 (*C*O$_2$CH$_3$); *m*/*z* (CI, NH$_3$) 350 (MH$^+$, 100%), 224 (MH − I + H, 16) and 222 (M − I, 14).

N-[3-(2-Iodophenyl)propyl]serine methyl ester 21

The general procedure was the same as described for the preparation of compound **20**. A solution of 3-(2-iodophenyl)-propanal **12** (4.46 g, 17.1 mmol) in dry isopropyl alcohol (10 cm^3) was added to a mixture of (±)-serine methyl ester hydrochloride (4.00 g, 25.7 mmol), potassium acetate (3.34 g, 34.2 mmol) and 3 Å molecular sieves (12 g) in dry isopropyl alcohol (70 cm^3) at room temperature. After stirring for 40 min, sodium cyanoborohydride (2.15 g, 34.2 mmol) was added in one portion to the opaque reaction mixture which was stirred for 14 h under nitrogen. It was then treated with 6 M aqueous hydrochloric acid and with saturated aqueous potassium carbonate. After filtration and evaporation of isopropyl alcohol *in vacuo*, it was extracted with ethyl acetate (3 × 150 cm^3). The combined organic layers were treated with dilute HCl (pH 1). Potassium carbonate was used to bring the acidic aqueous layers to pH 10 and the basic aqueous solution was extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated *in vacuo* to give the *title compound* as a colourless oil (3.80 g, 10.5 mmol, 61%) which slowly solidified to a white solid, mp 50.5–51.2 °C [Found: *m*/*z* (MH$^+$) 364.0385. $C_{13}H_{19}INO_3$ requires *M*, 364.0410]; ν_{max}(neat)/cm^{-1} 3400–3100br s (OH and NH) and 1737s (C=O); δ_H(270 MHz) 1.78–1.85 (2 H, m, C*H*$_2$CH$_2$N), 2.06–2.63 (1 H, m, ArC*H*H), 2.76–2.86 (3 H, m, CH$_2$N and ArCH*H*), 3.41 (1 H, dd, *J* 7, 5, C*H*CO$_2$CH$_3$), 3.61 (1 H, dd, *J* 11, 7, C*H*HOH), 3.77 (3 H, s, CO$_2$CH$_3$), 3.81 (1 H, dd, *J* 11, 5, CH*H*OH), 6.90 (1 H, ddd, *J* 8, 8, 2, H-5), 7.22 (1 H, dd, *J* 8, 2, H-3), 7.27 (1 H, ddd, *J* 8, 8, 1, H-4) and 7.83 (1 H, dd, *J* 8, 1, H-6); $\delta_C\{^1H\}$ (100 MHz) 30.6 (*C*H$_2$CH$_2$N), 38.3 (ArCH$_2$), 47.6 (CH$_2$N), 52.2 (CO$_2$*C*H$_3$), 62.3 (CH$_2$OH), 63.6 (*C*HCO$_2$CH$_3$), 100.5 (C-1), 127.8, 128.3, 129.3 (C-3, 4, 5), 139.5 (C-6), 144.3 (C-2) and 173.6 (*C*O$_2$CH$_3$); *m*/*z* (CI, NH$_3$) 364 (MH$^+$, 100%), 346 (MH − H$_2$O, 3), 332 (MH − CH$_2$OH, 6), 304 (M − CO$_2$Me, 5) and 236 (M − I, 21).

N-[4-(2-Iodophenyl)butyl]serine methyl ester 22

The general procedure was the same as described for the preparation of compound **20**. A solution of 4-(2-iodophenyl)-butanal **13** (5.62 g, 20.5 mmol) in dry isopropyl alcohol was added to a stirred mixture of (±)-serine methyl ester hydrochloride (4.79 g, 30.8 mmol), potassium acetate (4.03 g, 41.1 mol) and 3 Å molecular sieves (20 g) in isopropyl alcohol (100 cm^3) under nitrogen. The mixture was stirred at room temperature for 40 min, sodium cyanoborohydride (2.58 g, 41.1 mol) was added and stirring was continued for a further 14 h. Excess sodium cyanoborohydride was then hydrolysed by the sequential addition of 6 M aqueous hydrochloric acid and saturated aqueous potassium carbonate. The mixture was filtered through a sintered funnel and extracted with ethyl acetate. The combined organic layers were treated with dilute HCl (pH 1) and potassium carbonate was added to the combined aqueous layers. This basic solution was extracted with ethyl acetate and brine before being dried ($MgSO_4$) and evaporated *in vacuo* to give a colourless oil which solidified to a white solid (4.60 g, 12.2 mol, 60%), mp 62.3–63.1 °C (Found: C, 44.8; H, 5.3; N, 3.6. $C_{14}H_{20}NO_3$ requires C, 44.58; H, 5.34; N, 3.71%); ν_{max}(neat)/cm^{-1} 3400br s (OH and NH) and 1728s (C=O); δ_H(270 MHz) 1.56–1.62 (4 H, br m, ArCH$_2$C*H*$_2$C*H*$_2$), 2.10–2.40 (2 H, br, NH and OH), 2.53–2.60 (1 H, br m, ArC*H*H or C*H*HN), 2.69–2.79 (3 H, br m, 3 H of ArCH$_2$ and CH$_2$N), 3.38 (1 H, br dd, *J* 5, 7, C*H*CO$_2$CH$_3$), 3.57 (1 H, br dd, *J* 11, 7, C*H*HOH), 3.75–3.80 (4 H, m, CO$_2$CH$_3$ and CH*H*OH), 6.87 (1 H, dd, *J* 8, 8, H-5), 7.18–7.29 (2 H, m, H-3, 4) and 7.79 (1 H, d, *J* 8, H-6); $\delta_C\{^1H\}$ (67.5 MHz) 27.7, 29.6 (ArCH$_2$*C*H$_2$ and *C*H$_2$CH$_2$N), 40.4 (ArCH$_2$), 48.0 (CH$_2$N), 52.1 (CO$_2$*C*H$_3$), 62.3 (CH$_2$OH), 62.6 (*C*HCO$_2$CH$_3$), 100.5 (C-1), 127.6, 128.2, 129.2 (C-3, 4, 5), 139.4 (C-6), 144.7 (C-2) and 173.5 (*C*O$_2$CH$_3$); *m*/*z* (CI, NH$_3$) 378 (MH$^+$, 100%), 252 (MH − I + H, 88) and 148 [Ph(CH$_2$)$_4$NH + H, 92].

