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Stereoselective Cyclisation of the 2-Allyloxytetrahydropyran-3-yl Radical and Related Species: The Influence of Anomeric Effects

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Dedicated to the memory of Professor Sir Derek Barton

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Abstract: Ring closures of the 2-allyloxytetrahydropyran-3-yl radical **1b**, its mono-oxa analog **1d** and the all carbon system **1a** give mainly the cis-fused syn-substituted bicyclononylcarbinyl radicals **2b**, **2d** and **2a**, but the mono-oxa radical **1c** gives mainly the cis-fused anti-substituted radical **3c**. Molecular mechanics calculations show that the unexpected failure of the dioxa radical **1b** to reflect the influence of the anomeric effect on the stereochemistry of cyclisation arises from the loss of one stabilising anomeric interaction in the conversion of the conformer **17** into either of the transition structures **16** or **19**.

Recently,[1] we observed that anomeric interactions in suitably constituted hex-5-enyl-like radicals can stabilise pseudo-axially substituted cyclic transition structures sufficiently to induce preferential formation of cyclised products with stereochemistry the reverse of that usually observed.[2] In view of the importance of radical ring closure as a method for the generation of bi-and poly-cyclic structures[3] we decided to examine the cyclisation behaviour of a suitably substituted monocyclic radical so constituted as to allow anomeric affects to influence the stereochemistry of the cyclisation transition structure.

For the cyclisation of hex-5-enyl radicals and related species the observed stereoselectivity of exo ring formation reflects the fact that pseudo-equatorially substituted cyclohexane-like transition structures are generally more stable than their pseudo-axially substituted conformers.[2,4] The mechanistic rationale for the observed regio- and stereo-chemistry of cyclisation becomes somewhat more complex when part of the hex-5-enyl system resides in a pre-existing ring, because the ring imposes extra geometric and steric constraints on the system. The 2-(but-3-enyl)cyclohexyl radical **1a** and related species are formally 1,2-disubstituted hexenyl radicals and would be expected on the basis of the guidelines to preferentially afford trans-fused bicyclic products. Experiment shows, however, that this is not usually the case.[5,6] For example, cyclisation of the radical **1a** gave products derived from three exo ring-closed radicals **2a**-**4a** out of the four possible, but by far the major products were those derived from the cis-fused radicals **2a** and **3a**.[5] Accordingly, an additional guideline was advanced, namely that ring closures of the 2-butenylcyclohexyl radical and related species preferentially afford cis-fused bicyclic products.[5] Originally it was proposed that this type of stereoselectivity reflects the fact that π^*-SOMO overlap can only be attained if the olefinic substituent is axially oriented with respect to the cyclohexane ring in the transition structure.[5] However, it has recently been demonstrated that an efficient overlap can also occur with the olefinic substituent in an equatorial orientation.[6] Consideration of the usual chair-like and boat-like transition structures for cyclisation of the 2-butenylcyclohexyl radical **1a** indicated

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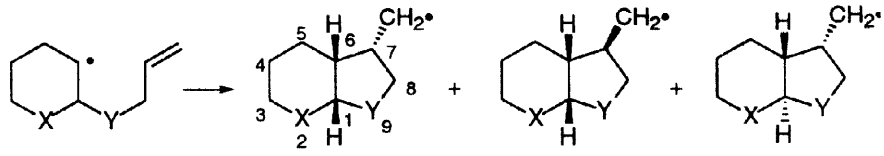
that the formation of the cis-fused product, **3a**, with the new radical centre attached to C-7 in an anti orientation proceeds via a chair-like transition structure **10** with an axially disposed olefinic substituent, whilst the formation of the cis-fused 7-syn product **2a** occurs via an equatorially substituted chair-like transition structure **12**.[6] These hypotheses were verified by experiments with conformationally locked substrates.[6]



a: X = CH_2, Y = CH_2; **b:** X = O, Y = O;
c: X = CH_2, Y = O; **d:** X = O, Y = CH_2

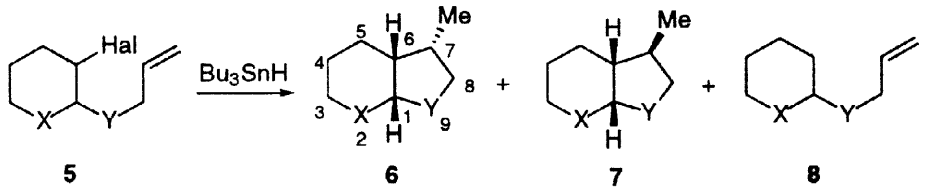
Herein, we describe the stereochemical outcome of the ring closure of the three radicals **1b**, **1c**, and **1d**, the first of which is subject to anomeric stabilisation. The cyclisation of **1b** has been previously described[7] but the stereoselectivity has not been discussed in the light of anomeric interactions. The results of the cyclisations of **1b**-**1d** are compared with those already reported for the all carbon analog **1a** and the intimate mechanisms involving the loss of anomeric interactions, or their retention, for each of the available alternative ring closure pathways have been considered with the aid of molecular mechanics calculations. Consequently, we are able to propose a mechanistic rationale for the stereochemical preferences exhibited by the various reactions.

