Pergamon

Tetrahedron 58 (2002) 1719–1737

TETRAHEDRON

Fused and bridged bi- and tri-cyclic lactams via sequential metallo-azomethine ylide cycloaddition–lactamisation

Paul Blaney,[a] Ronald Grigg,[a,*] Zoran Rankovic,[b] Mark Thornton-Pett[a] and Juan Xu[a]

[a]*Molecular Innovation, Diversity and Automated Synthesis (MIDAS) Centre, School of Chemistry, The University of Leeds, Leeds LS2 9JT, UK*

[b]*Organon Laboratories, Newhouse, Lanarkshire ML1 5SH, UK*

Received 25 October 2001; revised 29 November 2001; accepted 3 January 2002

Abstract—Aldimines of α-amino esters derived from aldehydes bearing an α-, β- or γ-protected amino group undergo $AgOAc/R_3N$ catalysed cycloaddition to electronegative olefins (dipolarophile). Subsequent unmasking of the amino group and lactamisation, spontaneous in most cases, generates 5–7 membered fused and bridged bi- and tri-cyclic lactams. The regioselectivity of the lactamisation is controlled by appropriate choice of the dipolarophile.

1. Introduction

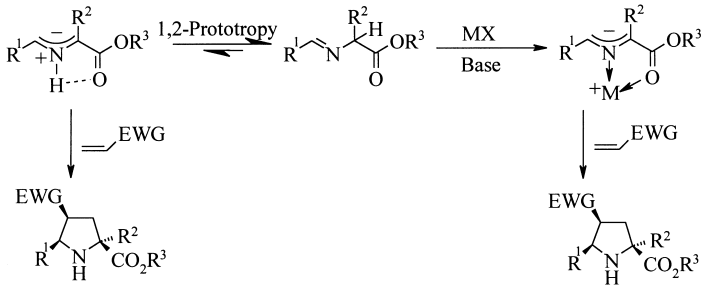
The 1,3-dipolar cycloaddition reaction of azomethine ylides is a powerful method for the synthesis of polysubstituted pyrrolidines, receiving much attention due to the presence of pyrrolidines in a number of alkaloids and in pharmaceutically important compounds.[1] There are a variety of ways to generate azomethine ylides,[2] with a number of the major routes having been extensively developed within our group. Two of these, the 1,2-prototropic[3] and *N*-metallation routes,[4] employ readily available aldimines of α-amino esters as the source of azomethine ylides (Scheme 1).

2. Results and discussions

The investigation described herein was devised to access fused and bridged polycyclic lactams incorporating a pyrrolidine and one or two additional 5–7 membered lactam rings via 1,3-dipolar cycloaddition of metallo-azomethine ylides using novel aldehydes incorporating a protected primary amino group which, upon deprotection, undergoes lactamisation.

2.1. *N*-Phthalimido protected amino aldehyde route to bicyclic lactams

2.1.1. 5- and 6-membered fused bicyclic lactams. *N*-Phthalimidoacetaldehyde **1a** and 3-(*N*-phthalimido)-propionaldehyde **1b**[5,6] were condensed with α-amino esters **2** to give aldimines **3a–h** (Scheme 2), which underwent 1,3-dipolar cycloaddition with acrylate esters **4** in toluene, mediated by $AgOAc–NEt_3$, to give pyrrolidine *endo*-isomers **5a–j** (Table 1). Hydrazinolysis of the phthalimide group gave the corresponding primary amines which spontaneously cyclised to lactams **6b**,**c** and **e–h** as the sole products reflecting the kinetic preference for

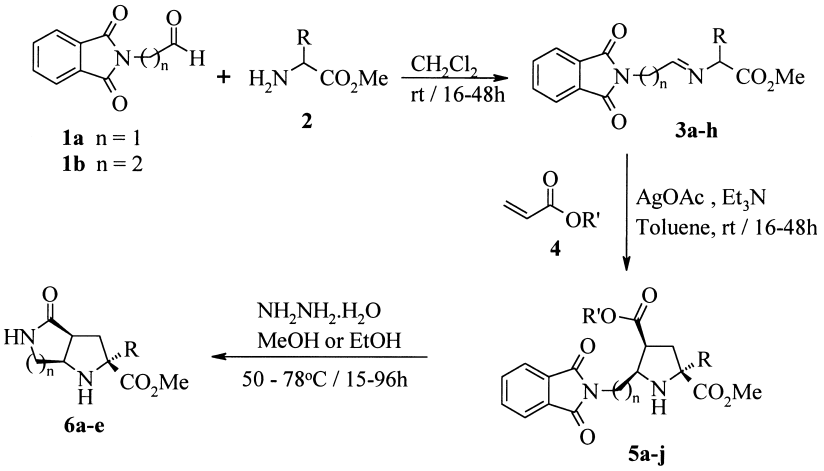


Scheme 1.

Keywords: azomethine ylide; cycloaddition; heterocycles; lactamisation; bridged and fused rings.

* Corresponding author. Tel./fax: +44-113-233-6501; e-mail: r.grigg@chem.leeds.ac.uk

0040–4020/02/$ - see front matter
PII: S0040-4020(02)00029-7

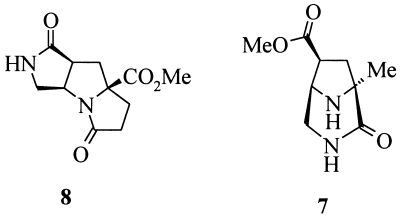


Scheme 2.

Table 1. Sequential 1,3-dipolar cycloaddition–lactamisation of imines **3a–h** (Scheme 2)

n	Imine	R′	R	Cycloadduct (%)	Lactam (%)
1	**3a**	Me	Me	**5a** (65)	**6a:7(1:1) 70** (70)
1	**3b**	Me	$(CH_2)_2SMe$	**5b** (70)	**6b** (96)
1	**3c**	Me	3-Indolylmethyl	**5c** (40)	**6c** (56)
1	**3d**	Me	$(CH_2)_2CO_2Me$	**5d** (92)	**8** (91)
1	**3e**	Me	Bn	**5e** (87)	**6e** (77)
1	**3e**	Bn	Bn	**5f** (52)	**6e** (83)
2	**3f**	Me	Bn	**5g** (72)	**6f** (72)
2	**3f**	Bn	Bn	**5h** (64)	**6f** (76)
2	**3g**	Me	Me	**5i** (71)	**6g** (80)
2	**3h**	Me	3-Indolylmethyl	**5j** (62)	**6h** (91)

5-membered ring formation. In the case of cycloadduct **5a** a 1:1 mixture of 5-membered fused, **6a**, and 6-membered bridged lactams **7** was obtained whilst in the case of cycloadduct **5d** [R=$(CH_2)_2CO_2Me$] hydrazinolysis afforded a [5.5.5]-tricyclic bis-lactam, **8**. The use of benzyl acrylate instead of methyl acrylate gave lower yields in the 1,3-dipolar cycloaddition step but, the lactamisation onto the benzyl ester gave higher yields than for the methyl ester. The structures of lactams **6a**, **6e** and **6f** were unequivocally established by single crystal X-ray analysis (Fig. 1).



8 **7**

2.1.2. Fused 7-membered bicyclic lactams. 7-Membered bicyclic lactams were accessed by the 1,3-dipolar cycloaddition/lactamisation protocol by employing **9** as the aldehyde component in imine formation (Scheme 3).

4-(*N*-Phthalimido)-butyraldehyde **9**[5], which was made from potassium phthalimide and 2-(3-chloropropyl)-1,3-dioxan,[7] was condensed with alanine and phenylalanine methyl ester (1.05 mol equiv.) in dichloromethane at room temperature for 22 h to give the imines **10a** and **10b**, which underwent 1,3-dipolar cycloaddition reactions with methyl acrylate (5 mol equiv.) in the presence of silver(I) acetate (1.1 mol equiv.) and triethylamine (1.1 mol equiv.) in toluene at room temperature over 18 h to give pyrrolidines **11a** and **11b** in 51 and 47% yield, respectively from the aldehyde **9**. When **11a** and **11b** were heated with hydrazine monohydrate (1.5 mol equiv.) in methanol at 55°C, the corresponding primary amines **12a** and **12b** were isolated in quantitative yield. Refluxing **12a**,**b** in methanol or toluene gave degradation products with no observable lactamisation whilst refluxing **12a**,**b** in methanol with sodium methoxide (1.5 mol equiv.) for 4.5 h induced lactamisation to give a 4:1 mixture (30%) of epimers **13a** and **14a** or a 9:1 (12%) mixture of **13b** and **14b**. Thus the lactamisation of the amino acid esters using sodium methoxide in refluxing methanol was low yielding and led to epimeric products. However an alternative approach circumvented these problems (Scheme 4). Thus **12b** was hydrolysed in refluxing 1 M HCl over 3.5 h to give the diamino diacid dihydrochloride **15** in quantitative yield. This was dissolved in dry acetonitrile (**15** is insoluble in neat thionyl chloride) followed by addition of excess thionyl chloride with stirring at room temperature for 16 h to give the diacid chloride **16**. The lactamisation was performed according to a similar literature example.[8] Two solutions comprising diacid chloride hydrochloride **16** dissolved in a minimum of dry acetonitrile and diluted with dry benzene and triethylamine (7 mol equiv.) dissolved in dry benzene were added dropwise simultaneously, with stirring, over 40 min at room temperature to dry benzene with overall high dilution (~0.002 M). This mixture was stirred for a further 2 h with subsequent addition of excess methanol and stirring at room temperature for 16 h to give the lactam **13b** in an overall yield of 90% from **12b**.

This sequence could not be applied to the analogous diacid dihydrochloride salt of **12a** since it was insoluble in both acetonitrile and neat thionyl chloride.

2.1.3. Bridged bicyclic lactams. The 1,3-dipolar cycloaddition/lactamisation protocol was extended to the synthesis of 6- and 7-membered bridged bicyclic lactams by employing *N*-methylmaleimide (Scheme 5) or phenyl vinyl sulfone (Scheme 6) as the dipolarophile. Use of these dipolarophiles forces lactamisation to take place on the ester derived from the amino acid moiety.

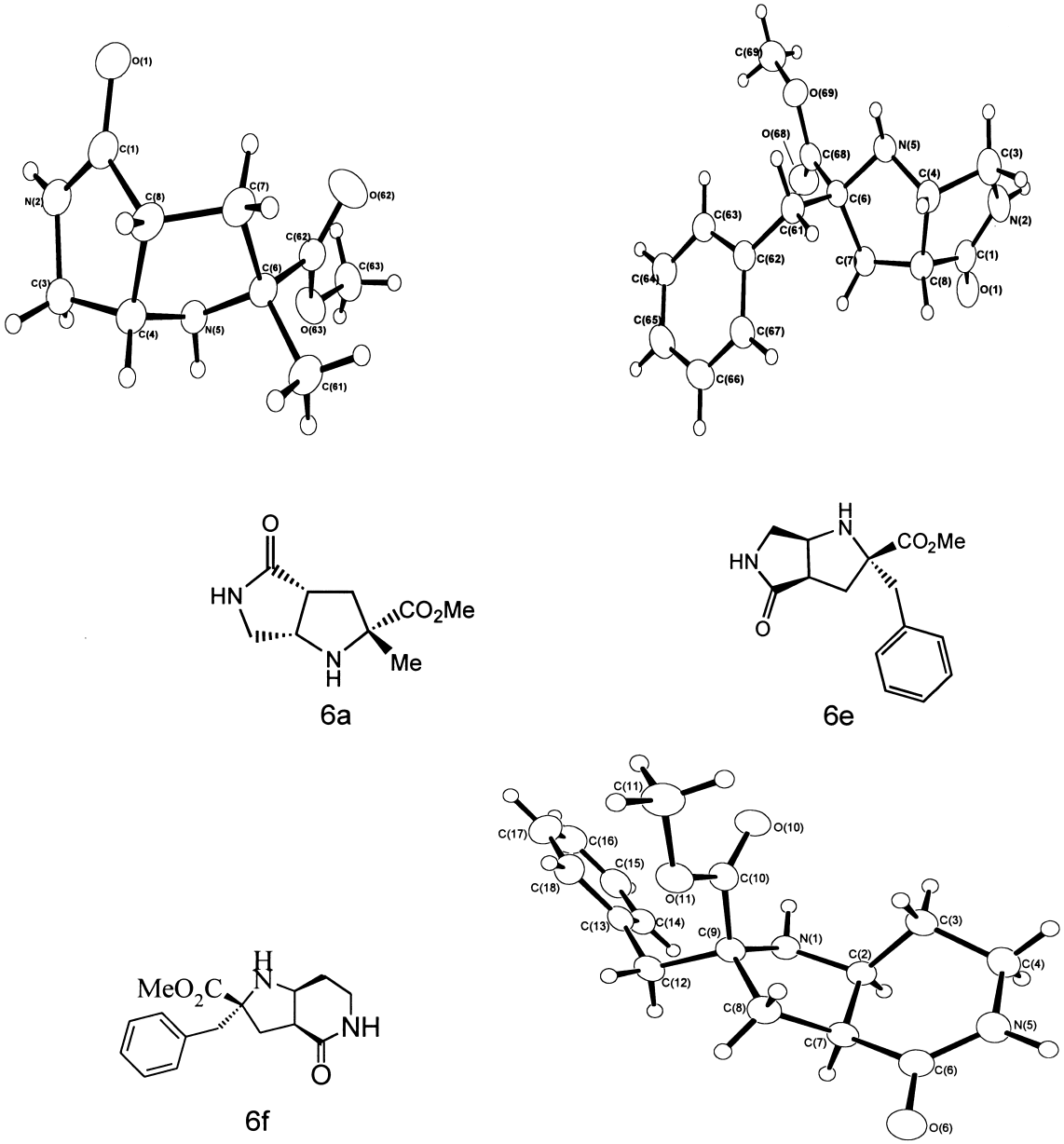


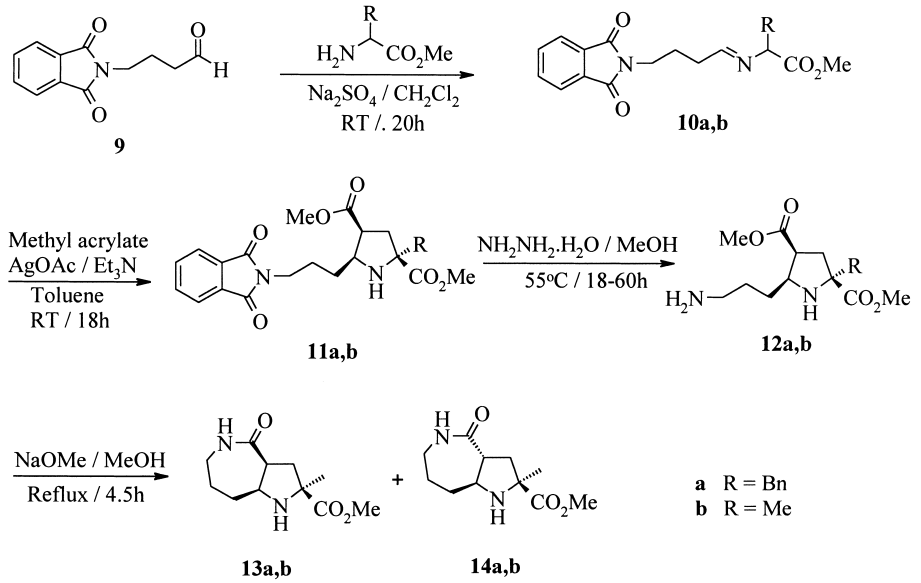
Figure 1. X-Ray crystal structures of **6a**, **6e** and **6f**.

The imines **3a**–**e** and **3e**,**f** underwent 1,3-dipolar cycloaddition with *N*-methylmaleimide and phenyl vinyl sulfone (1.05–1.5 equiv.), respectively using silver(I) acetate (1.05–1.2 equiv.) and triethylamine (1.05–1.2 equiv.) in toluene at room temperature. Deprotection of **17a**–**e** and **20** with hydrazine (50–78°C, 15–84 h) initiated lactamisation generating bridged-ring products **18a**–**e** (Scheme 5) and **21** (Scheme 6) in good yields. A second lactamisation occurred with **3d** [R=$(CH_2)_2CO_2Me$] to produce a tetracyclic bis-lactam **19**. Hydrazinolysis of the phthalimide group of **22** gave primary amine **23** in quantitative yield. Refluxing **23** in methanol with sodium methoxide (1 equiv.) induced lactamisation to give a 2:1 mixture (71%) of epimers **24** and **25** (Scheme 7).

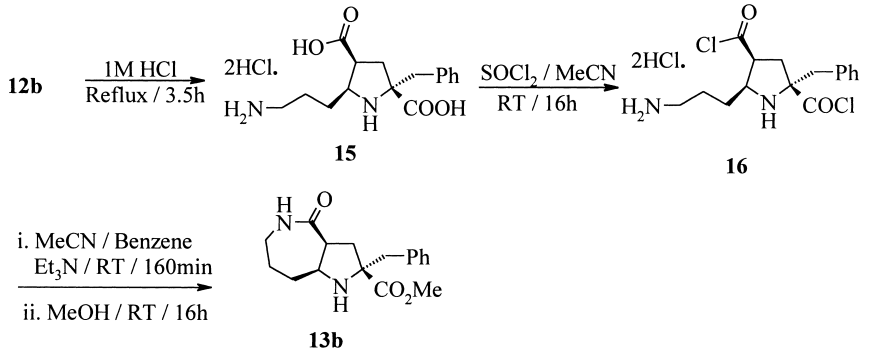
Where lactamisation does not occur spontaneously on the removal of the phthalimide protecting group, it is possible to use the primary amine in intermolecular reactions. This was exemplified by the synthesis of bicyclic urea **26** (Scheme 8). Amine **23** and triethylamine (2.2 mol equiv.) dissolved in THF (high dilution) were heated with phosgene (1.05 mol equiv. as a 20% solution in toluene) at 0°C and the reaction allowed to warm to room temperature with stirring over 16 h. Work up afforded bicyclic urea **26** in 56% yield.

2.2. *N*-Boc amino aldehyde route to bicyclic lactams

The Boc protecting group was evaluated as an alternative to the phthalimide group. Thus *N*-Boc-glycine **27a** and *N*-Boc-β-alanine **27b** were converted to their corresponding mixed anhydrides with *t*-butyl chloroformate (1.1 mol equiv.) and *N*-methyl morpholine (2.2 mol equiv.) in dichloromethane. Treatment with *N*,*O*-dimethylhydroxylamine hydrochloride (1 mol equiv.) at −15°C for 15 min then at room temperature for 18 h gave the Weinreb amides **28a**,**b** in quantitative yield. The Weinreb amides were reduced using lithium



Scheme 3.



