Easy access to medium rings by entropy/strain reduction. Part 2.[1] The ready availability of *cis*,*cis*-2,4-diene-1,6-diols and derived dibromides allows a simple and mild route to substituted 2,7-dihydro-1*H*-azepines

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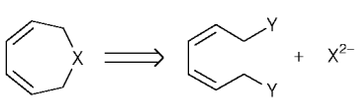
Hydride reduction of a series of substituted *cis*,*cis*-2,4-diene-1,6-dioates **1** provided the corresponding 1,6-diols **2**, most of which were converted to the 1,6-dibromides **3** with phosphorus tribromide. Reaction of a selection of these dibromides with primary alkylamines in the presence of sodium hydrogen carbonate provided a simple and mild synthesis of substituted dihydroazepines **4**. The cleanest products were obtained with toluene-*p*-sulfonamide as the nitrogen source. Bis(dihydroazepines) **5** were also synthesised from diamines while hydrazine yielded a hydrazinium salt **6**. Aniline could be induced to take part in the reaction in the presence of butyllithium furnishing a low yield of *N*-phenyldihydroazepines **8**.

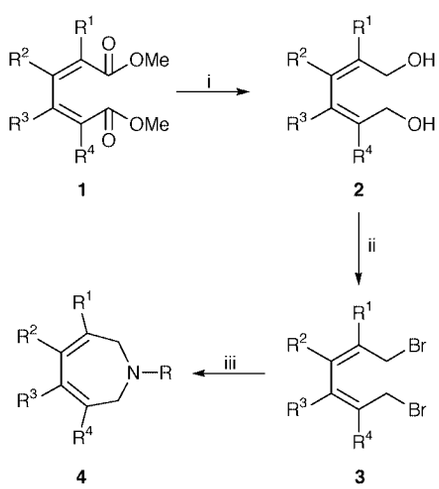
Introduction

The synthesis of medium rings has always been and remains a challenging problem.[2] We have previously communicated[1] an entropy/strain reduction strategy to overcome the low yields inherent in cycloaddition routes to medium rings. It is based on the use of a *cis*,*cis*-hexa-2,4-diene[3] unit as one of the components in the cycloaddition. This has the effect of (i) reducing the degrees of freedom in the chain; (ii) bringing the ends of the chain within reacting distance in certain conformations and (iii) reducing or eliminating eclipsing and transannular steric interactions in the product. Thus, for example, a seven-membered ring is readily constructed based on a [6 + 1] disconnection.



This strategy is crucially dependent on the ready availability of a precursor 1,6-bis-electrophile which has the correct *cis*,*cis*-stereochemistry of the double bonds. We have recently reported[4] the details of lead tetraacetate oxidative ring-opening of catechols which is an effective source of just such stereochemistry furnishing substituted *cis*,*cis*-2,4-diene-1,6-dioates **1** in high yields and free of any of the other alkene isomers. We report now full details[1] of the conversion of these esters, *via* the derived diols **2**, to the required dibromides **3** and the use of the latter for the construction of substituted 2,7-dihydroazepines **4** using primary amines as nucleophiles (Scheme 1).

This synthetic sequence provides ready access for the first time to the *cis*,*cis*-stereochemistry of 2,4-diene-1,6-diols and dibromides. There are some reports of diols **2** or their derivatives in the literature, mostly made by other routes[5–8] but there is only one report[8] of an open chain *cis*,*cis*-1,6-dihalo-2,4-diene. Although there is an extensive literature on azepines[9] which are an important class of heterocycle deserving a recent monograph,[9a] there is almost none on the 2,6-dihydro-derivatives, which could act as useful precursors to azepines. Thus, apart from our own previous work[1] and some other isolated reports[10] of species **4**, the few other known monocyclic 2,7-dihydroazepines are either 2-oxo derivatives made mostly by ring expansion[11] or 2,7-dioxo cases which are simply muconic acid imides.[12]



Scheme 1 *Reagents and conditions*: i, DIBAL-H, hexane–toluene, 25 °C, 12 h; ii, PBr_3, Et_2O, 0 °C, 12 h; iii, RNH_2, K_2CO_3, THF, 25 °C, 1–2 days. For R, R^1–R^4, see Tables 1 and 2.

Results and discussion

Reduction of substituted *cis*,*cis*-hexa-2,4-diene-1,6-diesters 1 to the corresponding diols 2

Exploratory experiments indicated that, not unexpectedly,[13] lithium aluminium hydride (LAH) caused over-reduction in certain cases and, after screening a number of systems, diisobutylaluminium hydride (DIBAL-H) solution in hexane was selected as the reducing agent in benzene or toluene at room temperature. The exception to this was the unsubstituted case **1a** where the solvent had to be dichloromethane, the use of toluene giving significantly reduced yields. Use of THF as solvent for the reduction using both LAH and DIBAL-H also led to reduced yields due to over-reduction. Table 1 shows the good yields of the diols **2** which can be achieved from reduction of diesters **1** using this system. The lower yields for entries **e**–**g**

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Table 1 Yields of diols **2** and dibromides **3** obtained from diesters **1** according to Scheme 1

Product	R^1	R^2	R^3	R^4	% Yield **2**[a]	% Yield **3**[f]
a	H	H	H	H	79[b]	50[b]
b	H	Bu^t	H	H	79[c]	82[c]
c	Bu^t	H	Bu^t	H	85[b]	84[c]
d	H	Me	H	H	70[c]	55[c]
e	Me	H	H	H	46[c,d]	23[c,g]
f	MeO	H	H	H	38[c,d]	43[c,g]
g	Mor[e]	H	H	Mor[e]	30[b,d]	nr

[a] Using DIBAL-H in hexane and with benzene or toluene as reaction solvent, except in **a** where the reaction solvent was dichloromethane, for procedures: see Experimental section. [b] Solid, yield after recrystallisation. [c] Liquid, yield after chromatography. [d] Unoptimised. [e] Mor: morpholinomethyl. [f] Using PBr_3 in Et_2O at 0 °C, for procedures: see Experimental section. [g] Impure material from one small scale experiment.

reflect an unoptimised extraction of the diols from the aqueous phase. Chromatographic analysis showed the presence of only one product irrespective of the overall yield.

All of the diols had spectroscopic characteristics in general agreement with that expected for the proposed structures. However, while the solid diols gave excellent elemental analyses, this was not so for some of the liquid diols, which were hygroscopic and polymerised on attempted drying. In the ^{1}H NMR spectra of compounds **2a** and **2b**, the all-important vicinal alkene coupling constants were both less than 12 Hz. In addition the data for diol **2a** may be compared with that obtained by Schneider and co-workers[6] whose chemical shift values are in agreement with that for the compound made in this work but whose $^3J_{H2,H3}$ (9.0 Hz here) was found to be 10 Hz. Naruta and co-workers[5] did not characterise this diol which they also prepared by DIBAL-H reduction (of monomethyl muconate) but immediately converted it to the *tert*-butyldimethylsilyl ether and characterised this latter compound as having the *cis*,*cis* configuration.

Allylic halogenation of *cis*,*cis*-hexa-2,4-diene-1,6-diols 2

For this conversion we were concerned that neither solvolysis/elimination nor allylic rearrangement of the product should occur.[14] Initial experiments with thionyl chloride–pyridine gave reaction mixtures with very complex ^{1}H NMR spectra but showing no diol or desired halide. However use of phosphorus tribromide following the method of Grieco and Masaki[15] for the conversion of *trans*-geraniol to *trans*-geranyl bromide was successful. This calls for direct treatment with freshly distilled phosphorus tribromide in anhydrous diethyl ether at 0 °C and when this procedure was applied to our range of hexa-2,4-diene-1,6-diols **2**, the corresponding hexa-2,4-diene-1,6-diyl dibromides **3** were successfully generated in moderate yields as shown in Table 1. Work-up was kept to a minimum with the usually dark and fuming crude reaction mixtures being purified by column chromatography to give material which was initally pure but which decomposed within days. No other products were detected by TLC apart from baseline material and we attribute lower yields to decomposition and/or polymerisation.

All the dibromides were liquids except for the unsubstituted analogue **3a** and all had spectroscopic characteristics in general agreement with those expected for the proposed structures. Satisfactory elemental analyses were obtained except for the 2-methyl- (**3e**) and 2-methoxy- (**3f**) products which were quite dark liquids on purification and turned black quickly once isolated while the 3-methyl analogue **3d** turned dark more slowly over a period of weeks. However this instability may be more apparent than real because of the possible presence of the phosphite ester intermediates whose conversion we did not optimise.[16] The dimorpholinomethyl diol **2g** was relatively insoluble in diethyl ether, so tetrahydrofuran, in which it was only slightly more soluble, was used. However no reaction was detected when it was treated with phosphorus tribromide and the diol was recovered unreacted.

