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Synthetic Approaches to Nortropanes and Nortrop-6-enes; Intramolecular Displacement by Nitrogen in 7-Membered Rings

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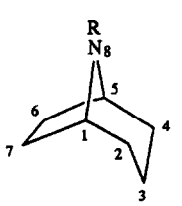
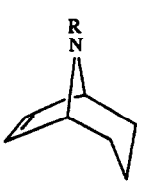
Abstract *The synthesis of simple nortropane and nortrop-6-ene derivatives from cyclohepta-1,3-diene is described. The key intermediates are trans-1-amino-4-chloro-cycloheptanes and -cyclohept-2-enes which are derived efficiently from the corresponding cis-amino-alcohols and undergo intramolecular cyclisation. Corresponding derivatisation of cyclohexa- and cycloocta-1,3-dienes is explored and attempts to achieve Pd-catalysed cyclisation of 1-amino-4-acetoxy-derivatives is described. Nitrogen inversion data for selected nortropane derivatives are included.*

Introduction

Our interest in nitrogen-bridged bicyclic molecules and, in particular, the unusual properties of the bridging nitrogen in 7-azabicyclo[2.2.1]heptyl derivatives[1] has led us to explore higher homologues. We have reported preliminary studies of a simple approach to 8-azabicyclo[3.2.1]octane (nortropane) and -oct-6-ene (nortrop-6-ene) derivatives including **(1b)**, **(1c)** and **(2c)**[2] and this has recently been extended to cover the next higher homologues, derivatives of the 9-azabicyclo[4.2.1]nonyl system.[3] We record here details of the scope of the method when applied to the synthesis of nortropane derivatives. The synthesis of substituted systems and further manipulation of the substituents at nitrogen will be reported separately.[4]



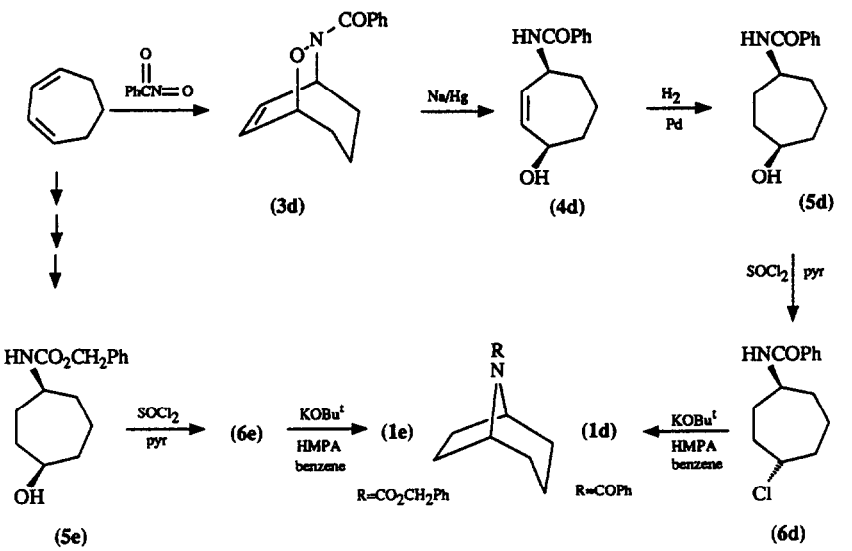
(1a) R=CH_3, tropane
(1b) R=H, nortropane
(1c) R=CH_2Ph
(1d) R=COPh
(1e) R=CO_2CH_2Ph
(1f) R=Cl



(2a) R=CH_3 trop-6-ene
(2b) R=H, nortrop-6-ene
(2c) R=CH_2Ph

The interesting pharmacological properties of derivatives of the tropane ring system are well known. A variety of synthetic approaches have been established since the pioneering work of Robinson[5a] with the major emphasis on derivatives incorporating an N-methyl substituent, an oxygen function at C_3, and a saturated 2-carbon bridge.[5] The Robinson route failed using substrates designed to incorporate a double bond or an epoxy-linkage into the C_6C_7 bridge and a number of recent schemes have addressed this problem by making use of [3+4] cycloaddition reactions with pyrroles as the 4π component.[6] However, these synthetic methods were often more successful for highly substituted tropane derivatives and the products usually retained a substituent on the nitrogen and an oxygen function at C_3. A novel approach by Kibayashi[7] was based on cycloaddition of nitroso compounds to cyclohepta-1,3-diene followed by reductive N-O cleavage and hydrogenation to give *cis*-1-aminocycloheptane-4-ol derivatives, e.g. (**5d**) and (**5e**) (scheme 1). Conversion into the chloro-compounds (**6d**) and (**6e**) followed by base-induced cyclisation led to (**1d**) and (**1e**), although the use of potassium *t*-butoxide in HMPA/benzene was necessary to achieve cyclisation. Tropane itself (**1a**) was available from (**1e**) by hydride reduction of the alkoxycarbonyl protecting group but attempted hydrolysis of (**1d**) to give nortropane (**1b**) was not successful and no attempts to produce 6-ene- derivatives (**2**) were reported. Bäckvall has reported a related approach based on 1,4-chloroacetoxylation of cycloheptadiene and derivatives followed by stereocontrolled conversion into the N-*p*-toluenesulphonyl derivatives of the *cis*- or *trans*- 1,4-aminoacetates. Subsequent base-induced cyclisation led to tropan-3-ol derivatives.[8] The approach has recently been applied successfully to the synthesis of the 6,7-epoxy derivatives scopine and pseudoscopine.[9]

Scheme 1



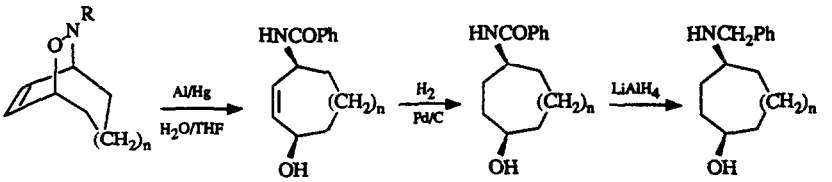
We sought a high-yield route to the tropane and trop-6-ene ring systems in order to extend our studies of nitrogen inversion in bridged bicyclic amines and stereoelectronic control in their reactions; we also required model compounds for the study of facial selectivity in reactions of π-bonds of unsaturated azabicycles with electrophiles, dienes and 1,3-dipoles. We felt that the intramolecular cyclisation approach offered the most attractive route to the parent compounds and also offered considerable potential for flexibility, allowing the preparation of non-natural tropane analogues. We chose to retain the advantages of the nitroso-cycloaddition route for the initial functionalisation of the 7-membered ring and thereby keep open the option of retaining unsaturation in the 2-carbon bridge. Modification of the nitrogen from amido- to *amino*- (and of the potential leaving group) prior to the intramolecular cyclisation step was intended to widen the scope of the cyclisation and the range of substituents at nitrogen in the azabicycles (**1**) and (**2**).

Results and Discussion

Nortropane and N-benzylnortropane

The cycloadduct (**3d**) was formed in 99% yield under the conditions described in reference 7, the nitroso-compound being formed *in situ* from benzohydroxamic acid and tetramethylammonium periodate. Similar cycloadditions using cyclohexa-1,3-diene and cycloocta-1,3-diene produced the adducts (**7**) and (**8**) in yields of 93% and 92% respectively (scheme 2). Each cycloadduct existed as a pair of rotamers. The rotational energy barriers about the amide C-N bonds were found by VT NMR to be 57.9 kJmol^{-1} for (**7**) and 55.6 kJmol^{-1} for (**3d**). The value for (**8**) could not be determined due to the intrusion of a second temperature-dependent process, presumably inversion of the 8-membered ring.

Scheme 2

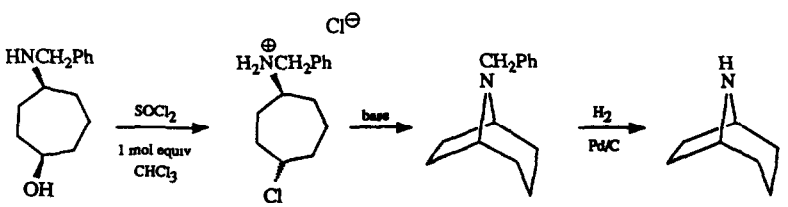


n=0:	(**7**)	(**9**)	(**11**)	(**13**)
n=1:	(**3d**)	(**4d**)	(**5d**)	(**14**)
n=2:	(**8**)	(**10**)	(**12**)	(**15**)

Reductive cleavage of the N-O bond in (**3d**), (**7**) and (**8**) could be achieved with 5% sodium amalgam.[7] However, we found the use of aluminium amalgam in aqueous THF[12] offered significant advantages; the yield of (**4d**), for example, was raised from 77%[7] to 92%. Hydrogenation gave the corresponding amido-alcohols in essentially quantitative yields. The route diverged from the path of earlier work at this point. Reduction with lithium aluminium hydride gave the corresponding benzyl amines (**13**), (**14**) and (**15**) in the hope that the more nucleophilic amino-nitrogen would facilitate the cyclisation step and also offer a simple route to the secondary amines *via* standard debenzylation procedures.

Attention was directed primarily at the cyclisation of (**14**), a potential precursor of the tropane skeleton, but treatment with thionyl chloride/pyridine failed to yield the *trans*-chloride. These initial difficulties (considerable difficulty with side-reactions had also been encountered in earlier conversions using thionyl chloride/pyridine[7]) were overcome by simply using 1 mole equivalent of thionyl chloride and no added base. Under these conditions, the amino-nitrogen acted as a very effective intramolecular base, neutralising the HCl formed in the reaction and ensuring efficient formation of chloride ion with which to achieve the substitution with clean inversion of configuration. The chloro-amine was formed as the hydrochloride salt (**16**) which could be isolated by evaporation of the solvent if desired; basification with pyridine was sufficient to liberate the free amine and induce cyclisation to yield (**1c**) in 88% yield from (**14**). Nortropane (**1b**) was then isolated in 94% yield after debenzylation of (**1c**) by catalytic hydrogenolysis (scheme 3). The presence of the bicyclic structure of (**1c**) and (**1b**) was immediately apparent from inspection of the ^{1}H and ^{13}C NMR spectra which indicated a high degree of symmetry.

