Addition of electrophiles to unsymmetric alkenes. Effects of β oxygen substituents on the stereo- and regio-chemistry of positive halogen addition

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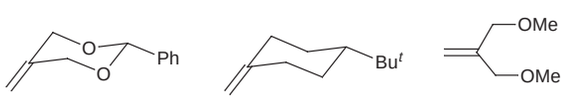
The stereo- and regio-chemistry of two step additions of positive halogen electrophiles to 5-methylene-2-phenyl-1,3-dioxane, 1-*tert*-butyl-4-methylenecyclohexane and 3-methoxy-2-(methoxymethyl)prop-1-ene have been determined. The direction of initial electrophile attack is in line with the frontier orbital and electrostatic considerations described by us previously. The regiochemistry of addition is strongly affected by hyperconjugative effects, acting between the intermediate epihalonium ion and the β C–X bonds. Where the β C–X bonds bear a fixed periplanar relation to the epihalonium ion and X is more electronegative than hydrogen, anti-Markownikoff addition is strongly promoted and becomes exclusive when two such β C–X bonds are present. If the β C–X bond is free to rotate away from periplanarity, then β C–H bonds will adopt the geometry required for hyperconjugation and Markownikoff regiochemistry will be favoured. The results are consistent with *ab initio* theoretical calculations and can be rationalised using a simple electrostatic model.

Our recent investigation into the stereochemistry of the addition of electrophiles to 1,1-disubstituted alkenes such as the 5-methylenedioxane **1** and the methylenecyclohexane **2** has



1 **2** **3**

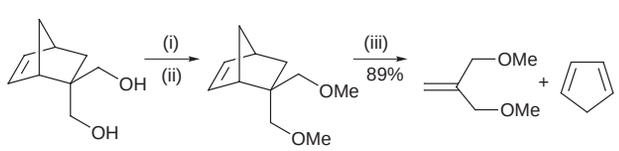
revealed that the hyperconjugative interaction of the correctly aligned β C–O, C–C and C–H bonds with the π system has a strong influence on the stereoreactivity of the system towards those electrophiles which add in a one step process.[1] We now report on the stereo- and, in particular, the regio-chemistry of additions to **1** and **2** of electrophiles which add in a two step manner.

It is to be expected that the Markownikoff rule will be obeyed in additions to the cyclohexane **2**. The expected result for addition to the dioxane, **1**, is less clear cut however. The two oxygens are, together, likely to exert a strong inductive effect which may act to destabilise any positive charge on the tertiary carbon of the double bond, during the formation and subsequent attack of a cationic intermediate. Alternatively the oxygen lone pairs could play some important role, perhaps by forming an oxygen bridged cationic intermediate. A third factor, of particular interest to us, was whether the β C–O bonds had some influence, mediated by hyperconjugation, that could affect the regiochemistry of addition. Our previous results had suggested that such an influence might be strong.[1] In addition theoretical calculations carried out some time ago by Radom *et al.* had predicted that a β C–O bond aligned with the p orbital of an adjacent carbocation would be poorer at stabilizing the cation hyperconjugatively than a β C–H or β C–C bond.[2] However, few experimental studies have unequivocally demonstrated this to be the case in practice.

Our primary aim was to identify any such hyperconjugative effect. It was necessary therefore to prepare a model compound analagous to **1** which would have no conformational restrictions on the geometry of the β substituents with respect to the double bond. 3-Methoxy-2-(methoxymethyl)prop-1-ene **3**, was accordingly chosen.

Results

The dioxane **1** was prepared by the method of Weiss *et al.*[3] as described previously, *via* the intermediate 2,2-bis(hydroxymethyl)norbornene **4**. Bis-methylation of **4**, followed by flash vacuum pyrolysis in a quartz tube cleanly afforded **3** (Scheme 1). The methylenecyclohexane **2** was prepared according to the method of Corey and Suggs.[4]



4 **5** **3**

Scheme 1 *Reagents and conditions*: (i) NaH, THF, (ii) MeI, (iii) 500 °C, 1 torr

The reagents employed and the results of the addition reactions are given in Tables 1 and 2. All the reagents chosen are sources of positive halogen and the reaction, in each case, is expected to proceed *via* an epihalonium ion. To ensure the validity of the results, it was essential that alternative radical mediated pathways be eliminated and also that the presence of any acidic by-products be excluded to prevent epimerisation of the dioxane ring in the products from **1**. To this end, all the reactions were carried out in the dark. Hypobromination and hypoiodination were performed in the presence of a sodium acetate or sodium carbonate buffer. Propylene oxide was employed to remove hydrohalogen acid in the bromination and iodochlorination reactions. Its use was essential in the reactions of **1**, for in its absence very different product ratios were observed. Thus bromination gave both possible dibromides and iodochlorination gave a mixture of all four possible chloroiodides, each of which was isolated. Additionally, the bromination was repeated in acetonitrile, a polar solvent, in the presence of a radical inhibitor (methylene blue) with the same results as those observed in CCl_4. The product mixtures were separated by flash column chromatography on silica and the individual components isolated and characterised. Product ratios were generally determined for the crude product mixture by measuring the integrated areas of characteristic peaks in the

Table 1 Products from addition of halohydrins to 5-methylene-2-phenyl-1,3-dioxane (**1**), 4-*tert*-butyl-1-methylenecyclohexane (**2**) and 3-methoxy-2-(methoxymethyl)prop-1-ene (**3**)

