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Synthesis and Tautomerism of 9-Azabicyclo[4.2.1]nonan-1-ols (Norhomotropan-1-ols), N-Alkyl and 7,8-Dehydro- Derivatives, and Oxabicyclic Analogues

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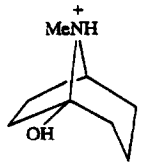
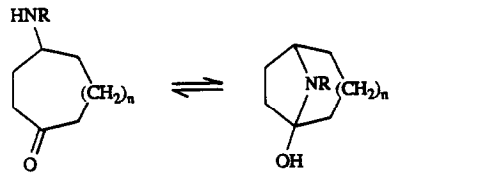
Abstract: *9-Methyl-9-azabicyclo[4.2.1]nonan-1-ol (homotropan-1-ol; homophysoperuvine) and -non-7-en-1-ol (homotrop-7-en-1-ol) have been synthesised together with the nor- systems and N-benzyl derivatives. The bicyclic amino-alcohols are shown to be in tautomeric equilibrium with the corresponding 4-aminocyclooctanones and -oct-2-enones; similar behaviour is also observed in oxabicyclic analogues. A rearrangement during attempted deprotection of the MEM ether derived from 9-benzyl-9-azabicyclo-[4.2.1]nonan-1-ol yielded N-benzyl-10-azabicyclo[3.3.2]dec-3-en-2-one. An attempt to introduce a 4-azido-substituent into a protected cyclooct-3-enone gave, instead, a novel tetracyclic triazoline.*

Introduction

The hydrochloride salt of the alkaloid physoperuvine exists in the bicyclic amino-alcohol form **(1)**[1] although there is spectroscopic evidence showing that the free base exists in tautomeric equilibrium with the monocyclic amino-ketone **(2 ⇄ 3)**.[1,2] Other natural derivatives of the nortropan-1-ol system, the calystegines, have been investigated recently and appear to exist entirely in the bicyclic form.[3] A synthesis of some higher homologues based on the novel 9-azabicyclo[4.2.1]nonan-1-ol ring system was reported recently in preliminary form; these compounds were shown to exist as mixtures of bicyclic/monocyclic tautomers **(4 ⇄ 5)** in solution.[4] We now report a fuller account of this work adding a wider range of N-alkyl- and 7,8-dehydro- derivatives and including details of our work with 9-oxabicyclo[4.2.1]nonan-1-ol and -non-7-en-1-ol which also exist in equilibrium with their respective monocyclic tautomers.



(1)



n=1: **(2)** **(3)**

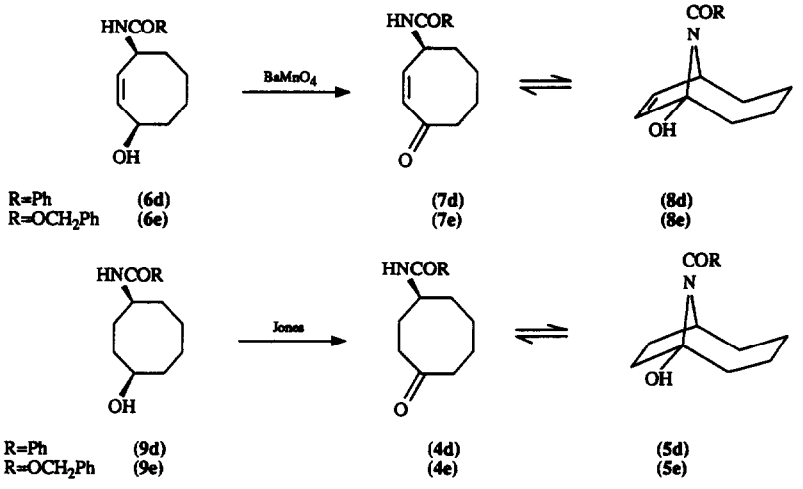
n=2: **(4)** **(5)**

a: R=Me
b: R=H
c: R=CH_2Ph
d: R=COPh
e: R=CO_2CH_2Ph

Synthesis

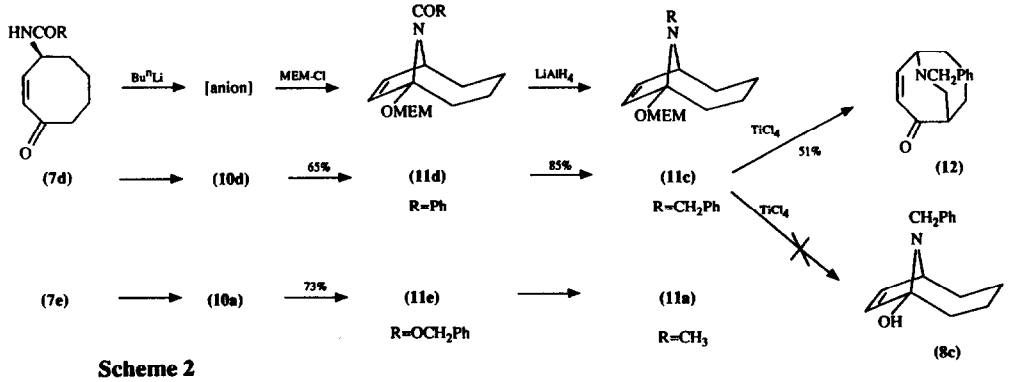
The synthesis of the key intermediates **(6d,e)** and **(9d,e)** was described earlier as part of a route to the parent homotropanes from cycloocta-1,3-diene.[5] Oxidation of **(6d,e)** provided the α,β-unsaturated ketones **(7d,e)** and the saturated analogues **(4d,e)** were available from oxidation of **(9d,e)** (scheme 1).

Scheme 1



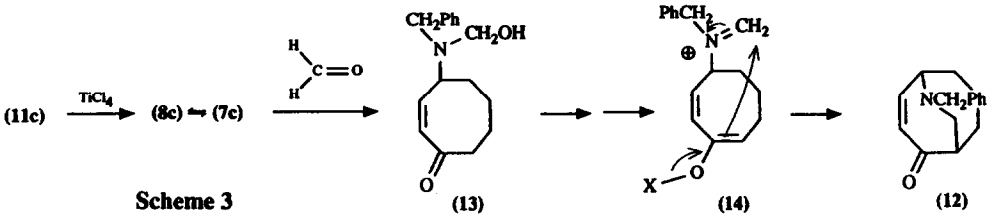
The oxidation of **(6d)** actually led to isolation of the monocyclic tautomer **(7d)** but earlier work had shown that the bicyclic tautomer **(8d)** was formed, and could be isolated, after an attempted Peterson olefination reaction on **(7d)**.[5] The sample of **(7d)** was therefore treated with n-butyl lithium followed by MEM-Cl and this allowed isolation of the bicyclic **(11d)** in its protected form (scheme 2).

Hydride reduction afforded **(11c)** but subsequent deprotection with $TiCl_4$ gave did not give the expected bicyclic product **(8c)**. Instead, the isolated product was shown by ^{13}C NMR spectroscopy and mass spectrometry to have suffered incorporation of an additional methylene group. The survival of the α,β-unsaturated ketone moiety and the N-benzyl group was easily demonstrated and the 10-azabicyclo[3.3.2]dec-3-en-2-one derivative **(12)** was consistent with all the data. The new carbon signal (C-9) appeared downfield at δ 52.7 and the attached protons showed the expected geminal coupling together with vicinal coupling to the bridgehead proton H-1. One of the methylene protons adjacent to nitrogen appeared as a doublet of doublet of doublets; the additional coupling was very small (J = 0.6 Hz) and was shown by a 2D NMR experiment to be due to w-coupling with the α-nitrogen bridgehead proton H-5.



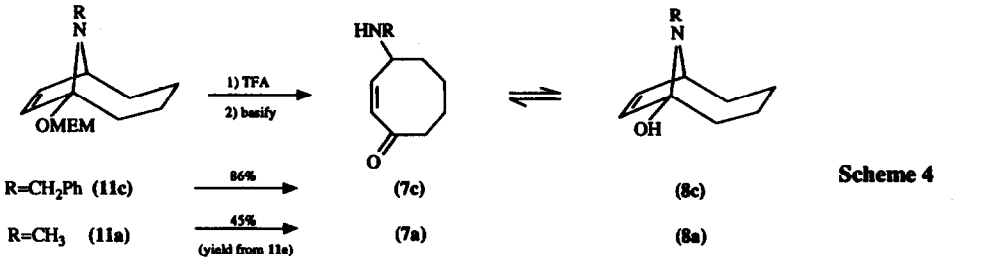
Scheme 2

The expected product (**8c**) was probably formed as an intermediate during the reaction but is assumed to have tautomerised to (**7c**) before reacting with methanal (which is known to be formed during cleavage of MEM ethers[6]) to produce the intermediate (**13**). Formation of an iminium ion is presumably facilitated by the $TiCl_4$ and the enolate (**14**) would lead to (**12**) via an intramolecular Mannich reaction. (scheme 3).



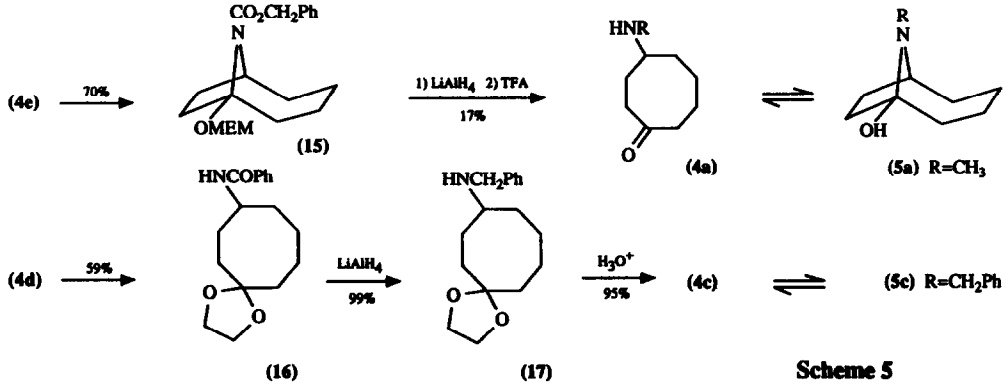
Scheme 3

An attempt was made to remove the MEM group using a large excess of TFA which was intended to protonate the amino-group, locking the product (**8c**) into the bicyclic form and reducing its reactivity with methanal. All solvent (and methanal product) was then removed under high vacuum. This strategy was successful; basification of the resulting salt led to the isolation of (**7c** ⇄ **8c**) in 86% yield (scheme 4).



Scheme 4

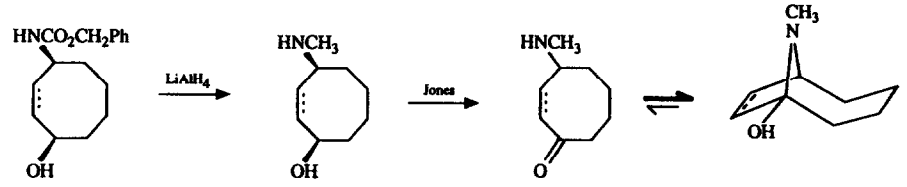
The same approach was used to convert (**7e**) into the N-methyl compound (**7a** ⇄ **8a**) via (**11a**) (schemes 2 and 4). The saturated analogue (**4e**) was converted similarly into the corresponding saturated N-methyl derivative (**4a** ⇄ **5a**) in poor yield via (**15**) (scheme 5). In each case, the equilibrium was weighted heavily towards the hemiaminal [(**8a**) and (**5a**) respectively]. Improved routes to both of these compounds are discussed below (scheme 6). The N-benzyl analogue was produced from (**4d**) via the acetal (**16**); hydride reduction gave (**17**) which was deprotected with aqueous trifluoroethanoic acid to yield (**4c** ⇄ **5c**).