Methyl 2-{*N*-[2-(2-iodophenyl)ethyl]-*N*-(*tert*-butoxycarbonyl)-amino}prop-2-enoate 8

Di-*tert*-butyl dicarbonate (7.63 g, 35.0 mmol) was added to a solution of *N*-[2-(2-iodophenyl)ethyl]serine methyl ester **20** (11.10 g, 31.8 mmol) in dry DCM (25 cm^3) in an ice bath under nitrogen. After 15 min, the reaction vessel was removed from the ice bath and the mixture was stirred at room temperature for 20 h. The solution was diluted with dry DCM (40 cm^3) and cooled to 0 °C. Tosyl chloride (9.10 g, 47.7 mmol) and triethylamine (13 ml, 95.4 mmol) were then added. The reaction mixture was stirred for 12 h at room temperature, washed with dilute HCl (pH 3) (3 × 50 cm^3), brine (50 cm^3), dried ($MgSO_4$) and evaporated *in vacuo* to give an oil. Purification by column chromatography (SiO_2; light petroleum–diethyl ether, 1:0 then 1:1) afforded the *title compound* as a colourless oil (10.73 g, 24.9 mmol, 78%) (Found: C, 47.5; H, 5.1; N, 3.5. $C_{17}H_{22}INO_4$ requires C, 47.35; H, 5.14; N, 3.25%); ν_{max}(neat)/cm^{-1} 1736vs (C=O), 1710vs (C=O) and 1634s (C=C); δ_H(300 MHz) 1.44 [9 H, s, C(CH$_3$)$_3$], 3.06 (2 H, t, *J* 8, ArCH$_2$), 3.67 (2 H, t, *J* 8, CH$_2$N), 3.80 (3 H, s, CO$_2$CH$_3$), 5.35 (1 H, br s, C=C*H*H), 5.92 (1 H, br s, C=CH*H*), 6.89–6.95 (1 H, m, Ar-H), 7.28–7.30 (2 H, m, Ar-H) and 7.81 (1 H, d, *J* 7.9, H-6); $\delta_C\{^1H\}$ (75 MHz) 28.1 [C(*C*H$_3$)$_3$], 39.4 (ArCH$_2$), 49.8 (CH$_2$N), 52.1 (CO$_2$*C*H$_3$), 81.0 [*C*(CH$_3$)$_3$], 100.3 (C-1), 117.6 (C=*C*H$_2$), 128.2, 128.4, 130.3 (C-3, 4, 5), 139.4 (C-6), 140.1, 141.6 (C-2, *C*=CH$_2$) 153.6 [*C*O$_2$C(CH$_3$] and 165.3 (*C*O$_2$CH$_3$); *m*/*z* (CI, NH$_3$) 449 (MNH$_4^+$, 21%), 432 (MH, 27), 393 [MNH$_4$ − C(CH$_3$)$_3$, 100], 376 [MNH$_4$ − OC(CH$_3$)$_3$, 12] and 332 [MH − CO$_2$C(CH$_3$)$_3$, 100].

Methyl 2-{*N*-[3-(2-iodophenyl)propyl]-*N*-(*tert*-butoxycarbonyl)-amino}prop-2-enoate 9

The general procedure was the same as described for the preparation of compound **8**. Di-*tert*-butyl dicarbonate (7.76 g, 35.6 mmol) was added to a solution of *N*-[3-(2-iodophenyl)propyl]-serine methyl ester **21** (9.28 g, 25.6 mmol) in dry DCM (27 cm^3) in an ice bath under nitrogen. After 15 min, the mixture was stirred at room temperature for 20 h. The solution was diluted with dry DCM (25 cm^3) and cooled to 0 °C. Tosyl chloride (5.85 g, 30.7 mmol) and triethylamine (10 ml, 76.8 mmol) were then added. The reaction mixture was stirred for 12 h at room temperature before being extracted with dilute HCl (pH 3) (3 × 50 cm^3), brine (25 cm^3), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by column chromatography (SiO_2; light petroleum–diethyl ether, 1:0 then 1:1) afforded the *title compound* as a colourless oil (7.44 g, 16.9 mmol, 66%) (Found: C, 48.3; H, 5.7; N, 3.4. $C_{18}H_{24}INO_4$ requires C, 48.55; H, 5.43; N, 3.15%); ν_{max}(neat)/cm^{-1} 1735vs (C=O), 1710vs (C=O) and 1631s (C=C); δ_H(300 MHz) 1.44 [9 H, s, C(CH$_3$)$_3$], 1.87–1.94 (2 H, m, C*H*$_2$CH$_2$N), 2.77 (2 H, t, *J* 8, ArCH$_2$), 3.60 (2 H, t, *J* 8, CH$_2$N), 3.81 (3 H, s, CO$_2$CH$_3$), 5.45 (1 H, br s, C=C*H*H), 5.94 (1 H, br s, C=CH*H*), 6.86–6.92 (1 H, m, ArH), 7.22–7.31 (2 H, m, ArH) and 7.81 (1 H, d, *J* 7.9, H-6); $\delta_C\{^1H\}$ (100 MHz) 28.0 [C(*C*H$_3$)$_3$], 28.6 (*C*H$_2$CH$_2$N), 37.9 (ArCH$_2$), 48.7 (CH$_2$N), 52.1 (CO$_2$*C*H$_3$), 80.9 [*C*(CH$_3$)$_3$], 100.4 (C-1), 117.0 (C=*C*H$_2$), 127.7, 128.3 and 129.2 (C-3, 4, 5), 139.3 (C-6), 139.9, 144.1 (C-2, *C*=CH$_2$) and

153.8 [$CO_2C(CH_3)_3$] and 165.5 (CO_2CH_3); *m*/*z* (CI, NH_3) 463 (MNH_4^+, 38%), 446 (MH, 28), 407 [$MNH_4 - C(CH_3)_3 + H$, 94], 346 [$MH - CO_2(CH_3)_3 + H$, 100] and 320 [$MH - I + H$, 22].