			Products				
				Markownikoff (%)		Anti-markownikoff (%)	
Entry	Substrate	Reagent	Structure	*exo*	*endo*	*exo*	*endo*
1	**1**	*N*-Bromoacetamide, aq. Bu^{t}OH, NaOAc	**6** R = H	0	0	71	0
			7 R = Ac			14	
			9 X = Y = Br			5	
2	**1**	*N*-Iodoacetamide, aq. Bu^{t}OH, NaOAc	**8** R = H	0	0	51	0
			10 R = Ac			36	
			11 X = Y = I			13	
3	**2**	*N*-Bromoacetamide, aq. Bu^{t}OH,	**14**, **15** X = Br	92	8[a]	0	0
4	**2**	*N*-Bromoacetamide, aq. Bu^{t}OH, NaOAc	**14** X = Br	>90			
5	**2**	*N*-Iodoacetamide, aq. Bu^{t}OH, NaOAc	**16**, **17** X = I	>90			
			18, **19**				
6	**2**	*N*-Iodoacetamide, aq. Bu^{t}OH, Na_2CO_3	**16**, **17** X = I	84	16	0	0
7	**3**	*N*-Bromoacetamide, aq. Bu^{t}OH, NaOAc	**12**, **13**	76		24	

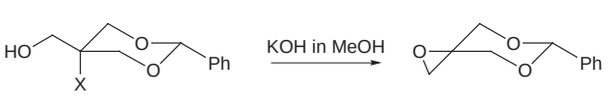
[a] Data from ref. 6.

Table 2 Products from addition of halogens to 5-methylene-2-phenyl-1,3-dioxane (**1**), 4-*tert*-butyl-1-methylenecyclohexane (**2**) and 3-methoxy-2-(methylenemethoxy)prop-1-ene (**3**)

			Products				
				Markownikoff (%)		Anti-markownikoff (%)	
Entry	Substrate	Reagent	Structure	*endo*	*exo*	*exo*	*endo*
1	**1**	Br_2 in CCl_4	**9**, **20** X = Y = Br	N/A	N/A	16	84
2	**1**	Br_2 in CCl_4 + propylene oxide		N/A	N/A	100	0
3	**1**	Br_2 in MeCN + propylene oxide		N/A	N/A	100	0
4	**1**	Br_2 in MeCN + propylene oxide + methylene blue		N/A	N/A	100	0
5	**1**	ICl_4 in CCl_4	**21**, **22**, **23**, **24** X = I, Y = Cl	7	20	3	70
6	**1**	ICl in CCl_4 + propylene oxide		0	0	100	0
7	**2**	Br_2 in CCl_4	**27**, **28** X = Y = Br	34	66	N/A	N/A
8	**2**	Br_2 in CCl_4 + propylene oxide		34	66	N/A	N/A
9	**2**	ICl in CCl_4 + propylene oxide	**29** X = I, Y = Cl	60		0	
			30 X = Y = Cl	40		N/A	
10	**3**	ICl in CCl_4 + propylene oxide	**25**, **26** X = I, Y = Cl	68		32	

^{1}H NMR spectrum (normally the peak due to the exocyclic methylene group).

The regiochemistry of hypobromination and hypoiodination of the dioxane **1** could be ascertained from the ^{1}H NMR spectrum of the single halohydrin isolated from each. A 6.5 Hz coupling between the hydroxy H and the exocyclic methylene hydrogens was clearly visible indicating that only the anti-Markownikoff adduct had formed in each case. The stereochemistry of the addition was determined by treating the isolated halohydrin (**6** or **8**) with KOH in methanol. Both halohydrins afforded exclusively the same epoxide **31** (Scheme 2),

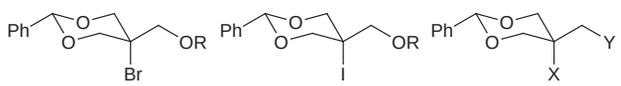


Scheme 2

which had been characterised previously,[1] indicating that the initial electrophilic attack by positive halogen had occurred on the *exo* (axial) face of the double bond. Both hypohalogenations gave a number of minor products (**7**, **9**, **10** and **11**), which result from capture of the intermediate epihalonium ion, on the route to the halohydrin, by acetate or halide. Acetylation of the halohydrins **6** and **8** gave rise to **7** and **10** respectively confirming their structures and stereochemistry.

The regiochemistry of hypobromination and hypoiodination of the methylenecyclohexane **2** was similarly evident from the ^{1}H and ^{13}C NMR spectra and the stereochemistry of the products was established by conversion to the corresponding epoxides, **35** and **36**, which are already known.[5] The result of hypobromination is in agreement with that reported previously.[6] Hypobromination of **3** gave both possible adducts, whose regiochemistry was defined by examination of their ^{13}C NMR spectra.

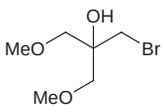
The isolation of all the possible isomers from the addition of bromine and iodine chloride to **1**, in the absence of propylene oxide, made the task of determining their stereo- and regiochemistry much easier. Comparison of the ^{13}C NMR shifts for the primary and tertiary iodine bearing carbons established the regiochemistry of the iodochlorination products. Their stereochemistry was assigned by making use of the results of Eliel and Enanoza,[7] who showed that for 5-substituted-1,3-dioxanes, a 5-equatorial methyl(ene) resonates substantially upfield of a 5-axial methyl(ene) in the ^{1}H NMR spectrum. This is a reversal of the situation observed for methylcyclohexanes. To confirm these assignments, samples of the pure compounds **9** and **23** were treated with acid. Epimerisation of the acetal group occurred rapidly to give a mixture of stereoisomers in a ratio similar to that obtained in the addition reactions carried out in the absence of propylene oxide. These experiments showed that the more thermodynamically stable epimer is that with the 5-methylene group *axial* rather than that with the 5-methylene group *equatorial*, which is the isomer formed as the major product in the addition reactions. For the case of **1**, this



6 R = H
7 R = Ac

8 R = H
10 R = Ac

9 X = Y = Br
11 X = Y = I
23 X = I, Y = Cl



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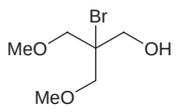

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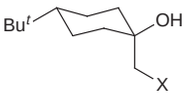
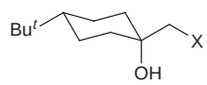
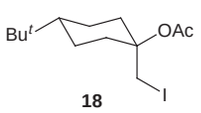


