Synthesis of the Alkaloid Homaline in (±) and Natural (*S,S*)-(−) Forms, using Amination and Transamidative Ring Expansion in Liquid Ammonia

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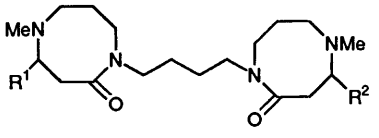
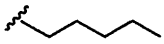
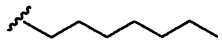
Synthesis of the alkaloid homaline in (±) and natural (*S,S*)-(−) forms is reported. Linking of 2-azacyclooctanone units either directly or successively using 1,4-dihalogenobutanes or 1,4-dihalogenobut-2-ynes is examined. (±)-5-Methyl-4-phenyl-1,5-diazacyclooctan-2-one is first made by a 2,2'-dithiodipyridine/triphenylphosphine-mediated cyclisation, and then by amination and transamidative ring expansion from *N*-(3-chloropropyl)-4-phenylazetidin-2-one in liquid ammonia, followed by *N*-methylation. Coupling through a 1,4-dihalogenobutane of either the *N*-methylated azalactam, or the unmethylated azalactam followed by methylation, gave homaline in (±) and *meso* forms.

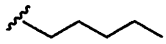
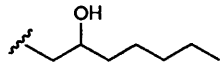
(*R*)-(−)-Phenylglycine was converted *via* (*S*)-β-phenyl-β-alanine into an (*S*)-β-lactam which was then alkylated with 1-bromo-3-chloropropane, and aminated and ring expanded in liquid ammonia. Coupling of the homochiral azalactam (2 mol) so formed with 1,4-dibromobutane, followed by *N*-methylation, gave (*S,S*)-(−)-homaline identical with the natural material.

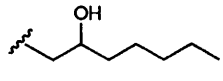
The *Homalium* (homaline) alkaloids constitute a group of alkaloids isolated from the leaves of an African *Homalium* species and *Homalium pronyense* Guillaum (Flacourtiacae) found in the forests of New Caledonia. They were investigated by Païs and colleagues and found to contain a spermine structural backbone. The best defined of these alkaloids is homaline **1**,[1-3] for which an X-ray single-crystal structure is available.[4] Also occurring with the latter are the unsymmetrical alkaloids hopromine **2**, hoprominol **3** and hopromalinol **4**.[5]

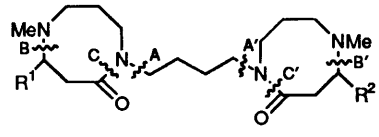


1 Homaline R^1 = (*S*)-Ph R^2 = (*S*)-Ph

2 Hopromine R^1 =  R^2 = 

3 Hoprominol R^1 =  R^2 = 

4 Hopromalinol R^1 = Ph R^2 = 



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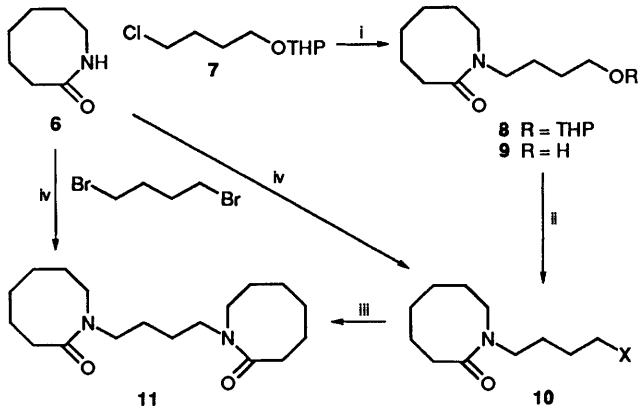
The alkaloids fall within a general structure pattern having obvious disconnections as shown in structure **5**. This paper deals with the synthesis of homaline in both the racemic and natural optically active forms. Our approach has been iterative, as we needed a method capable of dealing with the unsymmetrical alkaloids **2**–**4**: the synthetic work on these is discussed in the following paper. First we examined the linking of eight-membered lactams by a four-carbon chain using heptanolactam (2-azacyclooctanone) **6** as a model (Scheme 1).

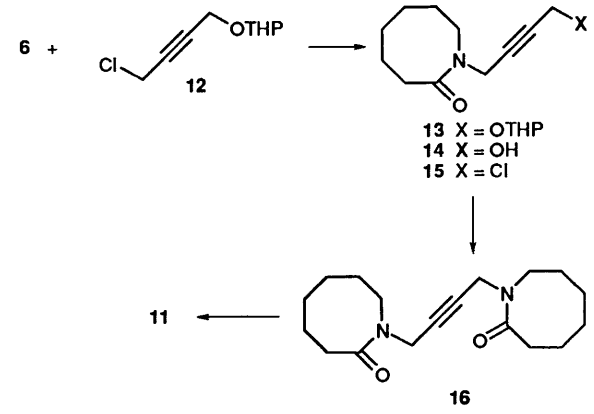


Scheme 1 Coupling of the heptanolactam model. *Reagents:* i, KI–KOH–DMSO; ii, Ph_3P–CCl_4; iii, KOH–DMSO–**6**; iv, KOH–DMSO–$Br[CH_2]_4Br$.

Results and Discussion

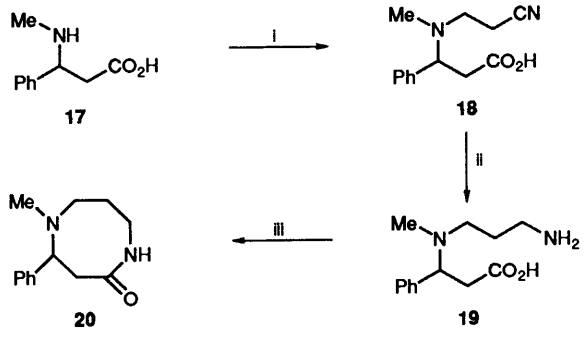
Alkylation of this lactam with the chlorotetrahydropyranyl ether **7** using potassium hydroxide in dimethyl sulfoxide (DMSO) in the presence of potassium iodide gave the lactam ether **8** (85%), and this was hydrolysed to the corresponding alcohol **9** (68%) by dilute mineral acid. Alcohol **9** was converted into its chloride **10** (X = Cl) (92%) by refluxing with triphenylphosphine in carbon tetrachloride. The chlorolactam **10** (X = Cl) could be coupled with a second lactam unit **6** in 65% yield to give the desired crystalline structure **11**, thus establishing an iterative procedure. Alternatively, the bis-lactam could be made by direct coupling through a four-carbon bridge. Treatment of lactam **6** with 1,4-dibromobutane (0.3 mol equiv.) in the presence of KOH–DMSO gave compound **11** in 70% yield. It was also found possible to carry out the dibromobutane reaction in a stepwise manner using the potassium hydroxide–DMSO system. Use of excess of dibromobutane gave the bromide **10** (X = Br) in 77% yield and this bromide could be coupled with a second molecule of heptanolactam in the same base system to give compound **11** in 76% yield.

The homaline alkaloids labelled with a hydrogen isotope would be useful both for analytical mass spectrometry and for biosynthetic purposes. The label could be introduced *via* an acetylene or an olefinic linkage (Scheme 2). By using alkylation