In the ^{1}H NMR spectra it was possible to determine the vicinal alkene coupling constant (again <12 Hz) only for the unsubstituted case **3a**. The data for the latter may be compared to that reported by Spangler and co-workers,[17] for the compound generated from the action of phosphorus tribromide on hexa-1,6-diene-3,4-diol, which they took to be the *trans*,*trans*-1,6-dibromide. The chemical shift values are similar but the only alkene coupling constant they reported was for the doublet generated by the allylic $-CH_2$, $^3J = 7$ Hz, which may be compared to $^3J = 8.1$ Hz found for the dibromide generated in this work. For dibromide **3a** it was also possible to determine the long range coupling constants, $^4J_{H2,H4} = {}^4J_{H3,H5} = 2.4$ Hz which is in the region determined by ourselves[4] and Jaroszewski and Ettlinger[18] for the precursor 3-methylhexa-2,4-diene-1,6-diester. A similar long range coupling constant, $^4J = 2.4$ Hz, was obtained for the unsubstituted diester. In addition Spangler's group[17] reported a melting point of 85–86 °C for the *trans*,*trans*-compound which was a potent lachrymator while the product reported here has a melting point of 91–94 °C and has no noticeable lachrymatory properties. From the information recorded thus far, especially the coupling constants, it seems reasonable to assume that the desired *cis*,*cis* configuration of the system has been maintained. Further confirmation comes from their conversion into cyclic products.

Reaction of dibromides 3 with primary amines and sulfonamide to give substituted dihydroazepines 4

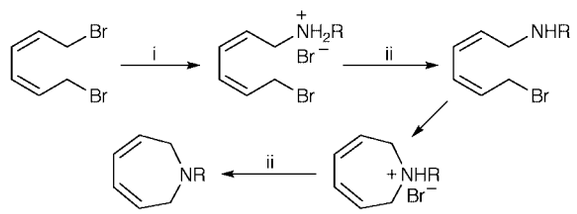
It was found that the primary amino group ($-NH_2$) provided an adequate and readily available source of the nitrogen heteroatom (Scheme 1). A very simple reaction system was used based on that described by Gleiter and co-workers[19] for their synthesis of large ring mixed heterocycles. This involves nothing more than the addition of a solution of the amine to a solution of dibromide, both in THF, in the presence of solid potassium carbonate. The reaction was also found to proceed in the absence of potassium carbonate but at a lower rate. Table 2 shows the yields obtained in the synthesis of dihydroazepines by the reaction of mostly *tert*-butyl substituted dibromides with butylamine, benzylamine, toluene-*p*-sulfonamide and aminoacetaldehyde dimethyl acetal.

For each of the reactions in Table 2, its progress was followed by TLC analysis which showed that, although the dihydroazepine was the major product, it was accompanied by at least one and sometimes more side-products which are the source of the lower yields. The exception to this was the dihydroazepines derived by reaction with toluene-*p*-sulfonamide which were solids and readily isolated and recrystallised. In these latter cases there were no side-products and the lower yields reflect a much more sluggish reaction which was worked up before completion with recovery of starting material. In all cases, attempted isolation of the side products was unsuccessful as they decomposed rapidly. Side-products are not hard to envisage if we consider that the likely course of the reaction is a set of sequential quaternisation–dehydrobrominations as shown in Scheme 2. There are therefore three points where the reaction

Table 2 Yields of dihydroazepines **4** obtained from dibromides **3** according to Scheme 1 [a]

Dibromide	R^1	R^2	R^3	R^4	R	% Yield of **4**
3c	Bu^t	H	Bu^t	H	Bu	41 [b]
3c	Bu^t	H	Bu^t	H	Bn	71 [b]
3c	Bu^t	H	Bu^t	H	Ts	49 [c]
3c	Bu^t	H	Bu^t	H	$(MeO)_2CHCH_2$	56 [b]
3b	H	^{t}Bu	H	H	Bu	66 [b]
3b	H	^{t}Bu	H	H	Ts	56 [c]
3b	H	^{t}Bu	H	H	$(MeO)_2CHCH_2$	74 [b]
3a	H	H	H	H	Bn	56 [b,d]

[a] Reaction in the presence of K_2CO_3 in THF at 25 °C for 1–2 days, except in the case of the toluene-*p*-sulfonamide derivatives which required either extended times or refluxing conditions, for procedures: see Experimental section. [b] Liquid, yield after chromatography. [c] Solid, yield after recrystallisation. [d] Impure.



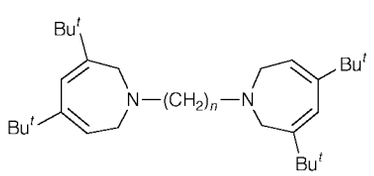
Scheme 2 i, RNH_2; ii, K_2CO_3, −HBr.

could be diverted, both by alternative eliminations and alternative sites of nucleophilic attack. We speculate that the absence of side-products in the case of sulfonamide is related to its reduced basicity leading to less side-products due to elimination.

The products were mainly liquids and had spectroscopic data and elemental analysis consistent with the dihydroazepine structures. NMR confirmed the retention of the alkene character with appropriate signals in both the ^{13}C and ^1H spectra with the latter having the same coupling patterns as for the precursor dibromides. The allylic $-CH_2$ unit also showed the expected shifts from the precursors: upfield for the hydrogens (from about 4 to 2.5–3.7 ppm depending on the nitrogen substituent) and downfield for the carbons (from 26–34 to 50–53 ppm).

Reaction of dibromides with primary diamines—substituted bis(dihydroazepines)

The dibromide **3c** was reacted with half an equivalent of both ethylenediamine and diaminopropane in THF in the presence of K_2CO_3 with a view to generating the ethylene or propylene bridged bis(dihydroazepine) compounds (**5**, $n = 2,3$).



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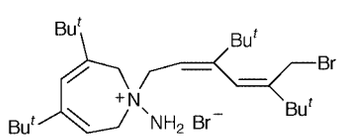
The strategy proved successful in that only one solid product was formed in each case in yields of 40% (**5**, $n = 2$) and 81% (**5**, $n = 3$). Both were found to be 2 : 1 adducts by elemental analysis and mass spectroscopy and NMR analysis was again fully consistent with the proposed structures. In the mass spectrum for both structures the expected parent molecular ion peak was detected with a fragmentation pattern consistent with the loss of the various substituents. A sizeable ion peak was recorded for the ethylene-bridged bis(dihydroazepine) corresponding to the splitting of the structure down the centre to give two equal fragments. The ^1H NMR of both products showed only two *tert*-butyl signals indicating that the structures were symmetrical with both heterocyclic fragments being able to rotate with respect to one another. That they may not be totally free to do so may be implied by a slight, but noticeable, broadening on the ^1H NMR signals.

Reaction of dibromides with hydrazines—hydrazinium salts

An obvious continuation of the previous section was the use of hydrazine with the hope of generating (**5**, $n = 0$). However, when the dibromide **3c** was reacted with hydrazine hydrate a heavy white precipitate was encountered during the work-up on addition of diethyl ether. This solid was fully characterised and shown not to be the hoped-for product. Although mass spectroscopy and elemental analysis showed the formation of a 1 : 2 adduct the presence of two bromine atoms showed that full ring closure had not occurred. The IR spectrum indicated the presence of an amine group by the presence of NH stretches at 3200 and 3080 cm^{-1}. In the ^1H NMR spectrum there were two very broad signals, almost hidden in the baseline, at roughly 3.0–3.9 ppm and 4.0–4.8 ppm with a singlet between them at 3.93 ppm. These signals correspond to the original allylic $-CH_2$ hydrogens in the starting material which have been drastically altered in terms of signal profile but are in roughly the same chemical shift region. Four *tert*-butyl signals confirmed the presence of two hexa-2,4-diene fragments, as did the expected alkene hydrogen signals with both sets of signals again broader than normal. From these observations the *N*-aminodihydroazepinium salt **6** is proposed as the structure of the 1 : 2 adduct. This



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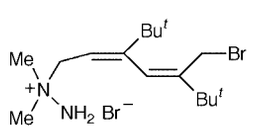

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would result from initial formation of *N*-aminodihydroazepine followed by its quaternisation with the least hindered side of another molecule of the dibromide **3c**. The broadness of the signals in the NMR spectrum could then be due to hydrogen exchange between the various allylic $-CH_2-$ sites and the amino group.

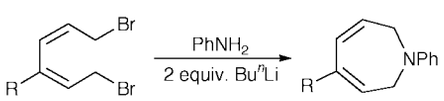
Monosubstituted alkyl hydrazines are known to be alkylated by simple alkyl halides at the substituted nitrogen atom providing steric effects do not interfere.[20] Thus a 1,1,1-trisubstituted hydrazine (hydrazinium salt) results when hydrazines react with excess alkyl halide. Further confirmation of the proposed structure was provided by the analogous reaction of 1,1-dimethylhydrazine with dibromide **3c**. Again during the work-up a white

solid precipitated, identified as the hydrazinium salt **7**. Mass spectroscopy and elemental analysis confirmed that in this case a 1 : 1 adduct had been formed but again showed the presence of two bromine atoms with the IR showing the presence of N–H. The ^{1}H NMR spectrum confirmed the presence of the hexa-2,4-diene group and the two *tert*-butyl groups with similar broadening effects as for product **6**. The main change in the ^{13}C NMR spectra of both **6** and **7** from that of the precursor dibromide **3c** is in the chemical shift of the allylic $-CH_2$ hydrogens. One of these is almost unchanged at 29.3 ppm but the other, previously at 32.0 ppm, is absent. Instead there are broad signals at approx. 60 ppm.

Reaction of dibromides with aniline–butyllithium—*N*-phenyldihydroazepines

No reaction was observed for aniline, acetamide, urea or dinitrophenylhydrazine with dibromide **3c** under the conditions of Scheme 1. This was undoubtedly a result of their reduced nucleophilicity. In an attempt to circumvent this restriction, an alternative set of conditions was investigated for aniline, namely reaction in the presence of butyllithium.

