# Cyclisation of 2-Substituted 2-Bromomethyl-1,3-dioxacyclohept-5-enes; Hydrogen Transfer Reactions of 1,3-Dioxacyclohept-5-enes and 1,3-Dithiacyclohept-5-enes

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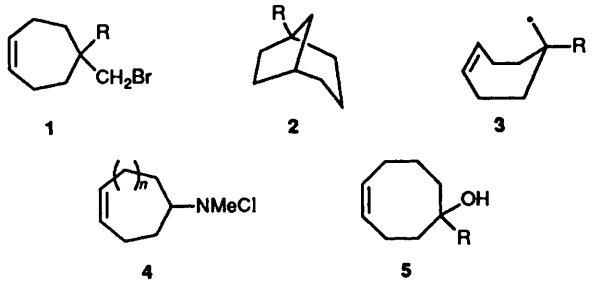
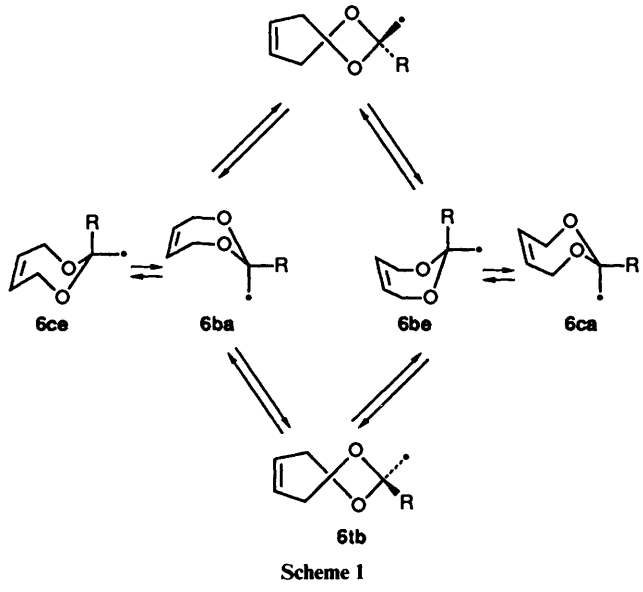
2-Bromomethyl-1,3-dioxacyclohept-5-enes (2-bromomethyl-4,7-dihydro-1,3-dioxepins), containing an additional substituent at the 2-position, cyclise to afford 1-substituted 2,7-dioxabicyclo[3.2.1]-octanes on treatment with tributyltin hydride. The rate constants for cyclisation of the 2-methyl- and 2-phenyl-4,7-dihydro-1,3-dioxepin-2-ylmethyl radicals are $8.4 \times 10^5$ and $4.9 \times 10^5$ $s^{-1}$ respectively at 298 K. Hydrogen is readily abstracted from the 4- and 7-positions of 4,7-dihydro-1,3-dioxepins by *tert*-butoxyl radicals to give 4,7-dihydro-1,3-dioxepin-4-yl radicals which have been characterised by EPR spectroscopy. The Arrhenius parameters for inversion of the 'flap' conformers have been determined from the exchange-broadened spectra of the 2,2-dimethyl and 2,2-diethyl radicals. The analogous radicals, expected on hydrogen abstraction from 1,3-dithiacyclohept-5-enes (4,7-dihydro-1,3-dithiepins), cannot be spectroscopically observed. Instead, the same spectrum, which we attribute to a degradation intermediate, is obtained from a series of 2,2-dialkyl-4,7-dihydro-1,3-dithiepins.

We showed recently[1] that 5-bromomethylcyclohept-1-enes (**1**) cyclised on treatment with tributyltin hydride to give useful yields of bicyclo[3.2.1]octanes (**2**). The reaction occurred *via* the intermediacy of cyclohept-4-enylmethyl radicals which have access to an axial boat conformation **3** in which the radical centre is very favourably placed for a transannular cyclisation. Several related processes have been reported, including the formation in low yield of 8-azabicycloalkanes from *N*-chloroamines[2] (**4**) and the formation of 9-oxabicyclo[4.2.1]nonane derivatives on treatment of cycloocten-5-ols (**5**) with ceric




ammonium nitrate.[3] We sought to extend the process to heterocyclic analogues of **1** containing oxygen or sulfur atoms in the seven-membered ring. The success of this type of transannular cyclisation depends critically on the conformations populated by the intermediate radicals and on their flexibility. The introduction of heteroatoms into a medium ring often leads to markedly different conformational preferences and free energy barriers.[4] NMR studies of 1,3-dioxacyclohept-5-enes (4,7-dihydro-1,3-dioxepins) showed that they have a preference for twist boat conformations which can invert by low energy pseudorotation processes through boat conformations.[5,6] A study of the conformational preferences of 1,3-dioxacyclohept-5-en-2-ylmethyl radicals (**6**) by EPR spectroscopy[7] showed that the preferred conformation depended on the type of substitution at C(2), and that conformational interconversion *via* axial boat conformations was a low energy pathway (Scheme 1). Because the axial boat conformation (**6ba**) should be readily accessible, it was obviously worthwhile to investigate transannular cyclisations of these species. In this paper we describe homolytic methods for the conversion of 2-




Scheme 1

substituted 4,7-dihydro-1,3-dioxepins to 1-substituted 2,7-dioxabicyclo[3.2.1]octanes. We also examined hydrogen abstraction from series of 2,2-disubstituted 2,7-dihydro-1,3-dioxepins and 2,7-dihydro-1,3-dithiepins.

## Results and Discussion

*Transannular Cyclisation of 2-Halomethyl-4,7-dihydro-1,3-dioxepins to 2,7-Dioxabicyclo[3.2.1]octanes.*—4,7-Dihydro-1,3-dioxepins (**7**) are readily prepared by condensation of (*Z*)-but-2-en-1,4-diol with an appropriate dimethylketal (Scheme 2). Successful condensations of ketals containing halomethyl groups have been reported in one or two instances.[8,9]

2-Halomethyl-4,7-dihydro-1,3-dioxepins (**7**), which could therefore be formed in a single step, were suitable precursors for free radical-mediated cyclisations. Reduction of **7a** with tributyltin hydride gave, however, only about 1% of the corresponding dioxabicyclo[3.2.1]octane, **8a**. The main product was 2-methyl-4,7-dihydro-1,3-dioxepin (**9a**) formed by simple reduction. A possible reason for the low yield of cyclised product was that cyclisation of the intermediate radical **6**

**Table 1** Product yields[a] from the reduction of 2-substituted 2-bromomethyl-1,3-dioxepins (**7**) with tributyltin hydride[b]

