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Synthetic Approaches to Homotropanes and Homotrop-7-enes using Intramolecular Displacement and Amidomercuration Strategies

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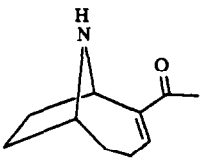
Abstract: *1,4-Functionalisation of cycloocta-1,3-diene using a nitroso-cycloaddition strategy is followed by intramolecular displacement by nitrogen to yield the 9-methyl-9-azabicyclo[4.2.1]nonane (homotropane) and -non-7-ene (homotrop-7-ene) systems and N-benzyl derivatives. The approach can be adapted to allow access to 1-methylhomotropanes and -7-enes via transannular amidomercuration/de-mercuration.*

Introduction

Recent interest in the homotropane (9-azabicyclo[4.2.1]nonane) ring system has been largely confined to the algal metabolite anatoxin-*a* (**1**) and many syntheses of this compound have been reported.[1] General routes to other derivatives of this ring system are rare although early work by Cope led to the formation of (**2**) by ring expansion of tropinone[2a] and selected examples have been produced in other studies.[2b] We have described an efficient synthesis of tropane derivatives from cyclohepta-1,3-diene[3] and have reported our initial attempts to extend this basic approach to the synthesis of homotropanes (**3**) and -7-enes (**4**) from cycloocta-1,3-diene.[4] We now describe in full the scope of the route to N-benzyl and N-methyl derivatives of these higher homologues together with an adaptation to yield the 1-methyl derivatives (**5**) and (**6**). Investigations into the removal of substituents at nitrogen to give the nor- systems (**5b**) and (**6b**) are currently being completed and will be described separately together with debenzylation reactions leading to (**3b**) and (**4b**)[4] and analogous routes to nortropanes and nortrop-6-enes.



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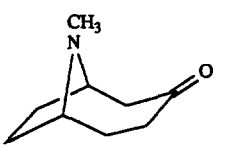

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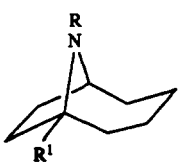
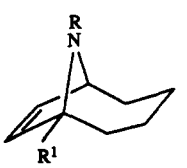




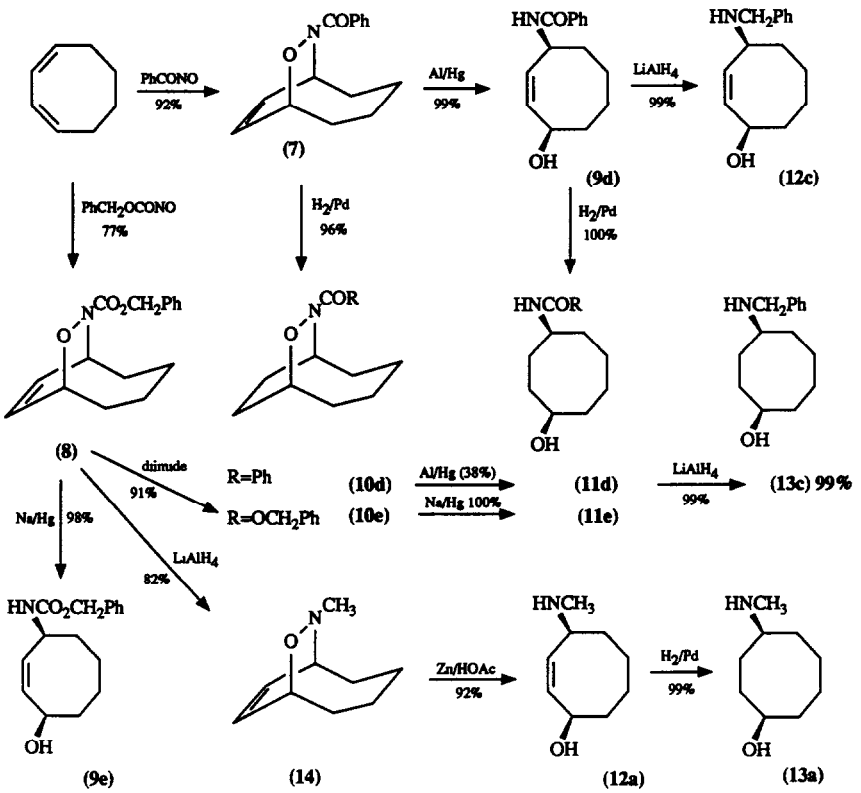
	R^1=H	R^1=CH_3	R^1=H	R^1=CH_3
R=CH_3	(3a)	(5a)	(4a)	(6a)
R=H	(3b)	(5b)	(4b)	(6b)
R=CH_2Ph	(3c)	(5c)	(4c)	(6c)
R=COPh	(3d)	(5d)	(4d)	(6d)
R=CO_2CH_2Ph	(3e)	(5e)	(4e)	(6e)

Synthesis of N-Substituted Homotropanes and Homotrop-7-enes

The cycloadducts (**7**) and (**8**) were produced from the appropriate nitroso-compounds which were generated *in situ* by standard methods[3] (scheme 1). The overall process is amenable to large-scale preparation of (**7**) and (**8**) since cycloocta-1,3-diene is inexpensive.

The NO bond in the cycloadduct (**7**) was cleaved reductively with aluminium amalgam to afford the *cis*-amido-alcohol (**9d**); hydrogenation of (**9d**) gave (**11d**) in quantitative yield. An approach to (**11d**) *via* (**10d**) was abandoned without optimisation following an initial attempt to cleave the N-O bond of (**10d**) which did not proceed to completion. The *cis*- amino-alcohols (**12c**) and (**13c**) were obtained by reduction with lithium aluminium hydride (scheme 1). Yields from (**7**) *via* (**9d**) were essentially quantitative. The adduct (**8**) was cleaved using sodium amalgam to give (**9e**) and hydride reduction of (**8**) yielded the bicyclic oxazine (**14**). The *cis*-N-methyl amino-alcohol (**12a**) was obtained by treatment with zinc/acetic acid and hydrogenation gave (**13a**).

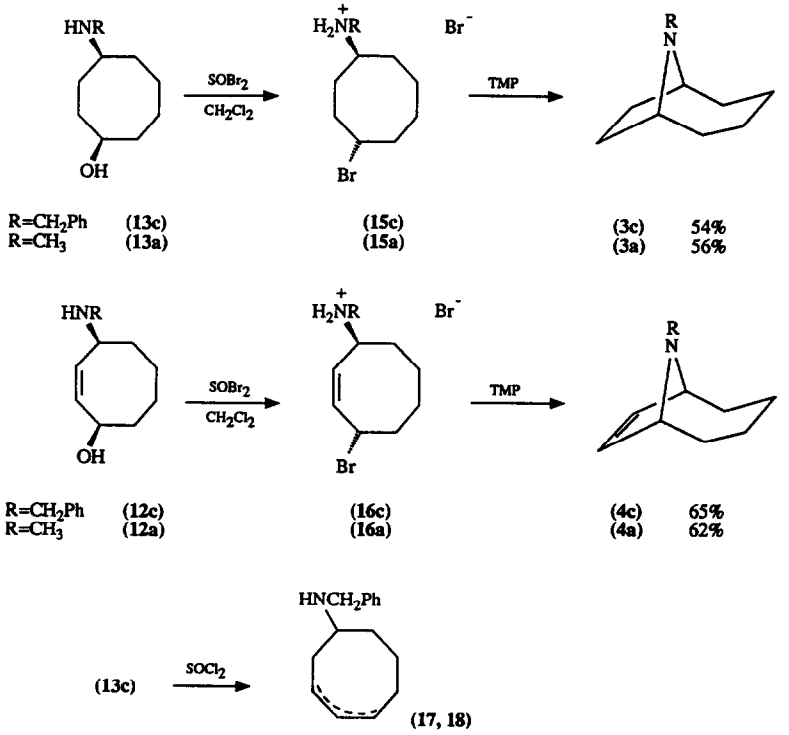
Scheme 1



The transannular cyclisation reactions are shown in scheme 2. Treatment of (**13c**) with thionyl chloride led to the appearance of new peaks in the ^{1}H NMR spectrum assigned to the alkyl chlorosulphite intermediate[3] but decomposition to yield the *trans*- 1,4-amino-chloride was not observed. The appearance of signals in the olefinic region suggested that elimination to (**17**) and (**18**) was probably occurring. The products were not characterised but analogous eliminations have been seen in work in 7-membered ring systems.[5] Successful conversion of the amino-alcohols (**13a,c**) into the hydrobromide salts of the *trans*-bromoamines (**15a,c**) was achieved using thionyl bromide.[3] No additional base was used in view of the presence of the amino- group which reacted with the HBr formed in the reaction and produced the bromide

ion necessary for the inversion of configuration at carbon 4. Initial experiments were performed in dry $CDCl_3$ in order to monitor decomposition of the intermediate bromosulphite; the subsequent cyclisation was achieved by basification with tetramethylpiperidine (TMP) which released the free bromoamine, as described earlier for the lower homologues.[3] N-Benzylnorhomotropane (**3c**) was obtained in an isolated yield of 41% after purification but this was improved subsequently. The structure of (**3c**) followed from the simple ^1H NMR spectrum in which the bridgehead protons were now equivalent (δ 3.29) and the simple ^{13}C NMR spectrum which showed only four signals due to the ring carbons. The same approach, when applied to the unsaturated analogue (**12c**) produced N-benzylnorhomotrop-7-ene (**4c**) (Scheme 2) in an initial yield of 38% after purification. The symmetrical structure of (**4c**) again followed from the simple NMR spectra. The competing 1,2-addition (S_N2' reaction) which had complicated the trop-6-ene cyclisations[3] was not a problem in these higher homologues.

In an attempt to increase the efficiency of the cyclisation reactions, treatment of (**13c**) with thionyl bromide was performed in purified chloroform solvent which was then removed and replaced by dry acetone prior to the cyclisation with TMP. The use of this more polar solvent led to a modest increase in yield (to 43%) but did not provide the substantial improvement noted in the tropane cyclisations.[3] However, the use of dry dichloromethane for both steps simplified the procedure and raised the overall yields to 54% for (**3c**) and 65% for (**4c**) after chromatography on silica. The lower yields in early experiments may be related to small amounts of water and/or alcohol in the chloroform solvent (although it was passed through a column of basic alumina prior to use[6]); in the case of dichloromethane, the complete absence of water was ensured by distillation from calcium hydride immediately prior to use.



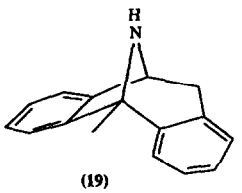
Scheme 2

The direct synthesis of the N-methyl compounds was investigated along similar lines. These compounds were of interest on their own right but were also seen as potential precursors of the nor- systems (by demethylation), bearing in mind the difficulties experienced in attempted debenzylation of the lower

homologues using non-hydrogenolytic conditions.[3] Cyclisation of (**13a**) using thionyl bromide in dichloromethane followed by addition of TMP gave a sample of homotropane (**3a**) in 56% yield which showed identical properties to those recorded for a sample prepared[7] using the method of Cope.[2a] The analogous reaction of (**12a**) gave homotrop-7-ene (**4a**) in 62% yield. The ^{1}H NMR spectrum of (**4a**) was similar to that of the N-benzyl drivative (**4c**) in all the important respects and the ^{13}C NMR spectrum showed the expected five signals. Once again, the aziridine isomer which might have been expected from 1,2-addition was, fortunately, absent. The overall yields in all of the cyclisation steps were reasonable and reproducible and the products were easily isolated in pure form by column chromatography.

Synthesis of 1-Methyl Derivatives

The 1-methylnortropane derivative MK-801 (**19**) is a selective ligand for brain cyclidine receptors which has attracted considerable attention as a potent anticonvulsive and neuroprotective agent.[8] A higher homologue (**20**) has recently been synthesised[9] which incorporates the 1-methylnorhomotropane skeleton but 1-methyl derivatives of neither skeleton have been found in nature to date. Following the successful transannular cyclisation reactions described above (which involve nucleophilic displacement at an sp^3 carbon), we decided to explore the possibility of cyclisation on to an sp^2 carbon of an *exo*-methylene group using mercury(II)- mediated amidocyclisation in order to generate 1-methyl derivatives of the homotropane and, if possible, homotrop-7-ene skeleta. The overall approach is summarised in scheme 3.