Methyl 2-{*N*-[4-(2-iodophenyl)butyl]-*N*-(*tert*-butoxycarbonyl)-amino}prop-2-enoate 10

The general procedure was the same as described for the preparation of compound **8**. Di-*tert*-butyl dicarbonate (3.84 g, 17.6 mmol) was added to a solution of *N*-[4-(2-iodophenyl)butyl]-serine methyl ester **22** (6.03 g, 16.0 mmol) in dry DCM (13 cm^3) in an ice bath, under nitrogen. The ice bath was removed after 15 min and the mixture was stirred at room temperature for 20 h. The solution was diluted with dry DCM (20 cm^3) and cooled to 0 °C. Tosyl chloride (4.57 g, 24.0 mmol) and triethylamine (6.7 ml, 48.0 mmol) were then added. The reaction mixture was stirred for 12 h at room temperature before being extracted with dilute HCl (pH 3) (3 × 50 cm^3), brine (50 cm^3), dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (SiO_2; light petroleum–diethyl ether, 9:1 and 5:1) gave the *title compound* as a pale yellow oil (5.61 g, 12.2 mmol, 76%) (Found: C, 49.8; H, 5.8; N, 3.2. $C_{19}H_{26}INO_4$ requires C, 49.68; H, 5.71; N, 3.05%); ν_{max}(neat)/cm^{-1} 1733vs (C=O), 1708vs (C=O) and 1631s (C=C); δ_H(500 MHz, at 50 °C) 1.22 [9 H, s, $C(CH_3)_3$], 1.14–1.50 (4 H, m, $ArCH_2CH_2CH_2$), 3.52 (2 H, t, *J* 7 $ArCH_2$), 3.34 (2 H, t, *J* 7, CH_2N), 3.55 (3 H, s, CO_2CH_3), 5.18 (1 H, s, C=CHH), 5.69 (1 H, s, C=CHH), 6.77 (1 H, ddd, *J* 8, 8, 2, ArH), 6.98–7.04 (2 H, m, ArH) and 7.56 (1 H, d, *J* 8, H-6); $\delta_C\{^1H\}$ (125 MHz) 26.7, 27.2 ($ArCH_2CH_2CH_2$), 27.5 [$C(CH_3)_3$], 39.7 ($ArCH_2$), 48.4 (CH_2N), 51.6 (CO_2CH_3), 80.0 [$C(CH_3)_3$], 100.0 (C-1), 116.4 (C=CH_2), 127.1, 127.7, 128.8 (C-3, 4, 5), 138.7 (C-6), 139.4 (*C*=CH_2), 144.1 (C-2), 153.0 [$CO_2C(CH_3)_3$] and 164.7 (CO_2CH_3); *m*/*z* (FAB positive) 460 (MH^+, 100%), 404 [$MH - C(CH_3)_3$, 2], 386 [$M - OC(CH_3)_3$, 8], 360 [$MH - CO_2C(CH_3)_3 + H$, 6], 300 [$MH - CO_2CH_3 - CO_2C(CH_3)_3$, 92] and 57 [$C(CH_3)_3$, 100].

General procedure for the intramolecular Heck reactions at various temperatures, concentrations and catalyst loadings

A solution of the Heck substrate **8**, **9** or **10** (200 mg) in dry nitrogen-saturated DMF (*x* cm^3 to give the required concentration) was stirred at room temperature for 30 min in the presence of 3 Å molecular sieves (20 mg cm^{-3}) under an atmosphere of nitrogen in a 25 cm^3 round-bottomed flask. Palladium acetate (0.01 to 0.2 equiv.), tetrabutylammonium chloride (1.0 equiv.) and sodium hydrogen carbonate (2.5 equiv.) were added together and the flask was fitted with a condenser. The reaction mixture was degassed and saturated with nitrogen repeatedly and then lowered into an oil bath preheated to the experiment temperature *T* °C. After stirring for 16 h at temperature *T*, the reaction mixture was cooled to room temperature and filtered through Kieselguhr (DCM) to give a brown oil. After evaporation of the solvents under reduced pressure, column chromatography (SiO_2; light petroleum–diethyl ether, 5:1) afforded the products as colourless oils. Spectroscopic data were identical to those obtained from fully characterised samples of **5**–**7**.

2-Methoxycarbonyl-3-(*tert*-butoxycarbonyl)-4,5-dihydro-3*H*-3-benzazepine 5. A solution of methyl 2-{*N*-[2-(2-iodophenyl)ethyl]-*N*-(*tert*-butoxycarbonyl)amino}prop-2-enoate **8** (1.007 g, 2.33 mmol) in dry nitrogen-saturated DMF (47 cm^3) was stirred at room temperature in the presence of 3 Å molecular sieves (0.94 g) for 30 min in a 100 cm^3 round-bottomed flask. Palladium acetate (52 mg, 0.232 mmol), tetrabutylammonium chloride (649 mg, 2.33 mmol) and sodium hydrogen carbonate (490 mg, 5.84 mmol) were added and the flask was fitted with a condenser. After saturating the reaction mixture with nitrogen, it was lowered into an oil bath preheated to 110 °C. After a few minutes the mixture could be seen to darken to deep brown. After stirring for 16 h at 110 °C under an atmosphere of nitrogen, the reation mixture was cooled to room temperature and filtered through Kieselguhr (DCM) to give a brown oil. After evaporation of the solvents under reduced pressure, column chromatography (SiO_2; light petroleum–diethyl ether, 5:1) afforded the *title compound* as a colourless oil (386 mg, 1.27 mmol, 55%) which crystallised as colourless crystals from hexane at −7 °C; mp 68–69 °C (Found: C, 67.6; H, 6.8; N, 4.6. $C_{17}H_{21}NO_4$ requires C, 67.31; H, 6.98; N, 4.62%); ν_{max}(neat)/cm^{-1} 1727vs (C=O), 1710vs (C=O) and 1637s (C=C); δ_H(300 MHz) 1.44 [9 H, s, $C(CH_3)_3$], 3.16 (2 H, t, *J* 5, $ArCH_2$), 3.81 (2 H, t, *J* 5, CH_2N), 3.86 (3 H, s, CO_2CH_3), 6.94 (1 H, s, CH=C), 7.24–7.28 (3 H, m, ArH) and 7.34–7.38 (1 H, m, H-6); $\delta_C\{^1H\}$ (125 MHz) 28.0 [$C(CH_3)_3$], 36.9 ($ArCH_2$), 45.5 (CH_2N), 52.2 (CO_2CH_3), 81.5 [$C(CH_3)_3$], 126.1 (C=*C*H), 126.3, 128.5, 130.5 (C-3, 4, 5), 131.8, 132.1, 140.0 (C-1, 2, *C*=CH), 133.6 (C-6), 152.6 [$CO_2C(CH_3)_3$] and 166.5 (CO_2CH_3); *m*/*z* (CI, NH_3) 304 (MH^+, 29%), 248 [$MH - C(CH_3)_3$, 51] and 204 [$MH - CO_2C(CH_3)_3$, 100].

