Synthesis of the Alkaloids Hopromine, Hoprominol and Hopromalinol, using Transamidation Methods

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Synthesis of the unsymmetrical *Homalium* alkaloids hopromine, hoprominol and hopromalinol, in diastereoisomeric mixture form, is reported. The component eight-membered azalactams are first prepared. *N*-(3-Halogenopropyl)-4-pentyl- and -4-heptyl-azetidin-2-ones are aminated and ring expanded in liquid ammonia to give, after reductive methylation, the corresponding 4-alkyl-5-methyl-1,5-diazacyclooctan-2-ones. Synthesis of the 4-(2-hydroxyheptyl)-5-methyl-1,5-diazacyclooctan-2-one required for hoprominol and hopromalinol is carried out *via* 4-allyl β-lactam ring expansion to the eight-membered 4-allylazalactam, followed by methylation, epoxidation and epoxide opening with lithium dibutylcuprate. A similar epoxidation–cuprate sequence was carried out on the epoxypropyl β-lactam, as its *N-tert*-butyldimethylsilyl derivative, and led to a convenient copper-catalysed *N*- to *O*-migration of the protection; this migration is examined. Alkylation gave *O*-TBDMS-protected *N*-(3-chloropropyl)-4-(2-hydroxyheptyl)azetidin-2-one which could be aminated and transamidated in excellent yield, to give, after methylation, a superior sequence to the required eight-membered hydroxy azalactam.

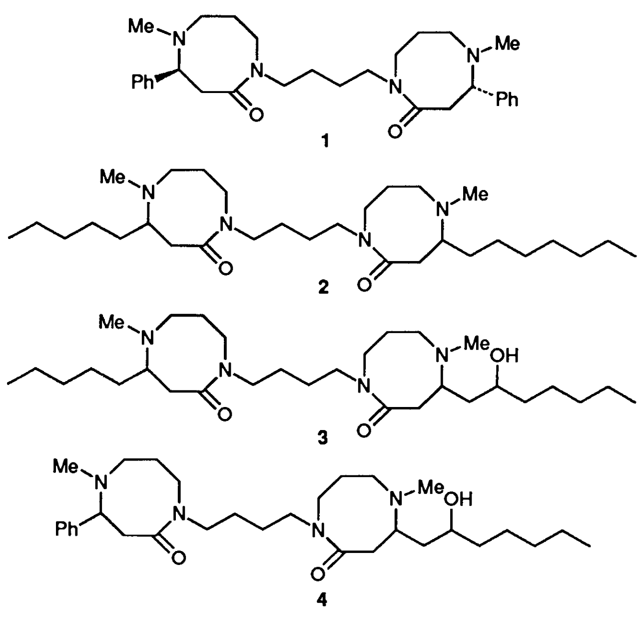
Although satisfactory for attachment of the first azalactam unit, a dibromobutane coupling system proved unreactive for the second. Couplings with unmethylated, methylated, and benzyloxycarbonyl-protected azalactams were examined using (*E*)-1,4-dibromobutene and (*Z*)-1,4-dichlorobutene as the bridging unit. Employing the latter, coupling the first *N*-methylated azalactam with potassium bis(trimethylsilyl)amide as the base, and then the second with bis(trimethylsilyl)amide–sodium hydride as the base system, provided a satisfactory synthetic outcome. Hydrogenation under acidic conditions gave the unsymmetrical structures hopromine, hoprominol and hopromalinol, as well as the more simple and symmetrical alkaloid, homaline.

The *Homalium* (homaline) alkaloids, isolated by Païs and her colleagues[1] from the leaves of the New Caledonian plant *Homalium pronyense* Guillaum, a member of the Flacourtiaceae family, comprise four members: homaline **1**, hopromine **2**, hoprominol **3**, and hopromalinol **4**. The best defined of these is homaline for which an X-ray single-crystal structure[2] and absolute configuration is available: a synthesis of (*S*,*S*)-(−)-homaline is reported in the preceding paper,[3] which also makes reference to previous work. The methods employed were based on a novel, mild ring-expansion of azetidin-2-ones[4] and were designed to be suitable for development to the remaining three alkaloids, which are unsymmetrical structures. We now report on our work in this area.[5]

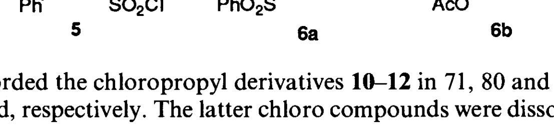
Results and Discussion

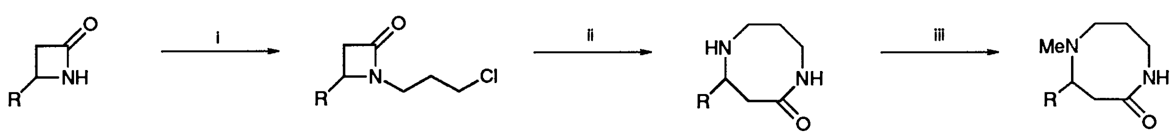
The first synthetic objectives were the three β-lactams **7–9** required for alkylation and ring expansion to form eight-membered terminal azalactam units of structures **2–4**. 4-Phenylazetidin-2-one **7** was made as before from the reaction between styrene and chlorosulfonyl isocyanate[6] which gave the chlorosulfonyl β-lactam **5** (73% yield), reduced to compound **7** by sodium sulfite (96%). The pentyl **8** and heptyl **9** β-lactams were prepared by addition at −70 °C of the appropriate Grignard reagent to 4-(phenylsulfonyl)azetidin-2-one **6a**[7] in 91 and 71% yield, respectively. The latter intermediate was made (73%) by addition of sodium benzenesulfinate to the well known 4-acetoxyazetidin-2-one **6b**,[8,9] itself a product of a similar chlorosulfonyl isocyanate reaction to that above, but using vinyl acetate in place of styrene.

Ring expansion of the three β-lactams was straightforward. Alkylation of the β-lactams with 1-bromo-3-chloropropane using potassium hydroxide in dimethyl sulfoxide (DMSO)[10] afforded the chloropropyl derivatives **10–12** in 71, 80 and 72% yield, respectively. The latter chloro compounds were dissolved



The *Homalium* alkaloids: **1**, homaline; **2**, hopromine; **3**, hoprominol; **4**, hopromalinol





7 R = phenyl
8 R = pentyl
9 R = heptyl

10 71%
11 80%
12 72%

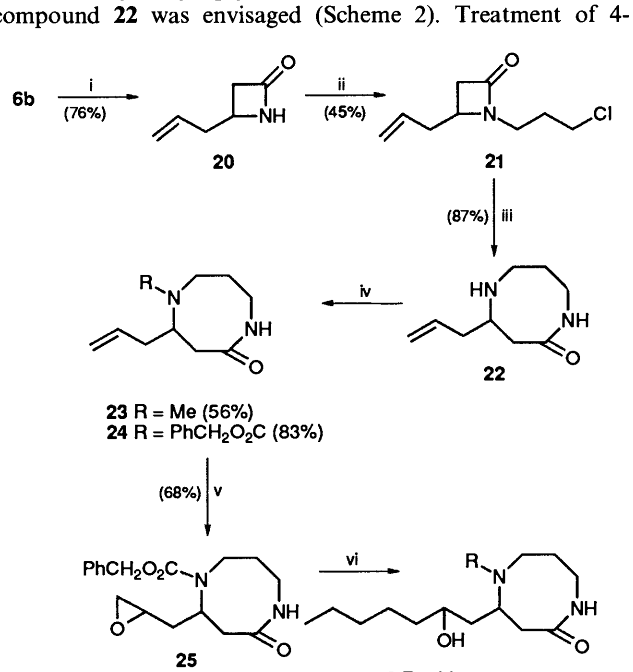
13 96%
14 96%
15 85%

16 97%
17 77%
18 83%

Scheme 1 Formation of the eight-membered lactams by way of transamidative ring expansion of azetidin-2-ones. *Reagents and conditions:* i, KOH–DMSO–Br[CH_2]$_3$Cl; ii, liq. NH_3, sealed tube, 20 °C, 7–10 days; iii, CH_2O–$NaBH_3CN$–H^+–MeCN.

in liquid ammonia at room temperature, when formation of the amine followed by transamidation[4] took place giving the required azalactams **13–15** in 96, 96 and 85% yields. The *N*(5)-methyl derivatives were made by reductive methylation[3] using formaldehyde and sodium cyanoborohydride to give compounds **16–18** in 97, 77 and 83% yield. This is summarised in Scheme 1.

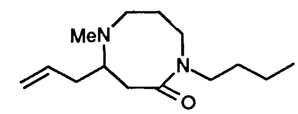
For the hydroxyheptylazalactam **19**, synthesis *via* an allyl compound **22** was envisaged (Scheme 2). Treatment of 4-



Scheme 2 Synthesis of the 2′-hydroxyheptyl azalactams *via* 4-allylazetidin-2-one. *Reagents and conditions:* i, allyltrimethylsilane–BF_3; ii, phase transfer, Br[CH_2]$_3$Cl; iii, liq. ammonia; iv, reductive methylation or $PhCH_2OCOCl$; v, MCPBA; vi, lithium dibutylcuprate.

acetoxyazetidin-2-one **6b** with allyltrimethylsilane in the presence of boron trifluoride[11] gave the 4-allyl β-lactam **20** (76%). Unfortunately, attempts to *N*-alkylate this material by our usual method (above) were not successful and an alternative phase-transfer method[12] gave at best a 45% yield of compound **21**. Transamidation, however, proceeded normally to give the heptanolactam **22** (87%). The *N*(5)-methyl derivative **23** was prepared (56%) by reductive methylation.

In order to model epoxidation, the tertiary amide **28** was made by alkylation of the lactam **23** (KOH–DMSO method; 65%). It has been reported that selective epoxidation of an olefin in the presence of a tertiary amine can be carried out with peroxytrifluoroacetic acid in trifluoroacetic acid[13] but when using either heptanolactam **28** or **22** as substrate, the reaction



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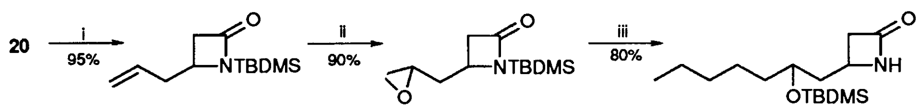
failed. On the supposition that the failure might be due to reactivity of the cyclic amine function, the benzyloxycarbonyl derivative **24** was made (83%) and epoxidation now proceeded smoothly using *m*-chloroperbenzoic acid (MCPBA) to give epoxide **25** in 68% yield. Treatment of the epoxide with lithium dibutylcuprate[14–16] opened it with the necessary regioselectivity to give protected azalactam **26** (56%) carrying the desired 2′-hydroxyheptyl side chain. Deprotection gave the desired azalactam **27**.

The low yields and capricious nature of the alkylation to form chloro compound **21** induced us to look at variants of the methodology, with the silyl ether **31** (Scheme 3) the key intermediate. Protection of the β-lactam **20** as the *N*-*tert*-butyldimethylsilyl derivative **29** (95%) and epoxidation (MCPBA, 90%) gave the epoxide **30** (90%). Treatment of this with lithium dibutylcuprate converted it in 80% yield, not into the expected *N*-silyl, but to the *O*-silyl hydroxyheptyl β-lactam **31**. This useful reaction accomplished three objectives: construction of the hydroxylated side-chain, deblocking of the amide nitrogen ready for alkylation, and concomitant blocking of the hydroxy group. If desired, the hydroxy group could be deblocked to give the heptan-2-ol **32** by using HF in aq. tetrahydrofuran (THF) (85% yield).

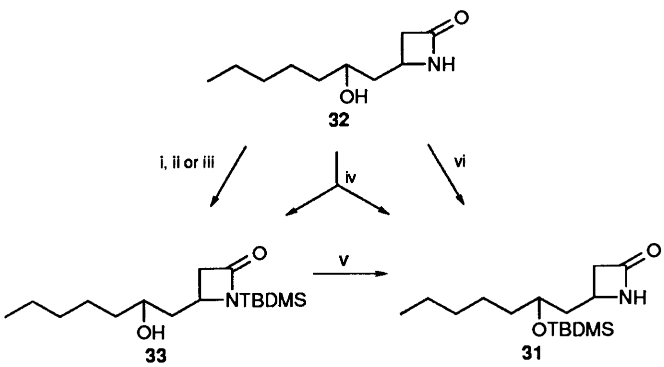
The use of lithium dimethylcuprate in the reaction with epoxide **30** also gave the lower homologue of **31** (64%), a result qualitatively similar to that obtained with the dibutyl compound, but a higher order mixed organocuprate '$Bu_2Cu(CN)Li_2$'[16] under identical conditions gave a mixture of *O*-silylated (52%) and *N*-silylated (17%) products. Direct silylation of the alcohol **32** (Scheme 4) under several sets of conditions (TBDMSCl–DBU; TBDMSCl–DMAP; TBDMSCl–butyllithium)* gave none of the desired *O*-silyl compound, only the *N*-silyl product **33** in 89, 95 and 96% yield, respectively. The migration of silyl groups during synthesis is precedented in prostaglandin,[17] carbohydrate[18] and nucleoside[19] examples and the main criterion for *O*-to-*O* migrations appears to be the

* *tert*-Butylchlorodimethylsilane (TBDMSCl), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 4-(dimethylamino)pyridine (DMAP).



29 **30** **31**

Scheme 3 *N*- to *O*-Rearrangement of TBDMS protecting group. *Reagents:* i, TBDMSCl, DBU, MeCN; ii, MCPBA; iii, lithium dibutylcuprate.



Scheme 4 *N*- and *O*-Protection by TBDMS and interconversions. *Reagents* (*yields*): i, DBU-MeCN-TBDMSCl (89%); ii, DMAP-CH_2Cl_2-TBDMSCl (95%); iii, BuLi-THF-TBDMSCl (96%); iv, $LiBu_2Cu$-THF-TBDMSCl; v, $LiBu_2Cu$-THF (88%); vi, BuLi-THF-TBDMSCl; then $LiBu_2Cu$ (77%).

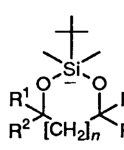
generation of an alkoxide ion leading to a penta-coordinate silicon anion in a five- or six-membered transition state, *e.g.* **34**, and producing a more stable alkoxide anion.[20] However, sodium hydride or n-butyllithium were ineffective in promoting the rearrangement of *N*-silyl **33** to *O*-silyl product **31** and it seems likely that the role of copper is to coordinate the anionic centre thereby facilitating the migration of the silyl group from intermediate **35** to species **36**, the more thermodynamically stable system. Copper(I) iodide is not itself effective in promoting the rearrangement though lithium dibutylcuprate is an efficient reagent (88% yield of *O*-silyl derivative **31** from *N*-silyl **33**).

Thus the most satisfactory procedure for direct *O*-silylation of the β-lactam possessing an alcohol side-chain, compound **32**, is a 'one pot *N*-silylation/migration' sequence effected by sequential addition of n-butyllithium, *tert*-butylchlorodimethylsilane (TBDMSCl) and lithium dibutylcuprate, when the *O*-silyl isomer **31** is formed in 77% yield. 4-(2-Hydroxyheptyl)azetidin-2-one **32**, obtained above, can also be prepared (Scheme 5) by treatment of 4-acetoxyazetidin-2-one **6b** with the trimethylsilyl ether of the kinetic enolate of heptan-2-one[20,21] (made in 72% yield using lithium diisopropylamide, Me_3SiCl, THF and triethylamine at −78 °C) in the presence of zinc chloride. The 4-(2-oxoheptyl)azetidin-2-one **37** obtained in 84% yield was then reduced to the alcohol **32** with sodium borohydride.

Following this excursion into *N*- and *O*-silyl migrations, the *O*-*tert*-butyldimethylsilylated 4-(2-hydroxyheptyl)azetidin-2-one **31** was alkylated with 1-bromo-3-chloropropane under phase-transfer conditions (KOH-Bu_4NHSO_4–THF) to give compound **38** in 77% yield and the latter was transamidated in liquid ammonia *via* amine **39** by our usual technique to give the azalactam **40** (79%). Only traces of the (ω-aminopropyl)-β-lactam **39** remained and the *tert*-butyldimethylsilyl group was unaffected by the conditions. The *N*(5)-methyl compound **41** was now prepared (92%) by our usual reductive methylation sequence, thus completing the synthesis of the four-component eight-membered azalactams required for synthesis of the *Homalium* alkaloid group.