Scheme 2 Stepwise heptanolactam coupling *via* propargylic halide

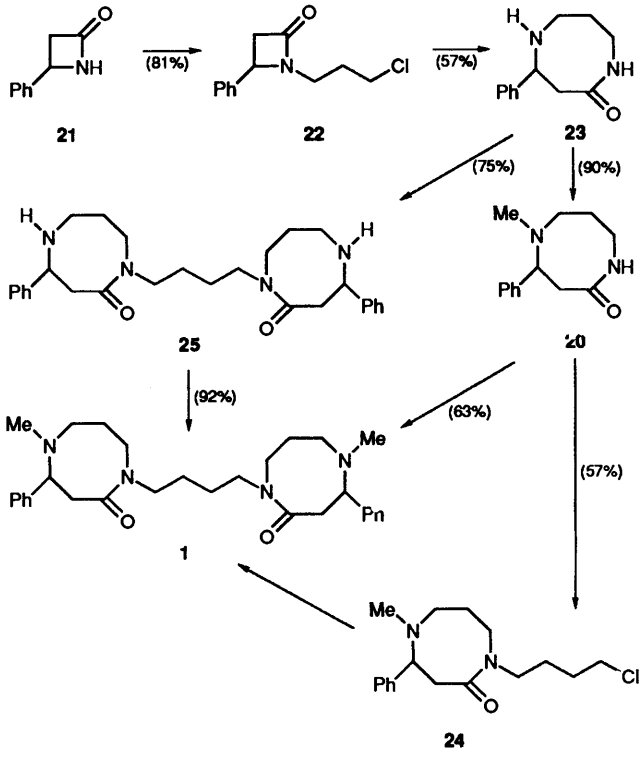
conditions similar to those above, the tetrahydropyranyl ether of 4-chlorobut-2-ynol, compound **12**, gave the acetylenic ether **13** (39%), which was hydrolysed (46%) to the alcohol **14** and converted into the acetylenic chloride **15** (30%) by the triphenylphosphine–carbon tetrachloride method. Alkylation of a second molecule of lactam **6** with the acetylenic chloride gave low yields of dimer **16** when attempted by the KOH–DMSO or NaH–dimethylformamide (DMF) methods. $NaNH_2$–liquid NH_3 also gave only a small yield (12%). Although the method requires further study in respect of yields, the feasibility of deuterium or tritium labelling in this way was shown by catalytic reduction (Pt) to the saturated bis-lactam **11**, identical with the above specimen, or to the corresponding *cis*-olefin (semihydrogenation, Pd).



Scheme 3 2,2′-Dithiodipyridine route to (±)-5-methyl-4-phenyl-1,5-diazacyclooctan-2-one. *Reagents:* i, acrylonitrile–aq. NaOH; ii, H_2–Pt–EtOH; iii, dipyridyl disulfide–PPh_3–MeCN.

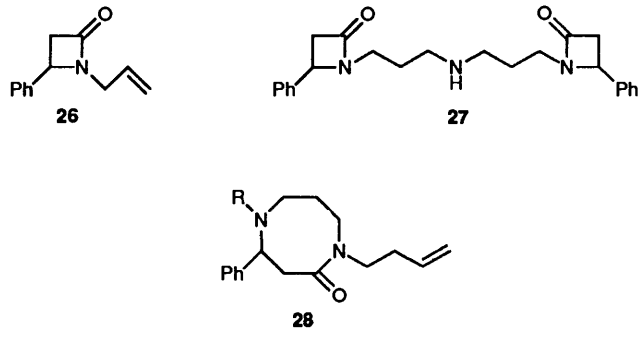
Initially, the lactam **20** required for homaline synthesis was made in racemic form by 2,2′-dithiodipyridine ('dipyridyl disulfide')[6]-mediated cyclisation from amino acid **19** (Scheme 3). (±)-*N*-Methyl-β-phenyl-β-alanine **17** was made by conjugate addition of malonic acid to benzalmethylamine[7,8] and was converted by cyanoethylation, followed by ion exchange, into the nitrile **18**. Catalytic hydrogenation (Pt/ethanol) gave *N*-methyl-*N*-(3-aminopropyl)-β-phenyl-β-alanine **19** as its hydrochloride. Ion exchange and crystallisation then gave the amino acid **19** in 59% yield. After trying a number of less successful methods, we found that cyclisation using 2,2′-dithiodipyridine–triphenylphosphine[6] in a large volume of acetonitrile cyclised amino acid **19** to the desired lactam **20** in high (94%) yield. However, at about this time the alternative transamidative β-lactam ring expansion method discussed in the preceding paper[9] was developed and this became our primary source of the eight-membered lactam **20**.

4-Phenylazetidin-2-one **21**[10,11] was alkylated (Scheme 4) by 1-bromo-3-chloropropane giving the chloride **22** in 81% yield by using the KOH (4 mol equiv.)–DMSO method.[12,13] A small quantity of the elimination product, the allyl compound **26**, was



Scheme 4 Synthesis of homaline as (±) and *meso* forms

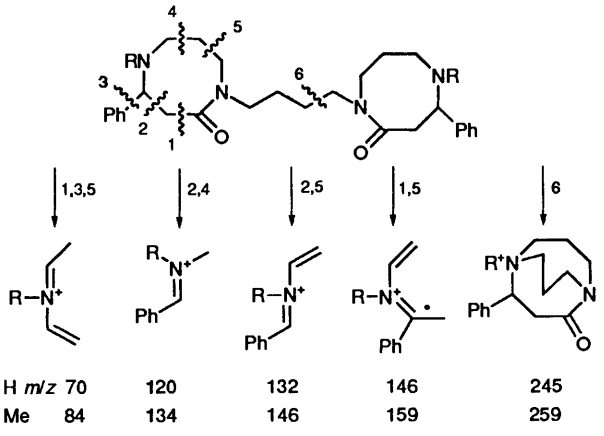
noted, but could be totally eliminated by using less KOH (3 mol equiv.). The use of 1-chloro-3-iodopropane, however, gave a poorer yield (41%). When *N*-(3-chloropropyl)-4-phenylazetidin-2-one **22** was kept in liquid ammonia in a Carius tube at 60 °C for 4 days the azalactam **23** was formed in 57% yield after chromatographic purification: no intermediate primary amine or coupled product **27**, formed from the primary amine by reaction with the chloride **22**, was observed. The azalactam was now *N*-methylated at C-5, to give the required compound **20**, by treatment with sodium cyanoborohydride and formaldehyde in acetonitrile at room temperature, the pH (indicator paper) being kept near 7 by careful addition of acetic acid.[14] The *N*-methylazalactam **20**, obtained in 90% yield after chromatography, was identical in all respects with the sample prepared by the 2,2′-dithiodipyridine cyclisation above.



When treated with 1,4-dibromobutane (0.5 mol equiv.) and KOH (4 mol equiv.) the azalactam **20** gave homaline **1** as a mixture of diastereoisomers, (±) and *meso*, in 63% yield, along with a little unchanged starting material and 6% of the butenyl by-product **28** (R = Me). Under similar conditions the use of 1,4-diiodobutane was less satisfactory. Large amounts of starting material were recovered and this was ascribed to double elimination to buta-1,3-diene before alkylation occurred. In order to establish the stepwise procedure the azalactam **20** was

treated with 1-bromo-4-chlorobutane (4 mol equiv.) in the presence of KOH (4 mol equiv.)–DMSO and gave the *N*-(4-chlorobutyl)azalactam **24** (57%) together with a small amount of unchanged starting material. Chlorolactam **24** could be coupled with a further molecule of lactam to give the homaline diastereoisomers, but these couplings by a stepwise procedure are more appropriately discussed further in the context of unsymmetrical homalium alkaloids in the following paper.[9]

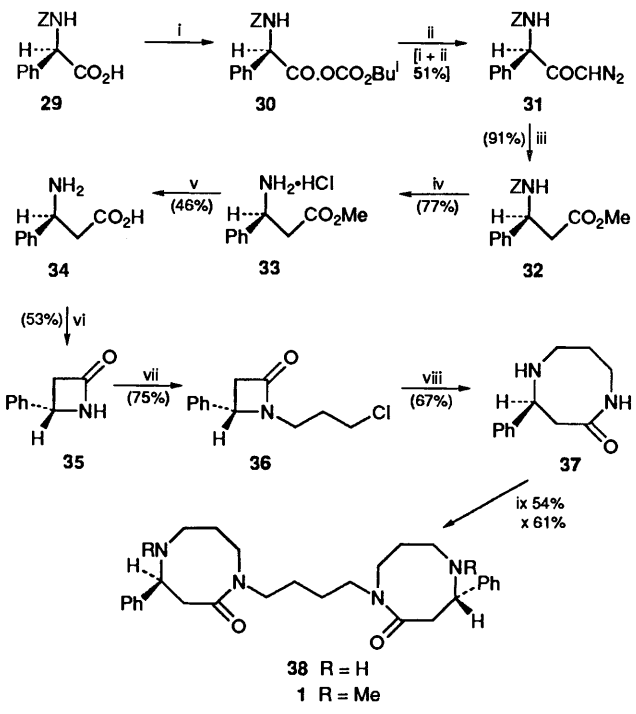
Synthesis of the (±)-homaline diastereoisomers was also carried out by the alternative sequence of treating the unmethylated azalactam **23** with 1,4-dibromobutane in the presence of KOH–DMSO, when 1,4-bis-(2-oxo-4-phenyl-1,5-diazacyclooctan-1-yl)butane **25** was obtained in 75% yield. The butenyl derivative **28** (R = H) was formed as a by-product (10%). The butane **25** was now reductively methylated (using formaldehyde, sodium cyanoborohydride and acetic acid) to give the homaline diastereoisomers (92%).