Scheme 3



(**14**) (**16**) (**1c**) (**1b**)

In parallel studies, thionyl chloride was also used in attempts to convert (13) and (15) into the lower and higher homologues of (1) but without success; interestingly, the reaction of (13) with thionyl chloride produced an unusually stable chlorosulphite intermediate which was only converted into the corresponding *trans*-chloride under prolonged heating. The use of thionyl bromide (to introduce a better leaving group) gave no improvement in the case of (13) and was not investigated further. Adaptation of the method to the synthesis of homotropanes by cyclisation of (15) was successful and has been developed separately.[3]

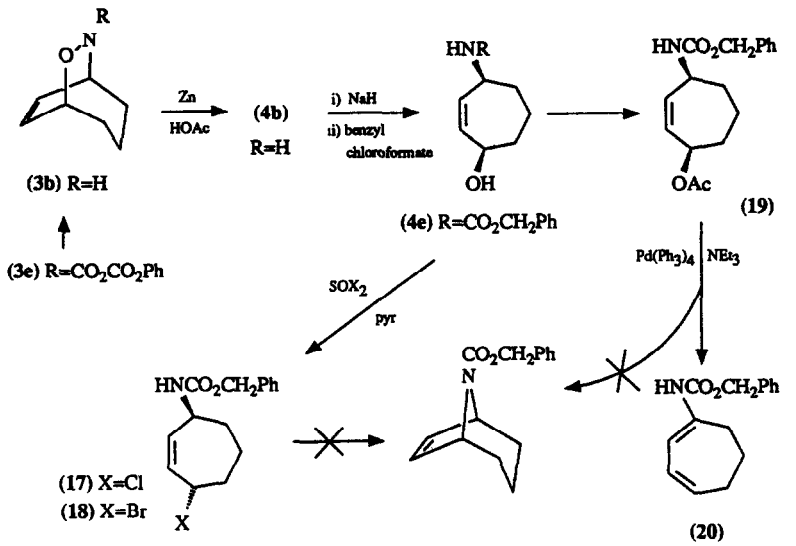
The conversion of (14) into (1c) appeared clean by NMR but, despite the use of NMR spectroscopy to ensure complete breakdown of the intermediate chlorosulphite in the thionyl chloride reaction, isolated yields of (1c) as low as 40% were sometimes obtained after chromatography. A polymer-supported base, 1,5,7-triazabicyclo[4.4.0]dec-5-ene on polystyrene crosslinked with 2% DVB (TABD), was used for the cyclisation step in order to simplify the separation of the tertiary amine product from the base in the work-up procedure. This constituted a simpler procedure and gave consistent, but lower, yields of approximately 40%.

The best overall yield for the 5-step process to nortropane (1b) from cyclohepta-1,3-diene via (1c) was 75%. We also prepared nortropane from (1e) by treatment with hydrogen bromide in ethanoic acid. Despite some improvements in the early stages of the synthesis of (1e)[7] from cycloheptadiene, the overall yield of (1b) by this route was 20%.

Approaches to nortrop-6-ene derivatives

Our early attempts to make derivatives of (2) started with the benzyloxycarbonyl-protected amino-alcohol (4e). Reductive cleavage of the cycloheptadiene/benzylnitrosoformate adduct (3e) in our hands gave only 7% of (4e) (the corresponding reduction of the ethoxycarbonyl analogue had earlier failed[7]). We achieved a higher overall yield of (4e) by the longer, but more efficient, route shown in scheme 4.

Scheme 4

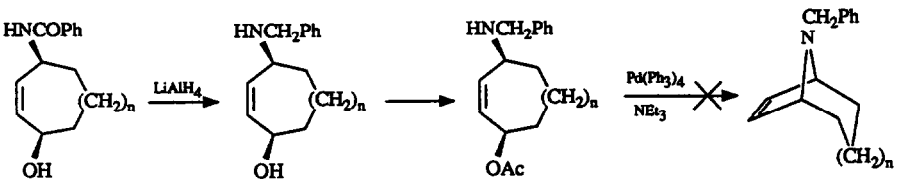


Treatment of (4e) with thionyl chloride/pyridine gave (17) but attempts to form (2e) by transannular cyclisation using a variety of bases and solvents failed. The incorporation of a better leaving group [bromide ion in (18)] was no more successful.

Palladium-catalysed cyclisation[10] was explored as a means of encouraging allylic substitution by nitrogen of a leaving group at the 4-position. Acetylation of (4e) gave the *cis*-acetoxy compound (19) which,

on treatment with $Pd(PPh_3)_4$ in the presence of triethylamine, gave not (**2e**) but rather the diene (**20**) *via* a Pd-catalysed elimination.[11] Palladium-induced cyclisation of the benzylamino-compounds was also investigated. The unsaturated amido alcohol (**4d**) was treated with lithium aluminium hydride to yield the corresponding amino alcohol (**21**). Reaction with ethanoic anhydride led to preferential acetylation at nitrogen and successful O-alkylation was only achieved following the addition of 1.1 equivalents of tetrafluoroboric acid to protonate the amino group. Careful work-up avoided O to N acetyl migration and afforded (**23**). Conversion of (**9**) into (**24**) was also carried out under similar conditions. Unfortunately, treatment with $Pd(PPh_3)_4$ in the presence of triethylamine gave no cyclisation products from either (**23**) or (**24**) (scheme 5).

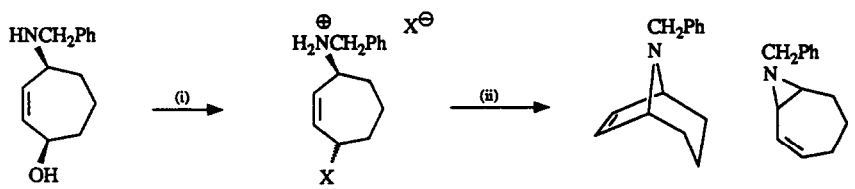
Scheme 5



n=1 (**4d**) (**21**) (**23**)
n=0 (**9**) (**22**) (**24**)

Successful cyclisation to give the trop-6-ene system (**2**) was achieved using the amino-alcohol (**21**). Application of the earlier cyclisation conditions, i.e. thionyl chloride at room temperature followed by pyridine, failed to give the desired bicyclic amines at first as did early experiments using anhydrous potassium carbonate as the base. However, when the heterogeneous mixture containing the hydrochloride (**25**) and potassium carbonate was sonicated, the 1,4-cyclisation product (**2c**) was formed together with the aziridine (**27**) from competitive 1,2- cyclisation (table 1).

Table 1



(**21**) (**25**) X=Cl (**26**) X=Br (**2c**) (**27**)

Reaction conditions		**Isolated yields**	
(i)	(ii)	(**2c**)	(**27**)
$SOCl_2/CHCl_3/RT$	pyridine	-	-
$SOCl_2/CHCl_3/0°C$	K_2CO_3	-	-
$SOCl_2/CHCl_3/0°C$	K_2CO_3/ultrasound	45%	20%
$SOCl_2/CHCl_3$/LiCl/0°C/u-sound	K_2CO_3/u-sound/24h	65%	10%
$SOCl_2/CDCl_3$/LiCl/0°C/u-sound	TABD/12h	33%	18%
$SOBr_2/CDCl_3/0°C \rightarrow RT/4h$	TMP/0→45°C	31%	
$SOBr_2/CDCl_3/0°C \rightarrow RT/5h$/evap	acetone/TMP/0→50°C/19h	58%	24%

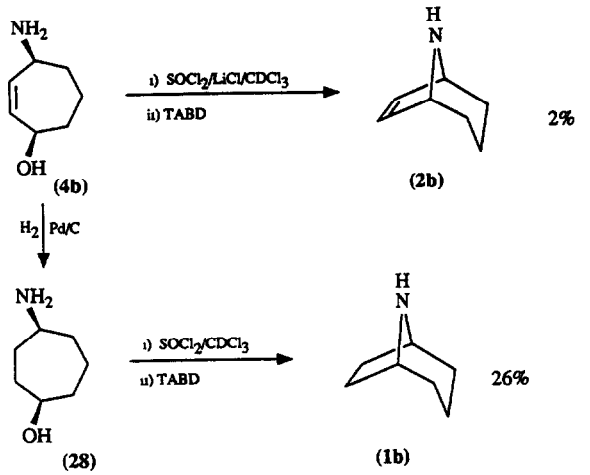
Again, some variations in isolated yields (down to 38%) occurred using anhydrous potassium carbonate despite careful attempts to achieve a constant quality of the reagents. Alternative conditions were explored and these are listed in table 1. Careful monitoring of the reaction using ^1H NMR ensured that the decomposition of the intermediate chlorosulphite (or bromosulphite) was complete before addition of the base. The addition of excess lithium chloride to the thionyl chloride reaction mixture led to an improvement, especially when the heterogeneous mixture was exposed to ultrasound. TABD led to poorer isolated yields as did the use of thionyl bromide and 2,2',6,6'- tetramethylpiperidine. The best and most consistent overall yield was obtained using thionyl bromide followed by evaporation of the solvent under vacuum and replacement with dry acetone prior to addition of TMP. The more polar solvent presumably assisted the intramolecular SN2 displacement of the bromide ion. Similar conditions have since been applied successfully in the homotropane series.[3]

Removal of the benzyl protecting group proved to be surprisingly difficult. Clearly, hydrogenolysis was inappropriate and the use of standard conditions including alkali metals in liquid ammonia, and chloroformates failed completely. A fuller study of the deprotection of bicyclic amino nitrogen is considered separately[4] and, in view of these problems, a more direct approach to nortrop-6-ene (and, concurrently, to nortropane) was sought.

A direct approach to nortropane and nortrop-6-ene.

The primary amino-alcohol (**4b**) was prepared as described in scheme 4 and hydrogenation gave (**28**) (scheme 6). Cyclisation of (**28**) occurred on treatment with thionyl chloride followed by TMP as shown by ^1H NMR but separation of the amine product from the TMP proved to be impossible by chromatographic means. The heterogeneous base TABD led to successful formation of (**1b**) but the yield of crude product was only 26% and further purification was not attempted. Similar conditions were applied to the cyclisation of (**4b**) but the yield of (**2b**) was only 2%. Variation of the reaction conditions including the use of potassium carbonate and ultrasound were unsuccessful and further attention was concentrated on the development of suitable removable protecting groups for the bridging nitrogen.[4]

Scheme 6



Inversion at Nitrogen in N-substituted nortropanes and -6-enes.