Continuation of the synthesis now required the attachment of a doubly functionalised four-carbon unit to the azalactam nitrogen, leaving one functionality unattacked. Using the 4-phenyl azalactam **13** as test compound, it was found that it could be alkylated by 1-bromobutane or 1,4-dibromobutane in the presence of potassium bis(trimethylsilyl)amide as base to give compounds **43** and **44** in unoptimised yields of 60 and 57%, respectively (some starting material was recovered in each case). The use of potassium hydroxide in DMSO was not satisfactory for amide alkylations of the N(5)-demethylazalactam **13**, though it was more useful when the amino nitrogen was masked as in the *N*-methyl or *N*-benzyloxycarbonyl derivatives. Thus, compounds **45** and **46** were formed in 29 and 72% yield, the improved yield in the latter case presumably reflecting the deactivation of the lone pair of electrons on nitrogen, and hence the diminution of side reactions involving this centre.

Test sequential couplings between 1,4-dibromobutane and 1-azacyclooctan-2-one (heptanolactam) in the presence of KOH–DMSO to give compound **47** (77%), followed by a second coupling (KOH, KI, DMSO) (76%) to give compound **48** were confirmed,[3] but a series of attempts to use bromides **45** and **46** in the second stage of the sequential coupling proved unsatisfactory. Reactions involving *N*(5)-methylazalactams gave a poor



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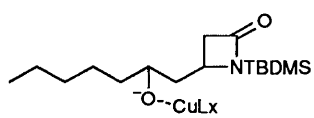

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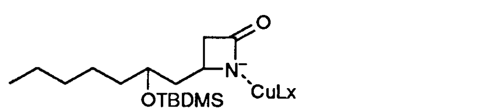

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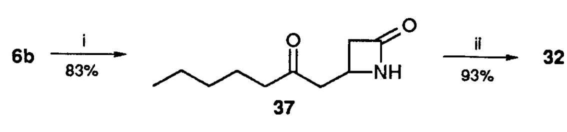
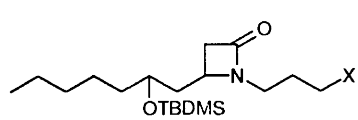
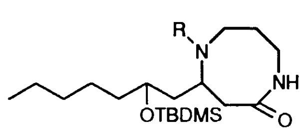


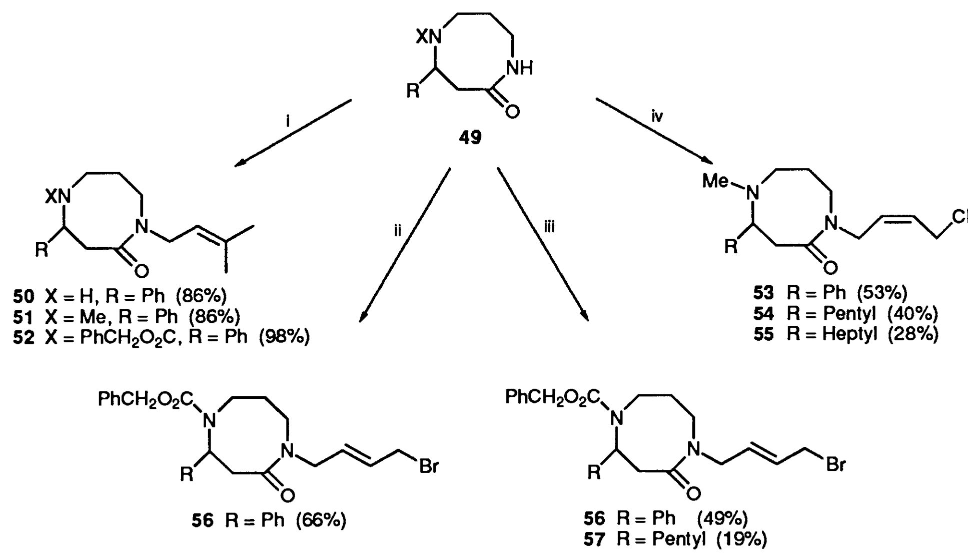
Scheme 5 Alternative synthesis of compound **32** *via* the protected enolate of heptan-2-one. *Reagents and conditions:* i, CH_2=C(OTMS)-$[CH_2]_4Me$-$ZnCl_2$-CH_2Cl_2; ii, $NaBH_4$-MeOH, 0 °C.



38 X = Cl
39 X = NH_2



40 R = H
41 R = Me
42 R = CO_2CH_2Ph

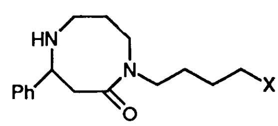


Scheme 6 Alkylation of various azalactams. *Reagents, products and yields:* i, For R = Ph: $Me_2C{=}CHCH_2Br$–$KN(TMS)_2$–THF; ii, For R = Ph, X = $PhCH_2O_2C$: (*E*)-$BrCH_2CH{=}CHCH_2Br$–$KN(TMS)_2$–THF; iii, For X = $PhCH_2O_2C$: (*E*)-$BrCH_2CH{=}CHCH_2Br$–NaH–THF; iv, For X = Me: (*Z*)-$ClCH_2CH{=}CHCH_2Cl$–$KN(TMS)_2$–THF.

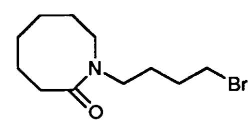
recovery of bromide and this might be due to some destruction by Hofmann elimination *via* bicycle **58**. However, the use of the *N*(5)-benzyloxycarbonyl derivative avoided the possibility of this side reaction whilst not improving the efficiency of the coupling. This implied that the primary bromide is not sufficiently activated towards alkylation of a second bulky amide nucleophile and that a more reactive electrophile was needed.

The matter of activation of the bridge-forming unit has been discussed in connection with our homaline synthesis (previous paper)[3] and initially the bis-allylic (*E*)-1,4-dibromobutene was chosen: it gave some success. The 4-phenyl compound **56** was obtained in 49% yield by using NaH–THF as the base but the 4-pentyl compound **57** was formed in only 19% yield (Scheme 6). Some elimination product **59**, as well as symmetrically coupled material, were by-products. Change of the base to potassium bis(trimethylsilyl)amide[22] gave excellent results in model alkylations using dimethylallyl bromide (Scheme 6, compounds **50–52**) and improved the yield of compound **56** to 66%, but alkylations using substrates 1,4-dibromobutane and **49**, R = Ph, X = H or Me were not improved. The failure to alkylate the *N*(5)-hydrogen- and methyl-containing systems tends to imply that the combination of an available pair of electrons on *N*(5)- and an over-reactive electrophile is a cause of the problem so a change to 1,4-dichlorobut-2-ene, readily available as the (*Z*)-isomer, was made. The *N*(5)-methyl systems **53**, **54** and **55** could now be obtained in 53, 40 and 28% yield, respectively: these are minimum yields as some starting material was recovered in each case. However, we were again unable to alkylate azalactams in which the *N*(5)-substituent was hydrogen.

Coupling of *N*(5)-benzoyloxycarbonylazalactams **49**, R = Ph and pentyl, X = CO_2CH_2Ph, and compound **42** with the appropriate *N*(1)-4-bromobut-2-enyl compounds **56** or **57** in the presence of sodium hydride in THF gave the coupled olefins **60**, **61** and **62** in 66, 47 and 21% yield, respectively. Catalytic hydrogenation of compound **60** (PtO_2–MeOH and conc. HCl) removed the protecting groups and saturated the olefinic linkage to give bisdemethylhomaline in 40% yield, and reductive methylation then gave the homaline structure as a mixture of (±)-homaline and *meso*-homaline. However, similar hydrogenation of the hopromalinol precursor **62** was less satisfactory. Although the fully deprotected product was tentatively identified, a mixture of products was obtained. The removal of the TBDMS grouping was probably effected by the acidic methanol and it was shown that when treated under similar conditions compound **42** was fully deprotected in 80% yield to give the corresponding alcohol.



43 X = H
44 X = Br



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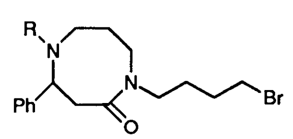
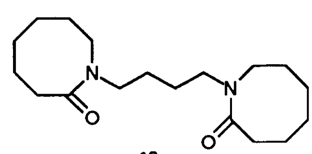


45 R = Me
46 R = CO_2CH_2Ph



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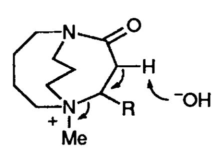
In the light of these results couplings with the *N*(5)-methyl group already in position were studied. The *N*-methylazalactams **63** did not couple satisfactorily with the allylic chlorides **64** (*i.e.* **53–55**) in the presence of potassium bis(trimethylsilyl)amide, but it was found that when sodium hydride was added to the mixture, reaction ensued to give compounds **65**, **66**, **67** and **68** in yields of 36, 29, 20 and 41%



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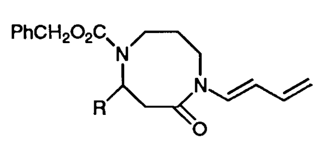

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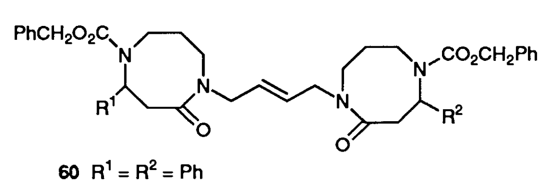
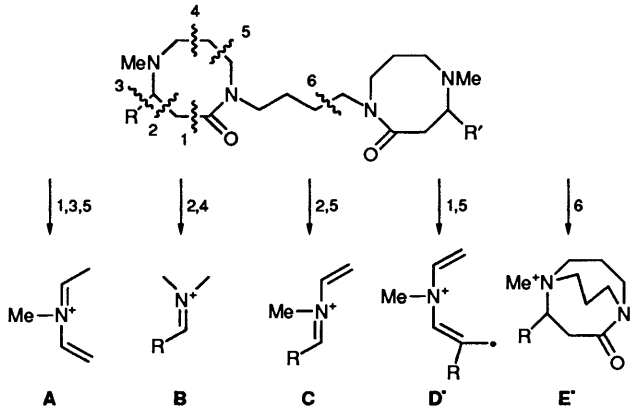


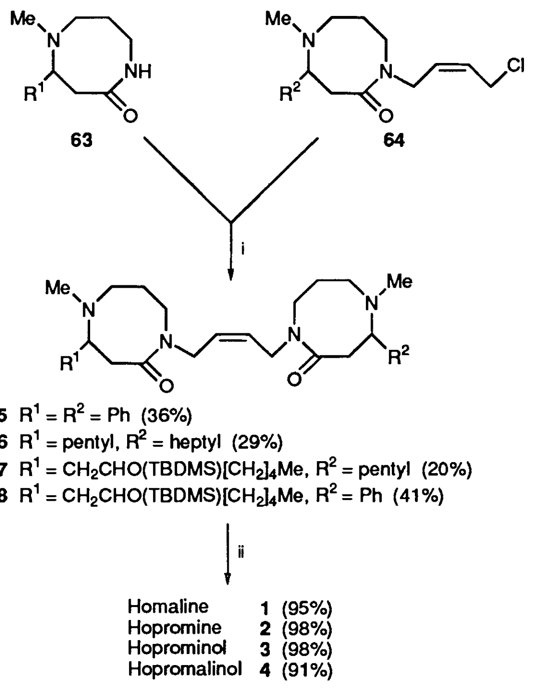
60 $R^1 = R^2$ = Ph
61 R^1 = pentyl, R^2 = heptyl
62 R^1 = Ph, R^2 = 2-(*tert*-butyldimethylsiloxy)heptyl

Table 1 Mass spectral data for natural and synthetic hopromine, hoprominol and hopromalinol



Alkaloid		M^+	$(M + 1)^+$	R or R′	A	B	C	D	E	(M − R or R′)
Hopromine	Natural	506		C_7H_{15} = 99	84	156	168	181	281	407
	Synthetic	506(85)	507(100%)		84(79)	156(35)	168(34)	181(41)	281(22)	407(99%)[a]
	Natural			C_5H_{11} = 71	84	128	140	153	253	435
	Synthetic				84(79)	128(35)	140(45)	153(53)	253(22)	435(76%)
Hoprominol	Natural	522		C_5H_{11} = 71	84	128	140	153	253	451
	Synthetic	522(51)	523(75%)		84(100)	128(55)	140(43)	153(58)	253(30)	451(49%)
	Natural			$C_7H_{15}O$ = 115	84	172	184	197	297	407
	Synthetic				84(100)	172(5)	184(15)	197(44)	297(8)	407(23%)
Hopromalinol	Natural	528		Ph = 77	84	134	146	159	259	
	Synthetic	528(14)	529(50%)		84(73)	134(58)	146(33)	159(71)	259(17%)	
	Natural			$C_7H_{15}O$ = 115	84	172	184	197	297	413
	Synthetic				84(73)		184(9)	197(21)	297(11)	413(100%)

[a] Data for synthetic alkaloids refer to chemical ionisation (CH_4) + ve ion spectra: % abundances are in parentheses. The fragment ions have been accurately mass measured and these data are given in the Experimental section.



Scheme 7 Final synthetic stages for the homaline alkaloids. *Reagents:* i, $KN(TMS)_2$–NaH–THF; ii, H_2/PtO_2–MeOH–H^+

(Scheme 7). Since starting materials were recovered in each example there is little doubt that each reaction would respond favourably to a yield-improvement programme. Catalytic hydrogenation under the conditions mentioned above then cleanly afforded homaline **1**, hopromine **2**, hoprominol **3** and hopromalinol **4** in 95, 98, 99 and 91% yield, respectively. As expected, hoprominol and hopromalinol were in desilylated form for the reasons given earlier.

The overall yields for the four alkaloids by the methods described in this paper were: homaline 12%, hopromalinol 13% (both based on 4-phenylazetidin-2-one **7**), hopromine 4% (based on 4-heptylazetidin-2-one **9**) and hoprominol 5% (based on 4-pentylazetidin-2-one **8**). Of the four natural alkaloids, only the stereochemistry of homaline **1** is known (see preceding paper).[3] As prepared here, the products are necessarily mixtures of stereoisomers and further work is required to deal with the stereochemical problems involved. Nonetheless, comparison of the ^1H NMR spectra of the synthetic products with those of the natural alkaloids kindly supplied by Dr. M. Païs[1] show a reassuring degree of correspondence. Mass spectra of the homaline alkaloids have been analysed by Païs *et al.* and are particularly valuable in the present context for comparing our diastereoisomers with the natural alkaloids, which have characteristic fragmentation patterns. Table 1 gives data for the natural alkaloids hopromine, hoprominol and hopromalinol alongside data for our synthetic materials. For the latter compounds % abundance is included (not available for the natural specimens) and all fragments gave accurate mass measurements (see Experimental section) to support the fragmentation scheme. Most of the fragment ions are of good strength with the exception of the ion at *m/z* 172 ($C_{10}H_{22}NO$) containing the hydroxyheptyl side-chain. This is only 5% in hoprominol and is below the cut-off level in hopromalinol. However, the hydroxylated side-chain appears satisfactorily in other fragment ions, and both hoprominol and hopromalinol have M − 18 peaks at *m/z* 504.439 ($C_{30}H_{56}N_4O_2$ requires *m/z* 504.439) and 510.389 ($C_{31}H_{50}N_4O_2$ requires *m/z* 510.393), respectively, due to loss of water derived from their hydroxy groups.