14 X = Br
16 X = I



15 X = Br
17 X = I



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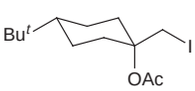

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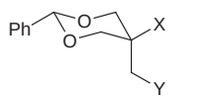
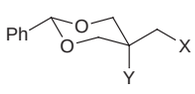
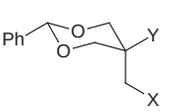


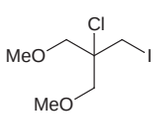
20 X = Y = Br
24 X = I, Y = Cl



21 X = I, Y = Cl



22 X = I, Y = Cl



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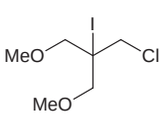

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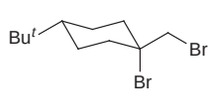

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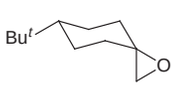

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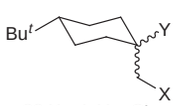
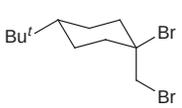


29 X = I, Y = Cl
30 X = Y = Cl



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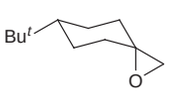

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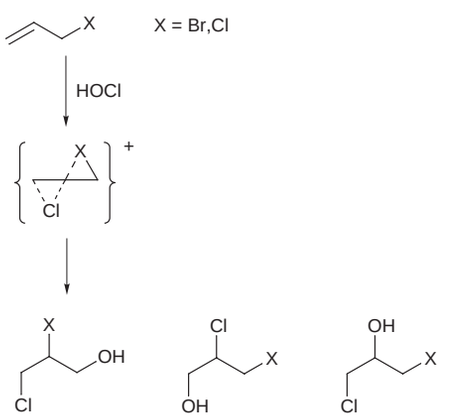
result shows conclusively that the addition reactions are under kinetic rather than thermodynamic control. We draw the inference that it is likely that this conclusion can be extrapolated to the products formed in the halohydrin additions. Hence we conclude that, under our experimental conditions, all the additions to the dioxane **1** are under kinetic control. It seems likely that this is also true for the other two substrates, **2** and **3**. (The thermodynamic preference for the 5-methylene group *axial* over *equatorial* in dioxanes has been noted previously by Eliel and Kaloustian.[8])

The ^{13}C NMR spectra enabled easy assignment of the regiochemistry of the iodochlorination products from the open chain ether **3**. For the methylenecyclohexane **2**, iodochlorination gave two rather unstable products. The major one, **29**, was an iodochloride which could be assigned Markownikoff regiochemistry on the basis of its ^{13}C NMR spectrum. The minor isomer, **30**, was a dichloride. The propensity for the formation of dichlorides during ICl addition has been noted before.[9] Unfortunately, no reliable assignment of stereochemistry could be made for either of these two compounds. Bromination of **2** gave a mixture of two dibromides. Their stereochemistry was determined by comparison of their ^{13}C NMR and IR spectra with those of previously reported bromomethylenecyclohexanes.[10,11] In neither the bromination nor the iodochlorination additions to **2** and **3** were the product ratios affected when propylene oxide was included in the reaction mixture.

Discussion

Our results indicate that whilst the methylenecyclohexane **2** undergoes exclusive Markownikoff addition as expected, the methylenedioxane **1** shows, conversely, complete anti-Markownikoff addition with positive halogen reagents. Further, assuming that *anti* opening of the epihalonium ion occurs, it is also clear that initial halogen attack on **1** must be overwhelmingly from the axial face, *i.e. exo*. Similar *exo* attack is also favoured for the hypohalogenation of the methylenecyclohexane **2**, although here some product does arise as a result of initial attack from the *endo* face. Molecular bromine adds to **2** with a preference for the *exo* face of 2 : 1, whereas for the methylenedioxane **1**, initial addition is still exclusively *exo*. (Based on the assumption that, as with the other reagents, bromine adds with anti-Markownikoff regiochemistry.) In comparing this aspect of the positive halogen additions to **1** and **2**, we note that the behaviour is similar to that observed with diimide, which reacts stereospecifically *exo* with 5-methylenedioxanes, but almost unselectively towards methylenecyclohexane.[1] For the reaction of diimide, this was most satisfactorily accounted for by invoking the pronounced difference in electrostatic potential field between the two faces of the double bond which calculations had shown for **1**. This difference gives a substantial bias for *exo* (axial) attack by an electrophile with an appreciable dipole, which, with the exception of bromine, is the case for the electrophiles that we have examined here. It has been argued previously that even uncharged but polarisable electrophiles, such as molecular bromine, can be directed by the electrostatic potential field because the field assists separation of charge within the electrophile,[12] or may act to 'guide in' the electrophile.[13]

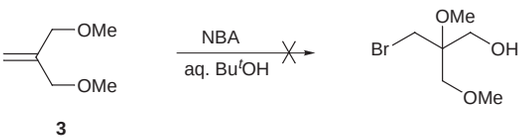
In considering the regiochemistry of addition of the unsymmetrical reagents to the two cyclic compounds, we note the remarkable propensity for the dioxane **1** to undergo anti-Markownikoff addition. This cannot be explained by invoking only an inductive effect, as otherwise 3-methoxy-2-(methoxymethyl)prop-1-ene **3** should also show exclusive anti-Markownikoff addition. However this molecule has a small preference for Markownikoff addition. An alternative rationalisation might be that described by de la Mare to account for the slight preference for anti-Markownikoff addition of hypochlorous acid to 3-chloro- and 3-bromo-propene.[14] This involves neighbouring group participation by the 3-halogen to form the double epihalonium ion shown in Scheme 3, followed by attack, preferred at the terminal sites, to afford **32** as the major product. For the propenes, this explanation is supported



32 **33** **34**

Scheme 3

by the formation of products in which the halogen initially at C-3 is found at C-2. However, in the reactions of **1** and **3**, neighbouring group participation by β-oxygen is unlikely to be occurring because, despite a careful search, in neither case could any similar rearrangement products be found (Scheme 4).