Scheme 5

Subsequently, it was shown that direct conversion of (**6e**) into homophysoperuvine (**7a** ⇄ **8a**) was possible by direct oxidation of the hydride reduction product (**6a**) with Jones reagent (63% yield) (scheme 6).

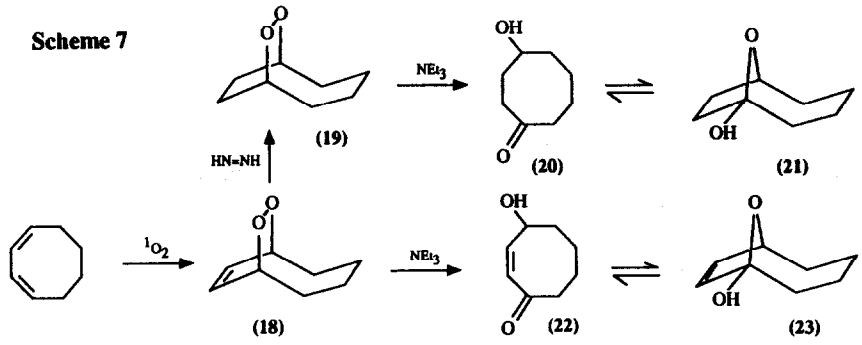
The same approach was obviously applicable to **(9e)** which was reduced to **(9a)** with hydride ion and afforded **(4a ⇄ 5a)** after oxidation. It is assumed that the same, direct oxidation of unprotected amino-alcohols will be successful if applied to the N-benzyl compounds but, since sufficient quantities of **(7c ⇄ 8c)** and **(4c ⇄ 5c)** were already available, this was not investigated further.[7]



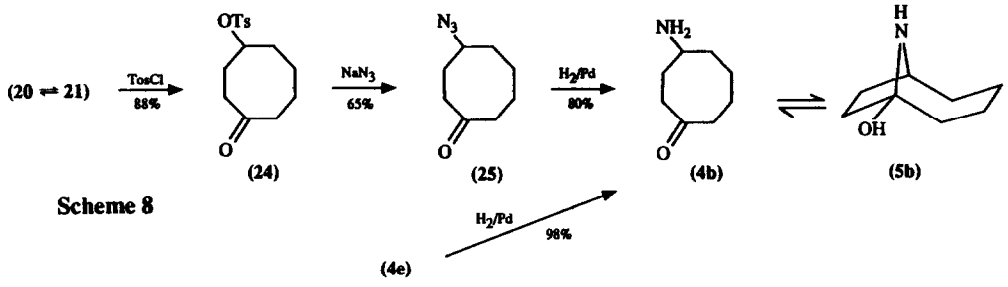
Scheme 6

Our initial approach to the nor- derivatives **(4b ⇄ 5b)** was based on the established addition of singlet oxygen to cycloocta-1,3-diene.[8] Reduction of the adduct **(18)** with diimide followed by treatment with triethylamine gave 4-hydroxycyclooctanone, formerly considered to be the monocycle **(20)**,[9] but which was seen using high-resolution NMR to be the minor tautomer in equilibrium with the oxabicycle **(21)** (scheme 7). Analysis of the ^{1}H NMR spectrum at 300 MHz allowed signals due to the two tautomers to be distinguished; diagnostic signals included peaks at δ 3.83 due to H-4 in **(20)**, and at δ 4.52 due to H-6 in **(21)** (earlier assigned, respectively, to the OH and H-4 in **(20)**[9]). The ^{13}C NMR spectrum showed the expected sixteen signals. Similar hydroxy-ketone / cyclic hemiacetal tautomerism has also been observed in 5-hydroxycyclooctanone, with the bicyclic tautomer predominating.[10]

Scheme 7



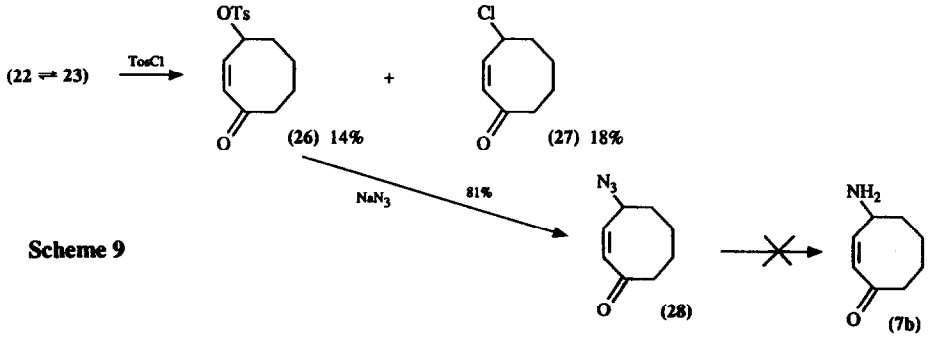
The action of triethylamine on **(18)** provided the unsaturated oxabicycle **(23)** which had formerly been thought to be formed irreversibly from the monocyclic tautomer **(22)**.[8,9] The major signals in the ^{13}C NMR spectrum were consistent with **(23)** and included peaks at δ 111.5 and 81.3 (H-1 and H-6 respectively). However, eight minor signals were also visible in the ^{13}C NMR spectrum which confirmed the presence of approximately 5% of the monocyclic tautomer **(22)**; these included peaks at δ 131.5, 148.8 and 202.0 typical of the α,β-unsaturated ketone system (supported by weak absorption at 1655 cm^{-1} in the IR spectrum). The ^{1}H spectrum showed minor signals assigned to **(22)** including the anticipated ABX system for H-2, H-3 and H-4 (with the addition of small w-coupling (0.8 Hz) between H_2 and one of the geminal pair on C-8). The nitrogen-bridged analogue **(4b ⇄ 5b)** was made from **(20 ⇄ 21)** via the tosylate **(24)**, displacement with azide ion, and hydrogenation (scheme 8). In later work, the availability of **(4e)** allowed direct conversion into **(4b ⇄ 5b)** by hydrogenolysis and this latter is clearly the simplest and most efficient route (scheme 8).



Scheme 8

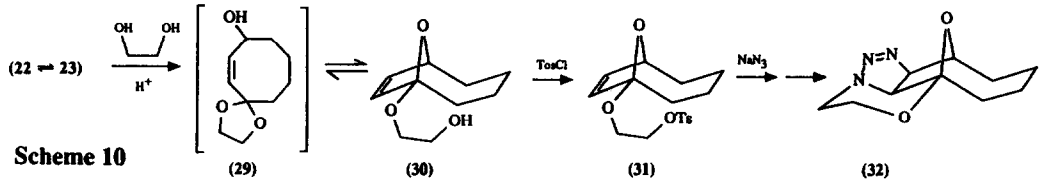
The ^{1}H and ^{13}C NMR spectra of (**4b** ⇄ **5b**) were broad at ambient temperature but the rate of interconversion slowed at lower temperatures and the two tautomers were distinguishable below -20°C. The VT NMR studies showed that the ratio was temperature-dependent and this was confimed by VT IR measurements which showed a gradual reduction in the intensity of the carbonyl signal at 1695 cm^{-1} as the temperature of a solution in dichloromethane was lowered (table).

An attempt was made to convert the unsaturated azide (**28**) into the unsaturated analogues (**7b** ⇄ **8b**) (scheme 9). Tosylation of (**22** ⇄ **23**) proceeded slowly and gave, after 16 days, a poor recovery of a mixture of the tosylate (**26**) and the allylic chloride (**27**) together with polymeric material. The azide (**28**) was produced in good yield from the tosylate and, more slowly, from the chloride (**27**). However, we were unable to convert (**28**) into the amine (**7b**) using, for example, Staudinger conditions; a mixture of products was obtained which showed no alkene proton signals in the ^{1}H NMR spectrum. A concurrent approach to derivatives of the 1-hydroxynortropane system[11] confirmed the sensitivity of similar cyclic allylic azides; in this case, epoxidation of the double bond in 4-azidocyclohept-2-enone was found to be necessary to suppress side reactions but the Staudinger reaction led to rearrangement.[11]



Scheme 9

A further attempt to make the unsaturated (**7b** ⇄ **8b**) from (**22** ⇄ **23**) via the acetal (**29**) was not successful but led to an unexpected and interesting result (scheme 10). Treatment of (**22** ⇄ **23**) with ethane-1,2-diol and acid gave a hydroxy-acetal which was converted readily into a tosylate which was reacted, in turn, with sodium azide. The highly crystalline product showed no evidence of either an azide group or a double bond and the ^{1}H NMR spectrum was complex. The available evidence led to proposal of structure (**32**) for the product from the azide reaction and this was confirmed by a crystal structure.[12] Clearly the hydroxy-acetal (**29**) was in equilibrium with the bicyclic tautomer (**30**) and the rapid reaction with tosyl chloride was consistent with the production of the primary tosylate (**31**) from (**30**) (rather than slower production of the required secondary tosylate from (**29**)). The primary azide derived from (**31**) had clearly been formed but had undergone a simple intramolecular 1,3-dipolar cycloaddition to yield the tetracyclic triazoline (**32**).

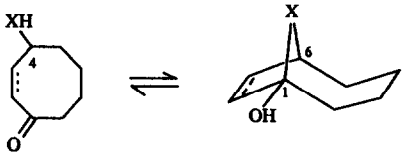


Scheme 10

Tautomeric Equilibria

The tautomeric ratios were measured by integration of the NMR signals under conditions of slow interconversion; the results are summarised in table 1. Spectra for the aza- compounds were broad at ambient temperature and VT NMR investigations are summarised in the table. Assignments in all cases were made on the basis of the key ^{13}C NMR chemical shifts shown, together with supporting ^{1}H NMR and other evidence. The shifts of the bridgehead carbons of norhomophysoperuvine (**5b**) (δ 93.1 and 52.4) are in very close agreement with published data for calystegine A_3[3a] (a hydroxy-derivative of norphysoperuvine) where the corresponding values are δ 93.0 and 54.0 respectively. The chemical shifts for C-6 in the oxa- and azabicyclic examples are in line with expectations based on homotropanes and 9-oxa-analogues.[13] The C_4 signals in the hydroxy-ketones (**20**) and (**22**) and the bridgehead carbon signals (C-1 and C-6) in the bicyclic tautomers (**21**) and (**23**) are pulled downfield by the presence of oxygen, as expected, when compared to the values for the corresponding nitrogen compounds.