Experimental

^1H NMR spectra were run in $CDCl_3$ unless specified otherwise, using a Perkin-Elmer R32 (90 MHz), a JEOL MH 100, a Bruker

WM 250, or a Bruker AM400 spectrometer. Tetramethylsilane (TMS) was used as an internal standard except for silicon-containing compounds, when external TMS was used. Acidic protons were identified by exchange with D_2O. Coupling constants *J* are in Hz. In ^{13}C NMR spectra, peaks cancelled or inverted by a DEPT (Distortionless Enhancement by Polarisation Transfer) pulse sequence are designated by italicisation. IR spectra were recorded on a Pye-Unicam SP3-100 IR spectrometer with polystyrene as standard. Mass spectra were recorded either on an AEI MS902 or a VG7070F instrument. Usually electron impact (EI) methods were used, though occasionally chemical ionisation (CI) (methane) or fast-atom bombardment (FAB) methods were employed using thioglycerol. All spectra were recorded in the positive-ion mode. Analytical TLC was carried out using 5 × 20 cm glass plates coated with silica gel HF 254 (0.25 mm) or pre-coated Polygram sheets. For preparative TLC (PLC) glass plates were 20 × 20 cm, coated with silica gel containing HF 254 fluorescer. All new compounds were checked for purity by TLC, running as one spot in several solvent systems. Drying normally implies the use of anhydrous sodium or magnesium sulfate. Evaporation was carried out under reduced pressure. For details of work with liquid ammonia in sealed containers see ref. 4

4-*Acetoxyazetidin*-2-*one* **6b**.—Chlorosulfonyl isocyanate (40 cm^3, 0.46 mol) was added over a period of 5 min to freshly distilled vinyl acetate (228 cm^3, 3.7 mol) under nitrogen, while the temperature was kept below 20 °C. After being stirred (30 min), the mixture was cooled to −40 °C and decomposed by adding it, using a double-ended needle and nitrogen pressure, to a stirred mixture of sodium hydrogen carbonate (104 g, 1.24 mol) and sodium sulfite heptahydrate (72 g, 0.29 mol) in water (200 cm^3)–ice (200 g) (foaming!). The quenching flask was packed in ice and more ice was added internally as required. The mixture was stirred until effervescence ceased, when the mixture was filtered through Celite. Subsequent operations were carried out at −5 °C in a cold room. The vinyl acetate layer was separated and washed twice with water and then discarded. The organic material of the combined aqueous phases was isolated with the aid of extraction (CH_2Cl_2) and, after evaporation at room temperature under reduced pressure, the oil obtained was dissolved in dry diethyl ether (50 cm^3), seeded, and stirred at −5 °C overnight. The crystals of 4-acetoxyazetidin-2-one (16.8 g), m.p. 38–39 °C, were filtered off, and the filtrate was evaporated to an oil (5.59 g). The latter, although nearly pure, was best used immediately, whilst crystalline material was stored at −10 °C. The combined yield was 22.39 g (38%) (Found: C, 46.5; H, 5.8; N, 11.1. Calc. for $C_5H_7NO_3$: C, 46.5; H, 5.5; N, 10.9%); ν_{max}(film)/cm^{-1} 1720–1780 (β-lactam and ester C=O) and 3300 (NH); δ_H 2.10 (3 H, s, MeCO), 2.95 (1 H, dm, J_d 15, 3-H), 3.25 (1 H, ddd, *J* 2.5, 4 and 15, 3-H′), 5.85 (1 H, dd, *J* 2.5 and 4, 4-H) and 7.25 (1 H, br s, NH); δ_C 20.8 (Me), *44.9* (C-3), 73.1 (C-4), *165.9* (amide C=O) and *171.2* (ester C=O).

4-(*Phenylsulfonyl*)*azetidin*-2-*one* **6a**.—A solution of 4-acetoxyazetidin-2-one **6b** (10.0 g, 0.078 mol) and sodium benzenesulfinate (12.73 g, 0.078 mol) in water (40 cm^3) was heated at 100 °C for 15 min, cooled in ice, and the crystalline 4-(phenylsulfonyl)azetidin-2-one (12.0 g, 73%) was isolated by filtration, δ_H($CDCl_3$/CD_3SOCD_3, 1:1) 2.90 (1 H, br s, NH), 3.30 (2 H, ABX, *J* 2, 5 and 15, CH_2), 5.00 (1 H, dd, *J* 2 and 5, 4-H) and 7.70–8.20 (5 H, m, Ph).

4-*Heptylazetidin*-2-*one* **9**.—Magnesium (3.53 g, 0.147 g-atom) was flame dried under nitrogen and a Grignard reagent was formed by addition of 1-bromoheptane (24 cm^3, 0.147 mol) to the metal in THF (120 cm^3) using iodine catalysis. The Grignard reagent was added, under nitrogen, to a solution of 4-(phenylsulfonyl)azetidin-2-one **6a** (6.21 g, 0.029 mol) in dry THF (120 cm^3) at −70 °C over a period of 35 min. After the mixture had attained room temperature it was stirred for 3.5 h and then quenched sequentially with water (200 cm^3) and chloroform (200 cm^3). After acidification, the product was recovered by extraction ($CHCl_3$). The extracts were washed successively with water and brine, dried and evaporated. The product was chromatographed on silica gel, and eluted with chloroform, and gave 4-*heptylazetidin*-2-*one* **9** (3.77 g, 71%), distilled at an oven temperature of 215 °C at 0.7 mmHg (Found: C, 70.6; H, 11.8; N, 7.9%; M^+, 169.148. $C_{10}H_{19}NO$ requires C, 71.0; H, 11.3; N, 8.3%; *M*, 169.147); ν_{max}(film)/cm^{-1} 1755 (C=O), 2950 and 3300; δ_H 0.90 (3 H, t, *J* 7, Me), 1.20–1.70 (12 H, m, 6 × CH_2), 2.55 (1 H, dm, J_d 15, 3-H_a), 3.05 (1 H, ddd, *J* 2, 5 and 15, 3-H_b), 3.60 (1 H, m, 4-H) and 6.47 (1 H, br s, NH); δ_C 14.0, *22.6*, *26.2*, *29.1*, *29.3*, *31.7*, *35.5*, 43.4 (C-3), 48.2 (C-4) and *168.7* (C=O).

4-*Pentylazetidin*-2-*one* **8**.—Prepared as above from magnesium (2.85 g, 0.12 g-atom), 1-bromopentane (14.7 cm^3, 0.12 mol) and 4-(phenylsulfonyl)azetidin-2-one **6a** (5.00 g, 0.024 mol), 4-*pentylazetidin*-2-*one* **8** (3.09 g, 91%), b.p. 190 °C (bath) at 0.5 mmHg was obtained (Found: $[M + H]^+$ (CI), 142.123. $C_8H_{16}NO$ requires [*M* + H], 142.123); ν_{max}(film)/cm^{-1} 1750 (C=O), 2900 and 3260; δ_H 0.90 (3 H, t, *J* 7, Me), 1.20–1.70 (8 H, m, 4 × CH_2), 2.55 (1 H, ddd, *J* 1, 2.5 and 15, 3-H_a), 3.05 (1 H, ddd, *J* 2, 5 and 15, 3H_b), 3.59 (1 H, m, 4-H) and 6.54 (1 H, br, NH); δ_C 13.9, *22.5*, *25.9*, *31.6*, *35.4*, *43.4* (C-3), *48.2* (C-4) and *168.8* (C=O).

1-(3-*Chloropropyl*)-4-*phenylazetidin*-2-*one* **10**.—This was prepared from 4-phenylazetidin-2-one **7** (8.00 g, 0.054 mol) and powdered potassium hydroxide (9.15 g, 0.163 mol) in DMSO (70 cm^3), by addition of a solution of 1-bromo-3-chloropropane (11 cm^3, 0.11 mol) in DMSO (140 cm^3), and stirring vigorously for 18 h. Work-up gave the title compound[4] (8.58 g, 71%), b.p. 168 °C at 2 mmHg (Found: C, 64.3; H, 6.3; N, 6.2%; M^+, 223.076. Calc. for $C_{12}H_{14}ClNO$: C, 64.4; H, 6.3; N, 6.25%; *M*, 223.076); ν_{max}(film)/cm^{-1} 1745 (C=O); δ_C *30.6*, *38.7*, *42.1*, *46.7*, 54.6 (C-4), 126.4, 128.7, 129.0, *138.1* and *167.5* (C=O).

1-(3-*Chloropropyl*)-4-*pentylazetidin*-2-*one* **11**.—The *pentyl compound* (4.25 g, 80%) was prepared in a manner similar to the above from 4-pentylazetidin-2-one **8** (3.55 g, 0.025 mol) and 1-bromo-3-chloropropane (5 cm^3, 0.05 mol) (Found: M^+, 217.122. $C_{11}H_{20}ClNO$ requires *M*, 217.123); ν_{max}(film)/cm^{-1} 1745 (C=O); δ_H 0.90 (3 H, t, *J* 7, Me), 1.20–1.90 (8 H, m, 4 × CH_2), 2.05 (2 H, m, CH_2CH_2Cl), 2.55 (1 H, dd, *J* 2.25 and 14.5, 3-H_a), 3.00 (1 H, dd, *J* 4.8 and 14.5, 3-H_b), 3.22–3.45 (2 H, m, CH_2N), 3.55 (1 H, m, 4-H) and 3.58 (2 H, t, *J* 7, CH_2Cl); δ_C 13.9, *22.5*, *25.2*, *31.2*, *31.7*, *33.0*, *38.2*, *42.3* (C-3), 52.1 (C-4) and *167.3* (C=O).

1-(3-*Chloropropyl*)-4-*heptylazetidin*-2-*one* **12**.—This was prepared in a manner analogous to the above from 4-heptylazetidin-2-one **9** (1.00 g, 0.006 mol) and 1-bromo-3-chloropropane (1.2 cm^3, 0.012 mol). Work-up, and chromatography on silica gel with hexane–chloroform (1:9) as eluent, gave the *title compound* (1.04 g, 72%), b.p. 225 °C (oven) at 0.4 mmHg (Found: C, 63.8; H, 10.2; N, 5.6%; M^+, 245.154. $C_{13}H_{24}ClNO$ requires C, 63.5; H, 9.85; N, 5.7%; *M*, 245.163); ν_{max}(film)/cm^{-1} 1740 (C=O); δ_H 0.80–1.90 (15 H, Me and 6 × CH_2), 2.05 (2 H, m, CH_2CH_2Cl), 2.50 (1 H, dd, *J* 2.3 and 14.6, 3-H_a), 3.00 (1 H, dd, *J* 4.5 and 14.6, 3-H_b), 3.23–3.44 (2 H, m, CH_2N), 3.50 (1 H, m, 4-H) and 3.58 (2 H, t, *J* 6.4, CH_2Cl); δ_C 14.1, *22.6*, *25.5*, *29.1*, *29.5*, *31.2*, *31.8*, *33.1*, *38.3*, *42.2*, *42.3*, 52.2 (C-4) and *167.4* (C=O).

4-Phenyl-1,5-diazacyclooctan-2-one **13**.—Chloropropyl compound **10** (8.00 g, 0.036 mol) was sealed with liquid ammonia (80 cm^3) for 8 days. The ammonia was allowed to evaporate off and water (300 cm^3) was added. Work-up by extraction with chloroform, followed by evaporation, gave the title compound (7.03 g, 96%), m.p. 128–130 °C after crystallisation (lit.,[4] 128–130 °C) (Found: C, 70.2; H, 8.2; N, 13.3%; M^+, 204.125. Calc. for $C_{12}H_{16}N_2O$: C, 70.55; H, 7.9; N, 13.7%; *M*, 204.126); ν_{max}(Nujol)/cm^{-1} 1610, 1650 and 3290; δ_H 1.65 (2 H, m, 7-H_2), 1.95 (1 H, br s, 5-H), 2.47 (1 H, dd, *J* 2.2 and 10.7, 3-H_a), 2.60 (1 H, m, 6-H_a), 2.90 (1 H, pseudo t, *J* 10.7, 3-H_b), 3.15 (2 H, m, 6-H_b, 8-H_a), 3.80 (1 H, m, 8-H_b), 4.05 (1 H, dd, *J* 2.2 and 10.7, 4-H), 6.63 (1 H, br s, 1-H) and 7.40 (5 H, m, Ph).

4-Pentyl-1,5-diazacyclooctan-2-one **14**.—The chloropropyl β-lactam **11** (3.75 g, 0.017 mol) was sealed for 10 days with liquid ammonia. Work-up, and chromatography on silica gel and elution with hexane–chloroform (3:17) to elute non-polar impurities, then with methanol–chloroform (1:32), gave *4-pentyl-1,5-diazacyclooctan-2-one* **14** (3.24 g, 96%) (Found: M^+, 198.173. $C_{11}H_{22}N_2O$ requires *M*, 198.173); ν_{max}(film)/cm^{-1} 1660 (C=O); δ_H 0.90 (3 H, t, *J* 7, Me), 1.20–1.90 (11 H, m, 4 × CH_2, 5-H, 7-H_2), 2.45 (3 H, m, 3-H_2, 6-H_a), 2.91 (1 H, m, 4-H), 3.13 (1 H, dm, J_d 14.9, 6-H_b), 3.23 (1 H, m, 8-H_a), 3.60 (1 H, m, 8-H_b) and 6.27 (1 H, br, 1-H); δ_C 13.9, *22.5*, *26.1*, *31.7*, *34.2*, *36.9*, *39.9*, *41.5*, *43.7*, 59.1 (C-4) and *177.0* (C=O).

4-Heptyl-1,5-diazacyclooctan-2-one **15**.—The chloropropyl β-lactam **12** (1.00 g, 0.004 mol) was sealed with liquid ammonia (20 cm^3) for 7 days at room temperature. Work-up, and chromatography [elution with methanol–chloroform (1:99; then 1:19)] as above, gave the *heptyl compound* **15** (0.79 g, 85%) (Found: M^+, 226.204. $C_{13}H_{26}N_2O$ requires *M*, 226.203); ν_{max}(film)/cm^{-1} 1645; δ_H 0.90 (3 H, t, *J* 7, Me), 1.20–1.80 (15 H, m, 6 × CH_2, 7-H_2, 5-H), 2.45 (3 H, m, 3-H_2 and 6-H_a), 2.91 (1 H, m, 4-H), 3.13 (1 H, dm, J_d 14.8, 6-H_b), 3.23 (1 H, m, 8-H_a), 3.60 (1 H, m, 8-H_b) and 6.25 (1 H, br, 1-H); δ_C 14.0, *22.7*, *26.4*, *29.2*, *29.5*, *31.7*, *34.2*, *37.1*, *40.0*, *41.5*, *43.7*, 59.1 and *177.0* (C=O).

5-Methyl-4-phenyl-1,5-diazacyclooctan-2-one **16**.—Aq. formaldehyde (37%; 1.2 cm^3, 0.016 mol) was added to a stirred solution of the 4-phenylazalactam **13** (2.04 g, 0.01 mol) in acetonitrile (30 cm^3). After the mixture had been stirred for 5 min at room temperature sodium cyanoborohydride (0.79 g, 0.012 mol) was added, followed after 15 min by sufficient acetic acid to attain pH 6. This pH was maintained (indicator paper) during the next 1 h by further additions of acetic acid. The solvent was evaporated off, and the residue was dissolved in aq. potassium hydroxide (2 mol dm^{-3}; 100 cm^3) and extracted with chloroform. After being washed successively with water and brine, the extracts were dried, evaporated, chromatographed on silica gel and eluted with methanol–chloroform (1:49) to give the *title compound* (2.12 g, 97%) (Found: M^+, 218.144. $C_{13}H_{18}N_2O$ requires *M*, 218.142); δ_H(250 MHz) 1.55–1.83 (2 H, m, 7-H_2), 2.33 (3 H, s, Me), 2.48 (1 H, dd, *J* 12.6 and 3.75, 3-H), 2.57 (1 H, m, 6-H), 3.05 (1 H, m, 6-H′), 3.11 (1 H, app. t, *J* 12.3, 3-H′), 3.30 (1 H, m, 8-H), 3.55 (1 H, m, 8-H′), 4.07 (1 H, dd, *J* 12.3 and 3.75, 4-H), 6.70 (1 H, br, NH) and 7.30 (5 H, m, Ph); δ_C(assignments by ^{13}C–^1H COSY) *32.3* (C-7), *39.7* (C-3), *42.4* (C-8), 43.7 (Me), *50.8* (C-6), 67.2 (C-4), 127.1, 127.5, 128.3, *141.3* and *176.7* (C=O).

5-Methyl-4-pentyl-1,5-diazacyclooctan-2-one **17**.—Employing azalactam **14** (2.80 g, 0.014 mol), the methylation was carried out as above using aq. formaldehyde (37%; 1.5 cm^3, 0.02 mol) and sodium cyanoborohydride (1.20 g, 0.019 mol). Chromatography on silica, and elution, first with chloroform to remove low-polarity impurities, then with methanol–chloroform (1:49), gave the *title diaza compound* **17** (2.28 g, 77%) (Found: M^+, 212.188. $C_{12}H_{24}N_2O$ requires *M*, 212.189); ν_{max}(film)/cm^{-1} 1645 (C=O); δ_H 0.88 (3 H, t, *J* 7, $[CH_2]_4Me$), 1.20–1.83 (10 H, m, 4 × CH_2, 7-H_2), 2.40 (2 H, m, 3-H_2), 2.49 (3 H, s, 5-Me), 2.53 (1 H, dm, J_d 15.3, 6-H_a), 2.95 (2 H, m, 6-H_b, 4-H), 3.30 (2 H, m, 8-H_2) and 6.17 (1 H, br, NH); δ_C(assignments by ^{13}C–^1H COSY) 14.0 (pentyl Me), *22.6*, *26.6*, *30.5*, *31.5* (C-7), *31.9*, *37.6* (C-3), 40.7 (NMe), *42.3* (C-8), *47.4* (C-6), 63.0 (C-4) and *177.0* (C=O).