Scheme 4.

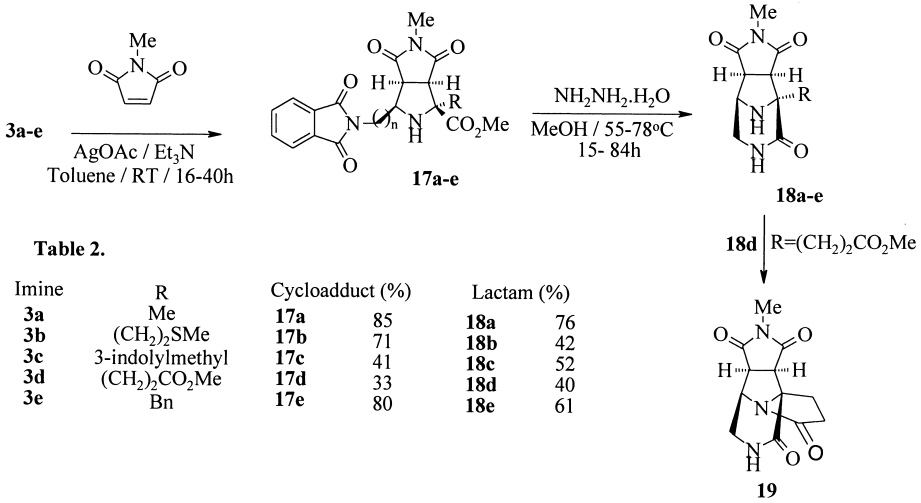
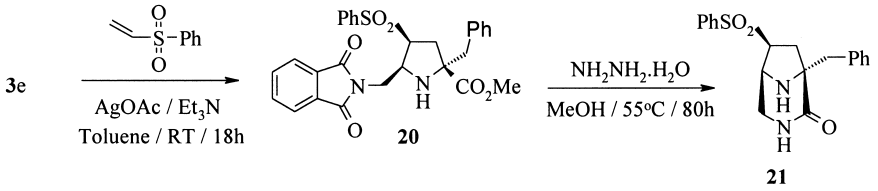


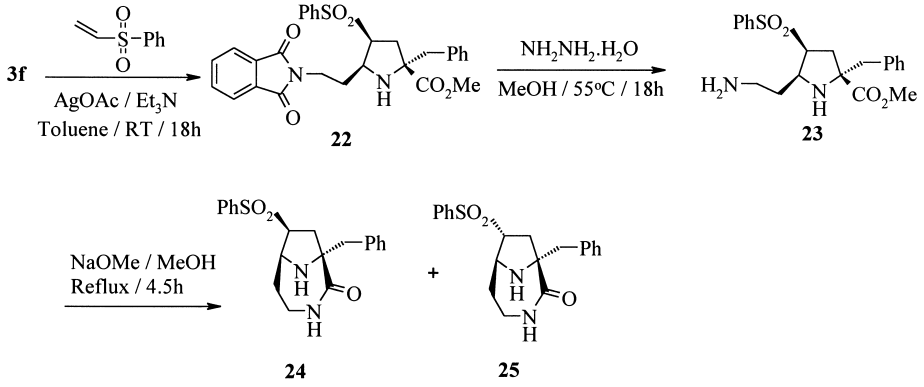
Table 2.

Imine	R	Cycloadduct (%)		Lactam (%)	
3a	Me	**17a**	85	**18a**	76
3b	$(CH_2)_2SMe$	**17b**	71	**18b**	42
3c	3-indolylmethyl	**17c**	41	**18c**	52
3d	$(CH_2)_2CO_2Me$	**17d**	33	**18d**	40
3e	Bn	**17e**	80	**18e**	61

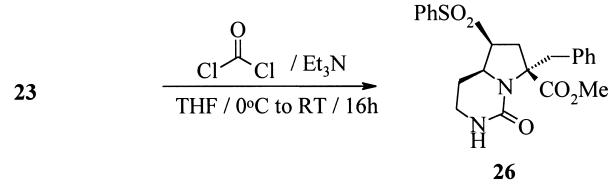
Scheme 5.



Scheme 6.

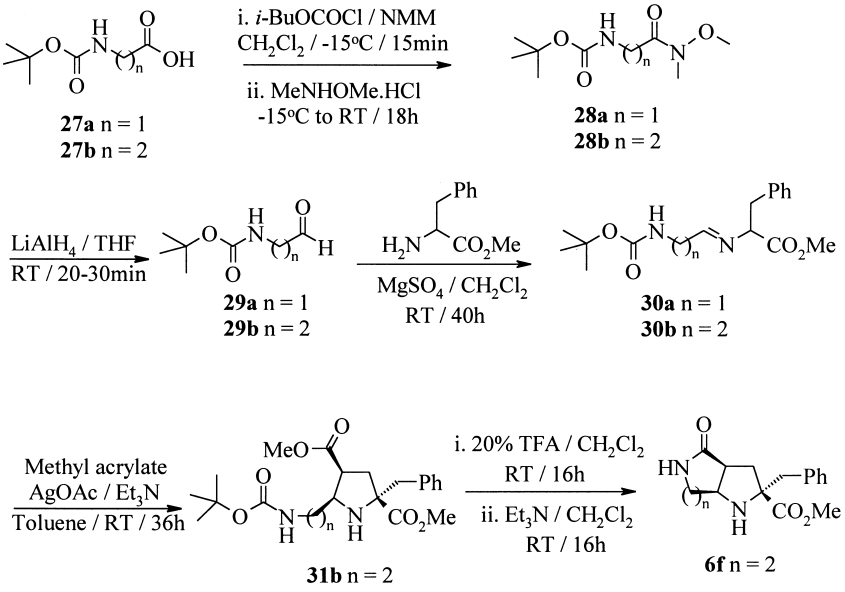


Scheme 7.

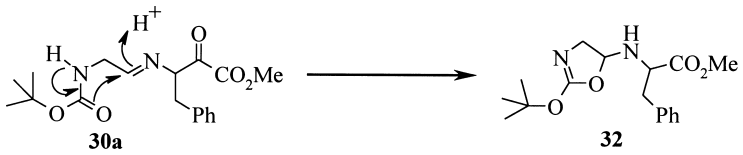


Scheme 8.

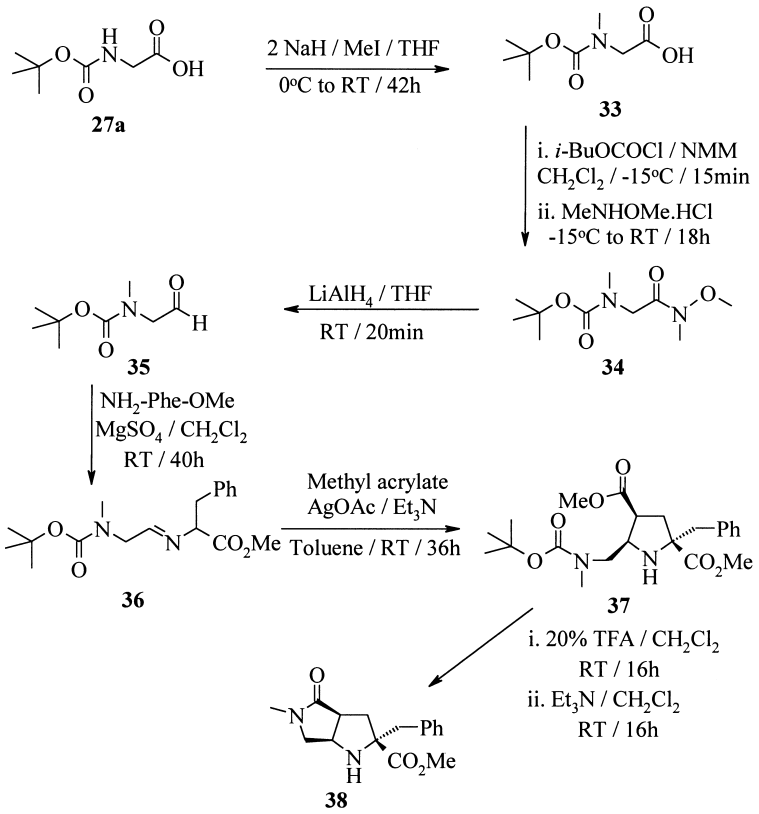
aluminium hydride (5 mol equiv.) in THF at room temperature for 20–30 min according to a literature procedure[9] to give the aldehydes **29a** and **29b** in 60 and 64% yield, respectively (Scheme 9). Condensation of aldehyde **29b** with phenylalanine methyl ester gave the imine **30b**. An analogous reaction with **29a** failed to give imine, and it was hypothesised that cyclisation of **30a** to **32** had occurred (Scheme 10). When this latter material was used in the 1,3-dipolar cycloaddition it was recovered unchanged. Thus the oxazoline tautomer **32**, if formed, was not in equilibrium with **30a**. Imine **30b** and methyl acrylate (5 mol equiv.) reacted, using silver(I) acetate (1.2 mol equiv.) and triethylamine (1.2 mol equiv.) in toluene at room temperature for 36 h, to give *endo*-pyrrolidine **31b** in 50% yield. A similar yield was obtained when leaving the reaction for 56 h (48%). The Boc-protecting group was removed using 20% TFA in dichloromethane at room temperature to give the



Scheme 9.



Scheme 10.



Scheme 11.

intermediate TFA salt, which was treated with triethylamine (2.2 mol equiv.) in dichloromethane at room temperature to give the bicyclic lactam **6f** in 82% yield.

The suggested cyclisation (Scheme 10) involves the Boc-oxygen atom and requires a Boc-*N*-H proton for formation of oxazoline **32**. If the Boc-nitrogen was alkylated this problem would be prevented and have the added advantage of introducing a further point of diversity. Several literature methods for the *N*-alkylation of Boc-protected amino acids using sodium hydride (>2 mol equiv.) and alkyl halides (>2 mol equiv.) were found.[10] The *N*-methylation of **27a** was carried out according to these literature examples using sodium hydride (4 mol equiv.) and methyl iodide (4 mol equiv.) in THF to give **33** in a 98% yield. This was then converted to the Weinreb amide **34** in 83% yield (Scheme 11). Reduction of **34** using lithium aluminium hydride (5 mol equiv.) in THF at room temperature gave the aldehyde **35** in 46% yield. This was condensed with phenylalanine methyl ester (1.1 mol equiv.) in dichloromethane to give the imine **36**, which underwent cycloaddition with methyl acrylate (5 mol equiv.) using silver(I) acetate (1.2 mol equiv.) and triethylamine (1.2 mol equiv.) in toluene at room temperature for 38 h to give the *endo*-pyrrolidine **37** in 53% overall yield from **35**. Lactamisation was achieved by removal of the Boc-group using 20% TFA in dichloromethane at room temperature to give the TFA salt of **38**, which was treated with triethylamine (2.2 mol equiv.) in dichloromethane at room temperature to give **38** in 63% yield.

In conclusion, processes for the synthesis of fused and bridged bicyclic 5–7 membered lactams have been developed. The phthalimide route is more convenient for the general synthesis of bicyclic lactams, but the Boc-protection route offers easy access to *N*-substituted lactams.

3. Experimental

3.1. General

Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. ^{1}H Nuclear magnetic resonance spectra were recorded at 250 MHz on a Bruker

AC 250 instrument, at 300 MHz on a Bruker DPX 300 instrument, at 400 MHz on a Bruker WP 400 instrument or at 500 MHz on a Bruker DRX 500 instrument, and referenced to tetramethylsilane or residual protonated solvent. Deuterochloroform was used as solvent unless stated otherwise, and chemical shifts are given in parts per million (δ) down field from tetramethylsilane. Assignments of ^{1}H signals were made with the aid of 2D COSY spectra where necessary. Microanalyses were obtained using a Carlo Erba Elemental Analyser MOD 1106 instrument. Infrared spectra were recorded as nujol mulls on a Nicolet FTIR spectrophotometer. Mass spectra were recorded on a V.G.-AutoSpec spectrometer using electron impact (EI) operating at 70 eV or by fast atom bombardment (FAB), as specified. Accurate molecular weights were determined using perfluorokerosene as an internal standard. X-Ray analysis was performed on a Stoe STADI 4-circle machine or a Nonius Kappa CCD area-detector diffractometer. Flash column chromatography was performed on silica gel 60 (Merk 230–400 mesh). Ether refers to diethyl ether and petroleum ether refers to the fraction with boiling point 40–60°C. All reagents and solvents were purified according to literature procedure.[11]

3.1.1. Phthalimidoacetaldehyde 1a. 6N HCl (60 ml) was added to a solution of phthalimidoacetaldehyde diethyl acetal (2.95 g, 1.5 mmol) in THF (60 ml) at room temperature with stirring and stirring was continued for 14 h. The solvent was then removed under reduced pressure, and the residue was treated with saturated aqueous $NaHCO_3$ and extracted with DCM. The organic layer was dried ($MgSO_4$), filtered, and the filtrate evaporated to afford the product **1a** (2.84 g) in quantitative yield as colourless needles from EtOAc–petroleum ether, mp 110–112°C. (Found: C, 63.30, H, 3.80, N, 7.45. $C_{10}H_7O_3N$ requires: C, 63.50, H, 3.70, N, 7.40%); δ 4.58 (s, 2H, CH_2), 7.77 and 7.90 (2×m, 2×2H, ArH) and 9.67 (s, 1H, CHO); *m/z* (%): 189 (M^+, 4), 160 (100), 147 (5), 133 (19), 104 (22), 76 (33) and 50 (24); ν_{max} (cm^{-1}): 3056, 2988, 1781 (C═O) and 1723 (C═O).

3.1.2. 3-(*N*-Phthalimido)-propionaldehyde 1b.[5,6] A solution of DMSO (2.06 ml, 29.04 mmol) in dichloromethane (20 ml) was added dropwise (15 min) to a stirred solution of oxalyl chloride (1.27 ml, 14.54 mmol) in dichloromethane (90 ml) at −70°C (isopropanol/dry ice) and the mixture was stirred at −70°C for 5 min. A solution *N*-(3-hydroxypropyl)-phthalimide (2.71 g, 13.22 mmol) in dichloromethane (40 ml) was added dropwise (15 min) and the solution was stirred at −70°C for 40 min. when triethylamine (9.33 ml, 66.10 mmol) was added dropwise (5 min) and the mixture stirred at −70°C for 5 min, then allowed to warm to room temperature. The mixture was washed with water (150 ml), 1 M HCL (80 ml), saturated sodium bicarbonate (80 ml) and water (80 ml). The organic layer was dried (Na_2SO_4) and the solvent evaporated. The residue was purified by flash column chromatography (3:2 v/v ether–petroleum ether) to afford the product (2.59 g, 97%) as a colourless solid, mp 125.5–126.5°C (lit. 126.0–127.0°C). δ (400 MHz): 2.87 (dt, *J*=1.0 and 7.0 Hz, 2H, CH_2CH_2CHO), 4.04 (t, *J*=7.0 Hz, 2H, NCH_2CH_2), 7.71–7.74 (m, 2H, ArH), 7.84–7.86 (m, 2H, ArH) and 9.82 (t, *J*=1.2 Hz, CH_2CHO); *m/z* (%): 203 (M^+, 9), 175 (56), 160 (100), 130 (20) and 105 (29); ν_{max} (cm^{-1}): 3056, 2988, 1775 (C═O) and 1717 (C═O).

3.1.3. 4-(*N*-Phthalimido)-butyraldehyde 9.[5] 2-(3-Chloropropyl)-1,3-dioxolane (3.92 ml, 29.70 mmol) was added to a stirred suspension of potassium phthalimide (5.00 g, 27.00 mmol) in DMF (200 ml) at 80°C and the suspension was stirred for 18 h. The mixture was allowed to cool, diluted with water (300 ml) and extracted with dichloromethane (3×150 ml). The combined organic layers were washed with 0.4 M NaOH (100 ml), dried ($MgSO_4$) and the solvent evaporated to afford 2-[3-(*N*-phthalimido)-propyl]-1,3-dioxolane (4.00 g, 54%) as a colourless solid, mp 109.5–111.0°C. (Found: C 63.85; H, 6.0; N, 5.25. $C_{15}H_{17}NO_4 \cdot 1/2H_2O$ requires: C, 63.4; H, 6.4; N, 4.95%); δ (250 MHz): 1.70–1.83 (m, 6H, $NCH_2CH_2CH_2CH$ and $OCH_2CH_2CH_2O$), 3.74 (t, *J*=6.9 Hz, 2H, NCH_2CH_2), 3.81–3.98 (m, 4H, $OCH_2CH_2CH_2O$), 4.91 (t, *J*=4.2 Hz, 1H, $CH_2CH(OCH_2)OCH_2$), 7.70–7.73 (m, 2H, ArH) and 7.83–7.86 (m, 2H, ArH). *m/z* (%): 275 (M^+, 0.2), 274 (1), 216 (5), 174 (16), 160 (56), 104 (24) and 73 (100); ν_{max} (cm^{-1}): 3056, 2985–2933, 1773 and 1713 (C═O).

The ketal (2.00 g, 7.27 mmol) was dissolved in acetone (60 ml) and 2 M HCl (30 ml) at room temperature and the resulting solution stirred for 16 h then poured into water (120 ml) and extracted with dichloromethane (3×80 ml). The combined organic layers were washed with saturated sodium bicarbonate, dried ($MgSO_4$) and the solvent evaporated to afford the product (1.14 g, 72%) as a pale yellow glass. δ (250 MHz): 2.02 (quintet, *J*=6.8 Hz, 2H, $CH_2CH_2CH_2$), 2.55 (t, *J*=7.2 Hz, 2H, CH_2CH_2CHO), 3.75 (t, *J*=6.8 Hz, 2H, NCH_2CH_2), 7.69–7.77 (m, 2H, ArH), 7.83–7.89 (m, 2H, ArH) and 9.78 (s, 1H, CHO); *m/z* (%): 217 (M^+, 1), 215 (11), 174 (46), 160 (100), 130 (14), 104 (21) and 76 (27); ν_{max} (cm^{-1}): 3057, 2985, 1774 (C═O) and 1714 (C═O).

3.2. General method for the preparation of imines 3a–h and 10a,b

Method A. Excess $MgSO_4$, Na_2SO_4 or 4 Å molecular sieves were added to a stirred solution of aldehyde (1 equiv.) and α-amino acid ester (1.05–1.1 equiv.) in dichloromethane at room temperature and the mixture was stirred for 16–48 h. The mixture was filtered and the filtrate evaporated to give the imines, which were used without purification.