Scheme 5 Major mass spectral fragmentations for synthetic bis-demethylhomaline and homaline

The mass spectral breakdown pattern of the homaline diastereoisomers and the demethyl precursor agrees with data for natural homaline[5] and is summarised in Scheme 5. The ^{13}C NMR spectrum of the pair of diastereoisomers was as expected, except that in the case of four signals in the proton-decoupled spectrum, double lines were observed instead of singlets. The lines on the high-field side of each doublet corresponded with those for (±)-natural homaline (*R,R/S,S*) and the proportion of the former to the (*R,S*)-(*meso*)-form was 55:45 (by NMR integration). One crystallisation from chloroform–acetone mixture gave a four-fold enrichment of the latter form but it proved difficult to isolate pure (*RR/SS*)-(±)-homaline from the mother liquors. A number of chromatographic methods were attempted, including the use of a chiral stationary phase, but without success. Presumably, the difficulty in separating these diastereoisomers originates from the remote relationship between the two chiral centres (twelve carbon and four nitrogen atoms apart, and separated by a flexible four-carbon chain). It was therefore decided to make natural (*S,S*)-(−)-homaline, starting from optically active (*S*)-(−)-4-phenylazetidin-2-one **35** and using the methodology above (Scheme 6).

(*R*)-(−)-Phenylglycine was protected as the benzyloxycarbonyl derivative **29** (82% yield) and this was then converted into a mixed anhydride **30**[15] which was not isolated but was instead converted into the diazo ketone **31** (51%) using diazomethane.[2] Wolff rearrangement (silver benzoate–MeOH–Et_3N) then gave ester **32** (91%), which was deprotected by hydrogenolysis (10% palladium on charcoal) to give (*S*)-β-phenyl-β-alanine as its methyl ester hydrochloride **33** (77%). The latter was hydrolysed (10% aq. sodium hydroxide) to obtain the amino acid **34** as its hydrochloride (74%). The free optically active (*S*)-amino acid **34** (63%) was obtained by ion-



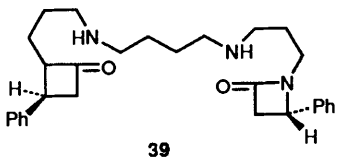
Scheme 6 Synthesis of natural (*S,S*)-homaline. *Reagents and conditions:* i, Bu^tO_2CCl–*N*-methylmorpholine–THF; ii, CH_2N_2; iii, AgOCOPh–MeOH; iv, Pd on C, H_2; v, 10% aq. NaOH, ion exchange; vi, 2,2′-dithiodipyridine–PPh_3–MeCN; vii, $Br[CH_2]_3Cl$–KOH–DMSO; viii, liq. NH_3 3 days, 20 °C; ix, $Br[CH_2]_4Br$–KOH–DMSO; x, CH_2O–$NaBH_3CN$–MeCN–AcOH.

exchange chromatography (Amberlite 120R, acid form, eluting with 15–20% w/v aq. ammonia). Cyclisation to the (*S*)-(−)-(β)-lactam **35** was effected in 53% yield by refluxing with 2,2′-dithiodipyridine and triphenylphosphine[6] in dry acetonitrile for 12 h: the product displayed an $[\alpha]_D^{21}$ -124×10^{-1} deg cm^2 g^{-1} (*c* 0.95, MeOH) in agreement, within experimental error, with the value for material prepared in a different manner.[16]

The synthesis of natural homaline then proceeded according to Scheme 6. Alkylation of (*S*)-(−)-4-phenylazetidinone **35** with 1-bromo-3-chloropropane gave the chloride **36** (75%) and this reaction was followed by amination and ring expansion in liquid ammonia (3 days; 20 °C) to give the demethylazalactam **37** (67%). A small amount of unconverted primary amine was also isolated. Coupling of two azalactam units with 1,4-dibromobutane by using KOH–DMSO gave homochiral di-demethylhomaline **38** in 54% yield. A substantial amount of the elimination product **28** (R = H) was formed (21%) and this could probably be largely diminished by adjustment of the reaction conditions. Reductive methylation by the method described above (CH_2O–$NaBH_3CN$)* gave (*S,S*)-(−)-homaline **1** in 61% yield after chromatography. It had m.p. 134–135 °C; $[\alpha]_D^{22}$ -32×10^{-1} deg cm^2 g^{-1} (*c* 0.95, $CHCl_3$) and was identical with natural homaline[1] in respect of mixed m.p., optical rotation, chromatographic behaviour and ^1H and ^{13}C NMR spectra. When synthetic (*S,S*)-homaline was added to *meso*-(*R,S*)-homaline (prepared above), the double lines appeared on the ^{13}C NMR spectrum as mentioned earlier, showing that it is the low-field lines that belong to the unnatural *meso*-form.

A synthesis of (*S,S*)-(−)-homaline has also been reported by Wasserman and his colleagues[16] and involves transamidation

* It has been reported[16] that this procedure causes some racemisation to give a product of $[\alpha]_D^{24}$ -16×10^{-1} deg cm^2 g^{-1}) (*c* 1.0, $CHCl_3$), but this was not observed in our work.



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using the symmetrical intermediate **39**. Elegant though this is in concept, our approach is shorter and milder, as the building of his intermediate **39**[16] requires eight stages from (*S*)-(−)-4-phenylazetidine-2-one **35** and its transamidative ring expansion to compound **38** requires severe conditions [refluxing quinoline (b.p. 237 °C) for 10 h], and gives a modest yield (25%): Eschweiler–Clark methylation (CH_2O–HCO_2H) then gave homaline in 33% yield. The immediate precursor of compound **39**, the bis-BOC-protected diamine, could also be pyrolysed [in air-saturated diphenyl ether (b.p. 259 °C) for 3 h] direct to compound **38** (28–36%). Wasserman's approach is not designed to be capable of extension to structurally unsymmetrical alkaloids of the homalium group whose synthesis is considered in the following paper.

Experimental

Unless stated otherwise ^1H NMR spectra were measured in $CDCl_3$, with $SiMe_4$ as internal standard, on a JEOL JMN-MH100 (100 MHz), a Perkin-Elmer R32 (90 MHz) or a Bruker WH250 (250 MHz) instrument. *J* Values are given in Hz. Exchangeable protons were located by using D_2O. ^{13}C NMR spectra were recorded on a Bruker WH250 spectrometer with $SiMe_4$ as internal standard. IR spectra were obtained using a Perkin-Elmer 710B spectrometer with polystyrene as a standard. Mass spectra were recorded on an upgraded AEI MS 902 and a VG7070F instrument. Optical rotations $[\alpha]_D$ given in 10^{-1} deg cm^2 g^{-1}) were measured on an Optical Activity AA-10 digital polarimeter. Analytical TLC was performed on silica gel HF254 plates with spots usually visualised under UV light or by exposure to iodine vapour. All new compounds showed a homogenous one spot on TLC. Preparative TLC (PLC) was carried out on silica gel HF254 coated on 20 × 20 cm glass plates at a thickness of 0.5 or 0.8 mm. Evaporation refers to evaporation under reduced pressure, and drying of solutions refers to the use of anhydrous sodium sulfate unless indicated otherwise.

1-*Chloro*-4-*tetrahydropyran*-2-*yloxy*)*butane* **7**.—4-Chlorobutan-1-ol (213 g, 53%) was prepared by passing dry hydrogen chloride through tetrahydrofuran at 0 °C. It had b.p. 52 °C at 0.9 mmHg (lit.,[17] 84–85 °C at 16 mmHg). Dihydropyran (8.4 cm^3, 92.2 mmol) was added to acidified 4-chlorobutan-1-ol (10 g, 92 mmol) and the mixture was stirred for 3 h while being cooled in an ice-bath. Distillation gave the title chloro compound (14.9 g, 83%), b.p. 100 °C at 16 mmHg (lit.,[18] 92 °C at 7 mmHg).