4-Heptyl-5-methyl-1,5-diazacyclooctan-2-one **18**.—Following the method above, the azalactam **15** (0.747 g, 0.003 mol), aq. formaldehyde (37%; 0.33 cm^3, 0.004 mol) and sodium cyanoborohydride (0.232 g, 0.004 mol) gave the *diazalactam* **18** (0.659 g, 83%) (Found: M^+, 240.219. $C_{14}H_{28}N_2O$ requires *M*, 240.220); ν_{max} (film)/cm^{-1} 1650; δ_H 0.90 (3 H, t, *J* 6.4, heptyl Me), 1.20–1.87 (14 H, m, 6 × CH_2, 7-H_2), 2.42 (2 H, m, 3-H_2), 2.45 (3 H, s, NMe), 2.55 (1 H, dm, J_d 15.4, 6-H_a), 2.87–3.05 (2 H, m, 6-H_b, 4-H), 3.20 (2 H, m, 8-H_2) and 6.12 (1 H, br, NH); δ_C 14.1 (heptyl Me), *22.6*, *27.0*, *29.2*, 29.8, *30.4*, *31.5* (C-7), *31.8*, *37.6* (C-3), 40.7 (NMe), *42.3* (C-8), *47.4* (C-6), 63.0 (C-4), and *177.1* (C=O).

4-(Prop-2-enyl)azetidin-2-one **20**.—Boron trifluoride–diethyl ether (5.85 cm^3, 0.048 mol) was added dropwise under nitrogen to a stirred solution of 4-acetoxyazetidin-2-one **6b** (5.00 g, 0.039 mol) and allyltrimethylsilane (12.4 cm^3, 0.078 mol) in dry dichloromethane (38 cm^3). After being stirred for 5.5 h the mixture was poured into brine and extracted with dichloromethane. The dried extract was evaporated and chromatographed on silica gel, with chloroform as eluent, to give *4-(prop-2-enyl)azetidin-2-one* **20** (3.28 g, 76%), which was distilled (oven 160 °C at 0.45 mmHg) (Found: M^+, 111.067. C_6H_9NO requires *M*, 111.068); ν_{max}(film)/cm^{-1} 1655 (C=C), 1750 (C=O) and 3250 (NH); δ_H 2.40 (2 H, tm, J_t 7, $CH_2CH=CH_2$), 2.60 (1 H, ddd, *J* 1.5, 2.5 and 15, 3-H_a), 3.13 (1 H, ddd, *J* 2, 5 and 15, 3-H_b), 3.70 (1 H, m, 4-H), 5.05–5.30 (2 H, m, CH_2=), 5.82 (1 H, m, $CH=CH_2$) and 7.10 (1 H, br s, NH); δ_C *39.4* ($CH_2CH=CH_2$), *42.8* (C-3), 47.1 (C-4), *117.9* ($CH_2=CH$), 133.4 ($CH=CH_2$) and *168.4* (C=O).

1-(3-Chloropropyl)-4-(prop-2-enyl)azetidin-2-one **21**.—A solution of allyl β-lactam **20** (1.34 g, 0.012 mol) in THF (10 cm^3) was added to a stirred suspension of powdered potassium hydroxide (1.00 g, 0.018 mol) and tetrabutylammonium hydrogen sulfate (0.41 g, 0.0012 mol) in THF (80 cm^3). This was immediately followed by 1-bromo-3-chloropropane (2.4 cm^3, 0.024 mol) and the mixture was stirred (18 h) at 20 °C. Work-up, and chromatography on silica gel, with chloroform as eluent, gave the *title chloro compound* **21** (1.03 g, 45%) (Found: M^+, 187.078. $C_9H_{14}ClNO$ requires *M*, 187.076); ν_{max}(film)/cm^{-1} 1650, 1680 and 1750; δ_H 2.07 (2 H, m, CH_2CH_2Cl), 2.30 and 2.55 (2 × 1 H, m, $CH_2CH=CH_2$), 2.60 (1 H, dd, *J* 2.3 and 14.6, 3-H_a), 3.00 (1 H, dd, *J* 4.9 and 14.6, 3-H_b), 3.22 and 3.45 (2 × 1 H, ABX_2, *J* 6.7, 6.72 and 13.4, NCH_2), 3.58 (2 H, t, *J* 6.4, CH_2Cl), 3.65 (1 H, m, 4-H), 5.10–5.20 (2 H, m, $CH_2=CH$) and 5.77 (1 H, m, $CH=CH_2$); δ_C *31.1*, *37.2*, *38.5*, *41.8*, *42.3* (C-3), 51.1 (C-4), *118.5* ($CH_2=CH$), 132.6 ($CH=CH_2$) and *167.1* (C=O).

4-(Prop-2-enyl)-1,5-diazacyclooctan-2-one **22**.—Chloropropyl β-lactam **21** (1.00 g, 0.005 mol) was sealed in liquid ammonia (30 cm^3) for 8 days at room temperature. Work-up, and chromatography on silica gel, with methanol–chloroform (1:32) as eluent, gave the *diaza compound* **22** (0.77 g, 87%) (Found: M^+, 168.126. $C_9H_{16}N_2O$ requires *M*, 168.126); ν_{max}(film)/cm^{-1} 1655 and 3500–3000; δ_H 1.65 (2 H, m, 7-H_2), 1.90 (1 H, s, 5-H), 2.00–2.70 (5 H, m, 6-H_a, 3-H_2 and $CH_2CH=CH_2$), 2.80–3.90 (4 H, m, 8-H_2, 4 H, 6-H_b), 5.00–5.30

(2 H, m, CH_2=CH), 5.60–6.07 (1 H, m, CH=CH_2) and 6.83 (1 H, br, 1-H).

5-Methyl-4-(prop-2-enyl)-1,5-diazacyclooctan-2-one **23**.—Prepared from azalactam **22** (0.684 g, 0.004 mol), aq. formaldehyde (37%; 0.4 cm^3, 0.005 mol) and sodium cyanoborohydride (0.284 g, 0.0045 mol), the methylated diaza compound **23** (0.408, 56%) was obtained after chromatography on silica gel, with methanol–chloroform (1:49) as eluent; δ_H 1.40–2.00 (2 H, m, 7-H_2), 2.05–3.43 (9 H, m), 2.50 (3 H, s, NMe), 5.00–5.25 (2 H, m, CH_2=CH), 5.65–6.12 (1 H, m, CH=CH_2) and 6.47 (1 H, br, NH). Unchanged aza lactam **22** (0.062 g, 10%) was recovered.

1-Butyl-5-methyl-4-(prop-2-enyl)-1,5-diazacyclooctan-2-one **28**.—A solution of the *N*-methyl azalactam **23** (1.127 g, 0.006 mol) in DMSO (10 cm^3) was added to a vigorously stirred suspension of powdered potassium hydroxide (1.05 g, 0.019 mol) in DMSO (10 cm^3). 1-Bromobutane (3.4 cm^3, 0.032 mol) was then added, and the mixture was stirred (18 h) before being poured into water and extracted with chloroform. The extracts were washed successively with water and brine, and dried and evaporated. Chromatography of the product on silica gel, with methanol–chloroform (1:49) as eluent, gave the *butyl derivative* **28** (0.964 g, 65%), b.p. 200 °C (oven) at 0.3 mmHg (Found: C, 70.2; H, 10.9; N, 11.4%; M$^+$, 238.202. $C_{14}H_{26}N_2O$ requires C, 70.5; H, 11.0; N, 11.75%; *M*, 238.204); ν_{max}(film)/cm^{-1} 1640; δ_H(assignments by ^1H–^1H COSY) 0.94 (3 H, t, *J* 7.3, $[CH_2]_3Me$), 1.31 (2 H, m, CH_2Me), 1.55 (3 H, m, 7-H_a, CH_2CH_2Me), 1.77 (1 H, m, 7-H_b), 2.18 and 2.33 (2 × 1 H, m, CH_2CH=CH_2), 2.44 (3 H, s, NMe), 2.52 (3 H, m, 3-H_2 and 6-H_a), 2.88 (1 H, ddd, *J* 3.1, 10.1 and 14.9, 6-H_b), 3.07 (1 H, m, 4-H), 3.23 (1 H, m, $NCH_aH[CH_2]_2Me$), 3.45 (3 H, m, 8-H_2, $NCHH_b[CH_2]_2Me$), 5.07 (2 H, m, CH=CH_2) and 5.84 (1 H, m, CH=CH_2); δ_C(assignments by ^{13}C–^1H COSY) 13.8 (butyl Me), *20.2*, *29.0* (C-7), *30.1*, *35.0* (CH_2CH=CH_2), *38.4* (C-3), 40.6 (NMe), *45.9*, *47.4* (C-6), *47.7* (C-8), 63.4 (C-4), *116.5* (CH_2=CH), 136.4 (CH=CH_2) and *173.2* (C=O).

5-(Benzyloxycarbonyl)-4-(prop-2-enyl)-1,5-diazacyclooctan-2-one **24**.—The azalactam **22** (0.445 g, 0.0027 mol), benzyl chloroformate (0.6 cm^3, 0.004 mol) and sodium hydroxide (0.4 g, 0.01 mol) were stirred vigorously (2.5 h) in chloroform (10 cm^3)–water (5 cm^3). The mixture was diluted with chloroform (100 cm^3) and washed successively with hydrochloric acid (2 mol dm^{-3}; 100 cm^3), water, and brine, and was then dried. Evaporation, and chromatography on silica gel, with methanol–chloroform (1.5:98.5) as eluent, gave the *benzyloxycarbonyl derivative* **24** (0.673 g, 83%) (Found: [M$^+$ − C_3H_5], 261.122. $C_{14}H_{17}N_2O_3$ requires *m/z*, 261.124); ν_{max}(film)/cm^{-1} ~ 1650br and ~ 3200br; δ_H 1.50 (1 H, br, 7-H_a), 1.80–3.84 (9 H, m, CH_2CH=CH_2, 7-H_b, 3-, 6- and 8-H_2), 4.50–5.25 (5 H, m, CH_2Ph, CH_2=CH and 4-H), 5.63 (1 H, br m, CH=CH_2), 6.75 (1 H, br, NH) and 7.31 (5 H, s, Ph).

5-(Benzyloxycarbonyl)-4-(2,3-epoxypropyl)-1,5-diazacyclooctan-2-one **25**.—The allylic azalactam **24** (0.618 g, 0.002 mol) and MCPBA (85%; 0.53 g, 0.0026 mmol) were stirred together in dichloromethane (15 cm^3) for 10 days at room temperature. The mixture was poured into aq. sodium thiosulfate and extracted with chloroform. The extract was washed successively with aq. sodium hydrogen carbonate and brine, and was then dried and evaporated. Chromatography on silica gel, with methanol–chloroform (1.5:98.5) as eluent, gave the *epoxide* **25** as a foam (0.452 g, 68%) (Found: M$^+$, 318.158, $C_{17}H_{22}N_2O_4$ requires *M*, 318.158); ν_{max}($CHCl_3$)/cm^{-1} 1650, 1680 and ~ 3400; δ_H 1.20–3.90 (13 H, complex series of overlapping multiplets), 4.70–5.22 (3 H, m, CH_2Ph, 4-H), 6.85 (1 H, br, NH) and 7.3 (5 H, s, Ph).

5-(Benzyloxycarbonyl)-4-(2-hydroxyheptyl)-1,5-diazacyclooctan-2-one **26**.—Butyllithium (1.42 mol dm^{-3} solution in hexanes; 3.77 cm^3, 0.0054 mol) was added to a suspension of copper(I) iodide (0.5 g, 0.0026 mol) in dry THF (15 cm^3) at −20 °C and the mixture was stirred (10 min) after which the epoxide **25** (0.333 g, 0.001 mol) was added. The mixture was allowed to warm to room temperature and was stirred for 25 h, after which it was poured into saturated aq. ammonium chloride (25 cm^3) and aq. ammonia (10 mol dm^{-3}; 50 cm^3) was added. Extraction with diethyl ether, followed by successive washings of the extract with water and brine, drying, and evaporation, gave a gum, which was chromatographed on silica gel and eluted with 1.5% methanol in chloroform (to remove low-polarity impurities), then with methanol–chloroform (1:19). The N-*protected hydroxyheptyl compound* **26** (0.219 g, 56%) had ν_{max}(film)/cm^{-1} 1665 and ~ 3300br (Found: M$^+$, 376.237. $C_{21}H_{32}N_2O_4$ requires *M*, 376.236); δ_H 0.87 (3 H, t, *J* 7, Me), 0.95–3.83 (20 H, overlapping complex multiplets), 4.80 (1 H, m, 4-H), 5.14 (2 H, m, CH_2Ph), 6.80 (1 H, m, NH) and 7.31 (5 H, s, Ph).

4-(2-Hydroxyheptyl)-1,5-diazacyclooctan-2-one **27**.—A solution of benzyloxy compound **26** (173 mg, 0.46 mmol) in methanol (5 cm^3) containing conc. hydrochloric acid (5 drops) and Adams catalyst (26 mg) was stirred under hydrogen (1 atm) at room temperature for 4 h. Filtration, evaporation, and chromatography on silica gel, with elution with isopropylamine–chloroform (1:19), gave the polar *hydroxyheptyl compound* **27** (46 mg, 42%) (Found: M$^+$, 242.199. $C_{13}H_{26}N_2O_2$ requires *M*, 242.199); ν_{max}(film)/cm^{-1} 1645 and 3600–3000; δ_H 0.90 (3 H, t, *J* 7, Me), 1.10–2.00 (12 H, m), 2.30–2.95 (3 H, m, 3-H_2, 6-H_a), 3.10–4.00 (7 H, m, 6-H_b, 8-H_2, 4-H, CHO, 5-H, OH) and 7.13 (1 H, m, 1-H).

*1-(*tert*-Butyldimethylsilyl)-4-(prop-2-enyl)azetidin-2-one* **29**.—A solution of the allyl β-lactam **20** (2.97 g, 0.027 mol) in dry acetonitrile (22 cm^3) was added to a mixture of DBU (5 cm^3, 0.033 mol) and TBDMSCl (4.88 g, 0.033 mol) in acetonitrile (40 cm^3). The mixture was stirred (3 h), then was poured into water and extracted with chloroform. The extract was washed successively with hydrochloric acid (2 mol dm^{-3}), saturated aq. sodium hydrogen carbonate and brine, dried, and evaporated. Distillation (oven 165 °C, 0.7 mmHg) gave the *silyl derivative* **29** (5.74 g, 95%) (Found: C, 63.7; H, 10.8; N, 5.8. $C_{12}H_{23}NOSi$ requires C, 63.9; H, 10.3; N, 6.2%); *m/z* 210 (M$^+$ − Me, 1%) and 168 (100) (Found: *m/z* 168.084. $C_8H_{14}NO^{28}Si$ [*i.e.*, *M*$^+$ − CMe_3] requires *m/z*, 168.084); ν_{max}(film)/cm^{-1} 1645 (C=C) and 1740 (C=O); δ_H 0.22 and 0.24 (2 × 3 H, $SiMe_2$), 0.96 (9 H, s, CMe_3), 2.17 and 2.55 (2 × 1 H, m, CH_2CH=CH_2), 2.64 (1 H, dd, *J* 2.7 and 15.3, 3-H_a), 3.08 (1 H, dd, *J* 5.4 and 15.3, 3-H_b), 3.59 (1 H, m, 4-H), 5.07 and 5.15 (2 H, dm, CH_2=CH) and 5.73 (1 H, m, CH=CH_2); δ_C −5.6 (Me), −5.3 (Me), *18.4* (CMe_3), 26.3 (CMe_3), *40.2* (CH_2CH=CH_2), *43.4* (C-3), 48.6 (C-4), *118.1* (CH_2=CH), 132.9 (CH=CH_2) and *172.3* (C=O).