Table Ratios of Monocyclic : Bicyclic Tautomers



X	Compound	Temp. (°C)	mono cyclic	:	bicyclic	^{13}C NMR (δ: selected data) mono-		bicyclic	
						C_4	CO	C_1	C_6
saturated series									
$NHCH_3$	(**4a ⇄ 5a**)	-30	~0	:	~100	-	-	92.0	58.1
NH	(**4b ⇄ 5b**)	-20	18	:	82				
		-30	11	:	89	50.7	218.8	93.1	52.4
		-50	5	:	95				
NCH_2Ph	(**4c ⇄ 5c**)	-30	70	:	30				
		-40	68	:	32				
		-50	66	:	34	56.1	218.6	92.2	54.2
O	(**20 ⇄ 21**)	25	31	:	69	70.7	217.0	108.3	76.0
unsaturated series									
$NHCH_3$	(**7a ⇄ 8a**)	-50	~0	:	~100	-	-	95.3	63.2
NCH_2Ph	(**7c ⇄ 8c**)	-55	58	:	42	55.3	203.3	94.7	60.1
O	(**22 ⇄ 23**)	25	5	:	95	69.2	202.0	111.5	81.3

The ratio of the two tautomers could not be measured at ambient temperature for any of the nitrogen-bridged systems; the figures quoted in the table refer to temperatures of -20°C or below. The heavy preference for the bicyclic tautomer (**5a**) of homophysoperuvine corresponds closely with the 98:2 preference measured for physoperuvine itself.[2] The similar, bicyclic preference in the case of the nor- system (**5b**) is in agreement with observations in lower homologues (norphysoperuvine[2] and many calystegines[3]) where the bridging nitrogen is also secondary. The N-benzyl system (**4c** ⇄ **5c**) differs somewhat, showing a modest preference for the monocyclic tautomer. The reason for the difference between the N-methyl and N-benzyl analogues is not clear and an additional complication is the variation of the ratios with temperature. Studies of the N-benzyl derivative of the corresponding lower homologue,[2,3a] concluded that there was a qualitative preference for the bicyclic tautomer but quantitative data could not be obtained.

Comparison of the figures for (**20** ⇄ **21**) and (**22** ⇄ **23**) suggests that the incorporation of a double bond into the ring results in a shift of the equilibrium towards the bicyclic tautomer. At first sight, this is surprising since the incorporation of a shorter C=C bond into the bicycle might be expected to lead to greater strain. Further, the bicyclic tautomer loses the apparent advantage of the stabilisation due to the α,β-unsaturated ketone system. Given our interest in the effects of incorporating π- bonds into azabicycles[14,15] we chose to examine the unsaturated nitrogen analogues. The N-methyl compounds (**4a** ⇄ **5a**) and (**7a** ⇄ **8a**) were both effectively bicyclic with or without the π-bond but the unsaturated N-benzyl compound (**7c** ⇄ **8c**) contained slightly more of the bicyclic tautomer than the saturated analogue (**4c** ⇄ **5c**).

The factors leading to the slight favouring of the hemiaminal form (**8c**) (relative to (**5c**)) and the hemiacetal (**23**) (relative to (**21**)) are not understood. The potential stabilisation of the monocyclic α,β-unsaturated ketones is not, in fact, a serious impediment since MMX calculations suggest that the preferred conformation of the monocycle gains little from π-delocalisation, the two π- bonds being close to orthogonal. Turning to factors which might stabilise the unsaturated bicyclic form, there is strong evidence that rigid bicyclic systems (such as 7-azabicyclo[2.2.1]hept-2-ene and -hepta-2,5-diene derivatives) experience a stabilising σ-π^* interaction between the bridging C-N bonds and the π-system and such an effect would conveniently rationalise the observed change in ratio. However, this approach fails when results from ^{15}N NMR spectroscopic studies are considered since it appears that this interaction is heavily attenuated in 8-azabicyclo[3.2.1]oct-6-enes (trop-6-enes) and actually plays no detectable part in the 9-azabicyclo[4.2.1]non-7-ene (homotrop-7-ene) ring system.[15] Complicating matters further, the available results show that incorporation of unsaturation into the 2-carbon bridge of the physoperuvine (tropan-1-ol) ring system (and the N-benzyl analogue) leads to a qualitative shift of equilibrium towards the monocycle[2] although the shorter C=C bond in this case may lead to greater strain in the bicyclic tautomer. The overall balance of factors influencing the relative stabilities of the two tautomers in both the physoperuvine and homophysoperuvine ring systems is clearly very complex and will not easily be unravelled. The influence of temperature on the position of equilibrium is an additional factor. The increase in the proportion of the monocyclic tautomer with increase in temperature in the examples shown in the table is to be expected in view of the increased disorder which results from the formation of the monocyclic from the bicyclic tautomer.

Acknowledgements

We thank the SERC for studentships to C.R.S. and D.J.; we are grateful to the SERC Mass Spectrometry Service at Swansea for some of the high-resolution mass spectra.

Experimental

Routine ^1H NMR spectra were recorded on Varian EM 390 (90 MHz) or Jeol JNM-PS100 (100 MHz) spectrometers. Higher field ^1H NMR (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker AM 300 spectrometer. Spectra were measured in $CDCl_3$ with tetramethylsilane (TMS) as internal reference unless indicated otherwise. Signal characteristics are described using standard abbreviations: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet), br (broad); protons identified as NH or OH were shown to be exchangeable with D_2O. Where data are quoted for two tautomers or rotamers, overlapping signals are shown in italics but may be quoted separately for reasons of clarity even though they are not fully resolved and assigned. In the ^{13}C spectra, C, CH, CH_2, CH_3 are used to indicate quaternary, methine, methylene and methyl carbons respectively, as shown by off-resonance decoupling or DEPT experiments.

IR spectra were recorded on PE 1604 FT or PE 298 IR spectrometers as solutions in CH_2Cl_2 unless indicated otherwise. Band intensities are described using standard abbreviations: s (strong), m (medium), w (weak), br (broad), v (very).

Mass spectra were measured routinely on a VG Micromass 14 spectrometer and were obtained using ionisation by electron impact except where chemical ionisation was used (shown CI); intensities are given as percentages of the base peak. Accurate mass measurements were obtained using a Kratos Concept mass spectrometer or through the SERC service at the University College of Swansea.

Melting point measurements were made using a Kofler hot stage apparatus and are uncorrected.

Combustion Analyses were performed by Butterworth Laboratories Ltd., Teddington, Middlesex.

Reactions were performed under dry nitrogen using solvents dried by standard methods. Diethyl ether was dried over sodium wire and distilled from $LiAlH_4$. Dichloromethane, toluene and benzene were distilled from calcium hydride. Petroleum ether and ethyl ethanoate were distilled prior to use. Methanol and ethanol were purified with magnesium and iodine.[16] Tetrahydrofuran was distilled from sodium-benzophenone. Triethylamine and pyridine were distilled from potassium hydroxide. All other solvents were dried and purified as described by Perrin *et al.*.[17] Flash chromatography was carried out according to the method of Still *et al.*[18] using Merck Kieselgel 60 (230 - 400 mesh). Thin-layer chromatography was conducted on standard commercial aluminium sheets pre-coated with a 0.2 mm layer of silica gel (Merck 60 - 254).

Compounds **(4d)**, **(4e)**, **(6a)**, **(7d)** and **(7e)** were prepared as described in reference 5.

1-(β-Methoxyethoxymethoxy)-N-benzoyl-9-azabicyclo[4.2.1]non-7-ene (11d)

n-Butyllithium (2.5 M solution in hexanes, 11.40 ml, 28.49 mmol) was added to a solution of **(7d)** (6.60 g, 27.13 mmol) in dry tetrahydrofuran (300 ml) at 0°C under dry N_2. The solution was stirred as it warmed to room temperature. After 15 min, methoxyethoxymethyl chloride (MEM-Cl; 4.31 ml, 37.81 mmol) was added and the solution was refluxed for 7 h. The solution was evaporated under reduced pressure and the residue dissolved in dichloromethane (400 ml) and washed with water (2 x 100 ml). The organic solution was dried over anhydrous magnesium sulphate and then evaporated under reduced pressure leaving an oil which was purified by flash chromatography (diethyl ether) to yield **(11d)** (5.37 g, 65%) as a yellow oil. δ_H (300 MHz, $CDCl_3$): 1.26 - 1.65 (series of m, 6H), 1.87 (m, 1H), 2.79 (m, 1H), 3.30 (s, 3H, MEM Methyl), 3.37 - 3.48 (m, 2H, MEM O-CH_2), 3.66 - 3.82 (m, 2H, MEM O-CH_2), 4.69 (brd, J = 5.0 Hz, 1H, H-6), 4.94, 4.98 (ABq, J = 7.3 Hz, 2H, MEM O-CH_2-O), 5.83 (s, 2H, alkenyl), 7.27 - 7.55 (series of m, 5H, aryl). δ_C (75 MHz, $CDCl_3$): 22.6, 23.6, 33.1, 35.5 (4 x CH_2), 58.8 (OCH_3), 63.6 (CH, C-6), 67.7 (MEM O-CH_2), 71.7 (MEM O-CH_2), 90.2 (MEM O-CH_2-O), 99.7 (C, C-1), 127.1, 128.3 (2 x Aryl CH), 129.8 (=CH), 130.9 (aryl CH), 134.0 (=CH), 137.2 (aryl C), 170.3 (C=O). ν_{max} (CH_2Cl_2): 2930m, 2890m, 2820w, 1765w, 1645m, 1630m, 1600m, 1575w, 1445m, 1390s, 1360m, 1345m, 1320w, 1200m, 1110brm, 1100m, 1070s, 1020s cm^{-1}. m/z (%): 332 (MH^+, 100), 256 (10), 243 (23), 226 (37), 122 (5), 105 (12), 94 (2), 59 (2), 44 (2); $C_{19}H_{26}NO_4$ [MH^+] requires 332.1862; observed 332.186.

1-β-Methoxyethoxymethoxy)-N-benzyl-9-azabicyclo[4.2.1]non-7-ene (11c)

A solution of **(11d)** (2.44 g, 7.36 mmol) in dry tetrahydrofuran (30 ml) was added dropwise to a slurry of lithium tetrahydroaluminate (421 mg, 11.04 mmol) in dry tetrahydrofuran (30 ml). The stirred slurry was refluxed for 6 h after which time decomposition of excess hydride was effected by addition of water. The inorganic solids were removed by filtration and washed with warm ethyl ethanoate. The combined organic solutions were evaporated under reduced pressure; the residue was dissolved in dichloromethane and dried over anhydrous magnesium sulphate. Evaporation under reduced pressure gave an oil which was purified by flash chromatography [65:35 petroleum ether (40 - 60°C): diethyl ether, saturated with gaseous ammonia] to yield **(11c)** (1.98 g, 85%) as a colourless oil. δ_H (300 MHz, $CDCl_3$): 1.37 - 1.45 (m, 1H), 1.52 - 1.76 (series of m, 4H), 1.91 - 2.16 (series of m, 3H), 3.35 (s, 3H, MEM CH_3), 3.48 - 3.62 (m, 3H, H-6 and MEM O-CH_2), 3.78 - 3.88 (m, 2H, MEM O-CH_2), 4.06, 4.14 (ABq, J = 14.5 Hz, 2H, benzyl CH_2), 4.54 (d, J = 6.8 Hz, 1H, MEM O-CH-O), 5.18 (d, J = 6.8 Hz, 1H, MEM O-CH-O), 5.92 (s, 2 H, alkenyl), 7.17 - 7.37 (series of m, 5 H, aryl). δ_C (75 MHz, $CDCl_3$): 23.0, 23.6, 29.5, 37.0 (4 x CH_2), 45.8 (benzyl CH_2), 58.9 (OCH_3), 59.8 (CH, C-6), 67.0 (MEM O-CH_2), 71.9 (MEM O-CH_2), 89.1 (MEM O-CH_2-O), 99.3 (C, C-1), 126.4, 128.0, 128.1 (3 x aryl CH), 133.7 (=CH), 135.8 (=CH), 140.4 (aryl C). ν_{max} (CH_2Cl_2): 2920m, 2880m, 1480w, 1445w, 1350brw, 1185brm, 1100m, 1050m, 1030m, 1015m, 985m cm^{-1}. m/z (%): 318 (MH^+, 100), 228 (8), 212 (77), 122 (4), 109 (4), 91 (7), 59 (4), 44 (3); $C_{19}H_{28}NO_3$ [MH^+] requires 318.2069; observed 318.207.