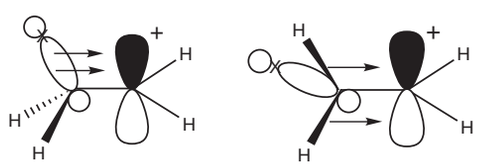


3

Scheme 4

The striking difference between the behaviour of the rigid methylenedioxane **1** and the flexible 3-methoxy-2-(methoxymethyl)prop-1-ane **3** points strongly to an effect dependent on the alignment of the β C–O bonds with the intermediate epihalonium ion. We suggest, therefore, that a hyperconjugative interaction between the β C–O bond and the epihalonium ion, analogous to that discussed in our previous paper,[1] is responsible for this difference.

The situation may be compared to those examined in the pioneering *ab initio* calculations of Radom and co-workers on the stability of carbonium ions β-substituted with a substituent X, where the stability of the carbocation depends both on the nature of X and the conformation of the C–X bond relative to the p-orbital on the cationic centre.[2,15] The calculations show that where the substituent X is more electropositive than hydrogen, the cation is best stabilised in the aligned conformation **A** shown in Scheme 5, so that extensive σ–π electron donation can occur. On the other hand, when X is more electronegative than hydrogen, the most stable conformation is that shown in **B** (Scheme 5) with the C–X bond in the plane perpendicular to the



A **B**

Scheme 5

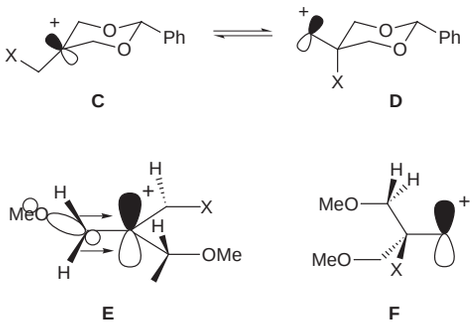
p-orbital and in which the C–H bonds can now act to stabilise the electron deficiency.

In addition to this entirely hyperconjugative effect, Radom and his colleagues were also able to demonstrate that there is an underlying inductive effect that, when X is more electronegative than H, destabilises the cation regardless of which conformation (**A** or **B**) it adopts. The inductive effect is still present in γ substituted cations, albeit somewhat reduced.

Our regiochemical results are very much as would be predicted on the basis of Radom's calculations if a simple carbocation mechanism were assumed. The equilibrium between the primary (**D**) and tertiary (**C**) cations formed by addition to the methylenedioxane **1** might well favour the primary cation (Scheme 6), for the tertiary one will be adversely affected by the C–O bonds. The tertiary carbocation formed by addition to the open chain **3** can, on the other hand, achieve the more stabilised conformation **E** predicted by Radom.

The fact that any anti-Markownikoff addition occurs at all with **3** could then be explained as a consequence of inductive destabilisation of the tertiary cation **E** by the β oxygens, with a resultant change in its energy to a level similar to that of the primary cation **F**.

However, none of the reactions discussed here are thought to proceed *via* a simple carbocation and therefore the direct application of the results of these calculations, though attractive, is not clear cut. We would suggest an electrostatic picture as a plausible alternative way of visualising how hyperconjugative



Scheme 6

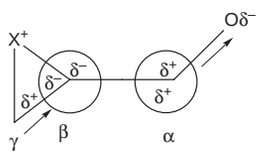


Fig. 1 Induced dipoles in the epihalonium ion resulting from axial attack on **1**

interactions might affect nucleophilic attack on the epihalonium ion formed by initial addition to the exocyclic bond of the dioxane **1**. The C_β–C_γ bond is close to antiperiplanar to the O–C_α bond. Therefore the dipole along the O–C_α bond is liable to induce a corresponding dipole along the C_β–C_γ bond. This is illustrated in Fig. 1. The arrows are intended to illustrate this charge shift and not the absolute charge on each atom which is likely to be positive for both C_β and C_γ. The transfer of charge from C_β to C_γ will make C_γ more electropositive than C_β and hence liable to nucleophilic attack. This C_β to C_γ charge transfer, mediated by hyperconjugation, will occur most strongly if the O–C_α bond is periplanar to the bonds of the epihalonium ring. If the O–C_α bond holds no fixed dihedral angle to the epihalonium ring, as in the intermediates from addition to **3**, then much less anti-Markownikoff addition would be expected.

Conclusions

For single step electrophilic additions to C–C double-bonds, we have already shown that the stereochemistry is profoundly influenced by the hyperconjugative interactions between the π system and a C–X bond situated β with respect to it.[1] We have here demonstrated that, for two step additions of positive halogen electrophiles, these same hyperconjugative effects, acting between an intermediate epihalonium ion and a β C–X bond, have a very significant influence on the regiochemistry of the process. Where X is more electronegative than hydrogen then, provided that the β C–X bond bears a fixed periplanar relation to the epihalonium ion, anti-Markownikoff addition is strongly promoted to the extent that it becomes exclusive when two such β C–X bonds are present. If the β C–X bond is free to rotate away from periplanarity, then it will do so, allowing alternative β C–H bonds to achieve the geometry required for hyperconjugation and hence favouring the Markownikoff regiochemistry. These results are consistent with *ab initio* theoretical calculations[14] and can be rationalised using a simple electrostatic model.

Experimental †

All solvents were dried and distilled before use. Flash column chromatography was carried out using a hand pump as air pres-

† The products have been named using *E* and *Z* terminology to describe the positions of the two substituents relative to the plane of the dioxane ring. *Z* indicates that the two substituents are located on the same side of the ring and *E* indicates that they are on opposite faces of the ring.

sure source and MN Kieselgel 60 (230–400) as the solid phase. Melting points were determined on a Gallenkamp solid block melting point apparatus and are uncorrected. Elemental analyses were performed at the microanalytical laboratory, University College, London. IR spectra were recorded on a Perkin-Elmer 298 Infrared Spectrophotometer, spectra were recorded in solution cells of 0.1 mm thickness (unless otherwise stated) in chloroform solvent. NMR spectra were recorded on a Varian Associates XL-100-12 with internal lock.