RESULTS

Precursors. The monocyclic precursors **5b** (73%) and **5c** (29%) were prepared by bromo-allyloxylation of dihydropyran and cyclohexene respectively with NBS and allyl alcohol,[8] while **5d** was prepared by the reaction of butenylmagnesium bromide with a mixture of isomeric 2,3-dibromotetrahydropyrans.[9] Only one diastereoisomer, tentatively identified as the trans product,[10] was isolated from each preparation.

Ring Closures. The various precursors were cyclised by treatment with tributylstannane. The precise conditions are given in the experimental section and are summarised in Table 1. Usually, the final conditions were chosen after running a number of test experiments designed to assess the efficiency of the work-up and analysis of the reactions mixtures. In order to ensure that no loss of any diastereoisomer occurred, the diastereomeric ratios of cyclised products were determined both on the crude reaction mixtures and after work-up. In general, analysis of the crude mixtures indicated that the reactions had proceeded cleanly and with high efficiency.

The nature of the reaction mixtures, isolated yields, and relative ratios of the products (GC) obtained from the tributylstannane reductions of the monocyclic substrates **5b**, **5c**, and **5d** are given in Table 1, which also includes for comparison literature data on the cyclisation of **5a**.[5] The rather poor *isolated* yields reflect the difficulty of separating products from their reaction mixtures rather than the efficiency of the reactions. For the dioxa substrate **5b** two small scale reductions (for analytical purposes only) were undertaken at low temperature with triethylborane/oxygen initiation.[12] For all preparative scale reductions, uncyclised and cyclised products were separated by flash chromatography.



5 **6** **7** **8**

a: X = CH_2, Y = CH_2, Hal = Cl
b: X = O, Y = O, Hal = Br
c: X = CH_2, Y = O, Hal = Br
d: X = O, Y = CH_2, Hal = Br

With the exception of **6c** and **7c** the stereochemistry of the cyclised products was unambiguously determined from a combination of COSY and 1D nOe experiments. Confirmation of the stereochemistry about the ring junctions in both **6c** and **7c** was less straight forward because the signals at H-1 and H-6 were masked by other resonances. Eventually, the cis-fused ring junctions of **6c** and **7c** were established by comparison of the observed NMR spectra with those previously reported for a trans-fused isomer.[13] Fortunately, the ^{1}H NMR signals for H-7 were distinguishable in both isomers, and 1D nOe irradiation at this centre confirmed the relative stereochemistry of **6c** and **7c** shown in the diagrams.

Table 1. Diastereomeric Ratios of Radical Cyclisation Products

Precursor	[Bu_3SnH] (mol/L)	Method[a]	Temp (^{0}C)	Products	Ratio **6/7**	Yield[b] (%)
5a[c]	0.1	A	65	**6a-8a**[c]	3.5[c]	*nd*
5b	0.2	B	40	**6b-8b**	7.8	75
5b	0.2	C	-20	**6b-8b**	20	*nd*
5b	0.2	C	-55	**6b-8b**	35	*nd*
5c	0.2	B	40	**6c-8c**	0.37	44
5d	0.1	B	40	**6d-8d**	14	46

[a] A: AIBN, benzene; B: pentane, $Bu^tON{=}NOBu^t$; C: Et_3B/O_2, hexane. [b] Total isolated yield of cyclised and uncyclised products (compounds **8a-c** isolated in yields ranging from 5 - 13%; see experimental); *nd*, not determined. [c] Data from reference 5. In addition **5a** afforded small quantities of the cylised product derived from **4a**.