1-Methoxyethyoxymethoxy-N-benzyloxycarbonyl-9-azabicyclo[4.2.1]non-7-ene (11e)

A solution of N-butyllithium (2.5 M in hexane; 1.44 ml, 3.60 mmol) was injected into a stirred solution of **(7e)**[5] (893 mg, 3.27 mmol) in THF (25 ml) at 0°C under a N_2 atmosphere. After 15 mins, methoxyethoxymethyl chloride (MEM-Cl; 0.52 ml, 4.58 mmol) was injected. The solution was allowed to warm to room temperature, then heated at reflux for 5 h. The solvent was removed under reduced pressure and the residue dissolved in dichloromethane (55 ml), washed with water (3 x 20 ml), separated and dried over anhydrous magnesium sulphate. Filtration and evaporation of solvent afforded a yellow oil which was purified by flash column chromatography (1 : 1 diethyl ether : petrol (b.p. 40 - 60°C) yielding **(11e)** (863 mg, 73%) as an oil. δ_H (300 MHz, $CDCl_3$) [Slow rotation about the N-CO bond was observed and signals due to the two rotamers are shown separately where they were resolved; where signals overlapped, δ values and integrals are shown in italics as if they were due to a single compound]: *1.29 - 1.60 (series of m, 5H)*, *1.81 (m, 1H)*, 2.03 (m, 1H), *2.29 (m, 1H)*, 2.50 (m, 1H), 3.35 (s, 3H, OMe), 3.38 (s, 3H, OMe), *3.53 (m, 2H)*, *3.63 - 3.87 (series of m, 2H)*, 4.58 and 4.88 (ABq, J = 6.9 Hz, 2H, O-CH_2-O), *4.70 (m, 1H, H-6)*, 4.72 and 4.91 (ABq, J = 7.2 Hz, 2H, O-CH_2-O), 5.15 (ABq, J = 12.4 Hz, 2H, benzyl CH_2), 5.21 (ABq, J = 12.8 Hz, 2H, benzyl CH_2), *5.77* (dd, J = 6.2, 0.6 Hz, 1H), 5.85 (dd, J = 6.2, 2.6 Hz, 1H), 5.88 (dd, J = 6.2, 2.6 Hz, 1H), *7.34 (m, 5H)*. Signal coalescence occurred at higher temperatures resulting in a simplified spectrum. δ_C (75 MHz, $CDCl_3$) 22.7, 23.0 (2 x CH_2), 23.1, 23.4 (2 x CH_2), 30.1, 31.5 (2 x CH_2), 35.7, 36.9 (2 x CH_2) 58.8, 58.9 (2 x CH_2), 61.0, 61.6 (2 x CH_2), 66.2, 66.6 (2 x CH_2), 67.4, 67.5 (2 x CH_2), *71.7 (CH_2)*, 89.9, 90.0 (2 x CH_2), 98.1, 99.0 (2 x C), *127.8 (C)*, 127.9, 128.1 (2 x aryl CH), *128.4 (aryl CH)*, 131.0, 131.4 (2 x =CH), 133.1, 133.8 (2 x =CH), *136.7 (C)*, 152.9, 154.3 (2 x C=O). ν_{max} (thin film): 3080w, 3060w, 3020w, 2920s, 2870s, 2800w, 1695brs, 1620w, 1580w, 1490w, 1440m, 1395s, 1345s, 1300s, 1250m, 1195m, 1170m, 1090brs, 1020s, 980s, 935m, 845w, 830w, 805w, 790m, 770m, 730m, 695m. m/z: 361 (M^+, 32), 285 (26), 274 (35), 273 (39), 256 (67), 241 (50), 228 (29), 212 (34), 199 (42), 186 (34), 165 (24), 150 (100), 138 (42). $C_{20}H_{27}NO_5$ requires: 361.1889; found 361.189.

N-Benzyl-10-azabicyclo[3.3.2]dec-3-en-2-one (12)

Titanium (IV) chloride (1.0 M solution in dichloromethane, 6.24 ml, 6.24 mmol) was added to a solution of **(11c)** (660 mg, 2.08 mmol) in dry dichloromethane (10 ml) at 0°C under N_2. After 2 h at room temperature, the solution was quenched with concentrated aqueous ammonia and extracted with dichloromethane. The organic solution was dried over anhydrous magnesium sulphate and evaporated under reduced pressure producing an oil which was purified by flash chromatography (1 : 1 petroleum ether (40 -

60°C); diethyl ether, saturated with gaseous ammonia) to yield (12) (255 mg, 51%) as a yellow oil. δ_H (300 MHz, $CDCl_3$): 1.19 (m, 1H, 1.51 - 1.82 (series of m, 4H), 2.05 (m, 1H), 2.63 (dd, J = 12.4, 1.3 Hz, 1H, bridging N-CH), 2.80 (m, 1H, bridgehead α-C=O), 3.01 (ddd, J = 12.4, 5.6, 0.6 Hz, 1H, bridging N-CH), 3.68 - 3.78 (m: ABq, 2H, benzyl CH_2 and 1H, bridgehead α-N), 6.26 (dd, J = 11.7, 1.9 Hz, 1H, alkenyl), 6.43 (dd, J = 11.7, 8.6 Hz, 1H, alkenyl), 7.20 - 7.35 (m, 5H, aryl). δ_C (75 MHz, $CDCl_3$): 20.6, 27.4, 32.8 (3 x CH_2), 49.1 (bridgehead CH-C=O), 52.7 (bridging N-CH_2), 58.8 (bridgehead CH-N), 62.5 (benzyl CH_2), 127.0, 128.2, 128.4 (3 x aryl CH), 135.4 (=CH), 139.4 (aryl C-1), 141.8 (=CH), 206.9 (C=O). ν_{max} (CH_2Cl_2): 3020w, 2940m, 2870m, 2820m, 1665s, 1490w, 1450w, 1390w, 1350m, 1235w, 1195m, 1160m, 1125m, 1105m cm^{-1}. m/z (%): 241 (M^+, 36), 214 (10), 213 (10), 171 (15), 170 (15), 158 (11), 150 (25), 122 (10), 91 (100), 85 (38), 83 (65), 76 (14), 65 (15), 51 (28), 49 (83); $C_{16}H_{19}NO$ [M^+] requires 241.1467; found 241.147.

Trifluoroethanoic acid salt of (12)

Compound (12) was acidified with one equivalent of trifluoroethanoic acid to observe the changes in chemical shift caused by protonation of the amino nitrogen: δ_H (300 MHz, $CDCl_3$): 1.30 (m, 1H), 1.75 - 1.85 (m, 2H), 1.99 (m, 1H), 2.19 (m, 1H), 2.42 (m, 1H), 3.03 (m, 1H, bridgehead α-C=O), 3.19 (brd, J = 13.8 Hz, 1H, bridging N-CH), 3.97 (brdd, J = 13.8, 5.1 Hz, 1 H, bridging N-CH), 4.20, 4.48 (ABq, J = 12.9 Hz, 2H, benzyl CH_2), 4.51 (m, 1H, bridgehead α-N), 6.31 (dd, J = 12.0, 8.4 Hz, 1H, alkenyl), 6.43 (dd, J = 12.0, 1.9 Hz, 1H, alkenyl), 7.33 - 7.56 (m, 5H, aryl). δ_C (75 MHz, $CDCl_3$): 19.5, 26.8, 28.1 (3 x CH_2), 47.5 (bridgehead CH-C=O), 51.4 (bridging N-CH_2), 59.6 (bridgehead CH-N), 62.0 (benzyl CH_2), 129.0 (C, aryl C-1), 129.5, 130.4, 131.2 (3 x aryl CH), 134.0 (=CH), 138.9 (=CH), 201.7 (C=O).

4-(Benzylamino)cyclooct-2-enone ⇌ N-benzyl-9-azabicyclo[4.2.1]non-7-en-1-ol (7c ⇌ 8c)

Trifluoroethanoic acid (2.23 ml, 28.9 mmol) was added in one portion to a solution of (11c) (920 mg, 2.89 mmol) in dichloromethane (20 ml) at 0°C. After 6h at room temperature, water (550 µl, 30.5 mmol) was added and the solution was left for a further 24 h at room temperature. The solution was evaporated under reduced pressure to remove solvent (ultimately at 0.4 mm Hg to remove hydrated methanal by-product). The residue was dissolved in water (50 ml) and extracted with diethyl ether (50 ml) followed by further washing of the aqueous layer with diethyl ether (2 x 10 ml). The aqueous layer was basified to pH 14 with 2M sodium hydroxide solution and then extracted with dichloromethane. The combined dichloromethane extracts were dried over anhydrous magnesium sulphate and evaporated under reduced pressure leaving an oil which was purified by flash chromatography [7 : 3 ethyl ethanoate : petroleum ether (40 - 60°C), saturated with gaseous ammonia] to yield (7c ⇌ 8c) (569 mg, 86%) as a colourless oil. ^1H and ^{13}C NMR spectra were broad at room temperature due to rapid interconversion of the two tautomers; data were therefore recorded at low temperature and are listed separately. The ratio (7c) : (8c) was found to be 42 : 58 at -55°C. Signals due to the exchangeable protons could not be assigned with confidence.

(7c): δ_H (300 MHz, $CDCl_3$, 218 K): 1.24 - 2.09 (series of m, 6H), 2.53 (m, 1H, α-C=O), 2.78 (m, 1H, α-C=O), 3.72, 3.90 (ABq, J = 12.7 Hz, 2H, benzyl CH_2), 4.23 (m, 1H, H-4), 6.25 (brd, J = 12.4 Hz, 1H, alkenyl), 6.40 (brdd, J = 12.4, 6.2 Hz, 1H, alkenyl), 7.18 - 7.74 (m, 5H, aryl).

δ_C (75 MHz, $CDCl_3$, 218 K): 22.7, 22.8, 31.3, 42.1 (4 x CH_2), 52.1 (CH_2, benzyl CH_2), 55.3 (CH, C-4), 127.2, 128.3, 128.5 (3 x aryl CH) 134.8 (=CH), 138.8 (aryl C), 149.9 (=CH), 203.3 (C=O).