The N-benzyl amines (**1c**) and (**2c**) together with the N-chloro derivative (**1f**) were studied by VT NMR. The ^1H NMR spectrum of (**1c**) showed substantial broadening at low temperature but was not analysable at 300 MHz. The ^{13}C spectrum of (**1c**) at -100°C showed two sets of signals in an integrated ratio of 95:5 which were assigned to the equatorial and axial invertomers respectively. ^{13}C chemical shifts were

assigned bearing in mind the compression shifts resulting from the γ-effect. Thus, the equatorial benzyl group induces an upfield shift for $C_{6,7}$ relative to the corresponding value for the axial ($\Delta\delta_{a\rightarrow e}$ = -2.7 ppm); the corresponding $\Delta\delta_{e\rightarrow a}$ value for $C_{2,4}$ is -10.1 ppm as the benzyl group moves *syn*- to the 3-carbon bridge. The compression appears greater for $C_{2,4}$ than $C_{6,7}$ and this is seen also in the $\Delta\delta_{e\rightarrow a}$ value of -7.5 ppm for the benzylic carbon itself. The chemical shift values are very similar to those reported for tropane.[13] Coalescence measurements led to a value of 36.3 kJ mol^{-1} for the inversion barrier (axial → equatorial) for N-benzylnortropane (**2c**) and this compares with the recorded value for tropane (38.3 kJ mol^{-1})[13] whilst being substantially less than for lower homologues such as N-methylazabicyclo[2.2.1]heptane (57.4 kJ mol^{-1})[14] and a variety of other N-substituted derivatives of this more rigid ring system.[1a] Similar investigations were carried out on the unsaturated N-benzyl derivative (**2c**) but the signals due to the minor invertomer were too small to assign with complete confidence in this case. We have established in lower homologues (derivatives of 7-azabicyclo[2.2.1]heptanes)[1a] that steric interactions between an ethano bridge and a substituent on the bridging nitrogen can raise the energy of an invertomer relative to the etheno-bridged analogue and it is therefore not surprising that the etheno bridge in (**2c**) allows the equilibrium to be displaced even further towards the equatorial invertomer in this case.

Table 2. Selected ^{13}C NMR and $\Delta G^{\neq}_{inv}$ Data for N-Substituted Nortropanes

	X	ratio %	$C_{1,5}$ δ	$C_{2,4}$	C_3	$C_{6,7}$	NCH_2	$\Delta G^{\neq}_{ax\rightarrow eq}$ kJmol^{-1}	$\Delta G^{\neq}_{eq\rightarrow ax}$ kJmol^{-1}	T_c °K
(1c)	*e*- CH_2Ph[a]	95	58.9	31.8	16.0	25.1	57.0		41.4±0.9	205
	a- CH_2Ph[a]	5	54.5	21.7	16.0	27.8	49.5	36.3±0.9		
(2c)	*e*- CH_2Ph[a,d]	>98	65.4	25.6	16.6		57.8			
(1f)	*e*- Cl[b]	98	70.9	34.2	15.4	27.2			77.1±1.1	373
	a- Cl[b]	2	61.8	24.8[e]	16.2	25.8[e]		67.3±1.1		
(1f)	*e*- Cl[c]	96	70.4	33.8	14.9	26.7				
	a- Cl[c]	4	61.5	24.3[e]	15.8	25.3[e]				

a. measured in $CFCl_3/CDCl_3$ at -100°C **b.** in d_8-toluene at 25°C **c.** in $CFCl_3/CDCl_3$ at -80°C
d. signals due to the minor invertomer could not be assigned with confidence. **e.** these assignments may be reversed
note: Values for $\Delta G^{\neq}_{inv}$ were calculated using T_c and rate constants at T_c derived using the Gutowsky approximation. Errors are pessimistic estimates and stem largely from uncertainty in T_c [±5K].

In view of our inversion measurements in other N-chloroazabicycles,[1b] we also looked at the N-chloroamine (**1f**), prepared by chlorination of (**1c**). The invertomer ratio differed little from that observed for the N-benzyl compound but a predictable increase in the inversion barrier was observed. The measured value of 67.3 kJ mol^{-1} (axial → equatorial) is substantially higher than expected on application of the Kessler approximation[15] which predicts a value for the N-chloroamine (**1f**) in this case of 49.0 kJ mol^{-1}. It has already been observed that where an intrinsic barrier is already high (for example in 7-azabicyclo[2.2.1]heptanes[1b] due to operation of the 'bicyclic effect'), the normal barrier-raising effect of chlorine is augmented substantially.[16] However, the deviation for (**1f**) is surprising in view of the modest intrinsic inversion barriers reported for N-alkyl derivatives of the 8-azabicyclo[3.2.1]octane system.[13]

Experimental

Routine ^{1}H NMR spectra were recorded on Varian EM 390 (90 MHz) or Jeol JNM-PS100 (100 MHz) spectrometers. Higher field ^{1}H NMR (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Bruker AM 300 spectrometer at Leicester and ^{1}H (400 MHz) spectra were recorded using facilities funded by the SERC at the University of Warwick. 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), exch (exchangeable with D_2O). Where data are quoted for two rotamers, overlapping signals are shown in italics but are quoted separately for reasons of clarity. In the ^{13}C spectra, s, d, t, q are used to indicate quaternary, methine, methylene and methyl carbons respectively, as shown by off-resonance or DEPT measurements. Temperature measurements on the NMR instruments used for the VT work were found to be accurate to within ± 1 K over the range used.

IR spectra were recorded as solutions in CH_2Cl_2 unless indicated otherwise. Band intensities are described using standard abbreviations: s (strong), m (medium), w (weak), br (broad).

Mass spectra were measured routinely on a VG Micromass 14 spectrometer; intensities are given as percentages of the base peak. Accurate mass measurements were obtained 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 CHN Analysis Ltd. of South Wigston, Leicester or 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 was distilled from calcium hydride. Petroleum ether was dried over sodium wire and then distilled. Methanol and ethanol were purified with magnesium and iodine.[17] Tetrahydrofuran and toluene were 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.*.[18] Flash chromatography was carried out according to the method of Still *et al.*[19] using Merck Kieselgel 60 (230 - 400 mesh).

N-Benzoyl-8-oxa-9-azabicyclo[3.2.2]non-6-ene (3d)[7]

This compound was prepared as described in reference 7. The crude orange gum was flash-chromatographed (50:50 diethyl ether : petrol [b.p. 40-60°C]) to give crystals, m.p. 100 - 101°C (lit.[7] m.p. 101 - 102°C). IR: ν_{max} (CH_2Cl_2) 3050m, 2950s, 2875w, 1640s, 1610s, 1568m, 1495w, 1440s, 1375m, 1308m, 1240m, 1210m, 1170m, 1155m, 1108s, 1022m, 998m, 970m, 950m, 910m, 865w, 828m cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 248K): major rotamer *(ca. 78%)* δ *1.25 - 1.95* (series of m, 6H), *4.59* (brs, 1H), 5.37 (brs, 1H), *6.15 - 6.29* (m, 2H), *7.25 - 7.70* (m, 5H); minor rotamer *(ca. 22%)* δ *1.25 - 1.95* (series of m, 6H), *4.59* (brs, 1H), 4.94 (brs, 1H), *6.03 - 6.18* (m, 2H), *7.25 - 7.70* (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, 248K): major rotamer, δ 17.6 (t), 27.7 (t), 28.4 (t), 50.2 (d), 75.9 (d), 125.8 (d), 126.8 (d), 127.8 (d), 129.2 (d), 129.5 (d), 133.4 (s), 164.1 (s); minor rotamer, δ 17.1 (t), 28.7 (t), 29.9 (t), 55.0 (d), 75.4 (d), 124.4 (d), 126.5 (d), 127.5 (d), 127.9 (d), 128.1 (d), 133.8 (s), 165.5 (s). MS: ^{m}/z 229 (6%) M^+, 138 (3), 122(5), 106 (9), 105 (100), 103 (3), 77 (33).

N-Benzoyl-7-oxa-8-azabicylo[2.2.2.]oct-5-ene (7)

The adduct (**7**) was prepared using a similar method to that for (**3d**). Cyclohexa-1,3-diene (3.2 ml, 33.6 mmol) was added to a suspension of tetramethylammonium metaperiodate (12.60 g, 47.5 mmol) in chloroform (450 ml). To this mixture at 0°C was added dropwise a solution of benzohydroxamic acid (6.52 g, 47.5 mmol) in dimethylformamide (35 ml) and chloroform (90 ml). The reaction mixture was stirred as it warmed to room temperature and was left to stand overnight. The chloroform was evaporated under vacuum and the product taken up in diethyl ether. The ethereal solution was washed with water (6 x 100 ml) to remove the dmf, dried over magnesium sulphate and the solvent evaporated to yield (**7**) (6.69 g, 93%) as an orange semi-crystalline solid. Crystallisation from chloroform/diethyl ether gave colourless crystals (84%) which were used in further work. Chromatographic separation on silica using 50:50 diethyl ether/petrol as eluant gave a sample which, after recrystallisation, had m.p. 107 - 109°C. Found: C, 72.81; H, 6.15; N,

6.56% $C_{13}H_{13}NO_2$ requires: C, 72.59; H, 6.09; N, 6.51%.[20] IR: ν_{max} (CH_2Cl_2) 3040m, 2975w, 2940m, 1630s, 1575m, 1450m, 1400m, 1365m, 1290w, 1235m, 1215w, 1165s, 1115w, 1085w, 1050m, 950m, 925m, 885m, 845w cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 248K): major rotamer *(ca. 58%)* δ *1.41 - 1.61* (m, 2H), *2.09 - 2.38* (m, 2H), 4.66 (m, 1H), 4.98 (brd, J = 6.4Hz, 1H), 6.43 (ddd, J = 6.4, 6.4, 1.0 Hz, 1H), 6.58 (ddd, J = 6.4, 6.4, 1.0 Hz, 1H), *7.32 - 7.52* (m, 5H); minor rotamer *(ca. 42%)* δ *1.38 - 1.61* (m, 2H), *2.02 - 2.38* (m, 2H), 4.75 (m, 1H), 5.44 (brd, J = 6.4 Hz, 1H), 6.52 (ddd, J=6.4, 6.4, 1.0 Hz, 1H), 6.72 (ddd, J=6.4, 6.4, 1.0 Hz, 1H), *7.32 - 7.52* (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$, 248K): major rotamer, δ 21.5 (t), 23.0 (t), 51.8 (d), 71.7 (d), 127.4 (d), 128.6 (d), 128.9 (d), 129.8 (d), 131.7 (d), 133.4 (s), 166.7 (s); minor rotamer, δ 20.4 (t), 22.9 (t), 46.3 (d), 71.9 (d), 127.2 (d), 129.6 (d), 130.6 (d), 131.3 (d), 132.6 (d), 133.6 (s), 167.7 (s). MS: m/z 215 (9%) M^+, 137 (18), 122 (40), 121 (9), 119 (17), 106 (16), 105 (100), 104 (6), 103 (36).