Method B. Excess $MgSO_4$ or Na_2SO_4 were added to stirred solution of aldehyde (1 equiv.), α-amino acid ester hydrochloride (1.05–1.1 equiv.) and triethylamine (1.05–1.1 equiv.) in dichloromethane at room temperature and the mixture was stirred for 16–20 h. The mixture was filtered and the filtrate was washed with saturated brine (×2). The organic layer was dried ($MgSO_4$) and the solvent evaporated to give the imines, which were used without purification.

3.2.1. Methyl (±) 2-[2-(*N*-phthalimido)ethylideneamino]-propionate 3a. Prepared according to the general procedure (Method A) from aldehyde **1a** (283 mg, 1.5 mmol) and alanine methyl ester (170 mg, 1.65 mmol) over 4 Å molecular sieves (1 g) in dichloromethane (10 ml) for 16 h

to afford the product **3a** as a pale yellow syrup (400 mg, 97%). δ 1.39 (d, J=6.8 Hz, 3H, Me), 3.71 (s, 3H, OMe), 4.08 (q, J=6.8 Hz, 1H, CH), 4.51 (d, J=3.0 Hz, 2H, CH_2), 7.74 (m, 3H, N=CH and 2×ArH) and 7.88 (m, 2H, ArH); m/z (%): 274 (M^+, 6), 259 (14), 231 (13), 215 (100), 197 (13), 170 (10), 161 (61), 147 (5), 133 (15), 114 (13), 104 (33), 88 (38), 76 (39), 68 (53) and 59 (33).

3.2.2. Methyl (±) 2-[2-(*N*-phthalimido)ethylideneamino]-4-methylsulfanylbutyrate 3b. Prepared according to the general procedure (Method A) from aldehyde **1a** (756 mg, 4 mmol) and methionine methyl ester (705 mg, 4.3 mmol) over $MgSO_4$ (2 g) in dichloromethane (20 ml) for 16 h to afford the product **3b** as a pale yellow syrup (1.34 g) in quantitative yield. δ 2.05 (s, 3H, SMe), 2.09 (m, 2H, CH_2), 2.51 and 2.70 (2×m, 2×1H, CH_2), 3.71 (s, 3H, OMe), 4.06 (dd, J=5.0 and 8.4 Hz, 1H, CH), 4.52 (d, J=2.8 Hz, 2H, NCH_2) and 7.74 and 7.87 (2×m, 5H, N=CH and 4×ArH); m/z (%): 334 (M^+, 3), 275 (15), 227 (10), 213 (8), 201 (16), 174 (100), 160 (24), 133 (8), 114 (12), 104 (29), 100 (12), 87 (11), 80 (17) and 61 (84).

3.2.3. Methyl (±) 2-[2-(*N*-phthalimido)ethylideneamino]-3-(3′-indolyl)propionate 3c. Prepared according to the general procedure (Method A) from aldehyde **1a** (869 mg, 4.6 mmol) and tryptophan methyl ester (1.1 g, 5 mmol) over $MgSO_4$ (2 g) in dichloromethane (25 ml) for 23 h to afford the product **3c** as an amorphous pale yellow solid (1.88 g) in quantitative yield. δ 3.06 (dd, J=9.3 and 14.4 Hz, 1H, C*H*H), 3.40 (dd, J=4.2 and 14.4 Hz, 1H, CH*H*), 3.72 (s, 3H, OMe), 4.04 (dd, J=4.2 and 9.3 Hz, 1H, CH), 4.36 (m, 2H, NCH_2) and 6.98–8.10 (m, 11H, N=CH and 10×ArH); m/z (%): 389 (M^+, 4), 229 (27), 169 (19), 160 (10), 130 (100), 115 (5), 103 (8), 84 (8), 77 (13) and 49 (10).

3.2.4. Methyl (±) 2-[2-(*N*-phthalimido)-ethylideneamino]-pentanedioate 3d. Prepared according to the general procedure (Method A) from aldehyde **1a** (718 mg, 3.8 mmol) and glutamic acid dimethyl ester (718 mg, 4.1 mmol) over $MgSO_4$ (2 g) in dichloromethane (20 ml) for 48 h to afford the product **3d** as a pale yellow syrup (1.28 g, 97%). δ 2.01–2.33 (m, 4H, 2×CH_2), 3.62 and 3.68 (2×s, 2×3H, 2×OMe), 3.91 (dd, J=4.8 and 8.3 Hz, 1H, CH), 4.50 (d, J=2.9 Hz, 2H, NCH_2), 7.66 (t, J=2.9, 1H, N=CH) and 7.73 and 7.86 (2×m, 2×2H, ArH); m/z (%): 346 (M^+, 2), 287 (10), 227 (6), 186 (8), 160 (23), 147 (12), 116 (8), 104 (24), 84 (100), 76 (29), 56 (24) and 41 (29).

3.2.5. Methyl (±) 2-[2-(*N*-phthalimido)-ethylidenamino]-3-phenylpropionate 3e. Prepared according to the general procedure (Method A) from aldehyde **1a** (850 mg, 4.5 mmol) and phenylalanine methyl ester (844 mg, 4.72 mmol) over $MgSO_4$ (2 g) in dichloromethane (20 ml) for 16 h to afford the product **3e** as a pale yellow syrup (1.62 g) in quantitative yield. δ 2.95 (dd, J=9.2 and 13.4 Hz, 1H, PhC*H*H), 3.21 (dd, J=4.5 and 13.4 Hz, 1H, PhCH*H*), 3.71 (s, 3H, OMe), 3.96 (dd, J=4.5 and 9.2 Hz, 1H, CH), 4.35 (dd, J=2.8 and 16.8 Hz, 1H, NC*H*H), 4.43 (dd, J=3.4 and 16.8 Hz, 1H, NCH*H*) and 7.08–7.86 (m, 10H, N=CH and 9×ArH); m/z (%): 350 (M^+, 3), 291 (18), 259 (70), 199 (46), 190 (28), 172 (19), 160 (37), 144 (32), 130 (22), 120 (73), 112 (11), 104 (32), 91 (75), 88 (100), 77 (31), 65 (20) and 51 (14).

3.2.6. Methyl (±) 2-[3-(*N*-phthalimido)-propylidenamino]-3-phenylpropionate 3f. Prepared according to the general procedure (Method A) from aldehyde **1b** (0.591 g, 2.910 mmol) and L-phenylalanine methyl ester (0.574 g, 3.207 mmol) over $MgSO_4$ (1.7 g) in dichloromethane (15 ml) for 16 h to afford the product **3f** (1.162 g, 100%) as a colourless syrup δ (400 MHz): 2.58 (dt, J=4.5 and 7.0 Hz, 2H, CH_2CH_2CH), 2.95 (dd, J=9.0 and 13.6 Hz, 1H, CHC*H*HPh), 3.21 (dd, J=5.5 and 13.6 Hz, 1H, CHCH*H*Ph), 3.63 (s, 3H, CO_2Me), 3.78–3.89 (m, 2H, NCH_2CH_2), 3.91–3.95 (m, 1H, $NCH(CO_2Me)CH_2$), 7.09–7.14 (m, 3H, *ortho* and *para* ArH), 7.16–7.24 (m, 2H, *meta* ArH), 7.35 (t, J=4.5 Hz, 1H, CH_2CH=N), 7.70–7.72 (m, 2H, ArH) and 7.82–7.84 (m, 2H, ArH); m/z (ES+, %): 365 ($M+H^+$, 9) and 180 (100).

3.2.7. Methyl (±) 2-[3-(*N*-phthalimido)propylidenamino]-propionate 3g. Prepared according to the general procedure (Method B) from aldehyde **1b** (0.400 g, 1.970 mmol), L-alanine methyl ester hydrochloride (0.289 g, 2.069 mmol) and triethylamine (0.30 ml, 2.069 mmol) over Na_2SO_4 (1 g) in dichloromethane (12 ml) for 16 h to afford the product **3g** (0.592 g, 100%) as a colourless syrup. δ (250 MHz): 1.33 (d, J=6.9 Hz, 3H, CHMe), 2.69 (dt, J=1.7 and 6.6 Hz, 2H, CH_2CH_2CH=N), 3.63 (s, 3H, OMe), 3.91 (q, J=6.9 Hz, 1H, NC*H*MeCO$_2$Me), 3.98 (t, J=6.7 Hz, 2H, NCH_2CH_2) and 7.70–7.86 (m, 5H, ArH and CH_2CH=N).

3.2.8. Methyl (±) 2-[3-(*N*-phthalimido)propylidenamino]-3-(3′-indolyl)propionate 3h. Prepared according to the general procedure (Method A) from aldehyde **1b** (0.225 g, 1.108 mmol) and L-tryptophan methyl ester (0.266 g, 1.219 mmol) over Na_2SO_4 (1 g) in dichloromethane (10 ml) for 16 h to afford the product **3h** (0.480 g, 100%) as a pale brown syrup. δ (250 MHz): 2.51–2.57 (m, 2H, NCH_2CH_2CH=N), 3.09 (dd, J=8.7 and 14.5 Hz, 1H, CHC*H*HAr), 3.38 (dd, J=5.0 and 14.4 Hz, 1H, CHCH*H*Ar), 3.65 (s, 3H, OMe), 3.79 (t, J=7.1 Hz, 2H, NCH_2CH_2CH), 4.03 (dd, J=5.2 and 8.7 Hz, 1H, NC*H*(CH_2)CO_2Me), 6.98–7.39 (m, 5H, ArH and CH_2CH=N), 7.60–7.64 (m, 2H, ArH), 7.78–7.86 (m, 2H, ArH) and 8.02 (br s, 1H, indole N*H*); m/z (%): 403 (M^+, 5), 229 (13), 169 (10) and 130 (100).

3.2.9. Methyl (±) 2-[4-(*N*-phthalimido)butylidenamino]-3-phenylpropionate 10a. Prepared according to the general procedure (Method A) from aldehyde **9** (0.805 g, 3.710 mmol) and L-phenylalanine methyl ester (0.697 g, 3.900 mmol) over Na_2SO_4 (1.7 g) in dichloromethane (20 ml) for 20 h to afford the product **10a** (1.410 g, 100%) as a colourless syrup. δ (250 MHz): 1.70–1.80 (m, 2H, $CH_2CH_2CH_2$), 2.21–2.24 (m, 2H, CH_2CH_2CH=N), 2.85–3.35 (m, 2H, $CHCH_2Ph$), 3.55–3.65 (m, 2H, NCH_2CH_2), 3.72 (s, 3H, OMe), 7.09–7.28 (m, 6H, ArH and CH_2CH=N), 7.69–7.73 (m, 2H, ArH) and 7.81–7.86 (m, 2H, ArH); m/z (%): 379 ($M+H^+$, 5), 295 (22), 160 (94), 120 (70) and 91 (100).

3.2.10. Methyl (±) 2-[4-(*N*-phthalimido)butylidenamino]-propionate 10b. Prepared according to the general procedure (Method B) from aldehyde **9** (0.268 g, 1.238 mmol), L-alanine methyl ester hydrochloride

(0.190 g, 1.362 mmol) and triethylamine (0.19 ml, 1.362 mmol) over Na_2SO_4 (1 g) in dichloromethane (8 ml) for 16 h to afford the product **10b** (0.379 g, 100%) as a colourless syrup. δ (250 MHz): 1.41 (d, J=6.8 Hz, 3H, CH*Me*), 1.71–1.83 (m, 2H, $CH_2CH_2CH_2$), 1.90–2.02 (m, 1H, CH_2CHHCH=N), 2.33–2.41 (m, 1H, CH_2CHHCH=N), 3.62–3.73 (m, 2H, NCH_2CH_2), 3.72 (s, 3H, OMe), 3.92 (q, J=6.8 Hz, 1H, CHMe), 7.67–7.76 (m, 3H, ArH and CH_2CH=N) and 7.81–7.86 (m, 2H, ArH).

3.3. General method for the preparation of cycloadducts 5a–j, 11a,b, 17a–e, 20 and 22

Silver(I) acetate (1.05–1.3 equiv.), dipolarophile [methyl acrylate (1.5–5 equiv.), benzyl acrylate (1.5 equiv.), *N*-methylmaleimide (1.2–2 equiv.), or phenyl vinyl sulfone (1.05–1.1 equiv.)] and triethylamine (1.05–1.3 equiv.) were added (in the dark for AgOAc) to a stirred solution of imine (1 equiv.) in toluene at room temperature and the mixture was stirred for 16–48 h. The mixture was diluted with dichloromethane and washed with saturated ammonium chloride (×2) and water. The organic layer was dried ($MgSO_4$) and the solvent evaporated. The residue was purified via flash column chromatography to afford the cycloadducts.

3.3.1. Dimethyl (±) *endo*-5-[(*N*-phthalimido)methyl]-2-methyl-pyrrolidine-2,4-dicarboxylate 5a. AgOAc (280 mg, 1.68 mmol), methyl acrylate (227 mg, 2.5 mmol), imine **3a** (385 mg, 1.4 mmol) and triethylamine (240 μl, 1.68 mmol) in toluene (10 ml) were reacted by the general procedure for 40 h. Flash chromatography (Et_2O) afforded the product **5a** (328 mg, 65%) as colourless prisms from Et_2O–petroleum ether, mp 117–119°C. (Found: C, 59.95, H, 5.55, N, 7.50. $C_{18}H_{20}N_2O_6$ requires: C, 60.00, H, 5.60, N, 7.75%); δ 1.34 (s, 3H, Me), 1.97 (dd, J=7.6 and 13.7 Hz, 1H, CHH), 2.67 (dd, J=4.9 and 13.7 Hz, 1H, CH*H*), 2.9 (br s, 1H, NH), 3.10 (m, 1H, CH), 3.66 (m, 1H, NCH), 3.69 and 3.78 (2×s, 2×3H, 2×OMe), 3.84 (m, 2H, NCH_2) and 7.71 and 7.83 (2×m, 2×2H, ArH); *m*/*z* (%): (FAB) 361 (M^++1, 100), 301 (50), 200 (9), 160 (12), 154 (5), 140 (6), 122 (10), 94 (25) and 82 (6).

3.3.2. Dimethyl (±) *endo*-5-[(*N*-phthalimido)-methyl]-2-(2-methylsulfanyl-ethyl)pyrrolidine-2,4-dicarboxylate 5b. AgOAc (250 mg, 1.5 mmol), methyl acrylate (542 μl, 6 mmol), imine **3b** (422 mg, 1.26 mmol) and triethylamine (209 μl, 1.5 mmol) in toluene (10 ml) were reacted by the general procedure for 16 h. Flash chromatography (2:1 v/v Et_2O–petroleum ether) afforded the product **5b** (363 mg, 70%) as colourless prisms from CH_2Cl_2/petroleum ether, mp 116–117°C. (Found: C, 57.15, H, 5.85, N, 6.65, S, 7.70. $C_{20}H_{24}N_2O_6S$ requires: C, 57.15, H, 5.75, N, 6.65, S, 7.60%); δ 1.72 (m, 1H, CHH), 1.84–2.00 (m, 5H, CH_2 and SMe), 2.22 and 2.52 (2×m, 2×1H, CH_2), 2.65 (dd, J=3.9 and 13.9 Hz, 1H, CH*H*), 2.89 (br s, 1H, NH), 3.04 (m, 1H, CH), 3.69 (s, 3H, OMe), 3.62–3.79 (m, 5H, NCH, NCHH and OMe), 3.90 (dd, J=3.6 and 12.6 Hz, 1H, NCH*H*) and 7.74 and 7.86 (2×m, 2×2H, ArH); *m*/*z* (%): 420 (M^+, 5), 361 (100), 345 (17), 313 (14), 260 (99), 228 (28), 214 (8), 186 (9), 160 (34), 152 (33), 138, (13), 126 (9), 104 (13), 94 (15), 77 (10) and 61 (68).

3.3.3. Dimethyl (±) *endo*-5-[(*N*-phthalimido)-methyl]-2-(3′-indolylmethyl)pyrrolidine-2,4-dicarboxylate 5c. AgOAc (300 mg, 1.8 mmol), methyl acrylate (677 μl, 7.5 mmol), imine **3c** (584 mg, 1.5 mmol) and triethylamine (251 μl, 1.8 mmol) in toluene (10 ml) were reacted by the general procedure for 40 h. Flash chromatography (3:1 v/v Et_2O–petroleum ether) afforded the product **5c** (282 mg, 40%) as colourless needles from CH_2Cl_2/petroleum ether, mp 158–160°C. (Found: C, 65.45, H, 5.40, N, 8.80. $C_{26}H_{25}N_3O_6$ requires: C, 65.70, H, 5.30, N, 8.85%); δ 2.20 (dd, J=7.4 and 13.8 Hz, 1H, CHH), 2.70 (dd, J=4.1 and 13.8 Hz, 1H, CH*H*), 2.91 (m, 2H, NH and CH), 2.98 and 3.15 (2×d, J=14.1 Hz, 2×1H, indole-CH_2), 3.51 (m, 1H, NCH), 3.60 (dd, J=9.5 and 13.6 Hz, 1H, NCHH), 3.66 and 3.69 (2×s, 2×3H, 2×OMe), 3.77 (dd, J=4.1 and 13.6 Hz, 1H, NCH*H*), 6.61 (t, J=7.8 Hz, 1H, ArH), 6.96 (m, 2H, ArH), 7.23 and 7.51 (2×d, J=7.8 Hz, 2×1H, ArH), 7.74 and 7.83 (2×m, 2×2H, ArH) and 8.06 (br s, 1H, NH); *m*/*z* (%): 476 (M^++1, <1), 416 (7), 345 (100), 253 (9), 160 (34), 138 (29), 130 (11), 104 (5), 84 (16) and 49 (47).

3.3.4. Dimethyl (±) *endo*-5-[(*N*-phthalimido)-methyl]-2-(2-methoxycarbonyl-ethyl)pyrrolidine-2,4-dicarboxylate 5d. AgOAc (300 mg, 1.8 mmol), methyl acrylate (677 μl, 7.5 mmol), imine **3d** (519 mg, 1.5 mmol) and triethylamine (251 μl, 1.8 mmol) in toluene (10 ml) were reacted by the general procedure for 48 h. Flash chromatography (Et_2O) afforded the product **5d** (596 mg, 92%) as colourless prisms from Et_2O–petroleum ether, mp 109–111°C. (Found: C, 58.10, H, 5.60, N, 6.65. $C_{21}H_{24}N_2O_8$ requires: C, 58.35, H, 5.60, N, 6.60%); δ 1.82 (m, 1H, CHH), 2.04 (3×m, 3×1H, CH*H* and CH_2), 2.38 (m, 1H, CHH), 2.64 (dd, J=3.7 and 13.9 Hz, 1H, CH*H*), 2.87 (br s, 1H, NH), 3.07 (m, 1H, CH), 3.52, 3.69 and 3.79 (3×s, 3×3H, 3×OMe), 3.68 (m, 2H, NCH and NCHH), 3.89 (dd, J=3.3 and 13.7 Hz, 1H, NCH*H*), 7.74 and 7.86 (2×m, 2×2H, ArH); *m*/*z* (%): 433 (M^++1, <1), 401 (5), 373 (92), 341 (16), 313 (13), 272 (100), 253 (6), 240 (27), 226 (12), 212 (10), 194 (7), 180 (26), 166 (18), 160 (86), 152 (24), 134 (49), 122 (7), 104 (30), 94 (17), 80 (50), 77 (27), 67 (12) and 55 (34).