Preparation of 5,5-bis(methoxymethyl)bicyclo[2.2.1]hept-2-ene, 5

A solution of 5,5-bis(hydroxymethyl)bicyclo[2.2.1]hept-2-ene, **4**, (16 g), in tetrahydrofuran (100 ml) was added dropwise, with stirring, to a slurry of sodium hydride (8.9 g, 60% in mineral oil, prewashed with pentane) in tetrahydrofuran (50 ml), under nitrogen. The mixture was heated to reflux for 60 min. and allowed to cool. Iodomethane (13.86 ml) was added dropwise and the mixture left overnight before being poured into brine. The organic solvent was removed under reduced pressure and the residue extracted with chloroform. The extracts were combined and washed with water. After drying, filtration and removal of solvent, an oil (17.7 g) was collected. Distillation yielded **5** as a colourless oil (14.6 g, 78%), bp 104.5–105.5 °C (22 mmHg). ν/cm^{-1} 2970, 2880, 1570, 1430, 1333, 1197, 1110, 975, 717; δ_H(100 MHz, $CDCl_3$) 0.75 (dd, *J* 12, 6, 1H), 1.5 (m, 3H), 2.62 (m, 1H), 2.78 (m, 1H), 3.05 (d, *J* 8, 1H), 3.20, (d, *J* 8, 1H), 3.26 (s, 3H), 3.36 (s, 3H), 3.35 (d, *J* 8, 1H), 3.5 (d, *J* 8, 1H), 6.15 (m, 2H).

Preparation of 2-methoxy-3-(methoxymethyl)prop-1-ene, 3

Vapourised 5,5-bis(methoxymethyl)bicyclo[2.2.1]hept-2-ene, **5**, (7 g) was passed through a quartz pyrolysis tube (50 × 1.5 cm), packed with quartz glass fragments and wound with nichrome resistance wire (5 Ω m^{-1}), with a pitch of 4 mm, on top of alumina cement (3 mm thick) heated to 500 °C, at a pressure of 1 mmHg. The collected pyrolysate was fractionally distilled under nitrogen to afford **3** as a mobile oil (3.97 g, 89%), bp 132–134 °C (760 mmHg). ν/cm^{-1} 2930, 1658, 1450, 1191, 923; δ_H(100 MHz, $CDCl_3$) 3.34 (s, 6H), 3.92 (d, *J* 1, 4H), 5.17 (s, 2H); δ_C(25.18 MHz, $CDCl_3$) 58.0, 73.4, 113.7, 143.

Addition of hypobromous acid to 5-methylene-2-phenyl-1,3-dioxane

5-Methylene-2-phenyl-1,3-dioxane (1.05 g, 5.97 mmol) and *N*-bromoacetamide (4.26 g, 28 mmol) were added, with stirring, to a mixture of sodium acetate (3.75 g, 46 mmol) in 50:50 water–*tert*-butyl alcohol. The reaction was left in the dark for 16 h, after which the organic solvent was evaporated off under reduced pressure and 1 M sodium hydroxide added (20 ml). The mixture was extracted with diethyl ether and the extracts combined, washed, dried, filtered and the solvent evaporated to afford a brown oil (1.35 g, 83%). The mixture was separated by flash column chromatography on silica using a solvent gradient from 50:50 toluene–CH_2Cl_2 to 80:20 CH_2Cl_2–EtOAc. Three major components were identified: (*Z*)-5-bromo-5-hydroxymethyl-2-phenyl-1,3-dioxane (845 mg), (*Z*)-5-acetoxymethyl-5-bromo-2-phenyl-1,3-dioxane (186 mg) and (*Z*)-5-bromo-5-bromomethyl-2-phenyl-1,3-dioxane (69 mg).

(*Z*)-5-Bromo-5-hydroxmethyl-2-phenyl-1,3-dioxane, 6. Recrystallised from cyclohexane, mp 95–96 °C. ν/cm^{-1} 3620, 3580, 2840, 1600, 1450, 1380, 1140, 1090, 905; δ_H(100 MHz, $CDCl_3$) 2.25 (t, *J* 6.5, 1H, disappears on D_2O shake), 3.78 (d, *J* 6.5, 2H), 4.03 (d, *J* 12, 2H), 4.29 (d, *J* 12, 2H), 5.51 (s, 1H), 7.48 (m, 5H); δ_C(25.18 MHz, $CDCl_3$) 64.5, 65.9, 73.4, 101.4, 126.2, 128.2, 129.2, 137.1; *m*/*z* 274.009 (calc. for $C_{11}H_{13}O_3{}^{79}Br^+$: 274.003).

(*Z*)-5-Acetoxymethyl-5-bromo-2-phenyl-1,3-dioxane, 7. Slow crystallising material. ν/cm^{-1} 2850, 2760, 1750, 1605, 1455; δ_H(100 MHz, $CDCl_3$) 1.17 (s, 3H), 4.088 (d, *J* 12, 2H), 4.257 (d, *J* 12, 2H), 4.40 (s, 2H), 5.53 (s, 1H), 7.48 (m, 5H).

(*Z*)-5-Bromo-5-bromomethyl-2-phenyl-1,3-dioxane, 9. Slow crystallising material. ν/cm^{-1} 2860, 1604, 1453, 1390, 1105, 980, 910; δ_H(100 MHz, $CDCl_3$) 3.81(s, 2H), 4.24 (s, 4H), 5.53 (s, 1H), 7.43 (m, 5H); (C_6D_6) 3.30 (s, 2H), 3.643 (d, *J* 12.5, 2H), 3.84 (d, *J* 12.5, 2H), 7.125 (s, 1H), 7.19 (m, 3H), 7.6 (m, 2H); δ_C(25.18 MHz, $CDCl_3$) 34.8, 59.4, 74.5, 101.6, 126.0, 128.5, 129.4, 137.0, *m*/*z* 333–338 (M^+).