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

Cycloocta-1,3-diene (1.02 g, 9.43 mmol) reacted with the nitroso compound generated from benzohydroxamic acid (1.80 g, 13.13 mmol) and tetramethylammonium metaperiodate (3.43 g, 12.94 mmol) according to the procedure described for (**7**). After stirring overnight, the solution was filtered and the solvent removed under reduced pressure yielding an oil which was dissolved in diethyl ether (200 ml) and washed with water (3 x 50 ml). The organic layer was separated, dried over magnesium sulphate and evaporated to yield (**8**) (2.10 g, 92%) as a yellow-orange oil. Purification by flash chromatography (3:2 petroleum ether [b.p. 40 - 60°C] diethyl ether) gave (**8**) as colourless crystals, m.p. 72.5 - 73.5°C from petrolem ether.[20] Found: C, 73.85; H, 7.06; N, 5.80% $C_{15}H_{17}NO_2$ requires: C, 74.05; H, 7.04; N, 5.76%. IR: ν_{max} (CH_2Cl_2) 3050w, 2930s, 2860w, 1620vs, 1575m, 1445m, 1425m, 1385w, 1320w, 1270w, 1215m, 1185m, 1025m, 1020m, 990w, 930w cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 218K): major rotamer *(ca. 60%)*, δ *1.46 - 2.27* (series of m, 8H), 4.82 (brs, 1H), *5.21* (brs, 1H), 6.23 (m, 2H), *7.34 - 7.51* (m, 5H); minor rotamer *(ca. 40%)* δ *1.37 - 2.27* (series of m, 8H), 4.51 (brs, 1H), *5.21* (brs, 1H), 5.90 (m, 1H), 6.06 (m, 1H), *7.34 - 7.51* (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): major rotamer, δ 21.7 (t), 25.5 (t), 30.8 (t), 34.8 (t), 55.4 (d), 78.7 (d), 126.8 (d), 127.9 (d), 128.1 (d), 128.9 (d), 129.8 (d), 133.2 (s), 167.0 (s); minor rotamer, 22.5 (t), 24.2 (t), 31.9 (t), 34.1 (t), 51.3 (d), 77.4 (d), 126.0 (d), 127.7 (d), 128.3 (d), 128.5 (d), 130.2 (d), 132.9 (s), 166.1 (s). MS: m/z 243 (82%) M^+, 226 (5), 225 (5), 138 (7), 122 (25), 107 (14), 106 (100), 103 (13).

cis-4-(Benzoylamino)cyclohept-2-enol (4d)[7]

A solution of (**3d**) (4.80 g, 20.9 mmol) in aqueous tetrahydrofuran (120 ml; THF:H_2O, 10:1) was cooled to 0°C with stirring under N_2. Aluminium amalgam prepared by sequential exposure (10 - 20 seconds) of small strips of aluminium foil (4.54 g, 170 mmol) to 1M (aq) potassium hydroxide solution, distilled water, 0.5% mercuric chloride, distilled water and tetrahydrofuran, was then added to the solution of Diels-Alder adduct. Stirring was continued at 0°C for 16h. The reaction mixture was diluted with tetrahydrofuran (350 ml), stirred vigorously for 1.5h, then filtered through a pad of celite. The filtrate was diluted with toluene and concentrated at reduced pressure to yield (**4d**) (4.45 g, 92%) as a white crystalline solid: m.p. 155 - 158°C (lit.[7] m.p. 157 - 159°C). IR: ν_{max} (CH_2Cl_2) 3350w, 3310w, 2955s, 2915s, 2860s, 2520w, 2460w, 2400w, 1620s, 1570m, 1450s, 1435m, 1375m, 1135w, 1080w, 1040m, 990w, 890w, 800w, 720m, 695m cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ 1.43 - 2.10 (series of m, 6H), 4.38 (brd, J = 10.5 Hz, 1H), 4.63 (brd, J = 10.5 Hz, 1H), 5.66 (ddd, J = 12.0, 2.6, 0.8 Hz, 1H), 5.79 (ddd, J = 12.0, 2.6, 1.1 Hz, 1H), 7.40 - 7.55 (m, 3H), 7.75 - 7.84 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD): 26.7 (t), 35.1 (t), 37.3 (t), 52.7 (d), 72.8 (d), 128.6 (d), 129.7 (d), 132.8 (d), 133.8 (d), 136.0 (s), 139.2 (d), 169.5 (s). MS: m/z 231 (16%) M^+, 229 (6), 214 (21), 213 (80), 212 (17), 205 (7), 201 (11), 123 (15), 122 (100), 121 (17).

cis-4-(Benzoylamino)cyclohex-2-enol (9)

The amido-alcohol (**9**) was prepared using a similar method to that described above for (**4d**). Reaction of (**7**) (3.92 g, 18.2 mmol) with aluminium amalgam (from 3.80 g, 140 mmol of aluminium foil) gave (**9**) as an oil (3.83 g, 97%). IR: ν_{max} (CH_2Cl_2) 3605m, 3440m, 3035w, 2950m, 2860w, 1670s, 1510s, 1485s, 1325m, 1245w, 1150w, 1080w, 1070m, 1050m, 985m, 950w, 835w cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.69 - 1.93 (series of m, 4H), 4.17 (m, 1H), 4.58 (m, 1H), 5.75 (ddd, J = 10.0, 3.2, 1.0 Hz), 5.94 (ddd, J = 10.0, 3.4, 1.8 Hz, 1H), 7.33 - 7.48 (m, 3H), 7.72 - 7.77 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.2 (t), 28.8 (t), 45.0 (d),

64.0 (d), 126.9 (d), 128.4 (d), 130.1 (d), 131.4 (d), 132.9 (d), 134.2 (s), 166.9 (s). MS: m/z 217 (17%) M^+ 215 (6), 201 (8), 200 (46), 199 (100), 198 (77), 197 (17), 173 (6), 148 (8), 122 (74), 121 (53).

cis-4-(Benzoylamino)cyclooct-2-enol (10)

Compound **(8)** (15.85 g, 65.2 mmol) reacted with aluminium amalgam (from 17.6 g, 652 mmol of aluminium foil) as described for **(4d)** to afford a white solid which crystallised from toluene to give **(10)** (15.82 g, 99%) as a white crystalline solid, m.p. 186 - 187°C after recrystallisation from ethyl acetate. Found: C, 73.25; H, 7.92; N, 5.69%. $C_{15}H_{19}NO_2$ requires: C, 73.44; H, 7.81; N, 5.71 %.[20] IR: ν_{max} (CH_2Cl_2) 3600m, 3410m, 3050w, 2915m, 2860w, 1665s, 1580w, 1510s, 1485m, 1365m, 1070w, 1025m, 965w cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.41 - 1.76 (m, 6H), 1.87 - 2.05 (m, 2H), 2.17 (brs, exch, OH), 4.75 (brm, 1H), 4.89 (brm, 1H), 5.37 (ddd, J = 10.8, 8.3, 1.7 Hz, 1H), 5.67 (ddd, J = 10.8, 6.9, 1.4 Hz, 1H), 6.20 (brd, J = 6.7 Hz, exch, NH), 7.39 - 7.52 (m, 3H), 7.71 - 7.80 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD): δ 24.5 (t), 25.4 (t), 37.2 (t), 39.7 (t), 49.3 (d), 70.1 (d), 128.2 (d), 129.4 (d), 129.8 (d), 132.5 (d), 135.8 (s), 136.0 (d), 169.3 (s). MS: m/z 245 (4%) M^+, 243 (4), 228 (17), 227 (61), 226 (11), 225 (6), 198 (17), 140 (6), 130 (34), 124 (75) 123 (14), 122 (84) 121 (37), 107 (11), 106 (100), 104 (98), 103 (18).

cis-4-(Benzoylamino)cycloheptanol (5d)[7]

A solution of **(4d)** (2.25 g, 9.73 mmol) in methanol (100 ml) was hydrogenated at 1 atm in the presence of 5% palladium on charcoal. After 16h, the catalyst was filtered off and the solvent was evaporated under reduced pressure to yield **(5d)** (2.24 g, 99%) as a white crystalline solid; m.p. 143 - 145°C (lit.[7] m.p. 143.5 - 145°C). IR: ν_{max} (CH_2Cl_2) 3330m, 3240m, 2930s, 2860s, 1630s, 1575m, 1530m, 1490w, 1460m, 1370m, 1325, 1290w, 1215w, 1120w, 1080w, 1030w, 980w, 805w, 760m, 700m cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ 1.30 - 2.05 (series of m, 10H), 3.88 (brm, 1H), 4.06 (brm, 1H), 7.36 - 7.53 (m, 3H), 7.76 - 7.83 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD): major rotamer, δ 21.8 (t), 29.5 (t), 33.8 (t), 36.3 (t), 38.3 (t), 52.2 (d), 72.1 (d), 128.5 (d), 129.6 (d), 132.6 (d), 136.2 (s), 169.3 (s); minor rotamer, δ 22.5 (t), 31.2 (t), 37.1 (t), 41.1 (t), 44.6 (t), 53.7 (d), 72.1 (d), 128.6 (d), 129.7 (d), 132.8 (d), 136.2 (s), 169.3 (s). MS: m/z 233 (7%) M^+, 215 (6), 122 (51), 106 (8), 105 (100), 94 (8).

cis-4-(Benzoylamino)cyclohexanol (11)