*1-(*tert*-Butyldimethylsilyl)-4-(2,3-epoxypropyl)azetidin-2-one* **30**.—Allyl β-lactam **29** (1.348 g, 0.006 mol) and MCPBA (85%; 1.50 g, 0.007 mol) were stirred together in dichloromethane (60 cm^3) for 8 days, by which time TLC showed complete consumption of the olefin. Work-up, and chromatography on silica gel, with hexane–chloroform (1:4) as eluent, gave the *title epoxide* **30** (1.295 g, 90%) as a mixture (~ 1:1) of diastereoisomers, b.p. (oven) 186 °C at 0.2 mmHg (Found: C, 59.7; H, 10.05; N, 5.8. $C_{12}H_{23}NO_2Si$ requires C, 59.7; H, 9.6; N, 5.8%); *m/z* 184 (Found: 184.083. $C_8H_{14}NO_2{}^{28}Si$ [*M*$^+$ − Bu^t] requires *m/z* 184.079]; ν_{max}(film)/cm^{-1} 1740; δ_H (diastereoisomerism causes additional splitting on most of the resonances) 0.25 (6 H, m, Me_2Si), 0.95 (9 H, s, Me_3C), 1.85 (1 H, pseudo t, diastereoisomeric side-chain CHH_aCHN), 1.58 (0.5 H, ddd) and 2.20 (0.5 H, dt, *J* 4 and 14; together diastereoisomeric side-chain CH_bHCHN), 2.50 (1 H, m, epoxide CHH_a), 2.72–2.90 (3 H, m, 3-H_a and epoxide CH_bH), 3.20 (1 H, dd, *J* 5.3 and 15.3, 3-H_b) and 3.71 (1 H, m, 4-H); δ_C (all resonances twinned; only the upfield signal of each pair is recorded) −5.6 (Me), −5.3 (Me), *18.3* (CMe_3), 26.2 (CMe_3), *38.9* (side-chain CH_2CHN), *44.2* (C-3), *46.3* (epoxide CH_2), 47.2 (epoxide CH), 49.1 (C-4) and *173.0* (C=O).

2-(*Trimethylsiloxy*)*hept*-1-*ene*.—Butyllithium (1.58 mol dm^{-3} in hexanes; 105 cm^3, 0.17 mol) was added to a stirred solution of diisopropylamine (24 cm^3, 0.17 mol) in dry THF (150 cm^3) at 0 °C. The mixture was stirred at 0 °C (5 min), then at −78 °C (10 min), and a solution of chlorotrimethylsilane (114 cm^3, 0.9 mol) in THF (130 cm^3) was added. The mixture was recooled to −78 °C and a solution of heptan-2-one (17.2 g, 0.15 mol) in THF (150 cm^3) was added over a period of 5 min. After a further 2 min, triethylamine (300 cm^3) was added, followed by aq. sodium hydrogen carbonate, and the product was extracted by light petroleum (boiling range 40–60 °C). The extract was washed successively with water and 0.033 mol dm^{-3} aq. citric acid, dried, evaporated, and distilled to give the title compound (20.22 g, 72%), b.p. 84–87 °C (oven) at 25 mmHg; δ_H 0.20 (9 H, s, Me_3Si), 0.90 (3 H, t, *J* 7, Me), 1.30–1.80 (6 H, m, $[CH_2]_3Me$), 2.05 (2 H, t, *J* 7.5, $CH_2C{=}CH_2$) and 4.10 (2 H, s, $CH_2{=}C$).

4-(2-*Oxoheptyl*)*azetidin*-2-*one* **37**.—2-(Trimethylsiloxy)hept-1-ene (20.20 g, 0.11 mol) in dichloromethane (70 cm^3) was added slowly to a stirred mixture of 4-acetoxyazetidin-2-one **6b** (7.02 g, 0.054 mol) and zinc chloride (3.8 g, 0.026 mol) in dichloromethane (100 cm^3) at room temperature. The mixture was stirred (20 h) and the reaction mixture was then diluted with ethyl acetate (500 cm^3) and washed successively with 2 mol dm^{-3} hydrochloric acid, aq. sodium hydrogen carbonate, water, and brine. After drying, the solvent was evaporated off, and the product was chromatographed on silica gel, with hexane–chloroform (1:1) as eluent, followed by methanol–chloroform (1:49), to give the *keto* β-*lactam* **37** (8.31 g, 84%), b.p. 235 °C (oven) at 0.3 mmHg, as a thick oil which eventually solidified when kept at 0 °C, m.p. ~45 °C (Found: C, 65.7; H, 9.7; N, 7.3. $C_{10}H_{17}NO_2$ requires C, 65.5; H, 9.35; N, 7.6%); *m/z* 127 (Found: *m/z*, 127.062. $C_6H_9NO_2$ [$M^+ - C_4H_8$] requires *m/z*, 127.063); ν_{max}(Nujol)/cm^{-1} 1700, 1750 and 3220; δ_H 0.89 (3 H, t, *J* 6.6, Me), 1.30 (4 H, m, CH_2CH_2Me), 1.58 (2 H, m, $CH_2[CH_2]_2Me$), 2.42 (2 H, t, *J* 7.4, CH_2COCH_2CHN), 2.60 (1 H, dm, J_d 14.9, 3-H_a), 2.70 (1 H, dd, *J* 8.8 and 17.9, $COCH_aHCHN$), 2.88 (1 H, dd, *J* 4.5 and 17.9, $COCHH_bCHN$), 3.15 (1 H, ddd, *J* 2.3, 5.1 and 14.9, 3-H_b), 3.95 (1 H, m, 4-H) and 6.44 (1 H, br, NH); δ_C 13.8 (Me), *22.3*, *23.3*, *31.3*, 43.3 (C-4), *43.4* ($COCH_2CHN$), *47.7* (C-3), *167.7* (ring C=O) and *209.1* (ketone C=O).

4-(2-*Hydroxyheptyl*)*azetidin*-2-*one* **32**.—Sodium borohydride (0.35 g, 0.009 mol) was added to a solution of the keto β-lactam **37** (1.26 g, 0.007 mol) in methanol (30 cm^3) at 0 °C and the mixture was stirred for 1 h. The product was poured into water and extracted with chloroform. Work-up and distillation gave the *alcohol* **32** (1.18 g, 93%), b.p. 250 °C (oven) at 0.25 mmHg (Found: C, 64.5; H, 10.6; N, 7.3. $C_{10}H_{19}NO_2$ requires C, 64.8; H, 10.3; N, 7.6%); *m/z* (EI) 167 (Found: 167.128. $C_{10}H_{17}NO$ [$M^+ - H_2O$] requires *m/z*, 167.131); *m/z* (CI) $(M + H)^+$ 186 (100%); ν_{max}(film)/cm^{-1} 1750 and 3600–3050br; δ_H (presence of diastereoisomers causes peaks to appear as multiplets) 0.85 (3 H, Me), 1.20–1.80 (10 H, 5 × CH_2), 2.30 (1 H, OH), 2.60 (1 H, 3-H_a), 3.10 (1 H, 3-H_b), 3.80 (2 H, 4-H, CHOH) and 6.70 (1 H, NH); δ_C (all peaks are twinned, and the resonances for the minor diastereoisomer are in brackets) 13.9 (13.9) (Me), *22.6* (*22.6*), *25.1* (*25.3*), *31.8* (*31.8*), *37.8* (*38.5*), *42.5* (*42.5*), *43.9* (*44.1*), 45.3 (46.8) (C-4), 69.6 (71.4) (CHOH) and *168.4* (*168.0*) (C=O).

1-(tert-*Butyldimethylsilyl*)-4-(2-*hydroxyheptyl*)*azetidin*-2-*one* **33** *by* N-*Silylation*.—(i) *Using butyllithium*. Butyllithium (158 mol dm^{-3} in hexanes; 1.2 cm^3, 0.0019 mol) was added to a solution of the hydroxyheptyl β-lactam **32** (0.3 g, 0.0016 mol) in dry THF (10 cm^3) at 0 °C and the mixture was stirred for 10 min prior to the addition of TBDMSCl (0.29 g, 0.0019 mol) in THF (6 cm^3). The mixture was stirred at 0 °C until consumption of the starting lactam was complete, as judged by TLC (6 h). The mixture was poured into saturated aq. ammonium chloride and extracted with chloroform. Washing (brine), drying, and evaporation gave the *N-TBDMS derivative* **33** (0.465 g, 96%) as a mixture of diastereoisomers (~1:1). Separation was achieved by chromatography on silica gel, with hexane–chloroform (1:4) as eluent.

Diastereoisomer 1 of compound **33**. {Found: $[M + H]^+$ (CI) 300 (100%). $C_{16}H_{33}NO_2Si$ requires *M*, 299}; *m/z* (EI) 242 [Found: *m/z* 242.158. $C_{12}H_{24}NO_2Si$ (*i.e.*, M − C_4H_9) requires *m/z*, 242.158]; ν_{max}(film)/cm^{-1} 1720 and 3420; δ_H 0.26 (6 H, apparent d, Me_2Si), 0.90 (9 H, s, Bu^t), 0.80–2.00 (13 H, m), 2.20 (1 H, br, OH), 2.65 (1 H, dd, *J* 3 and 15, 3-H_a), 3.20 (1 H, dd, *J* 5 and 15, 3-H_b) and 3.50–4.00 (2 H, m, 4-H, CHOH).

Diastereoisomer 2 of compound **33**: δ_H 0.30 (6 H, s, Me_2Si), 1.00 (9 H, s, Bu^t), 0.80–2.20 (13 H, m), 2.05 (1 H, br, OH), 2.90 (1 H, dd, *J* 2.5 and 16, 3-H_a), 3.30 (1 H, dd, *J* 5 and 16, 3-H_b) and 3.60–3.90 (2 H, m, 4-H and CHOH).

(ii) *Using DBU*. The β-lactam **32** (157 mg, 0.85 mmol), TBDMSCl (141 mg, 0.94 mmol) and DBU (0.16 cm^3, 1.1 mmol) were stirred together in dry acetonitrile (4 cm^3) at room temperature for 3.5 h. Work-up, and chromatography on silica gel, with hexane–chloroform (1:4) as eluent, gave the above mixture of diastereoisomers (~1:1) (223 mg, 89%).

4-[2-(tert-*Butyldimethylsiloxy*)*heptyl*]*azetidin*-2-*one* **31**.—(i) *From the epoxide* **30** *and lithium dibutylcuprate*. Butyllithium (1.5 mol dm^{-3} in hexanes; 4 cm^3, 0.006 mol) was added dropwise at −25 °C to a stirred suspension of copper(I) iodide (0.572 g, 0.003 mol) in dry THF (40 cm^3) and the resulting brownish suspension was stirred at −25 °C for 10 min prior to the introduction of the epoxide **30** (0.490 g, 0.002 mol) in THF (30 cm^3). The mixture was allowed to warm to room temperature, stirred (16 h), and was then poured into a solution of saturated aq. ammonium chloride (120 cm^3) and ammonia (10 mol dm^{-3}; 40 cm^3) and extracted with diethyl ether. Work-up, and chromatography on silica gel with chloroform as eluent, gave the *O*-silyl 2-hydroxyheptyl-β-lactam **31** (0.476 g, 80%), identical with the material below.

(ii) *From the epoxide* **30** *and a higher order mixed cuprate*. The epoxide (0.383 g, 0.0016) in THF (25 cm^3) was allowed to react with the higher order mixed cuprate Bu_2CuLi_2CN [from copper(I) cyanide (0.22 g, 0.0025 mol) and butyllithium (1.59 mol dm^{-3} in hexanes; 3.1 cm^3, 0.005 mol) in THF (30 cm^3)]. Work-up, and chromatography on silica gel with hexane–chloroform (1:9) as eluent, gave the *O*-silyl product **31** (0.245 g, 52%), followed by the *N*-silyl isomer **33** (0.081 g, 17%).

(iii) *One-pot* O-*silylation of* 4-(2-*hydroxyheptyl*)*azetidin*-2-*one* **32**. The reaction was not performed on >0.01 mol of the alcohol **32** and scale-up was by running more than one reaction simultaneously. Butyllithium (1.58 mol dm^{-3} in hexanes; 7.28 cm^3, 0.0115 mol) was added to a solution of the alcohol **32** (1.85 g, 0.01 mol) in THF (20 cm^3) at 0 °C and the mixture was stirred at this temperature (10 min) after which a solution of TBDMSCl (1.81 g, 0.012 mol) in THF (5 cm^3) was added. The mixture was allowed to warm to room temperature over a period of 6 h before being again cooled to 0 °C. Butyllithium (1.58 mol dm^{-3} in hexanes; 19.6 cm^3, 0.031 mol) was added to a suspension of copper(I) iodide (2.86 g, 0.015 mol) in dry THF (45 cm^3) at −20 °C and the mixture was stirred (10 min) at this temperature before the addition (syringe) of the above silylated preparation; the syringe was rinsed with further THF (5 cm^3) and this wash was added to the reaction mixture. The new reaction mixture was allowed to warm to room temperature during 16 h. Two such reaction mixtures were combined and worked up as under (i) above. Chromatography on silica gel with hexane–chloroform (1 : 9) as eluent gave the O-*silyl product* **31** (4.61 g, 77%), b.p. 230 °C (bath) at 0.3 mmHg {Found: [M + 1]$^+$ (CI), 300.237. $C_{16}H_{34}NO_2Si$ requires *m/z*, 300.236}; ν_{max}(film)/cm^{-1} 1745 and 3235; δ_H 0.05 (6 H, apparent d, Me_2Si), 0.90 (9 H, s, Bu^t), 0.90–1.50 (11 H, m, pentyl group), 1.77 (2 H, m, 4-CH_2), 2.60 (1 H, dm, J_d 14.3, 3-H_a), 3.10 (1 H, dm, J_d 14.3, 3-H_b), 3.75 (2 H, m, 4-H, CHOSi) and 6.00 (1 H, apparent d, NH); δ_C (some resonances show diastereoisomeric shifts and satellite peaks are in parentheses) −4.4 (MeSi), −4.2 (MeSi), 14.0 (chain Me), *18.0* (CMe_3), *22.6*, *24.9* (*24.6*), 25.9 (Me_3C), *31.9*, *37.7* (*37.2*), *42.1* (*41.9*), *44.3* (*44.0*), 45.8 (45.0) (C-4), 71.1 (70.7) (CO) and *168* (C=O).

4-[2-(tert-*Butyldimethylsiloxy)butyl*]*azetidin*-2-*one*.—A solution of the epoxide **30** (0.48 g, 0.002 mol) in THF (30 cm^3) was treated with lithium dimethylcuprate [0.003 mol in THF (40 cm^3) prepared and treated as for the dibutyl analogue above]. Work-up, and chromatography on silica gel with hexane–chloroform (1:9) as eluent, gave the *title compound* (0.329 g, 64%) {Found: [M + 1]$^+$ (CI) 258.189. $C_{13}H_{28}NO_2Si$ requires [*M* + 1], 258.189}; ν_{max}(film)/cm^{-1} 1750 and 3250; δ_H 0.20 (6 H, s, Me_2Si), 1.02 (3 H, t, *J* 7, Me), 1.03 (9 H, s, Bu^t), 1.50–2.00 [4 H, m, $CH_2CH(OR)CH_2$], 2.80 (1 H, dm, J_d 15, 3-H_a), 3.20 (1 H, dm, J_d 15, 3-H_b), 3.85 (2 H, m, 4-H, CHO) and 6.50 (1 H, br s, NH).

4-[2-(tert-*Butyldimethylsiloxy)heptyl*]-1-(3-*chloropropyl*)-*azetidin*-2-*one* **38**.—A suspension of the β-lactam **31** (0.450 g, 0.0015 mol), powdered potassium hydroxide (0.15 g, 0.0037 mol), tetrabutylammonium hydrogen sulfate (0.051 g, 0.00015 mol) and 1-bromo-3-chloropropane (0.24 cm^3, 0.0023 mol) in THF (16 cm^3) was stirred at room temperature for 3.5 days, then poured into water and extracted with chloroform. Work-up, and chromatography on silica gel with hexane–chloroform (1:4) as eluent, gave the title chloro compound **38** (0.435 g, 77%), ν_{max}(film)/cm^{-1} 1755; δ_H (the presence of diastereoisomers causes most resonances to appear as multiplets) 0.03 (6 H, s, Me_2Si), 0.80–1.00 (12 H, m, Bu^t and Me), 1.20–1.60 (8 H, m, $[CH_2]_4$), 2.00 (4 H, m, CH_2CH_2Cl and CH_2CH_2N), 2.57 (1 H, m, 3-H_a), 3.00 (1 H, m, 3-H_b), 3.17 (1 H, m, NC*H*H), 3.40 (1 H, m, NCH*H*), 3.53 (2 H, t, *J* 7, CH_2Cl) and 3.60–3.75 (2 H, m, 4-H, CHO); δ_C (doubled resonances through diastereoisomerism have second peak in parentheses) −4.48 (−4.25) (MeSi), −4.10 (−3.44) (MeSi), 14.15 (Me), *18.12* (CMe_3), *22.74*, *24.81* (*24.87*), 25.97 (Me_3C), *31.19*, *32.05*, *37.55* (*37.81*), *38.08* (*38.14*), *39.88* (*39.97*), *42.34* (*43.05*) *44.19*, 49.53 (49.90) (C-4), 69.85 (68.37) (CO) and *167.74* (C=O).