DISCUSSION

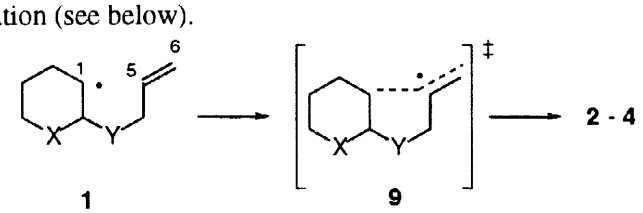
Free radical reduction of the bromo compounds **5b-d** by tributylstannane in a chain mechanism should involve the intermediacy of the radicals **1b-1d** of which only **1b** is appropriately constituted for the occurrence of an anomeric interaction. If RajanBabu's analysis[6] is correct, the radical **1b** derived from **5b** would be expected to afford preferentially the cis-fused anti-product **7b** because the anomeric effect[14] should ensure that the allyloxy substituent is axially oriented with respect to the tetrahydropyran ring. Conversely, the cyclisation of radicals **1c** and **1d** derived from the substrates **5c** and **5d** should preferentially afford cis-fused syn-substituted products since in these cases anomeric interactions cannot occur and the olefinic substituent should, therefore, be equatorial with respect to the tetrahydropyran ring.

The results presented in Table 1 show, however, that the stereochemistry and relative yields of the bicyclic products formed by radical cyclisation of **5b**, **5c**, and **5d** do not conform to expectation. Surprisingly, the dioxa precursor **5b** which is subject to anomeric stabilisation resembles the all-carbon analog **5a** in that it preferentially affords the 7-syn-substituted cis-fused product **6b**, although the selectivity is considerably higher.[5] Interestingly, the diastereoselectivity is quite strongly temperature dependent. Apparently the dominant factor determining the difference between the rates of formation of **6b** and **7b** is enthalpic rather than entropic. Like **5b**, the substrate **5d** containing an oxygen atom in the ring also behaved similarly to **5a** but with an even higher stereoselectivity. However, **5c** the precursor for the 2-allyloxycyclohexyl radical **1c**, did not conform to this general pattern but preferentially gave the anti-substituted cis-fused product **7c** on cyclisation.

According to RajanBabu's hypothesis[6] these results indicate that the anomerically stabilised radical **1b**, the mono-oxa radical **1d** and the all-carbon radical **1a** all react through transition structures in which the substituent is equatorially disposed with respect to the pre-existing ring, whereas the radical **1c** containing an oxygen atom in the side chain must react through an axially orientated transition structure. Since these conclusions are counter-intuitive we decided to use molecular mechanics calculations to examine the relative stabilities of the various ground states and transition structures.

For this purpose we used the computer mechanics program MODEL which incorporates Allinger's MM2 force-field.[15] The program was first tested by modelling the conformers of cyclohexanol and 2-hydroxytetrahydropyran. The difference in strain energy between the minimised values for the equatorial conformer of cyclohexanol (7.6 kcal/mol) and its axial conformer (8.2 kcal/mol) gave an A-value for the OH group of 0.6 kcal/mol (the accepted value is 1.25 kcal/mol),[14a,16] whilst for 2-hydroxytetrahydropyran the difference in strain energy between the equatorial conformer (12.5 kcal/mol) and the axial conformer (11.2 kcal/mol) was 1.3 kcal/mol in favour of the latter. Calculation of the magnitude of the anomeric effect, which is defined as the sum of these two values,[14,16] gave a value of 1.9 kcal/mol and is in good agreement with the accepted range of 0.7 - 3.0 kcal/mol.[14b,14c] The key feature of these results is that they correctly predict that 2-hydroxytetrahydropyran in its ground state conformer has the hydroxyl group in an axial configuration.[14a]

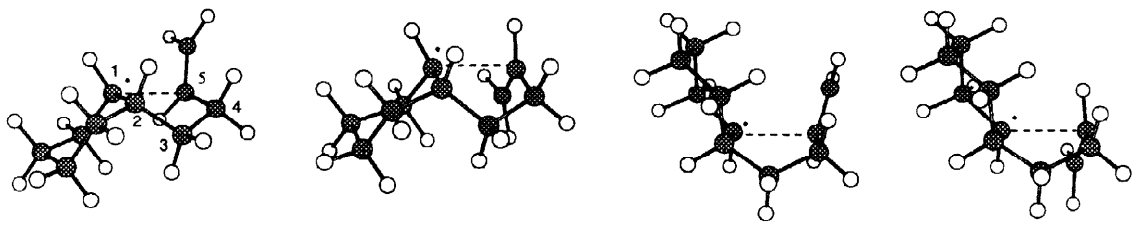
Modelling of all transition structures involved in the cyclisations was accomplished by approximating the radical centre with an sp^2-hybridised carbon atom and the expected transition states were modelled with the accepted geometry for a carbon-centred radical reaction with an olefinic system,[4a,b] i.e. $r(C_1\text{-}C_5) = 2.27$ Å; $r(C_5\text{-}C_6) = 1.38$ Å; $\angle(C_1,C_5,C_6) = 107°$; and $\angle(C_1,C_5,H_5) = 90°$, where the numbering system follows the usual convention for the hex-5-enyl radical and related species. In carrying out the minimisations care was taken to examine the various rotamers of the side chains in the ground state radicals. This is especially important for the dioxa-radical **1b**, in which rotation about the bond between the tetrahydropyran ring and the external oxygen can lower the anomeric stabilisation (see below).