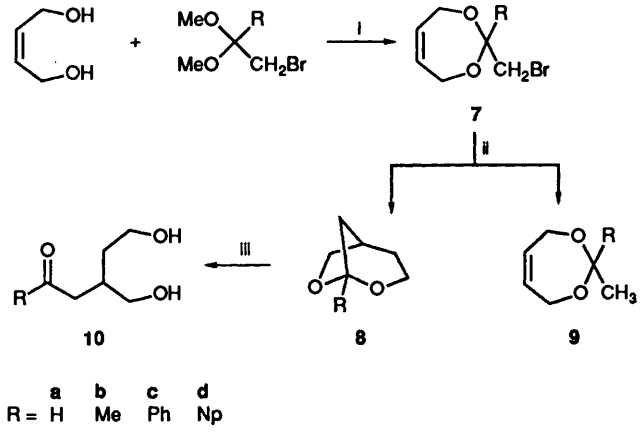
| R | T/°C | 8 (%) | 9 (%) |
|---|---|---|---|
| H | 97 | 1 | 49 |
| Me | 120 | 46 | 12 |
| Ph | 120 | 48 | 12 |
| Np[c] | 120 | — | — |

[a] Yields are mol% isolated products. [b] Dropwise addition. [c] Np = Naphthyl; gave hydrolysis products only.

**Table 2** Kinetics of the reduction of **7b** by tributyltin hydride in hexadecane[a]

| T/K | 8b (%) | 9b (%) | $(k_c/k_H)$/ mol dm$^{-3}$ |
|---|---|---|---|
| 272[b] | 39 | 61 | 0.16 |
| 305 | 67 | 33 | 0.45 |
| 336 | 80 | 20 | 0.85 |
| 364 | 88 | 12 | 1.61 |
| 394 | 94 | 6 | 3.7 |

[a] [**7b**] = 0.25 mol dm$^{-3}$, [$Bu_3SnH$] = 0.27 mol dm$^{-3}$; octane as internal standard. [b] In cyclopentane solvent.




**Scheme 2** *Reagents and conditions:* i, *p*-$MeC_6H_4SO_3H$/MeOH; ii, $Bu_3SnH$/*hν*; iii, 3.5% aq. HCl

could not compete with rapid hydrogen abstraction from the organotin hydride. Reactions of **7a** were therefore carried out with tris(trimethylsilyl)silane,[10] and triphenylsilane,[11] both of which transfer hydrogen more slowly than organotin hydrides. With both these reagents the yield of cyclised product (**8a**) remained negligible. It is most likely therefore that the low amount of cyclisation is due to the inaccessibility of the axial boat conformer **6ba** (Scheme 1). Of the two boat conformers, **6be** with its $CH_2$· group in the equatorial orientation, will be preferred, but this structure is not conducive to transannular cyclisation. We concluded therefore that 4,7-dihydro-1,3-dioxepins, containing substituents at the 2-position which were sterically larger than the $CH_2$· group, would cyclise much more efficiently because the $CH_2$· group would be forced into the axial orientation.

Several 2-substituted derivatives of **7** were examined and the results of preparative scale experiments are given in Table 1. Substantial yields of the 2,7-dioxabicyclo[3.2.1]octanes (**8**) were obtained from **7b** and **7c** and even higher yields were possible in higher temperature reductions. This demonstrated the considerable potential of this cyclisation as a synthetic route to 2,7-dioxabicyclo[3.2.1]octanes. The 2-naphthyl derivative **7d** was rather unstable and the only products isolated from its reduction were those from hydrolysis of the 4,7-dihydro-1,3-dioxepin. The main limitation of the reaction as a synthetic method was the instability of the haloalkyldihydrodioxepins. Thus, pure samples of **7**, R = Et, Pr$^i$, and other alkyl, could not be obtained from acid-catalysed condensations. Compounds containing this skeleton are known to be pharmaceutically active and have previously been prepared by multistage syntheses in which the key step was acid-catalysed cyclisation of functionalised 4-hydroxyalkyl-tetrahydropyrans or -dihydropyrans.[12,13]

**Table 3** Kinetics of the reduction of **7c** by tributyltin hydride in *tert*-butylbenzene[a]

| T/K | 8c (%) | 9c (%) | $(k_c/k_H)$/ mol dm$^{-3}$ |
|---|---|---|---|
| 298 | 34 | 66 | 0.28 |
| 323 | 47 | 53 | 0.43 |
| 348 | 57 | 53 | 0.67 |
| 373 | 80 | 20 | 2.0 |
| 398 | 80 | 20 | 2.0 |
| 423 | 88 | 12 | 3.5 |

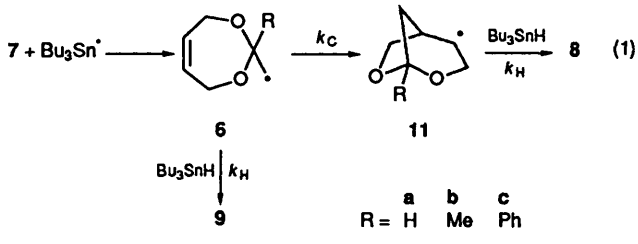
[a] [**7c**] = 0.54 mol dm$^{-3}$, [$Bu_3SnH$] = 0.54 mol dm$^{-3}$; hexadecane as internal standard.

**Table 4** Rate constants and Arrhenius parameters for transannular and related cyclisations

| Radical | $k_c/10^5$ s$^{-1}$ (298 K) | $E$/ kJ mol$^{-1}$ | log($A$/s$^{-1}$) |
|---|---|---|---|
| **3**[a] | 1.0 | 32.9 | 10.9 |
| **6a** | *ca.* 0.05[b] | — | — |
| **6b** | 8.4 | 37.5 | 12.5 |
| **6c** | 4.9 | 37.7 | 12.3 |
| Hex-5-enyl[c] | 2.5 | 28.6 | 10.4 |

[a] Data from ref. 1. [b] At 373 K. [c] Data from ref. 16.