4-[2-(tert-*Butyldimethylsiloxy)heptyl*]-1,5-*diazacyclooctan*-2-*one* **40**.—The chloropropyl β-lactam **38** (1.555 g, 0.004 mol) was kept in liquid ammonia (~40 cm^3) in a Carius tube for 13 days. Work-up, chromatography on silica gel, and elution, first, with chloroform, then with methanol–chloroform (1:19), gave the *diaza compound* **40** (1.149 g, 79%) (Found: M$^+$, 356.286. $C_{19}H_{40}N_2O_2Si$ requires *M*, 356.286); ν_{max}(film)/cm^{-1} 1657 and 3430–3100; δ_H 0.05 (6 H, m, Me_2Si), 0.80–0.90 (12 H, m, Bu^t and Me), 1.17–1.70 (12 H, $[CH_2]_4$, CH_2CHN and 7-H_2), 2.17 (1 H, br, 5-H), 2.25–2.55 (3 H, m, 3-CH_2 and 6-H_a), 2.95–3.25 (3 H, m, 6-H_b, 4-H and 8-H_a), 3.62 (1 H, m, 8-H_b), 3.81 (1 H, m, CHOSi) and 6.10 (1 H, br, 1-NH); δ_C (diastereoisomeric doubling of signals shown as before) −4.5 (−4.3) (MeSi), −4.2 (−4.1) (MeSi), 14.0 (Me), *18.0* (CMe_3), *22.6*, *24.3* (*25.1*), 25.9 (Me_3C), *32.0*, *34.4*, *37.1*, *38.1*, *40.4*, *42.8* (*42.6*), *43.7* (*43.3*), 55.6 (58.2) (C-4), 72.1 (70.2) (CHO) and *176.6* (C=O).

4-[2-(tert-*Butyldimethylsiloxy)heptyl*]-5-*methyl*-1,5-*diazacyclooctan*-2-*one* **41**.—*N*-Methylation was carried out as described above by using azalactam **40** (328 mg, 0.92 mmol), aq. formaldehyde (0.1 cm^3, 37%) and sodium cyanoborohydride (67 mg, 1.1 mmol) in acetonitrile (5 cm^3). Chromatography on silica gel, with methanol–chloroform (1.5:98.5) as eluent, gave the *title* N-*methyl compound* **41** (314 mg, 92%) (Found: M$^+$, 370.300. $C_{20}H_{42}N_2O_2Si$ requires *M*, 370.302); ν_{max}(film)/cm^{-1} 1657 and 3250; δ_H 0.03 (3 H, s, MeSi), 0.04 (3 H, s, MeSi), 0.87 (12 H, br s, Bu^t and Me), 1.15–1.90 (12 H, m), 2.42 (3 H, app. d, NMe), 2.30–2.50 (2 H, m, 3-H_2), 2.57 (1 H, dm, J_d 14.5, 6-H_a), 2.91 (2 H, m, 6-H_b and 4-H), 3.15 (1 H, m, 8-H_a), 3.27 (1 H, m, 8-H_b), 3.75 (1 H, m, CHOSi) and 6.23 (1 H, br, NH); δ_C (diastereoisomeric splitting shown as before) −4.3 (MeSi), −4.2 (MeSi), 14.1 (Me), *18.1* (CMe_3), *22.7*, *24.5*, 26.0 (Me_3C), *31.2* (*31.3*) (C-7), *32.1*, *37.1* (*37.4*), *37.5* (*37.6*), *37.8* (*38.0*), 41.5 (NMe), *41.8* (*41.9*) (C-8), *46.8* (C-6), 59.3 (59.5) (C-4), 69.8 (69.9) (CHO) and *176.6* (*176.7*) (C=O).

5-*Benzyloxycarbonyl*-4-*phenyl*-1,5-*diazacyclooctan*-2-*one* **49** (R = Ph, X = $PhCH_2O_2C$).—A solution of benzyl chloroformate (1.1 cm^3, 7.7 mmol) in chloroform (5 cm^3) was added to a vigorously stirred mixture of the azalactam **49** (R = Ph, X = H) (≡**13**) (1.00 g, 4.9 mmol) and sodium hydroxide (0.5 g, 12.5 mmol) in chloroform–water (1:2; 30 cm^3) and the mixture was stirred for 2.5 h. The phases were separated and the organic phase was washed successively with hydrochloric acid (20%; 25 cm^3), water and brine. Drying, evaporation, and chromatography on silica gel, with chloroform, then chloroform–methanol (32:1) as eluent, gave the *title compound* **49** (R = Ph, X = $PhCH_2O_2C$) as a foam (1.499 g, 91%); crystallisation from chloroform–hexane gave this compound with m.p. 140–142 °C (Found: C, 70.9; H, 6.6; N, 8.1%; M$^+$, 338.163. $C_{20}H_{22}N_2O_3$ requires C, 71.0; H, 6.55; N, 8.3%; *M*, 338.163); δ_H 1.50 (1 H, m, 7-H_a), 2.10 (1 H, m, 7-H_b), 2.50–4.00 (6 H, m), 5.22 (2 H, br s, $PhCH_2$), 6.00 (1 H, m, 4-H) and 6.90–7.40 (11 H, m, 2 × Ph, NH).

5-*Benzyloxycarbonyl*-4-*pentyl*-1,5-*diazacyclooctan*-2-*one* **49** (R = Pentyl, X = $PhCH_2O_2C$).—Formed by the method above, this was obtained in 41% yield after chromatography; δ_H 0.90–4.00 (19 H, m), 4.79–5.20 (3 H, m, $PhCH_2$ and 4-H), 6.55 (1 H, m, NH) and 7.40 (5 H, s, Ph).

5-*Benzyloxycarbonyl*-4-*heptyl*-1,5-*diazacyclooctan*-2-*one* **49** (R = Heptyl, X = $PhCH_2O_2C$).—Prepared in a manner analogous to the 4-phenyl compound, the 4-*heptyl title compound* was obtained in 83% yield after chromatography on silica gel and elution with methanol–chloroform (1:99) (Found: M$^+$, 360.241. $C_{21}H_{32}N_2O_3$ requires *M*, 360.241); ν_{max}(film)/cm^{-1} 1710–1645 and 3220; δ_H 0.80–1.70 (16 H, m), 1.75–3.80 (7 H, m), 4.63 (1 H, m, 4-H), 5.10 (2 H, s, $PhCH_2$), 6.60 (1 H, br, NH) and 7.31 (5 H, s, Ph).

5-*Benzyloxycarbonyl*-4-[2-(tert-*butyldimethylsiloxy)heptyl*]-1,5-*diazacyclooctan*-2-*one* **42**.—Prepared in a manner analogous to the phenyl compound above, the *title siloxyheptyl compound* was purified chromatographically and obtained in 79% yield {Found: [M$^+$ + H]$^+$ (CI) 491.329. $C_{27}H_{47}N_2O_4Si$ requires *m/z* 491.331}; δ_H 0.20 (6 H, m, Me_2Si), 1.00 (9 H, apparent d, Bu^t), 0.90–3.80 (22 H, m), 4.85 (1 H, m, 4-H), 4.80 and 5.20 (2 H, s for each diastereoisomer, $PhCH_2$), 6.70 (1 H, m, NH) and 7.40 (5 H, s, Ph).

5-Benzyloxycarbonyl-1-(4-bromobutyl)-4-phenyl-1,5-diazacyclooctan-2-one **46**.—Powdered potassium hydroxide (0.35 g, 0.006 mol), azalactam **49** (R = Ph, X = $PhCH_2O_2C$) (0.617 g, 0.002 mol) and 1,4-dibromobutane (1 cm^3) were stirred together in DMSO (15 cm^3) for 16 h at room temperature, then quenched with water and extracted with chloroform. The extract was washed successively with water and brine, dried, and evaporated. Chromatography on silica gel, and elution with chloroform, gave the *title compound* **46** (0.682 g, 72%) (Found: M^+, 472.138. $C_{24}H_{29}BrN_2O_3$ requires *M*, 472.136); ν_{max}(film)/cm^{-1} 1640 and 1695; δ_H 1.50–2.40 (6 H, m, 7-H_2, $CH_2CH_2CH_2Br$), 2.87 (2 H, m, 3-H_2), 3.05–3.85 (6 H, m, CH_2N and 6- and 8-H_2), 3.40 (2 H, t, *J* 7, CH_2Br), 5.10–5.35 (2 H, $PhCH_2$), 5.93 (1 H, m, 4-H) and 7.18–7.40 (10 H, m, 2 × Ph).

1-(4-Bromobutyl)-5-methyl-4-phenyl-1,5-diazacyclooctan-2-one **45**.—This was prepared by alkylation as above, using azalactam **49** (R = Ph, X = Me) (≡**16**) (0.865 g, 0.004 mol), potassium hydroxide (0.666 g, 0.012 mol), 1,4-dibromobutane (2.4 cm^3, 0.02 mol) and DMSO (17 cm^3). Chromatography on silica gel and elution with chloroform gave the *title compound* **45** (0.41 g, 29%), δ_H 1.80 (6 H, br m, $CH_2CH_2CH_2Br$ and 7-H_2), 2.35 (3 H, s, NMe), 2.50–4.00 (10 H, m), 4.10 (1 H, dd, *J* 4 and 11, 4-H) and 7.35 (5 H, s, Ph). Further elution with methanol–chloroform (1:49) gave recovered azalactam **16** (0.448 g, 51%).

1-(4-Bromobutyl)-5-methyl-4-pentyl-1,5-diazacyclooctan-2-one.—Prepared from azalactam **49** (R = pentyl, X = Me) (≡**17**) (0.500 g, 2.4 mmol), 1,4-dibromobutane (1.5 cm^3, 12 mmol), potassium hydroxide (0.41 g, 7.3 mmol) and DMSO (9 cm^3), the *title compound* (0.530 g, 63%) was purified by chromatography on silica gel and elution with methanol–chloroform (1:49), δ_H 0.90 (3 H, t, *J* 7, Me), 1.10–2.00 (14 H, m, $[CH_2]_4$, $CH_2CH_2CH_2Br$ and 7-H_2), 2.45 (3 H, s, NMe), 2.40–3.10 (5 H, m, 6- and 3-H_2, 4-H) and 3.30–3.60 (6 H, m, $NCH_2[CH_2]_2CH_2Br$ and 8-CH_2).

1-(4-Bromobutyl)-1-azacyclooctan-2-one **47**.—Prepared from heptanolactam (1.91 g, 0.015 mol), powdered potassium hydroxide (2.52 g, 0.045 mol), 1,4-dibromobutane (9 cm^3, 0.065 mol) and DMSO (45 cm^3), the *title halide* **47** (3.03 g, 77%) was purified by chromatography on silica gel and elution with methanol–chloroform (1:49), and then distillation, b.p. 170 °C (oven) at 0.4 mmHg; δ_H 1.50–2.20 (12 H, m), 2.55 (2 H, m, 3-H_2), 3.40–3.70 (6 H, m, 8-H_2 and $NCH_2[CH_2]CH_2Br$).

5-Benzyloxycarbonyl-1-[(E)-4-bromobut-2-enyl]-4-phenyl-1,5-diazacyclooctan-2-one **56**.—Azalactam **49** (R = Ph, X = $PhCH_2O_2C$) (0.338 g, 1 mmol) was treated with (*E*)-1,4-dibromobut-2-ene (0.43 g, 2 mmol) in the presence of potassium bis(trimethylsilyl)amide (1.05 mmol) in THF (27 cm^3) for 6 h at room temperature in a manner analogous to that for compound **43** (below). Work-up, and chromatography on silica gel with chloroform as eluent, gave the title bromo compound **56** (0.310 g, 66%), ν_{max}(film)/cm^{-1} 1630 and 1687; δ_H 1.60 (1 H, m, 7-H_a) 2.23 (1 H, m, 7-H_b), 2.40–4.33 (10 H, m), 5.27 (2 H, s, $PhCH_2$), 5.63–6.25 (3 H, m, CH=CH and 4-H) and 7.20–7.60 (10 H, m, 2 × Ph).

When the azalactam **49** (R = Ph, X = $PhCH_2O_2C$) (0.419 g, 1.24 mmol) in dry THF (11 cm^3) was alkylated using sodium hydride (55% dispersion, washed with hexane; 0.1 g, 2.3 mmol and prestirred with the azalactam for 30 min), followed by a solution of (*E*)-1,4-dibromobut-2-ene (0.40, 1.9 mmol) in THF (6 cm^3), the title compound was obtained in 49% yield (0.296 g).

5-Benzyloxycarbonyl-1-[(E)-4-bromobut-2-enyl]-4-pentyl-1,5-diazacyclooctan-2-one **57**.—Azalactam **49** (R = pentyl, X = $PhCH_2O_2C$) (0.777 g, 2.4 mmol) was alkylated with (*E*)-1,4-dibromobut-2-ene (1.29 g, 6 mmol) in the presence of sodium hydride (3.7 mmol) in THF (21 cm^3) to give the title compound **57** (0.204 g, 19%) after chromatography on silica gel and elution with chloroform; δ_H 1.60–4.00 (12 H, m), 4.65 (1 H, m, 4-H), 5.10 (2 H, m, $PhCH_2$), 5.70 (2 H, m, CH=CH) and 7.30 (5 H, s, Ph).

1-Butyl-4-phenyl-1,5-diazacyclooctan-2-one **43**.—Potassium bis(trimethylsilyl)amide (0.4 mol dm^{-3} solution in toluene; 2.6 cm^3, 0.001 mol) was added dropwise to a stirred solution of the azalactam **13** (0.204 g, 0.001 mol) in THF (10 cm^3) at 0 °C. After the mixture had been stirred at 0 °C for 30 min, 1-bromobutane (0.12 cm^3, 0.0011 mol) was added and the mixture was allowed to warm up during 16 h, and was then poured into water and extracted with chloroform. The extract was washed with brine, dried, and evaporated. Chromatography of the product on silica gel and elution with hexane–chloroform (1:4) gave the *title butyl compound* **43** (0.157 g, 60%) (Found: M^+, 260.189. $C_{16}H_{24}N_2O$ requires *M*, 260.189); ν_{max}(film)/cm^{-1} 1630 and 3315; δ_H 0.94 (3 H, t, *J* 7.2, Me), 1.20–1.80 (6 H, m, 7-H_2 and CH_2CH_2Me), 1.81 (1 H, s, NH), 2.38 (1 H, m, 6-H_a), 2.50 (1 H, dd, *J* 1.7 and 12.8, 3-H_a), 2.90 (1 H, m, NC*H*HPr), 3.00 (1 H, dd, *J* 11 and 12.8, 3-H_b), 3.20 (2 H, m, 6-H_b and 8-H_a), 3.82 (1 H, m, NCH*H*Pr), 4.05 (1 H, dd, *J* 1.7 and 11, 4-H), 4.12 (1 H, m, 8-H_b) and 7.30 (5 H, m, Ph); δ_C 13.9 (Me), *20.3*, *30.1*, *31.7*, *44.3*, *45.0*, *45.2*, *45.6*, 64.8 (C-4), 126.5, 127.5, 128.6, *145.1* and *172.9* (C=O). Continued elution gave starting lactam (0.035 g, 17% recovery).

1-(4-Bromobutyl)-4-phenyl-1,5-diazacyclooctan-2-one **44**.—Azalactam **13** (408 mg, 2 mmol) was alkylated with 1,4-dibromobutane (0.6 cm^3, 5 mmol) in THF (20 cm^3) using potassium bis(trimethylsilyl)amide (2.2 mmol) as the base, and a reaction time of 16 h. Chromatography on silica gel and elution with hexane–chloroform (1:4) gave the *bromobutyl compound* **44** (388 mg, 57%) (Found: $[M - Br]^+$, 259.179. $C_{16}H_{23}N_2O$ requires *m/z*, 259.181); ν_{max}(film)/cm^{-1} 1470, 1635 and 3220; δ_H 1.50–1.85 (6 H, m, 7-H_2 and $CH_2CH_2CH_2Br$), 1.85 (1 H, s, NH), 2.10–4.20 (11 H, m) and 7.30 (5 H, m, Ph). Continued elution gave unchanged azalactam (163 mg, 40% recovery).