Both the unsubstituted and 4-*tert*-butylhexa-2,4-diene-1,6-diyl dibromides **3a** and **3b** were employed as reactants with aniline, in the presence of 2 equivalents of butyllithium, and both produced a mixture of two compounds, as determined by TLC and ^{1}H NMR. These could be separated by column chromatography and in both cases the material of higher R_f (20–25% yield) was an unstable orange oil which decomposed too rapidly for definite identification. However in each case also, the material of lower R_f had characteristics consistent with the hoped-for *N*-phenyldihydroazepines (Scheme 3) (**8**, R = H



3a/b **8, R=H,Bu^t**

Scheme 3

or ^{t}Bu). Both were clear yellow oils, yields 40% (R = H) and 30% (R = ^{t}Bu), but both proved very unstable, decomposing rapidly within an hour or two, darkening in colour until black. This prevented the recording of mass spectra and elemental analysis. However ^{1}H and ^{13}C NMR spectra were collected and these were entirely consistent with the seven-membered heterocyclic product, being analogous to those of the alkyl-substituted analogues, discussed above.

Conclusions

In conclusion, this work represents a general synthesis of alkyl-substituted seven-membered nitrogen heterocycles. A useful feature is that the cleanest products are obtained for insertion of nitrogen bearing the sulfonamide group which would allow easier subsequent manipulation. Construction of halo-substituted dihydroazepines, other heterepins and cyclohexadienes will be the subjects of future papers.

Experimental

Elemental analyses were carried out commercially by the Microanalysis Department at University College Cork. IR spectra were obtained as potassium bromide discs or as a thin film between sodium chloride plates on a Perkin-Elmer 783 spectrophotometer. Mass spectra were obtained in the EI mode on an AEI 30 instrument and on a Kratos Profile machine. Mps were determined using a Reichart hot-stage apparatus and are uncorrected. Unless otherwise stated ^{1}H and ^{13}C NMR spectra were obtained in deuteriochloroform and were recorded using the Fourier transform mode at 80 MHz and 20 MHz respectively on a Bruker AC80 spectrometer using tetramethylsilane (TMS) as internal standard. Some ^{1}H NMR spectra were recorded at 270 MHz on a JEOL JNM-GX270 FT spectrometer (*J* values are given in Hz). Analytical TLC was performed on commercial silica-coated aluminium sheets with a fluorescent indicator (Merck-Art.5554) or on neutral aluminium oxide-coated aluminium sheets with fluorescent indicator (Merck-Art.5550). Realisation was by ultraviolet irradiation. Preparative chromatography was performed on Flash grade silica gel supplied by Aldrich Fine Chemicals (cat. no. 22,719-6,230-400 mesh) and neutral aluminium oxide (Aldrich cat. no. 19,997-4). The columns were pressurised using a fish pump which was found to be adequate for all diameters up to and including 4 cm. Solvents were dried using recognised procedures.[21] Oxygen-free nitrogen (Irish Industrial Gases) was dried by passage through concentrated sulfuric acid and then sodium hydroxide pellets. All of the starting substituted 2,4-hexadiene-1,6-diesters were prepared by oxidation of the appropriate catechol with lead tetraacetate according to our published procedures.[4] The catechols and all chemicals used, unless otherwise stated, were purchased from Aldrich Fine Chemicals Company.

Reduction of hexa-2,4-diene-1,6-diesters to the corresponding diols

General procedure. In a three-necked flask, equipped with a magnetic stirrer, nitrogen inlet and bubbler, was prepared a stirring solution of the diester[4] (1 equiv.) in anhydrous benzene, toluene or dichloromethane (DCM) (approx. 35 ml g^{-1} of diester), under an atmosphere of nitrogen at 0 °C. To this was added diisobutylaluminium hydride (DIBAL-H, 4 equiv. of a 1.5 M hexane solution) dropwise, *via* syringe, over 30 minutes. The solution was allowed to warm to room temperature and left to stir overnight. Any excess DIBAL-H remaining at the end of the reaction was destroyed by very careful addition of a small amount of methanol (*ca.* 2–4 ml), at 0 °C, until the mixture became paste-like with precipitated aluminium salts. A large volume of methanol was added (100 ml) and vigorous stirring undertaken to break up the paste-like salts (sometimes it was necessary to use a spatula to initially break up the paste). The use of methanol at this stage proves helpful later in the removal of the toluene, as an azeotrope is formed. The salt suspension was filtered and the filtrate set aside. The remaining pasty solids were ground in a mortar, resuspended in methanol and filtered again through a pad of Celite. This latter step was not performed in some cases (labelled unoptimised) leading to lower yields (~15%). The combined filtrate was dried over anhydrous sodium sulfate and evaporated to give the crude diol which was purified using column chromatography (alumina–diethyl ether, with a gradual change to 50 : 50 diethyl ether–methanol). Unreacted diester was eluted first, followed by the diol in the 50 : 50 diethyl ether–methanol fraction. The reactions were clean with the diol being the only product observed.

(2Z,4Z)-Hexa-2,4-diene-1,6-diol ***2a***. From dimethyl (2*Z*,4*Z*)-hexa-2,4-diene-1,6-dioate (8 g, 47 mmol) in DCM, recrystallised from ethyl acetate to give a white solid (4.24 g, 79%) which was stored in a freezer to prevent decomposition through polymerisation, mp 59–60 °C (lit.,[13] 62–63 °C); δ_H: 1.5 (br s, –OH), 4.33 (d, 4H, $-CH_2-$, ^3J = 6.4 Hz), 5.51–5.77 (m, 2H, –CH=CH–), 6.36 [d, 2H, –CH=CH–, ^3J = 9.0 Hz (lit.,[6] 10 Hz)]; δ_C (CD_3COCD_3): 59.2 ($-CH_2-$), 125.0, 134.1 (–CH=CH–).

(2E,4Z)-3-tert-butylhexa-2,4-diene-1,6-diol ***2b***. From dimethyl (2*E*,4*Z*)-3-*tert*-butylhexa-2,4-diene-1,6-dioate (8 g, 35 mmol) in toluene, as a clear yellow tinted oil (4.75 g, 79%) after chromatography (Found: C, 70.32; H, 10.74. Calc. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66%); ν_{max}/cm^{-1}: 3300, 3000, 2960, 2900, 2860, 1630, 1480, 1460, 990, 930, 730, 720; δ_H (270 MHz): 1.05 (s, 9H, *tert*-butyl), 2.0 (br s, –OH), 3.96 (dd, 2H, $-CH_2-$, ^3J = 7.4 Hz, ^4J = 0.5 Hz), 4.01 (dd, 2H, $-CH_2-$, ^3J = 7.7 Hz,

^5J = 0.5 Hz), 5.65 (td, 1H, –CH=CH–, ^3J = 7.7 Hz, ^4J = 0.9 Hz), 5.93 (unsymmetrical overlapped dt, 1H, –CH=CH–, ^3J = 11.5 Hz, ^3J = 7.4 Hz), 6.08 (unsymmetrical d, 1H, –CH=CH–, ^3J = 11.5 Hz); δ_C: 29.6 (–CH_3), 36.6 (–C–), 59.0, 60.1 (–CH_2–), 122.1, 131.9, 145.2, 149.7 (CH=CH); *m*/*z*: 170 (1.6%, M^+), 155 (3, $M^+ - CH_3$), 153 (8, $M^+ - OH$), 152 ($M^+ - H_2O$), 139 (65, $M^+ - CH_2OH$), 113 (36, M^+ – *tert*-butyl), 95 (99, M^+ – *tert*-butyl – H_2O), 57 (100, *tert*-butyl). This reduction was also performed with LAH in benzene which also gave **2b** as the sole product (63% yield, unoptimised; see general procedure). Use of LAH in THF resulted in two products: diene diol **2b** (14%, unoptimised) and another slightly impure liquid (*ca*. 30%) which appeared to be a partial overreduction product with ^{1}H and ^{13}C NMR spectra showing new signals in both the alkene and alkane regions: δ_H: 1.06 (s, 9H, *tert*-butyl), 1.60 (s, –OH), 2.46 (q, *J* = 6.7 Hz), 3.63 (t, *J* = 6.7 Hz), 4.90–5.43 (m), 6.05–6.41 (m); δ_C: 30.1 (–CH_3), 33.3, 36.1 (–C–), 63.5, 119.0, 119.2, 134.0, 151.2.