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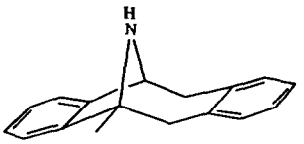

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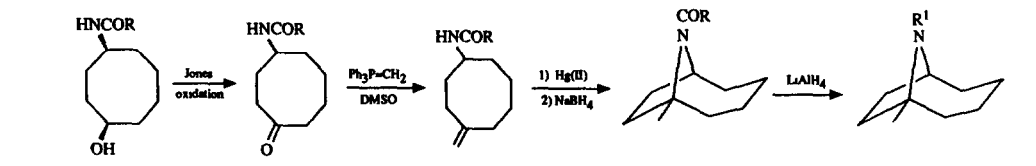
Scheme 3



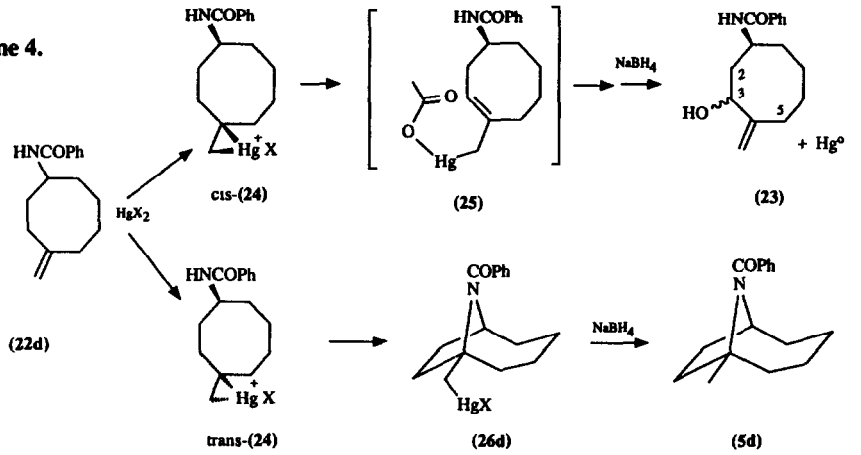
R=Ph (**11d**) (**21d**) 93% (**22d**) 89% (**5d**) 93% R^1=CH_2Ph (**5c**) 91%
R=OCH_2Ph (**11e**) (**21e**) 98% (**22e**) 52% (**5e**) 73% R^1=CH_3 (**5a**) 78%

The amido-alcohol (**11d**) was converted into (**21d**) by Jones oxidation. Wittig methylenation gave the amido-alkene (**22d**) in good yield. Initial cyclisation reactions were performed using a 1:1 mixture of mercury(II) acetate and mercury(II) trifluoroacetate in acetonitrile[10] followed by reduction with sodium borohydride in THF and led to the isolation of (**5d**) in 42% yield. This product showed no evidence of olefinic or NH signals in the NMR or IR spectra and the formation of a C-methyl group was confirmed by signals at δ 1.70 and δ 28.1 in the ^{1}H and ^{13}C spectra respectively. This homotropane derivative was accompanied by 22% of the allylic alcohol (**23**) (scheme 4).

The ^{1}H and ^{13}C NMR spectra of (**23**) were entirely in keeping with the proposed structure [the compound was a single stereoisomer but the configuration at C_3 was not assigned]. In particular, double-irradiation of the signal at δ 4.30 (assigned to the α-hydroxy proton H_3) revealed allylic coupling to the *exo*-methylene protons and to a pair of geminal protons which placed the hydroxyl at either the 3- or 5-position. Each member of this geminal pair appeared as a doublet of doublet of doublets (ddd) in the undecoupled spectrum and as a doublet of doublets (dd) on irradiation of H_3. This observation was consistent only with their assignment as the pair on C_2 since a 5-hydroxy compound would require each of the geminal

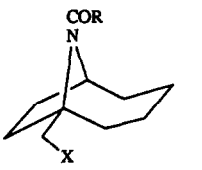
protons on C_6 to be coupled to each other, to H_5, and to *two* neighbours on C_7 leading to a dddd; irradiation of the α-hydroxy proton would have left a ddd. Only the *trans*- isomer of (**24**) is set up for cyclisation to (**26d**) and it was assumed that the inability of *cis*-(**24**) to undergo cyclisation allowed the intrusion of an alternative pathway leading to (**23**). A possible mechanism (scheme 4) is based on an initial elimination to give an intermediate (**25**) followed by solvolysis and allylic rearrangement.[14a]

Scheme 4.

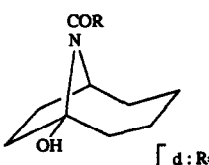


Attempts to repeat the experiment gave modest yields of (**5d**) but did not allow isolation of more (**23**); further investigation of the mechanism was therefore not possible. Nevertheless, the assumption that the yield of (**26d**) was limited by the formation of the unwanted *cis*-(**24**) was put to the test. The stereochemistry of formation of organomercury intermediates in aminomercuration[11] and amidomercuration[12] reactions has been shown to be dependent on the nature of the mercury(II) salt used; mercury(II) trifluoroacetate leads to reversible formation of the organomercury intermediate in contrast to the acetate salt itself. The amido-alkene (**22d**) was therefore treated with mercury(II) trifluoroacetate instead of the mixed mercury salts. The cyclisation product (**5d**) was obtained in 93% yield after treatment with borohydride confirming that more of the intermediate (**24**) had now attained the *trans*- stereochemistry and supporting the suggestion that the *cis*- isomer was formed reversibly. The N-benzoyl compound was subsequently reduced with lithium aluminium hydride to the N-benzyl derivative (**5c**) in 93% yield. The NMR spectra for (**5c**) were similar to those for (**3c**) although the destruction of the symmetry of the molecule led to the observation of extra signals and caused the diastereotopic protons of the benzyl CH_2 group to appear as an AB quartet.

The N-benzyloxycarbonyl compound (**5e**) was produced in corresponding fashion from (**11e**) (scheme 3). Oxidation of (**11e**) gave a high yield of the ketone (**21e**) which showed carbonyl absorption at 1720 cm^{-1} in the IR spectrum and a signal at δ 217 in the ^{13}C NMR spectrum. However on standing in solution over several hours, the bicyclic tautomer (**28e**) was detected by a characteristic signal at δ 93 due to C_1.[13] Conversion into (**22e**) was followed by cyclisation using Hg(II) trifluoroacetate in 73% yield but this was accompanied by ca. 25% of the 1-hydroxymethyl analogue (**27e**) which was presumably formed by oxidation of the intermediate (**26e**) during the borohydride reduction.[14] The NMR spectra of (**5e**) showed signals corresponding to two rotamers resulting from restricted rotation about the N-CO bond. Reduction of (**5e**) with lithium aluminium hydride gave the N-methyl compound (**5a**).



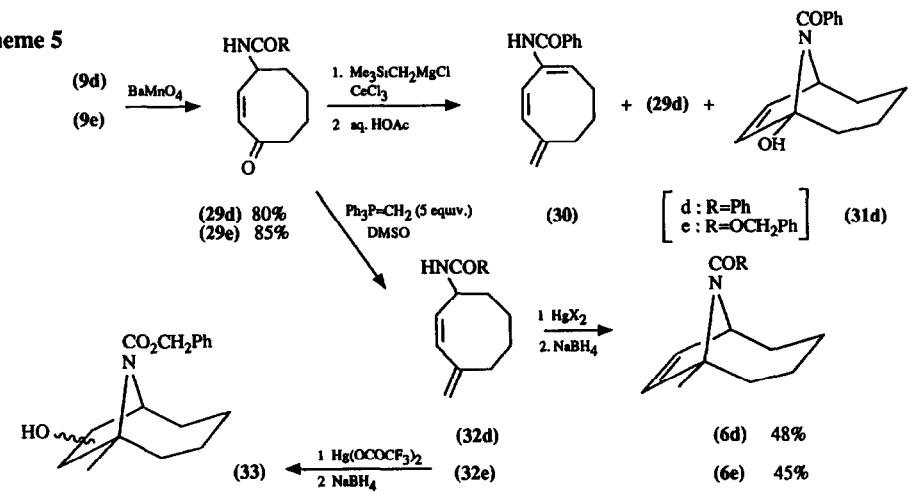
(**26**) X=Hg(OCOCF$_3$)
(**27**) X=OH



(**28**) [d : R=Ph ; e : R=OCH$_2$Ph]

Attention was turned to the formation of the corresponding unsaturated derivatives (**6**). Oxidation of (**9d**) to the α,β-unsaturated ketone (**29d**) was achieved in 40% yield using manganese dioxide but this was raised to 80% using barium manganate[15] (scheme 5). Peterson olefination using 2.5 equivalents of trimethylsilylmethylmagnesium chloride and cerium (III) chloride[16a] gave only 5% of the triene (**30**)[16b] together with 1-hydroxy-N-benzoyl-9-azabicyclo[4.2.1]non-7-ene (**31d**). When the experiment was repeated using 5 equivalents of Grignard reagent and $CeCl_3$ under oxygen-free conditions, more of the triene (**30**) was isolated (25%) together with (**31d**) and (**29d**) but none of the desired diene (**32d**) was obtained. In the absence of $CeCl_3$, only (**29d**) and (**31d**) were isolated. Interestingly, the bicyclic tautomer (**31d**) was stable enough to be purified by column chromatography and was characterised spectroscopically. In particular, the ^1H NMR spectrum showed two alkene protons as a singlet at δ 5.84 and an exchangeable 1-hydroxyl signal at δ 5.71; the ^{13}C NMR spectrum included alkene carbons at δ 129.9 and 132.9, C_6 at δ 63.2, and the quaternary carbon C_1 at δ 97.5 with no indication of a carbonyl carbon other than that due to the benzoyl group. A solution of (**31d**) in $CDCl_3$ reverted completely to the α,β-unsaturated ketone (**29d**) over a period of three weeks when monitored by NMR; the conversion occurred immediately in the presence of a small amount of aqueous acetic acid.

Scheme 5



Methylenation of (**29d**) to give (**32d**) was finally achieved in 79% yield using standard Wittig chemistry (scheme 5). The NMR spectra of (**32d**) are described fully in the experimental section and showed many features in common with the triene (**30**). Treatment of (**32d**) with mercury(II) trifluoroacetate (under the conditions described earlier for the successful cyclisation of (**22d**)) followed by borohydride reduction and chromatography led to the isolation of (**6d**) in 48% yield. The ^1H and ^{13}C NMR spectra of (**6d**) showed features in common with the saturated analogue (**5d**) but the presence of the ABX system due to H_6, H_7 and H_8 was confirmed with the aid of homonuclear spin-decoupling experiments.

The N-benzyloxycarbonyl-protected analogues were obtained similarly (scheme 5). The allylic alcohol (**9e**) was oxidised with barium manganate and the product (**29e**) also showed signals due to the bicyclic tautomer.[13] Wittig methylenation gave (**32e**) but treatment of this with mercury(II) trifluoroacetate followed by borohydride, as described earlier, gave the 7- and 8-hydroxy derivatives (**33**) (as shown by oxidation to yield a mixture of 7- and 8- keto derivatives), apparently as the *exo*- stereoisomers. However, in this case, treatment with two equivalents of mercury(II) acetate followed by borohydride reduction provided (**6e**) in 45% yield; starting material (33%) was also recovered. Compounds (**6d**) and (**6e**) were required for other studies and the conversions into (**6c**) and (**6a**) respectively were therefore not carried out. These conversions should be straightforward using the methods established earlier for (**5c**) and (**5a**).

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 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), ABq (AB quartet), 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 acetate were distilled prior to use. Methanol and ethanol were purified with magnesium and iodine.[6] 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 **(7)**, **(9d)**, **(11d)** and **(13c)** were prepared as described in reference 3.

N-(Benzyloxycarbonyl)-9-oxa-10-azabicyclo[4.2.2]dec-7-ene (8)

Cycloocta-1,3-diene (46.36 g, 53.35 ml, 428.5 mmol) was added to a suspension of tetramethylammonium periodate (116.62 g, 440 mmol) in chloroform (2.8 l). A solution of benzyl-N-hydroxycarbamate (73.56 g, 440 mmol) in chloroform (1.1l) was added to this mixture dropwise, with stirring, over 15 min. After stirring at room temperature for a further 17h, the solution was filtered and the solvent distilled at reduced pressure yielding an oil which was dissolved in diethyl ether (3.5 l) and washed with water (3 x 500 ml). The organic layer was separated, dried over anhydrous magnesium sulphate, and the solvent was evaporated at reduced pressure producing a yellow-orange oil which crystallised on standing to yield **(8)** (90.03 g, 77%) as colourless crystals, m.p. 61.0 - 61.5 °C (from petroleum ether (40 - 60°C)). In a similar experiment, separation by flash chromatography gave **(8)** in a yield of 61%. δ_H (300 MHz, $CDCl_3$): 1.49 - 1.82 (series of m, 5H), 1.91 - 2.18 (series of m, 3H), 4.66 (brm 1H), 4.91 (brm, 1H), 5.14, 5.19 (ABq, J = 12.4 Hz, 2H), 5.77 (dd, J = 10.5, 7.5 Hz, 1H), 6.33 (dd, J = 10.5, 9.0 Hz, 1H), 7.24 - 7.35 (m, 5H). δ_C (75 MHz, $CDCl_3$): 22.3, 25.5, 31.5, 34.3 (4 x CH_2), 53.9 (NCH), 67.6 (CH_2), 76.0 (OCH), 126.5 (=CH), 127.8, 128.0, 128.4 (3 x aryl CH), 131.7 (=CH), 136.2 (aryl C), 157.9 (C=O). ν_{max} (CH_2Cl_2): 3030w, 2920s, 2860m, 1705vs, 1495w, 1445m, 1380m, 1345m, 1330m, 1310m, 1300m, 1265s, 1205m, 1175m, 1070s cm^{-1}. m/z (%): 273 (M^+, 9), 229 (11), 186, (32), 149 (20), 138 (22), 108 (29), 92 (98), 91 (100), 80 (46), 79 (78), 77 (55), 65 (77). Found : C, 70.29; H, 6.84; N, 5.16%. $C_{16}H_{19}NO_3$ requires: C, 70.31; H, 7.01; N, 5.12%.