1 **9**

a: X = CH_2, Y = CH_2; **b:** X = O, Y = O;
c: X = CH_2, Y = O; **d:** X = O, Y = CH_2

Figure 1 shows the possible conformations of the all-carbon structure **9a** whilst the data in Table 2 indicates that the calculated strain energies for the various possible transition structures **9a-9d** are in complete accord with the experimental results. For the cyclisation of the radical **1a** the least strained transition structure is the chair-equatorial-chair form **12** which affords the cis-fused syn-product **2a**. Similarly, the radicals **1b** and **1d** preferentially undergo cyclisation through chair-equatorial-chair transition structures (analogous to **12**) to give **2b** and **2d** respectively. However, the least strained transition structure for the cyclisation of **1c** is in the chair-axial-chair form (analogous to **10**) which affords the cis-fused anti-product **3c**.



10 (chair-axial-chair) **11** (chair-axial-boat) **12** (chair-equatorial-chair) **13** (chair-equatorial-boat)

Figure 1. Transition structures for bicyclononane formation

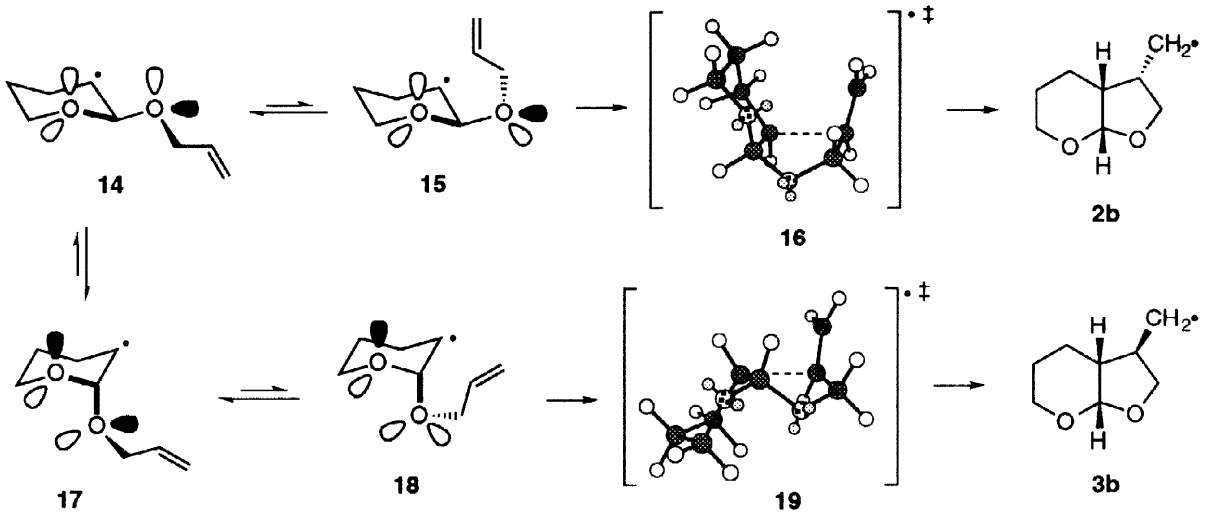
Table 2. Relative Strain Energies (MM2) for Cyclisation Transition Structures

Transition Structure	Conformation	Strain Energy[a] (kcal/mol)	Cyclised Radical	Transition Structure	Conformation	Strain Energy[a] (kcal/mol)	Cyclised Radical
9a	Chair-equatorial-chair	12.93	**2a**	**9b**	Chair-equatorial-chair	18.04	**2b**
	Chair-axial-chair	13.39	**3a**		Chair-axial-chair	18.43	**3b**
	Chair-equatorial-boat	13.66	**3a**		Chair-equatorial-boat	18.92	**3b**
	Chair-axial-boat	14.29	**2a**		Chair-axial-boat	19.12	**2b**
9c	Chair-axial-chair	13.23	**3c**	**9d**	Chair-equatorial-chair	13.58	**2d**
	Chair-axial-boat	13.84	**2c**		Chair-equatorial-boat	14.60	**3d**
	Chair-equatorial-chair	14.93	**2c**		Chair-axial-chair	16.45	**3d**
	Chair-equatorial-boat	15.49	**3c**		Chair-axial-boat	17.30	**2d**

[a] The Strain Energies listed here do not include components from the VDW interaction between C-1 and C-5 (5.7 kcal/mol) or the C-5 - C-6 bond vibration (1.6 kcal/mol) using the numbering system for the hex-5-enyl system (Figure 1). Since the ground state energy for each radical is different, strain energies are comparable within each set but are not comparable between different sets.