(8c): δ_H (300 MHz, $CDCl_3$, 218 K): 1.24 - 2.09 (series of m, 8H), 3.80 (br, 1H, H-6), 4.12, 4.30 (ABq, J = 14.6 Hz, 2H, benzyl CH_2), 5.93 (s, 2H, alkenyl), 7.18 - 7.74 (m, 5 H, aryl).

δ_C (300 MHz, $CDCl_3$, 218 K): 21.4, 23.0, 28.7, 36.3 (4 x CH_2), 45.7 (CH_2, benzyl CH_2), 60.1 (CH, C-6), 94.7 (C, C-1), 126.4, 127.9, 128.1 (3 x aryl CH), 133.2 (=CH), 137.4 (=CH), 140.6 (aryl C).

(7c ⇌ 8c): ν_{max} (CH_2Cl_2): 3560w, 3020w, 2930m, 2850m, 2820brw, 1690w, 1655m, 1490w, 1450m, 1350brw, 1205w cm^{-1}. m/z (%): 229 (M^+, 5), 211 (40, 210 (10), 183 (29), 182 (10), 91 (100), 77 (6), 65 (17), 44 (16), 36 (18). $C_{15}H_{19}NO$ [M^+] requires 229.1467; found 229.147.

N-Methyl-9-azabicyclo[4.2.1]non-7-en-1-ol (8a)

In flame-dried apparatus, a solution of **(11e)** in THF (12 ml) was injected into a slurry of $LiAlH_4$ (123 mg, 3.24 mmol) under nitrogen at 0°C. The mixture was subsequently heated at reflux for 4 h. Quenching of excess hydride with saturated ether, drying (Na_2SO_4), filtration through celite and distillation of solvent afforded an oil **(11a)** (292 mg) which was deprotected without further purification. The oil was dissolved in dichloromethane (11 ml) and trifluoroethanoic acid (0.52 ml, 6.77 mmol) was added. After stirring for 2 h, water (15 µl) was added, the mixture was stirred for a futher 10 minutes, and the solvent was removed under vacuum ensuring complete removal of methanal. The residue was dissolved in water (3 ml) and extracted with diethyl ether (2 x 4 ml) to remove benzyl alcohol. The pH of the aqueous layer was adjusted to pH 9 by additon of sodium hydroxide solution (2 M) and the product was extracted into dichloromethane (5 x 4 ml). Futher basification (pH 11) and extraction afforded a yellow solid (total 95 mg) after drying with $MgSO_4$ and evaporation of solvent. The crude product was recrystallised from petrol (b.p. 80 - 100°C) to afford **(8a)** (74 mg, 45% overall) as an off-white solid, m.p. 94 - 110°C. δ_H ($CDCl_3$; 298 K): 1.59 (m, 6H), 1.86 (m, 1H), 2.17 (m, 1H), 2.55 (s, 3H, CH_3), 3.87 (m, 1H, H-6), 5.90 (d, J = 7.8 Hz, 1H, alkenyl), 6.01 (dd, J = 7.8, 3.4 Hz, 1H, alkenyl). δ_C ($CDCl_3$; 298 K; the italicised signals were broadened at this temperature, presumably as a result of tautomerism involving a small concentration of the monocyclic form): 22.8 (CH_2), 23.3 (CH_2), *29.7* (CH_2), *31.0* (CH_2), *37.9* (CH_2), *62.4* (CH), *136.3* (CH). NMR spectra were also recorded at -50°C; the ^1H NMR spectrum was broad but the ^{13}C spectrum was sharp at this temperature and contained no significant signals in the regions expected for the minor tautomer **(7a)** (based on the signals observed for the N-benzyl analogue **(7c)** described above). δ_H ($CDCl_3$; 223 K): 1.45 - 2.18 (series of m, 8 H), 2.55 (s, 3 H), 3.78 (m, 1 H), 5.86 (br d, J ≈ 5.8 Hz), 5.98 (vbr d, J ≈ 5.8 Hz). δ_C ($CDCl_3$; 223 K): 22.5, 23.6, 28.3, 28.7, 35.6 (5 x CH_2), 62.9 (CH), 94.8 (C), 132.8, 137.4 (2 x =CH). ν_{max} (CH_2Cl_2): 3570w, 3055vbrs, 2940s, 1705m, 1645s, 1610s, 1400m, 1360w, 1305m, 1215w, 1135m, 1090m, 1055m, 1020m, 910m. m/z: 153 (M^+, 18), 125 (11), 110 (100), 97 (38), 96 (39), 70 (17), 68 (14). $C_9H_{15}NO$ [M^+] requires 153.1154; found 153.1156.

1-Methoxyethoxymethoxy-N-benzyloxycarbonyl-9-azabicyclo[4.2.1]nonane (15)

N-Butyllithium (0.58 ml, 2.5 M in hexanes) was injected into a stirred solution of **(4e)**[5] (364 mg, 1.32 mmol) in THF (13 ml) at 0°C. After 15 min, MEM-Cl (0.21 ml, 1.83 mmol) was added and the solution heated under reflux for 3 h. The bulk of the solvent was distilled in vacuo and the residual oil dissolved in dichloromethane (22 ml) and washed with water (2 x 10 ml). The organic layer was separated, dried with anhydrous $MgSO_4$, filtered and the solvent distilled. The crude product was purified by flash column chromatography (2 : 3 diethyl ether : petroleum ether (b.p. 40 - 60°C)) to afford **(15)** (336 mg, 70%) as a pale yellow oil. δ_H (300 MHz, $CDCl_3$; broadening and/or signal overlap due to slow N-CO rotation is indicated using italics as for compound **(11e)** above): *1.24 - 2.63 (series of m, 12H)*, 3.33 (s, 3H), 3.36 (s, 3H), *3.51 (m, 2H)*, 3.68 (m, 2H), 3.81 (m, 2H), 4.33 (m, 1H, H-6), *4.58, 4.77, 4.91 (series of m, 2H, O-CH_2-O (including H-6))*, *5.15 (m, 2H, CH_2Ph)*, *7.32 (m, 5H)*. δ_C (75 MHz, $CDCl_3$): *22.9 (CH_2)*, 23.6 (CH_2), 27.1, 27.7 (CH_2), 33.3, 35.0 (CH_2), 36.0, 36.6 (CH_2), 37.4, 38.4 (CH_2), 56.2, 57.0 (CH), *58.8 (CH_3)*, 66.2, 66.6 (CH_2), 66.7, 67.4 (CH_2), *71.7 (CH_2)*, 90.0 (CH), 95.6, 96.3 (C), *127.8, (CH)*, *127.9 (CH)*, *128.3 (CH)*, *136.8 (C)*, 153.6, 154.9 (C=O). ν_{max}(CH_2Cl_2): 2930m, 2895w, 1695s, 1500w, 1450w, 1395m, 1355w, 1335w, 1315w, 1275brw, 1215w, 1160w, 1115m, 1095m, 1030s, 995w, 955w, 935w, 910w, 850w. m/z: 363 (M^+, 2), 274 (14), 258 (25), 214 (10), 168 (18), 152 (39), 140 (11), 124 (10), 91 (100). $C_{20}H_{29}NO_5$ [M^+] requires 363.2050; found 363.2049.

N-Methyl-9-azabicyclo[4.2.1]nonan-1-ol (5a)

The protected carbamate **(15)** (290 mg; 1.20 mmol) was reduced with hydride and deprotected with trifluoroethanoic acid using identical procedures to those described for the preparation of **(8a)**. The product **(5a)** was isolated as an oil (21 mg, 17%).

An improved route to **(5a)** from **(9a)** is described below.

4-(Benzylamino)cyclooctanone ethylene acetal (16)

Ethane-1,2-diol (149 µl, 2.68 mmol) was added to a solution of **(4d)**[5] (600 mg, 2.44 mmol) in benzene (20 ml) contained in a 50 ml round-bottomed flask fitted with a Dean and Stark water separator and a reflux condenser. A few crystals of *p*-toluenesulphonic acid and a stirring bead were added, and the solution was heated to reflux and stirred vigorously for 3 h. The solution was allowed to cool to room temperature and the solvent was removed at reduced pressure to leave an oil which was dissolved in dichloromethane (20 ml). The resulting solution was washed with 5% sodium bicarbonate solution (5 ml), water (2 x 5 ml), and dried over anhydrous potassium carbonate. The solvent was evaporated under reduced pressure leaving an oil which was purified by flash chromatography (diethyl ether) to yield **(16)** (416 mg, 59%) as a white foam. δ_H (300 MHz, $CDCl_3$): 1.57 - 2.18 (series of m, 12H), 3.87 - 3.94 (m, 4H, acetal O-CH_2CH_2-O), 4.18 (M, 1H, H-4), 6 20 (brd, J = 7.4 Hz, exch -NH), 7.37 - 7.51 (m, 3H, aryl), 7.72 - 7.75 (m, 2H, aryl). δ_C (75 MHz, $CDCl_3$): 21.8, 23.3, 28.2, 30.4, 32.3, 33.5 (6 x CH_2), 50.0 (CH, C-4), 64.2 & 64.4 (2 x CH_2, acetal O-CH_2), 111.6 (C, acetal C), 126.8, 128.5, 131.2 (3 x aryl CH), 134.9 (aryl C), 166.4 (C=O). ν_{max} (CH_2Cl_2): 3430m, 3370brw, 2940m, 2880m, 1655s, 1600w, 1580m, 1510s, 1485m, 1315m, 1115m, 1090m cm^{-1}. m/z (%): 290 (MH^+, 100), 260 (5), 246 (42), 228 (7), 168 (5), 148 (2), 139 (2), 124 (9), 105 (23), 99 (7), 86 (6), 77 (2), 55 (2). $C_{17}H_{24}NO_3$ [MH^+] requires 290.1756; found 290.176.

4-(Benzylamino)cyclooctanone ethylene acetal (17)

A solution of **(16)** (340 mg, 1.17 mmol) in dry tetrahydrofuran (12 ml) was added dropwise to a stirred slurry of lithium tetrahydroaluminate (133 mg, 3.51 mmol) in dry tetrahydrofuran (6 ml). After 24 h at reflux, excess hydride was decomposed by careful addition of water. The inorganic solids were removed by filtration and washed with warm ethyl ethanoate. The combined organic solutions were evaporated under reduced pressure to yield **(17)** (320 mg, 99%) as a colourless oil. δ_H (300 MHz, $CDCl_3$): 1.36 - 2.02 (series of m, 12H and exch -NH, 1H), 2.74 (m, 1H, H-4), 3.75 (s, 2H, benzyl CH_2), 3.89 (s, 4H, O-CH_2CH_2-O), 7.18 - 7.37 (m, 5H, aryl). δ_C (75 MHz, $CDCl_3$): 22.2, 24.1, 28.3, 30.6, 31.6, 34.1 (6 x CH_2), 51.5 (CH_2, benzyl CH_2), 57.0 (CH, C-4), 64.1 & 64.3 (2 x CH_2, acetal O-CH_2), 112.1 (C, acetal C), 126.7, 128.0, 128.3 (3 x aryl CH), 140.7 (aryl C). ν_{max} (CH_2Cl_2): 3020w, 2930s, 2880m, 2820brm, 1465m, 1450m, 1360m, 1215w, 1150m, 1110m, 1090m, 1040m, 945m cm^{-1}. m/z (%): 276 (MH^+, 100), 232, (3), 214 (6), 184 (2), 169 (2), 159 (2), 146 (6), 129 (26), 108 (3), 99 (3), 91 (14), 55 (2). $C_{17}H_{26}NO_2$ [MH^+] requires 276.1964; found 276.196.