Cis-4-([Benzyloxycarbonyl]amino)cyclooct-2-enol (9e)

To a solution of the adduct (**8**) (4.80 g; 18 mmol) in dry ethanol (41 ml) was added sodium phosphate (11.40 g; 80 mmol). The suspension was stirred under a nitrogen atmosphere for 5 mins. Freshly powdered 6% sodium amalgam (47 g) was added and the mixture was stirred for 1 hour. The solution was filtered and the solvent removed under vacuum. The residual oil was partitioned between water (30 ml) and dichloromethane (40 ml). The organic layer was separated and the aqueous layer was extracted further with dichloromethane (2 x 40 ml). The combined organic layers were dried over magnesium sulphate, filtered, and the solvent removed under vacuum. The resulting oil was triturated with petrol to yield a white solid (4.74 g, 98%) which was recrystallised from toluene: petroleum ether (b.p. 40 - 60°C) to afford (**9e**) as a crystalline white solid, m.p. 127 - 128°C. δ_H (300 MHz, $CDCl_3$): 1.25 - 1.62 (m, 6H), 1.88 (m, 2H), 2.62 (brs, OH), 4.41 (brs, 1H, α-N), 4.62 (brm, 1H, α-O), 5.01 (d, J = 5.7 Hz, NH), 5.06 (s, 2H), 5.25 (ddd, J = 10.4, 8.3, 1.5 Hz 1H), 5.60 (dd, J = 10.4, 6.99 Hz, 1H), 7.33 (m, 5H). δ_C (75 MHz, $CDCl_3$): 23.4, 24.0, 36.5, 38.3 (4 x CH_2), 49.4 (NCH), 66.6 (CH_2Ph), 69.3 (OCH), 128.0 (2 x aryl CH), 128.4, (aryl CH), 129.4 & 139.4 (=CH), 136.4 (aryl C), 155.7 (C=O). ν_{max} (CH_2Cl_2): 3600m, 3430m, 3420m, 2930s, 2860w, 1715s, 1505s, 1450w, 1395w, 1315brw, 1235m, 1210m, 1130w, 1085w, 1045m, 1015m, 950w, 860w cm^{-1}. $^m/z$ (%): 275 (M^+, 1), 184 (19), 172 (6), 140 (13), 123 (5), 108 (9), 107 (5), 95 (4), 92 (9), 91 (100), 80 (4), 79 (7). Found : C, 69.87; H, 7.74; N, 5.08%. $C_{16}H_{21}NO_3$ requires: C, 69.79; H, 7.69; N, 5.09%.

N-Benzoyl-9-oxa-10-azabicyclo[4.2.2] decane (10d)

A solution of (**7**) (5.90 g, 24.27 mmol) in dry methanol (100 ml) was hydrogenated at 1 atm in the presence of 10% palladium on charcoal. After 6h, the solution was filtered through celite and then through a Millipore 0.2μ Millex-FG disposable filter giving a clear solution which was evaporated under reduced pressure yielding (**10d**) (5.69 g, 96%) as a white solid, m.p. 78 - 80°C (from petroleum ether (40 - 60°C)). δ_H (300 MHz, $CDCl_3$) : 1.44 - 2.45 (series of m, 12H), 4.45 (m, 1H), 4.90 (m, 1H), 7.31 - 7.45 (m, 3H), 7.63 - 7.73 (brdd, J = 7.4, 2.0 Hz, 2H). δ_C (75 MHz, $CDCl_3$): 20.7, 22.5, 23.9, 24.6, 32.5, 34.5 (6 x CH_2), 49.9 (NCH), 77.0 (OCH), 127.6, 128.6, 130.0 (3 x aryl CH), 134.5 (aryl C), 167.3 (C=O). ν_{max} (CH_2Cl_2): 3020w, 2930s, 2860m, 1615vs, 1575m, 1445s, 1425m, 1365m, 1340w, 1320w, 1295w, 1230w, 1200m, 1085m cm^{-1}. $^m/z$ (%): 245 (M^+, 6), 140 (3), 106 (20), 105 (100), 77 (50), 67 (6), 51 (17), 41 (11). Found: C, 73.22; H, 7.90; N, 5.69% $C_{15}H_{19}NO_2$ requires: C, 73.44; H, 7.81; N, 5.71%.

N-(Benzyloxycarbonyl)-9-aza-10-oxabicyclo[4.2.2]decane (10e)

To a stirred slurry of potassium azodicarboxylate (17.68 g; 92 mmol) and (**8**) in methanol (155 ml) at 0°C was added dropwise glacial acetic acid (10.53 ml; 184 mmol) over 40 mins. The mixture was allowed to warm to room temperature and stirred for 3 h when a further portion of potassium azodicarboxylate (7.28 g) was added and stirred for a further 2 h. Water (12 ml) was added and the bulk of the solvent removed under vacuum. The oily residue was partitioned between dichloromethane and 5% sodium bicarbonate solution (40 ml), washed with further bicarbonate solution (2 x 40 ml), and the organic layer was dried over magnesium sulphate. After filtration and removal of solvent under vacuum, the crude oil was purified by flash chromatography using 2:8 diethyl ether:petroleum ether (b.p. 40-60°C) to yield (**10e**) as a colourless oil (4.59 g; 91%). δ_H (300 MHz, $CDCl_3$): 1.51 - 1.79 (series of m, 10H), 1.99 (brm, 1H), 2.13 - 2.28 (brm, 1H), 4.48 (brm, 1H, α-N), 4.59 (brm, 1H, α-O), 5.21 (s, 2H), 7.28 - 7.37 (m, 5H). δ_C (75 MHz, $CDCl_3$) [Signals in italics were broadened due to rotation about the N-CO bond and values are approximate; the signal due to C_1 of the benzyl group was not visible.]: *20.5*, *22.3*, 23.7, 24.6, *33.0*, 34.4 (6 x CH_2), *51.2* (NCH), 67.1 (CH_2Ph), *76.5* (OCH), 127.8 (2 x aryl CH), 128.3 (aryl CH). ν_{max} (CH_2Cl_2): 3090w, 3060w, 3040w, 2930s, 2860m, 1725s, 1690s, 1590w, 1495w, 1400m, 1355m, 1330m, 1315m, 1290m, 1260m, 1210w, 1195m, 1150w, 1095s, 1070s, 1020m, 990w, 930w cm^{-1}. $^m/z$ (%): 275 (M^+, 13), 231 (7), 146 (5), 140 (7), 132 (10), 92 (14), 91 (100), 81 (4). $C_{16}H_{21}NO_3$ [M^+] requires $^m/z$ 275.1521; observed $^m/z$ 275.1525.

Cis-4-([Benzyloxycarbonyl]amino)cyclooctanol (11e)

To a solution of (**10e**) (1.26 g, 4.56 mmol) in dry ethanol (18 ml) was added sodium phosphate (3.12 g, 22 mmol). The suspension was stirred for 5 mins and freshly powdered 6% sodium amalgam (14 g) was added at 0°C under a nitrogen atmosphere. After stirring for 3 h and filtration, the solvent was removed under vacuum. The oil was dissolved in water (40 ml) and extracted into dichloromethane (3 x 20 ml). The

combined organic layers were dried over anhydrous magnesium sulphate and the solvent removed under vacuum to afford **(11e)** (1.26 g, 100%) as a colourless oil. δ_H (300 MHz, $CDCl_3$): 1.48 - 1.74 (brm, 12H), 2.15 (brs, OH), 3.65 (brm, 1H, α-N), 3.81 (brm, 1H, α-O), 4.94 (d, J = 7.3 Hz, NH), 5.06 (s, 2H), 7.26 - 7.37 (m, 5H). δ_C (75 MHz, $CDCl_3$): 22.0, 23.4, 28.0, 30.9, 31.2, 33.2 (6 x CH_2), 51.2 (NCH), 66.5 (CH_2Ph), 71.2 (OCH), 128.0 (2 x aryl CH), 128.4, (aryl CH), 136.6 (aryl C), 155.4 (C=O). ν_{max} (CH_2Cl_2): 3600m, 3420m, 3015w, 2930s, 2860m, 1710s, 1500s, 1450w, 1315brw, 1215s, 1080w, 1055s, 1010m, 975m, 910m cm^{-1}. m/z (%): 277 (M^+, 6), 168 (19), 146 (34), 142 (31), 126 (16), 125 (21), 124 (17), 123 (19), 114 (10), 112 (23), 110 (13), 109 (18), 108 (100), 107 (100), 105 (14); $C_{16}H_{23}NO_3$ [M^+] requires m/z 277.1680; observed m/z 277.168

Cis-4-(Benzylamino)cyclooct-2-enol (12c)

A solution of **(9)** (3.30 g, 14.26 mmol) in dry tetrahydrofuran (140 ml) was added dropwise to a stirred slurry of lithium aluminium hydride (2.16 g, 57.0 mmol) in dry tetrahydrofuran (80 ml). After refluxing for 24h, decomposition of excess hydride was effected by addition of water. The inorganic solids were removed by filtration and washed with warm ethyl acetate. The combined organic solutions were evaporated under reduced pressure to yield **(12c)** (3.25 g, 99%) as a white solid, m.p. 120.5 - 121.5°C (from ethyl acetate). δ_H (300 MHz, $CDCl_3$) : 1.34 - 1.91 (series of m, 10H, incl. 2H exch.), 3.48 (m, 1H), 3.63, 3.79 (ABq, J = 13.0 Hz, 2H), 4.47 (m, 1H) 5.42 (ddd, J = 11.0, 8.2, 1.7 Hz, 1H), 5.65 (ddd, J = 11.0, 6.9, 1.3 Hz, 1H), 7.21 - 7.36 (m, 5H). δ_C (75 MHz, CD_3OD): 24.8, 25.4, 37.0, 39.9 (4 x CH_2), 52.3 (CH_2Ph) 55.0 (NCH), 70.5 (OCH), 128.1, 129.4, 129.7 (3 x aryl CH), 132.1 & 137.4 (=CH), 140.5 (aryl C). ν_{max} (CH_2Cl_2) : 3600m, 3020w, 2930s, 2850m, 1490w, 1450m, 1195w, 1100m, 1035m cm^{-1}. m/z (%): 232 (9), 231 (M^+, 6), 173 (13), 172 (15), 147 (8), 146 (9), 141 (9), 140 (6), 92 (11), 91 (100). Found: C, 77.88; H, 9.31; N, 6.06%. $C_{15}H_{21}NO$ requires: C, 77.88; H, 9.15; N, 6.05%.

Cis-4-(Methylamino)cyclooct-2-enol (12a)

Zinc powder (52.35 g, 1.154 mol) was added to a stirred solution of **(14)** in glacial acetic acid (450 ml) at room temperature. The reaction mixture was heated at 60°C for 6h and then filtered. The residue was washed with glacial acetic acid (600 ml) and the filtrate evaporated under reduced pressure producing a residue which was dissolved in water (100 ml), washed with diethyl ether (3 x 50 ml) and basified to pH 14 with concentrated sodium hydroxide solution. The product was extracted into dichloromethane (5 x 100 ml), the combined organic layers were dried over anhydrous magnesium sulphate and the solvent evaporated under reduced pressure to yield **(12a)** (11.01 g, 92%) as a white solid, m.p. 125 - 126°C (from ethyl acetate). δ_H (300 MHz, $CDCl_3$): 1.26 - 1.93 (series of m, 8H plus 1H exch) 2.38 (s, 3H), 2.65 (brs, exch, 1H), 3.35 (m, 1H), 4.53 (m, 1H), 5.30 (ddd, J = 11.0, 8.1, 1.6 Hz, 1H), 5.63 (ddd, J = 11.0, 7.0, 1.3 Hz, 1H). δ_C (75 MHz, $CDCl_3$): 23.9 & 24.4 (CH_2), 34.5 (CH_3), 36.7 & 38.9 (CH_2), 57.7 (NCH), 69.1 (OCH), 132.1 & 136.0 (=CH). ν_{max} (CH_2Cl_2): 3600m, 3300brm, 3150brm, 3010m, 2930s, 2850m, 2790m, 1470m, 1445m, 1385w, 1140m, 1110m, 1030cm^{-1}. m/z (%): 155 (M^+, 4), 112 (12), 96 (45), 83 (12), 70 (100), 68 (19), 57 (23), 55 (14), 44 (22), 42 (26), 41 (26), 39 (18). Found: C, 69.58; H, 10.89; N, 9.16%. $C_9H_{17}NO$ requires: C, 69.63; H, 11.04; N, 9.02%.