Examination of the factors contributing to the strain energies of ground states and transition structures affords further insights into the features defining their preferred conformations. The ground state radicals **1a**, **1c**, and **1d** each preferentially assume the comformer with the substituent equatorially disposed. The major contributors to the higher strain energies of their axially substituted conformers are the 1,3-diaxial non-bonded interactions with protons on the ring. This is especially true for **1d** where the C-O bonds being shorter than C-C bonds increase the diaxial interactions with the substituent. As expected the anomeric effect stabilises the

axial conformer of **1b**, but it is noteworthy that this applies only to that particular side-chain rotamer **17** which allows *two* anomeric interactions (Scheme 1). The rotamer **18** which an axial side-chain must assume if it is to form the transition structure **19** allows only *one* anomeric interaction. Similarly there is only *one* stabilising anomeric interaction in the rotamer **14** which **1b** must assume in order to form the transition structure **16**.



Scheme 1. The thickened bonds and shaded orbitals indicate the antiperiplanar relation between the orbital and the C-O bond necessary for an effective anomeric interaction (lone pair to σ* -C-O).

The picture of the reaction profiles that emerges from the above considerations rests on the assumption that the Hammond postulate[17] holds for this system, i.e. that ring inversions and side chain rotations in the radicals **9a-d** are more rapid than cyclisation. All the available evidence[6,18] suggests that this is true. In these terms it is instructive to follow the course of the dioxa radical **1b** to its syn- and anti-bicyclic radicals, **2b** and **3b**. The first significant feature to note is that in the conformer **17** of the ground state radical **1b** *two* anomeric interactions are effective. In the alternative equatorially substituted ground state **14** there is only *one* anomeric effect. Similarly each of the transition structures **16** and **19** is stabilised by only one anomeric interaction regardless of whether the olefinic substituent is disposed axial with respect to the six-membered ring, as in **19**, or equatorial, as in **16**. Thus for the conversion of the conformer of **1b** of lowest energy **17** to either the axial transition structure **19** or its equatorial isomer **16**, the radical **17** must inevitably lose one stabilising anomeric interaction. This can be achieved either by a bond rotation process leading to the axial transition structure **19** via the rotamer **18** or, by a combination of both ring inversion and bond rotation to the equatorial transition structure **16** via the conformer **15**. Analyses by Deslongchamps[14b] of some simple 2-alkoxytetrahydropyranyl systems have shown that for the analogous interconversions the ring inversion/bond rotation pathway to an equatorial conformation is less energetically costly than a single rotation to a new axial conformation with only one stabilising anomeric interaction. Since in the absence of extra anomeric stabilisation, the steric demand of an equatorial substituent is smaller than that for an axial substituent[16] it is not surprising that cyclisation of **1b** proceeds via transition structure **16** to afford eventually **6b** as the major product.

CONCLUSION

The stereochemical outcome of the ring closure of three monocyclic radicals **1b**, **1c**, and **1d**, the first of which is subject to anomeric stabilisation, has been unambiguously determined and the results compared with those already reported for the all-carbon analogue **1a**. The unexpected preference for the dioxa radical **1b** to afford cis-fused bicycles with 7-syn stereochemistry is attributed to the loss of a stabilising anomeric effect in the conversion of the ground state radical **17** into either of the transition structures **16** or **19**. Molecular mechanics calculations revealed that the transition structure **16** with an equatorially disposed olefinic substituent is less strained than that **19** with an axially disposed olefinic substituent because of the smaller steric demand. A similar rationale was proposed for the behaviour of the mono-oxa substrate **1d** although in this case, the absence of stabilising anomeric effects required that only steric constraints need be considered. By contrast, molecular mechanics studies of the mono-oxa radical **1c** revealed that the steric and torsional strain across the hex-5-enyl substructure was exacerbated in transition states with equatorially disposed olefinic substituents. Hence cyclisation of **1c** preferentially affords the syn-fused bicyclic product with 7-anti stereochemistry. The results of a more extensive analysis of the modelling data and some kinetic studies on substrates **1b** and **1c** will be reported shortly.