4-(Benzylamino)cyclooctanone) ⇌ N-benzyl-9-azabicyclo[4.2.1]nonan-1-ol (4c ⇌ 5c)

A solution of **(17)** (175 mg, 0.64 mmol) in aqueous ethanoic acid (4 ml of 2 : 1 glacial ethanoic acid : water) was heated at 90°C for 2h. The solution was allowed to cool, washed with diethyl ether (2 x 1 ml), carefully neutralised and basified to pH 14 with 2 M sodium hydroxide solution, and then extracted with dichloromethane (5 x 10 ml). The combined organic solutions were washed with water (2 x 10 ml), dried over anhydrous magnesium sulphate, and evaporated under reduced pressure to yield **(4c ⇌ 5c)** 140 mg, 95%) as a pale yellow oil. Low-temperature NMR spectroscopy allowed the identification of signals due to both tautomers; the ratio of **(4c)** : **(5c)** was 66 : 34 at -50°C. The exchangeable protons could not be assigned with confidence.

(4c): δ_H (300 MHz, $CDCl_3$, 223 K): 1.23 - 2.48 (series of m, 12H), 2.73 (brm, 1H, H-4), 3.74, 3.78 (ABq, J = 13.4 Hz, 2H, benzyl CH_2), 7.28 - 7.35 (m, 5H, aryl).

δ_C (75 MHz, $CDCl_3$, 223 K): 22.7, 28.1, 28.5, 30.1, 40.0, 40.7 (6 x CH_2), 51.0 (CH_2, benzyl CH_2), 56.1 (CH, C-4), 126.9, 128.0, 128.4 (3 x aryl CH), 139.8 (aryl C), 218.6 (C=O).

(5c): δ_H (300 MHz, $CDCl_3$, 223 K): 1.23 - 2.48 (series of m, 12H), 3.31 (brm, 1H, H-6), 3.89, 4.17 (ABq, J = 14.2 Hz, 2H, benzyl CH_2), 7.28 - 7.35 (m, 5H, aryl).

δ_C (75 MHz, $CDCl_3$, 223 K): 22.6, 23.5, 26.0, 32.0, 38.2, 40.7 (6 x CH_2), 45.7 (CH_2, benzyl CH_2), 54.2 (CH, C-6), 92.2 (C, C-1), 126.4, 127.8, 128.0 (3 x aryl CH), 140.8 (aryl C).

(4c ⇌ 5c): ν_{max} (CH_2Cl_2): 3570w, 3020w, 2930s, 2860m, 2820brm, 1690m, 1490w, 1465m, 1450m, 1350m, 1205w, 1110m, 1070m, 1025w cm^{-1}. m/z (%): 232 (7), 231 (M^+, 8), 202 (9), 188 (3), 174 (13), 159

(8), 146 (100), 132 (13), 118 (3), 106 (6), 91 (92) 84 (6), 77 (3), 65 (11), 55 (5). $C_{15}H_{21}NO$ [M^+] requires 231.1623; found 231.162.

Cis-4-(Methylamino)cyclooct-2-enol (6a)

The protected amino-alcohol (**6e**) (308 mg; 1.12 mmol) was added to a slurry of lithium tetrahydroaluminate (83 mg; 2.18 mmol) in dry THF at 0°C following thorough evacuation/purging of the reaction flask with nitrogen. The mixture was heated at reflux for 2.5 h and excess hydride was then destroyed using water-saturated diethyl ether. Filtration through celite and distillation of solvent afforded a white solid which was repeatedly triturated with a 1:1 mixture of diethyl ether / petrol (b.p. 40 - 60°C) to remove benzyl alcohol. The product (**6a**) was obtained as a white solid, (145 mg; 85%), m.p. 124 - 127°C showing identical spectroscopic properties to a sample prepared previously by a different route (lit.[5] m.p. 125 - 126°C).

N-methyl-9-azabicyclo[4.2.1]non-7-en-1-ol (8a)

The allylic alcohol (**6a**) (297 mg; 1.92 mmol) was treated with Jones reagent using an identical procedure to that described below for conversion of (**9a**) into (**5a**). Extraction into trichloromethane using a Soxhlet apparatus gave a yellow solid which was recrystallised from petrol (b.p. 60 - 80°C) / toluene to afford (**8a**) (176 mg; 63%) as a slightly yellow solid which was identified by comparison of spectra with those of the sample obtained earlier from (**9a**).

Cis-4-(Methylamino)cyclooctanol (9a)

A 100 ml 2-necked flame dried flask was charged with lithium tetrahydroaluminate and stirred with dry THF (2 ml). The system was alternately charged and evacuated with nitrogen and cooled to 0°C. A solution of (**9e**) in THF (24 ml) was injected. After complete addition, the mixture was refluxed for 1 h. Excess hydride was destroyed by dropwise addition of water-saturated diethyl ether, the solution dried (Na_2SO_4) and filtered through celite. The solvent was distilled in vacuo and the residual oil purified by flash column chromatograpy (4 : 1 CH_2Cl_2 : MeOH (saturated with ammonia)) to afford product (**9a**) (709 mg, 92%) as a colourless oil which was identical to a sample prepared previously by hydrogenation of (**6a**).[5]

N-Methyl-9-azabicyclo[4.2.1]nonan-1-ol (5a)

To a stirred solution of (**9a**) (279 mg, 1.8 mmol) in propanone (12 ml) was added Jones reagent[19] (1 ml) dropwise. After 25 minutes, isopropanol was added until a permanent green colouration remained and the solution was then filtered through celite. The inorganic residues were washed further with methanol (2 x 10 ml). The solvent was distilled in vacuo and the residue dissolved in water (7 ml) and basified to pH 12 using sodium hydroxide solution (2 M). The water was removed in vacuo and the inorganic solids extracted with trichloromethane (80 ml), using a Soxhlet apparatus, for 18 hours. Distillation of solvent afforded (**4a**) as a waxy yellow solid (189 mg, 69%). δ_H (300 MHz, $CDCl_3$, 298 K): 1.46 (m, 1H), 1.61 (m, 6H), 1.86 (m, 1H), 2.11 (m, 5H), 2.45 (s, 3H), 3.17 (m, 1H), 4.30 (brs, 1H exch). δ_C (300 MHz, $CDCl_3$, 298 K; broad signals are italicised): 23.6 (CH_2), *24.0 (CH_2)*, 26.8 (CH_2), *30.1 (CH_2)*, 32.0 (CH_2), *38.4 (CH_2)*, 39.8 (CH_2), 58.7 (CH). δ_H (243 K, $CDCl_3$): 1.49 (m, 2H), 1.63 (m, 5H), 1.94 (m, 4H), 2.20 (m, 2H), 2.49 (s, 3H), 3.34 (m, 1H), 6.18 (vbrs, 1H). δ_C (243 K, $CDCl_3$): 22.4, 23.4, 25.9 (3 x CH_2), 28.8 (CH_3), 31.9, 37.4, 39.4 (3 x CH_2), 58.1 (CH), 92.0 (C). ν_{max} 3180vbr, 2940s, 2870m, 2800w, 1695m, 1470w, 1450w, 1365w, 1340w, 1230w, 1210w, 1180w, 1155w, 1130w, 1080w, 1055w, 1045w, 1005w, 975w, 940w, 915w, 865w, 835w, 815w. m/z 155 (M^+, 8), 149 (13), 141 (6), 137 (3), 126 (17), 112 (20), 108 (13), 98 (32), 94 (18), 70 (100). $C_9H_{17}NO$ requires: 155.1310; found 155.1311.

9,10-Dioxabicyclo[4.2.2]deca-7-ene (18)[8]

Haematoporphyrin (1.0 g) was added to a solution of cycloocta-1,3-diene (50 ml, 0.403 mol) in propanone (1.75 l) and oxygen bubbled vigorously through the stirred solution. The solution was exposed to

light from a 125 W sodium street lamp for 10 days during which time evaporation was minimised with the aid of a dry ice condenser attached to the apparatus. The solvent was removed under reduced pressure giving an oil which was purified by flash chromatography (4:1 petroleum ether (b.p. 40 - 60°C): diethyl ether) to yield **(18)** (14.5 g, 26%) as a pale yellow oil. δ_H (90 MHz, $CDCl_3$): 1.35 - 2.30 (series of m, 8H), 4.65 (brm, 2H, bridgehead H), 6.10 (dd, J = 3.6, 2.0 Hz, 2H, alkenyl).

9,10-Dioxabicyclo[4.2.2]decane (19)[8]

A solution of **(18)** (2.35 g, 16.76 mmol) in dry dichloromethane (45 ml) was added to a slurry of potassium azodicarboxylate (16.26 g, 83.78 mmol) in dry dichloromethane (110 ml) which had been cooled to 0°C. A solution of glacial ethanoic acid (12.48 ml, 0.218 mol) in dry dichloromethane (45 ml) was added to the stirred solution, dropwise, over a period of 30 min, and the mixture was stirred at room temperature for 24 h. Water (60 ml) was added to the mixture and the organic layer was washed with 5% sodium bicarbonate solution (3 x 50 ml) and water (50 ml). The organic layer was separated, dried over anhydrous magnesium sulphate, and the solvent evaporated at reduced pressure to leave an oil which was purified by flash chromatography [4 : 1 petroleum ether (b.p. 40 - 60°C) : diethyl ether] to yield **(19)** (2.10 g, 88%) as a pale yellow oil. δ_H (90 MHz, $CDCl_3$) : 1.40 - 2.35 (series of m, 12H), 4.50 (brm, 2H, bridgehead H).

4-Hydroxycyclooctanone ⇌ 9-oxabicyclo[4.2.1]nonan-1-ol (20 ⇌ 21)

The method of Kayama et al.[8] was used. A solution of triethylamine (1.37 ml, 9.84 mmol) in dichloromethane (24 ml) was added slowly to a solution of **(19)** (700 mg, 4.92 mmol) in dichloromethane (24 ml) which had been cooled to 0°C. After addition, the solution was heated under reflux for 24 h. The solvent was evaporated under reduced pressure leaving an oil which was purified by flash chromatography (95 : 5 dichloromethane : methanol) to yield **(20 ⇌ 21)** (560 mg, 80%) as a yellow oil. The ratio of **(20)** : **(21)** was measured by direct integration of NMR signals and was found to be 31 : 69 at ambient temperature.

(20): δ_H (300 MHz, $CDCl_3$): 1.29 - 2.57 (series of m, 12H), 3.20 (brs, exch -OH), 3.83 (dddd, J = 8.4, ~4.8, ~4.8, ~4.5 Hz, 1H, α-OH). δ_C (75 MHz, $CDCl_3$): 21.9, 28.7, 30.5, 33.6, 39.5, 40.2 (6 x CH_2), 70.7 (HC-OH), 217.0 (C=O).