3.3.5. Dimethyl (±) *endo* -5-[(*N*-phthalimido)-methyl]-2-benzyl-pyrrolidine-2,4-dicarboxylate 5e. AgOAc (300 mg, 1.8 mmol), methyl acrylate (677 μl, 7.5 mmol), imine **3e** (525 mg, 1.5 mmol) and triethylamine (251 μl, 1.8 mmol) in toluene (10 ml) were reacted by the general procedure for 16 h. Flash chromatography (2:1 v/v Et_2O–petroleum ether) afforded the product **5e** (570 mg, 87%) as colourless prisms from Et_2O–petroleum ether, mp 80–82°C. (Found: C, 65.95, H, 5.60, N, 6.30. $C_{24}H_{24}N_2O_6$ requires: C, 66.05, H, 5.55, N, 6.40%); δ 2.12 (dd, J=7.4 and 13.9 Hz, 1H, CHH), 2.68 (dd, J=5.0 and 13.9 Hz, 1H, CH*H*), 2.75 (br s, 1H, NH), 2.80 (d, J=13.1 Hz, 1H, PhCHH), 2.86 (m, 1H, CH), 2.94 (d, J=13.1 Hz, 1H, PhCH*H*), 3.66 (s, 3H, OMe), 3.68 (m, 3H, NCH and NCH_2), 3.72 (m, 3H, OMe), 7.10 (m, 5H, 5ArH) and 7.75 and 7.88 (2×m, 2×2H, ArH); *m*/*z* (%): (FAB) 437 (M^++1, 100), 377 (47), 345 (40), 276 (6), 198 (9), 170 (24), 160 (26) and 91 (31); ν_{max} (cm^{-1}): 3056–3033, 2988–2954, 1775 (C=O), 1717 (C=O), 1615 and 1496.

3.3.6. (±) *endo*-5-[(*N*-Phthalimido)-methyl]-2-benzyl-pyrrolidine-2-carboxylic acid methyl ester-4-carboxylic acid benzyl ester 5f. AgOAc (0.238 g, 1.425 mmol), benzyl

acrylate (0.963 ml, 5.94 mmol), imine **3e** (0.410 g, 1.188 mmol) and triethylamine (0.20 ml, 1.425 mmol) in toluene (15 ml) were reacted by the general procedure for 16 h. Flash chromatography (2:1 v/v Et_2O–petroleum ether) afforded the product **5f** (0.315 g, 52%) as a colourless syrup. (Found: C, 70.05; H, 5.70; N, 5.45. $C_{30}H_{28}N_2O_6$ requires: C, 70.30; H, 5.50; N, 5.45%); δ (250 MHz): 2.12 (dd, J=7.5 and 14.0 Hz, 1H, CHC*H*HC), 2.69 (dd, J=4.6 and 14.0 Hz, 1H, CHCH*H*C), 2.75 (br s, 1H, N*H*), 2.78 (d, J=13.1 Hz, 1H, CHC*H*HPh), 2.93 (d, J=12.9 Hz, 1H, CHCH*H*Ph), 2.90–2.94 (m, 1H, CHC*H*(CO_2Bn)CH_2), 3.63 (s, 3H, CO_2Me), 3.47–3.68 (m, 3H, NCH_2C*H*(NH)CH), 5.05 (d, J=12.1 Hz, PhC*H*HOCO), 5.13 (d, J=12.0 Hz, 1H, PCH*H*OCO), 7.09–7.34 (m, 10H, ArH) 7.71–7.74 (m, 2H, ArH) and 7.837.87 (m, 2H, ArH). *m/z* (ES+, %): 513 ($M+H^+$, 100); ν_{max} (cm^{-1}): 3056, 2988–2955, 1775 (C═O), 1717 (C═O) and 1496.

3.3.7. Dimethyl (±) *endo*-5-[2-(*N*-phthalimido)-ethyl]-2-benzyl-pyrrolidine-2,4-dicarboxylate 5g. AgOAc (0.192 g, 1.153 mmol), methyl acrylate (0.43 ml, 4.805 mmol), imine **3f** (0.350 g, 0.961 mmol) and triethylamine (0.16 ml, 1.153 mmol) in toluene (10 ml) were reacted by the general procedure for 18 h. Flash chromatography (2:1 v/v Et_2O–petroleum ether) afforded the product **5g** (0.310 g, 72%) as a colourless syrup. (Found: C, 66.75; H, 6.05; N, 6.00. $C_{25}H_{26}N_2O_6$ requires: C, 66.60; H, 5.85; N, 6.20%); δ (400 MHz): 1.71–1.77 (m, 2H, CH_2CH_2CH), 2.05 (dd, J=7.0 and 14.1 Hz, 1H, CHC*H*HC), 2.63 (dd, J=3.2 and 13.7 Hz, 1H, CHCH*H*C), 2.75 (br s, 1H, N*H*), 2.84 (d, J=13.0 Hz, 1H, CC*H*HPh), 2.89–2.93 (m, 1H, CHC*H*(CO_2Me)CH_2), 2.98 (d, J=13.0 Hz, 1H, CHCH*H*Ph), 3.48 (q, J=7.0 Hz, 1H, CHC*H*(CO_2Me)CH_2), 3.62 and 3.68 (2×s, 2×3H, 2×CO_2Me), 3.76–3.90 (m, 2H, NC$H_2$$CH_2$), 7.12–7.26 (m, 5H, *Ph*), 7.71–7.75 (m, 2H, ArH) and 7.82–7.87 (m, 2H, ArH); *m/z* (ES+, %): 451 ($M+H^+$, 100); ν_{max} (cm^{-1}): 3056, 2988–2954, 1773 (C═O) and 1714 (C═O).

3.3.8. (±) *endo*-5-[2-(*N*-Phthalimido)-ethyl]-2-benzyl-pyrrolidine-2-carboxylic acid methyl ester-4-carboxylic acid benzyl ester 5h. AgOAc (0.201 g, 1.206 mmol), benzyl acrylate (0.245 ml, 1.506 mmol), imine **3f** (0.366 g, 1.005 mmol) and triethylamine (0.17 ml, 1.206 mmol) in toluene (10 ml) were reacted by the general procedure for 18 h. Flash chromatography (2:1 v/v Et_2O–petroleum ether) afforded the product **5h** (0.340 g, 64%) as a colourless solid, mp 84.5–85.5°C. (Found: C, 70.45; H, 5.85; N, 5.15. $C_{31}H_{30}N_2O_6$ requires: C, 70.70; H, 5.75; N, 5.30%); δ ^{1}H (400 MHz): 1.63–1.69 (m, 2H, CH_2CH_2CH), 2.06 (dd, J=7.5 and 14.1 Hz, 1H, CHC*H*HC), 2.65 (dd, J=3.2 and 13.7 Hz, 1H, CHCH*H*C), 2.75 (br s, 1H, N*H*), 2.82 (d, J=13.0 Hz, 1H, CC*H*HPh), 2.97 (d, J=13.0 Hz, 1H, CCH*H*Ph), 2.95–2.99 (m, 1H, CHC*H*(CO_2Bn)CH_2), 3.09 (q, J=6.7 Hz, 1H, NHC*H*(CH_2)CH), 3.61 (s, 3H, CO_2Me), 3.66–3.76 (m, 1H, NC*H*HCH_2), 3.79–3.86 (m, 1H, NCH*H*CH_2), 5.03 (d, J=12.0 Hz, 1H, PhC*H*HOCO), 5.09 (d, J=12.0 Hz, 1H, PhCH*H*OCO), 7.09–7.31 (m, 10H, ArH), 7.70–7.75 (m, 2H, ArH), and 7.83–7.87 (m, 2H, ArH); *m/z* (ES+, %): 527 ($M+H^+$, 100); ν_{max} (cm^{-1}): 3057, 2988–2953, 1774 (C═O), 1713 (C═O) and 1496.

3.3.9. Dimethyl (±) *endo*-5-[2-(*N*-phthalimido)-ethyl]-2-methyl-pyrrolidine-2,4-dicarboxylate 5i. AgOAc (0.360 g, 2.156 mmol), methyl acrylate (0.88 ml, 9.800 mmol), imine **3g** (0.587 g, 1.960 mmol) and triethylamine (0.19 ml, 2.156 mmol) in toluene (20 ml) were reacted by the general procedure for 18 h. Flash chromatography (3:1 v/v Et_2O–petroleum ether) afforded the product **5i** (0.520 g, 71%) as a colourless solid, mp 97.0–98.0°C. (Found: C, 60.80; H, 5.95; N, 7.20. $C_{19}H_{22}N_2O_6$ requires: C, 60.95; H, 5.90; N, 7.50%); δ (250 MHz): 1.39 (s, 3H, CMe), 1.68–1.93 (m, 3H, NCH_2CH_2CH and N*H*), 1.92 (dd, J=7.5 and 13.8 Hz, 1H, CC*H*HCH), 2.63 (dd, J=3.5 and 13.9 Hz, 1H, CCH*H*CH), 3.06–3.12 (m, 1H, CHC*H*(CO_2Me)CH_2), 3.33–3.41 (m, 1H, NHC*H*(CH_2)CH), 3.65 and 3.77 (2×s, 2×3H, 2×CO_2Me), 3.82–3.89 (m, 2H, NC$H_2$$CH_2$), 7.70–7.74 (m, 2H, ArH) and 7.81–7.96 (m, 2H, ArH); *m/z* (%): 375 (M+1, 1), 359 (2), 315 (100), 255 (13), 200 (25), 160 (50) and 108 (42); ν_{max} (cm^{-1}): 3057, 2987–2954, 1774 (C═O), 1713.

3.3.10. Dimethyl (±) *endo*-5-[2-(*N*-phthalimido)-ethyl]-2-[3′-indolylmethyl]-pyrrolidine-2,4-dicarboxylate 5j. AgOAc (0.202 g, 1.210 mmol), methyl acrylate (0.50 ml, 5.500 mmol), imine **3h** (0.470 g, 1.100 mmol) and triethylamine (0.17 ml, 1.210 mmol) in toluene (10 ml) were reacted by the general procedure for 18 h. Flash chromatography (3:1 v/v Et_2O–petroleum ether) afforded the product **5j** (0.332 g, 62%) as a pale yellow solid, mp 67.5–69.0°C. (Found: C, 66.50; H, 5.60; N, 8.30. $C_{27}H_{27}N_3O_6$ requires: C, 66.25; H, 5.55; N, 8.60%); δ (250 MHz): 1.58–1.77 (m, 3H, NCH_2CH_2CH and N*H*), 2.13 (dd, J=7.5 and 13.8 Hz, 1H, CC*H*HCH), 2.66 (dd, J=3.5 and 13.8 Hz, 1H, CCH*H*CH), 2.91–2.97 (m, 1H, CHC*H*(CO_2Me)CH_2), 3.01 (d, J=14.2 Hz, 1H, CC*H*HAr), 3.15–3.22 (m, 1H, NHC*H*(CH_2)CH), 3.23 (d, J=14.2 Hz, 1H, CCH*H*Ar), 3.62 (s, 2×CO_2Me), 3.81 (dt, J=6.8 and 13.8 Hz, 2H, NC$H_2$$CH_2$), 7.03–7.14 (m, 2H, ArH), 7.21–7.29 (m, 2H, ArH), 7.64 (d, J=7.4 Hz, 1H, ArH), 7.70–7.74 (m, 2H, ArH), 7.80–7.86 (m, 2H, ArH) and 8.03 (br s, 1H, indole N*H*); *m/z* (%): 458 ($M-CO_2Me]^{1+}$, 1), 430 (7), 359 (100), 267 (20), 160 (52) and 130 (84); ν_{max} (cm^{-1}): 3056, 2988, 1775 (C═O), 1715 (C═O).

3.3.11. Dimethyl (±) *endo*-5-[3-(*N*-phthalimido)-propyl]-2-benzyl-pyrrolidine-2,4-dicarboxylate 11a. AgOAc (0.225 g, 1.347 mmol), methyl acrylate (0.55 ml, 6.125 mmol), imine **10a** (0.500 g, 1.225 mmol) and triethylamine (0.19 ml, 1.347 mmol) in toluene (8 ml) were reacted by the general procedure for 18 h. Flash chromatography (3:1 v/v Et_2O–petroleum ether) afforded the product **11a** (0.290 g, 51%) as colourless oil. (Found: C 66.65; H, 6.15; N, 6.25. $C_{26}H_{28}N_2O_6 \cdot 1/4H_2O$ requires: C, 66.60; H, 6.10; N, 5.95%); δ (500 gMHz): 1.39 (q, J=7.6 Hz, 2H, CH_2), 1.78–1.85 (br m, 3H, N*H* and CH_2), 2.04 (dd, J=7.6 and 13.9 Hz, 1H, $MeCO_2CHCH$*H*), 2.61 (dd, J=3.2 and 13.9 Hz, 1H, $MeCO_2CHCH$*H*), 2.82 (d, J=13.0 Hz, 1H, PhC*H*H), 2.81–2.84 (m, 1H, $MeCO_2CH$), 2.99 (d, J=13.0 Hz, 1H, PhCH*H*), 3.12 (q, J=6.8 Hz, 1H, NC*H*CH_2), 3.60 and 3.66 (2×s, 2×3H, 2×CO_2Me), 3.69–3.77 (m, 2H, NCH_2), 7.20–7.27 (m, 5H, ArH), 7.70–7.72 (m, 2H, ArH) and 7.82–7.85 (m, 2H, ArH); *m/z* (%): 465 ($M+H^+$, 41), 405 (48), 373 (100), 309 (19), 281 (42), 160 (53) and 91 (59); ν_{max} (cm^{-1}): 3057, 2985, 1715 (C═O).

3.3.12. Dimethyl (±) *endo*-5-[3-(*N*-phthalimido)-propyl]-2-methyl-pyrrolidine-2,4-dicarboxylate 11b. AgOAc

(0.223 g, 1.337 mmol), methyl acrylate (0.55 ml, 6.075 mmol), imine **10b** (0.370 g, 1.215 mmol) and triethylamine (0.19 ml, 1.34 mmol) in toluene (8 ml) were reacted by the general procedure for 18 h. Flash chromatography (2:1 v/v ethyl acetate/petroleum ether) afforded the product **11b** (0.220 g, 47%) as colourless oil. (Found: C 61.55; H, 6.15; N, 7.20. $C_{26}H_{28}N_2O_6$ requires: C, 61.85; H, 6.25; N, 7.20%); δ (500 MHz): 1.39 (s, 3H, CMe), 1.40–1.60 (m, 2H, CH_2), 1.78–1.88 (m, 2H, CH_2), 1.90 (dd, J=7.6 and 13.8 Hz, 1H, $MeCO_2CHCHH$), 2.15 (br s, 1H, N*H*) 2.59 (dd, J=3.6 and 13.8 Hz, 1H, $MeCO_2CHCHH$), 2.96–3.00 (m, 1H, $NCHCH_2$), 3.34 (q, J=7.4 Hz, 1H, $MeCO_2CH$), 3.62 and 3.75 (2×s, 2×3H, $2\times CO_2Me$), 3.70 (dt, J=2.2 and 6.9 Hz, 2H, NCH_2), 7.69–7.73 (m, 2H, ArH) and 7.81–7.85 (m, 2H, ArH); *m/z* (%): 389 ($M+H^+$, 56), 329 (100), 269 (32), 200 (42) and 160 (37); ν_{max} (cm^{-1}): 3054, 2985, 1774 (C═O), 1713 (C═O).

3.3.13. Methyl (±) *endo*-3-[(*N*-phthalimido)-methyl]-1,5-dimethyl-4,6-dioxo-octahydro-pyrrolo[3,4-*c*]pyrrole-1-carboxylate 17a. AgOAc (100 mg, 0.6 mmol), *N*-methylmaleimide (83 mg, 0.75 mmol), imine **3a** (137 mg, 0.5 mmol) and triethylamine (82 μl, 0.6 mmol) in toluene (4 ml) were reacted by the general procedure for 40 h. Flash chromatography (1:1 v/v EtOAc–CH_2Cl_2) afforded the product **17a** (164 mg, 85%) as colourless prisms from CH_2Cl_2, mp 217–219°C. (Found: C, 58.95, H, 5.15, N, 10.85. $C_{19}H_{19}N_3O_6$ requires: C, 59.20, H, 4.95, N, 10.90%); δ 1.41 (s, 3H, Me), 2.75 (d, J=11.9 Hz, 1H, NH), 3.01 (s, 3H, NMe), 3.25 (d, J=7.7 Hz, 1H, CH), 3.48 (t, J=7.7 Hz, 1H, CH), 3.79 (m, 5H, OMe, NCH and NC*H*H), 4.39 (dd, J=1.7 and 13.5 Hz, 1H, NCH*H*) and 7.72 and 7.85 (2×m, 2×2H, ArH); *m/z* (%): 386 (M^++1, 1), 326 (100), 238 (15), 225 (77), 193 (6), 179 (53), 165 (78), 160 (29), 138 (5), 133 (8), 130 (8), 122 (12), 108 (46), 104 (18), 94 (42), 80 (26), 53 (12) and 42 (12).

3.3.14. Methyl (±) *endo*-3-[(*N*-phthalimido)-methyl]-5-methyl-1-(2-methylsulfanyl-ethyl)-4,6-dioxo-octahydro-pyrrolo[3,4-*c*]pyrrole-1-carboxylate 17b. AgOAc (250 mg, 1.5 mmol), *N*-methylmaleimide (222 mg, 2.5 mmol), imine **3b** (422 mg, 1.26 mmol) and triethylamine (209 μl, 1.5 mmol) in toluene (10 ml) were reacted by the general procedure for 16 h. Flash chromatography (Et_2O) afforded the product **17b** (396 mg, 71%) as colourless prisms from CH_2Cl_2/petroleum ether, mp 162–164°C. (Found: C, 56.60, H, 5.30, N, 9.35, S, 6.95. $C_{21}H_{23}N_3O_6S$ requires: C, 56.60, H, 5.20, N, 9.45, S, 7.20%); δ 1.78 (m, 1H, C*H*H), 1.92 (s, 3H, NMe), 2.20 (m, 1H, CH*H*), 2.35 (m, 2H, CH_2), 2.73 (d, J=11.2 Hz, 1H, NH), 3.00 (s, 3H, SMe), 3.28 (d, J=7.5 Hz, 1H, CH), 3.50 (t, J=7.5 Hz, 1H, CH), 3.78 (m, 2H, NCH and NC*H*H), 3.80 (s, 3H, OMe), 4.35 (d, J=11.4 Hz, 1H, NCH_2) and 7.74 and 7.85 (2×m, 2×2H, ArH); *m/z* (%): 445 (M^+, 2), 386 (59), 370 (25), 338 (52), 285 (56), 253 (13), 239 (10), 224 (24), 211 (10), 191 (23), 178 (8), 168 (19), 160 (53), 138 (12), 130 (12), 106 (25), 94 (19), 77 (25) and 61 (100).