A solution of **(9)** (1.34 g, 6.17 mmol) in methanol (100 ml) was hydrogenated at 1 atm in the presence of 5% palladium on charcoal. After 14h, the catalyst was filtered off and the solvent was evaporated at reduced pressure to yield **(11)** (1.34 g, 99%) as a white solid. An analytical sample was prepared by recrystallisation from toluene to give colourless needles: m.p. 135 - 136°C. Found: C, 71.21; H, 7.81; N, 6.39% $C_{13}H_{17}NO_2$ requires: C, 71.32; H, 7.76; N, 6.33%. IR: ν_{max} (CH_2Cl_2) 3610m, 3440m, 3020w, 2940s, 2860w, 1650s, 1580m, 1515s, 1485m, 1450m, 1415m, 1360w, 1320w, 1130m, 1070m, 1030m, 970s, 910w, 800w cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.63 - 1.81 (m, 8H), 2.33 (brs, exch, 1H), 3.94 (m, 1H), 4.03 (m, 1H), 6.31 (brd, J = 7.5 Hz, exch, 1H), 7.35 - 7.51 (m, 3H), 7.70 - 7.77 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): major rotamer, δ 27.2 (t), 31.3 (t), 47.2 (d), 65.9 (d), 126.8 (d), 128.4 (d), 131.2 (d) 134.8 (s), 166.8 (s); minor rotamer, δ 27.2 (t), 31.3 (t), 47.1 (d), 65.8 (d), 126.7 (d), 128.4 (d), 131.3 (d), 134.9 (s), 166.7 (s). MS: m/z 219 (17%) M^+, 201 (9), 161 (5), 160 (4), 123 (5), 122 (55), 121 (6), 106 (8), 105 (100).

cis-4-(Benzoylamino)cyclooctanol (12)

A solution of **(10)** (0.98 g, 3.99 mmol) in methanol (50 ml) was hydrogenated at 1 atm in the presence of 5% palladium on charcoal as described for **(11)** to yield **(12)** (0.97 g, 98%) as a colourless oil. Recrystallisation from ethyl acetate gave crystals, m.p. 110.5 - 112°C (92%). Found: C, 72.72; H, 8.30; N, 5.68% $C_{15}H_{21}NO_2$ requires: C, 72.84; H, 8.56; N, 5.66%.[20] IR: ν_{max} 3600m, 3460m, 3020w, 2935s, 2860m, 1655s, 1580w, 1515s, 1485m, 1445w, 1365w, 1315w, 1270w, 1140w, 1075m, 1030m, 975w, 910m, 800w cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.50 - 1.89 (series of m, 12H), 2.14 (brs, exch, 1H), 3.88 (m, 1H), 4.11 (m, 1H), 6.30 (brd, J = 7.7 Hz, exch, 1H), 7.36 - 7.51 (m, 3H), 7.71 - 7.83 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9 (t), 23.5 (t), 27.8 (t), 30.8 (t), 31.3 (t), 33.1 (t), 49.9 (d), 71.0 (d), 126.8 (d), 128.4 (d), 131.2 (d), 134.9 (s), 166.4 (s). MS: m/z 247 (4%) M^+, 230 (5), 229 (29), 205 (12), 201 (10), 175 (5), 174 (5), 161 (8), 160 (7), 147 (11), 122 (88), 121 (100), 108 (37), 106 (41), 103 (22).

cis-4-(Benzylamino)cyclohexanol (13)

The amido-alcohol (**11**) (1.20 g, 5.47 mmol) was treated with lithium aluminium hydride (0.90 g, 23.7 mmol) as described for (**14**) to afford (**13**) (1.02 g, 91 %) as a colourless oil. IR: ν_{max} (CH_2Cl_2) 3605m, 3410w, 3015w, 2930s, 2855m, 1450m, 1370w, 1230w, 1120m, 1070m, 1060m, 1040m, 965s, 910s, 855w cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.50 - 1.78 (series of m, 8H), 2.14 (brs, exch, 2H), 2.59 (m, 1H), 3.78 (s, 2H), 3.85 (m, 1H), 7.21 - 7.33 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.5 (t), 31.0 (t), 50.9 (t), 53.9 (d), 67.0 (d), 126.8 (d), 128.0 (d), 128.3 (d), 140.5 (s). MS: $^m/z$ 205 (17%) M^+, 187 (6), 147 (3), 146 (100), 133 (14), 132 (12), 131 (5), 130 (5), 120 (7), 119 (6).

cis-4-(Benzylamino)cycloheptanol (14)

A solution of (**5d**) (0.85 g, 3.64 mmol) in dry diethyl ether (30 ml) was added dropwise to a stirred slurry of lithium aluminium hydride (0.60 g, 15.8 mmol) in diethyl ether (70 ml). After heating under reflux for 10h, decomposition of excess hydride was effected by cautious addition of water. The inorganic solids were removed by filtration, and the organic layer dried over anhydrous magnesium sulphate. The solvent was evaporated at reduced pressure to yield (**14**) (0.79 g, 99%) as colourless needles: m.p. 43- 45°C. IR: ν_{max} (CH_2Cl_2) 3610w, 3180brm, 3030m, 2960s, 2930s, 1500m, 1440w, 1215w, 1080m, 1065m, 1030m, 945m, 860w cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.30 - 2.01 (series of m, 10H), 2.69 (brs, exch, 1H), 2.98 (m, 1H), 3.69, 3.78 (AB quartet, J = 12.8 Hz, 2H), 4.00 (m, 1H), 7.21 - 7.41 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.2 (t), 28.7 (t), 32.6 (t), 34.3 (t), 35.5 (t), 51.5 (t), 55.1 (d), 69.1 (d), 127.0 (d), 128.0 (d), 128.4 (d), 139.6 (s). MS: $^m/z$ 219 (8%) M^+, 217 (8), 176 (5), 160 (6), 147 (8), 146 (61), 133 (8), 132 (10), 128 (7), 120 (8), 106 (15), 104 (5), 92 (10), 91 (100).

cis-4-(Benzylamino)cyclooctanol (15)

Reaction of (**12**) (0.85 g, 3.44 mmol) with lithium aluminium hydride (0.50 g, 13.2 mmol) as described for (**14**) afforded (**15**) (0.80 g, 99%) as a yellow oil. Crystallisation from toluene gave a sample of material which was pure by NMR (76%). An analytical sample was obtained by recrystallisation from ethyl acetate, m.p. 85.5 - 87.0°C. Found: C, 77.32; H, 10.02; N, 6.04% $C_{15}H_{23}NO$ requires: C, 77.21; H, 9.93; N, 6.00%.[20] IR: ν_{max} (CH_2Cl_2) 3600m, 3015w, 2920s, 2860m, 1470m, 1450m, 1365w, 1200w, 1100m, 1075w, 1055w, 1030m, 1005w, 975w, 825w cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 - 1.84 (series of m, 12H), 2.20 (brs, exch, 2H), 2.68 (m, 1H), 3.76 (s, 2H), 3.82 (m, 1H), 7.22 - 7.36 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.3 (t), 24.1 (t), 28.2 (t), 31.0 (t), 31.4 (t), 33.9 (t), 51.4 (t), 56.9 (d), 71.5 (d), 126.8 (d), 128.0 (d), 128.4 (d), 140.6 (s). MS: $^m/z$ 233 (20%) M^+, 176(11), 147 (21), 146 (100), 142 (11), 134 (11), 133 (96), 132 (33), 120 (21), 107 (14), 106 (36), 104 (11).

N-Benzylnortropane (1c) from (14) with thionyl chloride followed by base

a) To a solution of (**14**) (1.25 g, 5.70 mmol) in chloroform (20 ml) was added dropwise a solution of thionyl chloride (0.45 ml, 6.20 mmol) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for a further 24 h. After cooling to 0°C, pyridine (2 ml) was added dropwise and the solution stirred for 1 h. The reaction mixture was subsequently poured into 2M (aq) sodium hydroxide solution, and the aqueous layer extracted with dichloromethane (2 x 30 ml). The combined organic layers were dried over anhydrous sodium sulphate and the solvent evaporated at reduced pressure. The residue was purified by flash chromatography (90:9:1, petroleum ether [b.p. 40 - 60°C] : diethyl ether : triethylamine) to afford (**1c**) (1.01 g, 88%) as a colourless oil. [Lower yields (down to 40% in some cases) were obtained in some smaller-scale runs.] ^1H NMR (300 MHz, $CDCl_3$): δ 1.28 - 2.03 (series of m, 10H), 3.15 (brt, J = 3.2 Hz, 2H), 3.52 (s, 2H), 7.19 - 7.40 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): equatorial, δ 16.0 (t), 25.1 (t), 31.8 (t), 57.0 (t), 58.9 (d), 126.2 (d), 127.7 (d), 128.5 (d), 138.5 (s); axial, δ 21.7 (t), 27.8 (t), 34.0 (t), 49.5 (t), 54.5 (d), 127.2 (d), 127.8 (d), 128.1 (d), 137.9 (s). MS: observed accurate $^m/z$ 201.1511, calculated for $C_{14}H_{19}N$ 201.1517.

b. Thionyl chloride (14.0 μl, 0.19 mmol) was added gradually from a micro-syringe to a solution of (**14**) (0.0386 g, 0.18 mmol) in dry $CDCl_3$ (1 ml) at 0°C. The reaction was allowed to warm to room temperature and was monitored periodically by ^1H NMR. After 30 min, new signals corresponding to the intermediate chlorosulphite appeared [^1H NMR (90 MHz): δ 1.70 - 2.40 (brm, 10H), 2.98 (brm, 1H), 4.00 (brs, 2H) 5.35

(brm, 1H), 7.35 (brm, 3H), 7.58 (brm, 2H), 9.75 (brs, 2H, NH_2^+]. After 22 h, formation of the hydrochloride salt of the *trans*-1,4-chloroamine (**16**) was complete [^{1}H NMR (90 MHz): δ 1.40 - 2.30 (complex m, 10H), 2.92 (brm, 1H), 3.90 (brs, 2H) 4.06 (brm, 1H), 7.26 (brm, 3H), 7.48 (brm, 2H), 9.48 (brs, 2H, NH_2^+]. 1,5,7-triazabicyclo[4.4.0]dec-5-ene on polystyrene cross-linked with 2% DVB (TABD) (0.15 g) was then added and the suspension was rocked for 6 h. The base was removed by filtration under nitrogen and the filtrate was concentrated under vacuum. Chromatographic purification of the residue by flash chromatography (80:19:1, petroleum ether [b.p. 40 - 60°C] : diethyl ether : triethylamine) gave (**1c**) (0.015 g, 41%). ^{1}H NMR: δ 1.28 - 2.05 (complex, 10H), 3.15 (brm, 2H), 3.52 (s, 2H), 7.20 - 7.40 (m, 5H).