Treatment of (*Z*)-5-bromo-5-hydroxymethyl-2-phenyl-1,3-dioxane, 6, with methanolic potassium hydroxide

Bromohydrin **6** (214 mg, 0.784 mmol) was dissolved in methanol (2 ml) and a solution (0.82 M) of potassium hydroxide in methanol (1.85 ml) was added. After 7 days the solvent was removed under reduced pressure and the residue taken up in diethyl ether. This was washed (H_2O), dried and filtered. Evaporation of the solvent afforded material from which the *exo*-epoxide **31**[1] could be isolated by preparative TLC (silica, 90:10 $CHCl_3$–EtOAc). No *endo*-epoxide could be detected.

Addition of hypobromous acid to 1-*tert*-butyl-4-methylenecyclohexane

1-*tert*-Butyl-4-methylenecyclohexane, **2**, (168 mg, 1.1 mmol) and *N*-bromoacetamide (0.69 g, 5 mmol) were added, with stirring, to a mixture of sodium acetate (0.625 g, 7.6 mmol) in 30:70 water–*tert*-butyl alcohol. The reaction was left in the dark for 48 h. The organic solvent was evaporated off under reduced pressure and the residue extracted with diethyl ether. The combined extracts were washed (1 M NaOH, H_2O), dried, filtered and the solvent evaporated under reduced pressure to afford primarily a single compound (200 mg) by NMR spectroscopy. Preparative TLC (silica, $CHCl_3$) yielded a colourless crystalline solid (130 mg, 47%).

(*E*)-4-*tert*-Butyl-1-bromomethylcyclohexan-1-ol, 14. Recrystallised from hexane, mp 71–71 °C. ν/cm^{-1} 3570, 2950, 2870, 1600, 1450, 1365, 1050, 950; δ_H(100 MHz, $CDCl_3$) 0.89 (s, 9H), 1.0–2.0 (m, 9H), 2.15 (br s, 1H, disappears on D_2O shake), 3.33 (s, 2H).

Addition of hypobromous acid to 3-methoxy-2-methoxymethylprop-1-ene

3-Methoxy-2-methoxymethylprop-1-ene, **3**, (780 mg, 6.7 mmol) and *N*-bromoacetamide (2.74 g, 19.9 mmol) were added, with stirring, to a mixture of sodium acetate (3.7 g, 45 mmol) in 30:70 water–*tert*-butyl alcohol. The reaction was left in the dark for 1 h. The bulk of the organic solvent was evaporated off under reduced pressure and the residue extracted with diethyl ether. The combined extracts were washed (1 M NaOH, H_2O), dried, filtered and the solvent was removed under reduced pressure to afford an oil (0.90 g, 63%). Flash chromatography (silica, CH_2Cl_2–$CHCl_3$) afforded the two predominant constituents.

2-Bromomethyl-1,3-dimethoxypropan-2-ol, 12. ν/cm^{-1} 3550, 2930, 1447, 1111, 972; δ_H(100 MHz, $CDCl_3$) 2.90 (br s, 1H), 3.41 (s, 6H), 3.47 (s, 4H), 3.52 (s, 2H); δ_C(25.18 MHz, $CDCl_3$) 36.2, 59.5, 73.1, 73.9; *m*/*z* (CI with isobutane) 213.0177, 215.0146 (calc. for $C_6H_{13}{}^{79}BrO_3{}^+$ + H: 213.0127; for $C_6H_{13}{}^{81}BrO_3{}^+$ + H: 215.0106).

2-Bromo-3-methoxy-2-methoxymethylpropan-1-ol, 13. ν/cm^{-1} 3300 (br), 2920, 1110; δ_H(100 MHz, $CDCl_3$) 2.90 (1H, br s), 3.40 (8H, s), 3.73 (2H, s); δ_C(25.18 MHz, $CDCl_3$) 59.5, 66.9, 69.4, 75.3; *m*/*z* (CI with isobutane) 213.0125 (calc. for $C_6H_{13}{}^{79}BrO_3{}^+$ + H: 213.0127).

Addition of hypoiodous acid to 5-methylene-2-phenyl-1,3-dioxane

5-Methylene-2-phenyl-1,3-dioxane, **1**, (862 mg, 4.9 mmol) and *N*-iodosuccinimide (3.38 g, 21.3 mmol) were added, with stir-

ring, to a mixture of sodium acetate (3.64 g, 44 mmol) in 50:50 water–*tert*-butyl alcohol (100 ml). The reaction was left in the dark for 5 days. The organic solvent was evaporated off under reduced pressure in a foil enclosed flask. The aqueous residue was saturated with potassium carbonate and extracted with diethyl ether. The combined extracts were washed (0.2 M $Na_2S_2O_3$, H_2O), dried, filtered and the solvent evaporated under reduced pressure; to afford a brown oil (934 mg). This was separated by flash column chromatography, (CH_2Cl_2–$CHCl_3$–EtOAc gradient); into three components: (*Z*)-5-iodo-5-iodomethyl-2-phenyl-1,3-dioxane (93 mg), (*Z*)-5-acetoxymethyl-5-iodo-2-phenyl-1,3-dioxane (268 mg) and (*Z*)-5-iodo-5-hydroxymethyl-2-phenyl-1,3-dioxane (377 mg).

(*Z*)-5-Iodo-5-hydroxymethyl-2-phenyl-1,3-dioxane, 8. Recrystallised as colourless needles from cyclohexane. ν/cm^{-1} 3560, 2870, 1455, 1000, 700; δ_H(100 MHz, $CDCl_3$) 2.25 (t, *J* 7, 1H, disappears on D_2O shake), 3.72 (d, *J* 7, 2H), 3.75 (d, *J* 13, 2H), 4.29 (d, *J* 13, 2H), 5.48 (s, 1H), 7.45 (m, 5H); δ_C(25.18 MHz, $CDCl_3$) 52.3, 68.0, 75.9, 102.1, 126.6, 128.5, 129.4, 137.3; *m*/*z* 320 (M^+).