3.3.15. Methyl (±) *endo*-3-[(*N*-phthalimido)-methyl]-1-(1*H*-indol-3-ylmethyl)-5-methyl-4,6-dioxo-octahydro-pyrrolo[3,4-*c*]pyrrole-1-carboxylate 17c. AgOAc (50 mg, 0.3 mmol), *N*-methylmaleimide (67 mg, 0.6 mmol), imine **3c** (97 mg, 0.25 mmol) and triethylamine (42 μl, 0.3 mmol) in toluene (3 ml) were reacted by the general procedure for 10 h. Flash chromatography (4:1 v/v CH_2Cl_2–EtOAc) afforded the product **17c** (51 mg, 41%) as colourless needles from CH_2Cl_2/petroleum ether, mp 279–281°C. (Found: C, 64.90, H, 4.80, N, 10.95. $C_{27}H_{24}N_4O_6$ requires: C, 64.80, H, 4.85, N, 11.20%); δ 2.65 (br s, 1H, NH), 3.00 (s, 3H, NMe), 3.10 (d, J=14.6 Hz, 1H, indole-C*H*H), 3.43 (m, 2H, 2×CH), 3.46 (d, J=14.6 Hz, 1H, indole-CH*H*), 3.69 (dd, J=10.6 and 14.3 Hz, 1H, NC*H*H), 3.74 (s, 3H, OMe), 3.90 (m, 1H, NCH), 4.40 (dd, J=12.1 and 14.3 Hz, 1H, NCH*H*), 6.41 and 6.80 (2×t, J=8.1 Hz, 2×1H, ArH), 6.92 (d, J=2.0 Hz, 1H, ArH), 7.15 and 7.31 (2×d, J=8.1 Hz, 2×1H, ArH), 7.74 and 7.79 (2×m, 2×2H, ArH) and 8.0 (br s, 1H, NH); *m/z* (%): 500 (M^+, <1), 370 (100), 223 (8), 191 (15), 160 (27), 130 (66), 104 (9) and 77 (10).

3.3.16. Methyl (±) *endo*-3-[(*N*-phthalimido)-methyl]-1-(2-methoxycarbonyl-ethyl)-5-methyl-4,6-dioxo-octahydro-pyrrolo[3,4-*c*]pyrrole-1-carboxylate 17d. AgOAc (300 mg, 1.8 mmol), *N*-methylmaleimide (278 mg, 2.5 mmol), imine **3d** (519 mg, 1.5 mmol) and triethylamine (251 μl, 1.8 mmol) in toluene (10 ml) were reacted by the general procedure for 40 h. Flash chromatography (3:1 v/v Et_2O–EtOAc) afforded the product **17d** (231 mg, 33%) as colourless needles from CH_2Cl_2/petroleum ether, mp 175–177°C. (Found: C, 57.55, H, 5.10, N, 9.45. $C_{22}H_{23}N_3O_8$ requires: C, 57.75, H, 5.05, N, 9.20%); δ 1.99 (m, 1H, C*H*H), 2.14 (m, 2H, CH_2), 2.26 (m, 1H, CH*H*), 2.69 (d, J=11.1 Hz, 1H, NH), 3.00 and 3.18 (2×s, 2×3H, NMe and OMe), 3.24 (d, J=7.7 Hz, 1H, CH), 3.48 (t, J=7.7 Hz, 1H, CH), 3.69 (dd, J=11.3 and 14.1 Hz, 1H, NC*H*H), 3.80 (s, 3H, OMe), 3.82 (m, 1H, NCH), 4.37 (dd, J=2.2 and 14.1 Hz, 1H, NCH*H*) and 7.73 and 7.86 (2×m, 2×2H, ArH); *m/z* (%): 458 (M^++1, 1), 426 (7), 398 (56), 370 (12), 338 (47), 310 (9), 297 (83), 265 (19), 251 (33), 237 (15), 219 (13), 205 (30), 191 (15), 177 (61), 160 (100), 148 (11), 134 (22), 120 (30), 104 (45), 94 (28), 77 (43) and 59 (23).

3.3.17. Methyl (±) *endo*-1-benzyl-3-[(*N*-phthalimido)-methyl]-5-methyl-4,6-dioxo-octahydro-pyrrolo[3,4-*c*]-pyrrole-1-carboxylate 17e. AgOAc (300 mg, 1.8 mmol), *N*-methylmaleimide (278 mg, 2.5 mmol), imine **3e** (525 mg, 1.5 mmol) and triethylamine (251 μl, 1.8 mmol) in toluene (10 ml) were reacted by the general procedure for 16 h. Flash chromatography (Et_2O) afforded the product **17e** (551 mg, 80%) as colourless rods from Et_2O, mp 160–162°C. (Found: C, 65.15, H, 5.10, N, 9.40. $C_{25}H_{23}N_3O_6$ requires: C, 65.05, H, 5.00, N, 9.10%); δ 2.47 (d, J=9.3 Hz, 1H, NH), 2.85 (d, J=13.2 Hz, 1H, PhC*H*H), 3.01 (s, 3H, NMe), 3.36 (d, J=13.2 Hz, 1H, PhCH*H*), 3.37 (d, J=7.6 Hz, 1H, CH), 3.46 (t, J=7.6 Hz, 1H, CH), 3.76 (s, 3H, OMe), 3.83 (dd, J=10.7 and 14.0 Hz, 1H, NC*H*H), 3.95 (m, 1H, NCH), 4.35 (dd, J=2.4 and 14.0 Hz, 1H, NCH*H*), 6.81–7.00 (m, 5H, 5ArH) and 7.77 and 7.87 (2×m, 2×2H, ArH); *m/z* (%): (FAB) 461 (M^+, 100), 402 (37), 370 (57), 223 (5), 170 (11), 160 (15) and 91 (11).

3.3.18. Methyl (±) *endo*-5-[(*N*-phthalimido)-methyl]-4-benzenesulfonyl-2-benzyl-pyrrolidine-2-carboxylate 20. Prepared according to the general procedure from imine

3e (1.274 g, 3.448 mmol), silver(I) acetate (0.863 g, 5.172 mmol), phenyl vinyl sulfone (0.638 g, 3.793 mmol) and triethylamine (0.19 ml, 5.172 mmol) in toluene (40 ml) for 18 h. The residue was purified (3:1 v/v ether–petroleum ether) to afford the product **20** (0.610 g, 34%) as a yellow solid, mp 169.0–170.0°C. (Found: C 64.25; H, 5.10; N, 5.25; S, 6.30. $C_{28}H_{26}N_2O_6S{\cdot}1/4H_2O$ requires: C 64.30; H, 5.10; N, 5.35; S, 6.10%); δ (500 MHz): 2.06 (dd, J=7.5 and 14.5 Hz, 1H, SO_2CHCHH), 2.69 (d, J=13.2 Hz, 1H, PhC*H*H), 2.78 (dd, J=6.4 and 13.2 Hz, 1H, SO_2CHCHH), 2.83 (d, J=13.2 Hz, 1H, PhCH*H*), 3.16 (q, J=6.7 Hz, 1H, SO_2CH), 3.44–3.52 (m, 1H, NCH), 3.81 (s, 3H, CO_2Me), 4.15 (dd, J=3.2 and 14.3 Hz, 1H, NC*H*H), 4.24 (dd, J=11.1 and 14.3 Hz, 1H, NCH*H*), 6.96–6.98 (m, 4H, Ar*H*), 7.25–7.27 (m, 1H, Ar*H*), and 7.59–7.90 (m, 9H, Ar*H*). *m/z* (FAB, %): 541 ($M+Na^+$, 9), and 519 ($M+H^+$, 100); ν_{max} (cm^{-1}): 3056, 2987, 1772 (C=O), 1730 (C=O) and 1716 (C=O).

3.3.19. Methyl (±) *endo*-5-[(*N*-phthalimido)-ethyl]-4-benzenesulfonyl-2-benzyl-pyrrolidine-2-carboxylate 22. Prepared according to the general procedure from imine **3f** (0.990 g, 2.45 mmol), silver(I) acetate (0.429 g, 2.572 mmol), phenyl vinyl sulfone (0.432 g, 2.572 mmol) and triethylamine (0.19 ml, 2.572 mmol) in toluene (12 ml) for 18 h. The residue was purified (3:1 v/v ether–petroleum ether) to afford the product **22** (0.867 g, 67%) as a yellow solid, mp 86.5–88.0°C. (Found: C 65.3; H, 5.45; N, 5.0; S, 5.9. $C_{29}H_{28}N_2O_6S$ requires: C 65.4; H, 5.3; N, 5.25; S, 6.0%); δ (500 MHz): 2.05 (dd, J=7.7 and 14.8 Hz, SO_2CHCHH), 2.15–2.19 and 2.41–2.46 (2×m, 2×1H, $NCHCH_2$), 2.67 (dd, J=4.6 and 14.9 Hz, 1H, SO_2CHCHH), 2.75 (d, J=13.0 Hz, 1H, PhC*H*H), 2.90 (d, J=13.0 Hz, 1H, PhCH*H*), 3.01–3.05 (m, 1H, NCH), 3.41–3.45 (m, 1H, SO_2CH), 3.77 (s, 3H, OMe), 3.77–3.82 and 3.99–4.05 (2×m, 2×1H, NCH_2), 6.92–7.21 (m, 5H, ArH), 7.52–7.67 (m, 3H, ArH), and 7.73–7.92 (m, 6H, ArH); *m/z* (ES+, %): 533 ($M+H^+$, 49); ν_{max} (cm^{-1}): 3057, 2988, 1772 (C=O), 1714 (C=O), 1495, 1398 and 1146.

3.4. General method for the hydrazinolysis

Hydrazine monohydrate (1–2 equiv.) was added to a solution of the cycloadduct (1 equiv.) in methanol or ethanol and the solution was stirred at 50–78°C for 18–80 h. The solvent was removed and the residue was triturated with dichloromethane, filtered and the filtrate evaporated to give the product (5- and 6-membered fused and 6-membered bridged bicyclic lactams or primary amines). Products were purified via flash column chromatography (lactams) or used in the next step without purification (primary amines).

3.4.1. Methyl (±) *endo*-1-methyl-2-oxo-3,8-diaza-bicyclo-[3.2.1]octane-6-carboxylic acid methyl ester 7 and *endo*-2-methyl-4-oxo-octahydro-pyrrolo[3.4-*b*]pyrrole-2-carboxylate 6a. Reaction of **5a** (370 mg, 1.03 mmol) and hydrazine monohydrate (75 μl, 1.5 mmol) in methanol (15 ml) at reflux for 70 h afforded, after flash chromatography (Et_2O then 1:1 v/v EtOAc–MeOH), two separated regioisomers **7** and **6a** (142 mg, 70% combined yield) in a 1:1 ratio.

Isomer 7: obtained as colourless plates from MeOH/EtOAc/petroleum ether, mp 182–184°C. (Found: C, 54.30, H, 7.20, N, 14.05. $C_9H_{14}N_2O_3$ requires: C, 54.55, H, 7.10, N, 14.15%); δ 1.42 (s, 3H, Me), 1.85 (dd, J=12.2 and 13.3 Hz, 1H, C*H*H), 2.31 (br s, 1H, NH), 2.61 (dd, J=5.3 and 13.3 Hz, 1H, CH*H*), 3.14 (dd, J=2.4, and 13.0 Hz, 1H, NC*H*H), 3.35 (m, 1H, COCH), 3.49 (dd, J=4.5 and 13.0 Hz, 1H, NCH*H*), 3.70 (s, 3H, OMe), 3.94 (m, 1H, NCH) and 5.93 (br s, 1H, CONH); *m/z* (%): 198 (M^+, 10), 170 (5), 155 (9), 141 (66), 139 (29), 111 (7), 108 (5), 96 (45), 94 (22), 82 (100), 67 (8), 55 (10) and 42 (22).

Isomer 6a: obtained as colourless needles from CH_2Cl_2/petroleum ether, mp 111–113°C. (Found: C, 54.55, H, 7.20, N, 14.05. $C_9H_{14}N_2O_3$ requires: C, 54.55, H, 7.10, N, 14.15%); δ 1.39 (s, 3H, Me), 2.00 (dd, J=9.8 and 13.4 Hz, 1H, C*H*H), 2.42 (br s, 1H, NH), 2.64 (dd, J=2.5, 13.4 Hz, 1H, CH*H*), 2.79 (ddd, J=2.5, 6.7 and 9.8 Hz, 1H, COCH), 3.30 (d, J=10.7 Hz, 1H, NC*H*H), 3.59 (dd, J=6.7 and 10.7 Hz, 1H, NCH*H*), 3.70 (s, 3H, OMe), 4.08 (t, J=6.7 Hz, 1H, NCH) and 6.76 (br s, 1H, CONH); *m/z* (%): 198 (M^+, 6), 139 (100), 122 (12), 108 (5), 96 (55), 94 (70), 82 (91), 67 (18), 58 (21), 55 (20) and 42 (48).

3.4.2. Methyl (±) *endo*-2-(2-methylsulfanyl-ethyl)-4-oxo-octahydro-pyrrolo[3.4-*b*]pyrrole-2-carboxylate 6b. Reaction of **5b** (76 mg, 0.181 mmol) and hydrazine monohydrate (11 μl, 0.22 mmol) in ethanol (3 ml) at 78°C for 15 h afforded, after flash chromatography (Et_2O, then 3:1 v/v EtOAc–MeOH), the product **6b** (45 mg, 96%) as colourless prisms from CH_2Cl_2/petroleum ether, mp 87–89°C. (Found: C, 50.85, H, 7.05, N, 11.05, S, 12.50. $C_{11}H_{18}N_2O_3S$ requires: C, 51.15, H, 7.00, N, 10.85, S, 12.40%); δ 1.83 (m, 1H, C*H*H), 2.05 (dd, J=9.7 and 13.6 Hz, 1H, pyrrolidine C*H*H), 2.09 (s, 3H, SMe), 2.10 and 2.27 (2×m, 2×1H, CH_2), 2.42 (br s, 1H, NH), 2.49 (m, 1H, CH*H*), 2.61 (dd, J=1.9 and 13.6 Hz, 1H, pyrrolidine CH*H*), 2.95 (m, 1H, COCH), 3.30 (d, J=10.8 Hz, 1H, NC*H*H), 3.60 (dd, J=6.3 and 10.8 Hz, 1H, NCH*H*), 3.71 (s, 3H, OMe), 4.01 (t, J=6.3, 1H, NCH) and 6.67 (br s, 1H, CONH); *m/z* (%): 259 (M^++1, <1), 199 (100), 183 (15), 151 (40), 142 (18), 94 (22), 80 (15), 61 (39) and 41 (7).

3.4.3. Methyl (±) *endo*-2-(3′-indolylmethyl)-4-oxo-octahydro-pyrrolo[3.4-*b*]pyrrole-2-carboxylate 6c. Reaction of **5c** (156 mg, 0.33 mmol) and hydrazine monohydrate (20 μl, 0.4 mmol) in methanol (8 ml) at 50°C for 48 h afforded, after flash chromatography (3:1 v/v EtOAc–MeOH), the starting material **4e** (20 mg, 13%) and the product **6c** (57 mg, 56%) as colourless prisms from MeOH/CH_2Cl_2/petroleum ether, mp 171–173°C. Found: C, 65.30, H, 6.00, N, 13.55. $C_{17}H_{19}N_3O_3$ requires: C, 65.15, H, 6.10, N, 13.40%); δ 2.20 (dd, J=9.9 and 13.4 Hz, 1H, C*H*H), 2.60 (br s, 1H, NH), 2.66 (dd, J=1.9 and 13.4 Hz, 1H, CH*H*), 2.90 (m, 1H, CH), 3.02 (d, J=14.4 Hz, 1H, indole-C*H*H), 3.14 (d, J=10.7 Hz, 1H, NC*H*H), 3.28 (d, J=14.4 Hz, 1H, indole-CH*H*), 3.38 (dd, J=6.0, 10.7 Hz, 1H, NCH*H*), 3.54 (s, 3H, OMe), 3.98 (m, 1H, NCH), 6.53 (br s, 1H, NH), 6.96 (s, 1H, ArH), 7.11 (m, 2H, ArH), 7.29 and 7.54 (2×d, J=7.7 Hz, 2×1H, ArH) and 8.84 (br s, 1H, NH); *m/z* (%): 313 (M^+, 3), 254 (14), 183 (90), 151 (9), 130 (100), 126 (10), 123 (9), 103 (8), 82 (7), 80 (7) and 77 (8).

3.4.4. Polycyclic lactam 8. Reaction of **5d** (259 mg, 0.6 mmol) and hydrazine monohydrate (45 μl, 0.9 mmol) in methanol (7 ml) at 50°C for **4d** afforded, after flash chromatography (10:1–4:1 v/v EtOAc–MeOH), the starting material **5d** (10 mg, 5%), and the product **8** (130 mg, 91%) as colourless prisms from CH_2Cl_2/petroleum ether, mp 182–184°C. (Found: C, 55.25, H, 6.20, N, 11.45. $C_{11}H_{14}N_2O_4$ requires: C, 55.45, H, 5.90, N, 11.75%); δ 1.95 (dd, *J*=8.2 and 13.2 Hz, 1H, pyrrolidine C*H*H), 2.16 (m, 1H, C*H*H), 2.47 (m, 2H, CH*H* and COC*H*H), 2.82 (m, 1H, COCH*H*), 3.00 (d, *J*=13.2 Hz, 1H, pyrrolidine CH*H*), 3.27 (t, *J*=8.2 Hz, 1H, CH), 3.47 (d, *J*=11.0 Hz, 1H, NC*H*H), 3.72 (m, 4H, NCH*H* and OMe), 4.66 (t, *J*=8.2 Hz, 1H, NCH) and 7.34 (br s, 1H, NH); δ (^{13}C): (62.5 MHz) 176.3 (CO), 174.4 (CO), 173.1 (CO), 76.9 (C), 52.6, 52.5, 47.8 (CH_2), 47.6, 37.8 (CH_2), 33.6 (CH_2) and 32.9 (CH_2); *m*/*z* (%): 238 (M^+, <1), 179 (100), 134 (8), 122 (15), 82 (9), 55 (19) and 39 (5).