Nortropane (1b) from debenzylation of (1c)

A solution of (**1c**) (0.27 g, 1.34 mmol) in dry methanol (20 ml) was hydrogenated at 1 atm in the presence of 5% palladium on charcoal. After 4h, the catalyst was filtered off and the solvent was evaporated at reduced pressure to yield (**1b**) (0.14 g, 94%) as a colourless oil. ^{1}H NMR (90 MHz), $CDCl_3$): δ 1.12 - 1.91 (series of m, 10H), 3.02 (brs, exch, 1H), 3.29 (brs, 2H). The identity of (**1c**) was confirmed by comparison of the ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 17.1 (t), 29.0 (t), 32.8 (t), 54.6 (d) with the spectrum reported earlier.[21]

N-(Benzyloxycarbonyl)nortropane (1e)[7]

This compound was made from cyclohepta-1,3-diene as described in reference 7. The yield for the initial cycloaddition of 1-chloro-1-nitrosocyclohexane to cycloheptadiene was increased to 83% after recrystallisation (colourless needles, m.p. 178 - 180°C; lit.[7] m.p. 179 - 181°C) by extending the reaction time at -10°C from 2 days[7] to 5 days.

Nortropane (1b) from deprotection of (1e)

A solution of hydrogen bromide in glacial acetic acid (45% w/v, 3 ml) was added dropwise to (**1e**) (0.31 g, 1.26 mmol) at 0°C. The reaction mixture was allowed to warm to room temperature, stirred for a further 2h, and then poured into ice-water (20 ml). The aqueous layer was washed with diethyl ether (20 ml), cooled, and carefully basified with 2M (aq) sodium hydroxide solution. The resulting amine was extracted into diethyl ether (2 x 20 ml) and acidified by dropwise addition of concentrated HCl. The product was extracted into water (3 x 20 ml) and the solvent evaporated at reduced pressure to yield the hydrochloride salt: (**1b:HCl**) (0.18 g, 97%). ^{1}H NMR (90 MHz): δ 1.38 - 2.50 (series of m, 10H), 4.01 (brs, 2H), 9.23 (brs, exch, 2H).

Reactions of (13) and (15) with thionyl halides

The general method (**a**) [conversion of (**14**) into (**1c**) above] was followed. In each case, a slight excess of thionyl chloride or bromide was used in $CDCl_3$ solution and led to rapid reaction with the alcohol; the reaction mixture was left at room temperature for 24h to ensure conversion of the intermediate chlorosulphite or bromosulphite into the salt of the *trans*-4-haloamine. [The reaction was slower with thionyl chloride than with thionyl bromide and, in the case of (**13**), the mixture was heated at 50°C overnight and monitored by ^{1}H NMR until no further change was observed; the solution appeared to contain a single compound at this point which decomposed on aqueous work-up and was assumed to be the *trans*-4-chloroamine.] In each case, the solution was then cooled to 0°C and pyridine was added. The reaction mixtures were worked-up as described in (**a**) including flash chromatography of the reaction products. Reaction of (**13**) with thionyl chloride led to isolation of starting amino-alcohol (57%) and several minor, unidentified compounds, none of which had the characteristics of the required product, N-benzyl-7-azabicyclo[2.2.1]heptane. Similar results were obtained with (**13**) and thionyl bromide [74% recovery of (**13**)]; (**15**) and thionyl chloride [68% recovery of (**15**)]; and (**15**) with thionyl bromide [54% recovery of (**15**)].

N-(Benzyloxycarbonyl)-8-oxa-9-azabicyclo[3.2.2]non-6-ene (3e)

To a solution of cyclohepta-1,3-diene (3.5 ml, 32.3 mmol) and benzyl-N-hydrocycarbamate (5.79 g, 34.6 mmol) in dichloromethane (60 ml) was added a suspension of tetramethyl metaperiodate (9.27 g, 35.0 mmol) in dichloromethane (20 ml) over 30 min. at 0°C. After stirring at room temperature for 1.5h, the

reaction mixture was washed sequentially with aqueous sodium bisulphite (15%, 3 x 30 ml), saturated aqueous sodium hydrogen carbonate (2 x 30 ml), brine (30 ml), and dried over anhydrous magnesium sulphate. The solvent was evaporated at reduced pressure and the residue purified by flash chromatography (40:60 diethyl ether : petroleum ether [b.p. 40 - 60°C] to yield (**3e**) (7.54 g, 90%) as colourless needles: m.p. 20 - 21°C. Analysis. Found: C, 69.70; H, 6.71; N, 5.25%. $C_{15}H_{17}NO_3$ requires: C, 69.48; H, 6.61; N, 5.40%. IR: ν_{max} (CH_2Cl_2) 3040w, 2940m, 1690s, 1550w, 1500w, 1420s, 1355m, 1260s, 1205m, 1085m, 1030w, 970w, 895m, 760s cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 1.19 - 1.92 (series of m, 6H), 4.75 (brm, 2H), 5.15 (s, 2H), 6.20 (m, 2H), 7.28 (s, 5H). MS: m/z 259 (10%) M^+, 215 (24), 186 (7), 141 (5), 109 (6), 108 (38), 107 (32), 106 (13), 105 (11), 94 (35), 93 (16), 92 (54), 91 (100).

cis-4-([Benzyloxycarbonyl]amino)cyclohept-2-enol (4e)

To a solution of (**3e**) (1.15 g, 4.43 mmol) in ethanol (40 ml) was added Na_2HPO_4 (2.86 g, 20.15 mmol). To this suspension at 0°C was added 5% sodium amalgam (13.2 g) in small portions with stirring over 30 min. The reaction mixture was allowed to warm to room temperature and stirred for a further 2h. After filtration, the filtrate was concentrated at reduced pressure. The residue was dissolved in dichloromethane (100 ml), washed with water (50 ml) and dried over anhydrous magnesium sulphate. The solvent was evaporated at reduced pressure to yield (**4e**) (0.084 g, 7%) as a colourless oil. [An improved method is described below.] IR: ν_{max} (CH_2Cl_2) 3600m, 3435m, 3015w, 2930s, 2875w, 1710s, 1510m, 1495s, 1380m, 1305w, 1210m, 1125w, 1085m, 1045m, 1025s, 905w, 810w cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 - 2.04 (series of m, 6H), 4.26 (brd, J = 10.6 Hz, 1H), 4.39 (brd, J = 9.7 Hz, 1H), 5.03 (brs, exch, 1H), 5.09 (s, 2H), 5.54 (dddd, J = 12.0, 3.9, 2.2, 0.7 Hz, 1H), 5.77 (brdd, J = 12.0, 2.8 Hz, 1H), 7.20 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.2 (t), 33.9 (t), 36.0 (t), 51.9 (d), 66.7 (t), 71.4 (d), 128.1 (d), 128.5 (d), 133.0 (d), 133.7 (s), 136.4 (d), 137.4 (d), 169.3 (s). MS: m/z 261 (3%) M^+, 243 (10), 200 (10), 199 (6), 163 (13), 162 (11), 161 (77), 152 (30), 146 (19), 126 (62), 110 (36), 109 (26), 108 (75), 107 (46), 98 (20), 95 (18), 94 (100); observed accurate mass m/z 261.1371, calculated for $C_{15}H_{19}NO_3$ 261.1365.

8-Oxa-9-azabicyclo[3.2.2]non-6-ene (3b)

A solution of hydrogen bromide in glacial acetic acid (45%, 10.4 ml) was added dropwise to (**3e**) (1.73 g, 6.70 mmol) at 0°C. The reaction mixture was allowed to warm to room temperature, stirred for a further 2h, and then poured into ice-water (35 ml). The aqueous solution was washed with dichloromethane (25 ml), cooled, and then carefully basified with 2M (aq) sodium hydroxide solution. The product was extracted into dichloromethane (6 x 25 ml; multiple extraction was necessary to maximise the yield) and dried over anhydrous magnesium sulphate. Removal of the solvent at reduced pressure afforded (**3b**) (0.75 g, 90%) as a colourless oil. IR: ν_{max} (CH_2Cl_2) 3380w, 3055s, 2985m, 2940m, 1500w, 1420m, 1260s, 1155w, 1130w, 1090w, 1065w, 1030w, 995s, 760s cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 1.10 - 1.95 (series of m, 6H), 3.62 (m, 1H), 4.54 (m, 1H), 4.65 (brs, exch, 1H), 6.05 (brdd, J = 9.0, 6.5Hz, 1H), 6.43 (brdd, J = 9.0, 6.5 Hz, 1H). MS: m/z 125 (25%) M^+, 108 (14), 98 (6), 97 (21), 95 (35), 94 (28), 93 (9), 92 (42), 82 (6), 81 (11), 80 (13), 79 (100).

cis-4-Aminocyclohept-2-enol (4b)

To a solution of (**3b**) (3.10 g, 24.8 mmol) in glacial acetic acid (75 ml) at 0°C was added zinc powder (24.8 g, 0.38 mol). The reaction mixture was heated at 50 - 60°C for 4h and then filtered. The residue was washed with glacial acetic acid (100 ml) and the filtrate evaporated at reduced pressure. The residue was cooled, basified with concentrated ammonia solution and the product extracted into dichloromethane (10 x 30 ml). [Further, small, quantities of the water-soluble product could be obtained by continuous extraction of the aqueous layer with dichloromethane.] The combined organic layers were dried over anhydrous sodium sulphate and the solvent evaporated at reduced pressure to yield (**4b**) (2.02 g, 64%) as a pale yellow waxy solid. ^1H NMR (90 MHz, $CDCl_3$): δ 1.39 - 2.20 (series of m, 6H), 2.69 (brs, exch, 3H), 3.45 (m, 1H), 4.20 (m, 2H), 5.42 - 5.89 (m, 2H).

cis-4-([Benzyloxycarbonyl]amino)cyclohept-2-enol (4e)

To a suspension of sodium hydride (80% dispersion, 0.168 g) in dry diethyl ether (40 ml) was added dropwise a solution of (**4b**) (0.71 g, 5.59 mmol) in diethyl ether (10 ml). After stirring at room temperature

for 2 h, the reaction mixture was cooled to 0°C, and benzyl chloroformate (0.80 ml), 5.60 mmol) was added dropwise. The resulting solution was allowed to warm to room temperature, stirred for a further 2 h and then poured into water (40 ml). After separation of the organic layer, the aqueous layer was extracted with dichloromethane (3 x 20 ml) and the combined organic layers dried over anhydrous sodium sulphate. The solvent was evaporated at reduced pressure to yield (**4e**) (1.38 g, 95%) having identical properties to the sample prepared in low yield from (**3e**) as described above.

trans-1-([Benzyloxycarbonyl]amino)-4-chlorocyclohept-2-ene (17)