EXPERIMENTAL SECTION

General. General experimental details have been previously given.[1] Gas chromatography (GC) was conducted on a BP-10 capillary column (0.25 μm, 0.22 mm x 25 m). The temperature profile was: initial temp 50 °C for 3 min, ramped at 10 °C/min to 105 °C (held for 2 min), then ramped at 20 °C /min to 270 °C.

***trans*-3-Bromo-2-(prop-2'-enyl-1'-oxy)tetrahydropyran (5b).** A cooled solution (-20°C) of NBS (5.4 g, 30 mmol) and allyl alcohol (2 mL, 29 mmol) was treated with dihydropyran (2.7 mL, 29 mmol) for 2 h.[8a,b] The mixture was then warmed to rt, filtered through a glass sinter, and concentrated. Flash chromatography of the residue gave **5b**[7a] (tentatively identified as the trans isomer[11]) as a colourless oil (4.7 g, 73%). ^{1}H NMR ($CDCl_3$) δ 1.47 - 2.45 (m, 4H), 3.55 - 3.65 (m, 1H), 3.87 - 4.10 (m, 3H), 4.22 - 4.30 (ddt, 1H, J = 13.2, 6.6, 2.2 Hz), 4.65 (d, 1H, J = 5.1 Hz), 5.20 (dq, 1H, J = 11.0, 2.0 Hz), 5.33 (dq, 1H, J = 18.0, 2.0 Hz), 5.87 - 6.00 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 23.14, 29.96, 49.21, 62.40, 68.63, 100.12, 117.39, 133.76; IR (KBr) 2951, 2929, 2854, 1647, 1437, 1354, 1204, 1131, 1072, 1029, 994, 870, 730, 614 cm^{-1}; HRMS *m/z* calcd for $C_5H_8{}^{79}BrO$, $[M-C_3H_5O]^+$, requires: 162.9759. Found: 162.9758. Additional spectral data were consistent with those previously reported.[7a]

***trans*-2-Bromo-1-(prop-2'-enyl-1'-oxy)cyclohexane (5c).** A vigorously stirred suspension of NBS (6.5g, 37 mmol) in ice chilled allyl alcohol (15 mL) was treated with cyclohexene (3.7 mL, 37 mmol) as previously described.[8c] The reaction mixture was stirred at 0°C for 1 h, then warmed to rt. After being stirred for a further 3 h, the mixture was poured onto crushed ice and extracted with diethyl ether. Flash chromatography of the crude residue furnished the desired bromide **5c**[8c] (tentatively identified as the trans isomer[11]) as a colourless oil (2.14 g, 26%). ^{1}H NMR ($CDCl_3$) δ 1.24 - 2.49 (m, 8H), 3.34 - 3.45 (m, 1H), 3.94 - 4.08 (m, 1H), 4.08 - 4.15 (m, 2H), 5.13 - 5.22 (dm, 1H, J = 10.0 Hz), 5.27 - 5.36 (dm, 1H, J = 17.0 Hz), 5.87 - 6.04 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 23.10, 25.18, 30.73, 35.35, 55.50, 70.67, 80.89, 116.83, 135.01; IR (KBr) 2931, 2857, 1149, 1059, 1026, 1009, 957 cm^{-1}; HRMS *m/z* calcd for $C_9H_{14}{}^{79}BrO$, $[M-H]^+$, requires: 217.0228. Found: 217.0228.

***trans*-3-Bromo-2-(but-3'-enyl)tetrahydropyran (5d).** 3,4-Dihydro-2*H*-pyran was brominated in dry diethyl ether (12 mL) at -25°C to afford a 1 : 1 mixture of *cis*- and *trans*-2,3-dibromotetrahydropyran[9] which was cooled (ice) and added over 15 min with stirring to cooled but-3-enyl magnesium bromide (20 mmol) in ether (20 mL). The mixture was warmed slowly to rt, stirred for a further 3 h, then poured into a brine/diethyl

ether bilayer. After acidification with H_2SO_4 (10%), the ethereal phase was separated, and evaporated. Flash chromatography of the residue afforded **5d** as a colourless oil (967 mg, 28%). ^{1}H NMR ($CDCl_3$) δ 1.46 - 2.32 (m, 7H), 2.36 - 2.48 (m, 1H), 3.35 (td, 1H, J = 9.28, 1.77 Hz), 3.44 (td, 1H, J = 11.53, 2.56 Hz), 3.72 - 3.82 (m, 1H), 3.94 - 4.03 (m, 1H) 4.97 (dm, 1H, J = 8.36 Hz), 5.05 (dm, 1H, J = 17.27 Hz), 5.76 - 5.90 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.38, 29.13, 32.74, 35.90, 52.35, 68.02, 81.36, 114.61, 138.07. Anal. Calcd for $C_9H_{15}BrO$: C, 49.33; H, 6.90; Br, 36.47. Found: C, 49.65; H, 7.33; Br, 36.01.