Cis-4-(Methylamino)cyclooctanol (13a)

A solution of **(12a)** (2.08 g, 13.39 mmol) in dry methanol (100 ml) was hydrogenated at 1 atm in the presence of 10% palladium on charcoal. After 10h, 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 yielding **(13a)** (2.08 g, 99%) as a colourless oil. δ_H (300 MHz, $CDCl_3$): 1.40 - 1.79 (series of m, 12H), 2.37 (s, 3H), 2.49 (m, 1H), 2.66 (brs, exch, 2H), 3.79 (m, 1H). δ_C (75 MHz, $CDCl_3$): 22.4, 24.3, 27.9, 30.6, 31.4, 33.8 (6 x CH_2), 33.9 (CH_3), 59.7 (NCH), 70.9 (OCH). ν_{max} (CH_2Cl_2): 3600m, 3230brw, 2920s, 2850m, 2790m, 1470m, 1445m, 1365w, 1130m, 1095m, 1045m, 1005m cm^{-1}. m/z (%): 157 (M^+, 4) 100 (8), 98 (4), 96 (3), 84 (7), 71 (13), 70 (100), 67 (4), 58 (8), 57 (90), 55 (11), 44 (23), 42 (15), 41 (23); $C_9H_{19}NO$ [M^+] requires 157.1467; found 157.147.

N-Methyl-9-oxa-10-azabicyclo[4.2.2]dec-7-ene (14)

A solution of **(8)** (30.00 g, 109.76 mmol) in dry tetrahydrofuran (300 ml) was added to a slurry of lithium aluminium hydride (8.35 g, 220 mmol) in dry tetrahydrofuran (85 ml). After refluxing for 3h and

stirring at room temperature for a further 15h, decomposition of excess hydride was effected by addition of water. The inorganic solids were removed by filtration and washed with warm ethyl acetate. The combined organic solutions were evaporated under reduced pressure and the residue dissolved in dichloromethane. The solution was dried over anhydrous magnesium sulphate and evaporated under reduced pressure leaving an oil, contaminated with the benzyl alcohol by-product, which was purified by flash chromatography (diethyl ether) to yield **(14)** (13.78 g, 82%) as a colourless oil, b.p. 75°C (0.4 mm Hg). δ_H (300 MHz, $CDCl_3$): 1.48 - 1.79 (series of m, 5H), 1.87 - 2.17 (series of m, 3H), 2.70 (s, 3H), 3.28 (m, 1H), 4.56 (brm, 1H), 5.93 (dd, J = 10.15, 4.5 Hz, 1H), 6.12 (dd, J = 10.15, 6.8 Hz, 1H). δ_C (75 MHz, $CDCl_3$): 22.6, 25.6, 32.6, 34.8 (4 x CH_2), 44.6 (CH_3), 59.4 (NCH), 70.9 (OCH), 126.5 & 127.7 (=CH). ν_{max} (CH_2Cl_2): 3040w, 2950m, 2920s, 2890m, 2860m, 1440w, 1175m, 1140m, 1115m, 1055w, 1010m, 990m, 930m, 910s, 805m cm^{-1}. m/z (%): 153 (M^+, 23), 124, (7), 110 (67) 108 (16), 94 (31), 84 (40), 79 (79), 68 (37), 67 (42), 57 (41), 55 (44), 43 (100), 42 (74), 39 (57), 29 (100); $C_9H_{15}NO$ [M^+] requires 153.1154; found 153.115.

N-Benzyl-9-azabicyclo[4.2.1]nonane (3c)

Thionyl bromide (1.029 g, 383 µl, 4.95 mmol) was added dropwise to a solution of **(13c)** (1.10 g, 4.71 mmol) in dry dichloromethane (50 ml) with stirring at 0°C under dry N_2. The reaction mixture was allowed to warm to room temperature and stirred for a further 12h. After cooling to 0°C, dry tetramethylpiperidine (TMP) (700 mg, 836 µl, 4.95 mmol) was added and the solution was stirred for 24h at room temperature. The mixture was filtered and the filtrate was concentrated under reduced pressure giving a yellow-orange oil which was purified by flash chromatography (1:1 petroleum ether (40 - 60 °C): diethyl ether, saturated with gaseous ammonia) to yield **(3c)** (547 mg, 54%) as a pale yellow oil, b.p. 140°C (0.4 mm Hg). δ_H (300 MHz, $CDCl_3$): 1.22 - 2.17 (series of m, 12H), 3.29 (brm, 2H), 3.74 (s, 2H), 7.17 - 7.40 (m, 5H). δ_C (75 MHz, $CDCl_3$): 24.9, 30.7, 35.9 (3 x CH_2), 59.4 (CH), 62.6 (CH_2), 126.4, 128.0, 128.1 (3 x aryl CH), 141.5 (aryl C). ν_{max} (CH_2Cl_2): 3080w, 3020w, 2920s, 1600w, 1495m, 1470m, 1450m, 1385w, 1345w, 1205w, 1150m, 1130m, 1100m, 1070m, 1030m, 945m cm^{-1}. m/z (%): 216 (10), 215 (M^+, 18), 167 (31), 149 (94), 91 (100), 71 (42), 57 (71); $C_{15}H_{21}N$ [M^+] requires: 215.1674; found 215.167.

N-Methyl-9-azabicyclo[4.2.1]nonane (Homotropane) (3a)

Thionyl bromide (1.659 g, 618 µl, 7.98 mmol) was added dropwise to a solution of **(13a)** (1.20 g, 7.60 mmol) in dry dichloromethane (65 ml) with stirring at 0°C under dry N_2. The reaction mixture was allowed to warm to room temperature and stirred for a further 12h. After cooling to 0°C, dry TMP (1.127 g, 1.347 ml, 7.98 mmol) was added and the solution was stirred for 24h at room temperature. The mixture was worked up and chromatographed as described for **(3c)**. The fractions containing product were acidified with dry hydrogen chloride gas, and the combined fractions were evaporated under reduced pressure yielding **(3a:HCl)** (813 mg, 61%) as a white, hygroscopic solid. On basification with sodium hydroxide solution, extraction into dichloromethane, and drying over anhydrous magnesium sulphate, **(3a)** (592 mg, 56%) was obtained as a pale yellow oil, b.p. 156°C, after distillation at atmospheric pressure. δ_H (300 MHz, $CDCl_3$): 1.34 - 1.63 (series of m, 8H), 1.79 - 1.86 (m, 2H), 2.08 - 2.28 (m, 2H), 2.42 (s, 3H), 3.24 (m, 2H). δ_C (75 MHz, $CDCl_3$): 24.6, 30.2, 35.5 (3 x CH_2), 42.9 (CH_3), 64.6 (CH). ν_{max} (CH_2Cl_2): 3030w, 2920s, 2860m, 2810m, 1625brw, 1470m, 1445m, 1370w, 1350w, 1320w, 1210m, 1175m, 1130m, 1115m, 1090m, 1080m, 985m, 945m, cm^{-1}. m/z (%): 140 (MH^+, 100), 126 (4), 110 (2), 96 (7), 82 (8), 58 (4), 44 (8); $C_9H_{17}N$ [M^+] requires: 139.1361; found: 139.136.

The picrate of **(3a)** was prepared in 95% ethanol, m.p. 272 - 273 °C (decomp.) from 1:1 ethanol:propanone (lit.[2a] m.p. 272 - 273°C). Found: C, 49.18; H, 5.47; N, 14.96%. $C_9H_{17}N.C_6H_3N_3O_7$ requires: C, 48.91; H, 5.47; N, 15.21%.

N-Benzyl-9-azabicyclo[4.2.1]non-7-ene (4c)

Thionyl bromide (2.328 g, 868 µl, 11.20 mmol) was added dropwise to a solution of **(12c)** 2.47 g, 10.67 mmol) in dry dichloromethane (100 ml) with stirring at 0°C under dry N_2. The reaction mixture was allowed to warm to room temperature and stirred for a further 12h. After cooling to 0°C, dry TMP (1.582 g, 1.896 ml, 11.20 mmol) was added and the solution was stirred for 24h at room temperature. The mixture was worked up and chromatographed as described for **(3c)** above to yield **(4c)** (1.47 g, 65%) as a pale yellow oil, b.p. 150 °C (0.4 mm Hg). δ_H (300 MHz, $CDCl_3$): 1.26 - 1.36 (m, 2H), 1.43 - 1.55 (m, 2H), 1.66 - 1.78 (m, 4H), 3.63

(ddd, J = 7.6, 1.7, 1.0 Hz, 2H), 3.66 (s, 2H), 5.69 (d, J = 1.0 Hz, 2H), 7.17 - 7.43 (m, 5H). δ_C (75 MHz, $CDCl_3$): 25.0, 33.1, 61.4 (3 x CH_2), 69.4 (CH), 126.4, 128.0, 128.1 (3 x aryl CH), 131.2 (=CH), 141.5 (aryl C). ν_{max} (CH_2Cl_2): 3080w, 3060m, 3020m, 2920s, 2850m, 2800m, 1720w, 1600w, 1490m, 1435m, 1370w, 1350m, 1335m, 1320m, 1195m, 1120m, 1100m, 1080m, 1070m, 1025m, 970m, 910s cm^{-1}. m/z (%) 214 (14), 213 (M^+, 72), 184 (7), 171 (67), 170 (100), 157 (9), 92 (23), 91 (100), 80 (13), 65 (29); $C_{15}H_{19}N$ [M^+] requires 213.1518; found 213.152.

N-Methyl-9-azabicyclo[4.2.1]non-7-ene (4a)

Thionyl bromide (8.139 g, 3.033 ml, 39.15 mmol) was added dropwise to a solution of **(12a)** (5.79 g, 37.29 mmol) in dry dichloromethane (330 ml) with stirring at 0°C under dry N_2. The reaction mixture was allowed to warm to room temperature and stirred for a further 12h. After cooling to 0°C, dry TMP (5.530 g, 6.607 ml, 39.15 mmol) was added and the solution was stirred for 24h at room temperature. The mixture was worked up and chromatographed as described for **(3c)**. The fractions containing product were acidified with dry hydrogen chloride gas, and the combined fractions were evaporated under reduced pressure yielding **(4a: HCl)** (4.20 g, 65%) as a white, hygroscopic solid. On basification with sodium hydroxide solution, extraction with dichloromethane, and drying over anhydrous magnesium sulphate, **(4a)** (3.17 g, 62%) was obtained as a pale yellow oil, b.p. 170°C, after distillation at atmospheric pressure. δ_H (300 MHz, $CDCl_3$): 1.32 - 1.64 (series of m, 6H), 1.73 - 1.83 (m, 2H), 2.35 (s, 3H), 3.53 (ddd, J = 6.3, 1.6, 1.0 Hz, 2H), 5.66 (d, J = 1.0 Hz 2H). δ_C (75 MHz, $CDCl_3$): 24.7 & 32.6 (CH_2), 45.7 (CH_3), 71.9 (CH), 130.4 (=CH). ν_{max} (CH_2Cl_2): 3030w, 2920s, 2850m, 2790m, 1660w, 1440m, 1360w, 1340m, 1320m 1305w, 1200m, 1120m, 1100m 1080m, 1005m, 970m, 865m, 795 cm^{-1}. m/z (%): 138 (MH^+, 100), 124 (2), 108 (3), 94 (16), 91 (3), 81 (4), 58 (3), 44(2); $C_9H_{15}N$[M^+] requires: 137.1204; found: 137.120.

The picrate of **(4a)** was prepared in 95% ethanol, m.p. 265 - 266°C (decomp.) from 1:1 ethanol:propanone. Found: C, 49.49; H, 4.97; N, 15.18%. $C_9H_{15}N$. $C_6H_3N_3O_7$ requires C, 49.18; H, 4.95; N, 15.29%.