(2Z,4E)-2,4-Di-tert-butylhexa-2,4-diene-1,6-diol ***2c***. From dimethyl (2*Z*,4*E*)-2,4-di-*tert*-butylhexa-2,4-diene-1,6-dioate (8 g, 28 mmol) in toluene, recrystallised from diethyl ether–hexane (1 : 1) to give a white solid (5.06 g, 85%), mp 99–101 °C (Found: C, 74.38; H, 11.80. Calc. for $C_{14}H_{26}O_2$: C, 74.28; H, 11.57%); ν_{max}/cm^{-1}: 3320, 3240, 2980, 2890, 1480, 1420, 1400, 980, 960, 880, 690; δ_H: 1.06 (s, 9H, *tert*-butyl), 1.26 (s, 9H, *tert*-butyl), 2.4 (br s, –OH), 4.04 (d, 2H, –CH_2–, ^3J = 9.2 Hz), 4.09 (s, 2H, –CH_2–), 5.61 (t, 1H, –CH=CH–, ^3J = 9.2 Hz), 6.10 (s, 1H, –CH=CH–); δ_C (CD_3COCD_3): 30.2, 31.6 (–CH_3), 37.1, 37.3 (–C–), 59.7, 60.3 (–CH_2–), 123.4, 123.0, 151.1, 151.7 (–CH=CH–); *m*/*z*: 209 (4%, $M^+ + 1 - H_2O$), 208 (17, $M^+ - H_2O$), 195 (22, $M^+ - CH_2OH$), 193 (11, $M^+ - H_2O - CH_3$), 180 (11, $M^+ - CH_2OH - CH_3$), 169 (40, M^+ – *tert*-butyl), 151 (87, M^+ – *tert*-butyl – H_2O), 139 (67), 57 (100, *tert*-butyl). Repetition in benzene gave a comparable yield (77%, unoptimised; see general procedure) while use of diethyl ether gave a slightly lower yield (66%, unoptimised). This reduction was also performed with LAH in diethyl ether (57%, unoptimised) and THF (34%, unoptimised).

(2Z,4Z)-3-Methylhexa-2,4-diene-1,6-diol ***2d***. From dimethyl (2*Z*,4*Z*)-3-methylhexa-2,4-diene-1,6-dioate (8 g, 43.5 mmol) in toluene as a clear yellow tinted oil (3.9 g, 70%) after chromatography (Found: C, 65.10; H, 9.66. Calc. for $C_7H_{12}O_2$: C, 65.60; H, 9.43%); ν_{max}/cm^{-1}: 3300, 3000, 2920, 2860, 1700, 1440, 1430, 1000, 730; δ_H: 1.79 (s, 3H, –CH_3), 3.5 (br s, –OH), 3.82–4.15 (m, 4H, –CH_2–), 5.40–6.10 (m, 3H, –CH=CH–); δ_C: 24.2 (–CH_3), 59.1, 59.6 (–CH_2–), 127.1, 130.7, 130.8, 136.3 (–CH=CH–); *m*/*z*: 128 (1.4%, M^+), 110 (23, $M^+ - H_2O$), 97 (100, $M^+ - CH_2OH$), 95 (51, $M^+ - H_2O - CH_3$), 82 (33, $M^+ - CH_2OH - CH_3$), 81 (59), 79 (38).

(2Z,4Z)-2-Methylhexa-2,4-diene-1,6-diol ***2e***. From dimethyl (2*Z*,4*Z*)-2-methylhexa-2,4-diene-1,6-dioate (1.0 g, 54 mmol) in benzene as a clear liquid (0.32 g, 46%, unoptimised; see general procedure) after chromatography (Found: C, 65.29; H, 9.57. Calc. for $C_7H_{12}O_2$: C, 65.60; H, 9.43%); ν_{max}/cm^{-1}: 3300, 3020, 2920, 2860, 1650, 1450, 1430, 1010, 980; δ_H: 1.84 (s, 3H, –CH_3), 3.0 (br s, –OH), 4.16 (s, 2H, –CH_2–), 4.22 (d, 2H, –CH_2–, ^3J = 8.6 Hz), 5.24–6.30 (m, 3H, –CH=CH–); δ_C (CD_3COCD_3): 22.5 (–CH_3), 59.0, 61.5 (–CH_2–), 122.7, 125.5, 131.4, 140.6 (–CH=CH–); *m*/*z*: 128 (2.4%, M^+), 110 (43, $M^+ - H_2O$), 97 (100, $M^+ - CH_2OH$), 95 (31, $M^+ - H_2O - CH_3$), 82 (47, $M^+ - CH_2OH - CH_3$).

(2E,4Z)-2-Methoxyhexa-2,4-diene-1,6-diol ***2f***. From dimethyl (2*E*,4*Z*)-2-methoxyhexa-2,4-diene-1,6-dioate (0.92 g, 46 mmol) in benzene as a pale yellow tinged liquid (0.25 g, 38%, unoptimised; see general procedure) after chromatography (Found: C, 58.08; H, 8.26. Calc. for $C_7H_{12}O_3$: C, 58.32; H, 8.39%); ν_{max}/cm^{-1}: 3400, 2940, 1640, 1610, 1460; δ_H (CD_3COCD_3): 3.58 (s, 3H, –OCH_3), 4.17 (s, 2H, –CH_2–), 4.21 (m, 2H, –CH_2–), 5.20–5.63 (m, 2H, –CH=CH–), 6.08–6.55 (m, 1H, –CH=CH–); δ_C: 55.4 (–OCH_3), 60.0, 62.1 (–CH_2–), 123.5, 131.3, 136.9, 140.0 (–CH=CH–); *m*/*z*: 144 (1.1%, M^+), 126 (25, $M^+ - H_2O$), 113 (100, $M^+ - OCH_3$ or $M^+ - CH_2OH$).

(2Z,4Z)-2,5-Bis(morpholin-4-ylmethyl)hexa-2,4-diene-1,6-diol ***2g***. From dimethy1 (2*Z*,4*Z*)-2,5-bis(morpholin-4-ylmethyl)hexa-2,4-diene-1,6-dioate (1.0 g, 27 mmol) in benzene, recrystallised from a large volume of chloroform to give a white solid (0.25 g, 30%, unoptimised; see general procedure), mp 170–172 °C (Found: C, 61.42; H, 8.88; N, 9.25. Calc. for $C_{16}H_{28}N_2O_4$: C, 61.51; H, 9.03; N, 8.97%); ν_{max}/cm^{-1}: 3200, 2960, 2860, 2820, 1460, 910, 890, 870, 790; δ_H: 2.49 (t, 8H, –CH_2N–, ^3J = 4.6 Hz), 3.16 (s, 4H, –CH_2N–), 3.68 (t, 8H, –CH_2O–, ^3J = 4.6 Hz), 4.41 (s, 4H, –CH_2O–), 4.5 (br s, –OH), 6.10 (s, 2H, –CH=CH–); δ_C: 53.0 (–NCH_2–), 62.3 (–CH_2N–), 66.8 (–CH_2O–), 67.3 (–CH_2O–), 124.3, 137.0 (–CH=CH–); *m*/*z*: 313 (23%, $M^+ + 1$), 227 (52, $M^+ + 1 - NCH_2CH_2O$), 226 (71, $M^+ - NCH_2CH_2O$), 225 (58), 140 (14, $M^+ - 2 \times NCH_2CH_2O$), 122 (37, $M^+ - 2 \times NCH_2CH_2O - H_2O$), 100 (100, $CH_2NCH_2CH_2O$), 86 (84, NCH_2CH_2O).

Conversion of hexa-2,4-diene-1,6-diols to the corresponding dibromides

General procedure. To a stirred suspension of the diol (1 equiv.) in dry diethyl ether (*ca.* 1 g/30 ml) at 0 °C under a nitrogen atmosphere was added phosphorus tribromide (0.66 equiv.) in dry diethyl ether (1 g/30 ml) over five minutes. During the addition there was some initial fuming but this subsided with time and the reaction mixture became orange tinted or brown in colour. After 4–6 hours stirring the solvent was evaporated to leave usually a crude viscous orange or black oil. This was purified *via* column chromatography on silica using diethyl ether as eluent to yield the pure hexa-2,4-diene-1,6-dibromides. In all cases the dibromide was the first fraction eluted from the column. The dibromides were found to be unstable and decomposed at varying rates. The *tert*-butyl and methyl substituted cases decomposed over a week or two, darkening in colour. The solid dibromides were stable for longer periods (up to several months) once they had been recrystallised. Storage in a freezer slowed decomposition considerably.

(2Z,4Z)-1,6-Dibromohexa-2,4-diene ***3a***. From (2*Z*,4*Z*)-hexa-2,4-diene-1,6-diol **2a** (6.0 g, 53 mmol), recrystallised from hexane (6.32 g, 50%) to give a beige solid, mp 91–93 °C (lit.,[17] 85–86 °C for the (*E*,*E*)-isomer) (Found: C, 29.98; H, 3.40; Br, 67.10. Calc. for $C_6H_8Br_2$: C, 30.03; H, 3.36; Br, 66.61%); ν_{max}/cm^{-1}: 1440, 1190, 760, 570, 350; δ_H: 4.09 (d, 4H, –CH_2–, ^3J = 8.1 Hz), 5.74–6.06 (m, 2H, –CH=CH–), 6.37–6.50 (dd, 2H, –CH=CH–, ^3J = 7.6 Hz, ^4J = 2.4 Hz); δ_C: 26.8 (–CH_2–), 126.3, 129.6 (–CH=CH–); *m*/*z*: 242 (4%, $M^+ + 4$), 240 (10, $M^+ + 2$), 238 (4, M^+), 161 (38, M^+ – Br), 159 (44, M^+ – Br), 82 (23), 81 (13), 80 (77), 79 (100).