1-(4-Chlorobutyl)-4-phenyl-1,5-diazacyclooctan-2-one.—Azalactam **13** (1.5 g, 7.4 mmol) was alkylated with 1-bromo-4-chlorobutane (2.2 cm^3, 19 mmol) in THF (60 cm^3) in the presence of potassium bis(trimethylsilyl)amide (8.4 mmol), with a reaction time of 24 h. Work-up, and chromatography on silica gel with hexane–chloroform (1:9), then (1:3) as eluent, gave the chloro compound[4] (1.91 g, 88%) (Found: M^+, 294.150. Calc. for $C_{16}H_{23}ClN_2O$: *M*, 294.150); ν_{max}(film)/cm^{-1} 1627 and 3320; δ_H 1.60–1.90 (7 H, m, $CH_2CH_2CH_2Cl$, 7-H_2, NH), 2.37 (1 H, ddd, *J* 3.8, 11.8 and 15.2, 6-H_a), 2.50 (1 H, dd, *J* 1.7 and 10.9, 3-H_a), 2.90 (1 H, m, NC*H*H$[CH_2]_3$Cl), 2.95 (1 H, t, *J* 10.9, 3-H_b), 3.20 (2 H, m, 6-H_b, 8-H_a), 3.60 (2 H, t, *J* 6.1, CH_2Cl), 3.85 (1 H, m, NCH*H*$[CH_2]_3$Cl), 4.03 (1 H, dd, *J* 1.7 and 10.9, 4-H), 4.15 (1 H, m, 8-H_b) and 7.20–7.40 (5 H, m, Ph); δ_C *25.2*, *30.0*, *31.5*, *44.2*, *44.5*, *44.7*, *45.0*, *45.4*, 64.7 (C-4), 126.4, 127.5, 128.6, *144.9* and *173.1* (C=O).

1-(3-Methylbut-2-enyl)-4-phenyl-1,5-diazacyclooctan-2-one **50**.—The azalactam **13** (0.21 g, 1 mmol) in THF (10 cm^3) was converted into the anion by treatment with potassium bis(trimethyl)silylamide (1.05 mmol), 3,3-dimethylallyl bromide (0.14 cm^3, 1.3 mmol) was added, and the mixture was stirred at 20 °C until no further starting azalactam remained (TLC). The product was poured into water and extracted with chloroform. Work-up, and chromatography on silica gel with hexane–chloroform (1:4) as eluent, gave the *title 3-methylbutenyl compound* **50** (0.232 g, 86%) (Found: M^+, 272.189. $C_{17}H_{24}N_2O$

requires *M*, 272.189); ν_{max}(film)/cm^{-1} 1625 and 3315; δ_H 1.70 (2 H, m, 7-H_2), 1.72 (6 H, 2 × Me), 1.87 (1 H, s, 5-H), 2.41 (1 H, m, 6-H_a), 2.50 (1 H, dd, *J* 1.7 and 12.6, 3-H_a, 2.99 (1 H, dd, *J* 11.1 and 12.6, 3-H_b), 3.20 (2 H, m, 6-H_b), 3.63 (1 H, dd, *J* 8 and 14.5, NC*H*HC=), 4.03 (1 H, dd, *J* 1.7 and 11.1, 4-H), 4.07 (1 H, m, 8-H_b), 4.40 (1 H, dd, *J* 6.2 and 14.5, NCH*H*C=), 5.20 (1 H, m, CH=C) and 7.35 (5 H, m, Ph); δ_C 17.8 (Me), 25.7 (Me), *31.5* (C-7), *42.5*, *44.0*, *44.3*, *45.5*, 64.8 (C-4), 120.1 (*C*H=C), 126.4, 127.4, 128.6, *135.7* (CH=*C*Me_2), *145.0* and *172.8* (C=O).

*5-Methyl-*1-*(3-methylbut-2-enyl)-4-phenyl-*1,5-*diazacyclooctan-2-one* **51**.—The 5-methylazalactam **16** (0.218 g, 1 mmol) was treated with a solution of potassium bis(trimethylsilyl)amide (1.05 mmol) in THF (10 cm^3), followed by 3,3-dimethylallyl bromide (0.14 cm^3), and was then worked up as above. The *product* **51**, an oil after chromatography, crystallised slowly in plates (0.245 g, 86%), m.p. 76–78 °C (Found: M^+, 286.204. $C_{18}H_{26}N_2O$ requires *M*, 286.205); ν_{max}($CDCl_3$)/cm^{-1} 1620; δ_H 1.60–1.80 (2 H, m, 7-H_2), 1.75 (3 H, s, Me), 1.78 (3 H, s, Me), 2.30 (3 H, s, NMe), 2.55 (2 H, m, 6- and 3-H_a), 2.97 (1 H, m, 6-H_b), 3.20 (1 H, t, *J* 11.6, 3-H_b), 3.35 (1 H, dt, *J* 3.7 and 15.3, 8-H_a), 3.78 (2 H, m, 8-H_b, NC*H*HCH=C), 4.05 (1 H, dd, *J* 3.1 and 11.6, 4-H), 4.42 (1 H, dd, *J* 6 and 14.6, NCH*H*CH=C), 5.20 (1 H, m, CH=C) and 7.35 (5 H, m, Ph); δ_C 17.7 (Me), 25.7 (Me), *29.6* (C-7), *41.4*, *43.1*, 43.6 (5-Me), *46.7*, *51.3*, 68.3 (C-4), 120.3, 127.0, 127.4, 128.3, *135.7* (CMe_2), *142.3* and *173.2* (C=O).

*5-Benzyloxycarbonyl-*1-*(3-methylbut-2-enyl)-4-phenyl-*1,5-*diazacyclooctan-2-one* **52**.—The *compound* (0.199 mg, 98%) was prepared in a similar way to the *N*-methyl analogue **51**, from compound **49** (R = Ph, X = $PhCH_2O_2C$) (0.17 g, 0.5 mmol) (Found: M^+, 406.227. $C_{25}H_{30}N_2O_3$ requires *M*, 406.226); δ_H(250 MHz) (all resonances show extra complexity, presumably because of hindered rotation of the benzyloxycarbonyl group) 1.50 (1 H, m, 7-H), 1.70 (6 H, m, 2 × Me), 2.10–2.40 (1 H, m, 7-H′), 2.83 (2 H, m, 3-H_2), 3.26 (2 H, app. t, C*H_2*CH=C), 3.50–3.83 (3 H, m, 6-H_2 and 8-H), 4.17 (1 H, m, 8-H′), 5.10 (1 H, m, C*H*=CMe_2), 5.25 (2 H, app. m, PhC*H_2*), 5.90 (1 H, m, 4-H) and 7.15–7.40 (10 H, m, 2 × Ph).

1-[(Z)-4-*Chlorobut-2-enyl*]-5-*methyl-4-phenyl-*1,5-*diazacyclooctan-2-one* **53**.—Prepared from azalactam **16** (0.958 g, 4.4 mmol) and (*Z*)-1,4-dichlorobut-2-ene (1.2 cm^3, 11.4 mmol) in THF (40 cm^3) using potassium bis(trimethylsilyl)amide (5.3 mmol) as the base, and a reaction time of 36 h, the *title chloride* **53** was obtained (0.715 g, 53%) after chromatography on silica gel [eluent hexane–chloroform (1:4)] (Found: M^+, 306.151. $C_{17}H_{23}ClN_2O$ requires *M*, 306.150); ν_{max}(film)/cm^{-1} 1628; δ_H 1.60–1.90 (2 H, m, 7-H_2), 2.27 (3 H, s, NMe), 2.50 (1 H, m, 6-H_a), 2.56 (1 H, dd, *J* 3.3 and 11.7, 3-H_a), 3.00 (1 H, m, 6-H_b), 3.20 (1 H, t, *J* 11.7, 3-H_b), 3.35 (1 H, dt, *J* 3.6 and 15.4, 8-H_a), 3.80–3.95 (2 H, m, 8-H_b and NC*H*HCH=C), 4.00 (1 H, dd, *J* 3.3 and 11.7, 4-H), 4.18 (2 H, m, CH_2Cl), 4.43 (1 H, dd, *J* 6.4 and 14.9, NCH*H*CH=C), 5.70–5.90 (2 H, m, CH=CH) and 7.30 (5 H, m, Ph); δ_C *29.7*, *38.7*, *41.0*, *42.4*, 43.6 (5-Me), *47.7*, *51.0*, 68.1 (C-4), 127.2, 127.5, 128.3, 128.4, 130.5, *141.7* and *173.4* (C=O). Inspection of the crude reaction product indicated the presence of ~25% of unchanged starting material, but it was not isolated during the chromatographic purification. Approximate yield allowing for unconverted starting material: 71%.

1-[(Z)-4-*Chlorobut-2-enyl*]-5-*methyl-4-pentyl-*1,5-*diazacyclooctan-2-one* **54**.—Using azalactam **17** (0.99 g, 4.7 mmol), (*Z*)-1,4-dichlorobut-2-ene (1.2 cm^3) and potassium bis(trimethylsilyl)amide (6.1 mmol) in THF (40 cm^3), and a reaction time of 48 h at 20 °C, the *title pentyl compound* **54** was obtained (0.562 g, 40%) after chromatography [silica gel; elution hexane–chloroform (1:9)] (Found: M^+, 300.197. $C_{16}H_{29}ClN_2O$ requires *M*, 300.197); ν_{max}(film)/cm^{-1} 1627; δ_H 0.70–1.95 (13 H, m, pentyl chain and 7-H_2), 2.41 (3 H, s, 5-Me), 2.40–3.10 (5 H, m, 3- and 6-H_2 and 4-H), 3.43 (2 H, t, *J* 7, 8-H_2), 3.97–4.30 (4 H, m, NC*H_2*CH=CHC*H_2*Cl) and 5.50–5.90 (2 H, m, CH=CH). Continued elution of the column gave starting azalactam (0.234 g, 23% recovery). Yield corrected for recovered starting material: 52%.

1-[(Z)-4-*Chlorobut-2-enyl*]-4-*heptyl-5-methyl-*1,5-*diazacyclooctan-2-one* **55**.—Azalactam **18** (0.713 g, 3 mmol) was alkylated for 50 h using (*Z*)-1,4-dichlorobut-2-ene (0.8 cm^3, 7.5 mmol) in THF (40 cm^3) in the presence of potassium bis(trimethylsilyl)amide (4 mmol). Work-up and chromatography as above gave the *title heptyl compound* **55** (0.278 g, 28%) (Found: M^+, 328.225. $C_{18}H_{33}ClN_2O$ requires *M*, 328.228); ν_{max}(film)/cm^{-1} 1630; δ_H 0.70–1.90 (17 H, m, heptyl side chain and 7-H_2), 2.41 (3 H, s, 5-Me), 2.40–3.10 (5 H, m, 3- and 6-H_2, 4-H), 3.41 (2 H, t, *J* 7, 8-H_2), 3.80–4.30 (4 H, m, NC*H_2*CH=CHC*H_2*Cl) and 5.50–5.97 (2 H, m, CH=CH). Continued elution gave recovered starting azalactam (0.378 g, 52%): yield, corrected for recovered starting material: 58%.

1,4-*Bis-(2-oxo-*1-*azacyclooctanyl)butane* **48**.—Heptanolactam (0.48 g, 3.8 mmol), powdered potassium hydroxide (0.86 g, 15.3 mmol), potassium iodide (0.79 g, 4.75 mmol), and the bromobutyl lactam **47** (1.00 g, 3.8 mmol) were stirred together in DMSO for 16 h at room temperature and the mixture was then poured into water and extracted with chloroform. Work-up, and chromatography on silica gel with methanol–chloroform (1:49) as eluent, gave the title bis-compound **48** (0.885 g, 76%), m.p. 79 °C (from acetone–hexane) (lit.,[3] 79–80 °C).

(E)-1,4-*Bis-(5-benzyloxycarbonyl-2-oxo-4-phenyl-*1,5-*diazacyclooctanyl)but-2-ene* **60** (*Homaline Precursor*).—A solution of the azalactam **49** (R = Ph, X = $PhCH_2O_2C$) (0.43 g, 1.3 mmol) in THF (9 cm^3) was added to a suspension of sodium hydride (55% dispersion; 0.1 g, 2.3 mmol, hexane washed) in THF (2 cm^3). The mixture was stirred at room temperature (30 min) and a solution of the bromide **56** (0.6 g, 1.3 mmol) in THF (9 cm^3) was added. After being stirred for 28 h, the product was worked up, and chromatographed on silica gel with methanol–chloroform (1:99) as eluent to give the title compound, a mixture of diastereoisomers, as a foam (0.613 g, 66%) {Found: $[M + 1]^+$ (FAB), 729. (EI) *m/z*, 390.195. $C_{24}H_{26}N_2O_3$ requires *m/z*, 390.194}; ν_{max}($CDCl_3$)/cm^{-1} 1630 and 1685; δ_H (resonances show the presence of diastereoisomers) 1.30–1.70 (2 H, m, 2 × 7-H), 1.95–2.33 (2 H, m, 2 × 7-H′), 2.60–3.00 (4 H, m), 3.22 (4 H, app. t, *J* 11.4), 3.30–4.20 (8 H, m), 5.10–5.20 (4 H, m, 2 × PhC*H_2*), 5.21–5.50 (2 H, m, CH=CH), 5.83–6.05 (2 H, m, 2 × 4-H) and 7.15–7.40 (20 H, m, 4 × Ph).

(E)-1-*(5-Benzyloxycarbonyl-4-heptyl-2-oxo-*1,5-*diazacyclooctan-*1-*yl)-4-(5-benzyloxycarbonyl-2-oxo-4-pentyl-*1,5-*diazacyclooctanyl)but-2-ene* **61** (*Hopromine Precursor*).—The compound was prepared (reaction time 48 h) and chromatographed as above from azalactam **49** (R = heptyl, X = $PhCH_2O_2C$) (0.100 g, 0.28 mmol), sodium hydride (0.57 mmol) and 1-(4-bromobut-2-enyl) azalactam **57** (0.131 g, 0.28 mmol) in THF (12 cm^3) to give the *title compound* **61** (0.097 g, 47%) {Found: $[M + 1]^+$ (FAB), 745; $C_{44}H_{65}N_4O_6$ requires *m/z* 745}; δ_H 0.80–4.00 (46 H, m, Me, CH_2), 4.60 (2 H, m, 2 × ring 4-H), 5.11 (4 H, m, PhC*H_2*), 5.20–5.50 (2 H, m, CH=CH) and 7.30 (10 H, s, 2 × Ph). Continued elution gave recovered starting azalactam **49** (R = heptyl, X = $PhCH_2O_2C$) (0.023 g, 23%). Correcting for recovered starting material, the yield was 61%.

(E)-1-{5-*Benzyloxycarbonyl*-4-[2-(tert-*butyldimethylsiloxy*)-*heptyl*]-2-*oxo*-1,5-*diazacyclooctanyl*}-4-(5-*benzyloxycarbonyl*-2-*oxo*-4-*phenyl*-1,5-*diazacyclooctanyl*)*but*-2-*ene* **62** (*Hopromalinol romalinol Precursor*).—This was prepared using azalactam **42** (0.506 g, 1.03 mmol), sodium hydride (1.5 mmol) and 1-(4-bromobut-2-enyl) azalactam **56** (0.490, 1 mmol) in THF (14 cm^3) with a reaction time of 48 h. Chromatography gave the title diastereoisomers **62** (0.191 g, 21%), δ_H 0.20 (6 H, s, 2 × Me), 0.90 (9 H, apparent d, Bu^t), 0.90–4.20 (35 H, m), 4.50–6.10 (7 H, m, 2 × CH_2Ph, PhC*H*, CH=CH) and 7.20–7.50 (15 H, m, 3 × Ph). Continued elution of the column gave recovered substrate **42** (0.077 g, 15%). Yield, taking into consideration recovered material, was 25%.