*Kinetics of the Cyclisations of* 4,7-*Dihydro*-1,3-*dioxepin*-2-*ylmethyl Radicals* (**6**).—The rates of these cyclisations were determined by quantitative analysis of the products of the tributyltin hydride reductions of **7b** and **7c**. Photochemical




reductions were carried out in hydrocarbon solution in the temperature range 0–150 °C, and the product proportions are given in Tables 2 and 3. The ratio of the cyclisation rate constant $k_c$ to the rate constant for hydrogen abstraction from $Bu_3SnH$ by the uncyclised radical, $k_H$ [eqn.(1)] was evaluated at each temperature by the usual method.[14,15] The $k_H$ value of Ingold and co-workers[16] was used to derive absolute $k_c$ values which, together with the corresponding Arrhenius parameters, are compared in Table 4 with kinetic data for related reactions. The rate constant for cyclisation of **6a** is very much smaller than that for the analogous hydrocarbon radical (**3**) (Table 4). There are several possible explanations of this difference. First, the C–O bonds in **6** will be shorter than the C–C bonds in **3**. This may introduce more strain into the transition state and hence disfavour cyclisation of **6a**. Second, the smaller rate constant for **6** might be a consequence of a lower population of axial boat

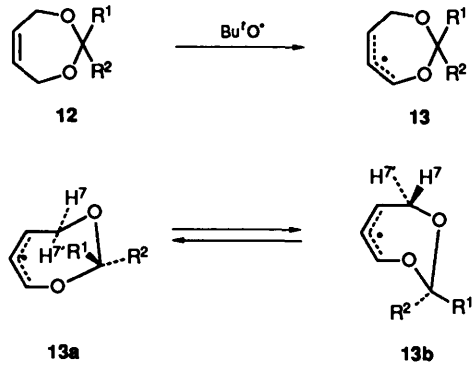
**Table 5** EPR parameters[a] for 4,7-dihydro-1,3-dioxepin-4-yl radicals (**13**)

| Radical **13** | | | hfs | | | | |
|---|---|---|---|---|---|---|---|
| $R^1$ | $R^2$ | $T$/K | H(4, 6) | H(5) | H(7) | H(7′) | Other |
| Me | Me | 150 | 1.39 | 0.28 | 2.00 | 2.51 | |
| Et | Et | 220 | 1.39 | 0.33 | 1.97 | 2.48 | |
| Ph | Ph | 210 | 1.41 | 0.34 | 4.29 [H(7 + 7′)] | | |
| H | $CH_2Br$ | 220 | 1.42 | 0.31 | 1.81 | 2.42 | 0.31 (1 H) |
| Me | $CH_2Br$ | 220 | 1.42 | 0.31 | 1.72 | 2.45 | |
| Ph | $CH_2Br$ | 225 | 1.35 | 0.35 | 1.75 | 2.45 | |
| Np | $CH_2Br$ | 225 | 1.35 | 0.35 | 1.72 | 2.50 | |

[a] All $g$-factors 2.003 ± 0.001; hfs in mT.

**Table 6** Best fit rate constants for inversion of 2,2-dimethyl- and 2,2-diethyl-4,7-dihydro-1,3-dioxepin-4-yl radicals (**13**)

| $R^1 = R^2 = Me$ | | $R^1 = R^2 = Et$ | |
|---|---|---|---|
| $T$/K | $k/10^6$ s$^{-1}$ | $T$/K | $k/10^6$ s$^{-1}$ |
| 206 | 0.8 | 195 | 1.0 |
| 226 | 2.0 | 206 | 3.0 |
| 236 | 4.0 | 217 | 6.0 |
| 256 | 20 | 228 | 9.0 |
| 295 | 200 | 239 | 15 |
| 312 | 300 | 256 | 35 |
| 328 | 600 | 273 | 80 |
| 351 | 790 | 289 | 180 |
| 373 | 1300 | 306 | 400 |




conformers **6ba**. The proportion of **6ba** could not be determined by EPR spectroscopy,[7] however, this evidence suggested that dihydrodioxepinylmethyl radicals have greater preferences for twist boat conformers than the analogous cyclohepten-5-ylmethyl radicals.

That the orientation of the $CH_2$· group was very important, was indicated by the greatly increased $k_c$ values for **6b** and **6c**, where the $CH_2$· group is constrained to occupy an axial or pseudoaxial orientation. For both **6b** and **6c** $k_c$(298) was greater than $k_c$(298) for the hex-5-enyl radical.[16] This is probably partly an entropic effect because the cycloalkenylmethyl radicals are conformationally much more constrained than hex-5-enyl radicals.

The product bicycloketals (**8**) were readily hydrolysed with dilute acid to give ketodiols **10**. The overall reaction is equivalent to intermolecular addition of a ketone, $RCOCH_2$–H, to (*Z*)-but-2-en-1,4-diol, which is accomplished *via* an intramolecular cyclisation. The overall process resembles the conjugate addition of carbanions to α,β-unsaturated ketones.

*Generation and Conformational Analysis of* 4,7-*Dihydro*-1,3-*dioxepin*-4-*yl Radicals*.—In 4,7-dihydro-1,3-dioxepins (**12**) the hydrogens at C(4) and C(7) are allylic and adjacent to oxygen so they are highly activated towards hydrogen abstraction. No products derived from 4,7-dihydro-1,3-dioxepin-4-yl radicals (**13**) were detected in the tributyltin hydride reductions of 2-halomethyl derivatives but, when *tert*-butoxyl radicals were used as initiating species, the main attack took place at C(4) or C(7) and radicals **13** were easily detected by EPR spectroscopy. The EPR parameters of a series of 2-substituted-4,7-dihydrodioxepin-4-yl radicals, obtained in this way, are recorded in Table 5. The magnitudes of the hyperfine splittings (hfs) were about normal for allyl type radicals. For each radical the hydrogen atoms at the ends of the allyl system [H(4) and H(6)] were non-equivalent, but their hfs were so similar that they were not resolved, except in several cases where partial resolution was observed. It is probable that the three carbon atoms of the allyl system will stay planar, because this will maximize the resonance delocalisation of the unpaired electron, thus lowering the electronic energy. This structural restraint severely restricts the ring conformations available to **13** and models indicate that the 'flap' conformations (structures **13a** and **13b**) will be the main ones populated.

For all the radicals studied the hydrogens attached to C(7) were found to be non-equivalent at temperatures below *ca.* 220 K. When **13a** and **13b** are at the limit of conformational immobility H(7) and H(7′) will be non-equivalent. Thus, one hydrogen [H(7) in **13a** and H(7′) in **13b**] will lie close to the nodal plane of the allyl π-system and so will have a small hfs, whereas the other hydrogen will overlap the allyl π-system substantially and so should have a large hfs. In the temperature range 150–220 K all of the radicals exhibited non-equivalent H(7) and H(7′) with hfs differing in magnitude by 0.6 to 0.8 mT (Table 5). At higher temperatures most of the spectra weakened rapidly so that line broadening was difficult to distinguish. However, for the 2,2-dimethyl (**13**, $R^1 = R^2$ = Me) and the 2,2-diethyl radicals (**13**, $R^1 = R^2$ = Et) selective line broadening of the EPR spectra was observed in the range 200–320 K (Fig. 1). For both radicals the fast exchange limit spectra showed a triplet hfs from equivalent H(7) and H(7′). We attribute this line broadening to the 'flapping' inversion which interconverts **13a** and **13b** and thus makes H(7) and H(7′) equivalent. The exchange broadening was simulated using a modified version of Heinzer's program,[17] assuming a 'two jump' model. Good correspondence between experimental and simulated spectra was obtained (see Fig. 1) and the best fit rate constants are recorded in Table 6. The Arrhenius parameters derived from the rate constants were, for the dimethyl radical, $\log(A/s^{-1})$ = 13.7 ± 0.5, $E$/kJ mol$^{-1}$ = 31 ± 6, and for the diethyl radical, $\log(A/s^{-1})$ = 12.8 ± 0.4, $E$/kJ mol$^{-1}$ = 25 ± 4. Thus, the pre-exponential factors were fairly close to $10^{13}$ s$^{-1}$, which is normal for unimolecular conformational changes. The magnitude of the inversion barrier between the 'flap' conformations of **13** was therefore 5–10 kJ mol$^{-1}$ greater than the barrier to interconversion of the parent 4,7-dihydro-1,3-dioxepins.[5,6] This is not unexpected because the planar three-carbon allyl unit in **13**