(*Z*)-5-Acetoxymethyl-5-iodo-2-phenyl-1,3-dioxane, 10. ν/cm^{-1} 3000, 1710, 1600, 1270, 1040; δ_H(60 MHz, $CDCl_3$) 3.9 (d, *J* 13, 2H), 4.3 (d, *J* 13, 2H), 4.45 (s, 2H), 5.5 (s, 1H), 7.5 (m, 5H).

(*Z*)-5-Iodo-5-iodomethyl-2-phenyl-1,3-dioxane, 11. Obtained as an oil that coloured violet on standing, too unstable to characterize with certainty; δ_H(60 MHz, $CDCl_3$) 4.2 (s, 2H), 4.5 (s, 4H), 5.6 (s, 1H), 7.4 (s, 5H).

Treatment of crude hypoiodous acid adduct of 5-methylene-2-phenyl-1,3-dioxane with methanolic potassium hydroxide

Crude product from the previous reaction (174 mg) was dissolved in methanol (5 ml). A solution of methanolic potassium hydroxide was added (8 ml, 0.27 M) and the mixture stirred for 2 days. The solvent was evaporated off and the residue taken up in diethyl ether. The diethyl ether extracts were washed (H_2O), dried, filtered and the solvent removed under reduced pressure to afford an oil (92 mg, 96%) that consisted of two components, separable by preparative TLC. One was *exo*-epoxide **31**, the other had spectral properties consistent with it being the ring opened product of methoxide attack on **31**. No *endo*-epoxide was found.

Addition of hypoiodous acid to 1-*tert*-butyl-4-methylenecyclohexane

1-*tert*-Butyl-4-methylenecyclohexane, **2** (0.50 g, 3.25 mmol), and sodium bicarbonate (3.125 g) were dissolved in 50:50 water–*tert*-butyl alcohol. *N*-iodosuccinimide (3.75 g, 16.7 mmol) was added and the mixture stirred for 15 min. The bulk of the organic solvent was evaporated off under reduced pressure in a foil enclosed flask. The residue was taken up in diethyl ether and washed (0.2 M $Na_2S_2O_3$, H_2O) and the washings back extracted. The diethyl ether extracts were combined and the solvent removed under reduced pressure to yield an oil (608 mg, 63%). This was separated by flash column chromatography [silica, 10:90 diethyl ether–light petroleum (bp 40–60 °C)] into two major fractions. The first fraction (219 mg) largely consisted of epoxides formed *in situ* by base catalysed ring closure of the initially formed iodohydrins. The second fraction (152 mg) was identified as iodohydrin **16**, (*E*)-4-*tert*-butyl-1-iodomethylcyclohexan-1-ol. Unidentified by-products (95 mg) were also isolated.

The reaction was repeated using sodium acetate instead of sodium bicarbonate as buffer. This led to the isolation of two major fractions, one **16**, the other iodoacetate (*Z*)-1-acetoxy-4-*tert*-butyl-1-iodomethylcyclohexane, **18**.

(*E*)-4-*tert*-Butyl-1-iodomethylcyclohexan-1-ol, 16. Recrystallised from hexane, mp 99.5–100.5 °C (dec) (Found: C, 45.7; H, 7.35; I, 41.7. $C_{11}H_{21}IO$ requires: C, 44.6; H, 7.15; I, 42.8%); ν/cm^{-1} 3560, 2910, 2870, 1455, 1368, 1190, 1038; δ_H(100 MHz, $CDCl_3$) 0.88 (s, 9H), 1.3–1.9 (m, 6H), 1.96 (m, 3H), 2.64 (s, 1H), 3.50 (s, 2H); δ_C(25.18 MHz, $CDCl_3$) 23.8, 24.5, 27.6, 32.2, 37.5, 47.5, 69.9; *m*/*z* 278 ($M^+ - 17$).

(*Z*)-1-Acetoxy-4-*tert*-butyl-1-iodomethylcyclohexane, 18. ν/cm^{-1} 2960, 1731, 1370, 1254, 1022; δ_H(60 MHz, $CDCl_3$) 0.8 (s, 9H), 1.0–2.0 (m, 7H), 2.0 (s, 3H), 2.5 (m, 2H), 3.9 (s, 2H).

Treatment of crude hypoiodous acid adduct of 1-*tert*-butyl-4-methylenecyclohexane with methanolic sodium hydroxide

Crude product from the previous reaction (55 mg) was dissolved in methanol (6 ml) containing sodium hydroxide (60 mg) and the mixture stirred for 3 h. Solvent was evaporated off and the residue taken up in diethyl ether. This was washed, dried, filtered and the diethyl ether removed to yield an oil (20 mg, 70%) consisting of *exo*-and *endo*-epoxides **35** and **36** in the ratio 84:16. The spectral data were identical with those previously reported;[4] δ_H(100 MHz, $CDCl_3$) of epoxide mixture 0.9 (s, 9H), 1.2–2.2 (m, 9H), 2.40 (s, 1.6H), 2.46 (s, 0.4H). Repetition of this process with pure iodohydrin **16** afforded solely epoxide **35**.

Bromination of model compounds: general procedure

A solution of bromine (0.95 equiv. Br_2 w.r.t. olefin) in carbon tetrachloride, or benzene, was gradually added to a stirred solution of the alkene in the dark under nitrogen, with or without co-reagents. When the solution had almost completely decolourised, it was washed (sat. $NaHCO_3$, $Na_2S_2O_3$, H_2O), dried, filtered and the solvent evaporated under reduced pressure to give crude product mixture.