4-(Benzoylamino)cyclooctanone (21d)

A solution of **(11d)** (9.00 g, 36.38 mmol) in propanone (400 ml) was titrated at room temperature with a solution of chromic acid prepared from chromium trioxide (12.35 g, concentrated sulphuric acid (11.5 ml) and water (20 ml). A persistant orange-brown colouration indicated the end-point. Ethanol was added to this solution which on filtering gave a green solution. The solvent was removed under reduced pressure, dichloromethane was added to the green oil, and the solution was passed down a short column of silica to remove chromium residues. The eluted solution was dried over anhydrous magnesium sulphate and the solvent evaporated under reduced pressure to yield **(21d)** (8.33 g, 93%) as a white solid, m.p. 138 - 139°C (from toluene). δ_H (300 MHz, $CDCl_3$): 1.37 - 1.50 (m, 1H), 1.55 - 2.16 (series of m, 6H), 2.28 - 2.62 (series of m, 5H), 4.22 (m, 1H), 6.48 (brd, J = 7.2 Hz, NH), 7.37 - 7.51 (m, 3H), 7.70 - 7.79 (m, 2H). δ_C (75 MHz, $CDCl_3$): 23.9, 28.0, 28.6, 31.3, 39.7, 40.7 (6 x CH_2), 49.6 (NCH), 126.9, 128.5, 131.4 (3 x aryl CH), 134.6 (aryl C), 166.7 (NC=O), 217.0 (CC=O). ν_{max} (CH_2Cl_2): 3440m, 3370brw, 3040w, 2940m, 2860m, 1695s, 1655vs, 1600m, 1580m, 1515vs, 1485s, 1465m, 1445m, 1350m, 1315m, 1225w, 1205w cm^{-1}. m/z (%) 245 (M^+, 1), 163 (8), 141 (5), 122 (26), 106 (10), 105 (100), 77 (53), 74 (18), 44 (24). Found: C, 73.25; H, 7.81; N, 5.55%. $C_{15}H_{19}NO_2$ requires: C, 73.44; H, 7.81; N, 5.71%.

4-([Benzyloxycarbonyl]amino)cyclooctanone (21e)

Chromic acid, prepared form chromium trioxide (12.35 g), concentrated sulphuric acid (11.5 ml) and water (20 ml), was added dropwise to a solution of **(11e)** (1.23 g, 4.45 mmol) in dry acetone (36 ml). A persistent orange colouration indicated complete oxidation. Excess oxidant was destroyed by dropwise addition of ethanol. The mixture was filtered through celite, dried over magnesium sulphate, and the solvent removed under vacuum to yield **(21e)** (1.21 g, 98%) which after recrystallisation from petroleum ether (b.p. 80-100°C) had m.p. 117 - 118°C. Data for the bicyclic tautomer **(28e)** are given separately below; figures in italics are common to both tautomers.

Monocyclic **(21e)**: δ_H (300 MHz, $CDCl_3$): *1.33 - 1.65 (series of m, 4H), 1.82 - 2.04 (series of m, 2H), 2.07 - 2.31 (brm, 2H), 2.34 - 2.50 (brm, 3H),* 3.75 (m, 1H), 4.96 (brd, J = 6.9 Hz, NH), 5.07 (s, 2H), *7.34 (s, 5H).* δ_C (75 MHz, $CDCl_3$): 23.4, 28.2, 28.4, 31.2, 39.8, 40.4 (6 x CH_2), 50.8 (NCH), 66.5 (CH_2Ph), 128.0 (2 x

aryl CH), 128.4, (aryl CH), 136.5 (aryl C), 155.4 (NC=O), 217.0 (CC=O). ν_{max} (CH_2Cl_2): 3440m, 3340brw, 3060w, 3015w, 2940s, 2860m, 1720vs, 1505s, 1465m, 1450m, 1405w, 1340m, 1310m, 1215w, 1150w, 1125w, 1085m, 1060w, 1035m, 1025w, 1005w, 980w, 845w cm^{-1}. m/z (%) 275 (M^+, 10), 184 (6), 146 (7), 140 (15), 108 (9), 92 (9), 91 (100), 84 (14). Found: C, 69.93; H, 7.46; N, 5.10%. $C_{16}H_{21}NO_3$ requires: C, 69.79; H, 7.69; N, 5.09%.

The bicyclic tautomer (**28e**) showed signals as shown in italics above, together with signals at δ 4.32 (m, 1H), 5.11 & 5.17 (ABq, J = 12.4 Hz, 2H) in the ^1H NMR spectrum and at δ 23.0, 23.7, 27.8, 34.7, 37.7, 40.0 (6 x CH_2), 55.4 (NCH), 66.6 (CH_2Ph), 92.9 (COH), 127.7, 128.0, 128.5, (3 x aryl CH), 136.4 (aryl C), 155.1 (NC=O) in the ^{13}C NMR spectrum.

4-Methylene-(benzoylamino)cyclooctane (22d)

A 250 ml three-necked round-bottom flask was charged with sodium hydride (2.054 g, 85.59 mmol) which was washed with several portions of dry petroleum ether (40 - 60°C) to remove the mineral oil. The flask was equipped with rubber septum caps, a reflux condenser fitted with a three-way tap, and a magnetic stirring bead. The system was alternately evacuated and filled with N_2; dry DMSO (50 ml) was introduced *via* a syringe, and the mixture was heated at 75 - 80°C for 45 min. The resulting solution of methylsulphinyl carbanion was cooled in an ice-water bath, and methyltriphenylphosphonium bromide (30.58 g, 85.59 mmol) in warm, dry DMSO (60 ml) was added. The resulting orange-green solution of the ylide was stirred at room temperature for 10 min before use. A solution of (**21d**) (7.00 g, 28.53 mmol) in dry DMSO (75 ml) was added to the ylide and the resulting solution was stirred for 15h at room temperature. The solvent was removed under reduced pressure, the residue extracted with dichloromethane, and the organic solution filtered. The filtrate was evaporated at reduced pressure giving a brown oil which was purified by flash chromatography (diethyl ether) to yield (**22d**) (6.18 g, 89%) as white crystals, m.p. 97°C (from petroleum ether (80 - 100°C)). δ_H (300 MHz, $CDCl_3$): 1.53 - 1.91 (series of m, 7H), 1.99 - 2.09 (m, 1H), 2.15 - 2.44 (series of m, 4H), 4.18 (m, 1H), 4.82 and 4.85 (each m, 1H, $=CH_2$; $J_{gem} \approx 0.8$ Hz), 6.24 (brd, J = 6.9 Hz, NH), 7.36 - 7.50 (m, 3H), 7.70 - 7.78 (m, 2H). δ_C (75 MHz, $CDCl_3$): 23.7, 29.9, 30.6, 32.1, 32.7, 33.9 (6 x CH_2), 49.9 (CH), 111.8 ($=CH_2$), 126.8, 128.4, 131.2 (3 x aryl CH), 135.1 (aryl C), 150.9 ($C=CH_2$), 166.3 (C=O). ν_{max} (CH_2Cl_2): 3440m, 3320brw, 3070w, 2930s, 2860m, 1655vs, 1600m, 1580m, 1515vs, 1485s, 1445m, 1315m, 1140m, 1095m, 1075w, 1030w, 910m, 890m cm^{-1}. m/z (%): 243 (M^+, 1), 215 (2), 174 (2), 122 (39), 106 (9), 105 (100), 93 (12), 77 (54), 51 (13), 41 (9). Found : C, 78.84; H, 8.80; N, 5.73%. $C_{16}H_{21}NO$ requires: C, 78.98; H, 8.70; N, 5.76%.

4-Methylene-([benzyloxycarbonyl]amino)cyclooctane (22e)

The method described for the preparation of (**22d**) was used. Sodium hydride (80% dispersion, 0.082 g, 2.73 mmol) was heated with dry DMSO (2.7 ml) and, after cooling, methyltriphenylphosphonium bromide (0.975 g, 2.73 mmol) in dry DMSO (2.5 ml) was added. The protected keto-amine (**21e**) (0.25 g, 0.905 mmol) in dry DMSO (2.8 ml) was added and the mixture was stirred for 18 h. After flash chromatography using 1:10 diethyl ether:petroleum ether (b.p. 40-60°C), (**22e**) (0.104 g, 52%) was isolated as a colourless oil. δ_H (300 MHz, $CDCl_3$): 1.49 - 1.81 (brm, 7H), 1.95 (m, 1H), 2.14 - 2.23 (m, 3H), 2.34 (m, 1H), 3.73 (m, 1H, α-N), 4.78 and 4.80 (each s, 1H, $=CH_2$)), 4.88 (d, J = 6.8 Hz, NH), 5.06 (s, 2H), 7.25 - 7.34 (m, 5H). δ_C (75 MHz, $CDCl_3$): 23.4, 30.2, 30.4, 32.0, 32.5, 33.6 (6 x CH_2), 51.1 (NCH), 66.4 (CH_2Ph), 111.6 ($=CH_2$), 128.0, 128.1, 128.4 (3 x aryl CH), 136.6 (aryl C), 150.9 ($C=CH_2$), 155.4 (C=O). ν_{max} (CH_2Cl_2): 3330m, 3065w, 3030w, 2925s, 2850m, 1695s, 1640w, 1530s, 14850m, 1405w, 1315m, 1235s, 1145w, 1100w, 1075w, 1035w, 970w, 885m, 740m, 695m cm^{-1}. m/z (%) (CI): 274 (MH^+, 100), 230 (52), 140 (20), 138 (24), 123 (22), 108 (32), 91 (73); $C_{17}H_{24}NO_2$ [MH^+] requires m/z 274.1807; observed 274.181.

N-Benzoyl-1-Methyl-9-azabicyclo[4.2.1]nonane (5d)

Mercury(II) trifluoroacetate (753 mg, 1.75 mmol) was added to a stirred solution of (**22d**) (406 mg, 1.67 mmol) in dry acetonitrile (30 ml) at room temperature. The mercury salt dissolved forming a colourless solution which was stirred for 2.5h and then filtered. The filtrate was evaporated under reduced pressure to give an oil which was dissoved in dry tetrahydrofuran (40 ml). Sodium borohydride (126 mg, 3.34 mmol) was added to this solution with stirring at -78°C, and the solution was allowed to warm to room temperature. After stirring for 3.5h at room temperature, water was added and the solution was filtered. The filtrate was

evaporated under reduced pressure and the residue purified by flash chromatography (1:1 petroleum ether (40 - 60°C); diethyl ether) to yield **(5d)** (377 mg, 93%) as a white, waxy solid, m.p. 68 - 69°C (from petroleum ether 40 - 60°C)). δ_H (300 MHz, $CDCl_3$): 1.19 - 1.70 (series of m, 8H + brs, 3H), 1.93 - 2.22 (series of m, 3H), 2.45 (brm, 1H) 4.21 (brm, 1H), 7.27 - 7.42 (m, 5H). δ_C (75 MHz, $CDCl_3$): 23.5 & 25.4 (CH_2), 28.1 (CH_3), 29.0, 36.0, 38.3, 40.8 (4 x CH_2), 60.7 (CH), 65.0 (C), 126.6, 128.1, 129.1 (3 x aryl CH), 138.7 (aryl C), 171.1 (C=O). ν_{max} (CH_2Cl_2): 2960m, 2930m, 2860w, 1625s, 1445m, 1440s, 1370w, 1355w, 1200m cm^{-1}. m/z (%): 244 (6), 243 (M^+, 36), 186 (7), 139 (6), 138 (65), 106 (8), 105 (100), 77 (46); $C_{16}H_{21}NO$ [M^+] requires m/z 243.1623; observed 243.162.

3-Hydroxy-4-methylene-(benzoylamino)cyclooctane (23)

The first attempt to cyclise **(22d)** using a 1:1 mixture of mercury(II) acetate : mercury(II) trifluoroacetate in dry acetonitrile (using conditions as described for the production of **(5d)** above) resulted in the isolation of **(5d)** (42%), unchanged **(22d)** (28%), and **(23)** (22%). Numerous attempts to repeat the experiment in order to isolate more **(23)** for full characterisation were unsuccessful and only ^1H and ^{13}C NMR spectra for **(23)** were recorded: δ_H (300 MHz, $CDCl_3$) : 1.47 - 1.84 (series of m, 6H), 2.00 - 2.09 (m, 2H including 1H ddd, J = 15.0, ~5.2, ~2.2 Hz), 2.23 (ddd, J = 15.0, 6.6, 3.4 Hz, 1H), 2.41 (m, 1H), 4.14 (m, 1H, H_1), 4.30 (ddd J ≈ 5.2, 3.4, 1.5, 1.0 Hz, 1H), 4.50 (vbrs, OH), 4.96 (m, 1H, =CH), 5.32 (dd, J ≈ 1.5, 1.5 Hz, 1H, =CH), 6.55 (brd, J = 6.7 Hz, NH), 7.30 - 7.52 (m, 3H), 7.67 - 7.77 (m, 2H). Double irradiation of the ^1H signal at δ 4.30 (H_3; α-OH) led to removal of vicinal coupling to the H_2 protons [leaving signals at δ ~2.04 (dd, J = 15.0, ~2.2 Hz, 1H), and 2.23 (dd,J = 15.0, 6.6 Hz, 1H)], and removal of allylic coupling to the *exo*-methylene protons [leaving signals at δ 4.96 (brd, J ≈ 1.5 Hz, 1H, =CH) and 5.32 (d, J ≈ 1.5 Hz)]. δ_C (75 MHz, $CDCl_3$): 22.7, 28.6, 30.6, 33.5, 40.0 (5 x CH_2), 45.4 (NCH), 72.5 (OCH), 114.0 ($C=CH_2$), 126.9, 128.5, 131.5 (3 x aryl CH), 134.2 (aryl C), 151.1 ($C=CH_2$), 167.3 (C=O).