(21): δ_H (300 MHz, $CDCl_3$): 1.29 - 2.57 (series of m, 12H), 3.20 (brs, exch - OH), 4.52 (dddd, J = 8.4, 6.9, ~2.0, ~2.0 Hz, 1H, H-6). δ_C (75 MHz, $CDCl_3$): 23.3, 23.8, 31.2, 36.4, 37.1, 41.7 (6 x CH_2), 76.0 (CH, C-6), 108.3 (C, C-1).

(20 ⇌ 21) : ν_{max} (CH_2Cl_2): 3580m, 3400brm, 3050w. 2940s, 2860m, 1695s, 1470m, 1450m, 1355m, 1330m, 1220m, 1130m, 1080m, 995m, 930m cm^{-1}. m/z (%): 142 (M^+, 2), 124 (7), 113 (25), 96 (18), 85 (47), 83 (68), 67 (41), 57 (57), 55 (100), 43 (77), 41 (93).

4-Hydroxycyclooct-2-enone ⇌ 9-oxabicyclo[4.2.1]non-7-en-1-ol (22 ⇌ 23)

The method of Kayama et al.[8] was used. A solution of triethylamine (29 ml, 209 mmol) in dichloromethane (200 ml) was added slowly to a solution of **(18)** (14.5 g, 104 mmol) in dichloromethane (500 ml) which had been cooled to 0°C. After addition, the solution was refluxed for 24 h. The solvent was evaporated at reduced pressure leaving an oil which was purified by flash chromatography (95 : 5 dichloromethane : methanol) to yield **(22 ⇌ 23)** (11.3 g, 78%), as a white solid, m.p. 92 - 93°C (lit.[9] m.p. 92 - 93°C) [from petroleum ether (b.p. 80 - 100°C)]. The ratio of **(22)** : **(23)** was found to be 5 : 95.

(22): δ_H (300 MHz, $CDCl_3$): 1.43 - 1.70 (m, 6H), 2.53 (vbr dd, J = 13.2, 6.3 Hz, 1 H), 2.72 (ddd, J = 13.2, 11.8, 6.9 Hz, 1H), 3.97 (brs, exch -OH), 5.20 (vbr m, 1 H, H-4), 6.03 (ddd, J = 12.7, 1.9, 0.8 Hz, 1H, alkenyl), 6.38 (dd, J = 12.7, 5.5 Hz, 1H, alkenyl). δ_C (75 MHz, $CDCl_3$): 22.2, 23.0, 33.6, 42.1 (4 x CH_2), 69.2 (C-4), 131.5 (=CH), 148.8 (=CH), 202.0 (C=O).

(23): δ_H (300 MHz, $CDCl_3$): 1.43 - 1.70 (m, 5H), 1.85 - 2.02 (m, 3H), 4.26 (brs, exch -OH), 4.96 (dddd, J = 6.3, 1.9, 1.9, 1.2 Hz, 1H, H-6), 5.78 (dd, J = 5.8, 1.2 Hz, 1H, alkenyl), 5.96 (dd, J = 5.8, 1.9 Hz, 1H, alkenyl).

(22 ⇌ 23): ν_{max} (CH_2Cl_2): 3560m, 3360brw, 2930s, 2860m, 1655w, 1440w, 1365m, 1350m, 1300w,

1205m, 1130m, 1110m, 1090m, 1070s, 1035m, 1000m, cm^{-1}. m/z (%): 140 (M^+, 2), 111 (11), 97 (100), 95 (18), 84 (37), 80 (55), 67 (27), 55 (66), 53 (21), 43 (26), 41 (45), 39 (50).

4-Tosyloxycyclooctanone (24)

Pyridine (1.068 ml, 13.2 mmol) was added to a solution of **(20 ⇌ 21)** (941 mg, 6.6 mmol) in trichloromethane (8 ml), which had been passed through an alumina column immediately prior to use. The solution was cooled in an ice-bath at 0°C and *p*-toluenesulphonyl chloride (1.881 g, 9.90 mmol) was then added in small portions with constant stirring. After 3.5 days at room temperature, trichloromethane (30 ml) and water (6 ml) were added and the organic layer was washed successively with 2 M HCl, 5% sodium bicarbonate solution, and water, and then dried over anhydrous magnesium sulphate. The tosylate was purified by flash chromatography (using dichloromethane to remove excess *p*-toluenesulphonyl chloride, then 98 : 2 dichloromethane : methanol) to yield **(24)** (1.72 g, 88%) as a white solid, m.p. 84.5 - 86°C. δ_H (300 MHz, $CDCl_3$): 1.41 - 1.54 (m, 2H), 1.61 - 1.92 (m, 4H), 2.14 - 2.31 (m, 3H), 2.34 - 2.57 [m, 6H (incl. 2.44, s, 3H, tosyl methyl)], 4.61 (m, 1H, H-4), 7.34 (d, J = 8.3 Hz, 2H, aryl), 7.77 d, J = 8.3 Hz, 2H, aryl). δ_C (75 MHz, $CDCl_3$): 21.6 (CH_3, tosyl methyl), 21.7, 28.1, 28.6, 30.8, 38.8, 40.1 (6 x CH_2), 81.9 (C-4), 127.5 (CH, aryl C-2/C-6), 129.8 (CH, aryl C-3/C-5) 134.3 (C, aryl C-4), 144.7 (C, aryl C-1), 215.4 (C=O). ν_{max} (CH_2Cl_2): 3060w, 2950s, 2870m, 1700vs, 1600m, 1495w, 1470m, 1450m, 1410m, 1355s, 1230m, 1190s, 1175s, 1120m, 1100s, 910s, 820s, 655s, cm^{-1}. m/z (%): 296 (M^+, 5), 172 (12), 155 (20), 141 (19), 124 (57), 105 (20), 96 (27), 95 (40), 91 (64), 75 (69), 67 (59), 54 (53), 32 (43), 28 (100). $C_{15}H_{20}SO_4$ [M^+] requires 296.1082; found 296.108.

4-Azidocyclooctanone (25)

Sodium azide (168 mg, 2.54 mmol) was added in small portions at room temperature to a stirred solution of **(24)** (630 mg, 2.12 mmol) in dimethylformamide (15 ml), and the solution was warmed to 40°C for 10 h. The solvent was evaporated under reduced pressure, the residue was dissolved in dichloromethane (50 ml) and the solution was washed repeatedly with water. The solution was dried over anhydrous magnesium sulphate and evaporated under reduced pressure giving an oil which was purified by flash chromatography [3 : 2 petroleum ether (b.p. 40 - 60°C) : diethyl ether] to yield **(25)** (233 mg, 65%) as a yellow oil. δ_H (300 MHz, $CDCl_3$): 141 - 1.97 (series of m, 6H), 2.05 - 2.26 (m, 2H), 2.30 - 2.58 (m, 4H), 3.63 (m, 1H, H-4). δ_C (75 MHz, $CDCl_3$): 22.5, 27.7, 28.3, 29.8, 39.9, 40.2 (6 x CH_2), 61.2 (C-4), 215.8 (C=O). ν_{max} (CH_2Cl_2): 2940s, 2860m, 2480w, 2090vs, 1695vs, 1465m, 1450m, 1410w, 1360m, 1340m, 1320m, 1240m, 1200m, 1150w, 1115w cm^{-1}. m/z (%): 185 (MH^+, 14), 168 (11), 157 (13), 141 (85), 140 (100), 122 (27), 110 (21), 97 (10), 84 (18), 69 (11), 55 (16). CI: $C_8H_{17}N_4O$ [MNH_4^+] requires 185.1402; found 185.140.

4-Aminocyclooctanone ⇌ 9-azabicyclo[4.2.1]nonan-1-ol (4b ⇌ 5b)

a) From (25): A solution of **(25)** (160 mg, 0.94 mmol) in dry methanol (10 ml) was hydrogenated at 1 atm pressure in the presence of 10% palladium on charcoal. After 5 h, the solution was filtered through celite and then through a Millipore 0.2μ Millex-FG disposable filter unit giving a clear solution which was evaporated under reduced pressure. The residue was dissolved in 1 M HCl (4 ml) and washed with diethyl ether (3 x 4 ml). The aqueous layer was basified to pH 14 with concentrated sodium hydroxide solution, extracted with dichloromethane (5 x 5 ml) and the combined organic solutions were dried (K_2CO_3) and evaporated under reduced pressure to yield **(4b ⇌ 5b)** (106 mg, 80%) as a colourless oily solid. NMR spectra were broad and unhelpful at ambient temperature but signals due to both tautomers were resolved at -30°C (although the weak signals due to the minor tautomer were still broad); the ratio of **(4b)** : **(5b)** estimated from the ^1H NMR spectrum was 11 : 89 at this temperature. The positions of the signals due to the amino- and hydroxy- protons varied considerably with concentration and temperature.

(4b): δ_H (300 MHz, $CDCl_3$, 243 K): 1.48 - 2.47 (series of brm, 12H) 3.04 (br, 1H, H-4). δ_C (75 MHz, $CDCl_3$, 243 K): 21.9, 28.7, 30.7, 33.5, 40.1, 40.5 (6 x CH_2), 50.7 (C-4), 218.8 (C=O).

(**5b**): δ_H (300 MHz, $CDCl_3$, 243 K): 1.48 - 2.47 (series of brm, 12H), 3.59 (brm, 1H, H-6). δ_C (75 MHz, $CDCl_3$, 243 K): 22.6, 23.9, 31.1, 36.4, 37.8, 43.1 (6 x CH_2), 52.4 (CH, C-6), 93.1 (C, C-1).

(**4b** ⇌ **5b**): ν_{max} (CH_2Cl_2): 3580m, 3160brm, 3040m, 2930s, 2860m, 1695s, 1465m, 1410m, 1330m, 1205m, 1165w, 1100m, 1085m, 985m cm^{-1}. I.R. measurements were made at different temperatures and it was found that the intensity of the carbonyl signal at 1695 cm^{-1} was gradually reduced as the temperature of the solution in CH_2Cl_2 was lowered. $^m/z$ (%): 141 (M^+, 27), 113 (22), 112 (22), 99 (17), 98 (53), 85 (41), 84 (30), 57 (30), 56 (100). $C_8H_{15}NO$ [M^+] requires 141.1154; found 141.115.

b) From (4e) A solution of (**4e**) (330 mg, 0.8 mmol) in dry ethanol (18 ml) was hydrogenolysed at 1 atmosphere pressure in the presence of a catalytic quantity of 5% palladium on charcoal. After 2 h the solution was filtered through a Millipore 0.2 μl Millex-FG disposable filter. Distillation of solvent under reduced pressure left (**4b**) ⇌ (**5b**) as an off-white solid (165 mg, 98%).

4-Tosyloxycyclooct-2-enone (26)

Pyridine (1.973 ml, 24.39 mmol) was added to a solution of (**22** ⇌ **23**) (1.14 g, 8.13 mmol) in trichloromethane (12 ml) (which had been passed through an alumina column immediately prior to use), and cooled in an ice-bath at 0°C. This was followed by the addition of *p*-toluenesulphonyl chloride (2.317 g, 12.20 mmol) in small portions with constant stirring. After 16 days at room temperature, the solution was evaporated under reduced pressure giving a dark brown oil which was flash chromatographed to yield (**26**) (382 mg, 14%) and 4-chlorocyclooct-2-enone (**27**) (228 mg, 18%) as colourless oils.