1-[4-(*Tetrahydropyran*-2-*yloxy*)*butyl*]-1-*azacyclooctan*-2-*one* **8**.—Powdered potassium hydroxide (1.0 g, 16.7 mmol) was added to DMSO (8.5 cm^3) at room temperature and, after being stirred (5 min), the mixture was treated with 1-azacyclooctan-2-one **6** (0.53 g, 4.2 mmol) along with potassium iodide (0.16 g, 0.95 mmol) followed immediately by the chloro compound **7** (1.54 g, 8 mmol). The mixture was kept overnight, poured into water, and extracted with chloroform. Drying ($MgSO_4$), evaporation, and chromatography on silica gel, and elution with chloroform–methanol (24:1), gave the *title compound* **8** (0.95 g, 85%) (Found: M$^+$, 283.211. $C_{16}H_{29}NO_3$ requires *M*, 283.215); ν_{max}(film)/cm^{-1} 1640 (lactam); $\delta_H(CCl_4)$ 1.16 (18 H, m, 9 × CH_2), 2.40 (2 H, t, *J* 8, CH_2CO), 3.58 (8 H, m, 2 × CH_2N, 2 × CH_2O) and 4.56 (1 H, t, *J* 2, OCHO).

1-(4-*Hydroxybutyl*)-1-*azacyclooctan*-2-*one* **9**.—The tetrahydropyranyl (THP) derivative **8** (0.4 g, 3.32 mmol) was vigorously stirred with aq. hydrochloric acid (20 cm^3; 2 mol dm^{-3}) for 30 min and then made alkaline with potassium hydroxide and extracted with diethyl ether. Evaporation and chromatography on silica gel, and elution with chloroform–methanol (24:1), gave the recovered THP ether **8** (0.33 g, 35%), followed by the *title alcohol* **9** (0.29 g, 44%) (Found: M$^+$, 199.158. $C_{11}H_{21}NO_2$ requires *M*, 199.157); ν_{max}(film)/cm^{-1} 1640 (amide) and 3300–3600 (OH); $\delta_H(CCl_4)$ 1.1–2.0 (12 H, m, 6 × CH_2), 2.40 (2 H, t, *J* 8, CH_2CO), 3.40 (6 H, m, 2 × CH_2N and CH_2O) and 4.30 (1 H, s, OH).

1-(4-*Chlorobutyl*)-1-*azacyclooctan*-2-*one* **10** (X = Cl).—The hydroxy compound **9** (69 mg, 0.35 mmol) and triphenylphosphine (0.11 g, 0.42 mmol) in carbon tetrachloride (10 cm^3) were heated under reflux for 3 h. After filtration, the filtrate was concentrated under reduced pressure and the residue was repeatedly extracted with light petroleum (boiling range 60–80 °C). Evaporation of the latter extracts gave the *chloro compound* **10** (70 mg, 92%) (Found: M$^+$, 217.122. $C_{11}H_{20}ClNO$ requires *M*, 217.123); ν_{max}(film)/cm^{-1} 1640 (amide); $\delta_H(CCl_4)$ 1.20–2.10 (12 H, m, 6 × CH_2), 2.30 (2 H, t, *J* 8, CH_2CO) and 3.00–3.60 (6 H, m, 2 × CH_2N and CH_2Cl).

1,4-*Bis*-(2-*oxo*-1-*azacyclooctanyl*)*butane* **11** (*Stepwise Method*).—1-Azacyclooctan-2-one **6** (0.12 g, 0.95 mmol) was stirred with powdered potassium hydroxide (0.20 g, 3.8 mmol) in DMSO (2 cm^3) for 5 min, followed by addition of a solution of 1-(4-chlorobutyl)-1-azacyclooctan-2-one **10** (X = Cl) (0.21 g, 0.97 mmol) in DMSO (1 cm^3) and potassium iodide (20 mg, 1.2 mmol). After being stirred overnight, the product was poured into water, worked up, and chromatographed on silica gel, and eluted with chloroform–methanol (24:1) to give, after crystallisation from acetone, the title butane **11**, m.p. 77–78 °C, identical with material prepared and characterised by the hydrogenation route below.

1,4-*Bis*-(2-*oxo*-1-*azacyclooctanyl*)*butane* **11** (*Direct Method*).—Powdered potassium hydroxide (0.87 g, 15.6 mmol) was added to DMSO (8 cm^3) and after the mixture had been stirred (5 min) azacyclooctan-2-one **6** (0.5 g, 3.9 mmol) and 1,4-dibromobutane (0.26 g, 1.2 mmol) were introduced and the mixture was stirred overnight. Work-up and chromatography on silica gel, and elution with chloroform–methanol (19:1), gave the title butane (0.20 g, 70%), crystallised from acetone, m.p. 79–80 °C, identical with the material above (for spectral data see later).

1-*Chloro*-4-(*tetrahydropyran*-2-*yloxy*)*but*-2-*yne* **12**.—4-Chlorobut-2-yn-1-ol was prepared from but-2-yne-1,4-diol (86 g, 1 mol) in dry benzene (100 cm^3) containing pyridine (86.9 g, 1.1 mol) by addition of thionyl dichloride (130.9 g, 1.1 mol) at 10–20 °C over a period of 6 h. Work-up and distillation gave 4-chlorobut-2-yn-1-ol (51.3 g, 49%), b.p. 85 °C at 5 mmHg (lit.,[19] 50 °C at 0.5 mmHg); ν_{max}(film)/cm^{-1} 2400 (C≡C), 3400br and 3600 (OH). Also isolated was 1,4-dichlorobut-2-yne (23.5 g, 24%), b.p. 42 °C at 5 mmHg).

Dihydropyran (3.2 g, 38 mmol) was added to stirred and cooled 4-chlorobut-2-yn-1-ol (4.0 g, 38 mmol) and, after being stirred (2.5 h), the mixture was distilled to give 1-chloro-4-(tetrahydropyran-2-yloxy)but-2-yne **12** (4.1 g, 88%), b.p. 87 °C at 0.7 mmHg (lit.,[19] 130 °C at 14 mmHg); δ_H 1.68 (6 H, m, 3 × CH_2), 3.56 (1 H, m, CH_aHO), 3.80 (1 H, m, CHH_bO), 4.24 (2 H, s, C≡CCH_2O), 4.28 (2 H, s, C≡CCH_2Cl) and 4.80 (1 H, s, OCHO).

1-[4-(*Tetrahydropyran*-2-*yloxy*)*but*-2-*ynyl*]-1-*azacyclooctan*-2-*one* **13**.—Powdered potassium hydroxide (1.0 g, 4 mol equiv.

with respect to lactam) was stirred with DMSO (10 cm^3) at 20 °C for 5 min. 1-Azacyclooctan-2-one **6** (0.60 g, 0.47 mmol), together with potassium iodide (0.44 g) and 1-chloro-4-(tetrahydropyran-2-yloxy)but-2-yne (2.0 g, 10.6 mmol) were added and the mixture was stirred for 1 h, poured into ice–water, and extracted with methylene dichloride. Work-up and column chromatography on silica gel, and elution with chloroform–methanol (49:1), gave the *title compound* **13** (0.5 g, 39%) (Found: M^+, 279.181. $C_{16}H_{25}NO_3$ requires *M*, 279.183); $\nu_{max}(CHCl_3)/cm^{-1}$ 1630 (amide) and 2400 (C≡C); $\delta_H(CCl_4)$ 1.46 (14 H, m, 7 × CH_2), 2.40 (2 H, t, *J* 8, CH_2CO), 3.60 (4 H, m, CH_2N and CH_2O), 4.08 (4 H, s, C≡CCH_2N and C≡CCH_2O) and 4.66 (1 H, s, OCHO).

1-(4-*Hydroxybut*-2-*ynyl*)-1-*azacyclooctan*-2-*one* **14**.—The tetrahydropyranyl derivative **13** (1.37 g, 4.9 mmol) was stirred in aq. sulfuric acid (10 cm^3; 50% w/v) for 12 h, basified with aq. potassium hydroxide (10%) and extracted with chloroform. Chromatography on silica gel, and elution with chloroform–methanol (97:3), gave the *hydroxy compound* **14** (0.4 g, 46%) (Found: M^+, 195.127. $C_{11}H_{17}NO_2$ requires *M*, 195.126); $\nu_{max}(CHCl_3)/cm^{-1}$ 1680 (amide), 2415 (C≡C), 3500br and 3680 (OH); δ_H 1.62 (8 H, m, 4 × CH_2), 2.46 (2 H, t, *J* 8, CH_2CO), 3.42 (1 H, s, OH), 3.62 (2 H, t, *J* 8, CH_2N) and 4.22 (4 H, s, C≡CCH_2N and C≡CCH_2O).