N-(Benzyloxycarbonyl)-1-Methyl-9-azabicyclo[4.2.1]nonane (5e)

Mercury(II) trifluoroacetate (0.152 g, 0.36 mmol) was added to a stirred solution of **(22e)** (0.092 g, 0.34 mmol) in dry acetonitrile (11.5 ml) as decribed above for **(5d)**. Following treatment with sodium borohydride (0.026 g, 0.66 mmol) the product was isolated as described for **(5d)** and purified by flash chromatography using 1:4 diethyl ether:petrol (b.p. 40-60°C) to give **(5e)** (0.057 g, 61%) as an oil together with **(27e)** (36%). In subsequent experiments, whe yield of **(5e)** was increased to 73%. **(5e)**: δ_H (300 MHz, $CDCl_3$): major rotamer *1.33 - 1.56* (series of m, 6H), *1.60* (s, 3H), *1.80 - 2.15* (brm, 6H), 4.34 (brt, J = 7.2 Hz, 1H), *5.03 & 5.2* (AB, J = 12.5 Hz, 2H), *7.25 - 7.37* (m, 5H); minor rotamer *1.33 - 1.56* (series of m, 6H), *1.60* (s, 3H), *1.80 - 2.15* (brm, 6H), 4.41 (m, 1H), *5.03 & 5.2* (AB, J = 12.5 Hz, 2H), *7.25 - 7.37* (m, 5H); δ_C (75 MHz, $CDCl_3$): major rotamer, 23.6 & *25.0* (CH_2), 28.6 (CH_3), *29.4*, 34.8, 38.8, 39.6 (4 x CH_2), 57.7 (CH), 63.9 (C), 66.0 (CH_2), *127.7, 127.8, 128.4* (3 x aryl CH), *137.2* (aryl C), *154.3* (C=O); minor rotamer, 23.5 & *25.0* (CH_2), 29.7 (CH_3), *29.4*, 33.1, 40.4, 41.2 (4 x CH_2), 58.7 (CH), 63.1 (C), 66.6 (CH_2), *127.7, 127.8, 128.4* (3 x aryl CH), *137.2* (aryl C), *154.3* (C=O) ν_{max} (CH_2Cl_2): 2930s, 2850m, 2690w, 1700s, 1450m, 1440m, 1340m, 1320m, 1120m, 1060m cm^{-1}. m/z (%) (CI): 274 (MH^+, 22), 173 (10), 172 (14), 138 (29), 91 (100); $C_{17}H_{24}NO_2$ requires m/z 274.1807 [MH^+]; observed 274.181.

N-(Benzyloxycarbonyl)-1-hydroxymethyl-9-azabicyclo[4.2.1]nonane (27e)

The hydroxymethyl compound **(27e)** (0.036 g, 36%) was isolated as a byproduct during chromatographic separation of a crude sample of **(5e)** prepared as described above. δ_H (300 MHz, $CDCl_3$): 1.26 - 1.66 (m, 7H), 1.81 (m, 2H), 2.08 (m, 2H), 2.31 (m, 1H), 3.60 & 3.70 (ABq, J = 12.2 Hz, 2H), 4.38 (m, 1H), 5.08 & 5.16 (ABq, J = 12.4 Hz, 2H), 7.28 - 7.36 (m, 5H). δ_C (75 MHz, $CDCl_3$): 24.0, 24.1, 29.1, 33.9, 34.2, 35.8 (6 x CH_2), 58.6 (CH), 67.0 (CH_2Ph), 68.7 (C), 68.9 (CH_2OH), 127.8, 128.0, 128.5 (3 x aryl CH), 136.6 (aryl C), 156.0 (C=O). ν_{max} (CH_2Cl_2): 3385brs, 3075w, 3060w, 3030w, 2930s, 2850m, 1675s, 1545w, 1455m, 1410m, 1345m, 1325m, 1280m, 1233m, 1205m, 1165m, 1120m, 1080m, 1060m, 1020m, 980w, 965w, 910w, 770m cm^{-1}. m/z (%): 289 (M^+, 5), 181 (49), 154 (19), 153 (65), 152 (52), 138 (11), 137 (11), 136 (11), 125 (15), 124 (24), 122 (12), 110 (10), 109 (61), 108 (100), 107 (87), 106 (12), 105 (14), 95 (100) 91 (100); $C_{17}H_{24}NO_2$ [M^+] requires m/z 289.1678; observed 289.168.

N-Benzyl-1-methyl-9-azabicyclo[4.2.1]nonane (5c)

A solution of **(5d)** (0.445 g, 1.83 mmol) in dry THF (7 ml) was added dropwise to a stirred slurry of lithium aluminium hydride (0.139 g, 3.66 mmol) in dry THF (7 ml). After 10 h at reflux, excess hydride was decomposed by addition of wet diethyl ether. The inorganic solids were removed by filtration and washed with warm ethyl acetate. The combined organic solutions were evaporated under reduced pressure to give a residue which was dissolved in HCl (1M, 10 ml) and washed with diethyl ether (3 x 10 ml). The aqueous layer was basified to pH 14 with concentrated aqueous NaOH, extracted with dichloromethane (5 x 10 ml), and the combined organic extracts were dried with magnesium sulphate and evaporated under reduced pressure to yield **(5c)** (0.38 g, 91%) as a pale yellow oil. δ_H (300 MHz, $CDCl_3$): 1.21 (s, 3H), 1.33 - 1.88 (series of m, 10H), 1.94 - 2.13 (m, 2H), 3.33 (m, 1H) 3.81, 3.87 (ABq, J = 14.6 Hz, 2H) 7.10 - 7.37 (m, 5H). δ_C (75 MHz, $CDCl_3$): 24.8 & 25.2 (CH_2), 29.3 (CH_3), 29.8, 32.8, 38.5, 41.2 (4 x CH_2), 47.3 (CH_2Ph), 57.1 (CH), 62.9 (C), 126.3, 127.9, 128.0 (3 x aryl CH), 141.8 (aryl C). ν_{max} (CH_2Cl_2): 3020w, 2950m, 2920s, 2860m, 1620m, 1490w, 1445m, 1400m, 1355w, 1205m, 1155m, 1025w cm^{-1}. $^m/z$ (%): 230 (7), 229 (M^+, 32), 186 (46), 173 (35), 172 (50), 104 (20), 91 (100), 82 (39), 65 (14), 57 (19), 55 (27), 41 (32); $C_{16}H_{23}N$ [M^+] requires $^m/z$ 229.1830; observed 229.183.

N-Methyl-1-methyl-9-azabicyclo[4.2.1]nonane (5a)

A solution of **(5e)** (0.102 g, 0.37 mmol) in dry THF (4 ml) was added dropwise to a stirred slurry of lithium aluminium hydride (0.028 g, 0.73 mmol) in dry THF (1 ml) under nitrogen at 0°C. The system was allowed to warm to ambient temperature, stirred for 3 h, then heated at reflux for 1 h. The excess hydride was destroyed by addition of water-saturated diethyl ether and the solution was dried with sodium sulphate and filtered through celite. The solution was cooled to 0°C, acidified with gaseous HCl, and the solvent was evaporated under reduced pressure. The resulting oil was repeatedly triturated with diethyl ether to remove benzyl alcohol and to induce crystallisation of **(5a:HCl)** as a pale yellow solid (0.054 g, 78%) which was recrystallised from toluene. δ_H (300 MHz, $CDCl_3$): 1.61 (s, 3H), 1.7 - 1.9 (m, 6H), 1.95 - 2.2 (m, 3H), 2.30 (m, 1H), 2.5 - 2.9 (m, 2H), 2.73 (d, $J_{Me,\ NH}$ = 4.4 Hz, 3H), 4.08 (bm, 1H), 11.62 (NH); in addition, small signals at δ 3.85 and 11.06 corresponded to H6 and the NH protons of the minor stereoisomeric quaternary salt. δ_C (75 MHz, $CDCl_3$, major stereoisomer): 22.7, 23.6 (2 x CH_2), 24.8 (CH_3), 28.1, 28.2, (2 x CH_2), 29.3 (CH_3), 34.6 (CH_2), 37.1 (CH_2), 62.7 (CH), 70.0 (C). ν_{max} (CH_2Cl_2): 3680w, 3380br, 3025m, 2940s, 2870m, 2390vbr, 1465m, 1445m, 1380m, 1265w, 1215w, 1205w, 1100m, 1085w, 1065w, 1045w, 1010w, 995w, 970w, 905s, 845w cm^{-1}. $^m/z$ (%): 153 (-HCl, M^+, 28), 152 (5), 126 (6), 124 (20), 111 (12), 110 (95), 98 (6), 97 (69), 96 (100), 82 (6), 81 (6), 71 (5), 56 (26), 55 (10); $C_{10}H_{19}N$ [M^+] requires 153.1517; found: 153.1516.

4-(Benzoylamino)cyclooct-2-enone (29d)

Barium manganate[15] (81.0 g, 344 mmol) was added to a stirred solution of **(9d)** (9.70 g, 39,54 mmol) in dry dichloromethane (1 l). After 18 h, the solution was filtered through a sintered glass funnel and the residue washed with ethyl acetate. The combined organic solutions were evaporated under reduced pressure to give an oil which was purified by flash chromatography (diethyl ether) to yield **(29d)** (7.65 g, 80%) as a colourless oil. [NMR data for the bicyclic tautomer **(31d)** are given separately as part of a later experiment]. **(29d)**: δ_H (300 MHz, $CDCl_3$): 1.47 - 2.03 (series of m, 6H), 2.53 (brm, 1H), 2.89 (ddd, J = 14.1, 10.2, 7.0 Hz, 1H), 5.43 (m, 1H, α-N), 6.03 (ddd, J = 12.6, 1.8, 0.9 Hz, 1H), 6,84 (brd, J = 7.4 Hz, 1H), 6.84 (brd, J = 7.4 Hz, NH), 7.38 - 7.80 (m, 5H). δ_C (75 MHz, $CDCl_3$): 22.5, 22.6, 30.7, 42.0 (4 x CH_2), 49.3 (NCH), 127.1, 128.4, 131.6 (3 x aryl CH), 132.6 (=CH), 134.0 (aryl C), 144.2 (=CH), 167.1 (PhC=O), 203.7 (C=O). ν_{max} (CH_2Cl_2): 3440m, 3320w, 2940m, 2860w, 1660vs, 1600m, 1580m, 1510s, 1485m, 1455m, 1390w, 1350m, 1320m, cm^{-1}. $^m/z$ (%) (CI): 244 (MH^+, 100), 226 (6), 139 (24), 123 (8), 122 (89), 105 (14), 94 (3); $C_{15}H_{17}NO_2$ [MH^+] requires 244.1338; observed 244.134.