3.4.5. Methyl (±) *endo*-2-benzyl-4-oxo-octahydropyrrolo[3.4-*b*]pyrrole-2-carboxylate 6e. *From* ***5e***. Reaction of **5e** (174 mg, 0.4 mmol) and hydrazine monohydrate (28 μl, 0.56 mmol) in methanol (7 ml) at 50°C for **3d** afforded, after flash chromatography (EtOAc, then 5:1 v/v EtOAc–MeOH), the starting material **5e** (29 mg 13%), and the product **6e** (80 mg, 77%).

From ***5f***. Reaction of **5f** (0.253 g, 0.494 mmol) and hydrazine monohydrate (0.041 ml, 0.741 mmol) in methanol (8 ml) at 50°C for 66 h afforded, after flash chromatography, the product **6e** (0.112 g, 83%) as colourless prisms from CH_2Cl_2/petroleum ether, mp 161–163°C. (Found: C, 65.65, H, 6.70, N, 10.40. $C_{15}H_{18}N_2O_3$ requires: C, 65.70, H, 6.60, N, 10.20%); δ 2.17 (dd, *J*=9.7 and 13.4 Hz, 1H, C*H*H), 2.47 (br s, 1H, NH), 2.64 (dd, *J*=2.5 and 13.4 Hz, 1H, CH*H*), 2.82 (d, *J*=13.3 Hz, 1H, PhC*H*H), 2.93 (m, 1H, CH), 3.12 (d, *J*=13.3 Hz, 1H, PhCH*H*), 3.24 (d, *J*=10.7 Hz, 1H, NC*H*H), 3.52 (dd, *J*=6.4 and 10.7 Hz, 1H, NCH*H*), 3.62 (s, 3H, OMe), 4.02 (t, *J*=6.4 Hz, 1H, NCH), 6.68 (br s, 1H, NH), 7.10 (m, 2H, ArH) and 7.27 (m, 3H, ArH); *m*/*z* (%): 275 (M^++1, <1), 215 (54), 183 (100), 170 (7), 158 (5), 151 (10), 126 (14), 123 (13), 91 (38), 82 (10), 80 (11) and 65 (8); ν_{max} (cm^{-1}): 3056, 2988, 1731 (C═O), 1702 (C═O).

3.4.6. Methyl (±) 2-benzyl-4-oxo-octahydro-pyrrolo[3.4-*b*]-pyridine-2-carboxylate 6f. *From* ***5g***. Reaction of **5g** (0.270 g, 0.600 mmol) and hydrazine monohydrate (0.052 ml, 0.900 mmol) in methanol (10 ml) at 50°C for 66 h afforded, after flash chromatography (5:1 v/v ethyl acetate–methanol), the product **6f** (0.125 g, 72%).

From ***5h***. Reaction of **5h** (0.265 g, 0.504 mmol) and hydrazine monohydrate (0.042 ml, 0.756 mmol) in methanol (8 ml) at 50°C for 66 h afforded, after flash chromatography, the product **6f** (0.110 g, 76%) as colourless needles, mp 123.5–124.5°C. (Found: C 66.55; H, 6.95; N, 9.85. $C_{16}H_{20}N_2O_3$ requires: C 66.65; H, 7.00; N, 9.70%); δ (400 MHz): 1.66–1.74 (m, 1H, CH_2C*H*HCH), 1.85–1.92 (m, 1H, CH_2CH*H*CH), 2.40 (dd, *J*=9.0 and 13.6 Hz, 1H, CHC*H*HC), 2.50 (dd, *J*=7.0 and 13.6 Hz, 1H, CHCH*H*C), 2.81–2.87 (m, 1H, CHC*H*(CO)CH_2), 2.88 (d, *J*=13.6 Hz, 1H, CC*H*HPh), 3.11 (d, *J*=13.1 Hz, 1H, CCH*H*Ph), 3.12–3.18 (m, 1H, NHC*H*HCH_2), 3.41–3.48 (m, 1H, NHCH*H*CH_2), 3.67 (m, 4H, NHC*H*(CH_2)CH and CO_2Me), 6.11 (br s, 1H, CON*H*), 7.14–7.16 (m, 2H, *meta* ArH), and 7.20–7.29 (m, 3H, *ortho* and *para* ArH); *m*/*z* (ES+, %): 289 ($M+H^+$, 100); ν_{max} (cm^{-1}): 3056, 2988–2955, 1730 (C═O), 1662 (C═O).

3.4.7. Methyl (±) 2-methyl-4-oxo-octahydropyrrolo[3.4-*b*]-pyridine-2-carboxylate 6g. Reaction of **5i** (0.169 g, 0.452 mmol) and hydrazine monohydrate (0.030 ml, 0.62 mmol) in methanol (8 ml) at 55°C for 22 h afforded, after flash chromatography (4:1 v/v ethyl acetate–methanol), the product **6g** (0.077 g, 80%) as colourless needles, mp 106.5–108.0°C. (Found: C 55.30; H, 7.70; N, 13.15. $C_{10}H_{16}N_2O_3$·1/4H_2O requires: C 55.40; H, 7.70; N, 12.95%); δ (250 MHz): 1.41 (s, 3H, CMe), 1.70–1.79 (m, 1H, CH_2C*H*HCH), 1.88–2.00 (m, 1H, CH_2CH*H*CH), 2.17 (br s, 1H, N*H*), 2.19 (dd, *J*=9.0 and 13.4 Hz, 1H, CC*H*HCH), 2.49 (dd, *J*=7.3 and 13.4 Hz, 1H, CCH*H*CH), 2.91–3.00 (m, 1H, CHC*H*(CO_2Me)CH_2), 3.17–3.24 (m, 1H, NHC*H*(CH_2)CH), 3.43–3.51 (m, 1H, NC*H*HCH_2), 3.67–3.75 (m, 1H, NCH*H*CH_2), 3.72 (s, 3H, OMe) and 6.33 (br s, 1H, CON*H*); *m*/*z* (%): 213 ($M+H^+$, 1), 153 ($M-CO_2Me^+$, 100) and 108 (72); ν_{max} (cm^{-1}): 3056, 2988, 1730 (C═O), 1662 (C═O).

3.4.8. Methyl (±) 2-(3′-indolylmethyl)-4-oxo-octahydropyrrolo[3.4-*b*]-pyridine-2-carboxylate 6h. Reaction of **5j** (0.150 g, 0.307 mmol) and hydrazine monohydrate (0.018 ml, 0.365 mmol) in methanol (8 ml) at 55°C for 42 h afforded, after flash chromatography (3:1 v/v ethyl acetate–methanol), the product **6h** (0.091 g, 91%) as pale yellow needles, mp 139.5–141.0°C. (Found: C 63.85; H, 6.60; N, 12.30. $C_{18}H_{21}N_3O_3$·1/2H_2O requires: C 64.25; H, 6.60; N, 12.50%); δ (250 MHz): 1.59–1.69 (m, 1H, CH_2C*H*HCH), 1.75–1.90 (m, 1H, CH_2CH*H*CH), 2.43–2.60 (m, 2H, CC*H*$_2$CH), 2.76 (br s, 1H, N*H*), 2.82–2.94 (m, 1H, CHC*H*(CO_2Me)CH_2), 3.04–3.14 (m, 1H, NHC*H*(CH_2)CH), 3.08 (d, *J*=14.4 Hz, 1H, CC*H*HAr), 3.30 (d, *J*=14.4 Hz, 1H, CCH*H*Ar), 3.39–3.51 (m, 1H, NC*H*HCH_2), 3.60 (s, 3H, OMe), 3.60–3.73 (m, 1H, NCH*H*CH_2), 6.55 (br s, 1H, CON*H*), 7.05–7.2) (m, 2H, ArH), 7.31 and 7.58 (2×d, *J*=7.7 Hz, 2×1H, ArH) and 8.66 (br s, 1H, ArN*H*); *m*/*z* (ES+, %): 350 ($M+Na^+$, 20), 328 ($M+H^+$, 100) and 197 (45); ν_{max} (cm^{-1}): 3056, 2988–2932, 1728 (C═O), 1660 (C═O).

3.4.9. Dimethyl (±) *endo*-5-[3-aminopropyl]-2-benzylpyrrolidine-2,4-dicarboxylate 12a. Reaction of **11a** (0.133 g, 0.286 mmol) and hydrazine monohydrate (0.023 ml, 0.486 mmol) in methanol (8 ml) at 55°C for 18 h afforded the product **11a** (0.073 g, 76%) as a colourless oil. δ (250 MHz): 1.25–1.85 (m, 5H, CH_2C*H*$_2$CH, N*H* and N*H*$_2$), 2.05 (dd, *J*=7.6 and 14.0 Hz, 1H, CC*H*HCH), 2.60 (dd, *J*=3.7 and 13.9 Hz, 1H, CCH*H*CH), 2.71–2.85 (m, 2H, NH_2CH_2C*H*$_2$CH$_2$), 2.82 (d, *J*=13.0 Hz, 1H, CC*H*HPh), 2.99 (d, *J*=13.0 Hz, 1H, CCH*H*Ph), 3.07–3.15 (m, 1H, CHC*H*(CO_2Me)CH_2), 3.55–3.99 (m, 3H, NH_2C*H*$_2$CH$_2$, and NHC*H*(CH_2)CH), 3.59 and 3.68 (2×s, 2×3H, 2×OMe) and 7.22–7.28 (m, 5H, ArH).

3.4.10. Dimethyl (±) *endo*-5-[3-aminopropyl]-2-methylpyrrolidine-2,4-dicarboxylate 12b. Reaction of **11b**

(0.118 g, 0.304 mmol) and hydrazine monohydrate (0.018 ml, 0.365 mmol) in methanol (8 ml) at 55°C for 18 h afforded the product **12b** (0.068 g, 87%) as a colourless oil. δ (250 MHz): 1.32–1.66 (m, 4H, $CH_2CH_2CH_2CH$), 1.41 (s, 3H, CMe), 1.92 (dd, *J*=7.5 and 13.8 Hz, 1H, CC*H*HCH), 1.99 (br s, 3H, N*H* and NH_2), 2.60 (dd, *J*=3.6 and 13.8 Hz, 1H, CCH*H*CH), 2.70 (t, *J*=6.8 Hz, 2H, $NH_2CH_2CH_2$), 2.97–3.04 (m, 1H, $CHCH(CO_2Me)CH_2$), 3.29–3.37 (m, 1H, $NHCH(CH_2)CH$) and 3.65 and 3.77 (2×s, 2×3H, 2×OMe).

3.4.11. (±) *endo*-4,7-Dimethyl-4,9,11-triaza-tricyclo-[5.3.1.0 2,6]undecane-3,5,8-trione 18a. Reaction of **17a** (177 mg, 0.46 mmol) and hydrazine monohydrate (25 μl, 0.51 mmol) in methanol (10 ml) at 50°C for 90 h afforded, after flash chromatography (1:1 v/v EtOAc–MeOH), the product **18a** (78 mg, 76%) as colourless prisms from MeOH, mp 256–258°C. (Found: C, 53.65, H, 5.90, N, 18.90. $C_{10}H_{13}N_3O_3$ requires: C, 53.80, H, 5.85, N, 18.80%); δ 1.50 (s, 3H, Me), 2.0 (br s, 1H, NH), 2.98 (s, 3H, NMe), 3.18 (m, 2H, 2×COCH), 3.32 (dd, *J*=5.9 and 10.3 Hz, 1H, NC*H*H), 3.46 (dd, *J*=5.0 and 10.3 Hz, 1H, NCH*H*), 4.32 (m, 1H, NCH) and 5.94 (br s, 1H, NH); *m/z* (%): 223 (M^+, 62), 195 (25), 180 (10), 166 (42), 164 (60) 138 (71), 123 (16), 107 (50), 94 (57), 81 (100), 67 (6), 53 (11) and 40 (14).

3.4.12. (±) *endo*-4-Methyl-7-(2-methylsulfanyl-ethyl)-4,9,11-triaza-tricyclo[5.3.1.0 2,6]undecane-3,5,8-trione 18b. Reaction of **17b** (113 mg, 0.25 mmol) and hydrazine monohydrate (20 μl, 0.4 mmol) in ethanol (5 ml) at 78°C for 48 h afforded, after flash chromatography (EtOAc then 3:1 v/v EtOAc–MeOH), the product **18b** (30 mg, 42%) as colourless fine needles from $MeOH/CH_2Cl_2$/petroleum ether, mp 146–148°C. (Found: C, 50.60, H, 6.30, N, 14.65, S, 11.40. $C_{12}H_{17}N_3O_3S$ requires: C, 50.85, H, 6.05, N, 14.85, S, 11.30%); δ 2.06 (m, 2H, CH_2), 2.11 (s, 3H, SMe), 2.49 (m, 3H, CH_2 and NH), 2.98 (s, 3H, NMe), 3.19 (d, *J*=10.7 Hz, 1H, NC*H*H), 3.31 (m, 2H, 2×COCH), 3.47 (dd, *J*=4.8 and 10.7 Hz, 1H, NCH*H*), 4.29 (s, 1H, NCH) and 5.78 (br s, 1H, NH); *m/z* (%): 283 (M^+, 27), 268 (12), 236 (11), 209 (100), 181 (30), 177 (15), 165 (27), 151 (31), 137 (22), 123 (12), 106 (10), 94 (31), 84 (32), 80 (79), 74 (11), 67 (8), 61 (21), 53 (18) and 40 (10).

3.4.13. (±) *endo*-7-(3-Indolyl-methyl)-4-methyl-4,9,11-triaza-tricyclo[5.3.1.0 2,6]undecane-3,5,8-trione 18c. Reaction of **17c** (37 mg, 0.074 mmol) and hydrazine monohydrate (7.5 μl, 0.15 mmol) in ethanol (7 ml) at reflux for 3 d afforded, after flash chromatography (4:1 v/v EtOAc–MeOH), the product **18c** (13 mg, 52%) as colourless prisms from $CHCl_3$, mp 147–149°C. (Found (HRMS): 338.1379. $C_{18}H_{18}N_4O_3$ requires: 338.1380); δ 2.80 (s, 3H, NMe), 3.16 (m, 2H, 2×COCH), 3.21 and 3.34 (2×d, *J*=14.2 Hz, 2×1H, indole-CH_2), 3.39 (dd, *J*=5.0 and 10.3 Hz, 1H, NC*H*H), 3.46 (d, *J*=10.3 Hz, 1H, NCH*H*), 4.03 (m, 1H, NCH), 5.51 (br s, 1H, CONH), 7.18 (m, 3H, ArH), 7.38 and 7.60 (2×d, *J*=7.5 Hz, 2×1H, ArH) and 8.22 (br s, 1H, NH); *m/z* (%): 338 (M^+, 10), 130 (100), 86 (12), 84 (20), 77 (5) and 49 (12).

3.4.14. Polycyclic lactam 19. Reaction of **17d** (120 mg, 0.26 mmol) and hydrazine monohydrate (25 μl, 0.5 mmol) in methanol (5 ml) at reflux for 84 h afforded, after flash chromatography (EtOAc then 4:1 v/v EtOAc–MeOH), the product **19** (31 mg, 40%) as colourless needles from $MeOH/CH_2Cl_2$/petroleum ether, mp >290°C. (Found: C, 54.60, H, 4.95, N, 15.80. $C_{12}H_{13}N_3O_4$ requires: C, 54.75, H, 5.00, N, 15.95%); δ 2.29, 2.41 and 2.53 (3×m, 3H, CH_2 and COC*H*H), 2.99 (s, 3H, NMe), 3.16 (m, 1H, COCH*H*), 3.30 (d, *J*=9.9 Hz, 1H, COCH), 3.42 (d, *J*=11.3 Hz, 1H, NC*H*H), 3.68 (m, 2H, NCH*H* and COCH), 4.81 (m, 1H, NCH) and 6.00 (br s, 1H, NH); *m/z* (%): 263 (M^+, 100), 235 (22), 204 (25), 178 (43), 164 (6), 149 (63), 134 (34), 121 (39), 106 (9), 93 (21), 80 (22), 67 (10), 55 (16) and 39 (13).

3.4.15. (±) *endo*-7-Benzyl-4-methyl-4,9,11-triaza-tricyclo-[5.3.1.0 2,6]undecane-3,5,8-trione 18e. Reaction of **17e** (102 mg, 0.22 mmol) and hydrazine monohydrate (17 μl, 0.32 mmol) in ethanol (4 ml) at 78°C for 48 h afforded, after flash chromatography (EtOAc, then 4:1 v/v EtOAc–MeOH), the product **18e** (40 mg, 61%) as colourless prisms from CH_2Cl_2/petroleum ether, mp 199–201°C. (Found: C, 63.95, H, 5.85, N, 14.25. $C_{16}H_{17}N_3O_3$ requires: C, 64.20, H, 5.70, N, 14.05%); δ 2.78 (s, 3H, NMe), 2.97 and 3.11 (2×d, *J*=13.5 Hz, 2×1H, $PhCH_2$), 3.14 (m, 2H, COCH and NC*H*H), 3.39 (m, 2H, COCH and NCH*H*), 3.96 (t, *J*=5.2 Hz, 1H, NCH), 6.56 (br s, 1H, NH), 7.15 (m, 3H, ArH) and 7.28 (m, 2H, ArH); *m/z* (%): 299 (M^+, 4), 208 (100), 156 (9), 151 (63), 123 (23), 91 (18), 80 (29), 65 (7) and 53 (8).

3.4.16. Phenyl (±) 1-benzyl-2-oxo-3,8-diaza-bicyclo-[3.2.1]octane-6-sulfone 21. Reaction of **20** (0.300 g, 0.579 mmol) and hydrazine monohydrate (0.039 ml, 0.811 mmol) in methanol (15 ml) at 55°C for 80 h afforded, after flash chromatography (5:1 v/v ethyl acetate–methanol), the product **21** (0.125 g, 61%) as pale yellow needles, mp 190.0–191.0°C. (Found: C 63.50; H, 5.75; N, 7.95. $C_{19}H_{20}N_2O_3S{\cdot}1/4H_2O$ requires: C 63.25; H, 5.70; N, 7.95%); δ ^{1}H (250 MHz): 1.82–1.87 (m, 1H, CHC*H*HC), 2.00 (br s, 1H, CHN*H*C), 2.52 (dd, *J*=6.2 and 13.6 Hz, 1H, CHCH*H*C), 2.96 (d, *J*=13.9 Hz, CC*H*HPh), 3.43 (dd, *J*=4.6 and 12.2 Hz, 1H, CHC*H*HNH), 3.62–3.72 (m, 1H, $CHCH(SO_2Ph)CH_2$), 3.98–4.06 (m, 2H, CHC*H*(NH)CH*H*NH), 5.66 (br s, 1H, CON*H*), 7.21–7.31 (m, 5H, ArH), 7.61–7.68 (m, 3H, ArH *ortho* and *para* to S) and 7.88–7.90 (m, 2H, ArH *meta* to S); *m/z* (FAB, %): 379 ($M+Na^+$, 12), 357 ($M+H^+$, 100) and 158 (70); ν_{max} (KBr disc, cm^{-1}): 3373, 3275, 3056–3027, 2964–2853, 1668 (C=O) and 1146.