(2E,4Z)-3-tert-Butyl-1,6-dibromohexa-2,4-diene ***3b***. From (2*E*,4*Z*)-3-*tert*-butylhexa-2,4-diene-1,6-diol **2b** (6 g, 35 mmol) as a light brown liquid (8.4 g, 82%) after chromatography (Found: C, 40.81; H, 5.69; Br, 53.72. Calc. for $C_{10}H_{16}Br_2$: C, 40.57; H, 5.45; Br, 53.98%); ν_{max}/cm^{-1}: 2970, 2870, 1620, 1480, 1460, 860, 770; δ_H (270 MHz): 1.07 (s, 9H, *tert*-butyl), 3.87–3.89 (m, 2H, –CH_2–), 3.95 (d, 2H, –CH_2–, ^3J = 8.1 Hz), 5.73 (br t, 1H, –CH=CH–, ^3J = 8.1 Hz), 5.98–6.02 (m, 2H, –CH=CH–); δ_C: 29.6 (–CH_3), 29.1, 31.2 (–CH_2–), 37.0 (–C–), 121.1, 129.1, 130.0, 149.3 (–CH=CH–); *m*/*z*: 298 (0.7%, $M^+ + 4$), 296 (2, $M^+ + 2$), 294 (0.8, M^+), 217 (77, M^+ – Br), 215 (79, M^+ – Br), 136 (11, $M^+ - 2 \times$ Br), 93 (84, –CH_2Br), 79 (93, Br or $M^+ - 2 \times CH_2Br$), 57 (100, *tert*-butyl).

(2E,4Z)-1-Bromo-5-(bromomethyl)-3-tert-butyl-6,6-dimethylhepta-2,4-diene ***3c***. From (2*Z*,4*E*)-2,4-di-*tert*-butylhexa-2,4-diene-1,6-diol **2c** (6 g, 26.5 mmol) as a clear faintly coloured orange–yellow liquid (7.8 g, 84%) after chromatography (Found: C, 48.78; H, 7.10; Br, 44.40. Calc. for $C_{14}H_{24}Br_2$: C, 47.75; H, 6.87; Br, 45.38%); ν_{max}/cm^{-1}: 2960, 2880, 1450, 1460, 1430, 870, 860; δ_H: 1.07 (s, 9H, *tert*-butyl), 1.28 (s, 9H, *tert*-

butyl), 3.97 (d, 2H, $-CH_2-$, $^3J = 8.2$ Hz), 4.02 (s, 2H, $-CH_2-$), 5.72 (t, 1H, –CH=CH–, $^3J = 8.2$ Hz), 6.11 (s, 1H, –CH=CH–); δ_C: 30.1, 31.5 ($-CH_3$), 29.7, 32.0 ($-CH_2-$), 37.1, 37.3 (–C–), 120.7, 127.4, 147.3, 151.5 (–CH=CH–); *m/z*: 354 (1.3%, $M^+ + 4$), 352 (3.2, $M^+ + 2$), 350 (1.4, M^+), 273 (12), 271 (12, $M^+ - Br$), 215 (24, $M^+ - Br$ – *tert*-butyl), 135 (100, $M^+ - 2 \times Br$ – *tert*-butyl), 57 (65, *tert*-butyl).

(2Z,4Z)-1,6-Dibromo-3-methylhexa-2,4-diene ***3d***. From (2*Z*,4*Z*)-3-methylhexa-2,4-diene-1,6-diol **2d** (6 g, 3.9 mmol) as an orange–brown liquid (6.4 g, 55%) after chromatography (Found: C, 32.83; H, 4.13; Br, 62.77. Calc. for $C_7H_{10}Br_2$: C, 33.10; H, 3.97; Br, 62.93%); ν_{max}/cm^{-1}: 2980, 2960, 2920, 2860, 1450, 1430, 960, 760, 660; δ_H: 1.88 (s, 3H, $-CH_3$), 3.87–4.15 (m, 4H, $-CH_2-$), 5.68–6.22 (m, 3H, –CH=CH–); δ_C: 23.9 ($-CH_3$), 28.8, 30.1 ($-CH_2-$), 125.4, 126.0, 130.9, 137.3 (–CH=CH–); *m/z*: 256 (16%, $M^+ + 4$), 254 (31, $M^+ + 2$), 252 (17, M^+), 175 (79, $M^+ - Br$), 173 (79, $M^+ - Br$), 95 (18), 94 (62, $M^+ - 2 \times Br$), 93 (64), 79 (75, $M^+ - 2 \times Br - CH_3$).

(2Z,4Z)-1,6-Dibromo-2-methylhexa-2,4-diene ***3e***. From (2*Z*,4*Z*)-2-methylhexa-2,4-diene-1,6-diol **2e** (0.2 g, 1.6 mmol) as an impure dark brown liquid (0.09 g, 23%) which was not analysed further.

(3Z,1E)-1,6-Dibromo-2-methoxyhexa-2,4-diene ***3f***. From (2*E*,4*Z*)-2-methoxyhexa-2,4-diene-1,6-diol **2g** (0.27 g, 1.9 mmol) as an impure dark brown liquid (0.22 g, 43%) which was not analysed further.

Attempted preparation of 4-[(2Z,4Z)-6-bromo-2-(bromomethyl)-5-(morpholin-4-ylmethyl)hexa-2,4-dienyl]morpholine ***3g***. From (2*Z*,4*Z*)-2,5-bis(morpholin-4-ylmethyl)hexa-2,4-diene-1,6-diol **2g** (0.3 g, 0.96 mmol) subjected to general procedure in THF (100 ml). Starting material was recovered quantitatively.

Attempted preparation of (4Z,2E)-3-tert-butyl-1-chloro-5-(chloromethyl)-6,6-dimethylhepta-2,4-diene using thionyl chloride. (2*Z*,4*E*)-2,4-Di-*tert*-butylhexa-2,4-diene-1,6-diol (0.5 g, 2.2 mmol) was dissolved in dry pyridine (10 ml) and to this stirred cooled solution was added slowly a slight excess of thionyl chloride (0.28 g 2.35 mmol). This led to a slight warming and the formation of a cloudy yellow solution which was stirred at room temperature overnight. The reaction mixture was then extracted with diethyl ether (5 × 20 ml). The extracts were then dried over $MgSO_4$ and reduced to a clear pale yellow liquid (0.38 g). NMR analysis of this crude product showed a complex spectrum but without the presence of diol or dihalide: δ_H: 0.93 (s, 9H, *tert*-butyl), 1.10 (s, 9H, *tert*-butyl), 4.60 (d), 4.90–5.45 (m), 5.85–6.30 (m). As the reaction did not provide the desired product no attempt was made to purify this crude material.

Synthesis of substituted dihydroazepines

General procedure. The precursor dibromide (1 equiv.) was dissolved in anhydrous THF (*ca*. 1 g/50 ml), potassium carbonate (1 equiv.) was added and the resultant mixture stirred under dry nitrogen at room temperature. To this mixture over about 10 minutes was slowly added the relevant amine (1 equiv.) dissolved in anhydrous THF (*ca.* 1 g/75 ml) and the resultant solution stirred under a blanket of dry nitrogen. Usually the reaction became cloudy and sometimes coloured depending on the reagents involved. Likewise, the time-scale of each reaction depended on the type of reagent involved so they were monitored by TLC. In some cases the addition of extra amine also proved necessary. The work-up involved the removal of potassium salts by careful filtration and evaporation of the resultant filtrate. The crude product mixture was analysed by NMR and TLC and the various components separated by column chromatography and characterised.

3,5-Di-tert-butyl-1-butyl-2,7-dihydro-1H-azepine. From (2*E*,4*Z*)-1-bromo-5-(bromomethyl)-3-*tert*-butyl-6,6-dimethylhepta-2,4-diene **3c** (0.5 g, 1.4 mmol), potassium carbonate (0.2 g, 1.5 mmol) and butylamine (0.11 g, 1.5 mmol) over 48 h. The cloudy white solution was worked up yielding a clear yellow tinged liquid, TLC and NMR analysis of which revealed the absence of starting material and the presence of three products. Column chromatography on silica with elution by chloroform followed by acetone enabled isolation of the title compound from the acetone fraction as a brown liquid (0.15 g, 41%) (Found: C, 81.78; H, 12.55; N, 5.36. Calc. for $C_{18}H_{33}N$: C, 82.06; H, 12.62; N, 5.32%); ν_{max}/cm^{-1}: 3040, 2960, 2860, 2800, 1630, 1460, 860, 840, 730, 660; δ_H: 0.81–1.60 (m, 7H, $-CH_2CH_2CH_3$), 1.07 (s, 9H, *tert*-butyl), 1.16 (s, 9H, *tert*-butyl), 2.38–2.52 (m, 2H, $-NCH_2-$), 2.86 (s, 2H, $-CH_2-$), 2.90 (d, 2H, $-CH_2-$, $^3J = 6.6$ Hz), 5.88 (t, 1H, –CH=CH–, $^3J = 6.6$ Hz), 6.16 (s, 1H, –CH=CH–); δ_C: 14.6 ($-CH_3$), 21.3, 30.7 ($-CH_2-$), 30.1, 30.4 ($-CH_3$), 35.9, 36.7 (–C–), 51.4 ($2 \times -NCH_2-$), 56.5 ($-NCH_2$), 118.0, 124.7, 152.2, 155.0 (–CH=CH–); *m/z*: 264 (12%, $M^+ + 1$), 263 (49, M^+), 248 (61, $M^+ - CH_3$), 220 (38, $M^+ - CH_2CH_2CH_3$), 206 (100, M^+ – *tert*-butyl or $M^+ - CH_2CH_2CH_2CH_3$), 180 (11), 150 (19).