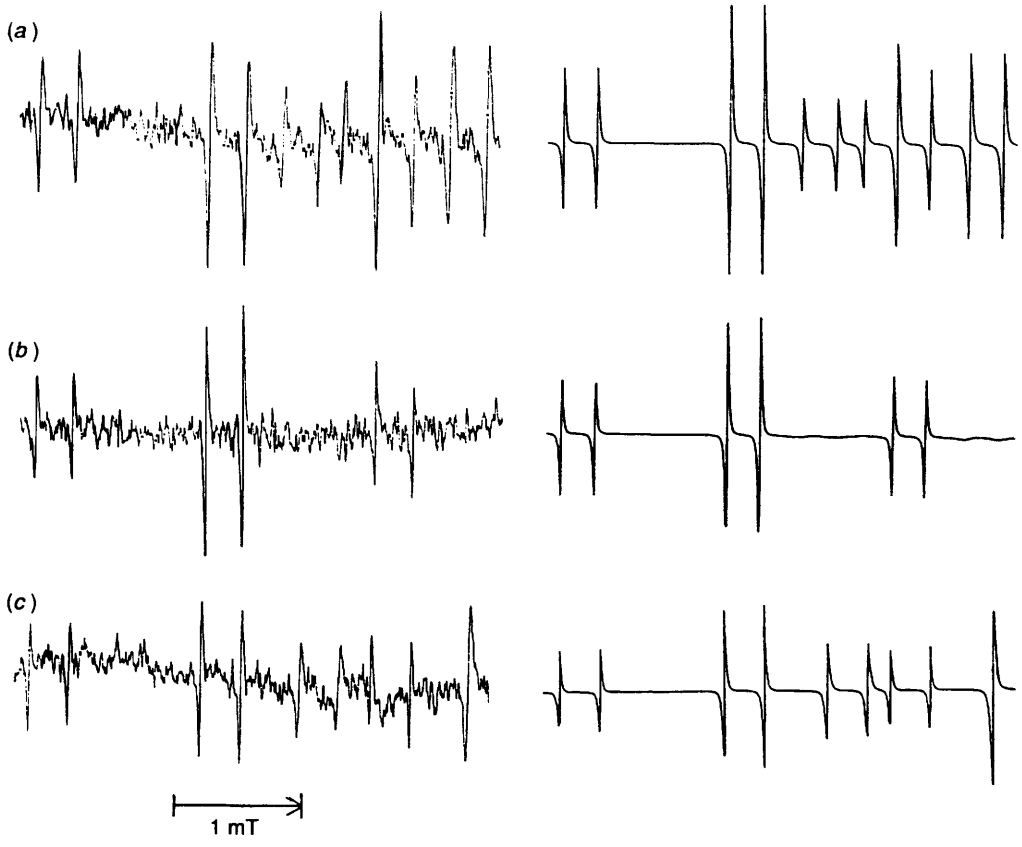



Fig. 1 Low field halves of the 9.3 GHz EPR spectra of the 2,2-dimethyl-1,4-dihydro-1,3-dioxepin-4-yl radical (**13**, $R^1 = R^2 = Me$) in *tert*-butylbenzene at various temperatures. From the top, (*a*) 206 K; at the right is a computer simulation with $k = 0.8 \times 10^6$ s$^{-1}$, (*b*) 256 K; at the right is a computer simulation with $k = 19.9 \times 10^6$ s$^{-1}$, (*c*) 328 K; at the right is a computer simulation with $k = 603 \times 10^6$ s$^{-1}$.

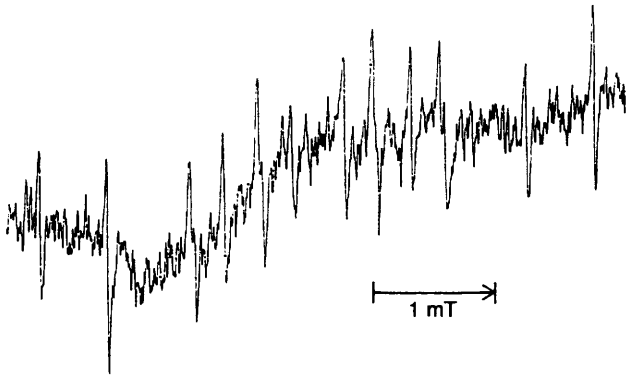
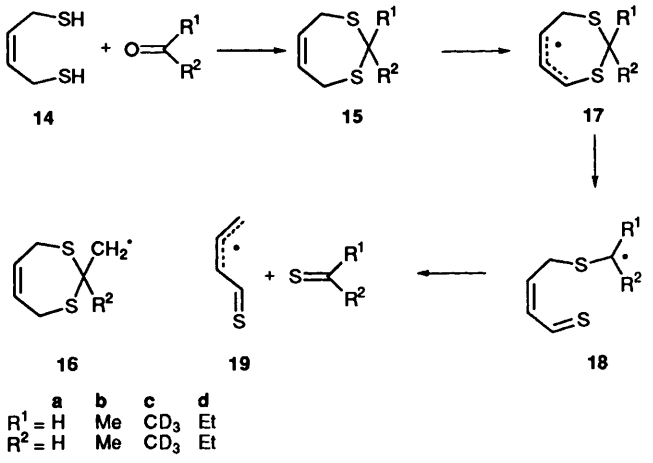



Fig. 2 9.3 GHz EPR spectrum, in *tert*-butylbenzene at 280 K, of the radical obtained on hydrogen abstraction from 2,2-dimethyl-1,3-dithiepin (**15b**)

restricts the number of internal bond rotation modes which are available to execute the inversion. Surprisingly, the EPR spectrum of the analogous hydrocarbon allyl radical, *i.e.* the cyclohept-3-enyl radical, has been reported to be independent of temperature in solution[18,19] so that its inversion barrier must be considerably lower.