***cis-syn-* and *cis-anti*-7-Methyl-2,9-dioxabicyclo[4.3.0]nonane (6b, 7b).** Tributyltin hydride (1.5 mL, 5.4 mmol) was added to a deaerated solution of bromo acetal **5b** (1.0 g, 4.5 mmol) and t-butyl hyponitrite (7.5 mg, 45 μmol) in dry pentane (23 mL). The mixture was refluxed for 16 h, after which time the solvent was removed under reduced pressure and the residue was subjected to a DBU work-up[19] and repetitive flash chromatography (3 : 1 hexane/diethyl ether) to furnish three colourless oils (482 mg, 75%). The least polar fraction (86 mg, 13%) comprised exclusively 2-allyloxytetrahydrofuran **8b**.[20] ^{1}H NMR ($CDCl_3$) δ 1.45 - 1.90 (m, 6H), 3.46 - 3.55 (m, 1H), 3.83 - 3.92 (m, 1H), 3.92 - 4.02 (dd, 1H, J = 12.86, 6.43 Hz), 4.20 - 4.30 (dd, 1H, J = 12.86, 6.43 Hz), 4.65 (t, 1H, J = 3.21 Hz), 5.18 (dm, 1H, J = 10.71 Hz), 5.30 (dm, 1H, J = 17.14 Hz), 5.88 - 6.01 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 19.31, 25.55, 30.47, 62.04, 67.86, 97.78, 116.65, 134.55. Additional spectral data were consistent with those previously reported.[20] Anal. Calcd for $C_8H_{14}O_2$: C, 67.57: H, 9.92. Found: C, 67.90; H, 10.20.

The second and third fractions contained the cyclised bicyclononanes **6b** and **7b**[7a] (395 mg, 61%). ^{1}H NMR ($CDCl_3$) δ 7-syn: 0.96 (d, 3H, J = 6.96 Hz), 1.32 - 1.72 (m, 4H), 1.85 -1.95 (m, 1H), 2.36 - 2.51 (m, 1H), 3.58 - 3.65 (m and superimposed t, 2H, J = 8.06 Hz), 3.70 - 3.78 (m, 1H), 3.94 (t, 1H, J = 7.94 Hz), 5.27 (d, 1H, J = 3.85 Hz); 7-anti: 1.02 (d, 3H, J = 6.63 Hz), 1.30 - 1.39 (dm, 1H, J = 14.0 Hz), 1.60 - 1.75 (m, 2H), 1.80 - 1.87 (m, 2H), 2.31 - 2.46 (m, 1H), 3.37 - 3.49 (dt and partially superimposed t, 2H, J = 11.41, 2.6, 8.15 Hz), 3.87 (dt, 1H, J = 12.07, 3.1 Hz), 4.27 (t, 1H, J = 8.15 Hz), 5.00 (d, 1H, J = 3.57 Hz); ^{13}C NMR ($CDCl_3$) δ 7-syn: 11.50, 19.28, 23.03, 35.01, 37.67, 61.01, 71.53, 102.09; 7-anti: 15.67, 20.57, 21.79, 32.17, 45.41, 64.38, 75.30, 102.12. Additional spectral data were consistent with those previously reported.[7a] Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.91; H, 10.21.

In a second experiment tributyltin hydride (30 μL, 0.1 mmol) was added to a deaerated solution of **5b** (20 mg, 90 μmol) in freshly distilled hexane (5 mL) and the mixture was cooled to -20°C in a cryogenic bath and stirred for 10 min. Triethylborane in hexane (20 μL, 1 M, 20 mol%) was then added followed by dry air (1 mL) introduced through a syringe with the tip of the needle just above the level of the mixture.[12] The progress of the reaction was monitored by GC analysis of small aliquots, and additional portions of triethylborane (20 μL, 1 M solution in hexane, 20 mol%) and dry air (1 mL) were added at 4 and 6 h respectively. After 28 h, the mixture was warmed to rt and analyzed by GC. The ratio of the two cyclised products **6b : 7b** was 20 : 1 while that of the combined cyclised material relative to 2-allyloxytetrahydrofuran **8b** was 18 : 1. Repetition of the experiment at -55°C gave a ratio between **6b** and **7b** of 35 : 1 whilst that of the combined cyclised material versus **8b** was 6.8 : 1.