1-(4-*Chlorobut*-2-*ynyl*)-1-*azacyclooctan*-2-*one* **15**.—(i) *Using thionyl dichloride.* A solution of the hydroxy compound **14** (1.0 g, 5.1 mmol) in dry benzene (5 cm^3)–dry pyridine (4.5 cm^3, 5.2 mmol) was added slowly to stirred thionyl dichloride (0.66 g, 5.6 mmol) at 18–20 °C. After further stirring (1 h) the product was poured into water and extracted with diethyl ether. The organic layers were separated, washed with aq. sodium hydrogen carbonate, dried, evaporated, and chromatographed on silica gel, and eluted with chloroform–methanol (99:1) to give *chloro compound* **15** (100 mg, 10%) (Found: M^+, 213.087. $C_{11}H_{16}ClNO$ requires *M*, 213.092); ν_{max}(film)/cm^{-1} 1635 (amide) and 2325 (C≡C); δ_H 1.62 (8 H, m, 4 × CH_2), 2.80 (2 H, t, *J* 7, CH_2CO), 3.40 (2 H, t, *J* 7, CH_2N), 4.22 (2 H, s, C≡CCH_2N) and 4.24 (2 H, s, C≡CCH_2Cl).

(ii) *Using triphenylphosphine and carbon tetrachloride.* The hydroxy compound **14** (0.31 g, 1.6 mmol) and triphenylphosphine (0.54 g, 2.0 mmol) were refluxed together in carbon tetrachloride (10 cm^3) for 2.5 h. The volume of the solution was reduced to 5 cm^3 by evaporation and the residue was then refrigerated, the resulting precipitate being filtered off. Evaporation and chromatography, as above, gave the chloro compound **15** (100 mg, 30%), identical with the specimen above.

1,4-*Bis*-(2-*oxo*-1-*azacyclooctanyl*)*but*-2-*yne* **16**.—(i) *Using sodium hydride–DMF.* Sodium hydride (0.15 g, 3.2 mmol; 50% suspension in oil) was thoroughly washed with dry hexane and was then suspended in dry DMF (7 cm^3). After this mixture had been stirred for 1 h at 50 °C, 1-azacyclooctan-2-one **6** (0.33 g, 2.6 mmol) and potassium iodide (0.26 g, 1.6 mmol) were added. The mixture was stirred for a further hour, when a solution of the chloroacetylene **15** (0.77 g, 3.6 mmol) in dry DMF (5 cm^3) was added dropwise. The mixture was stirred (2 h) and the product was poured into water and extracted with chloroform. Work-up, and chromatography on silica gel, with chloroform–methanol (19:1) as eluent, gave 1,4-bis-(2-*oxo*-1-*azacyclooctanyl*)*but*-2-*yne* **16** (20 mg) (Found: M^+, 304.213. $C_{18}H_{28}N_2O_2$ requires *M*, 304.215); ν_{max}(film)/cm^{-1} 1620 (amide); $\delta_H(CCl_4)$ 1.62 (16 H, m, 8 × CH_2), 2.42 (4 H, t, *J* 7, CH_2CO), 3.48 (4 H, t, *J* 7, CH_2N) and 4.00 (4 H, s, C≡CCH_2N).

(ii) *Using sodamide in liquid ammonia.* Sodamide (0.17 g, 4.3 mmol) was formed from sodium (0.10 g, 4.3 mmol) and liquid ammonia (20 cm^3) in the presence of iron(III) nitrate catalyst. 1-Azacyclooctan-2-one **6** (0.45 g, 3.5 mmol) was added, and the mixture was stirred for 1 h. Potassium iodide (0.30 g, 2 mmol) was then added, followed immediately by a solution of 1-(4-chlorobut-2-ynyl)-1-azacyclooctan-2-one **15** (0.89 g, 4.10 mmol) in diethyl ether (5 cm^3). After the mixture had been stirred (4 h), the ammonia was allowed to evaporate off and the residue was taken up in chloroform (50 cm^3), filtered, and evaporated. PLC, developing with chloroform–methanol (19:1), followed by column chromatography using a similar system, gave the title 1,4-bis-compound **16** (0.13 g, 12%), identical with the material above.

1,4-*Bis*-(2-*oxo*-1-*azacyclooctanyl*)*butane* **11** *by Hydrogenation.*—The butyne **16** (0.4 g, 1.32 mmol) in ethanol (45 cm^3) was hydrogenated at atmospheric pressure over a palladium catalyst (100 mg; 5% on charcoal) for 3 h. Filtration and evaporation, followed by chromatography on silica gel, with chloroform–methanol (99:1) as eluent, gave, first, unchanged acetylene (45 mg, 11%), followed by 1,4-bis-(2-oxo-1-azacyclooctanyl)but-2-ene (170 mg, 43%), $\delta_H(CCl_4)$ 1.46 (16 H, m, 8 × CH_2), 2.40 (4 H, t, *J* 8, CH_2CO), 3.42 (4 H, t, *J* 8, CH_2N), 4.00 (4 H, d, *J* 4, C=CCH_2N) and 5.4 (2 H, t, *J* 4, CH=CH). Continued elution gave 1,4-bis-(2-oxo-1-azacyclooctanyl)butane **11** (100 mg, 24.7%) identical with authentic material. The but-2-ene above (170 mg, 0.55 mmol) was further hydrogenated over a platinum oxide catalyst (10 mg) in methanol and gave the *butane* **11** (total crop 280 mg, 69%), m.p. 79 °C after crystallisation from acetone–chloroform (Found: C, 69.8; H, 10.5; N, 8.75%; M^+, 308.244. $C_{18}H_{32}N_2O_2$ requires C, 70.1; H, 10.45; N, 9.1%; *M*, 308.346); ν_{max}(KBr)/cm^{-1} 1640 (amide C=O); $\delta_H(CCl_4)$ 1.46 (20 H, m, 10 × CH_2), 2.46 (4 H, t, *J* 7, CH_2CO) and 3.52 (8 H, m, CH_2N).

The butyne **16** (45 mg, 0.16 mmol) was hydrogenated in methanol (30 cm^3) over platinum oxide (10 mg) at room temperature and pressure. When uptake of hydrogen was complete, the catalyst was filtered off and the filtrate was evaporated to give the butane **11** (44 mg, 97%), identical with the specimen above.

(R,S)-N-*Methyl*-β-*phenyl*-β-*alanine* **17**.—Methylamine (454 cm^3, 3.2 mol; 22% solution) was added dropwise to stirred benzaldehyde (70.6 g, 0.67 mol) and the mixture was stirred further (3 h), and then kept for 12 h. After saturation with sodium chloride, the product was thoroughly extracted with diethyl ether and the extracts were dried and evaporated. Distillation gave benzalmethylamine (62 g, 78%), b.p. 30 °C at 0.1 mmHg (lit.,[7] 90–91 °C at 30 mmHg).

The latter (62 g) was added to a solution of malonic acid (50 g, 0.48 mmol) in benzene (230 cm^3) and heated on a boiling water-bath for 12 h. The precipitate was filtered off and recrystallised from ethanol to give (*R*,*S*)-*N*-methyl-β-phenyl-β-alanine **17** (32 g, 39%), m.p. 174–175 °C (lit.,[8] 167–168 °C); ν_{max}(KBr)/cm^{-1} 1640 (C=O); $\delta_H(CD_3OD)$ 2.28 (3 H, s, MeN), 2.68 (2 H, t, *J* 8, CH_2CO), 4.24 (1 H, dd, *J* 4 and 8, PhC*H*N) and 7.24 (5 H, s, Ph). Methylcinnamamide (1.8 g, 2%), m.p. 112–113 °C, crystallised from the filtrate (lit.,[20] 111–112 °C).

(R,S)-N-(3-*Aminopropyl*)-N-*methyl*-β-*phenyl*-β-*alanine* **19**.—A solution of (*R*,*S*)-*N*-methyl-β-phenyl-β-alanine (20 g, 0.11 mol) in water (100 cm^3) was mixed with aq. potassium hydroxide (10 cm^3; 50% w/v) and stirred (5 min). Acrylonitrile (4.2 cm^3, 0.12 mol) was added to the stirred mixture, which was stirred for a further 3 h and then kept overnight. The solution was acidified with hydrochloric acid (6 mol dm^{-3}) and evaporated under reduced pressure on a steam-bath. The residue was taken up in chloroform–methanol (17:3) and filtered to remove inorganic salts. The filtrate was concentrated and passed

through a column of ion-exchange resin (Amberlite-225, acid form), and eluted with aq. ammonia (15% w/v), to give (*R,S*)-*N*-(2-cyanoethyl)-*N*-methyl-β-phenyl-β-alanine **18** (23 g, 89%), m.p. 88–89 °C (lit.,[3] 88 °C); ν_{max}(mull)/cm^{-1} 1595, 1700, 2800, 2850, 2950, 3025 and 3400; δ_H 2.12 (3 H, s, MeN), 2.20–3.00 (6 H, m, CH_2CN, CH_2N, CH_2CO), 4.12 (1 H, br, PhC*H*N) and 7.10 (5 H, s, Ph).