1,3-*Dithiacyclohept*-5-*enes* (4,7-*Dihydro*-1,3-*dithiepins*).—Only a few 4,7-dihydro-1,3-dithiepins (**15**) have been reported. A variable temperature NMR study of **15a** and **15b** showed that the free energies of activation for interconversion of the chair and twist-boat conformations were 36 and 34 kJ mol$^{-1}$ respectively.[20] We prepared **15a–d** by the *p*-toluenesulfonic acid-catalysed condensation of (*Z*)-but-2-en-1,4-dithiol (**14**) with appropriate ketones. However, this method failed with other ketones, including chloroacetone, benzophenone, phenacyl bromide and phenacyl chloride. Alternative condensation procedures of ketones and ketals were also unsuccessful. Thus, the method frequently employed for formation of 1,3-dithianes[21] *i.e.* reaction of **14**, and an α-haloalkyl ketone, with boron trifluoride etherate in glacial acetic acid also failed, as did the lanthanum(III) chloride-catalysed condensation, which had been successful in the preparation of 1,3-dithiolanes.[22] Consequently, we were unable to obtain a suitable precursor to 4,7-dihydro-1,3-dithiepin-2-ylmethyl radicals (**16**), or to investigate their transannular cyclisations.

When a mixture of **15b** and di-*tert*-butyl peroxide, in *tert*-butylbenzene or cyclopropane as solvent, was photolysed in the cavity of an EPR spectrometer broad, ill-defined signals were obtained at lower temperatures (< 200 K). However, after several minutes photolysis at higher temperatures, a weak but well resolved spectrum was obtained (Fig. 2). This was well matched by a computer simulation having $a$(1 H) = 1.53, $a$(1 H) = 1.24, $a$(1 H) = 1.22, $a$(1 H) = 0.55 mT. This spectrum showed hfs from only four hydrogens and hence it was not due to a 4,7-dihydro-1,3-dithiepin-4-yl radical (**17**). No signals were obtained from a similar reaction of **15a**, but **15c** and **15d** gave the same spectrum as **15b**, although the intensities were very weak and developed only after several minutes of photolysis. The fact that the same spectrum was obtained from **15b–d** indicated that the EPR active hydrogens in this radical were derived exclusively from the butenyl unit of **15**. The delay in the appearance of this spectrum suggested that it was due to a secondary radical formed in a degradation process. One possibility is indicated in Scheme 3. Initial hydrogen abstraction is expected to give **17** which may ring open to give tertiary radical **18** and hence, by a further β-scission, afford allyl type radical **19** and a thioketone. This sequence explains the absence of signals from **15a** because **18a** would be a less stabilised primary radical which would form much less readily. The observed hfs are reasonable for an allyl radical like **19**. The hydrogen of the




Scheme 3

thioaldehyde group will be in the nodal plane of the allyl π-system, because of conjugation with the C=S group, and hence it will not couple significantly with the unpaired electron. Radicals of type **19** (or its oxygen analogue) have not been observed previously, so this proposal needs to be confirmed by independent generation of **19**.

## Experimental

$^1$H NMR spectra were obtained with Bruker WP 80 (80 MHz) and Bruker AM 300 (300 MHz) spectrometers. The latter instrument, operating at 75 MHz, was used for $^{13}$C NMR spectra. Samples were dissolved in $CHCl_3$; $Me_4Si$ was used as internal standard; *J* values are in Hz. EPR spectra were recorded at 9.3 GHz with a Bruker ER 200D instrument employing 100 kHz modulation. Samples were prepared in Spectrosil quartz tubes in cyclopropane solution on a vacuum line, or in *tert*-butylbenzene and degassed by bubbling nitrogen for 10 min. They were photolysed in the spectrometer cavity with light from a 500 W super pressure mercury arc. GC–MS analyses were carried out with a Finnigan Incos 50 quadrupole mass spectrometer coupled to a Hewlett-Packard HP 5890 capillary gas chromatograph fitted with a column coated with methylsilicone stationary phase. Preparative GLC was carried out with a Pye-Unicam 105 chromatograph.

2,2-*Diphenyl*-4,7-*dihydro*-1,3-*dioxepin*. (*Z*)-But-2-ene-1,4-diol (5.45 g, 0.062 mol), benzophenone dimethyl ketal (14.12 g, 0.062 mol) and *p*-toluenesulfonic acid (0.58 g, 5 mol%) were dissolved in methanol (40 cm$^3$) and refluxed for 1 h. The methanol was allowed to distil off during a further 1 h to leave the title compound as a pale yellow liquid (3.04 g, 20%), b.p. 205 °C/22 Torr (lit.,[23] 157 °C/1.2 Torr). Further purification was achieved by preparative TLC using a solvent mixture of 10% diethyl ether in light petroleum (b.p. 40–60 °C); $\delta_H$ 4.15–4.30 (4 H, m), 5.6–5.8 (2 H, m), 7.0–7.8 (10 H, m).

2,2-*Diethyl*-4,7-*dihydro*-1,3-*dioxepin*. (*Z*)-But-2-ene-1,4-diol (6.67 g, 0.076 mol) and 3,3-dimethoxypentane (10.0 g, 0.076 mol) were mixed with *p*-toluenesulfonic acid (0.72 g, 5 mol%). The mixture was warmed to *ca.* 60 °C for 0.5 h and the methanol formed was distilled off. The residual liquid was distilled to yield the title compound as a colourless liquid (4.87 g, 41%), b.p. 86 °C/12 Torr (lit.,[23] 108 °C/57 Torr); $\delta_H$ 0.7 (6 H, t, *J* 7), 1.7 (4 H, q, *J* 7), 4.2 (4 H, m), 5.65 (2 H, m); $\delta_C$ 8.1, 24.3, 60.9, 101.1, 129.7.

2,2-*Dimethyl*-4,7-*dihydro*-1,3-*dioxepin*. (*Z*)-But-2-ene-1,4-diol (15.2 g, 0.17 mol) and 2,2-dimethoxypropane (18.0 g, 0.17 mol) were condensed as described above for the 2,2-diethyl analogue. The product was purified by distillation on a Kugelrohr at 90 °C/24 Torr (7.37 g, 33%), (lit.,[23] 41 °C/6 Torr); $\delta_H$ 1.3–1.5 (6 H, bs), 4.2 (4 H, m), 5.6 (2 H, m).