A solution of thionyl chloride (0.27 ml, 3.72 mmol) in chloroform (5 ml) was added dropwise to a solution of (**4e**) (0.30 g, 1.15 mmol) and pyridine (0.76 ml, 9.48 mmol) in chloroform (20 ml) at 0°C. After stirring for 1 h at 0°C, the reaction mixture was poured into ice-water (30 ml) and the aqueous layer was extracted with chloroform (2 x 30 ml). The combined organic extracts were dried over anhydrous magnesium sulphate. The solvent was evaporated at reduced pressure to yield (**17**) (0.25 g, 78%) as a yellow oil. IR: ν_{max} (CH_2Cl_2): 3415m, 3040w, 2915m, 1715s, 1505s, 1445w, 1320m, 1300w, 1215m, 1100w, 1070w, 1025w, 975w, 945w, 775m, 750m cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 1.46 - 2.27 (series of m, 6H), 4.31 (m, 1H), 5.02 (br s, exch, 1H), 5.07 (s, 2H), 5.16 (m, 1H), 5.58 - 5.88 (m, 2H), 7.33 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.3 (t), 33.5 (t), 33.8 (t), 51.5 (d), 66.6 (t), 72.9 (d), 128.0 (d), 128.4 (d), 132.7 (d), 135.1 (d), 136.3 (s), 137.8 (d), 155.4 (s). MS: $^m/_z$ 281 (2%), 279 (6%) M^+, 243 (15), 200 (8), 199 (6), 182 (10), 153 (9), 152 (51), 134 (10), 124 (10), 109 (20), 108 (76), 107 (44), 94 (25), 93 (21), 92 (100).

trans-1-([Benzyloxycarbonyl]amino)-4-bromocyclohept-2-ene (18)

A solution of thionyl bromide (88 µl, 1.14 mmol) in chloroform (1 ml) was added dropwise to a solution of (**4e**) (100 mg, 0.38 mmol) and pyridine (0.25 ml, 3.12 mmol) in chloroform (10 ml) at 0°C. After stirring for 1h at 0°C, the reaction mixture was poured into ice-water (20 ml) and the aqueous layer extracted with chloroform (2 x 20 ml). The combined organic extracts were dried over anhydrous magnesium sulphate and the solvent evaporated at reduced pressure to yield a pale yellow residue which was purified by chromatography (50:50 diethyl ether : petroleum ether [b.p. 40 - 60°C]). The first fraction afforded (**18**) (37 mg, 30%) as a pale yellow oil. IR: ν_{max} (CH_2Cl_2): 3410m, 3020m, 2910m, 1710s, 1510s, 1445w, 1440w, 1335m, 1305w, 1220m, 1105w, 1075w, 975w, 750m, 735m cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 1.40 - 2.02 (series of m, 6H), 4.28 (m, 1H), 4.50 (m, 1H), 4.80 (brs, exch, 1H), 4.92 (s, 2H), 5.52 - 5.78 (m, 2H), 7.29 (s, 5H). MS: $^m/_z$ 325 (2%), 323 (2%) M^+, 243 (20), 200 (6), 199 (5), 153 (11), 152 (62), 93 (25), 92 (100). Further elution of the column yielded recovered starting material (**4c**) (21 mg, 21%).

cis-1-([Benzyloxycarbonyl]amino)-4-acetoxycyclohept-2-ene (19)

Acetyl chloride (0.27 g, 3.80 mmol) was added dropwise to a solution of (**4e**) (0.57 g, 2.20 mmol) and pyridine (0.60 ml, 7.49 mmol) in dry dichloromethane (25 ml) at 0°C. The reaction mixture was stirred for 2 h at 0°C, and then washed with saturated sodium bicarbonate solution (2 x 20 ml), copper sulphate solution (2 x 20 ml) and water (20 ml). The organic extract was dried over anhydrous potassium carbonate and the solvent evaporated at reduced pressure to yield (**19**) (0.62 g, 93%) as a colourless oil. IR: ν_{max} (CH_2Cl_2) 3440m, 3035w, 2940m, 2860w, 1720s, 1500s, 1440m, 1420s, 1370m, 1300m, 1260s , 1230s, 1150w, 1110m, 1065w, 1025m, 985w, 895s, 750s cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 1.39 - 1.98 (series of m, 6H), 2.01 (s, 3H), 4.25 (m, 1H), 4.90 (brs, exch, 1H), 5.05 (s, 2H), 5.30 (m, 1H), 5.55 - 5.65 (m, 2H), 7.27 (s, 5H). MS: $^m/_z$ 303 (6%) M^+, 244 (25), 243 (41), 200 (14), 199 (19), 157 (6), 156 (16), 152 (17), 126 (12), 110 (19), 109 (18), 108 (35), 107 (16), 95 (10), 94 (100), 93 (15), 92 (55); observed accurate mass $^m/_z$ 303.1465, calculated for $C_{17}H_{21}NO_4$ 303.1470.

1-([Benzyloxycarbonyl]amino)cyclohepta-2,4-diene (20)

To a solution of (**19**) (0.62 g, 2.04 mmol) and triethylamine (0.29 ml, 2.08 mmol) in dry tetrahydrofuran (10 ml) was added $Pd_2(dba)_3.CHCl_3$ (0.10 g, 0.10 mmol) and triphenylphosphine (0.21 g, 0.80 mmol) under N_2. The reaction mixture was heated at reflux for 14 h, filtered through a short column of silica, and then the solvent was evaporated at reduced pressure. The residue was purified by flash chromatography (30:70, diethyl ether : petroleum ether [b.p. 40 - 60°C]) to yield (**20**) (0.31 g, 64%) as a pale yellow oil. IR: ν_{max} (CH_2Cl_2):

3440m, 3035s, 2935w, 1715s, 1500s, 1450w, 1400w, 1340w, 1310m, 1215s, 1130w, 1100w, 1050m, 1025w, 920w cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.76 - 2.43 (series of m, 4H), 4.49 (m, 1H), 5.02 (brs, exch, 1H), 5.08 (s, 2H), 5.66 - 5.96 (m, 4H), 7.31 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.3 (t), 31.3 (t), 51.6 (d), 66.6 (t), 124.3 (d), 125.8 (d), 127.9 (d), 128.4 (d), 132.6 (d), 135.2 (d), 136.4 (s), 155.2 (s). MS: m/z 243 (8%) M^+, 182 (12), 152 (75), 135 (8), 134 (15), 120 (13), 109 (9), 108 (69), 107 (44), 106 (18), 93 (6), 92 (19), 91 (100); observed accurate mass m/z 243.1251, calculated for $C_{15}H_{17}NO_2$ 243.1259.

cis-4-(Benzylamino)cyclohept-2-enol (21)

The amino-alcohol (**21**) was prepared using a similar method to that used for (**14**). Reaction of (**4d**) (2.26 g, 9.77 mmol) with lithium aluminium hydride (1.50 g, 39.5 mmol) afforded (**21**) (2.07 g, 97%) as a white crystalline solid. An analytical sample was prepared by recrystallisation from petroleum ether (b.p. 80 - 100°C) to give colourless needles: m.p. 115 - 116°C. Found: C, 77.45; H, 8.66; N, 6.44%. $C_{14}H_{19}NO$ requires: C, 77.38; H, 8.81; N, 6.45%. IR: ν_{max} (CH_2Cl_2): 3610w, 3200brw, 3025m, 2930s, 2850s, 1500m, 1450w, 1320w, 1210w, 1110m, 1085s, 1055m, 1030m, 995m, 950w, 910w cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.50 - 1.87 (series of m, 5H), 2.17 - 2.35 (m, 1H), 3.29 (ddd, J = 6.3, 6.3, 1.7 Hz, 1H), 3.40 (brs, exch, 2H), 3.69, 3.79 (AB quartet, J = 12.8 Hz, 2H), 4.22 (ddd, J = 6.3, 6.3, 1.7 Hz, 1H), 5.87 (dd, J = 11.4, 6.3 Hz, 1H), 6.18 (dd, J = 11.4, 6.3 Hz, 1H), 7.22 - 7.42 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1 (t), 31.8 (t), 34.2 (t), 51.6 (t), 55.1 (d), 68.1 (d), 127.1 (d), 128.2 (d), 128.5 (d), 134.4 (d), 139.0 (d), 139.4 (s). m/z 217 (13%) M^+, 199 (7), 172 (9), 170 (9), 146 (14), 133 (5), 132 (5), 126 (5), 108 (8), 106 (12), 92 (10), 91 (100).

cis-4-(Benzylamino)cyclohex-2-enol (22)

Reaction of (**9**) (1.67 g, 7.69 mmol) with lithium aluminium hydride (1.20 g, 31.6 mmol) as described for (**21**) afforded (**22**) (1.44 g, 92%) as a colourless oil. IR: ν_{max} (CH_2Cl_2): 3600m, 3420m, 3015m, 2940s, 2860m, 1500w, 1450s, 1440m, 1395w, 1355w, 1215m, 1150w, 1105w, 1060m, 1035w, 995m, 970m, 945m, 860w cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.62 - 1.79 (m, 4H), 2.50 (brs, exch, 2H), 3.12 (m, 1H), 3.78 3.85 (AB quartet, J = 13.0 Hz, 2H), 4.08 (m, 1H). 5.78 - 5.82 (m, 2H), 7.21 - 7.33 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7 (t), 29.0 (t), 51.0 (t), 52.1 (d), 64.3 (d), 126.9 (d), 128.0 (d), 128.3 (d), 130.9 (d), 132.3 (d), 140.0 (s). MS: m/z 203 (14%) M^+, 185 (7), 186 (6), 175 (39), 160 (11), 159 (100), 146 (11), 144 (14), 133 (13), 108 (17), 106 (22).

cis-1-(Benzylamino)-4-acetoxycyclohept-2-ene (23)

A solution of (**21**) (0.37 g, 1.70 mmol) in dichloromethane (8 ml) was added to a solution of tetrafluoroboric acid-dimethyl ether complex (0.25 g, 1.88 mmol) in dichloromethane (2 ml) at 0°C. Acetic anhydride (0.20 ml, 2.12 mmol) was subsequently added at 0°C and the solution allowed to warm to room temperature. The reaction mixture was stirred for a further 7h, and then poured into ice-water (40 ml). The solution was cooled, carefully basified to pH 8 with sodium bicarbonate solution and dried over anhydrous potassium carbonate. The solvent was evaporated at reduced pressure to yield (**23**) (0.41 g, 93%) as a pale yellow oil. IR: ν_{max} (CH_2Cl_2): 3440w, 3035w, 2935m, 2850w, 1730s, 1495w, 1450m, 1370m, 1240s, 1100w, 1085w, 1025m, 980w, 810m, cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 1.3 - 1.95 (series of m, 6H), 2.02 (s, 3H), 3.29 (brd, J = 9.0 Hz, 1H), 3.72 (s, 2H), 5.31 (brd, J = 9.0 Hz, 1H), 5.51 - 5.75 (m, 2H), 7.21 (s, 5H). MS: m/z 259 (5%) M^+, 200 (10), 199 (21), 170 (12), 156 (13), 108 (13), 106 (12), 105 (11), 92 (14), 91 (100).