2-Methoxycarbonyl-3-(*tert*-butoxycarbonyl)-3,4,5,6-tetrahydro-3-benzazocine 6. The general procedure was the same as described for the preparation of compound **5**. A mixture of methyl 2-{*N*-[3-(2-iodophenyl)propyl]-*N*-(*tert*-butoxycarbonyl)amino}prop-2-enoate **9** (1.00 g, 2.25 mmol), palladium acetate (25 mg, 0.111 mmol), sodium hydrogen carbonate (0.47 g, 5.62 mmol), tetrabutylammonium chloride (0.62 g, 2.25 mmol) and 3 Å molecular sieves (0.9 g) in dry nitrogen-saturated DMF (45 cm^3) was stirred and heated at 105 °C for 16 h under nitrogen. The dark brown solution was cooled and filtered through Kieselguhr. Flash chromatography (SiO_2; light petroleum–diethyl ether, 4:1) afforded the *title compound* as a colourless oil (0.523g, 1.65 mmol, 73%) which crystallised as colourless needles from hexane at −7 °C; mp 65–67 °C (Found: C, 68.4; H, 7.5; N, 4.5. $C_{18}H_{23}NO_4$ requires C, 68.12; H, 7.30; N, 4.41%); ν_{max}(neat)/cm^{-1} 1729s (C=O), 1710s (C=O) and 1626m (C=C); δ_H(500 MHz, C_6D_6, 80 °C) 1.30 [9 H, s, $C(CH_3)_3$], 1.70 (2 H, quintet, *J* 6, CH_2CH_2N), 2.52 (2 H, t, *J* 6, $ArCH_2$), 3.41 (2 H, t, *J* 6, CH_2N), 3.55 (3 H, s, CO_2CH_3), 6.89–7.02 (4 H, m, H-3, 4, 5, 6) and 7.27 (1 H, s, C=CH); $\delta_C\{^1H\}$ (75 MHz) 25.9 ($ArCH_2CH_2$), 27.9 [$C(CH_3)_3$], 32.1 ($ArCH_2CH_2$), 45.6 (CH_2N), 52.2 (CO_2CH_3), 80.7 [$C(CH_3)_3$], 125.9 (C=*C*H), 129.3, 129.3, 129.9, 130.4 (C-3, 4, 5, 6), 132.7, 133.1, 140.1 (C-1, 2, *C*=CH), 152.8 [$CO_2C(CH_3)_3$] and 166.3 (CO_2CH_3); *m*/*z* (CI, NH_3) 318 (MH^+, 10%), 262 [$MH - C(CH_3)_3 + H$, 26], 218 [$MH - CO_2C(CH_3)_3 + H$, 100], 217 [$MH - CO_2C(CH_3)_3$, 93], 158 [$MH - CO_2C(CH_3)_3 - CO_2CH_3$, 21] and 57 [$C(CH_3)_3$, 37].

2-Methoxycarbonyl-3-(*tert*-butoxycarbonyl)-4,5,6,7-tetrahydro-3*H*-3-benzazonine 7. The general procedure was the same as described for the preparation of compound **5**. A mixture of methyl 2-{*N*-[4-(2-iodophenyl)butyl]-*N*-(*tert*-butoxycarbonyl)amino}prop-2-enoate **10** (1.011 g, 2.20 mmol), palladium acetate (12.4 mg, 0.0551 mmol), sodium hydrogen carbonate (463 mg, 5.51 mmol), tetrabutylammonium chloride (612 mg, 2.20 mmol) and 3 Å molecular sieves (0.9 g) in dry nitrogen-saturated DMF (44 cm^3) was stirred and heated at 110 °C for 16 h under nitrogen. The dark brown solution was cooled to room temperature and filtered through Kieselguhr. Flash chromatography (SiO_2; light petroleum–diethyl ether, 5:1) gave the *title compound* as a colourless oil (625 mg, 1.89 mmol, 86%) (Found: C, 68.6; H, 7.5; N, 4.2. $C_{19}H_{25}NO_4$ requires C, 68.86; H, 7.60; N, 4.23%); ν_{max}(neat)/cm^{-1} 1728vs (C=O), 1703vs (C=O) and 1645s (C=C); δ_H(300 MHz, two rotamers) 1.28 [9 H, s, $C(CH_3)_3$, minor rotamer], 1.31 [9 H, s, $C(CH_3)_3$, major rotamer], 1.54–1.59 (2 H, m, $ArCH_2CH_2CH_2$), 1.60–1.87 (2 H, m, $ArCH_2CH_2CH_2$), 3.71 (2 H, t, *J* 7, $ArCH_2$), 3.23–3.29 (2 H, br m, CH_2N), 3.83 (3 H, s, CO_2CH_3), 7.05 (1 H, d, *J* 8, ArH), 7.15–7.28 (3 H, m, ArH), 7.68 (1 H, C=CH, major rotamer), 7.75 (1 H, C=CH, minor rotamer); $\delta_C\{^1H\}$ (125 MHz) 25.8, 26.0 ($ArCH_2CH_2$ rotamers), 28.0 [$C(CH_3)_3$], 28.1, 28.4 ($ArCH_2CH_2$ rotamers), 30.3, 30.7 (CH_2CH_2N rotamers), 47.0, 47.3 (CH_2N rotamers), 52.2 (CO_2CH_3), 79.8 [$C(CH_3)_3$], 125.4 (C=*C*H), 125.9, 128.0, 128.2, 128.3, 128.9 × 2, (C-3, 4, 5 rotamers), 138.5, 139.6 (C-6 rotamers), 133.2, 133.5, 134.4, 134.5, 139.2 × 2, (C-1, 2, *C*=CH