2-*Bromomethyl*-4,7-*dihydro*-1,3-*dioxepin* (**7a**). (*Z*)-But-2-en-1,4-diol (8.8 g, 0.10 mol) and bromoacetaldehyde dimethyl acetal (33.8 g, 0.20 mol) were mixed with *ca.* 2 mg of *p*-toluenesulfonic acid and warmed in a distillation apparatus. Methanol and the excess bromoacetaldehyde dimethyl acetal were removed by distillation. The residue was purified by distillation at 75 °C/1 Torr on a Kugelrohr to give **7a** (13.8 g, 72%); $\delta_H$ 3.4 (2 H, d, *J* 6), 4.0–4.7 (4 H, m), 5.0 (1 H, t, *J* 6), 5.7 (2 H, t, *J* 2 Hz); $\delta_C$ 31.4, 65.7, 102.2, 129.2; *m*/*z* (%) 125 (21), 123 (25), 99 (29), 69 (30), 53 (10), 41 (100).

2-*Bromomethyl*-4,7-*dihydro*-2-*methyl*-1,3-*dioxepin* (**7b**). This was prepared from 1-bromo-2,2′-dimethoxypropane, in 91% yield, as described for **7a**, and distilled at 84 °C/1 Torr on a Kugelrohr (lit.,[9] 116 °C/10 Torr); $\delta_H$ 1.55 (3 H, s), 3.5 (2 H, s), 4.3 (4 H, d, *J* 2), 5.65 (2 H, t, *J* 2); $\delta_C$ 20.9, 34.7, 62.0, 101.7, 129.1; *m*/*z* (%) 139 (7), 123 (2), 121 (3), 113 (55), 93 (3), 69 (9), 57 (10), 43 (100).

2-*Bromomethyl*-4,7-*dihydro*-2-*phenyl*-1,3-*dioxepin* (**7c**). (*Z*)-But-2-ene-1,4-diol (2.64 g, 0.030 mol), phenacyl bromide dimethyl acetal (7.3 g, 0.030 mol), *p*-toluenesulfonic acid (0.28 g) and methanol (40 cm$^3$) were mixed together and refluxed for 90 min. The apparatus was rearranged to allow the methanol to distil off over a period of 1 h. The title compound was obtained as a grey-green solid (4.61 g, 57%), m.p. 59–60 °C; $\delta_H$ 3.5 (2 H bs), 4.1 (4 H, m), 5.55 (2 H, m), 7.1–7.6 (5 H, m); *m*/*z* (%) 106 (8), 105 (100), 91 (19), 77 (65), 65 (12), 51 (74), 50 (36), 42 (11), 39 (18).

2-*Bromomethyl*-2-*naphthyl dimethyl acetal*. 2-Bromo-2-acetonaphthone (bromomethyl 2-naphthyl ketone) (5.0 g, 0.02 mol) and trimethyl orthoformate (2.13 g, 0.02 mol) were mixed together in methanol (2.44 cm$^3$, 0.06 mol), 2 drops of ethanolic HCl were added, and the mixture was stirred at room temperature for *ca.* 19 h. Two further drops of ethanolic HCl were added, and the mixture stirred for a further 5 h. The methanol was removed under reduced pressure to leave the title compound (4.18 g, 81%), m.p. 80–82 °C. No further purification was undertaken; $\delta_H$ 3.2 (6 H, s), 3.7 (2 H, s), 7.3–8.1 (7 H, m).

2-*Bromomethyl*-4,7-*dihydro*-2-*naphthyl*-1,3-*dioxepin* (**7d**). 2-Bromomethyl-2-naphthyl dimethyl acetal (5.21 g, 0.018 mol), (*Z*)-but-2-ene-1,4-diol (1.55 g, 0.018 mol) and *p*-toluenesulfonic acid (0.17 g) were mixed together and warmed to 80 °C for *ca.* 1 h. The methanol produced was removed under pressure, during which time the dark brown solution turned pale brown in colour. The residual solid was purified by recrystallisation from light petroleum (b.p. 40–60 °C)/ethyl acetate to give **7d** (0.64 g, 11%), m.p. 86–87 °C; $\delta_H$ 3.65 (2 H, s), 4.1–4.2 (4 H, bs), 5.5–5.6 (2 H, bs), 7.2–8.0 (7 H, m).

*Reduction of* **7a** *with tributyltin hydride*. The 4,7-dihydro-1,3-dioxepin (**7a**) (1.0 g, 52 mmol) was placed in a pyrex tube, heated to 97 °C, and degassed by bubbling nitrogen. To the tube, which was irradiated with light from a 250 W medium pressure Hg arc, was added dropwise over 20 min $Bu_3SnH$ (1.6 g, 55 mmol) under nitrogen. Photolysis was continued for a further 100 min at 97 °C. The products were distilled directly out of the reaction mixture on a Kugelrohr at 80 °C/760 Torr (0.3 g, 51%). GC analysis showed one major and several minor components which were separated by preparative GC on a 4.5 m × 1 cm Carbowax 20M column at 150 °C. The major component was 4,7-dihydro-2-methyl-1,3-dioxepin (97 rel. %); $\delta_H$ 1.4 (3 H, d, *J* 6), 4.1 (2 H, d, *J* 14), 4.4 (2 H, d, *J* 14), 5.0 (1 H, q, *J* 6), 5.7 (2 H, m); $\delta_C$ 20.0 (1 C), 64.7 (2 C), 101.2 (1 C), 129.9 (2 C); *m*/*z* (%) 73 (3), 69 (18), 53 (6), 45 (100), 41 (77), 39 (97). A minor component was identified as 2,7-dioxabicyclo[3.2.1]octane (**8a**) (1%); $\delta_H$ 1.4–2.0 (4 H, m), 2.6 (1 H, bs), 3.4–4.0 (4 H, m), 5.0 (1 H, m); $\delta_C$ 30.0, 32.4, 38.5, 59.4, 72.4, 99.3; *m*/*z* (%) 114 ($M^+$, 15), 84 (25), 67 (97), 55 (100), 41 (78).

*Reduction of* **7a** *with triphenyltin hydride*. The bromide (0.5 g, 26 mmol) was placed in a pyrex tube at 155 °C, degassed by

bubbling nitrogen, and $Ph_3SnH$ (1.0 g, 28 mmol) was added over 30 min while the mixture was irradiated with light from a 250 W medium pressure Hg arc. After a further 1.5 h irradiation the product mixture was examined by GC and GC–MS which showed the major component (> 95%) to be 4,7-dihydro-2-methyl-1,3-dioxepin by comparison with an authentic sample.

*Reduction of* **7a** *with tris(trimethylsilyl)silane.* The bromide **7a** (0.5 g, 26 mmol) and tris(trimethylsilyl)silane (0.7 g, 28 mmol) were dissolved in hexadecane (2 $cm^3$) in a pyrex tube, degassed by bubbling nitrogen, heated to 80 °C, and irradiated as above for 45 min. Although the mixture had turned black, GC analysis indicated that most of the **7a** had not reacted. The major product (> 95 rel. %) was shown to be 4,7-dihydro-2-methyl-1,3-dioxepin.