A solution of the latter compound (9.10 g, 39 mmol) in absolute ethanol (364 cm^3) was treated with 2 mol dm^{-3} hydrochloric acid (25 cm^3) and hydrogenated over a platinum catalyst (PtO_2, 230 mg) at room temperature and atmospheric pressure (18 h). After filtration and evaporation, the residue was dissolved in water, made alkaline with aq. ammonia (36% w/v), and extracted with chloroform. The aqueous solution was then acidified to pH 5 with hydrochloric acid and extracted with chloroform. These extracts were evaporated, and the residue was taken up in chloroform–ethanol (17:3), filtered to remove inorganic salts, and the filtrate was again evaporated and the residue was dissolved in water (150 cm^3). The solution was passed through a column of Amberlite-225 (acid form) resin and eluted with aq. ammonia (15% w/v). Evaporation, and crystallisation from absolute ethanol, gave the title compound **19** (4.6 g, 59%), m.p. 193–195 °C (lit.,[3] 194–195 °C); ν_{max}(KBr)/cm^{-1} 1580 (C=O), 2900br and 3350; δ_H(CD_3OD) 1.82 (2 H, m, CH_2), 2.22 (3 H, s, NMe), 2.20–3.40 (6 H, m, 2 × CH_2N and CH_2CO), 4.20 (1 H, dd, *J* 5 and 8, PhC*H*N) and 7.26 (5 H, m, Ph).

(R,S)-5-*Methyl*-4-*phenyl*-1,5-*diazacyclooctan*-2-*one* **20**.—(i) *From amino acid* **19** *by cyclisation using ethyl chloroformate and triethylamine.* A solution of (*R,S*)-*N*-(3-aminopropyl)-*N*-methyl-β-phenyl-β-alanine **19** (3.7 g, 15.8 mmol) in water (30 cm^3) was treated with hydrochloric acid (3.2 cm^3, 31.6 mmol; 36% w/v). The solvent was evaporated off and the residue, after drying over anhydrous Na_2SO_4 at 0.5 mmHg for 8 h, was dissolved in dry DMF (1 dm^3). The solution was cooled to −15 °C and dry pyridine (1.27 cm^3, 15.8 mmol) and ethyl chloroformate (1.46 cm^3, 15.8 mmol) were added. After the mixture had been stirred at −15 °C for 30 min, dry triethylamine (8.7 cm^3, 63.2 mmol) was added over a period of 30 min. The reaction mixture was stirred (3 h), the solvent was evaporated off, and the residue was taken up in chloroform (50 cm^3). The compound was extracted into aq. hydrochloric acid (3 × 30 cm^3; 0.1 mol dm^{-3}) and then re-extracted into chloroform after basification with aq. ammonia. The chloroform extracts were dried and evaporated and the residue was chromatographed on silica gel, with chloroform–methanol (49:1) as eluent, to give (*R,S*)-5-methyl-4-phenyl-1,5- diazacyclooctan-2-one **20** (0.78 g, 22%). After storage in chloroform for 3–5 weeks, the compound crystallised, m.p. 92–93 °C (lit.,[3] 96 °C) (Found: M$^+$, 218.142. Calc. for $C_{13}H_{18}N_2O$: *M*, 218.142); ν_{max}(KBr)/cm^{-1} 1640 (C=O); δ_H 1.70 (2 H, m, CH_2), 2.38 (3 H, s, MeN), 2.30–3.90 (6 H, m, 2 × CH_2N and CH_2O), 4.16 (1 H, dd, *J* 4 and 10, PhC*H*N), 7.10 (1 H, br, NHCO) and 7.40 (5 H, s Ph).

(ii) *By cyclisation of amino acid* **19** *using* 2,2′-*dithiodipyridine and triphenylphosphine.* The amino acid **19** (15 mg, 0.05 mmol) was refluxed with 2,2′-dithiodipyridine (19 mg, 0.06 mmol) and triphenylphosphine (16 mg, 0.06 mmol) in dry acetonitrile (50 cm^3) for 12 h. The solvent was evaporated off and the residue was chromatographed on silica gel, and eluted first with diethyl ether (100 cm^3), then with diethyl ether–methanol (19:1) (200 cm^3), then with diethyl ether–methanol (9:1) (100 cm^3), to give the title diazacyclooctanone **20** (13 mg, 94%), identical with the sample above.

(iii) *By reductive methylation of* (R,S)-4-*phenyl*-1,5-*diazacyclooctan*-2-*one* **23**. (*R,S*)-4-Phenylazetidin-2-one **21**, m.p. 106–107 °C, was prepared in 82% yield, converted (81%) into the *N*-3-chloropropyl derivative **22**, and this was aminated and transamidated using the methods described previously[9] to give (*R,S*)-4-phenyl-1,5-diazacyclooctan-2-one **23** (57%). The latter (0.3 g, 1.47 mmol) with aq. formaldehyde (0.12 cm^3, 1.48 mmol; 37% w/v) in acetonitrile (4.4 cm^3) was added to sodium cyanoborohydride (93 mg, 1.48 mmol). After the mixture had been stirred for 15 min, glacial acetic acid was added to attain near neutral pH. The mixture was stirred for 45 min, with the pH kept near neutral (indicator paper) by occasional addition of acetic acid. After removal of the solvent, aq. potassium hydroxide (20 cm^3; 2 mol dm^{-3}) was added to the residue and the aqueous solution was extracted with chloroform. Evaporation of the extracts and purification by column chromatography on silica gel, with chloroform–methanol (49:1 to 19:1) as eluent, gave the title compound **20** (288 mg, 90%), m.p. 94 °C, identical with the specimen above.

(R,S)-1-(4-*Chlorobutyl*)-5-*methyl*-4-*phenyl*-1,5-*diazacyclooctan*-2-*one* **24**.—Powdered potassium hydroxide (71 mg, 1.28 mmol) was added to DMSO (1.5 cm^3), the mixture was stirred (5 min), and (*R,S*)-5-methyl-4-phenyl-1,5-diazacyclooctan-2-one **20** (71 mg, 0.32 mmol), followed by 1-bromo-4-chlorobutane, were introduced. The mixture was stirred (6 h), when water (20 cm^3) was added and the product was extracted with chloroform. Evaporation of the extracts, followed by chromatography on silica gel, with ethyl acetate as eluent, gave the *title chloro compound* **24** (56 mg, 57%) (Found: M$^+$, 308.166. $C_{17}H_{25}ClN_2O$ requires *M*, 308.166); ν_{max}(film)/cm^{-1} 1640 (C=O); δ_H 1.76 (6 H, m, 3 × CH_2), 2.24 (3 H, s, NMe), 2.24–4.10 (11 H, m, CH_2CO, 3 × CH_2N, CH_2Cl, PhC*H*N) and 7.20 (5 H, s, Ph).

Diastereoisomers of 1,4-*Bis*-(2-*oxo*-4-*phenyl*-1,5-*diazacyclooctanyl*)*butane* **25**.—Powdered potassium hydroxide (0.7 g, 12.8 mmol) and DMSO (6.4 cm^3) were stirred together for 5 min and (*R,S*)-4-phenyl-1,5-diazacyclooctan-2-one **23** (0.65 g, 3.2 mmol) and 1,4-dibromobutane (0.34 g, 1.6 mmol) were added. The mixture was stirred for 6 h, water (30 cm^3) was added, and the precipitate, collected by filtration, was crystallised from chloroform–acetone. The filtrate was extracted with chloroform, combined with the crystallisation mother liquors, and evaporated. The residue was chromatographed on silica gel, with chloroform–methanol (19:1) as eluent, and combined with the crystallised precipitate to give the *title mixture of diastereoisomers* **25** (560 mg, 75%), m.p. 195 °C (Found: C, 72.15; H, 8.35; N, 12.0%; M$^+$, 462.299. $C_{28}H_{38}N_4O_2$ requires C, 72.7; H, 8.3; N, 12.1%; *M*, 462.300); ν_{max}(KBr)/cm^{-1} 1620; δ_H 1.80 (8 H, m, 4 × CH_2), 2.40 (2 H, s, 2 × NH), 2.50–4.50 (18 H, 6 × CH_2N, 2 × CH_2CO, 2 × PhC*H*N) and 7.50 (10 H, m, 2 × Ph).