3,5-Di-tert-butyl-1-benzyl-2,7-dihydro-1H-azepine. From (2*E*,4*Z*)-1-bromo-5-(bromomethyl)-3-*tert*-butyl-6,6-dimethylhepta-2,4-diene **3c** (0.68 g, 1.9 mmol), potassium carbonate (0.53 g, 3.8 mmol) and benzylamine (0.25 g, 2.3 mmol) over 36 h. The work-up yielded a thick yellow liquid which proved difficult to purify by chromatography. Eventually, slow elution with toluene gave an analytically consistent sample when characterised (0.41 g, 71%) (Found: C, 84.55; H, 10.21; N, 4.45. Calc. for $C_{21}H_{31}N$: C, 84.79; H, 10.50; N, 4.71%); ν_{max}/cm^{-1}: 3060, 3030, 2960, 2870, 2800, 1670, 1630, 1600, 1500, 1480, 1450, 980, 900, 880, 860, 740, 700, 670; δ_H: 1.07 (s, 9H, *tert*-butyl), 1.12 (s, 9H, *tert*-butyl), 2.85 (s, 2H, $-CH_2N-$), 2.90 (d, 2H, $-CH_2N-$, $^3J = 7.6$ Hz), 3.65 (s, 2H, $-NCH_2-$), 5.86 (t, 1H, –CH=CH–, $^3J = 7.6$ Hz), 6.14 (s, 1H, –CH=CH–), 7.20–7.30 (m, 5H, Ar); δ_C: 30.3, 30.4 ($-CH_3$), 35.0, 36.9 (–C–), 50.9, 52.3 ($-CH_2N-$), 61.1 ($-NCH_2-$), 119.4, 124.1, 152.7, 154.6 (–CH=CH–), 127.4, 128.8, 129.5, 140.7 (Ar); *m/z*: 298 (3%, $M^+ + 1$), 297 (11, M^+), 282 (15, $M^+ - CH_3$), 240 (53, M^+ – *tert*-butyl), 214 (9), 158 (14), 91 (100, benzyl), 57 (39, *tert*-butyl).

3,5-Di-tert-butyl-1-[(4-methylphenyl)sulfonyl]-2,7-dihydro-1H-azepine. From (2*E*,4*Z*)-1-bromo-5-(bromomethyl)-3-*tert*-butyl-6,6-dimethylhepta-2,4-diene **3c** (0.5 g, 1.4 mmol), potassium carbonate (0.38 g, 2.75 mmol) and toluene-*p*-sulfonamide (0.25 g, 1.46 mmol). After 72 h, TLC and NMR analysis showed no product formation, so the reaction mixture was refluxed for 48 h. Work-up in the usual manner gave a yellow tinted semi-solid. TLC and NMR analysis showed the presence of three compounds, the two starting materials and a single product. These were separated by column chromatography [silica, dichloromethane–pentane (1 : 1)] to yield the title compound as a white solid (0.47 g, crude) which was recrystallised from chloroform (0.25 g, 49%), mp 118–120 °C (Found: C, 69.44; H, 8.78; N, 3.70; S, 8.55. Calc. for $C_{21}H_{31}NSO_2$: C, 69.76; H, 8.64; N, 3.87; S, 8.87%); ν_{max}/cm^{-1}: 2960, 3860, 1600, 1470, 940, 930, 870, 850, 820, 800, 760, 730, 660, 640, 610, 550; δ_H: 0.86 (s, 9H, *tert*-butyl), 1.16 (s, 9H, *tert*-butyl), 2.42 (s, 3H, $-CH_3$), 3.43 (s, 2H, $-CH_2-$), 3.64 (d, 2H, $-CH_2-$, $^3J = 7.2$ Hz), 5.27 (t, 1H, –CH=CH–, $^3J = 7.2$ Hz), 6.10 (s, 1H, –CH=CH–), 7.24–7.76 (m, 4H, –Ar); δ_C: 22.1 ($-CH_3$), 29.8, 30.0 ($-CH_3$), 35.7, 37.4 (–C–), 44.4, 44.7 ($-CH_2N-$), 116.7, 125.5, 149.1, 155.9 (–CH=CH–), 128.3, 130.1, 136.9, 143.8 (–Ar); *m/z*: 362 (4%, $M^+ + 1$), 361 (26, M^+), 346 (5, $M^+ - CH_3$), 305 (19, $M^+ + 1$ – *tert*-butyl), 304 (100, M^+ – *tert*-butyl), 206 (48, $M^+ - CH_3C_6H_4SO_2$), 150 (92, $M^+ + 1 - CH_3C_6H_4SO_2$ – *tert*-butyl), 91 (44, $CH_3C_6H_4$), 57 (64, *tert*-butyl).

3,5-Di-tert-butyl-1-(2,2-dimethoxyethyl)-2,7-dihydro-1H-azepine. From (2*E*,4*Z*)-1-bromo-5-(bromomethyl)-3-*tert*-butyl-6,6-dimethylhepta-2,4-diene **3c** (0.5 g, 1.42 mmol), potassium carbonate (0.4 g, 2 mmol) and aminoacetaldehyde dimethyl acetal (0.15 g, 1.42 mmol) over 48 h. The usual work-up yielded a clear yellow liquid, TLC analysis of which showed the presence of two main products. These were separated by column

chromatography [silica, diethyl ether–pentane (1 : 1)] with the first fraction being a mixture of impurities and the second being the title product, a yellow tinged liquid (0.2 g, 56%) (Found: C, 72.89; H, 11.19; N, 4.70. Calc. for $C_{18}H_{33}O_2N$: C, 73.17; H, 11.26; N, 4.74%); ν_{max}/cm^{-1}: 2960, 2900, 2880, 2830, 1730, 1630, 1470, 970, 730; δ_H: 1.06 (s, 9H, *tert*-butyl), 1.15 (s, 9H, *tert*-butyl), 2.69 (d, 2H, –CH_2–, ^3J = 5.2 Hz), 2.94 (d, 2H, –CH_2–, ^3J = 6.7 Hz), 2.95 (s, 2H, –CH_2–), 3.36 (s, 6H, –OCH_3), 4.47 (t, 1H, –CH–, ^3J = 5.2 Hz), 5.79 (t, 1H, –CH=CH–, ^3J = 6.7 Hz), 6.14 (s, 1H, –CH=CH–); δ_C: 30.1, 30.3 (–CH_3), 35.9, 36.8 (–C–), 51.8, 52.6, 63.2 (–CH_2N), 58.6 (–OCH_3), 104.1 (–CH–), 119.4, 124.2, 152.4, 154.5 (–CH=CH–); *m*/*z*: 296 (42%, M^+ + 1), 295 (68, M^+), 280 (16, $M^+ - CH_3$), 264 (35, $M^+ - OCH_3$), 221 [70, $M^+ + 1 - CH(OCH_3)_2$, 220 (100, $M^+ - CH(OCH_3)_2$, 164 (38, $M^+ + 1 - CH(OCH_3)_2$ − *tert*-butyl], 108 (72).

4-tert-Butyl-1-butyl-2,7-dihydro-1H-azepine. From (2*E*,4*Z*)-3-*tert*-butyl-1,6-dibromohexa-2,4-diene **3b** (0.33 g, 1.1 mmol), potassium carbonate (0.31 g, 2.2 mmol) and butylamine (0.08 g, 1.1 mmol) over 24 h. TLC and NMR analysis of the resulting yellow paste showed the absence of starting dibromide and the presence of two products. The mixture was subjected to column chromatography (silica, petroleum ether followed by diethyl ether). The first product was slowly eluted with the petroleum ether giving a yellow tinged liquid, while the title product and major component, a brown viscous liquid, was quickly eluted with the diethyl ether (0.31 g, 66%) (Found: C, 80.86; H, 11.88; N, 6.57. Calc. for $C_{14}H_{25}N$: C, 81.09; H, 12.15; N, 6.75%); ν_{max}/cm^{-1}: 2960, 2940, 2880, 1480, 1460, 750, 670; δ_H: 0.80–1.60 (m, 7H, –$CH_2CH_2CH_3$), 1.11 (s, 9H, *tert*-butyl), 2.42–2.63 (m, 2H, –NCH_2–), 2.96–3.12 (m, 4H, –CH_2N–), 5.78–6.47 (m, 3H, –CH=CH–); δ_C: 14.6 (–CH_3), 21.4, 30.6 (–CH_2–), 30.0 (–CH_3), 35.7 (–C–), 51.9, 53.3 (–CH_2N–), 55.7 (–NCH_2–), 122.1, 131.4, 132.0, 152.6 (–CH=CH–); *m*/*z*: 208 (12%, M^+ + 1), 207 (40, M^+), 192 (53, $M^+ - CH_3$), 164 (77, $M^+ - CH_2CH_2CH_3$), 150 (78, M^+ − *tert*-butyl or *n*-$CH_3CH_2CH_2CH_2$), 107 (16, M^+ − *tert*-butyl-$CH_2CH_2CH_3$), 57 (100, *tert*-butyl or *n*-CH_3CH_2-CH_2CH_2).