*Reduction of* **7b** *with tributyltin hydride.* The bromide **7b** (1.0 g, 48 mmol) was photochemically reduced with $Bu_3SnH$ as described above for **7a**. The reaction mixture was extracted with diethyl ether (10 $cm^3$). The ether solution was washed with dilute aqueous KF solution (5 $cm^3$), dried ($Na_2SO$), and distilled on a Kugelrohr at 85–110 °C/15 Torr to give a colourless liquid (0.38 g, *ca.* 58%). GC analysis showed two major components which were separated on a 15 × 2 cm neutral alumina column eluted with 120 $cm^3$ of 2% diethyl ether in pentane, 100 $cm^3$ of 10% diethyl ether in pentane and 50 $cm^3$ of diethyl ether. The first component (20 rel. %), eluted in the second fraction, was 4,7-dihydro-2,2-dimethyl-1,3-dioxepin (**12**, $R^1 = R^2 =$ Me); $\delta_H$ 1.4 (6 H, s), 4.2 (4 H, m), 5.8 (2 H, m) (lit.[24]); $\delta_C$ 24.0 (2 C), 61.4 (2 C), 101.9 (1 C), 129.5 (2 C); *m/z* (%) 113 (8), 69 (25), 59 (100), 43 (72). The second component, which was eluted in the third fraction, was 1-methyl-2,7-dioxabicyclo[3.2.1]octane (**8b**) (80 rel. %); $\delta_H$ 1.4 (3 H, s), 1.45 (1 H, bs), 1.6–1.9 (3 H, m), 2.6 (1 H, bs), 3.7–4.0 (4 H, m); $\delta_C$ 23.8 ($CH_3$), 29.6 ($CH_2$), 34.5 (CH), 42.5 ($CH_2$), 60.4 ($CH_2$), 72.9 ($CH_2$), 105.1 (C); *m/z* (%) 128 ($M^+$, 8), 97 (15), 83 (32), 67 (20), 55 (17), 43 (100).

*Reduction of* **7c** *with tributyltin hydride.* 2-Bromomethyl-4,7-dihydro-2-phenyl-1,3-dioxepin (**7c**) (1.0 g, 37 mmol) was placed in a pyrex tube, degassed by bubbling nitrogen, heated to 130 °C and irradiated with light from a 250 W medium pressure Hg arc, while $Bu_3SnH$ (1.08 g, 37 mmol) was added over 10 min. Photolysis was continued for a further 2 h. The reaction mixture was extracted with diethyl ether (10 $cm^3$) and the extract was washed with dilute KF solution (5 $cm^3$), dried ($Na_2SO_4$), and evaporated. The residual liquid (2.4 g) was chromatographed as described above for **7b**. Two major components were separated. The first component, eluted in the second fraction, was 2-methyl-4,7-dihydro-2-phenyl-1,3-dioxepin (35 rel. %); m.p. 49–50 °C (lit.,[9] b.p. 104 °C/2 Torr); $\delta_H$ 1.58 (3 H, s), 4.20 (4 H, m), 5.61 (2 H, t, *J* 2), 7.28 (3 H, m), 7.5 (2 H, m); $\delta_C$ 26.20 (1 C), 62.13 (2 C), 103.60 (1 C), 125.89 (2 C), 127.58 (1 C), 128.01 (2 C), 129.42 (1 C), 143.31 (2 C). The second component, eluted in the third fraction was 1-phenyl-2,7-dioxabicyclo[3.2.1]octane (**8c**) (65 rel. %); m.p. 52–53 °C; $\delta_H$ 1.5–1.7 (2 H, m), 1.9–2.1 (2 H, m). 2.73 (1 H, bs), 3.9–4.25 (4 H, m), 7.3 (3 H, m), 7.55 (2 H, m); $\delta_C$ 29.65, 34.71, 44.13, 60.86, 73.49, 106.01, 125.46, 128.05, 128.12, 128.64; *m/z* (%) 190 ($M^+$, 15), 160 (14), 159 (12), 145 (21), 105 (100), 77 (75), 68 (17), 67 (32) 51 (23).

*Reduction of* **7c** *with triethylsilane.* **7c** (1.34 g, 5 mmol), triethylsilane (1.16 g, 10 mmol), dilauroyl peroxide (0.1 g), dodecane-1-thiol (0.02 g, 2 mol%) and cyclohexane (50 $cm^3$) were mixed together and heated at reflux under $N_2$ for *ca.* 1 h. The mixture was allowed to cool and diluted with cyclohexane (50 $cm^3$) and washed successively with water (100 $cm^3$), 6 mol $dm^{-3}$ NaOH (100 $cm^3$) and water again (100 $cm^3$) and dried ($MgSO_4$). After filtration and removal of the solvent under reduced pressure, the crude product appeared as a green-yellow solid (0.66 g) which was found to be the unchanged starting bromide. The same result was obtained using 10 mol% dilauroyl peroxide and on heating the mixture at reflux for *ca.* 6 h.

*Hydrolysis of* 1-*methyl*-2,7-*dioxabicyclo*[3.2.1]*octane* (**8b**). **8b** (70 mg, 0.55 mmol) was mixed with 3.5% aq. HCl (5 $cm^3$) and refluxed for 1 h. The solution was neutralised with aq. $NaHCO_3$ and evaporated. The residue was extracted with diethyl ether (20 $cm^3$) which was then dried and evaporated to give 6-hydroxy-4-(hydroxymethyl)hexan-2-one (**10b**) as a clear liquid (10 mg, 63%); $\delta_H$ 1.8 (1 H, bs, $D_2O$ exch.), 2.2 (5 H, m), 2.7 (3 H, m), 3.42 (1 H, dd, *J* 8, 6), 3.84 (1 H, m), 3.92 (1 H, m), 4.06 (1 H, dd, *J* 8, 6); $\delta_C$ 30.1 (CH), 32.1 ($CH_3$), 47.4 ($CH_2$), 67.6 ($CH_2$), 73.0 ($CH_2$), 207.6 (CO); *m/z* (%), 111 (1), 97 (1), 83 (3), 70 (71), 58 (5), 55 (17), 43 (100); $\nu$/$cm^{-1}$ 3370 (br, OH).