3.4.17. Methyl (±) *endo*-5-[2-aminoethyl]-4-benzenesulfonyl-2-benzyl-pyrrolidine-2-carboxylate 23. Reaction of **22** (0.150 g, 0.282 mmol) and hydrazine monohydrate (0.023 ml, 0.479 mmol) in methanol (9 ml) at 55°C for 18 h afforded the product **23** (0.118 g, 100%) as a colourless oil. δ (250 MHz): 1.85–2.40 (m, 6H, CH_2CH_2CH, CC*H*HCH, N*H* and NH_2), 2.64 (dd, *J*=4.5 and 14.7 Hz, 1H, CCH*H*CH), 2.77 (d, *J*=13.0 Hz, 1H, CC*H*HPh), 2.84–2.91 (m, 2H, $NHCH(CH_2)CH(SO_2Ph)CH_2$), 2.91 (d, *J*=13.0 Hz, CCH*H*Ph), 3.23–3.30 (m, 2H, $NH_2CH_2CH_2$), 3.74 (s, 3H, OMe), 7.12–7.22 (m, 5H, ArH), 7.55 (t, *J*=7.4 Hz, 2H, ArH *meta* to SO_2), 7.62 (t, *J*=7.3 Hz, 1H, ArH *para* to SO_2) and 7.78 (d, *J*=7.5 Hz, 2H, ArH *ortho* to SO_2).

3.5. General procedure for the base catalysed lactamisation of amino esters

Sodium methoxide (1 equiv.) was added to a stirred solution of primary amino ester (1 equiv.) in methanol and the mixture was heated to reflux for 4.5–16 h. The mixture was allowed to cool, the solvent evaporated, the residue dissolved in dichloromethane and washed with saturated ammonium chloride (2×) and brine. The organic layer was dried ($MgSO_4$) and the solvent evaporated. The residue was purified via flash column chromatography to afford the product.

3.5.1. Methyl (±) 2-benzyl-4-oxodecahydropyrrolo[3,2-*c*]azepine-2-carboxylate 13a and methyl (±) 2-benzyl-4-oxodecahydropyrrolo[3,2-*c*]azepine-2-carboxylate 14a. Prepared according to the general procedure from primary amino ester **12a** (0.162 g, 0.431 mmol), and sodium methoxide (0.024 g, 0.431 mmol) in methanol (8 ml) at reflux for 4.5 h. The residue was purified (5:1 v/v ethyl acetate–methanol) to afford a 4:1 mixture of **13a** and **14a** (0.037 g, 30%) as a colourless gum. Further purification gave pure epimers **13a** (0.005 g) and **14a** (0.003 g) for analysis. (Found: C 65.00; H, 7.50; N, 8.45. $C_{17}H_{22}N_2O_3{\cdot}3/4H_2O$ requires: C 64.65; H, 7.50; N, 8.80%); *m/z* (ES+, %): 325 ($M+Na^+$, 15), 303 ($M+H^+$, 100) and 243 (85); ν_{max} (cm^{-1}): 3056, 2988, 1733 (C═O), 1669 (C═O).

Compound **13a**: δ (500 MHz): 1.50–1.61 (m, 2H, CH_2CH_2CH), 1.75–1.79 (m, 1H, CH_2CHHCH_2), 1.96–2.00 (m, 1H, CH_2CHHCH_2), 2.02 (br hump, 1H, NH), 2.12 (dd, *J*=8.8 and 13.5 Hz, 1H, CCHHCH), 2.87 (d, *J*=13.3 Hz, 1H, CCHHPh), 2.88 (dd, *J*=5,6 and 13.5 Hz, 1H, CCHHCH), 3.14 (d, *J*=13.4 Hz, 1H, CCHHPh), 3.14–3.22 (m, 2H, $CHCH(CO)CH_2$ and $NHCHHCH_2$), 3.28–3.34 (m, 1H, $NHCHHCH_2$), 3.44–3.48 (m, 1H, $NHCH(CH_2)CH$), 3.70 (s, 3H, OMe), 5.57 (br t, *J*=6.4 Hz, 1H, CONH) and 7.17–7.27 (m, 5H, ArH).

Compound **14a**: δ (500 MHz): 1.49–1.56 (m, 2H, CH_2CH_2CH), 1.82–1.85 (m, 1H, CH_2CHHCH_2), 2.05 (br hump, 1H, NH), 2.26–2.29 (m, 1H, CH_2CHHCH_2), 2.47 (dd, *J*=7.8 and 13.5 Hz, 1H, CCHHCH), 2.54 (dd, *J*=10.9 and 13.6 Hz, CCHHCH), 2.67–2.73 (m, 1H, $CHCH(CO_2\text{-}Me)CH_2$), 2.93 (d, *J*=13.3 Hz, 1H, CCHHPh), 3.04 (dt, *J*=3.4 and 10.3 Hz, $NHCH(CH_2)CH$), 3.16 (d, *J*=13.3 Hz, 1H, CCHHPh), 3.17–3.20 (m, 1H, $NHCHHCH_2$), 3.25–3.28 (m, 1H, $NHCHHCH_2$), 3.67 (s, 3H, OMe), 6.07 (br s, 1H, CONH) and 7.18–7.26 (m, 5H, ArH).

3.5.2. Methyl (±) 2-methyl-4-oxodecahydropyrrolo[3,2-*c*]azepine-2-carboxylate 13b and methyl (±) 2-methyl-4-oxodecahydropyrrolo[3,2-*c*]azepine-2-carboxylate 14b. Prepared according to the general procedure from primary amino ester **12b** (0.098 g, 0.380 mmol), and sodium methoxide (0.021 g, 0.380 mmol) in methanol (8 ml) at reflux for 4.5 h. The residue was purified (3:1 v/v ethyl acetate–methanol) to afford a 10:1 mixture of **13b** and **14b** (0.010 g, 12%) as a colourless gum. (HRMS: $M+H^+$ $C_{11}H_{19}N_2O_3$ requires 227.1395; found 227.1396); *m/z* (%): 227 ($M+H^+$, 1), 167 ($M-CO_2Me^+$, 100), 139 (11) and 122 (34); ν_{max} (cm^{-1}): 3056, 2988, 1733 (C═O), 1669 (C═O). The quantity of **14b** was too small to collect spectroscopic data.

Compound **13b**: δ (250 MHz): 1.40 (s, 3H, CMe), 1.45–2.09 (m, 6H, $CH_2CH_2CH_2CH$, CCHHCH and NH), 2.73 (dd, *J*=6.6 and 13.8 Hz, 1H, CCHHCH), 3.14–3.49 (m, 4H, $NHCH_2CH_2$ and $NHCH(CH_2)CH(CO)CH_2$), 3.76 (s, 3H, OMe) and 5.84 (br s, 1H, CONH).

3.5.3. Phenyl (±) 1-benzyl-2-oxo-3,9-diaza-bicyclo-[4.2.1]octane-7-sulfone 24 and phenyl (±) 1-benzyl-2-oxo-3,9-diaza-bicyclo[4.2.1]octane-7-sulfone 25. Prepared according to the general procedure from primary amino ester **23** (0.124 g, 0.308 mmol), and sodium methoxide (0.017 g, 0.308 mmol) in methanol (8 ml) at reflux for 4.5 h. The residue was purified (5:1 v/v ethyl acetate–methanol) to afford a 2:1 mixture of **24** and **25** (0.081 g, 71%) as a pale yellow solid, mp 104.0–106.0°C. (Found: C 64.35; H, 5.95; N, 7.70; S, 8.35. $C_{20}H_{22}N_2O_3S{\cdot}1/4H_2O$ requires: C 64.05; H, 6.00; N, 7.45; S, 8.35%); *m/z* (%): 370 (M^+, 1), 279 (2), 229 (36), 201 (26), 158 (98) and 91 (100); ν_{max} (cm^{-1}): 3056, 2987, 1652 (C═O) and 1140.

Compound **24**: δ (250 MHz): 2.00–2.17 (m, 1H, CH_2CHHCH), 2.07 (dd, *J*=8.5 and 13.7 Hz, 1H, CCHHCH), 2.48–2.57 (m, 1H, CH_2CHHCH), 2.64 (dd, *J*=11.3 and 13.7 Hz, 1H, CCHHCH), 2.90 (d, *J*=13.9 Hz, 1H, CCHHPh), 2.98–3.06 (m, 1H, $CHCH(SO_2Ph)CH_2$), 3.29 (d, *J*=13.9 Hz, 1H, CCHHPh), 3.43–3.51 (m, 2H, $NHCH_2CH_2$), 3.86–3.92 (m, 1H, $NHCH(CH_2)CH$), 6.04 (br s, 1H, CONH), 7.10–7.32 (m, 5H, ArH) and 7.53–7.77 (m, 5H, ArH).

Compound **25**: δ (250 MHz): 1.70–1.81 (m, 1H, CH_2CHHCH), 2.19–2.23 (m, 1H, CCHHCH), 2.39 (dd, *J*=8.0 and 13.4 Hz, 1H, CCHHCH), 2.75–2.81 (m, 1H, CH_2CHHCH), 2.93 (d, *J*=14.1 Hz, 1H, CCHHPh), 3.41–3.50 (m, 1H, $CHCH(SO_2Ph)CH_2$), 3.57 (d, *J*=13.9 Hz, 1H, CCHHPh), 3.70–3.85 (m, 2H, $NHCH_2CH_2$), 4.23–4.29 (m, 1H, $NHCH(CH_2)CH$), 6.16 (br s, 1H, CONH), 7.10–7.32 (m, 5H, ArH) and 7.53–7.77 (m, 5H, ArH).

3.6. Lactamisation via acid chloride

3.6.1. (±) *endo*-5-[3-Aminopropyl]-2-benzyl-pyrrolidine-2,4-dicarboxylic acid dihydrochloride 15. A stirred solution of primary amino ester **12a** (0.072 g, 0.215 mmol) in 1 M HCl (10 ml) was heated to reflux for 3.5 h. The solution was allowed to cool and the solvent evaporated, azeotroping the residue with toluene (×3) to afford the *product* (0.088 g, 100%) as brown gum. This was used without further purification.

3.6.2. Methyl (±) 2-benzyl-4-oxodecahydropyrrolo[3,2-*c*]azepine-2-carboxylate 13b. Excess thionyl chloride (5 ml) was added to a stirred solution of diacid dihydrochloride **15** (0.048 g, 0.126 mmol) in acetonitrile (5 ml) at room temperature and the solution was stirred for 16 h. The solvent was evaporated and the residue was dissolved in acetonitrile (10 ml) and transferred to a dropping funnel, diluting with benzene (15 ml). This was added dropwise (40 min) to a 3-necked flask containing benzene (30 ml) with simultaneous dropwise addition (40 min) of a solution

of triethylamine (0.12 ml, 0.846 mmol) in benzene (15 ml) at room temperature. The mixture was stirred for 2 h followed by the addition of methanol (5 ml) and stirring for a further 16 h. The solvents were evaporated and the solid residue was extracted with toluene (×2), filtered and the filtrate evaporated. The residue was purified via flash column chromatography (5:1 v/v ethyl acetate–methanol) to afford the *product* (0.034 g, 90%) as a colourless gum. Analytical data as previously described for **13b**.

3.7. Synthesis of bicyclic ureas

3.7.1. Methyl (±) 7-benzyl-1-oxo-5-(phenylsulfonyl)-octahydropyrrolo[1,2-*c*]pyrimidine-7-carboxylate 26. Phosgene (0.085 ml, 0.162 mmol as a 20% solution in toluene) was added dropwise to a stirred solution of primary amine **23** (0.062 g, 0.154 mmol) and triethylamine (0.047 ml, 0.340 mmol) in THF (8 ml) at 0°C (ice/water) and the mixture was stirred for 1 h, then at room temperature for 15 h. The mixture was diluted with chloroform and washed with saturated sodium bicarbonate (×2). The organic layer was dried ($MgSO_4$) and the solvent evaporated. The residue was purified via flash column chromatography (ethyl acetate→95:5 v/v ethyl acetate–methanol) to give the *product* (0.037 g, 56%) as a colourless foam. (HRMS: $M+H^+$ $C_{22}H_{25}N_2O_5S$ requires 429.1484; found 429.1484); δ (d_6-DMSO, 300 MHz): 1.87 (dd, J=7.7 and 13.0 Hz, 1H, CHC*H*HC), 1.94–2.05 (m, 1H, NHCH$_2$C*H*HCH), 2.28–3.36 (m, 1H, NHCH$_2$CH*H*CH), 2.69 (dd, J=9.6 and 13.0 Hz, 1H, CHCH*H*C), 2.83 (br s, 1H, N*H*CO), 2.95 (d, J=13.1 Hz, 1H, CC*H*HPh), 2.99–3.40 (m, 4H, NC*H*(CH$_2$C*H*$_2$NH)C*H*(SO$_2$)CH$_2$), 3.27 (d, J=13.2 Hz, 1H, CCH*H*Ph), 3.63 (s, 3H, CO_2Me), 7.02–7.32 (m, 5H, ArH) and 7.61–7.84 (m, 5H, ArH); *m*/*z* (FAB, %): 429 ($M+H^+$, 57), 227 (7); ν_{max} (cm^{-1}): 3056, 2987–2955, 1741 (C=O), 1667 (C=O), 1495 and 1152.

3.8. Synthesis of bicyclic lactams: Boc-amino-aldimine route

General procedure for the synthesis of Weinreb amides. Isobutyl chloroformate (1.1 equiv.) was added dropwise to a stirred solution of Boc-amino acid (1 equiv.) and *N*-methylmorpholine (2.2 equiv.) in dichloromethane (70–100 ml) at −15°C (ice/methanol) and the mixture was stirred for 15 min. *N*,*O*-Dimethylhydroxylamine hydrochloride (1 equiv.) was added and stirring was continued at −15°C for 15 min, then at room temperature for 16 h. The mixture was washed with 0.2 M potassium bisulfate (50–100 ml), the organic layer separated and the aqueous extracted with dichloromethane (×2). The combined organic layers were dried ($MgSO_4$) and the solvent evaporated to afford the product.

3.8.1. *N*-Boc-glycine-*N*′-methyl-*N*′-methoxyamide 27a.[12] Prepared according to the general procedure from Boc-glycine (2.50 g, 14.27 mmol), *N*-methylmorpholine (3.45 ml, 31.40 mmol), isobutylchloroformate (2.10 ml, 15.70 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (1.39 g, 14.27 mmol) in dichloromethane (100 ml) to afford the product (3.04 g, 97%) as a colourless solid, mp 77.0–78.0°C. δ (250 MHz): 1.46 (s, 9H, CMe_3), 3.21 (s, 3H, NMe), 3.72 (s, 3H, OMe), 4.08 (d, J=4.7 Hz, 2H, NHCH_2CO) and 5.30 (br s, 1H, N*H*); *m*/*z* (FAB, %): 241 ($M+Na^+$, 11), 219 ($M+H^+$, 75) and 163 (100).

3.8.2. *N*-Boc-β-alanine-*N*′-methyl-*N*′-methoxyamide 27b.[12] Prepared according to the general procedure from Boc-β-alanine (2.50 g, 13.21 mmol), *N*-methylmorpholine (3.19 ml, 29.06 mmol), isobutylchloroformate (1.88 ml, 14.53 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (1.29 g, 13.21 mmol) in dichloromethane (100 ml) to afford the *product* (3.15 g, 100%) as a colourless oil. δ (250 MHz): 1.43 (s, 9H, CMe_3), 2.64 (t, J=5.4 Hz, 2H, CH$_2$C*H*$_2$CO), 3.19 (s, 3H, NMe), 3.42 (q, J=5.9 Hz, 2H, NHC*H*$_2$CH$_2$), 3.68 (s, 3H, OMe), and 5.25 (br s, 1H, N*H*); *m*/*z* (FAB, %): 255 ($M+Na^+$, 8), 233 ($M+H^+$, 53), 177 (87), 133 (88), and 73 (100).

3.8.3. *N*-Boc-*N*-methylamino-*N*′-methyl-*N*′-methoxy acetamide 33.[13] Prepared according to the general procedure from Boc-sarcosine[10] (1.297 g, 6.862 mmol), *N*-methylmorpholine (1.66 ml, 15.096 mmol), isobutylchloroformate (0.98 ml, 7.584 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (0.669 g, 6.862 mmol) in dichloromethane (70 ml) to afford the product (1.320 g, 83%) as a colourless oil. δ (250 MHz): 1.45 (d, J=13.2 Hz, 9H, CMe_3), 2.93 (s, 3H, BocNMe), 3.19 (s, 3H, NMe), 3.72 (s, 3H, OMe) and 4.12 (d, J=18.9 Hz, 2H, NCH_2CO); *m*/*z* (%): 172 (6), 159 (13), 116 (30), 88 (19), 57 (100) and 44 (78).

General procedure for the reduction of Weinreb amides. Lithium aluminium hydride (5 equiv.) was added to a stirred solution of Weinreb amide (1 equiv.) in THF at room temperature and the mixture was stirred for 20 min. The reaction was quenched with 0.2 M potassium bisulfate (25 ml) and extracted with ether (×3). The combined organic layers were washed with 2 M HCl (×3), saturated sodium bicarbonate (×3) and brine (×3). The organic layer was dried ($MgSO_4$) and the solvent removed to afford the product which was used directly for the next step.

3.8.4. *N*-Boc-aminoacetaldehyde 29a.[12] Prepared according to the general procedure from Weinreb amide **28a** (0.500 g, 2.290 mmol) and lithium aluminium hydride (0.109 g, 2.867 mmol) in THF (25 ml) to afford the product (0.218 g, 60%) as a colourless oil. δ (300 MHz): 1.44 (s, 9H, CMe_3), 4.07 (br d, J=4.4 Hz, 2H, NHCH_2CO), 5.10 (br s, 1H, N*H*) and 9.65 (s, 1H, C*H*O).