4-tert-Butyl-1-[(4-methylphenyl)sulfonyl]-2,7-dihydro-1H-azepine. From (2*E*,4*Z*)-3-*tert*-butyl-1,6-dibromohexa-2,4-diene **3b** (0.4 g, 1.35 mmol), potassium carbonate (0.37 g, 2.67 mmol) and toluene-*p*-sulfonamide (0.25 g, 1.46 mmol) over 7 d. The reaction solution was reduced to a yellow pasty solid, TLC analysis of which showed the presence of two compounds, starting sulfonamide and one product which was separated by column chromatography [silica, diethyl ether–pentane (1 : 2)] and recrystallised from pentane (0.23 g, 56%), mp 82–84.5 °C (Found: C, 66.56; H, 7.64; N, 4.73; S, 10.53. Calc. for $C_{17}H_{23}NSO_2$: C, 66.85; H, 7.60; N, 4.58; S, 10.48%); ν_{max}/cm^{-1}: 3320, 3240, 3120, 1600, 1570, 900, 800, 700, 650, 550, 530; δ_H: 0.94 (s, 9H, *tert*-butyl), 2.41 (s, 3H, –CH_3), 3.55–3.71 (m, 4H, –CH_2–), 5.50–6.30 (m, 3H, –CH=CH–), 7.26–7.75 (m, 4H, –Ar); δ_C: 22.0, 30.0 (–CH_3), 35.8 (–C–), 44.3, 45.6 (–CH_2N–), 121.3, 130.4, 132.1, 151.3 (–CH=CH–), 128.6, 130.7, 134.9, 138.2 (–Ar); *m*/*z*: 306 (9%, M^+ + 1), 305 (44, M^+), 290 (14, $M^+ - CH_3$), 248 (56, M^+ − *tert*-butyl), 150 (100, $M^+ - CH_3C_6H_4SO_2$), 94 (87), 91 (93, $CH_3C_6H_4$), 57 (72, *tert*-butyl).

4-tert-Butyl-1-(2,2-dimethoxyethyl)-2,7-dihydro-1H-azepine. From (2*E*,4*Z*)-3-*tert*-butyl-1,6-dibromohexa-2,4-diene **3b** (0.5 g, 1.68 mmol), potassium carbonate (0.46 g, 3.38 mmol) and aminoacetaldehyde dimethyl acetal (0.18 g, 1.68 mmol) over 24 h. Work-up gave a yellow viscous liquid which TLC and NMR analysis showed to be one predominant product which was purified by column chromatography (silica, chloroform) and isolated as a clear brown viscous liquid (0.30 g, 74%) (Found: C, 69.93; H, 10.34; N, 5.68. Calc. for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85%); ν_{max}/cm^{-1}: 2950, 2900, 2820, 1460, 1390, 1360, 970, 870, 810, 750; δ_H: 1.08 (s, 9H, *tert*-butyl), 2.67 (d, 2H, –CH_2–, ^3J = 5.2 Hz), 3.06–3.21 (m, 4H, –CH_2–), 3.31 (s, 6H, –OCH_3), 4.48 (t, 1H, –CH–, ^3J = 5.2 Hz), 5.75–6.45 (m, 3H, –CH=CH–); δ_C: 29.7 (–CH_3), 35.4 (–C–), 52.4, 53.8, 56.5 (–NCH_2–), 53.5 (–OCH_3), 103.5 (–CH–), 122.0, 131.4, 131.5, 151.9 (–CH=CH–); *m*/*z*: 240 (31%, M^+ + 1), 239 (78, M^+), 224 (32, $M^+ - CH_3$), 208 (54, $M^+ - OCH_3$), 182 (38, M^+ − *tert*-butyl), 164 [100, $M^+ - CH(OCH_3)_2$], 107 (61), 75 (86), 57 (70, *tert*-butyl).

1-Benzyl-2,7-dihydro-1H-azepine. From (2*Z*,4*Z*)-1,6-dibromohexa-2,4-diene **3a** (0.7 g, 2.88 mmol), potassium carbonate (1.0 g, 7.22 mmol) and benzylamine (0.32 g, 2.88 mmol) over 7 h. The solution was evaporated under reduced pressure and the sticky semi-solids were resuspended in dichloromethane (30 ml). The solids were filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography [silica, dichloromethane–hexane (1 : 1)] to yield a clear, yellow tinted oil which darkened rapidly in colour, turning black in an hour or two. Rapid analysis by ^{1}H NMR showed it to be the desired heterocycle (0.3 g, 56%). However, the product decomposed too fast to allow for ^{13}C analysis. δ_H: 3.50 (d, 4H, –C=C–CH_2–), 3.63 (s, 2H, –CH_2–N), 5.70–6.45 (m, 4H, –CH=CH–), 7.25–7.35 (m, 5H, Ar).

*3,5-Di-tert-butyl-1-[2-(3,5-di-tert-butyl-2,7-dihydro-1H-azepin-1-yl)ethyl]-2,7-dihydro-1H-azepine (**5**, n = 2).* From (2*E*,4*Z*)-1-bromo-5-(bromomethyl)-3-(*tert*-butyl)-6,6-dimethylhepta-2,4-diene **3c** (0.25 g, 0.71 mmol), potassium carbonate (0.10 g, 0.35 mmol) and ethylenediamine (0.02 g, 0.35 mmol) over 48 h. The cloudy white reaction mixture was evaporated and the residue treated with diethyl ether and filtered to remove the insoluble salts. The clear faintly yellow tinged liquid was dried with $MgSO_4$ and reduced to a viscous clear orange tinted liquid which overnight solidified to a white–pale brown solid which was purified by column chromatography (silica, diethyl ether followed by acetone) with isolation of the title compound in the acetone fraction as a white solid recrystallised from acetone (0.06 g, 40%), mp 66–68 °C (Found: C, 80.31; H, 11.72; N, 6.17. Calc. for $C_{30}H_{52}N_2$: C, 81.75; H, 11.89; N, 6.36%); ν_{max}/cm^{-1}: 2960, 2940, 2920, 2860, 2800, 1570, 1560, 1540, 1360, 860, 850, 810; δ_H: 1.07 (s, 18H, *tert*-butyl), 1.16 (s, 18H, *tert*-butyl), 2.69 (s, 4H, –NCH_2–), 2.91 (s, 4H, –CH_2N–), 2.95 (d, 4H, –CH_2N, ^3J = 5.5 Hz), 5.88 (t, 2H, –CH=CH–, ^3J = 5.5 Hz), 6.15 (s, 2H, –CH=CH–); δ_C: 30.2, 30.4 (–CH_3), 36.0, 36.9 (–C–), 51.6, 52.6 (–CH_2N–), 55.6 (–NCH_2), 119.4, 124.4, 152.4, 154.7 (–CH=CH–); *m*/*z*: 441 (3%, M^+ + 1), 440 (100, M^+), 383 (62, M^+ − *tert*-butyl), 251 (23), 220 [66, $M^+ - (C_4H_9)_2C_6H_6NCH_2$], 164 (12), 150 (14), 109 (23).

*3,5-Di-tert-butyl-1-[3-(3,5-di-tert-butyl-2,7-dihydro-1H-azepin-1-yl)]propyl]-2,7-dihydro-1H-azepine (**5**, n = 3).* From (2*E*,4*Z*)-1-bromo-5-(bromomethyl)-3-(*tert*-butyl)-6,6-dimethylhepta-2,4-diene **3c** (0.5 g, 1.42 mmol), potassium carbonate (0.2 g, 1.44 mmol) and diaminopropane (0.05 g, 0.71 mmol) over 24 h. Work-up yielded a yellow viscous liquid, NMR analysis of which showed the presence of one main product which was purified by column chromatography (silica, acetone) to give an off-white solid which was recrystallised from diethyl ether (0.26 g, 81%), mp 173–174 °C (Found: C, 81.59; H, 11.87; N, 5.90. Calc. for $C_{31}H_{54}N_2$: C, 81.87; H, 11.97; N, 6.16%); ν_{max}/cm^{-1}: 2960, 2920, 2880, 1470, 1450, 1380, 1360, 870, 840; δ_H: 1.07 (s, 18H, *tert*-butyl), 1.16 (s, 18H, *tert*-butyl), 1.55–2.00 (m, 2H, –CH_2–), 2.62 (t, 4H, –CH_2N, ^3J = 7.2 Hz), 2.92 (s, 4H, –CH_2N–), 2.96 (d, 4H, –CH_2N–, ^3J = 6.6 Hz), 5.88 (t, 2H, –CH=CH–, ^3J = 6.6 Hz), 6.19 (s, 2H, –CH=CH–); δ_C: 27.6 (–CH_2–), 30.1, 30.3 (–CH_3), 35.9, 36.8 (–C–), 51.6, 51.7, 55.0 (–CH_2N–), 119.4, 124.3, 152.4, 154.5 (–CH=CH–); *m*/*z*: 455 (5%, M^+ + 1), 454 (73, M^+), 439 (10, $M^+ - CH_3$), 398 (6, $M^+ + 1 -$ *tert*-butyl), 397 (33, M^+ − *tert*-butyl), 263 (48), 220 (83), 164 (66), 57 (100, *tert*-butyl).