*Hydrolysis of* 1-*phenyl*-2,7-*dioxabicyclo*[3.2.1]*octane* (**8c**). **8c** (16.3 mg, 0.085 mmol) was hydrolysed using the procedure described for **8b**. Evaporation of the diethyl ether gave 5-hydroxy-3-(hydroxymethyl)-1-phenylpentan-1-one (**10c**) as a white solid (12 mg, 70%); m.p. 142 °C (decomp.); $\delta_H$ 2.15–2.25 (2 H, m), 2.77–2.90 (1 H, m), 3.05–3.2 (2 H, m), 3.46 (2 H, dd), 4.05 (2 H, dd), 7.3–7.6 (3 H, m), 7.9–8.0 (2 H, m); $\delta_C$ 30.1 (CH), 32.1 ($CH_2$), 47.4 ($CH_2$), 67.6 ($CH_2$), 70.3 ($CH_2$), 125.5 (CH), 128.0 (CH), 128.2 (CH), 128.6 (C), 207.6 (CO).

*Kinetics of the tributyltin hydride reductions of* 2-*bromomethyl*-4,7-*dihydro*-1,3-*dioxepins* (**7b, c**). The solvent [hexadecane (0.5 $cm^3$) for **7b** and *tert*-butylbenzene (0.25 $cm^3$) for **7c**] was placed in a pyrex tube, heated to the desired temperature, and degassed by bubbling nitrogen. To this was added **7b** (20 $mm^3$) [or **7c** (50 mg)] and an internal standard [octane for **7b**, and hexadecane for **7c**]under nitrogen. The solution was irradiated with light from 240 W medium pressure Hg arc for 1–2 h. The solutions were analysed by GC and the values of $k_c/k_H$ were obtained at each temperature from the initial $Bu_3SnH$ concentration and the final product concentrations, using an integrated rate equation.[14,15] The best values of $k_c/k_H$ were located with an iterative computer program based on NAG routine C05AXF.

(*Z*)-But-2-ene-1,4-dithiol (**14**). KOH (5.9 g, 0.10 mol) was dissolved in methanol (100 $cm^3$) and added dropwise over 0.5 h to (*Z*)-but-2-ene-1,4-dithiol diacetate[25] (10.7 g, 0.05 mol) also in methanol (100 $cm^3$). Upon completion of the addition, 2 mol $dm^{-3}$ HCl was added until the mixture was neutral. Water (100 $cm^3$) was added, the mixture was extracted with diethyl ether (3 × 150 $cm^3$) and the combined ether extracts were dried over $MgSO_4$. Evaporation of the solvent gave **14** as a pale yellow liquid (4.7 g, 78%) which was purified by distillation on a Kugelrohr at 80 °C/0.6 Torr (lit.,[25] 55–56 °C/0.2 Torr); $\delta_H$ 1.5–1.6 (2 H, t, *J* 3), 3.1–3.3 (4 H, m), 5.5–5.7 (2 H, m); $\delta_C$ 21.2, 130.0.

4,7-*Dihydro*-1,3-*dithiepin* (**15a**). To a solution of dimethoxymethane (1.90 g, 0.025 mol) in benzene (100 $cm^3$) containing 5 mg of *p*-toluenesulfonic acid was added (*Z*)-but-2-ene-1,4-dithiol (3.0 g, 0.025 mol). The mixture was heated at *ca.* 45 °C for 18 h, then a Dean-Stark trap was attached and the mixture refluxed for a further 3 h, the methanol produced being separated off. The remaining solution was allowed to cool and then washed with 10% aq. NaOH (2 × 100 $cm^3$), water (2 × 100 $cm^3$), and dried over $MgSO_4$. The solvent was removed under reduced pressure, leaving **15a** as a pale yellow liquid (2.39 g, 72%). The product did not require further purification and solidified at *ca.* 20 °C (lit.,[26] m.p. 26–27 °C); $\delta_H$ 3.45 (4 H, d, *J* 3), 4.0 (2 H, s), 5.95 (2 H, t, *J* 3); $\delta_C$ 29.3, 38.0, 129.3; *m/z* (%) 132 ($M^+$, 12), 85 (100), 78 (25), 45 (67), 39 (27), 27 (34).

4,7-*Dihydro*-2,2-*dimethyl*-1,3-*dithiepin* (**15b**). To a solution of acetone (1.45 g, 0.025 mol) in benzene (70 $cm^3$), containing 5 mg of *p*-toluenesulfonic acid, was added (*Z*)-but-2-ene-1,4-dithiol (3.0 g, 0.025 mol). The mixture was heated under reflux for 18 h while the water formed was removed by a Dean-Stark trap. The

mixture was cooled and washed successively with 10% aq. NaOH (2 × 75 $cm^3$), water (2 × 100 $cm^3$), and dried over $MgSO_4$. The solvent was evaporated to leave the crude product as a yellow-orange liquid (3.46 g). The product was purified by distillation at 79 °C/0.7 Torr (lit.,[25] b.p. 58–61 °C/0.4 Torr) on a Kugelrohr (1.1 g, 28%). The dithiepin was dissolved in boiling pentane and recrystallised at low temperature (dry ice–ethanol bath). The crystals were filtered through a pre-chilled apparatus, however, when the product warmed up to ambient temperature it reverted to being a pale yellow liquid; $\delta_H$ 1.70 (6 H, s), 3.3–3.5 (4 H, m), 5.8–6.0 (2 H, m); $\delta_C$ 27.2, 32.0, 54.6, 130.8; $\lambda_{max}$(cyclohexane)/nm ($\varepsilon$) 227 (840), 257 (398); *m/z* (%) 160 ($M^+$, 9), 106 (42), 95 (13), 85 (32), 74 (27), 57 (100), 45 (48), 41 (51), 39 (44), 27 (32).

2,2-*Diethyl*-4,7-*dihydro*-1,3-*dithiepin* (**15d**). This was prepared using the method outlined above for **15b** and purified by low temperature crystallisation from pentane (27%); m.p. 27–28 °C; $\delta_H$ 0.9–1.1 (6 H, t, *J* 7), 1.8–2.0 (4 H, q, *J* 7), 3.3 (4 H, d, *J* 2, 5.8–5.9 (2 H, m); $\delta_C$ 9.7, 26.8, 31.4, 63.9, 130.5; *m/z* (%) 188 ($M^+$, 5), 134 (15), 102 (18), 85 (17), 73 (80), 69 (100), 45 (64), 41 (52), 39 (33), 27 (41).

4,7-*Dihydro*-2,2-*bis*(*trideuteriomethyl*)-1,3-*dithiepin* (**15c**). This was prepared from [$^2H_6$]acetone by the method outlined above and purified by low temperature recrystallisation from pentane (31%); the product was liquid at room temperature; $\delta_H$ 3.3–3.4 (4 H, m), 5.9–6.0 (2 H, m); $\delta_C$ 26.7, 31.1, 53.8, 130.2; *m/z* (%) 166 ($M^+$, 7), 110 (27), 85 (49), 61 (87), 45 (100), 39 (42), 27 (47).

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