rotamers), 153.4, 153.8 [$CO_2C(CH_3)_3$ rotamers] and 165.2, 165.6 (CO_2CH_3 rotamers); *m*/*z* (FAB positive) 332 (MH^+, 12%), 276 [MH − $C(CH_3)_3$ + H, 49], 232 [MH − $CO_2(CH_3)_3$ + H, 98], 172 [MH − $CO_2C(CH_3)_3$ − CO_2CH_3, 91] and 57 [$C(CH_3)_3$, 100].

2-Methoxycarbonyl-3-(*tert*-butoxycarbonyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine 23

A Schlenk tube was charged with 2-methoxycarbonyl-3-(*tert*-butoxycarbonyl)-4,5-dihydro-3*H*-3-benzazepine **5** (850 mg, 2.801 mmol), palladium on charcoal (10%) (85 mg, 10% w/w) and a stirrer bar. The Schlenk tube was evacuated and filled with nitrogen ten times and then methanol (56 cm^3), saturated with nitrogen *via* a nitrogen–freeze–pump–thaw cycle, was transferred into it *via* a cannula. The reaction mixture was degassed and saturated with hydrogen ten times before being firmly clamped in a sonicator bath. Sonication for 24 h followed by filtration through Kieselguhr (methanol), gave a colourless solution. Removal of the solvent by evaporation *in vacuo* gave the *title compound* as a colourless oil (836 mg, 2.740 mmol, 98%) (Found: C, 66.9; H, 7.4; N, 4.5. $C_{17}H_{23}NO_4$ requires C, 66.86; H, 7.59; N, 4.59%); ν_{max}(neat)/cm^{-1} 1776vs (C=O) and 1698vs (C=O); δ_H(300 MHz, 9:7 mixture of rotamers) 1.40, 1.46 [9 H, 2 × s, $C(CH_3)_3$ rotamers], 2.87–3.40 (5 H, m, $ArCH_2CH_2$, $ArCH_2CHCO_2Me$, $CHHN$), 3.65, 3.67 (3 H, 2 × s, CO_2CH_3 rotamers), 4.21, 4.48 (1 H, 2 × dt, *J* 15, 5, $CHHN$ rotamers), 4.96, 5.28 (1 H, 2 × dd, *J* 8, 4, $CHCO_2CH_3$ rotamers) and 7.10–7.19 (4 H, m, ArH); $\delta_C\{^1H\}$ (125 MHz) 28.0 [$C(CH_3)_3$], 35.0, 35.5, 36.6, 36.8 ($ArCH_2CH_2$, $ArCH_2CHCO_2CH_3$ rotamers), 41.1, 42.2 (CH_2N rotamers), 51.5 (CO_2CH_3), 56.9, 57.7 ($CHCO_2CH_3$ rotamers), 80.0 [$C(CH_3)_3$], 126.0, 126.1, 126.7, 126.9, 129.0, 129.3, 130.0, 130.2 (C-3, 4, 5, 6 rotamers), 135.7, 136.0, 139.6, 139.7 (C-1, 2 rotamers), 154.8, 155.4 [$CO_2C(CH_3)_3$ rotamers] and 171.1, 171.2 (CO_2CH_3 rotamers); *m*/*z* (CI, NH_3) 306 (MH^+, 22%), 250 [MNH_4 − $OC(CH_3)_3$, 17], 206 [MH − $CO_2C(CH_3)_3$ + H, 31], 146 [MH − CO_2CH_3 − $CO_2C(CH_3)_3$, 100] and 57 [$C(CH_3)_3$, 74].

2-Methoxycarbonyl-3-(*tert*-butoxycarbonyl)-1,2,3,4,5,6-hexahydro-3-benzazocine 24

A Fischer–Porter bottle was charged with 2-methoxycarbonyl-3-(*tert*-butoxycarbonyl)-3,4,5,6-tetrahydro-3-benzazocine **6** (720 mg, 2.271 mmol), palladium on charcoal (10%) (145 mg, 20% w/w) and a stirrer bar. It was evacuated and filled with nitrogen ten times and then methanol (10 cm^3), saturated with nitrogen *via* a nitrogen–freeze–pump–thaw cycle, was added *via* a cannula. The reaction vessel was evacuated and filled with hydrogen three times. Stirring for 24 h under hydrogen at a pressure of 50 psi† followed by filtration through Kieselguhr and evaporation of the solvent *in vacuo* afforded the *title compound* as a colourless oil (699 mg, 2.191 mmol, 96%) (Found: C, 67.7; H, 7.6; N, 4.3. $C_{18}H_{25}NO_4$ requires C, 67.69; H, 7.89; N, 4.39%); ν_{max}(neat)/cm^{-1} 1746vs (C=O) and 1696vs (C=O); δ_H(500 MHz, C_6D_6, 40 °C, 7:5 mixture of rotamers) 1.17, 1.27 [9 H, 2 × s, $C(CH_3)_3$ rotamers], 1.35–3.08 (7 H, m, $ArCH_2CH_2$, $ArCH_2CH_2$, $ArCH_2CHCO_2Me$, $CHHN$), 3.30, 3.34 (3 H, 2 × s, CO_2CH_3 rotamers), 3.68–3.72 and 3.96–3.98 (1 H, 2 × d, *J* 15, $CHHN$ rotamers), 4.90–4.92, 5.40–5.42 (1 H, 2 × m, $CHCO_2CH_3$ rotamers), 6.91–6.93 (1 H, m, ArH), 6.98–7.01 (2 H, m, ArH) and 7.09–7.11 (1 H, m, ArH); $\delta_C\{^1H\}$ (75 MHz) 28.0, 28.3 [$C(CH_3)_3$ rotamers], 29.6, 30.7 (CH_2CH_2N rotamers), 32.2, 33.1 ($ArCH_2CH_2$ rotamers), 34.4 ($ArCH_2CHCO_2CH_3$), 45.4, 45.7 (CH_2N rotamers), 52.0, 52.2 (CO_2CH_3), 59.2, 60.8 ($CHCO_2CH_3$ rotamers), 79.8, 79.9 [$C(CH_3)_3$], 126.3, 126.5, 127.2 × 2, 129.2, 129.4, 129.7, 130.1 (C-3, 4, 5, 6 rotamers), 136.2, 136.3, 141.4, 142.3 (C-1, 2 rotamers), 154.4, 155.7 [$CO_2C(CH_3)_3$ rotamers] and 172.0 (CO_2CH_3); *m*/*z* (CI, CH_4) 640 (2 MH^+, 3%), 539 [2 MH − $CO_2C(CH_3)_3$ + 2 H, 11], 320 (MH, 47), 220 [MH − $CO_2(CH_3)_3$ + H, 65], 160 [MH − $CO_2C(CH_3)_3$ − CO_2CH_3, 79] and 57 ($C(CH_3)_3$, 100).