4-([Benzyloxycarbonyl]amino)cyclooct-2-enone (29e) and N-Benzyloxycarbonyl-1-hydroxy-9-azabicyclo[4.2.1]non-7-ene (31e)

Barium manganate[15] (48.0 g, 180 mmol) was added to a stirred solution of **(9e)** (4.56 g, 16.6 mmol) in dry dichloromethane (215 ml) under nitrogen. The suspension was stirred at room temperature for 48 h. Dichloromethane (100 ml) was added with stirring and the mixture was filtered through celite. The solvent was removed under vacuum and the resulting oil purified by flash chromatography using 1:4 diethyl

ether:petrol (b.p. 40-60°C) to yield (**29e**) (3.83 g, 85%) as a yellow oil. Data for the monocyclic (**29e**) and bicyclic (**31e**) tautomers are given separately below; where signals due to two rotamers were visible, figures given italics are common to both rotamers. δ_H (300 MHz, $CDCl_3$); **bicyclic tautomer**: *1.27 - 1.66* (series of m, 5H), *1.89* (m, 1H), *2.02* (m, 1H), *2.29* (m, 1H), 4.71 (m, 1H, α-N, major rotamer), 4.75 (m, 1H, α-N, minor rotamer), *5.13, 5.20* (ABq, J = 12.2 Hz, 2H, CH_2Ph), 5.71 (d, J = 6.2 Hz, 1H, =CH, minor rotamer), 5.74 (dd, J = 6.2, 1.0 Hz, 1H, =CH, major rotamer), 5.86 (dd, J = 6.2, 2.6 Hz, 1H, =CH, major rotamer), 5.89 (dd, J = 6.2, 2.6 Hz, 1H, =CH, minor rotamer), 7.30 - 7.37 (m, 5H); **monocyclic tautomer**: 1.44 - 2.01 (series of m, 6H), 2.54 (m, 1H), 2.84 (m, 1H), 4.95 (m, NH), 5.01 (m, 1H, α-N) 5.12 (s, 2H), 6.09 (m, 2H, =CH). δ_C (75 MHz, $CDCl_3$); **bicyclic tautomer**: 23.2, 23.6, 30.8, 38.7 (4 x CH_2), 60.8 (CH), 66.4 (CH_2Ph), 95.7 (COH), 127.8, 128.0, 128.4, (3 x aryl CH), 131.6 & 132.3 (=CH), 136.4 (aryl C), 154.0 (C=O); **monocyclic tautomer**: 22.4, 22.6, 31.0, 42.0 (4 x CH_2), 50.6 (CNH), 67.0 (CH_2Ph), 128.16, 128.22, 128.5, (3 x aryl CH), 132.7 (=CH), 136.1 (aryl C), 144.1 (=CH), 155.6 (NC=O), 203.4 (α,β-unsaturated CO). ν_{max} (CH_2Cl_2); **bicyclic tautomer**: 3470brw, 2930m, 2850w, 1670s, 1415m, 1350m, 1320m, 1190m, 1125m, 1095m, 1040w, 1020w, 995m, 945w, 835w cm^{-1}; **monocyclic tautomer**: 3430m, 2950m, 2860m, 1715s, 1660m, 1500m, 1350w, 1320brm, 1215m, 1170w cm^{-1}. m/z (%): 23 (M^+, 13), 229 (10), 186 (34), 165 (12), 138 (23), 137 (11), 124 (16), 122 (22), 121 (21), 120 (17), 109 (26), 108 (87), 107 (61), 106 (10), 105 (30), 91 (100); $C_{16}H_{19}NO_3$ [M^+] requires 273.1365; observed 273.136.

2-(Benzoylamino)-5-methylenecycloocta-1,3-diene (30)
N-Benzoyl-1-hydroxy-9-azabicyclo[4.2.1]non-7-ene (31d)

Anhydrous cerium chloride[19] (2.93 g, 12.3 mmol) in a two-neck flask was heated gradually to 135 - 140°C. After 1 h at this temperature, a magnetic stirrer bar was placed in the flask and the cerium chloride was dried completely by stirring under vacuum at the same temperature for an additional 2 h. Dry nitrogen was introduced into the hot flask which was then cooled in an ice bath. Freshly distilled THF (10 ml) was added in one portion with vigorous stirring, the ice bath was removed, and the suspension was stirred under nitrogen for 20 h at room temperature. Magnesium turnings (299 mg, 12.3 mmol) were placed in a two-neck flask fitted with a reflux condenser and a nitrogen bubbler. A crystal of iodine was added followed by chloromethyltrimethylsilane (252 μl, 1.81 mmol) in dry THF (0.5 ml). When the reaction started, the stirrer was set in motion and a solution of chloromethyltrimethylsilane (1.464 ml, 10.49 mmol) in dry THF (3.5 ml) was added over 20 min. The flask containing the cerium chloride was immersed in an ice/water bath and the Grignard reagent (12.3 mmol) was added. After stirring the suspension for 1.5 h at 0°C, a solution of (**29d**) (598 mg, 2.46 mmol) in dry THF (5 ml) was added and the stirring was continued for 30 min at 0°C. A 10% solution of aqueous acetic acid (25 ml) was added and the product was extracted into diethyl ether, washed with sodium bicarbonate solution, water, then dried over magnesium sulphate. The solvent was evaporated under reduced pressure to leave an orange oil which was purified by flash chromatography yielding (**30**) (141 mg, 25%) as a yellow oil, together with starting material (**29d**) (299 mg, 50%) and the bicyclic tautomer (**31d**) (132 mg, 22%) as a colourless oil.

(**30**): δ_H (300 MHz, $CDCl_3$): 1.60 - 1.69 (brm, 2H), 2.27 - 2.35 (brm, 2H), 2.50 - 2.60 (brm, 2H), 4.95 (brd, J = 0.8 Hz, 1H, $=CH_2$), 5.02 (brm, 1H, $=CH_2$), 5.49 (d, J = 12.2 Hz, 1H, alkene), 6.03 (dd, J = 8.7, 8.6 Hz, 1H, alkene), 6.15 (d, J = 12.2 Hz, 1H, alkene), 7.20 - 7.87 (series of m, 5H). δ_C (75 MHz, $CDCl_3$): 25.1, 29.1, 30.2 (3 x CH_2), 120.1 (=CH), 120.3 ($C=CH_2$), 122.1 (=CH), 126.9, 128.3, 131.2 (3 x aryl CH), 134.2 (aryl C), 134.7 (=C), 134.9 (=CH), 147.3 ($C=CH_2$), 166.1 (PhC=O). ν_{max} (CH_2Cl_2): 3420m, 2930m, 2860m, 1670s, 1600m, 1580m, 1510s, 1480m, 1450m, 1345m, 1325m, 1295w, 1205w cm^{-1}. m/z (%) (CI): 240 (MH^+, 100), 207 (7), 194 (13), 167 (4), 139 (12), 122 (41), 105 (20), 90 (13), 71 (2); $C_{16}H_{18}NO$ [MH^+] requires 240.1388; observed 240.139.

(**31d**) δ_H (300 MHz, $CDCl_3$): 1.22 - 1.70 (series of m, 6H), 1.96 (m, 1H), 2.55 (m, 1H), 4.72 (brd, J = 5.6 Hz, 1H), 5.71 (brs, OH), 5.84 (s, 2H 2H, alkene), 7.33 - 7.55 (m, 5H). δ_C (75 MHz, $CDCl_3$): 23.1, 23.9, 31.8, 38.5 (4 x CH_2), 63.2 (CH), 97.5 (COH), 126.5 & 128.5, (aryl CH), 129.9 (=CH), 131.0 (aryl CH), 132.9 (=CH), 135.6 (aryl C), 170.7 (PhC=O). ν_{max} (CH_2Cl_2): 3440brw, 2930m, 2860w, 1635m, 1610s, 1600s, 1575m, 1490w, 1440m, 1400m, 1325w, 1230w, 1195m, 1150m, 1130m, 1115m cm^{-1}. A solution of (**31d**) in $CDCl_3$ reverted completely to (**29d**) over a period of 3 weeks, as indicated by ^1H NMR spectroscopy.

4-Methylene-(benzoylamino)cyclooct-2-ene (32d)

A 50 ml three-neck round-bottom flask was charged with sodium hydride (0.384 g, 16 mmol) which had been washed with several portions of dry petroleum ether to remove the mineral oil. The flask was equipped with rubber septum caps, a reflux condenser fitted with a three-way tap, and a magnetic stirring bead. The system was alternately filled and evacuated with nitrogen; dry DMSO (4 ml) was introduced via a syringe, and the mixture was heated at 75 - 80°C for 45 min. The resulting solution of methylsulphinyl carbanion[20] was cooled in an ice-water bath, and methyltriphenylphosphonium bromide (5.72 g, 16 mmol) in warm, dry DMSO was added. The resulting orange-green solution of the ylide was stirred at room temperature for 10 min. A solution of (**29d**) (0.710 g, 2.91 mmol) in dry DMSO (5 ml) was added to the ylide and the reaction mixture was stirred for 15 h at room temperature. The solvent was removed under reduced pressure, the residue dissolved in dichloromethane, and the solution washed with water. After drying over magnesium sulphate, the solution was evaporated under reduced pressure leaving an oil which was purified by flash chromatography using 1:1 diethyl ether; petrol ether (b.p. 40-60°C) to yield (**32d**) (0.555 g, 79%) as white crystals, m.p. 147.5 - 148.5°C from toluene. δ_H (300 MHz, $CDCl_3$): 1.46 (m, 1H), 1.60 - 1.77 (m, 4H), 1.98 (m, 1H), 2.39 (brdd, J = 14.4, 6.5 Hz, 1H), 2.83 (m, 1H), 4.90 (brs, 1H, $=CH_2$), 4.98 (brd, J = 1.9 Hz, 1H, $=CH_2$), 5.19 (dd, J = 12.1, 6.7 Hz, 1H, =CH), 5.62 (m, 1H, α-N), 6.22 (brd, J = 12.1 Hz, 1H, =CH), 6.39 (brd, J = 7.5 Hz, NH), 7.26 - 7.49 (m, 3H), 7.72 - 7.80 (m, 2H). δ_C (75 MHz, $CDCl_3$): 21.7, 28.2, 33.6, 34.3 (4 x CH_2), 48.2 (NCH), 118.9 ($C=CH_2$), 126.9 & 128.4 (CH, aryl), 129.7 (=CH), 131.3 (aryl CH), 134.4 (=CH), 134.6 (aryl C), 146.1 ($C=CH_2$), 166.7 (PhC=O). ν_{max} (CH_2Cl_2): 3440m, 2940m, 2850m, 1660s, 1600w, 1590m, 1580m, 1515s, 1485m, 1325m, 1180w, 1140w cm^{-1}. m/z (%): 241 (M^+, 8), 213 (3), 146 (3), 136 (6), 120 (11), 106 (10), 105 (100), 91 (17), 77 (87), 65 (6), 51 (25), 41 (6). Found: C, 79.60; H 7.95; N, 5.73%. $C_{16}H_{19}NO$ requires C, 79.63; H, 7.94: N, 5.80%.

4-Methylene-([benzyloxycarbonyl]amino)cyclooct-2-ene (32e)

The exo-methylene derivative (**32e**) was prepared using the method described for (**32d**) from sodium hydride(80% dispersion, 0.384 g, 12.8 mmol) in dry DMSO (8 ml), methyltriphenylphosphonium bromide (4.75 g, 13 mmol) in DMSO (12.5 ml), and (**29e**) (0.698 g, 2.56 mmol) in DMSO (7.5 ml). After flash chromatography using 1:9 diethyl ether:petrol ether (b.p. 40-60°C) (**32e**) was obtained as a white solid (0.397 g, 57%) which had m.p. 94 -95°C after recrystallisation from petrol (b.p. 80 - 100°C). δ_H (300 MHz, $CDCl_3$): 1.31 (m, 1H), 1.60 (m, 4H), 1.90 (m, 1H), 2.36 (m, 1H), 2.68 (m, 1H), 4.87 (s, 1H, $=CH_2$), 4.90 (s, NH), 4.96 (d, J = 1.0 Hz, 1H, $=CH_2$), 5.08, (s, 2H, CH_2Ph), 5.09 (m, 1H, =CH), 5.15 (m, 1H, α-N), 6.18 (d, J = 11.5 Hz, 1H, =CH), 7.32 (m, 5H). δ_C (75 MHz, $CDCl_3$): 21.6, 28.1, 33.6, 34.4 (4 x CH_2), 49.6 (NCH), 66.6 (CH_2Ph), 118.9 ($C=CH_2$), 128.0, 128.1, 128.4 (3 x aryl CH), 130.1 (=CH), 134.1 (=CH), 136.5 (aryl C), 146.0 ($C=CH_2$), 155.7 (C=O). ν_{max} (CH_2Cl_2): 3430m, 3010, 2940m, 2850w, 1715s, 1590w, 1505s, 1470w, 1460w, 1320w, 1220m, 1040m, 1030m, 975w, 895w cm^{-1}. m/z (%) (CI): 272 (MH^+, 100), 228 (91), 211 (20), 136 (22), 121 (36), 108 (25), 91 (17); $C_{17}H_{22}NO_2$ (MH^+) requires m/z 272.1651; found 272.165. Found: C, 75.19; H, 7.97; N, 5.17%. $C_{17}H_{21}NO_2$ requires C, 75.24; H, 7.80; N, 5.16%.

N-(Benzyloxycarbonyl)-1-methyl-9-azabicyclo[4.2.1]nonan-7-ol and -8-ol (33)

The cyclisation of (**32e**) was carried out according to the method described for (**5d**) using mercury(II) trifluoroacetate (0.216 g, 0.51 mmol) and (**32e**) (0.131 g, 0.48 mmol) in dry acetonitrile (8.3 ml). The reduction was carried out using sodium borohydride (0.037 g, 0.98 mmol) in dry THF (13.5 ml) to give (**33**) (0.076 g, 54%) after flash chromatography using 2:3 diethyl ether:petrol ether (b.p. 40-60°C). δ_H (90 MHz, $CDCl_3$): 1.2 - 1.8 (m, 9H including CH_3), 1.8 - 2.4 (series of m, 5H), 3.8 - 4.4 (m, 1H), (s, 2H, CH_2Ph), 7.30 (s, 5H). The high-resolution ^1H and ^{13}C NMR spectra of the mixture were complicated at ambient temperature due to slow rotation around the N-CO bond. ν_{max} (CH_2Cl_2): 3440br, 2930s, 2960m, 1680s, 1575w, 1530w, 1500w, 1450m, 1335m, 1235m, 1200m, 1160m, 1135m, 1050m cm^{-1}. m/z (%): 289 (M^+, 17), 271 (6), 228 (6), 184 (8), 154 (24), 110 (11), 108 (13), 107 (12), 106 (13), 105 (12), 91 (100); $C_{17}H_{23}NO_3$ (M^+) requires m/z 289.1680; found 289.168. Partial analysis of the ^1H NMR spectra of a mixture of the secondary amines derived from deprotection of (**33**) supported the structural assignments but subtle conformational effects appear to be operating and further study is needed in view of the variations in J values.