N-Benzylnortop-6-ene (2c) from (21) via the chloro-amine (25); cyclisation using K_2CO_3

Variations in reaction conditions using K_2CO_3 as base are summarised in table 1; the most successful procedure is described here.

To a solution of (**21**) (1.10 g, 5.06 mmol) and lithium chloride (1.0 g) in chloroform (20 ml) was added dropwise a solution of thionyl chloride (0.40 ml, 5.51 mmol) in chloroform (5 ml) at 0°C. The reaction mixture was sonicated for 1.5 h. Anhydrous potassium carbonate (3.0 g) was subsequently added and the reaction mixture further sonicated for 24 h. Filtration and evaporation of the solvent at reduced pressure yielded a pale yellow oil which was purified by flash chromatography (90:9:1, petroleum ether [b.p. 40 - 60°C] : diethyl ether : triethylamine). The first fraction afforded (**27**) (0.10 g, 10%) as a colourless oil. IR: ν_{max} (CH_2Cl_2): 3010w, 2960m, 2930s, 2875m, 1495m, 1450m, 1350m ,1125m, 1095s, 1075m, 1040m, 1025s, 800s cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.50 - 2.28 (series of m, 8H), 3.36, 3.79 (AB quartet, J = 13.9 Hz,

2H). 5.65 (dddd, J = 11.4, 6.5, 3.5, 0.4 Hz, 1H), 5.82 (dddd, J = 11.4, 6.5, 1.3, 1.3 Hz, 1H), 7.20 - 7.37 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.5 (t), 29.8 (t), 31.2 (t), 42.4 (d), 47.6 (d), 65.1 (t), 126.2 (d), 126.7 (d), 127.6 (d). 128.2 (d), 133.4 (d), 139.6 (s). MS: ^{m}/z 199 (6%) M^+, 195 (7), 194 (7), 106 (12), 105 (54), 104 (7), 92 (18), 91 (100), 90 (6). Further elution afforded (2c) (0.66 g, 65%) as a colourless oil. IR: ν_{max} (CH_2Cl_2): 3020, 2940s, 1495m, 1450m, 1365m, 1330m, 1095m, 1075w, 1055s, 1030m, 995w, 915w, 845m cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24 - 1.76 (series of m, 6H) 3.45 (br s, 2H), 3.49 (s, 2H), 5.91 (s, 2H), 7.18 - 7.37 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ equatorial- 16.6 (t), 25.6 (t), 57.8 (t), 65.4 (d), 126.5 (d), 128.0 (d). 128.6 (d), 129.2 (d), 139.0 (s); the very small signals due to the axial invertomer (<2%) could not be assigned with complete confidence. MS: ^{m}/z 199 (32%) M^+, 171 (11), 170 (53), 156 (6), 108 (5), 104 (4), 92 (8), 91 (100), 89 (7); observed accurate ^{m}/z 199.1353, calculated for $C_{14}H_{17}N$ 199.1361.

Formation of (2c) from (21) via the chloro-amine (25); cyclisation with TABD

Thionyl chloride (10.78 μl, 0.15 mmol) was added gradually to a stirred solution of (21) (0.03 g, 0.14 mmol) and anhydrous lithium chloride (0.03 g) in dry $CDCl_3$ (1 ml) at 0°C. The reaction mixture was sonicated and after 3 h, the hydrochloride salt (25) was the only product present, as judged by ^{1}H NMR. TABD (0.1 g) was added and the suspension was rocked for 12 h. After primary filtration, gaseous ammonia was added to the solution and the resulting white precipitate was filtered off. The solvent was removed from the filtrate under vacuum. Chromatographic purification as described above gave (27) (0.005 g, 18%) and (2c) (0.009 g, 33%) as colourless oils.

Formation of (2c) from (21) via the bromo-amine (26); cyclisation with TMP

Thionyl bromide (21.5 μl, 0.28 mmol) was added gradually to a solution of (21) (0.055 g, 0.25 mmol) in dry $CDCl_3$ (1 ml) at 0°C. After 20 min, the ^{1}H NMR spectrum contained new signals which were assigned to the bromosulphite intermediate: ^{1}H NMR (90 MHz, $CDCl_3$): δ 1.68 - 2.55 (brm, 6H), 4.14 (brm, 3H), 5.30 (brm, 1H), 6.12 (brm, 2H), 7.38 (brs, 3H), 7.58 (brs, 2H), 9.25 (brs, 2H, NH_2^+). After 4h, the NMR spectrum indicated that conversion into the HBr salt (26) was complete: δ 1.80 - 2.60 (brm, 6H), 4.18 (brm, 3H), 4.85 (brm, 1H), 6.18 (brs, 2H), 7.48 (brs, 3H), 7.70 (brs, 2H), 9.45 (brs, 2H, NH_2^+). After cooling to 0°C, anhydrous tetramethylpiperidine (TMP) (140 μl) was added, the solution was allowed to warm to room temperature, and was then heated at 45°C for 19 h. The solvent was removed under vacuum and the residue was triturated with diethyl ether. The combined ethereal extracts were treated with gaseous ammonia and the mixture filtered. Evaporation of solvent and chromatographic purification yielded (2c) (0.016 g, 31%).

Formation of (2c) from (21) via the bromo-amine (26); cyclisation with TMP in acetone.

Thionyl bromide (97 μl, 1.25 mmol) was added gradually to a stirred solution of (21) (0.25 g, 1.15 mmol) in dry $CDCl_3$ (10 ml) at 0°C. After 5h, the hydrobromide salt (26) was shown to have been formed as described above. The solvent was removed under vacuum and replaced with dry acetone (10 ml). After cooling to 0°C, anhydrous TMP (650 μl) was added; the solution was allowed to warm to room temperature and then heated at 50°C for 19 h. The mixture was worked up as described above and chromatographed to give (27) (0.054 g, 24%) and (2c) (0.133g, 58%).

cis-4-Aminocycloheptanol (28)

A solution of (4b) (0.38 g, 3.02 mmol) in methanol (20 ml) was hydrogenated over 5% Pd/C at atmospheric pressure. After 16h, the catalyst was removed by filtration and the solvent was evaporated under vacuum to afford (28) as a colourless oil (0.39 g, 99%). IR: ν_{max} (CH_2Cl_2) 3605w, 3200w, 2930s, 2860m, 1580w, 1450w cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD): δ 1.25 - 1.99 (series of m, 10H), 2.88 (m, 1H), 3.78 (m, 1H). ^{13}C NMR (75 MHz, CD_3OD): δ 21.4 (t), 31.5 (t), 33.0 (t), 38.2 (t), 38.6 (t), 53.0 (d), 72.0 (d). The salt (28:HCl)[7] was also prepared from (4b:HCl) to give a sample, m.p. 170 - 171°C (lit.[7] m.p. 171 - 173°C).

Nortropane (1b) from (28) with thionyl chloride followed by base

Thionyl chloride (21.3 μl, 0.29 mmol) was added dropwise to a solution of (28) (0.035 g, 0.27 mmol) in dry $CDCl_3$ at 0°C. The reaction mixture was allowed to warm to room temperature and its progress was monitored periodically by ^{1}H NMR. After 30 min, the chlorosulphite was observed [(90 MHz) δ 1.65 - 2.40 (brm, 10H), 3.38 (brm, 1H), 5.45 (brm, 1H), 8.22 (brs, 3H, NH_3^+)]. After 20h, complete decomposition had

occurred to give the hydrochloride salt of the *trans*-1,4-chloroamine [δ 1.58 - 2.52 (brm, 10H), 3.32 (brm, 1H), 4.15 (brm, 1H), 8.13 (brs, 3H, NH_3^+)]. At this point, the base TABD (0.25g) was added and the suspension was rocked for 6h. The base was filtered off under nitrogen and direct NMR measurement on the solution in $CDCl_3$ confirmed the formation of (**1b**) (0.008 g, 26%; quantified relative to an internal standard). The product was not purified further.

Nortrop-6-ene (2b) from (4b) using thionyl chloride followed by base

Thionyl chloride (19.6 μl, 0.27 mmol) was added dropwise to a solution of (**4b**) (0.031 g, 0.25 mmol) and anhydrous lithium chloride (0.0487 g) in dry $CDCl_3$ (1 ml) at 0°C. The reaction mixture was sonicated for 25 h during which time it was monitored periodically by ^1H NMR to ensure complete decomposition of the intermediate chlorosulphite. After 25 h, TABD (0.2 g) was added and the suspension was rocked for 4 h. After removal of the base, the filtrate was basified with gaseous ammonia and filtered again. A 300 MHz NMR spectrum confirmed the presence of 2% of (**2b**) [δ 1.42 - 2.17 (series of m, 6H), 4.28 (brs, 2H), 6.10 (s, 2H): by direct comparison with an authentic sample[4]] but the product was not isolated.

N-Chloronortropane (1f)

A solution of (**1b**) (0.10 g, 0.68 mmol) in water (10 ml) was treated with sodium hypochlorite (5% chlorine content, 15 ml) and stirred at room temperature for 1 h. The product was extracted into trichlorofluoromethane (3 x 10 ml) and the combined organic layers dried over anhydrous magnesium sulphate. The solvent was evaporated in a gentle stream of nitrogen to yield (**1f**) (0.099 g, *ca.* 100%) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$): equatorial, δ *0.95 - 1.15* (m, 4H), *1.31 - 1.39* (m, 2H), *1.63 - 1.77* (m, 2H), *2.13 - 2.33* (m, 2H); axial, δ *0.83 - 1.15* (m, 4H), *1.24 - 1.39* (m, 2H), *1.63 - 1.77* (m, 2H), *2.13 - 2.25* (m, 2H), 3.24 (m, 2H). ^{13}C NMR data are summarised in table 2. MS: m/z 110 (12%) M^+-Cl, 96 (6), 95 (37), 94 (100), 84 (6), 83 (16), 82 (56), 71 (27). Accurate mass (M^+-Cl) 110.0917, calculated for $C_7H_{12}N$ 110.0917.

References and Notes

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