2-Methoxycarbonyl-3-(*tert*-butoxycarbonyl)-2,3,4,5,6,7-hexahydro-1*H*-3-benzazonine 25

The general procedure was the same as described for the preparation of compound **24**. A Fischer–Porter bottle was charged with 2-methoxycarbonyl-3-(*tert*-butoxycarbonyl)-4,5,6,7-tetrahydro-3*H*-3-benzazonine **7** (773 mg, 2.335 mmol), palladium on charcoal (10%) (230 mg, 30% w/w) and a stirrer bar and evacuated and filled with nitrogen ten times. Nitrogen-saturated methanol (10 cm^3) was added *via* a cannula. The reaction vessel was evacuated and filled with hydrogen. Stirring for 24 h under hydrogen at a pressure of 100 psi, followed by filtration through Kieselguhr and evaporation of the solvent *in vacuo* gave the *title compound* as a white solid (758 mg, 2.276 mmol, 97%), mp 103–104 °C (Found: C, 68.3; H, 7.9; N, 4.1. $C_{19}H_{27}NO_4$ requires C, 68.44; H, 8.16; N, 4.20%); ν_{max}(neat)/cm^{-1} 1748vs (C=O) and 1703vs (C=O); δ_H(300 MHz, 5:4 mixture of rotamers) 1.30–2.03 (4 H, m, $CH_2CH_2CH_2N$), 1.46, 1.48 [9 H, 2 × s, $C(CH_3)_3$ rotamers], 2.74–4.12 (7 H, m, $ArCH_2CH_2$, CH_2N, $ArCH_2CH$-CO_2CH_3), 3.76 (3 H, s, CO_2CH_3) and 7.13–7.28 (4 H, m, H-3, 4, 5, 6); $\delta_C\{^1H\}$ (75 MHz) 22.8, 23.9 ($ArCH_2CH_2$ rotamers), 28.3 [$C(CH_3)_3$], 28.8, 29.3 (CH_2CH_2N rotamers), 30.1, 30.6 ($ArCH_2CH_2$ rotamers), 33.3, 35.0 ($ArCH_2CHCO_2CH_3$ rotamers), 47.4, 47.8 (CH_2N rotamers), 52.1 (CO_2CH_3), 62.0, 62.2 ($CHCO_2CH_3$ rotamers), 79.9, 80.4 [$C(CH_3)_3$ rotamers], 126.5, 126.9, 127.2, 129.1, 129.3, 130.6, 130.7 (C-3, 4, 5 rotamers), 138.6, 138.7, 140.5, 140.7 (C-1, 2 rotamers), 154.4, 159.8 [$CO_2C(CH_3)_3$ rotamer] and 172.0 (CO_2CH_3); *m*/*z* (CI, NH_3) 334 (MH^+, 43%), 278 [MH − $C(CH_3)_3$ + H, 100], 263 [MH − $C(CH_3)_3$ − CH_3 + H, 9], 234 [MH − $CO_2(CH_3)_3$ + H, 68] and 174 [MH − $CO_2C(CH_3)_3$ − CO_2CH_3, 36].

2,3,4,5-Tetrahydro-1*H*-3-benzazepine-2-carboxylic acid hydrochloride 26

A suspension of 2-methoxycarbonyl-3-(*tert*-butoxycarbonyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine **23** (849 mg, 2.783 mmol) in 3 M HCl (28 cm^3) was stirred vigorously for 4 h at 90 °C in a 100 cm^3 flask fitted with an air condenser. The solvent was evaporated *in vacuo* to give the *title compound* as a white powder (615 mg, 2.709 mmol, 97%), mp 242–245 °C (decomp.) (Found: C, 58.0; H, 5.9; N, 6.1. $C_{11}H_{14}ClNO_2$ requires C, 58.03; H, 6.20; N, 6.15%); ν_{max}(Nujol)/cm^{-1} 1733s (C=O); δ_H(270 MHz; D_2O) 3.00–3.20 (3 H, m, $ArCH_2CH_2N$, $ArCHHCHCO_2H$), 3.22–3.40 (2 H, m, $ArCH_2CHHN$, $ArCHHCHCO_2H$), 3.55–3.60 (1 H, m, $ArCH_2CHHN$), 3.99 (1 H, dd, *J* 10, 2, $CHCO_2H$) and 7.15–7.25 (4 H, m, ArH); $\delta_C\{^1H\}$ (125 MHz, D_2O) 34.0 ($ArCH_2CH_2$), 37.4 ($ArCH_2CHCO_2H$), 47.5 (CH_2N), 60.6 ($CHCO_2H$), 130.5, 130.9, 132.3, 133.0 (C-3, 4, 5, 6), 138.9, 141.9 (C-1, 2) and 173.8 (CO_2H); *m*/*z* (EI, 70 eV, 220 °C) 191 (M^+ − HCl, 0.6%), 146 (M − HCl − CO_2H, 60) and 36 (HCl, 100).