1,4-*Bis*-(2-*oxo*-4-*phenyl*-1,5-*diazacyclooctanyl*)*butane*.—The bis-benzyloxycarbonyl olefin **60** (602 mg, 0.83 mmol) was hydrogenated in methanol (30 cm^3) containing hydrochloric acid (conc. 0.6 cm^3) over Adams catalyst (150 mg) at room temperature for 4.5 h. Work-up, and chromatography on silica gel with, first, methanol–chloroform (1:99), then (3:97) as eluent, gave the *title compound* (0.153 g, 40%) {Found: [M + 1]$^+$ (FAB), 463 $C_{28}H_{39}N_4O_2$ requires *m*/*z* 463}; ν_{max}($CHCl_3$)/cm^{-1} 1617 and 3370; δ_H 1.50–2.50 (10 H, m, CH_2, NH), 2.50–4.50 (18 H, m, CH_2N, CH_2O, PhC*H*N) and 7.50 (10 H, m, 2 × Ph).

Treatment of the TBDMS Derivative **40** *with Acidic Methanol*.—4-[2-(*tert*-Butyldimethylsiloxy)heptyl]-1,5-diazacyclooctan-2-one **40** (0.209 g, 0.59 mmol) was stirred in methanol (10 cm^3) containing conc. hydrochloric acid (0.3 cm^3) for 3 h. Work-up gave 4-(2-hydroxyheptyl)-1,5-diazacyclooctan-2-one **27** (134 mg, 95%), identical with that prepared from azalactam **26**.

(Z)-1,4-*Bis*-(5-*Methyl*-2-*oxo*-4-*phenyl*-1,5-*diazacyclooctan yl*)*but*-2-*ene* **65**.—Potassium bis(trimethylsilyl)amide (0.34 mol dm^{-3} solution in toluene; 3 cm^3, 1.02 mmol) was added to a mixture of the azalactam **63** (R^1 = Ph) (≡**16**) (180 mg, 0.83 mmol) and potassium iodide (anhydrous; 175 mg, 1.05 mmol) in dry THF (10 cm^3) at 0 °C and the suspension was stirred for 30 min before the addition of a solution of the chloro olefin **64** (R^2 = Ph) (≡**53**) (254 mg, 0.83 mmol) in THF (7 cm^3). The mixture was stirred for 14 h at 20 °C, by which time TLC showed that little reaction had taken place. Sodium hydride (50% dispersion; ~150 mg, 3 mmol NaH) was then added, and the mixture was stirred for 48 h at room temperature. After being poured into water, the mixture was worked up and the product was chromatographed on silica gel, with hexane–chloroform (1:9), then with methanol–chloroform (1:49) as eluent, to give the title compound **65** (145 mg, 36%) as a mixture of diastereoisomers (~1:1), ν_{max}($CHCl_3$)/cm^{-1} 1630; δ_H 1.40–2.03 (4 H, m, 2 × ring 7-H_2), 2.23 (6 H, 2 × NMe), 2.30–4.00 (14 H, m, 2 × CH_2CO, 4 × CH_2N, 2 × NC*H*H=CH), 4.01 (2 × 1 H, dd, *J* 4 and 11, 2 × PhC*H*N), 4.43 (2 H, m, NCH*H*-CH=CH), 5.61 (2 H, m, CH=CH) and 7.27 (10 H, m, 2 × Ph).

(Z)-1-(4-*Heptyl*-5-*methyl*-2-*oxo*-1,5-*diazacyclooctanyl*)-4-(5-*methyl*-2-*oxo*-4-*pentyl*-1,5-*diazacyclooctanyl*)*but*-2-*ene* **66** (*Hopromine Precursor*).—The compound was prepared as before by using 4-pentyl-5-methyl-1,5-diazacyclooctan-2-one **63** (R^1 = pentyl) (≡**17**) (166 mg, 0.78 mmol), potassium bis(trimethylsilyl)amide (1.17 mmol), the chloride **64** (R^2 = heptyl) (≡**55**) (257 mg, 0.78 mmol), and THF (20 cm^3) with a reaction time of 24 h at 20 °C, before the addition of sodium hydride (55% dispersion; ~3 mmol NaH). After being stirred for 10 days the mixture was worked up and chromatographed by the usual procedures to give the *title compound* **66** (114 mg, 29%) as a mixture of diastereoisomers {Found: [M + H]$^+$ (FAB), 505 $C_{30}H_{57}N_4O_2$ requires *m*/*z* 505 ν_{max}(film)/cm^{-1} 1625; δ_H (resonances show additional diastereoisomeric splitting) 0.87 (6 H, m, 2 × Me), 1.15–1.90 (24 H, m, 12 × CH_2), 2.42 (6 H, s, 2 × NMe), 2.40–2.60 (6 H, m, 2 × ring 6-H_a, 2 × ring 3-H_2), 2.80–3.05 (4 H, m, 2 × ring 4-H, 2 × ring 6-H_b), 3.20–3.65 (4 H, m, 2 × ring 8-H_2), 3.80–4.40 (4 H, m, NCH_2CH=CHCH_2N) and 5.56 (2 H, apparent singlet, CH=CH); δ_C 14.09 (Me), 14.13 (Me), *22.66*, *26.66*, *27.00*, *28.80*, *29.31*, *29.69*, *30.87*, *31.86*, *31.92*, *38.38*, 39.84 (br 2 × NMe), *42.42*, *47.36*, 63.33 (2 × ring C-4), 128.61 (CH=CH) and 173.61 (2 × C=O).

(Z)-1-{4-[2-(tert-*Butyldimethylsiloxy*)*heptyl*]-5-*methyl*-2-*oxo*-1,5-*diazacyclooctanyl*}-4-(5-*methyl*-2-*oxo*-4-*pentyl*-1,5-*diazacyclooctanyl*)*but*-2-*ene* **67** (*Hoprominol Precursor*).—This was prepared using 4-[2-(*tert*-butyldimethylsiloxy)heptyl]-5-methyl-1,5-diazacyclooctan-2-one **41** (521 mg, 1.41 mmol), potassium bis(trimethylsilyl)amide (2.1 mmol) and the chloride **64** (R^2 = pentyl) (≡**54**) (457 mg, 1.52 mmol) in THF (40 cm^3). After the mixture had been stirred for 20 h, sodium hydride (from 55% dispersion; ~7 mmol) was added and the mixture was stirred for another 9 days. The customary work-up and chromatography gave the *title* olefin **67** (174 mg, 20%) {Found: [M + 1]$^+$ (FAB), 635 $C_{36}H_{71}N_4O_3Si$ requires *m*/*z* 635}; ν_{max}(film)/cm^{-1} 1630br; δ_H (diastereoisomeric broadening of signals) 0.05 (6 H, s, Me_2Si), 0.87 (15 H, br s, Bu^t, heptyl Me, pentyl Me), 1.10–2.00 (22 H, m, 11 × CH_2), 2.40 (6 H, s, 2 × NMe), 2.30–4.20 (19 H, m, 6 × CH_2N, 2 × CH_2CO, CHOSi, and 2 × NCH) and 5.53 (2 H, app. singlet, CH=CH).

(Z)-1-{4-[2-(tert-*Butyldimethylsiloxy*)*heptyl*]-5-*methyl*-2-*oxo*-1,5-*diazacyclooctanyl*}-4-(5-*methyl*-2-*oxo*-4-*phenyl*-1,5-*diazacyclooctanyl*)*but*-2-*ene* **68** (*Hopromalinol Precursor*).—The compound was prepared as before, using 4-[2-(*tert*-butyldimethylsiloxy)heptyl]-5-methyl-1,5-diazacyclooctan-2-one **41** (600 mg, 1.62 mmol), potassium bis(trimethylsilyl)amide (2.5 mmol), the chloride **64** (R^2 = Ph) (≡**53**) (500 mg, 1.62 mmol) and THF (40 cm^3) with an initial reaction time of 24 h. Sodium hydride (55% dispersion; ~8 mmol) was added and the mixture was stirred for 17 days at 20 °C. Work-up, and chromatographic purification as above, gave the *title compound* **68** (420 mg, 41%) as a mixture of diastereoisomers {(Found: [M + H]$^+$ (FAB), 641 $C_{37}H_{65}N_4O_3Si$ requires *m*/*z* 641}; ν_{max}(film)/cm^{-1} 1627; δ_H (resonances show extra splitting due to stereoisomerism) 0.05 (6 H, m, Me_2Si), 0.83 (12 H, m, Bu^t and heptyl Me), 1.10–2.00 (14 H, m, 7 × CH_2), 2.21 (3 H, s, NMe), 2.47 (3 H, s, NMe), 2.30–4.50 (19 H, m, 6 × CH_2N, 2 × CH_2CO, PhC*H*N, CH_2C*H*N and CHOSi), 5.54 (2 H, m, CH=CH) and 7.22 (5 H, m, Ph).

(±)-*Homaline* **1** *and* epi-*Homaline*: 1,4-*Bis*-(5-*methyl*-2-*oxo*-4-*phenyl*-1,5-*diazacyclooctanyl*)*butane*.—The olefin **65** (130 mg, 0.27 mmol) was hydrogenated in methanol (5 cm^3) containing conc. hydrochloric acid (0.1 cm^3) over Adams catalyst (32 mg) for 3 h at room temperature and atmospheric pressure. The mixture was filtered through Celite and the methanol was evaporated off. The residue was dissolved in chloroform (50 cm^3) previously saturated with sodium-dried ammonia gas. The suspension was filtered and the filtrate was evaporated to give a solid (124 mg, 95%), the spectrum of which was identical with that of the mixture of (±)-homaline and *epi*-homaline prepared in the previous paper[3] {Found: [M + 1]$^+$ (FAB), 491 $C_{30}H_{43}N_4O_2$ requires *m*/*z* 491}; ν_{max}($CHCl_3$)/cm^{-1} 1625; δ_H 1.40–2.00 (8 H, m, 4 × CH_2), 2.25 (6 H, s, 2 × NMe), 2.40–3.90 (16 H, m, 6 × CH_2N and 2 × CH_2CO), 4.00 (2 H, dd, *J* 4 and 12, 2 × PhC*H*) and 7.30 (10 H, s, 2 × Ph).

Hopromalinol Diastereoisomers 1-[4-(2-*Hydroxyheptyl*)-5-*methyl*-2-*oxo*-1,5-*diazacyclooctan*-1-*yl*]-4-(5-*Methyl*-2-*oxo*-4-

phenyl-1,5-diazacyclooctan-1-yl)butane **4**.—The olefin **68** (196 mg, 0.3 mmol) was hydrogenated in methanol (10 cm^3) containing hydrochloric acid (0.2 cm^3) over a platinum catalyst in the manner of the preceding experiment to give the *hoprimalinol diastereoisomers* **4** (147 mg, 91%), elision of the silyl group accompanying olefin hydrogenation {Found: $[M + H]^+$ (FAB), 529; $[M^+ + H]$ (CI), 529.412. $C_{31}H_{53}N_4O_3$ requires *m/z*, 529.412}; *m/z* (CI) [Found: 84.083 (73%). $C_5H_{10}O$ requires *m/z* 84.081; 134.097 (58%). $C_9H_{12}N$ requires *m/z*, 134.097; 146.096 (33%). $C_{10}H_{12}N$ requires *m/z*, 146.097: 159.103 (71%). $C_{10}H_{12}N$ requires *m/z*, 159.105; 259.183 (17%). $C_{16}H_{23}N_2O$ requires *m/z*, 259.181; and 184.168 (9%). $C_{11}H_{22}NO$ requires *m/z*, 184.170; 197.171 (21%). $C_{12}H_{23}NO$ requires *m/z*, 197.178; 413.289 (100%). $C_{24}H_{37}N_4O$ requires *m/z*, 413.292]; ν_{max}(film)/cm^{-1} 1635br and 3380br; δ_H (not sharply resolved) 0.88 (3 H, m, heptyl Me), 1.10–3.90 (38 H, 17 × CH_2, CHOH and 2 × CHN), 2.26 (3 H, s, NMe), 2.46 (3 H, s, NMe) and 7.10–7.50 (5 H, Ph).

Hopromine Diastereoisomers: 1-(4-*Heptyl*-5-*methyl*-2-*oxo*-1,5-*diazacyclooctanyl*)-4-(5-*methyl*-2-*oxo*-4-*pentyl*-1,5-*diazacyclooctanyl*)*butane* **2**.—The olefin **66** (85.6 mg, 0.17 mmol) in methanol (7 cm^3) containing conc. hydrochloric acid (0.1 cm^3) was hydrogenated as above over Adams catalyst (21 mg). Work-up gave the *hopromine diastereoisomers* **2** (83.9 mg, 98%) (Found: $[M + H]^+$ (FAB), 507. $[M + H]^+$ (CI), 507.463. $C_{30}H_{59}N_4O_2$ requires *m/z*, 507.464); *m/z* (CI) [Found: 84.085 (79%). $C_5H_{10}N$ requires *m/z*, 84.081; 156.173 (35%). $C_{10}H_{22}N$ requires *m/z*, 156.175; 168.173 (34%). $C_{11}H_{22}N$ requires *m/z*, 168.175; 181.180 (41%). $C_{12}H_{23}N$ requires *m/z*, 181.183; 281.258 (22%). $C_{17}H_{33}N_2O$ requires *m/z*, 281.259; 407.339 (99%). $C_{23}H_{43}N_4O_2$ requires *m/z*, 407.339; and 128.142 (35%). $C_8H_{18}N$ requires *m/z*, 128.144; 140.143 (49%). $C_9H_{18}N$ requires *m/z*, 140.144; 153.150 (53%). $C_{10}H_{19}N$ requires *m/z* 153.152; 253.225 (22%). $C_{15}H_{29}N_2O$ requires *m/z*, 253.223; 435.380 (76%). $C_{25}H_{47}N_4O_2$ requires *m/z*, 435.370]; ν_{max}(film)/cm^{-1} 1625; δ_H (not sharply resolved) 0.88 (6 H, m, 2 × CH_2*Me*), 1.10–2.00 (28 H, m, 14 × CH_2), 2.41 (6 H, s, 2 × NMe) and 2.45–3.60 (18 H, m, 6 × CH_2N, 2 × CH_2CO, 2 × ring 4-H); δ_C 14.06 (Me), 14.10 (Me), *22.65*, *25.29*, *26.66*, *27.00*, *28.69*, *29.30*, *29.68*, *30.88*, *31.85*, *31.91*, *38.46*, 39.75 (2 × NMe), *45.48*, *47.13*, *47.66*, 63.26 (2 × ring C-4) and *173.67* (2 × C=O).

Hoprominol Diastereoisomers: 1-[4-(2-Hydroxyheptyl)-5-methyl-2-oxo-1,5-diazacyclooctanyl]-4-(5-methyl-2-oxo-4-pentyl-1,5-diazacyclooctanyl)butane **3**.—The olefin **67** (131.5 mg, 0.21 mmol) in methanol (7 cm^3) containing conc. hydrochloric acid (0.15 cm^3) was hydrogenated over Adams catalyst (33 mg) and worked up as before to give the *hoprominol diastereoisomers* **3** (107 mg, 99%) {Found: $[M + H]^+$ (FAB), 523; $[M + 1]^+$ (CI), 523.459. $C_{30}H_{59}N_4O_3$ requires *m/z*, 523.459}; *m/z* (CI) [Found: 84.081 (100%). $C_5H_{10}N$ requires *m/z*, 84.081; 128.140 (55%). $C_8H_{18}N$ requires *m/z*, 128.144; 140.140 (42%). $C_9H_{18}N$ requires *m/z*, 140.144; 153.147 (58%). $C_{10}H_{19}N$ requires *m/z*, 153.152; 253.322 (30%). $C_{15}H_{29}N_2O$ requires *m/z*, 253.223; 451.365 (49%). $C_{25}H_{47}N_4O_3$ requires *m/z*, 451.365; and 172.158 (5%). $C_{10}H_{22}NO$ requires *m/z*, 172.170; 184.166 (15%). $C_{11}H_{22}NO$ requires *m/z*, 184.170; 197.171 (44%). $C_{12}H_{23}NO$ requires *m/z*, 197.178; 297.252 (8%). $C_{17}H_{33}N_2O_2$ requires *m/z*, 297.254; 407.342 (53%). $C_{23}H_{43}N_4O_2$ requires *m/z*, 407.339]; ν_{max}(film)/cm^{-1} 1625 and 3375br; δ_H (not sharply resolved) 0.90 (6 H, m, 2 × CH_2*Me*), 1.00–2.00 (26 H, m, 13 × CH_2), 2.41 (3 H, s, NMe), 2.45 (3 H, s, NMe) and 2.30–3.90 (20 H, m, 6 × CH_2N, 2 × CH_2CO, CHOH, and 2 × ring-4-H).

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