Diastereoisomers of 1,4-*Bis*-(5-*methyl*-2-*oxo*-4-*phenyl*-1,5-*diazacycloctanyl*)*butane* **1**.—(i) *From azalactam* **20** *and* 1,4-*dibromobutane.* Powdered potassium hydroxide (132 mg, 2.36 mmol) and DMSO (1.2 cm^3) were stirred together (5 min), (*R,S*)-5-methyl-4-phenyl-1,5-diazacyclooctan-2-one **20** (130 mg, 0.59 mmol) and 1,4-dibromobutane (63.7 mg, 1.2 mmol) were introduced, and the mixture was stirred (7 h). Work-up by addition of water, extraction ($CHCl_3$), and chromatography on silica gel, with diethyl ether–methanol (49:1) as eluent, gave the *title* (±)-*diastereoisomers* **1** (92 mg, 63%), m.p. 199–200 °C (Found: C, 73.15; H, 8.8; N, 11.25%; M$^+$, 490.331. $C_{30}H_{42}N_4O_2$ requires C, 73.45; H, 8.55; N, 11.4%; *M*, 490.331); ν_{max}(KBr/cm^{-1} 1620 (NC=O) δ_H 1.50–1.90 (8 H, m, 4 × CH_2), 2.26 (6 H, s, 2 × NMe), 2.44–3.96 (16 H, m, 6 × CH_2N, 2 × CH_2O), 4.00 (2 H, dd, *J* 11.6 and 3.2, PhC*H*) and 7.30 (10 H, s, 2 × Ph); δ_C 25.4 and 25.5 ($NCH_2CH_2CH_2CH_2N$), 29.85 and 30.0 ($NCH_2CH_2CH_2N$), 41.25 (CH_2CO), 43.65 (NMe), 45.8 and 46.05 (CH_2NCHPh), 47.9 and 48.0 ($NCH_2CH_2CH_2$-

NCO), 51.15 ($NCH_2CH_2CH_2CH_2N$), 68.15 (PhCHN), 127.15, 127.55, 128.35 (aromatic CH), 142.0 (aromatic CCH) and 173.4 (NC=O).

(ii) *From* (R,S)-1-(4-*chlorobutyl*)-5-*methyl*-4-*phenyl*-1,5-*diazacyclooctan*-2-*one* **24**.—As before, powdered potassium hydroxide (200 mg, 3.64 mmol) was stirred with DMSO (15 cm^3) and the (*R*,*S*)-diaza compound **20** (200 mg, 0.91 mmol) was added, followed by the chlorobutyl compound **24** (284 mg, 0.92 mmol) and potassium iodide (20 mg, 0.12 mmol), the mixture being stirred for 6 h. Work-up gave the diastereoisomeric mixture (17 mg), indistinguishable from that above after crystallisation from chloroform–acetone.

(iii) *From methylation of the diastereoisomers* **25**. The latter sample (86 mg, 0.19 mmol) and aq. formaldehyde (0.15 cm^3, 1.85 mmol; 37%) in acetonitrile (1.2 cm^3) was treated with sodium cyanoborohydride (116 mg, 1.85 mmol). The methylation was conducted as above, the pH being kept near neutral by addition of glacial acetic acid, and the product was worked up to give, after crystallisation, a mixture of diastereoisomers (84 mg, 92%), indistinguishable from that above.

(S)-(−)-N-*Benzyloxycarbonyl*-β-*phenyl*-β-*alanine Methyl Ester* **32**.—A solution of (*R*)-(−)-α-phenylglycine (5.0 g, 32 mmol) in aq. sodium hydroxide (17 cm^3; 2 mol dm^{-3}), was treated at 0 °C with benzyl chloroformate (4.8 g, 32 mmol) and aq. sodium hydroxide (17 cm^3; 2 mol dm^{-3}) over a period of 45 min by dropwise alternate addition. Further stirring (1 h) and work-up gave (*R*)-(−)-*N*-benzyloxycarbonyl-α-phenylglycine **29** (7.48 g, 82%), m.p. 132–133 °C (lit.,[2] 131–132 °C); $[\alpha]_D^{21}$ −124.7 (*c* 0.42, $CHCl_3$) {lit.,[2] $[\alpha]_D$ −125° (*c* 1.7, $CHCl_3$)}.

The benzyloxycarbonyl compound **29** (4.4 g, 15.5 mmol) and dry tetrahydrofuran (THF) (44 cm^3) were treated with *N*-methylmorpholine (2.7 cm^3, 25 mmol) and isobutyl chloroformate (5.96 cm^3, 46 mmol) at −5 °C for 30 min to form the mixed anhydride **30**.

The morpholine hydrochloride was filtered off, washed with dry THF (44 cm^3), and the combined filtrates were treated at 0 °C with ethereal diazomethane (1.9 g, 46 mmol; made from nitrosomethylurea) and set aside overnight. Filtration, washing with aq. sodium hydrogen carbonate, drying, and evaporation gave, after chromatography on silica gel, and elution, first with toluene and then with chloroform, (*R*)-(−)-α-benzyloxycarbonylamino)benzyldiazomethyl ketone **31** (2.42 g, 51%), m.p. 87–88 °C (lit.,[2] 88 °C); $[\alpha]_D^{21}$ −243 (*c* 1.16, $CHCl_3$) {lit.,[2] $[\alpha]_D^{21}$ −270° (*c* 1.0, $CHCl_3$)}; ν_{max}(KBr)/cm^{-1} 1635 (C=O), 1690 (C=O), 2050 ($N^+{=}N^-$), 3100 and 3350 (NHCO); δ_H 5.05 (2 H, s, $PhCH_2O$), 5.20 (2 H, s, $COCHN_2$, PhCHN), 6.25 (1 H, d, *J* 7, NHCO) and 7.35 (10 H, s, 2 × Ph).

A solution of the diazo ketone (8.0 g, 25.8 mmol) in dry methanol (100 cm^3)–triethylamine (20 cm^3) was treated with silver benzoate catalyst (1.2 g) and was stirred for 3 h. Filtration through Kieselguhr, and washing with methanol, gave a solution, which was evaporated. The residue was taken up in chloroform and washed successively with aq. sodium hydrogen carbonate and water. Drying, evaporation, and chromatography on silica gel with chloroform–methanol (99:1) as eluent gave the title ester **32** (7.4 g, 91%), m.p. 65 °C (lit.,[2] 66 °C); $[\alpha]_D^{21}$ −15.8 (*c* 0.55, $CHCl_3$) {lit.,[2] $[\alpha]_D$ −19° (*c* 1.0, $CHCl_3$)}; ν_{max}(KBr)/cm^{-1} 1520, 1720 (C=O), 2950, 3050 and 3350 (NHCO); δ_H 2.80 (2 H, d, *J* 8, CH_2CO), 3.55 (3 H, s, OMe), 5.05 (2 H, s, $PhCH_2O$), 5.25 (1 H, t, *J* 8, PhCHN), 6.05 (1 H, d, *J* 9, NHCO) and 7.30 (10 H, s, 2 × Ph).

(S)-(+)-β-*Phenyl*-β-*alanine* **34** *and its Methyl Ester Hydrochloride* **33**.—The benzyloxycarbonyl compound **32** (7.2 g, 23 mmol) in methanol (170 cm^3) containing conc. hydrochloric acid. (1.72 cm^3) was hydrogenated at 1 atmosphere pressure over palladium catalyst (1.84 g; 10% Pd/C) for 3–4 h at room temperature. Filtration, evaporation, and crystallisation from ethanol gave the title methyl ester hydrochloride **33** (3.8 g, 77%), m.p. 142–143 °C; $[\alpha]_D^{21}$ +11 (*c* 0.21, MeOH) {lit.,[2] $[\alpha]_D$ +7.8° (*c* 2.0, MeOH)}; ν_{max}(KBr)/cm^{-1} 1510, 1590, 1720 (ester C=O), 2000 and 2900br; $\delta_H(D_2O)$ 3.15 (2 H, d, *J* 9, CH_2CO), 3.60 (3 H, s, MeO), 4.80 (1 H, t, *J* 9, PhCHN) and 7.45 (5 H, s, Ph).