1,2,3,4,5,6-Hexahydro-3-benzazocine-2-carboxylic acid hydrochloride 27

The general procedure was the same as described for the preparation of compound **26**. A suspension of 2-methoxycarbonyl-3-(*tert*-butoxycarbonyl)-1,2,3,4,5,6-hexahydro-3-benzazocine **24** (817 mg, 2.561 mmol) in 3 M HCl (26 cm^3) was stirred vigorously for 4 h at 100 °C. The solvent was evaporated *in vacuo* to give the *title compound* as a white powder (608 mg, 2.522 mmol, 98%), mp 225–227 °C (decomp.) (Found: C, 59.4; H, 6.5; N, 5.6. $C_{12}H_{16}ClNO_2$ requires C, 59.63; H, 6.67; N, 5.79%); ν_{max}(KBr dispersion)/cm^{-1} 1737s (C=O); δ_H(300 MHz; D_2O) 1.93–1.95 (2 H, m, $ArCH_2CH_2$), 2.81–2.83 (2 H, m, $ArCH_2CH_2$), 2.99–3.08 (1 H, m, $CHHN$) and 3.20–3.77 (3 H, m, $CHHN$ and $ArCH_2$-$CHCO_2H$), 4.16 (1 H, t, *J* 6, $CHCO_2H$) and 6.89–7.02 (4 H, m, ArH); $\delta_C\{^1H\}$ (75 MHz, D_2O) 27.9 ($ArCH_2CH_2$), 30.1, 30.9

† 1 psi = 6894.76 Pa.

(Ar*C*H_2CH$_2$, Ar*C*H_2CHCO$_2$H), 45.4 (CH$_2$N), 61.8 (*C*HCO$_2$H), 127.7, 128.8, 130.3, 130.5 (C-3, 4, 5, 6), 132.8 (C-2), 140.5 (C-1) and 170.9 (CO$_2$H); *m*/*z* (CI, NH$_3$) 206 (MH$^+$ − HCl, 100%) and 160 (M − HCl − CO$_2$H, 19).

2,3,4,5,6,7-Hexahydro-1*H*-3-benzazonine-2-carboxylic acid hydrochloride 28

The general procedure was the same as described for the preparation of compound **26**. A suspension of 2-methoxycarbonyl-3-(*tert*-butoxycarbonyl)-2,3,4,5,6,7-hexahydro-1*H*-3-benzazonine **25** (846 mg, 2.540 mmol) in 3 M HCl (28 cm^3) was stirred vigorously for 4 h at 110 °C. The solvent was evaporated *in vacuo* to give the *title compound* as a white powder (639 mg, 2.506 mmol, 99%), mp 198–201 °C (decomp.) (Found: C, 61.3; H, 7.2; N, 5.3. $C_{13}H_{18}ClNO_2$ requires C, 61.15; H, 7.11; N, 5.49%); ν_{max}(KBr dispersion)/cm^{-1} 1736s (C=O); δ_H(300 MHz; D$_2$O) 1.37–1.45 (1 H, m, ArCH$_2$C*H*H), 1.58–1.75 (2 H, m, ArCH$_2$CH*H* and C*H*HCH$_2$N), 1.82–1.92 (1 H, m, CH*H*-CH$_2$N), 2.57–2.76 (2 H, m, ArC*H*$_2$CH$_2$), 3.09 (2 H, t, *J* 6, CH$_2$C*H*$_2$N), 3.24 (1 H, dd, *J* 16, 6, ArC*H*HCHCO$_2$H), 3.36 (1 H, dd, *J* 16, 6, ArCH*H*CHCO$_2$H), 4.72 (1 H, t, *J* 6, C*H*CO$_2$H) and 7.07–7.22 (4 H, m, ArH); δ_C{^{1}H} (75 MHz, D$_2$O) 21.8 (ArCH$_2$*C*H$_2$), 27.0 (*C*H$_2$CH$_2$N), 29.8 (Ar*C*H$_2$CH$_2$), 31.1 (Ar*C*H$_2$CO$_2$H), 44.5 (CH$_2$*C*H$_2$N), 59.8 (*C*HCO$_2$H), 127.2, 128.5, 130.2, 130.6 (C-3, 4, 5, 6), 133.6 (C-2), 141.0 (C-1) and 171.0 (CO$_2$H); *m*/*z* (CI, NH$_3$) 220 (MH$^+$ − HCl, 100%) and 174 (M − HCl − CO$_2$H, 42).

2,3,4,5-Tetrahydro-1*H*-3-benzazepine-2-carboxylic acid (Sic) 1

The hydrochloride salt **26** (615 mg, 2.709 mmol) was dissolved in ethanol (14 cm^3) in a 100 cm^3 round-bottomed flask fitted with a condenser and propene oxide (2.1 cm^3, 29.8 mmol) was added. The solution was stirred at 50 °C for 4 h. The solvent was evaporated *in vacuo* to give a white solid which was left under vacuum for a day to afford the *title compound* as an insoluble white powder (515 mg, 2.696 mmol, 100%), mp 267–274 °C (decomp.) (Found: C, 68.8; H, 6.6; N, 7.0. $C_{11}H_{13}NO_2$ requires C, 69.08; H, 6.86; N, 7.33%); ν_{max}(KBr dispersion)/cm^{-1} 1605vs (C=O); *m*/*z* (CI, NH$_3$) 192 (MH$^+$, 100%) and 146 (M − CO$_2$H, 68).

1,2,3,4,5,6-Hexahydro-3-benzazocine-2-carboxylic acid (Hic) 2

The general procedure was the same as described for the preparation of compound **1**. Propene oxide (1.9 cm^3, 27.7 mmol) was added to a solution of the hydrochloride salt **27** (608 mg, 2.523 mmol) in ethanol (13 cm^3). The solution was stirred at 50 °C for 4 h. The solvent was evaporated *in vacuo* to give a white solid which was left under vacuum for a day to afford the *title compound* as an insoluble white powder (503 mg, 2.453 mmol, 97%), mp 221–223 °C (decomp.) (Found: C, 70.4; H, 7.3; N, 6.7. $C_{12}H_{15}NO_2$ requires C, 70.22; H, 7.37; N, 6.82%); ν_{max}(KBr dispersion)/cm^{-1} 1617m (C=O); *m*/*z* (CI, NH$_3$) 206 (MH$^+$, 100%) and 160 (M − CO$_2$H, 35).