*1-Amino-1-[(4Z,2E)-5-(bromomethyl)-3-tert-butyl-6,6-dimethylhepta-2,4-dien-1-yl]-3,5-di-tert-butyl-2,7-dihydro-1H-azepinium bromide **6**.* From (2*E*,4*Z*)-1-bromo-5-(bromomethyl)-3-(*tert*-butyl)-6,6-dimethylhepta-2,4-diene **3c** (0.5 g, 1.42 mmol), potassium carbonate (0.2 g, 1.45 mmol) and hydrazine hydrate (0.05 g, 1 mmol) over 24 h. Work-up yielded

a yellow tinged, white pasty solid which, on treatment with diethyl ether, precipitated a large amount of white solid which was recrystallised from chloroform–diethyl ether (1:1), and characterised as the title compound (0.39 g, 95%) mp 183–186 °C (Found: C, 58.59; H, 8.83; N, 4.63; Br, 27.90. Calc. for $C_{28}H_{50}N_2Br_2$: C, 58.53; H, 8.77; N, 4.87; Br, 27.81%); ν_{max}/cm^{-1}: 3200, 3080, 2960, 2910, 2860, 1630, 1460, 1400, 1360, 960, 940, 870, 850, 800, 700, 620, 500; δ_H: 1.10 (s, 9H, *tert*-butyl), 1.15 (s, 9H, *tert*-butyl), 1.27 (s, 9H, *tert*-butyl), 1.29 (s, 9H, *tert*-butyl), 3.0–3.8 (br, $-CH_2-$), 3.93 (s, 2H, $-CH_2-$), 4.0–4.7 (br, $-CH_2-$), 5.90–5.92 (m, 2H), 6.10 (s, 1H), 6.64 (s, 1H); δ_C: 29.3 ($-CH_2-$), 30.0 (2×), 30.4, 31.2 ($-CH_3$), 36.2, 36.9, 37.4, 38.0 (–C–), 60–64 (br), 64.6 ($-CH_2N-$), 114.3, 116.3, 126.3, 130.9, 148.7, 150.1, 159.0, 162.0 (–CH=CH–); *m/z*: 438 (0.4%), 436 (0.5, $M^+ - tert$-butyl), 395 (3), 393 (3), 381 (2), 379 (2, $M^+ - 2 \times tert$-butyl), 356 (13), 355 (40), 206 (100, $M^+ - C_{14}H_{24}Br - NH_2$), 205 (90), 192 (58), 190 (100), 150 (100), 57 (100, *tert*-butyl).

1-[(4Z,2E)-5-(Bromomethyl)-3-tert-butyl-6,6-dimethylhepta-2,4-dien-1-yl]-1,1-dimethylhydrazinium bromide ***7****.* From (2*E*,4*Z*)-1-bromo-5-(bromomethyl)-3-*tert*-butyl-6,6-dimethyl hepta-2,4-diene **3c** (0.5 g 1.42 mmol), potassium carbonate (0.2 g, 1.44 mmol) and dimethylhydrazine (0.086 g; 1.48 mmol) over 12 h. Work-up resulted in a white paste which gave a white solid on treatment with diethyl ether. This was recrystallised from chloroform–diethyl ether (1:1) and characterised as the title compound (0.35 g, 60%), mp 139–141 °C (Found: C, 46.99; H, 7.98; N, 6.70; Br, 38.33. Calc. for $C_{16}H_{32}N_2Br_2$: C, 46.62; H, 7.82; N, 6.79; Br, 38.76%); ν_{max}/cm^{-1}: 3220, 3100, 3000, 2980, 2860, 1620, 1480, 1400, 750, 720, 690, 630, 570, 510, 490; δ_H: 1.13 (s, 9H, *tert*-butyl), 1.30 (s, 9H, *tert*-butyl), 3.48 (s, 6H, $2 \times -CH_3$), 3.92 (s, 2H, $-CH_2-$), 4.05–4.45 (br, 2H, $-CH_2-$), 5.79 (bt, 1H, –CH=CH–, $J = 7.5$ Hz), 6.08 (s, 1H, –CH=CH–); δ_C: 29.0 ($-CH_2-$), 29.8, 31.2 ($-CH_3$), 36.9, 38.1 (–C–), 53–56 (br, $-CH_2N-$), 68.0 [$-N(CH_3)_2$], 111.6, 126.3, 148.8, 159.2 (–CH=CH–); *m/z*: 273 (2.6%), 271 (2.5%) [$M^+ - NH_2N(CH_3)_2$], 237 (11), 236 (41, $M^+ - Br - CH_3$), 180 (75, $M^+ - Br - tert$-butyl $- CH_3$), 123 (54, $M^+ - Br - 2 \times tert$-butyl $- CH_3$), 57 (20, *tert*-butyl).

Attempted reaction of (2E,4Z)-1-bromo-5-(bromomethyl)-3-(tert-butyl)-6,6-dimethyl hepta-2,4-diene ***3c*** *with acetamide, 2,4-dinitrophenylhydrazine and aniline.* In each case the dibromide (0.25 g, 0.7 mmol) was dissolved in THF (25 ml), stirred with potassium carbonate (0.10 g, 0.72 mmol) and treated with the other reactant (0.71 mmol) in THF (15 ml) and left stirring for 12 h. In each case NMR and TLC analysis showed that no reaction had taken place and the starting materials were recovered quantitatively.

*4-tert-Butyl-1-phenyl-2,7-dihydro-1H-azepine (****8****,* $R = Bu^t$). Freshly distilled aniline (202 mg, 2.18 mmol) was placed in a dry, 100 ml, three-necked flask, fitted with a rubber septum and magnetic stirrer, which was then flooded with dry nitrogen. Dry THF (15 ml) was then added, *via* syringe, and stirring begun. The solution was brought to 0 °C by immersion of the flask in an ice bath. To this stirred solution was added butyllithium (1.74 ml of a 2.5 M solution, 4.35 mmol), *via* syringe, over 5 minutes. The solution turned bright yellow. (2*E*,4*Z*)-3-*tert*-Butyl-1,6-dibromohexa-2,4-diene **3b** (646 mg, 2.18 mmol), dissolved in dry THF (10 ml), was then added slowly over 10 minutes, by syringe, to the reaction flask. This resulted in a colour change to dark red–orange. After 4 hours stirring, a few drops of methanol were added to ensure that all the butyllithium had been destroyed, and the solution was evaporated under reduced pressure. The crude solids were purified by column chromatography (silica, hexane) to give two separate products, both of which decomposed upon standing for more than 1 h, precluding the collection of data other than NMR. Material of higher R_f: unidentified orange–red liquid (105 mg, 21%); δ_H (270 MHz): 1.16 (s, 9H, *tert*-butyl), 4.00 (dt, 1H, CH_2, $J = 13.7$ Hz, $J = 2.2$ Hz), 4.17–4.19 (m, 1H), 4.92–4.70 (m, 1H), 5.20–5.37 (m, 2H), 5.60–5.73 (m, 2H), 6.57–6.68 (m, 3H, Ph), 7.17–7.23 (m, 2H, Ph); δ_C (67.8 MHz): 30.2 ($-CH_3$), 32.8 (–C–), 54.5 ($-CH_2-$), 68.1 (–CH–), 111.9, 115.6 (–CH=CH–), 117.0 ($C=CH_2$), 118.3, 128.9, 138.8 (–CH=CH–), 146.3, 151.7 (–C–, alkene). Material of lower R_f: clear pale yellow liquid (160 mg, 32%); this fraction had ^1H and ^{13}C NMR spectra consistent with the title compound but, due to poor quality of the sample, the quaternary alkene carbon signals could not be distinguished from the baseline noise with absolute certainty and are, therefore, not reported: δ_H (270 MHz): 1.11 (s, 9H, *tert*-butyl), 3.73 (d, 2H, $-CH_2N$), 3.82 (d, 2H, $-CH_2N$), 5.98–6.03 (m, 1H, –CH=CH–), 6.09–6.17 (m, 1H, –CH=CH–), 6.30–6.35 (m, 1H, –CH=CH–), 6.68–6.79 (m, 3H, Ar), 7.17–7.26 (m, 2H, Ar); δ_C (67.8 MHz): 29.3 ($-CH_3$, *tert*-butyl), 47.7, 50.0 ($-CH_2-$), 113.8, 117.1, 121.9, 129.0, 130.5, 130.9 (–CH=C–).

*1-Phenyl-2,7-dihydro-1H-azepine (****8****,* $R = H$). From aniline (243 mg, 2.61 mmol) in dry THF (10 ml) treated with butyllithium (2.09 ml of a 2.5 M solution, 5.23 mmol) and (2*Z*,4*Z*)-1,6-dibromohexa-2,4-diene (627 mg, 2.61 mmol) in dry THF (10 ml) in the same manner as the previous experiment. After overnight stirring, work-up and chromatography again gave two fractions, identified as separate products (by ^1H NMR), both of which decomposed upon standing within 30 minutes, allowing the collection of only ^1H NMR: material of higher R_f: (105 mg, 24%); δ_H (270 MHz): 5.60–5.83 (m), 5.85–6.15 (m), 6.48–6.83 (m), 6.99–7.20 (m). Material of lower R_f: (179 mg, 40%); this fraction had ^1H NMR consistent with the title compound, δ_H (270 MHz): 3.88 (d, 4H, $-CH_2-$), 5.58–6.03 (m, 4H, –CH=CH–), 6.39–6.82 (m, 3H, Ar), 7.21–7.24 (m, 2H, Ar).

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