However, the presence of two isomeric hydroxy- compounds was confirmed by Jones oxidation to a mixture of two keto- derivatives:

N-(Benzyloxycarbonyl)-1-methyl-9-azabicyclo[4.2.1]nonan-7-one and -8-one.

The high-resolution ^1H and ^{13}C NMR spectra of the mixture were complicated at ambient temperature due to slow rotation around the N-CO bond. δ_H (90 MHz, $CDCl_3$): 0.7 - 2.8 (complex; CH_2, CH_3), 4.1 - 4.7 (H_6), 5.0 - 5.25 (CH_2Ph), 7.30 (bs, CH_2Ph). Partial ^1H NMR data obtained at higher temperature in toluene-d_8 are recorded here (300 MHz, 363 K): ***7-keto-***: δ_H 4.0 (bd, $J_{5,6}$ = 8.4 Hz, H_6), 2.02, 1.83 (ABq, J ≈ 18 Hz, H_{8x},H_{8n}) [double irradiation at δ 4.0 sharpened one half of the AB quartet (w-coupling) but the lack of vicinal coupling confirmed the assignments of H_8 and H_6 and the position of the CO at C7]. ***8-keto-***: δ_H 4.3 (v broad & complex, H_6), 2.2 (dd, J_{gem} = 17.4, $J_{6,7x}$ = 8.7 Hz, H_{7x}) [double irradiation at δ 4.3 removed the vicinal coupling between H_6 and H_{7x} leaving a doublet J = 17.4 Hz and confirming the placing of the CH_2 at C7 and the carbonyl at C8]. ν_{max} (CH_2Cl_2): 1753s, 1695vs cm^{-1}. m/z (%): 287 (M^+, 4), 259 (7), 151 (6), 149 (4), 124 (11), 92 (9), 91 (100), 65 (6); $C_{17}H_{21}NO_3$ (M^+) requires m/z 287.1521; found 287.1521.

N-Benzoyl-1-methyl-9-azabicyclo[4.2.1]non-7-ene (6d)

The cyclisation of **(32d)** was carried out according to the method described for **(5d)** using mercury(II) trifluoroacetate (0.374 g, 0.87 mmol) and **(32d)** (0.200 g, 0.83 mmol) in dry acetonitrile (15 ml). The reduction was carried out using sodium borohydride (0.0627 g, 1.66 mmol) in dry THF (20 ml) to give **(6d)** (0.095 g, 48%) as a pale yellow oil after flash chromatography using 2:3 diethyl ether:petrol ether (b.p. 40-60°C). A small amount of unchanged **(32d)** (0.010 g, 10%) was also recovered but other, minor, products were not characterised. Spectroscopic data for **(6d)**: δ_H (300 MHz, $CDCl_3$): 1.20 - 1.36 (m, 2H), 1.43 - 1.76 (series of m, 5H), 1.76 (s, 3H), 2.43 (m, 1H), 4.70 (brddd, J = 5.4, 2.2, 1.6 Hz, 1H), 5.58 - 5.62 (AB of ABX system, J_{AB} ≈ 6.1 Hz, J_{BX} ≈ 2.2 Hz, J_{AX} ≈ 0 Hz, 2H, alkene), 7.33 - 7.49 (m, 5H). [Double irradiation of the alkene proton signals at δ 5.58 - 5.62 led to collapse of the brddd at δ 4.70 to a brdd, J = 5.4, 1.6 Hz (vicinal coupling to CH_2 at C-5). Conversely, irradiation of the bridgehead proton at δ 4.70 collapsed the alkene signals to a simple AB system, J ≈ 6.1 Hz]. δ_C (75 MHz, $CDCl_3$): 23.2 (CH_2), 24.1 (CH_3), 25.3, 33.0, 36.2 (3 x CH_2), 65.4 (CH), 69.9 (C), 126.9, (aryl CH), 127.3, (=CH), 128.2 & 129.4 (aryl CH), 137.5 (=CH), 137.6 (aryl C), 170.3 (C=O). ν_{max} (CH_2Cl_2): 2930s, 2860m, 1640s, 1615s, 1615s, 1580m, 1510w, 1480w, 1445m, 1405s, 1360m, 1325m, 1205m, 1170m cm^{-1}. m/z (%): 242 (7), 241 (M^+, 13), 198 (4), 136 (2), 120 (6), 106 (10), 105 (100), 94 (4), 77 (41), 65 (2), 51 (7); $C_{16}H_{19}NO$ (M^+) requires m/z 241.1467; found 241.147.

N-(Benzyloxycarbonyl)-1-methyl-9-azabicyclo[4.2.1]non-7-ene (6e)

The cyclisation of **(32e)** was carried out according to the method described for **(5d)** using mercury(II) acetate (0.190 g, 0.60 mmol) and **(32e)** (0.080 g, 0.30 mmol) in dry acetonitrile (19 ml). The reduction was carried out using sodium borohydride (0.023 g, 0.61 mmol) in dry THF (12 ml) to give **(6e)** (0.036 g, 45%) after flash chromatography using 1:9 diethyl ether:petrol ether (b.p. 40-60°C) together with unchanged **(32e)** (0.026 g). δ_H (300 MHz, $CDCl_3$, δ values in italics refer to overlapping signals due to major and minor rotamers): *1.26 - 1.61* (m, 6H), 1.52 (s, 3H, minor rotamer), 1.65 (s, 3H, major rotamer), *1.97* (m, 1H), *2.16* (m, 1H), 4.72 (ddm, J = ca. 6.0, 2.6 Hz, 1H, major rotamer), 4.79 (dm, J = ca. 5.4 Hz, 1H, minor rotamer), 5.07, 5.18 (ABq, J = 12.5 Hz, 2H, CH_2Ph, major rotamer), 5.18 (s, 2H, CH_2Ph, minor rotamer), 5.47 (d, J = ca. 6.2 Hz, 1H, minor rotamer), 5.49 (dd J = 6.2, 0.8 Hz, 1H, major rotamer), 5.64 (dd, J = 6.2, 2.6 Hz, major rotamer), 5.67 (dd, J = ca. 6.2, 2.6 Hz, 1H, minor rotamer), *7.5*, (m, 5H). δ_C (75 MHz, $CDCl_3$), major rotamer: 23.7 (CH_2), 24.3 (CH_3), 24.8, 31.7 & 37.0 (3 x CH_2), 62.8 (CH), 66.1 (CH_2Ph), 68.8 (CCH_3), 127.75 (=CH), 127.8, 128.0 & 128.4 (3 x aryl CH), 136.4 (=CH), 137.0 (aryl C); minor rotamer: 23.4 & 25.0 (CH_2), 25.6 (CH_3), 30.3 & 38.1 (CH_2), 63.8 (CH), 66.6 (CH_2Ph), 68.0 (CCH_3), 127.7 (aryl CH), 127.8 (=CH), 128.1 & 128.5 (aryl CH), 137.1 (=CH), 137.1 (aryl C); the CO signals were too weak to be resolved. ν_{max} (CH_2Cl_2): 3025m, 2865w, 1695s, 1630w, 1570w, 1560w, 1550w, 1520w, 1510w, 1505w, 1445w, 1405s, 1235m, 1155w, 1100m, 1040m, 935 cm^{-1}. m/z (%): 271 (M^+, 5), 185 (7), 92 (8), 91 (42), 44 (39), 32(100); $C_{17}H_{21}NO_2$ (M^+) requires m/z 271.1572; found 271.157.

References.

1. Carmichael, W.W.; Biggs, D.F.; Gorham, P.R. *Science*, **1975**, *187*, 542; Sardina, F.J.; Howard, M.H.; Morningstar. M.; Rapoport, H. *J.Org. Chem.*, **1990**, 55, 5025 and references therein.
2. **a.** Cope, A,C.; Nace, H.R.; Estes, L.L. Jr., *J.Amer.Chem.Soc.*, **1950**, *72*, 1123.
   b. Derivatives have also been produced from 8-ring precursors (though often as mixtures with other by-products) by:
   addition of cyanogen azide to cyclooctatetraene [Anastassiou, A.G. *J.Amer.Chem.Soc.*, **1968**, *90*, 1527;
   Ag(I)-catalysed transannular cyclisation of N-chloro-N-methylcyclooct-4-enamines [Bastable, J.W.; Hobson, J.D.; Riddell, W.D. *J.Chem.Soc.Perkin 1.*, **1972**, 2205];
   intramolecular Hg(II)-catalysed reactions of N-substituted cyclooctenyl aziridines [Barrelle, M.; Apparu, M. *Tetrahedron*, **1977**, *33*, 1309];
   1,4-cyclo-arylamination of cycloocta-1,3-diene [Barluenga, J.; Pérez-Prieto, J.; Asensio, G. *J.Chem.Soc.Chem.Commun.*, **1982**, 1181];
   treatment of cycloocta-1,5-diene with cyanamide and N-bromosuccinimide [Haufe, G.; Kleinpeter, E. *Tetrahedron Lett.*, **1982**, *23*, 3555].
3. Naylor (née Bathgate), A.; Howarth, N.; Malpass, J.R. *Tetrahedron*, **1993**, *49*, 451 and references therein.
4. Smith, C.R.; Malpass, J.R. *Tetrahedron Lett.*, **1992**, *33*, 273.
5. H. Iida, Y. Watanabe and C. Kibayashi, *J.Org.Chem.*, **1985**, *50*, 8516.
6. Vogel's Textbook of Practical Organic Chemistry, 5th Edition, Longman, London, **1989**.
7. Barrelle, M.; Apparu, M.; Gey, C. *Can.J.Chem.*, **1978**, *56*, 85; Scheiber, P.; Nádor, K. *Liebigs Ann.Chem.*, **1985**, 913.
8. Lamanec, T.R.; Bender, D.R.; DeMarco, A.M.; Karady, S.; Reamer, R.A.; Weinstock, L. *J.Org.Chem.*, **1988**, *53*, 1768 and references to earlier work cited therein.
9. Leeson, P.D.; James, K.; Baker, R. *J.Chem.Soc.Chem.Commun.*, **1989**, 433.
10. Takacs, J.M.; Helle, M.A.; Takusagawa, F. *Tetrahedron Lett.*, **1989**, *30*, 7321.
11. Barluenga, J.; Pérez-Prieto, J.; Bayón, A.M.; Asensio, G. *Tetrahedron*, **1984**, *40*, 1199.
12. Harding, K.E.; Marman, T.H. *J.Org.Chem.*, **1984**, *49*, 2838; Harding, K.E.; Burks, S.R. *J.Org.Chem.*, **1984**, *49*, 40.
13. For preliminary results concerning tautomerism in some of these systems, see Smith, C.R.; Malpass, J.R. *Tetrahedron Lett.*, **1992**, *33*, 277. A fuller discussion of this topic is in hand: Smith, C.R.; Justice D.; Malpass, J.R. manuscript in preparation.
14. **a.** Larock, R.C. Organomercury Compounds in Organic Synthesis, Ch. 4, Springer-Verlag, Berlin, **1985** and references therein.
    b. Quirk, R.P. *J.Org.Chem.*, **1972**, *37*, 3554.
15. Firouzabadi, H.; Ghaderi, E. *Tetrahedron Lett.*, **1978**, *34*, 839.
16. **a.** Peterson, D.J.; *J.Org.Chem.*, **1968**, *33*, 780.
    b. The isolation of **(30)** was unexpected; further work is required to resolve the precise conditions and mechanism leading to formation of this triene.
17. Perrin, D.D.; Armarego, W.L.F. *Purification of Laboratory Chemicals*, 3rd Edition, Pergamon, Oxford, **1988**.
18. Still, W.C.; Kahn, M.; Mitra, A. *J.Org.Chem.*, **1978**, *43*, 2923.
19. Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, Y.; Kamiya, Y. *J.Amer.Chem.Soc.*, **1989**, *111*, 4392.
20. Greenwald, R.; Chaykovsky, M.; Corey, E.J. *J.Org.Chem.*, **1963**, *28*, 1128.