2,3,4,5,6,7-Hexahydro-1*H*-3-benzazonine-2-carboxylic acid (Nic) 3

The general procedure was the same as described for the preparation of compound **1**. Propene oxide (1.8 cm^3, 27.3 mmol) was added to a solution of the hydrochloride salt **28** (633 mg, 2.48 mmol) in ethanol (12 cm^3). The solution was stirred at 40 °C for 4 h. The solvent was evaporated *in vacuo* to give a white solid which was left under vacuum for a day to afford the *title compound* as an insoluble white powder (539 mg, 2.46 mmol, 99%), mp 174–176 °C (decomp.) (Found: C, 70.9; H, 7.6; N, 6.3. $C_{13}H_{17}NO_2$ requires C, 71.21; H, 7.81; N, 6.39%); ν_{max}(KBr dispersion)/cm^{-1} 1638s (C=O); *m*/*z* (CI, NH$_3$) 220 (MH$^+$, 100%) and 174 (M − CO$_2$H, 34).

Acknowledgements

The authors thank the James Black Foundation for financial support (N. G.), the EPSRC for a studentship (R. J. M.) and the Erasmus Exchange Programme for a bursary (A. T.). Liang L. K. Ke and Stephen P. Keen are very gratefully acknowledged for technical assistance and exploratory experiments.

References

1 A. Giannis and T. Kolter, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1244.
2 (*a*) W. M. Kazmierski, H. I. Yamamura and V. J. Hruby, *J. Am. Chem. Soc.*, 1991, **113**, 2275; (*b*) P. W. Schiller, G. Weltrowska, T. M. D. Nguyen, C. Lemieux, N. N. Chung, B. J. Marsden and B. C. Wilkes, *J. Med. Chem.*, 1991, **34**, 3125; (*c*) D. J. Kyle, J. A. Martin, R. M. Burch, J. P. Carter, S. Lu, S. Meeker, J. C. Prosser, J. P. Sullivan, J. Togo, L. Noronha-Blob, J. A. Sinsko, R. F. Walters, L. W. Whaley and R. N. Hiner, *J. Med. Chem.*, 1991, **34**, 2649; (*d*) M. Feletou, P. Robineau, M. Lonchampt, E. Bonnardel, C. Thurieau, J. L. Fauchere, P. Widdowson, J. P. Mahieu, B. Serkiz, J. P. Volland, C. Martin, E. Naline, C. Advenier, J. F. Prost and E. Canet, *J. Pharm. Expt. Therap.*, 1995, **273**, 1071; (*e*) B. C. Wilkes and P. W. Schiller, *Biopolymers*, 1995, **37**, 391.
3 C. Wang and H. I. Mosberg, *Tetrahedron Lett.*, 1995, **36**, 3623.
4 M. Okada, T. Takahashi, M. Yokota, T. Kawasaki and S. Nagaoka, *Jpn. Kokai Tokkyo Koho*, Japanese Patent JP 02103071 A2 900731 Heisei.
5 (*a*) J. W. Zhang, J. Y. Guo and X. T. Liang, *Chin. Chem. Lett.*, 1995, **6**, 651; (*b*) H. Bieraugel, H.-P. Soetens and U. K. Pandit, *Heterocycles*, 1977, **7**, 37.
6 (*a*) M. Cutolo, V. Fiandanese, F. Naso and O. Sciacovelli, *Tetrahedron Lett.*, 1983, **24**, 4603; (*b*) A.-S. Carlström and T. Frejd, *Synthesis*, 1989, 414; (*c*) A.-S. Carlström and T. Frejd, *Acta Chem. Scand.*, 1992, **46**, 163; (*d*) J. H. Dygos, E. E. Yonan, M. G. Scaros, O. J. Goodmonson, D. P. Getman, R. A. Periana and G. R. Beck, *Synthesis*, 1992, 741.
7 S. E. Gibson (née Thomas) and R. J. Middleton, *J. Chem. Soc., Chem. Commun.*, 1995, 1743.
8 (*a*) D. A. Heerding, C. Y. Hong, N. Kado, G. C. Look and L. E. Overman, *J. Org. Chem.*, 1993, **58**, 25, 6947; (*b*) G. H. Posner, K. S. Webb, E. Asirvatham, S. S. Jew and A. Degl'Innocenti, *J. Am. Chem. Soc.*, 1988, **110**, 4754.
9 M. A. Ciufolini and M. E. Browne, *Tetrahedron Lett.*, 1987, **28**, 171.
10 E. Campaigne and M. P. Georgiadis, *J. Heterocycl. Chem.*, 1969, **6**, 339.
11 R. Grigg, V. Sridharan, P. Stevenson, P. Teasdale, M. Thornthon-Pett and T. Worakun, *Tetrahedron*, 1991, **47**, 9703.
12 (*a*) C. E. Castro, R. Havlin, V. K. Honwad, A. Malte and S. Mojé, *J. Am. Chem. Soc.*, 1969, **91**, 6464; (*b*) M. A. Ciufolini, H. B. Qui and M. E. Browne, *J. Org. Chem.*, 1988, **53**, 4149.
13 S. E. Gibson (née Thomas) and R. J. Middleton, *Contemp. Org. Synth.*, 1996, **3**, 447.
14 See, for example, (*a*) J. J. Masters, D. K. Jung, W. G. Bornmann, S. J. Danishefsky and S. de Gala, *Tetrahedron Lett.*, 1993, **34**, 7253; (*b*) D. C. Horwell, P. D. Nichols, G. S. Ratcliffe and E. Roberts, *J. Org. Chem.*, 1994, **59**, 4418; (*c*) S. Ma and E. Negishi, *J. Org. Chem.*, 1994, **59**, 4730; (*d*) S. Ma and E. Negishi, *J. Am. Chem. Soc.*, 1995, **117**, 6345; (*e*) J. H. Rigby, R. C. Hughes and M. J. Heeg, *J. Am. Chem. Soc.*, 1995, **117**, 7834.

Paper 6/05286J
Received 29*th July* 1996
Accepted 11*th September* 1996