(**26**): δ_H (300 MHz, $CDCl_3$): 1.39 - 2.06 (series of m, 6H), 2.37 - 2.65 [m, 5H incl 2.44 (s, 3 H, tosyl methyl)], 5.78 (m, 1H, H-4), 5.95 (ddd, J = 13.0, 1.9, 0.8 Hz, 1H, alkenyl), 6.12 (dd, J = 13.0, 5.3 Hz, 1H, alkenyl), 7.38 (d, J = 8.2 Hz, 2H, aryl), 7.81 (d, J = 8.2 Hz, 2H, aryl). δ_C (75 MHz, $CDCl_3$): 21.6 (CH_3, tosyl methyl), 21.8, 22.4, 30.6, 42.0 (4 x CH_2), 79.3 (C-4), 127.7 (CH, aryl C-2/C-6), 130.0 (=CH), 132.6 (CH, aryl C-3/C-5), 133.7 (C, aryl C-4), 139.5 (=CH), 145.2 (C, aryl C-1), 202.0 (C=O). ν_{max} (CH_2Cl_2): 3060w, 2940m, 2860w, 1665s, 1595m, 1490w, 1450m, 1390m, 1360s, 1305m, 1210m, 1190s, 1175vs, 1120m, 1095m, 950s, 850m, 815m cm^{-1}. $^m/z$ (%): No M^+ observed at low resolution, 212 (97), 155 (22), 139 (20), 122 (26), 108 (43), 107 (56), 94 (32), 91 (100), 79 (53), 75 (36), 65 (70), 39 (60). $C_{15}H_{18}SO_4$ [M^+] requires 294.0926; found 294.093.

4-Chlorocyclooct-2-enone (27): δ_H (300 MHz, $CDCl_3$): 1.65 - 2.03 (series of m, 5H), 2.16 (m, 1H), 2.48 - 2.70 (m, 2H), 5.08 (m, 1H, H-4), 5.92 (ddd, J = 13.0, 1.9, 0.8 Hz, 1H, alkenyl), 6.28 (dd, J = 13.0, 5.4 Hz, 1H, alkenyl). δ_C (75 MHz, $CDCl_3$): 21.7, 24.3, 33.2, 42.7 (4 x CH_2), 57.6 (C-4), 130.1 (=CH), 140.3 (=CH), 204.7 (C=O). ν_{max} (CH_2Cl_2): 2940m, 2860w, 1655s, 1450m, 1385m, 1320w, 1205w, 1170w, 1130w cm^{-1}. $^m/z$ (%): 160 (^{37}Cl M^+, 3), 158 (^{35}Cl M^+, 10), 123 (25), 122 (18), 115 (42), 95 (48), 81 (100), 80 (86), 79 (70), 67 (46), 55 (48), 53 (58). $C_8H_{11}O^{35}Cl$ [M^+] requires 158.0498; found 158.050.

4-Azidocyclooct-2-enone (28)

Sodium azide (199 mg, 3.00 mmol) was added in small portions at room temperature to a stirred solution of (**25**) (175 mg, 0.60 mmol) in dimethylformamide (2 ml). The solution was stirred at room temperature for 17 h, filtered, and evaporated under reduced pressure to leave a residue which was dissolved in dichloromethane (20 ml), washed with water (2 ml), and dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure giving an oil which, after purification by flash chromatography (3 : 2 petroleum ether : diethyl ether) yielded (**28**) (80 mg, 81%) as a pale yellow oil. δ_H (300 MHz, $CDCl_3$): 1.50 - 2.09 (series of m, 6H), 2.55 (m, 1H), 2.71 (ddd, J = 14.2, 11.0, 6.4 Hz, 1H), 4.80 (m, 1H, H-4), 6.08 - 6.19 (m, 2H, H-2/H-3). δ_C (75 MHz, $CDCl_3$): 22.5, 22.7, 30.1, 42.3 (4 x CH_2), 60.2 (C-4), 133.2 (CH, C-2), 140 (CH, C-3), 202.9 (C=O). ν_{max} (CH_2Cl_2): 2940m, 2860m, 2100vs, 1670vs, 1450m, 1385m, 1340m, 1240m, 1215m, 1170w, 1120w, 1090 cm^{-1}. $^m/z$ (%): No M^+ observed at low resolution, 149 (12), 139 (19), 123 (37), 122 (100), 105 (20), 95 (79), 94 (72), 93 (44), 91 (78), 79 (54), 77 (49), 67 (48), 65 (40), 55 (49), 41 (75). CI: $C_8H_{15}N_4O$ [MNH_4^+] requires 183.1246; found 183.125.

1-(β-Hydroxyethoxy)-9-oxabicyclo[4.2.1]non-7-ene (30)

Ethane-1,2-diol (388 µl, 7.00 mmol) was added to a solution of **(22 ⇌ 23)** (891 mg, 6.36 mmol) in benzene (20 ml) contained in a 50 ml round-bottomed flask fitted with a Dean and Stark water separator and a reflux condenser. A few crystals of *p*-toluenesulphonic acid and a stirring bead were added, the solution was heated to reflux and stirred for 1 h. When the solution had cooled to room temperature, the solvent was removed under reduced pressure producing an oil which was purified by flash chromatography (94 : 5 : 1 dichloromethane : methanol : triethylamine) and **(30)** (750 mg, 65%) was isolated as a colourless oil. δ_H (300 MHz, $CDCl_3$): 1.44 - 1.71 (m, 5H), 1.81 - 2.04 (m, 3H), 3.32 (brs, exch -OH), 3.50 - 3.75 (m, 4H, O-CH_2CH_2-O), 5.01 (dddd, J = 6.3, 1.9, 1.9, 1.5 Hz, 1H, H-6), 5.74 (dd, J = 5.9, 1.5 Hz, 1H, alkenyl), 6.05 (dd, J = 5.9, 1.9 Hz, 1H, alkenyl). δ_C (75 MHz, $CDCl_3$): 23.2, 23.8, 33.6, 39.1 (4 x CH_2), 62.1 (O-CH_2), 64.7 (O-CH_2), 81.5 (CH, C-6), 115.1 (C, C-1), 131.0 (=CH), 135.0 (=CH). ν_{max} (CH_2Cl_2): 3600w, 3420brw, 2940s, 2860m, 1590w, 1440w, 1345m, 1210w, 1155m, 1130m, 1085m, 1060s, 1040m, 1010m, 940m, 910s cm^{-1}. m/z (%): 185 (MH^+, 26), 167 (14), 155 (3), 141 (18), 140 (100), 124 (32), 123 (100), 95 (9), 91 (5), 85 (5), 65 (1), 53 (3). $C_{10}H_{16}O_3$ [M^+] requires 184.1099; found 184.110.

1-(β-Tosyloxyethoxy)-9-oxabicyclo[4.2.1]non-7-ene (31)

Pyridine (530 µl, 6.54 mmol) was added to a solution of **(30)** (602 mg, 3.27 mmol) in trichloromethane (6 ml) (which had been passed through an alimina column immediately prior to use), and cooled in an ice-bath at 0°C. *p*-Toluenesulphonyl chloride (933 mg, 4.91 mmol) was added in small portions with constant stirring. After 2 h at room temperature, the solvent was removed under reduced pressure and the resulting oil was purified by flash chromatography (dichloromethane to remove excess *p*-toluenesulphonyl chloride, then 98 : 2 dichloromethane : methanol) to yield **(31)** (740 mg, 67%) as a colourless oil. δ_H (300 MHz, $CDCl_3$): 1.41 - 2.04 (series of m, 8H), 2.44 (s, 3H, tosyl methyl), 3.53 - 3.73 (m, 2H, O-CH_2), 4.12 - 4.16 (m, 2H, O-CH_2), 4.94 (dddd, J = 6.2, 1.9, 1.9, 1.5 Hz, 1H, H-6), 5.64 (dd, J = 5.9, 1.5 Hz, 1H, alkenyl), 6.01 (dd, J = 5.9, 1.9 Hz, 1H, alkenyl), 7.33 (d, J = 8.2 Hz, 2H, aryl), 7.79 (d, J = 8.2 Hz, 2H, aryl). δ_C (75 MHz, $CDCl_3$): 21.6 (CH_3, tosyl methyl), 23.1, 23.7, 33.7, 38.8 (4 x CH_2), 60.1 (O-CH_2), 69.7 (O-CH_2), 81.7 (CH, C-6), 115.0 (C, C-1), 127.9 (CH, aryl C-2/C-6), 129.7 (CH aryl C-3/C-5), 130.8 (=CH), 133.1 (C, aryl C-4), 135.3 (=CH), 144.6 (C, aryl C-1). ν_{max} (CH_2Cl_2): 3060w, 2940m, 2860m, 1600m, 1500w, 1455m, 1360s, 1300w, 1215m, 1195vs, 1180vs, 1160m, 1130m, 1100m, 1080m, 1060m, 1025m, 1010m, 930s, 820s cm^{-1}. m/z/ (%): No observed M^+ at low resolution, 217 (3), 199 (74), 167 (20), 155 (29), 139 (6), 123 (89), 91 (100), 79 (55), 65 (49), 55 (61), 41 (35). $C_{16}H_{26}NSO_5$ [MNH_4^+] requires 356.1532; found 356.153.

Tetracyclic triazoline (32)

Sodium azide (119 mg, 1.82 mmol) was added in small portions at room temperature to a solution of **(31)** (440 mg, 1.30 mmol) in dimethyl sulphoxide (4 ml). After stirring at room temperature for 1 day, the solution was evaporated under reduced pressure, the residue was dissolved in dichloromethane (20 ml), and the solution was dried over anhydrous magnesium sulphate. The solvent was evaporated under reduced pressure giving an oil which was purified by flash chromatography (diethyl ether) to yield **(32)** (238 mg, 87%) as white crystals, m.p. 116 - 117°C. δ_H (300 MHz, $CDCl_3$): 1.26 - 1.41 (m, 1H), 1.51 - 2.00 (series of m, 6H), 2.07 - 2.19 (m, 1H), 3.49 - 3.77 (complex m, 4H), 4.13 (brdd, J = 13.6, 2.4 Hz, 1H), 4.46 (brd, J = 7.2 Hz, 1H), 4.85 (dd, J = 9.7, 1.6 Hz, 1H). δ_C (75 MHz, $CDCl_3$): 22.4, 23.6, 34.7, 41.5, 44.5 (5 x CH_2), 57.8 (CH), 58.5 (CH_2), 80.3 (CH), 90.0 (CH), 108.0 (C). ν_{max} (CH_2Cl_2): 3050w, 2940s, 2860m, 1590brm, 1490m, 1455m, 1350w, 1320m, 1245m, 1210m, 1165m, 1155m, 1120m, 1095s, 1060m, 1040m, 1000m, 965s, 955m cm^{-1}. Found: C, 57.17; H, 7.41; N, 20.30%; $C_{10}H_{15}N_3O_2$ requires: C, 57.40; H, 7.22; N, 20.08%.

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