Cyclisation of *trans*-2-Bromo-1-(prop-2'-enyl-1'-oxy)cyclohexane (5c). A solution of bromo ether **5c** (400 mg, 1.8 mmol) t-butyl hyponitrite (3 mg, 18 μmol) and tributyltin hydride (0.5 mL, 2.0 mmol) in dry pentane (9 mL) was heated under reflux for 14 h, then worked up as described above. Repetitive flash chromatography (10 : 1 pentane/diethyl ether) furnished two colourless oils (114 mg, 44%). The least polar fraction (12 mg, 5%) contained only allyloxycyclohexane **8c**.[21] ^{1}H NMR ($CDCl_3$) δ 1.12 - 1.35 (m, 5H), 1.48 - 1.57 (m, 1H), 1.66 - 1.80 (m, 2H), 1.88 - 1.98 (m, 2H), 3.23 - 3.32 (1H, m, H-1), 4.01 (dt, 2H, J = 5.55, 1.38 Hz), 5.15 (dm, 1H, J = 10.29 Hz), 5.27 (dm, 1H, J = 17.25 Hz), 5.87 - 6.00 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 24.10, 25.70, 32.18, 68.68, 76.87, 116.19, 135.57. Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.44; H, 11.83.

The second fraction (102 mg, 39%) contained the two cyclised oxabicyclononanes **6c** and **7c** as an inseparable mixture. ^{1}H NMR (C_6D_6) δ 7-anti: 0.97 (d, 3H, J = 6.71 Hz), 1.15 - 2.11 (m, 10H), 3.51 (dd, 1H, J = 8.42, 5.37 Hz), 4.05 (m, 1H), 4.29 (t, 1H, J = 7.64 Hz). 7-syn: 0.91 (d, 3H, J = 6.83 Hz), 1.15 - 2.11 (m, 8H), 2.28 - 2.40 (m, 2H), 3.63 (dd, 1H, J = 10.01, 7.93 Hz), 4.05 - 4.13 (m, 2H); ^{13}C NMR (C_6D_6) δ 7-anti:

18.92, 22.11, 24.30, 27.70, 29.40, 38.72, 45.95, 74.36, 76.38. 7-syn: 12.02, 21.36, 22.65, 25.36, 29.40, 38.63, 42.03, 72.78, 78.64; IR (KBr) 2931, 2857, 1149, 1059, 1026, 1009, 957 cm^{-1}. Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.14; H, 11.50.

Cyclisation of *trans*-3-Bromo-2-(but-3'-enyl)tetrahydropyran (5d). A deaerated solution of **5d** (779 mg, 3.6 mmol), t-butyl hyponitrite (6.2 mg, 36 μmol) and tributyltin hydride (1.15 mL, 4.3 mmol) in dry pentane (43 mL) was heated under reflux for 4.5 h. The usual work up and repetitive flash chromatography (15 : 1 pentane/diethyl ether) furnished two colourless oils, the least polar of which (33 mg, 7%) was identified as the 2-(but-3'-enyl)tetrahydropyran **8d**.[22] ^1H NMR ($CDCl_3$) δ 1.14 - 1.33 (m, 1H), 1.37 - 1.67 (m, 6H), 1.74 - 1.86 (m, 1H), 1.98 - 2.25 (m, 2H), 3.17 - 3.29 (m, 1H), 3.40 (td, 1H, J = 14.23, 2.87 Hz), 3.96 (dt, 1H, J = 11.26, 2.20 Hz), 4.94 (dm, 1H, J = 11.11 Hz), 5.01 (dm, 1H, J = 17.09 Hz), 5.72 - 5.90 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 23.45, 26.09, 29.63, 31.75, 35.64, 68.37, 77.04, 114.32, 138.57; HRMS *m/z* calcd for $C_9H_{17}O$, $[M+H]^+$, requires: 141.1279. Found: 141.1278.

The second fraction (193 mg, 39%) comprised the two cyclised bicyclononanes **6d** and **7d** as an inseparable mixture. ^1H NMR ($CDCl_3$) δ 0.96 (d, 0.51H, J = 6.45 Hz), 0.97 (d, 2.49H, J = 7.08 Hz), 1.07 - 1.54 (m, 3H), 1.54 - 1.91 (m, 6H), 1.91 - 2.16 (m, 1H), 3.29 - 3.42 (m, 0.17H), 3.42 - 3.54 (m, 0.83H), 3.68 - 3.77 (m, 0.83H), 3.80 - 3.90 (m, 0.17H), 4.03 - 4.11 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 7-syn: 16.53, 20.01, 23.96, 27.62, 30.47, 35.00, 40.21, 63.05, 79.23. 7-anti: 18.77, 21.15, 22.05, 31.35, 31.70, 32.57, 46.91, 67.41, 80.99. Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.95; H, 11.93.

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