3.8.5. 3-(*N*-Boc-amino)-propionaldehyde 29b.[12] Prepared according to the general procedure from Weinreb amide **28b** (0.610 g, 2.625 mmol) and lithium aluminium hydride (0.125 g, 3.281 mmol) in THF (18 ml) to afford the product (0.292 g, 64%) as a colourless oil. δ (300 MHz): 1.43 (s, 9H, CMe_3), 2.71 (t, J=5.8 Hz, 2H, CH$_2$C*H*$_2$CHO), 3.42 (q, J=5.9 Hz, 2H, NHC*H*$_2$CH$_2$), 4.90 (br s, 1H, N*H*) and 9.81 (s, 1H, C*H*O). *m*/*z* (FAB, %): 174 ($M+H^+$, 3), 173 (17), 147 (14) and 73 (100).

3.8.6. *N*-Boc-*N*-methylglycinal 35.[14] Prepared according to the general procedure from Weinreb amide **34** (0.600 g, 2.586 mmol) and lithium aluminium hydride (0.123 g, 3.232 mmol) in THF (18 ml) to afford the product (0.205 g, 46%) as a colourless oil. δ (250 MHz): 1.55 (d,

J=12.5 Hz, 9H, CMe_3), 2.97 (d, J=8.2 Hz, 3H, NMe), 4.00 (d, J=25.0 Hz, 2H, NCH_2CHO) and 9.63 (s, 1H, CHO). *m/z* (FAB, %): 174 ($M+H^+$, 11), 147 (13), 144 (24), 131 (8), 118 (23) and 57 (100).

General procedure for the preparation of imines. Excess $MgSO_4$ was added to a stirred solution of aldehyde (1 equiv.) and phenylalanine methyl ester (1.1 equiv.) in dichloromethane at room temperature and the mixture was stirred for 40 h, filtered and the filtrate evaporated to give the imines, which were used without purification.

3.8.7. Methyl (±) 2-[3-(*N*-Boc-amino)-propylidene-amino]-3-phenyl propionate 30b. Prepared according to the general procedure from aldehyde **29b** (0.283 g, 1.636 mmol) and L-phenylalanine methyl ester (0.322 g, 1.799 mmol) over $MgSO_4$ (1.0 g) in dichloromethane (20 ml) for 40 h to afford the product (0.622 g, 100%) as a colourless gum. δ (300 MHz): 1.44 (s, 9H, CMe_3), 2.31–2.36 (m, 2H, $NHCH_2CH_2$), 2.99–3.07 (m, 1H, CHCHHPh), 3.26–3.32 (m, 2H, CHCHHPh and CH_2CHHC=N), 3.51 (d, J=5.2 Hz, 1H, CH_2CHHC=N), 3.76 (s, 3H, CO_2Me), 3.94 (dd, J=4.3 and 9.8 Hz, 1H, $NCH(CH_2)CO_2Me$), 4.90 (br s, 1H, NH) and 7.11–7.31 (m, 6H, ArH and CH_2CH=N); *m/z* (FAB, %): 335 ($M+H^+$, 17), 311 (29), 218 (31), 199 (36) and 57 (100).

3.8.8. Methyl (±) 2-[2-(*N*-Boc-*N*-methylamino)-ethyl-idenamino]-3-phenylpropionate 36. Prepared according to the general procedure from aldehyde **35** (0.196 g, 1.133 mmol) and L-phenylalanine methyl ester (0.233 g, 1.246 mmol) over $MgSO_4$ (1.0 g) in dichloromethane (10 ml) for 40 h to afford the product (0.393 g, 100%) as a colourless gum. δ (250 MHz): 1.42 (br s, 9H, CMe_3), 2.63 (br d, J=7.3 Hz, 3H, NMe), 3.03 (dd, J=9.6 and 13.5 Hz, 1H, CCHHPh), 3.29 (dd, J=4.6 and 13.5 Hz, 1H, CHCHHPh), 3.72 (d, J=3.0 Hz, 2H, NCH_2CH=N), 3.76 (s, 3H, CO_2Me), 4.00 (dd, J=4.5 and 9.6 Hz, 1H, $NCH(CH_2Ph)CO_2Me$), and 7.11–7.34 (m, 6H, ArH and CH=N); *m/z* (FAB, %): 369 (20), 281 (6), 221 (7), 147 (21) and 69 (100).

General procedure for the 1,3-dipolar cycloaddition of Boc-aminoaldimines. Silver(I) acetate (1.3 equiv.), methyl acrylate (5 equiv.), and triethylamine (1.3 equiv.) were added to a stirred solution of imine (1 equiv.) in toluene (10–15 ml) at room temperature and the mixture was stirred for 36 h. The mixture was diluted with dichloromethane (50 ml) and washed with saturated ammonium chloride (×2) and water. The organic layer was dried ($MgSO_4$) and the solvent evaporated. The residue was purified via flash column chromatography to afford the cycloadducts.

3.8.9. Dimethyl (±) *endo*-2-benzyl-5-[2-(*N*-Boc-amino)-ethyl]-pyrrolidine-2,4-dicarboxylate 31b. Prepared according to the general procedure from imine **30b** (0.622 g, 1.630 mmol), silver(I) acetate (0.408 g, 2.445 mmol), methyl acrylate (0.73 ml, 8.150 mmol) and triethylamine (0.34 ml, 2.445 mmol) in toluene (15 ml) for 36 h. The residue was purified (2:1 v/v ether–petroleum ether) to afford the product (0.342 g, 50%) as a colourless solid, mp 94.5–96.0°C. (Found: C 63.00; H, 7.75; N, 6.85. $C_{10}H_{16}N_2O_3$ requires: C 62.85; H, 7.65; N, 6.65%); δ (500 MHz): 1.42–1.45 (m, 1H, NCH_2CHH), 1.46 (s, 9H, CMe_3), 1.70–1.78 (m, 1H, NCH_2CHH), 2.06 (dd, J=7.4 and 14.0 Hz, 1H, $MeCO_2CHCHH$), 2.60 (dd, J=3.0 and 14.0 Hz, 1H, $MeCO_2CHCHH$), 2.81–2.85 (m, 1H, $MeCO_2CH$), 2.83 (d, J=13.1 Hz, 1H, PhCHH), 2.99–3.04 (m, 1H, $NCHCH_2$), 3.02 (d, J=13.1 Hz, 1H, PhCHH), 3.15–3.22 (m, 1H, NCHH), 3.25–3.33 (m, 1H, NCHH), 3.62 and 3.71 (2×s, 2×3H, 2×CO_2Me), 5.11 (br s, 1H, NHCO) and 7.20–7.30 (m, 5H, ArH); *m/z* (%): 421 ($M+H^+$, 1), 361 (1), 347 (13), 329 (14), 273 (50), 229 (100), 186 (73), 91 (88) and 57 (87); ν_{max} (cm^{-1}): 3056, 2985–2954,1731 (C=O), 1708 (C=O) and 1508.

3.8.10. Dimethyl (±) *endo*-5-[(*N*-Boc-*N*-methylamino)-methyl]-2-benzylpyrrolidine-2,4-dicarboxylate 37. Prepared according to the general procedure from imine **36** (0.393 g, 1.130 mmol), silver(I) acetate (0.245 g, 1.469 mmol), methyl acrylate (0.51 ml, 5.650 mmol) and triethylamine (0.21 ml, 1.469 mmol) in toluene (10 ml) for 36 h. The residue was purified (2:1 v/v ether–petroleum ether) to afford the product (0.240 g, 51%) as a colourless gum. (Found: C 62.20; H, 7.55; N, 6.65. $C_{22}H_{32}N_2O_6 \cdot 1/4H_2O$ requires: C 62.15; H, 7.70; N, 6.60%); δ (500 MHz): 1.46 (s, 9H, CMe_3), 2.07 (dd, J=7.5 and 13.8 Hz, 1H, $MeCO_2CHCHH$), 2.59–2.64 (m, 1H, $MeCO_2CHCHH$), 2.76–2.85 (m, 2H, PhCHH and $MeCO_2CH$), 2.90 (s, 3H, NMe), 2.92–3.19 (m, 2H, PhCHH and NH), 3.15–3.25 (br m, 2H, NCHH), 3.30–3.50 (br m, 1H, $NCHCH_2$), 3.63–3.69 (2×s, 2×3H, 2×CO_2Me), and 7.23 (s, 5H, ArH); *m/z* (FAB, %): 421 ($M+H^+$, 100), 321 (28), 276 (62), 229 (32) and 91 (55); ν_{max} (cm^{-1}): 3057, 2985, 1736 (C=O), 1691 (C=O).

3.9. General procedure for Boc-deprotection/lactamisation

Cycloadduct (1 equiv.) was dissolved in dichloromethane and TFA at room temperature and the solution was stirred for 16 h. The solvents were evaporated and the residue was dissolved in dichloromethane, followed by the addition of triethylamine (2.2 equiv.) and stirring for 16 h at room temperature. The mixture was diluted with dichloromethane and washed with water (×3). The organic layer was dried ($MgSO_4$) and the solvent evaporated. The residue was purified via flash column chromatography to afford the bicyclic lactams.

3.9.1. Methyl (±) 2-benzyl-4-oxo-octahydro-pyrrolo[3.4-*b*]-pyridine-2-carboxylate 6f. Prepared according to the general procedure from cycloadduct **31b** (0.08 g, 0.19 mmol) in dichloromethane (8 ml) and TFA (2 ml), then dichloromethane (10 ml) and triethylamine (0.06 ml, 0.42 mmol). The residue was purified (5:1 v/v ethyl acetate–methanol) to afford the *product* (0.045 g, 82%) as colourless prisms, mp 123.5–124.5°C. Analytical data as previously described for **6f**.

3.9.2. Methyl (±) 2-benzyl-4-oxo-octahydro-*N*-methyl-pyrrolo[3.4-*b*]pyrrole-2-carboxylate 38. Prepared according to the general procedure from cycloadduct **37** (0.16 g, 0.38 mmol) in dichloromethane (8 ml) and TFA (2 ml), then dichloromethane (10 ml) and triethylamine (0.18 ml, 0.84 mmol). The residue was purified (10:1 v/v ethyl

acetate–methanol) to afford the *product* (0.069 g, 63%) as a colourless syrup. (Found: C 62.60; H, 7.05; N, 9.00. $C_{22}H_{32}N_2O_6{\cdot}H_2O$ requires: C 62.70; H, 7.25; N, 9.15%); δ (250 MHz): 2.15 (dd, J=9.3 and 13.3 Hz, 1H, CC*H*HC), 2.68–2.71 (m, 1H, CHCH*H*C), 2.73 (s, 3H, NMe), 2.81 (d, J=13.2 Hz, 1H, CC*H*HPh), 2.97–3.04 (m, 1H, CHC*H*(CO_2Me)CH_2), 3.21 (d, J=11.3 Hz, 1H, NMeC*H*HCH), 3.52–3.61 (m, 2H, NMeCH*HCH*), 7.08–7.12 (m, 2H, ArH *meta*) and 7.21–7.31 (m, 3H, ArH *ortho* and *para*); *m/z* (FAB, %): 311 ($M+Na^+$, 16), 289 ($M+H^+$, 62), 229 (100), 197 (33), 147 (18), and 73 (80); ν_{max} (cm^{-1}): 3056, 2987–2883, 1732 (C=O), 1683 (C=O), 1605 and 1496.

3.10. Single crystal X-ray diffraction analysis of 6a, 6e and 6f

Crystallographic data for all three compounds were collected on a Nonius KappaCCD area-detector diffractometer using 1° ϕ- and omega-slices. All structures were solved by direct methods using SHELXS-86[15]and were refined by full-matrix least-squares (based on F^2) using SHELXL-97.[16] The weighting scheme used in all refinements was $w=[\sigma^2(F_o^2)+(xP)^2+yP]^{-1}$ where $P=(F_o^2+2F_c^2)/3$. In all cases all non-hydrogen atoms were refined with anisotropic displacement parameters whilst hydrogen atoms were constrained to predicted positions. All refinements included an isotropic extinction parameter, x, so that $F'_c=kF_c[1+0.001xF_c^2\lambda^3]^{-1/4}$ where k is the overall scale factor. The residuals wR_2 and R_1, given below, are defined as $wR_2=(\sum[w(F_o-F_c^2)^2]/\sum[wF_o^4])^{1/2}$ and $R_1=\sum||F_o|-|F_c||/\sum|F_o|$.

3.10.1. Crystal data for 6a. $C_9H_{14}N_2O_3$, 0.48×0.46×0.19 mm^3, M=546.53, monoclinic, space group $C2/c$, a=17.3718(3), b=11.7339(3), c=11.2632(2) Å, β=122.9790(13)°, U=1925.94(7) $Å^3$, Z=8, D_c=1.37 Mg m^{-3}, μ=0.10 mm^{-1}, F(000)=848, T=190 K.

Data collection. Graphite monochromated Mo Kα radiation, λ=0.71073 Å. The detector was positioned with 2θ=0° and a 180° rotation of 1.0° ϕ-slices were measured at χ=0°. 'Cusp' data was measured at χ=90° and comprised 1° omega-slices over 55°; $6.94<2\theta<60.4°$, 8682 data collected 2263 of which were unique, R_{int}=0.0385, R_{sig}=0.0306. There were 1967 reflections with $F_o>4.0\sigma(F_o)$.

Structure refinement. Number of parameters=138, isotropic extinction parameter x=0.044(6), goodness of fit s=1.081; weighting parameters x, y=0.0672, 0.4792; wR_2=0.1163, R_1=0.0389.

3.10.2. Crystal data for 6e. $C_{15}H_{18}N_2O_3$, 0.55×0.35×0.28 mm^3, M=274.31, monoclinic, space group $P2_1/c$, a=13.6998(5), b=6.2380(1), c=17.0575(6) Å, β=110.9180(14)°, U=1361.65(7) $Å^3$, Z=2, D_c=1.34 Mg m^{-3}, μ=0.09 mm^{-1}, F(000)=584, T=190 K.

Data collection. As for **6a** above with $6.36<2\theta<56.92°$, 10031 data collected 2772 of which were unique, R_{int}=0.0562, R_{sig}=0.0683. There were 1815 reflections with $F_o>4.0\sigma(F_o)$.

Structure refinement. Number of parameters=329, isotropic extinction parameter x=0.034(4), goodness of fit s=0.864; weighting parameters x, y=0.0388, 0.0000; wR_2=0.0876, R_1=0.0340.

3.10.3. Crystal data for 6f. $C_{16}H_{20}N_2O_3$, 0.50×0.20×0.11 mm^3, M=288.34, triclinic, space group $P\bar{1}$, a=5.9152(2), b=9.9712(2), c=13.6560(4) Å, α=73.133(1), β=78.563(1), γ=75.759(2)°, U=740.09(4) $Å^3$, Z=2, D_c=1.29 Mg m^{-3}, μ=0.09 mm^{-1}, F(000)=308, T=150 K.

Data collection. As for **6a** above with $1.0<2\theta<52.0°$, 11777 data collected 2900 of which were unique [R_{int}=0.048]. There 2426 reflections with $F_o>4.0\sigma(F_o)$.

Structure refinement. Number of parameters=200, isotropic extinction parameter x=0.063(9), goodness of fit s=1.043; weighting parameters x, y=0.0469, 0.1349; wR_2=0.1008, R_1=0.0381.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 172732 (compound **6a**), CCDC 172733 (compound **6e**) and CCDC 172734 (compound **6f**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2) 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

We thank the ORS and Tetley and Lupton for a scholarship (to J. X.) and the EPSRC, Leeds University and Organon Laboratories for support.

References

1. (a) Massioltz, G.; Delaude, C. *The Alkaloids* **1986**, *27*, 269–322. (b) Patvardhan, S. P.; Joshi, K. S.; Vadlamudi, R. V. S. V.; Deshpande, S. G. *Ind. J. Pharm. Sci.* **1998**, *60*, 384. (c) Gupta, P.; Butler, P.; Shepperson, N. B.; McHarg, A. *Eur. J. Pharmacol.* **2000**, *398*, 73. (d) Bauer, J. H. *Am. J. Med.* **1984**, *77*, 43. (e) Sternsfeld, F.; Guibin, A. R.; Jelley, R. A.; Matassa, V. G.; Reeve, A. J.; Hunt, P. A.; Beer, M. S.; Heald, A.; Stanton, J. A.; Sohal, B.; Watt, A. P.; Street, L. J. *J. Med. Chem.* **1999**, *42*, 677.
2. Tsuge, O.; Kanemasa, S. *Adv. Heterocycl. Chem.* **1989**, *45*, 232.
3. Grigg, R. *Chem. Soc. Rev.* **1987**, *16*, 89.
4. Grigg, R.; Sridharan, V. *Adv. Cycloaddition* **1993**, *3*, 161.
5. Li, A-H.; Moro, S.; Forsyth, N.; Melman, N.; Ji, X-D.; Jacobson, K. A. *J. Med. Chem.* **1999**, *42*, 706.
6. Prabhakaran, P. C.; Gould, S. J.; Orr, G. R.; Coward, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 5779.
7. (a) Ismaid, A. M.; Angeles, J. D. L.; Teitler, M.; Ingher, S.; Glennon, R. A. *J. Med. Chem.* **1993**, *36*, 2519. (b) Mann, J.; Shervington, L. A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2961.
8. von Vavrecka, M.; Hesse, M. *Helv. Chim. Acta* **1989**, *72*, 847.
9. Fehrentz, J. A.; Castro, B. *Synthesis* **1983**, 676.

10. (a) Mouna, A. M.; Nguyen, C.; Rage, I.; Xie, J.; Nee, G.; Mezaleyrat, J. P.; Wakselman, M. *Synth. Commun.* **1994**, *24*, 2429. (b) Dado, G. P.; Gellman, S. H. *J. Am. Chem. Soc.* **1993**, *115*, 4228. (c) McDermott, J. R.; Benoiton, N. L. *Can. J. Chem.* **1973**, *51*, 1915.
11. Leonard, J.; Lygo, B.; Procter, G. *Advanced Practical Organic Chemistry*; Blachie A and P: London, 1990.
12. Bitan, G.; Muller, D.; Kasher, R.; Gluhov, E. V.; Gilon, C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1501.
13. Baum, J. C.; Gleason, J. G.; Pendrak, I.; Serau, H. M.; Schmidt, D. B. *J. Med. Chem.* **1993**, *36*, 3333.
14. Kato, S.; Haroda, H.; Marie, T. *J. Chem. Soc., Perkin Trans. 1* **1997**.
15. Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–473.
16. Sheldrick, G. M. *SHELXL 97*, Program for refinement of crystal structures; University of Göttingen, 1997.