The methyl ester (1.2 g, 5.5 mmol) was stirred for 3 h with aq. sodium hydroxide (13 cm^3; 10%) and the solution was acidified to pH 4 with hydrochloric acid and then evaporated. The residue was crystallised from chloroform–ethanol (17:3) to give (*S*)-(+)-β-phenyl-β-alanine hydrochloride (0.69 g, 74%). The free amino acid **34** (0.58 g, 63%) was obtained by ion-exchange chromatography on Amberlite-120R with aq. ammonia (15–30% w/v) as eluent, and was crystallised from water, m.p. 225 °C (lit.,[2] 225 °C); $[\alpha]_D^{22}$ +9.6 (*c* 0.94, 1 mol dm^{-3} HCl); ν_{max}(KBr)/cm^{-1} 1540, 1620 (C=O), 2150, 2400–3100br (CO_2H) and 3450 (NH); $\delta_H(D_2O)$ 2.90 (2 H, d, *J* 9, CH_2CO), 4.20 (1 H, t, *J* 9, PhCHN) and 7.55 (5 H, s, Ph).

(S)-(−)-4-*Phenylazetidin*-2-*one* **35**.—Finely powdered (*S*)-(+)-β-phenyl-β-alanine **34** (750 mg, 4.5 mmol) was heated at reflux with 2,2′-dithiodipyridine (1.2 g, 5.4 mmol) and triphenylphosphine (1.43 g, 5.4 mmol) in dry acetonitrile (450 cm^3) for 12 h. The solvent was evaporated off and the residue was chromatographed on a silica gel column, eluted with diethyl ether–hexane (19:1; 150 cm^3), and crystallised from methanol. (*S*)-(−)-4-Phenylazetidin-2-one **35** (356 mg, 53%) had m.p. 109–110 °C (lit.,[16] 115.5–116 °C); $[\alpha]_D^{21}$ −124 (*c* 0.51, MeOH) {lit.,[16] $[\alpha]_D^{24}$ −128°, $[\alpha]_D^{24}$ −132° (both *c* 1.0, MeOH)}. Spectral data were identical with those given earlier for (*R*,*S*)-4-phenylazetidin-2-one **21**.

(S)-*N*-(3-*Chloropropyl*)-4-*phenylazetidin*-2-*one* **36**.—Powdered potassium hydroxide (560 mg, 9.9 mmol) and DMSO (6.6 cm^3) were stirred for 5 min and (*S*)-(−)-4-phenylazetidin-2-one **35** (490 mg, 3.3 mmol) was introduced, followed by 1-bromo-3-chloropropane (0.98 cm^3, 9.9 mmol). The reaction mixture was stirred overnight and was then poured into water and extracted with chloroform. Washing (water), drying, and evaporation of the extracts gave a residue, which was chromatographed on silica gel and eluted with chloroform–hexane (49:1) to give (*S*)-*N*-(3-chloropropyl)-4-phenylazetidin-2-one **36** (545 mg, 75%), having spectral data identical with those of the (*R*,*S*)-form **22** (above).

(S)-(−)-4-*Phenyl*-1,5-*diazacyclooctan*-2-*one* **37**.—The chloroazetidin-2-one **36** (540 mg, 2.42 mmol) was kept in liquid ammonia (50 cm^3) in a Carius tube at room temperature for 3 days. The ammonia was allowed to evaporate off and the residue was taken up in chloroform (50 cm^3) and the solution was washed with water, dried, and evaporated. The residue was chromatographed on silica gel, with chloroform–methanol (19:1) as eluent, to give (*S*)-(−)-4-phenyl-1,5-diazacyclooctan-2-one **37** (330 mg, 67%), m.p. 166–168 °C (from chloroform–diethyl ether); $[\alpha]_D^{22}$ −10.7 (*c* 0.65, $CHCl_3$). Spectral data were identical with those of the (*R*,*S*)-form **23** described earlier.

1,4-*Bis*-[(S)-(−)-2-*oxo*-4-*phenyl*-1,5-*diazacyclooctanyl*]-*butane* **38**.—Powdered potassium hydroxide (349 mg, 6.24 mmol) was stirred with DMSO (3 cm^3) for 5 min. (*S*)-(−)-4-Phenyl-1,5-diazacyclooctan-2-one **37** (318 mg, 1.56 mmol) was then introduced, followed immediately by 1,4-dibromobutane (168 mg, 0.78 mmol) and the mixture was stirred overnight. Water (50 cm^3) was added, and the product was extracted with chloroform, the latter extracts being washed with water, dried, and evaporated. The product was chromatographed on silica gel and eluted with diethyl ether–methanol (19:1) to give 1,4-

bis-[(*S*)-(−)-2-oxo-4-phenyl-1,5-diazacyclooctanyl]butane **38** (197 mg, 54%) having spectral data closely similar to those of the mixture of diastereoisomers **25** prepared above. A by-product eluted in the early fractions was found to be (S)-1-(*but*-3-*enyl*)-4-*phenyl*-1,5-*diazacyclooctan*-2-*one* (*S*)-**28** (R = H) (88 mg, 21%) (Found: M^+, 258.172. $C_{16}H_{22}N_2O$ requires *M*, 258.173); δ_H 1.80 (2 H, m, $CH_2CH_2CH_2$), 1.95 (1 H, s, NH), 2.20–4.40 (11 H, m, CH_2CO, 3 × CH_2N, CH_2CH=C, PhC*H*N), 5.15 (2 H, t, *J* 9, CH=CH_2) and 5.85 (1 H, m, *J* 4 and 9, C*H*=CH_2), 7.40 (5 H, s, Ph).

1,4-*Bis*-[(S)-(−)-5-*methyl*-2-*oxo*-4-*phenyl*-1,5-*diazacyclooctanyl*]*butane* (*Homaline*) **1**.—A solution of 1,4-bis-(*S*)-(−)-2-oxo-4-phenyl-1,5-diazacyclooctanyl]butane **38** (197 mg, 0.42 mmol) in acetonitrile (2.5 cm^3) was stirred with aq. formaldehyde (0.34 cm^3, 4.25 mmol; 37% w/v) and sodium cyanoborohydride (85 mg, 1.36 mmol) for 15 min. It was then adjusted to pH 7 by addition of acetic acid and was stirred for 45 min, during which time acetic acid was added to maintain the pH near to neutrality. The solvent was evaporated off, water (50 cm^3) was added, and after basification the product was extracted into chloroform. The extracts were washed successively with 0.1 mol dm^{-3} aq. sodium hydroxide and water, dried, and evaporated. Chromatography on neutral alumina (Grade II), and elution with diethyl ether–methanol (19:1), gave crude product (188 mg, 91%). The latter was further purified by PLC on a silica gel plate developed with diethyl ether–methanol (9:1), to give 1,4-bis-[(*S*)-(−)-5-methyl-2-oxo-4-phenyl-1,5-diazacyclooctanyl]butane (homaline) **1** (128 mg, 61%), m.p. 134–135 °C (from diethyl ether–hexane) (lit.,[5] for natural homaline 132 °C); $[\alpha]_D^{22}$ −32 (*c* 0.95, $CHCl_3$) {for natural homaline: lit.,[5] $[\alpha]_D$ −34° (*c* 1.00, $CHCl_3$); lit.[16] $[\alpha]_D$ −31 (*c* 0.40, $CHCl_3$)}; ν_{max}(KBr)/cm^{-1} 1625 (NC=O); δ_H 1.50–1.90 (8 H, m, 4 × CH_2), 2.26 (6 H, s, 2 × NMe), 2.45–3.90 (16 H, m, 6 × CH_2N, 2 × CH_2CO), 4.00 (2 H, dd, *J* 3.2 and 11.6, PhC*H*N) and 7.30 (10 H, s, 2 × Ph); δ_C 25.4 ($NCH_2CH_2CH_2CH_2N$), 29.9 ($NCH_2CH_2CH_2N$), 41.3 (CH_2CO), 43.6 (NMe), 45.8 (CH_2NCHPh), 47.9 ($NCH_2CH_2CH_2CH_2N$), 51.1 ($NCH_2CH_2CH_2$), 68.1 (PhCHN), 127.1, 127.5 and 128.3 (aromatic CH), 142.2 (aromatic *C*CH) and 173.4 (C=O).

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