Bromination of 5-methylene-2-phenyl-1,3-dioxane in carbon tetrachloride without propylene oxide

Compound **1** (1.035 g, 5.9 mmol), and bromine [19.1 ml of 0.273 M soln. in CCl_4, (5.214 mmol)] were reacted together as above in carbon tetrachloride (50 ml). The reaction took 1 h and, after work up, yielded a brown oil (1.783 g, 90%). Separation using flash column chromatography (silica, toluene–$CHCl_3$) gave two isomeric fractions; the major: (*E*)-5-bromo-5-bromomethyl-2-phenyl-1,3-dioxane, **20**, and the minor: (*Z*)-5-bromo-5-bromomethyl-2-phenyl-1,3-dioxane, **9**, previously described. Small quantities of decomposition products, including benzaldehyde, were also obtained.

(*E*)-5-Bromo-5-bromomethyl-2-phenyl-1,3-dioxane, 20. Recrystallised from cyclohexane–hexane, mp 42.5–43.5 °C. (Found: C, 39.1; H, 3.55; Br, 47.7. $C_{11}H_{12}Br_2O_2$ requires: C, 39.3; H, 3.60; Br, 47.6%); ν/cm^{-1} 2870, 1600, 1450, 1390, 1100, 1020, 980, 930; δ_H(100 MHz, $CDCl_3$) 4.165 (2H, s), 4.18 (d, *J* 10.25, 2H), 4.40 (d, *J* 10.25, 2H), 5.46 (s, 1H), 7.58 (m, 5H); δ_C(25.18 MHz, $CDCl_3$) 38.7, 57.2, 74.1, 102.2, 125.9, 128.3, 129.3, 136.7.

Bromination of 5-methylene-2-phenyl-1,3-dioxane in carbon tetrachloride with propylene oxide

Compound **1** (107 mg, 0.61 mmol), propylene oxide (53 mg) and bromine were reacted together as above in carbon tetrachloride (35 ml). Work up afforded the *Z* dibromide, **9** (162 mg, 79%) only.

Bromination of 5-methylene-2-phenyl-1,3-dioxane in acetonitrile with propylene oxide

Compound **1** (110 mg, 0.62 mmol), propylene oxide (53 mg) and bromine [Br_2 soln. in benzene (0.6 ml, 0.95 equiv.)] were reacted together in acetonitrile (2 ml). Work up afforded an oil (160 mg) that was estimated, by ^{1}H NMR spectroscopy, to contain **9** (68%), unreacted starting material (18%) and unidentified material (14%) (possibly Ritter type adducts).

Bromination of 5-methylene-2-phenyl-1,3-dioxane in acetonitrile with propylene oxide and methylene blue

Compound **1** (103 mg, 0.585 mmol), propylene oxide (50 mg),

methylene blue (10 mg) and bromine (0.95 equiv.) were reacted together in acetonitrile (2 ml) for 3 h. Evaporation of the solvent afforded an oil that was examined by ^{1}H NMR spectroscopy. Only one dibromide, **9**, was identified as being present, along with unreacted starting material.

Bromination of 1-*tert*-butyl-4-methylenecyclohexane

Compound **2** (0.9 g, 6.2 mmol) and bromine (20.1 ml of a 0.273 M soln. in CCl_4) were reacted together as above in carbon tetrachloride (50 ml). After 18 h, the reaction was worked up to afford an oil (1.9 g) which was separated by flash column chromatography [silica, light petroleum (bp 60–80 °C)] to afford the dibromides (*Z*)- and (*E*)-1-bromo-1-bromomethyl-4-*tert*-butylcyclohexane **27** and **28**. Repetition of the experiment with propylene oxide (50 mg) present made no difference to the final isomer ratio.

(*Z*)-1-Bromo-1-bromomethyl-4-*tert*-butylcyclohexane, 27. Colourless oil. ν/cm^{-1} 2980, 1440, 1366, 1222, 1091, 845, 788, 668, 626, 603; δ_H(100 MHz, $CDCl_3$) 0.93 (s, 9H), 1.5–2.0 (m, 9H), 3.94 (s, 2H); δ_C(25.18 MHz, $CDCl_3$) 23.8, 27.5, 32.4, 38.4, 44.4, 46.4, 72.5.

(*E*)-1-Bromo-1-bromomethyl-4-*tert*-butylcyclohexane, 28. Colourless oil. ν/cm^{-1} 2980, 1450, 1365, 1010, 895, 685; δ_H(100 MHz, $CDCl_3$) 0.88 (s, 9H), 1.0–2.6 (m, 9H), 3.90 (s, 2H); δ_C(25.18 MHz, $CDCl_3$) 25.2, 27.4, 32.3, 41.2, 41.9, 46.8, 67.4; *m*/*z* 311 ($M^+ - H$), 231 ($M^+ - Br$).

Iodochlorination of model compounds: general procedure

A solution of iodine monochloride in carbon tetrachloride (1.0 equivs. ICl w.r.t. olefin) was added to a stirred solution of the unsaturated substrate in the dark under nitrogen, with or without co-reagents. The solution generally changed colour from brown to violet over the space of 1 h. It was washed (0.2 M $Na_2S_2O_3$, H_2O), dried, filtered and the solvent evaporated under reduced pressure to give crude product mixture.

Iodochlorination of 5-methylene-2-phenyl-1,3-dioxane in carbon tetrachloride without propylene oxide

1 (1.00 g, 5.68 mmol) and iodine monochloride (1 equiv.) were reacted together in carbon tetrachloride (70 ml) as above for 40 min yielding an oily material (1.7 g, 88%). Flash column chromatography [silica, light petroleum (bp 60–80 °C)–diethyl ether] afforded four fractions. The first fraction (1.00 g of an oil) was identified as a mixture of the adducts (*E*)-5-chloro-5-iodomethyl-2-phenyl-1,3-dioxane, **22**, and (*E*)-5-chloromethyl-5-iodo-2-phenyl-1,3-dioxane, **24**. The second fraction (0.2 g) consisted largely of benzaldehyde. The third (40 mg of yellow crystals) and the fourth (87 mg) were identified as (*Z*)-5-chloromethyl-5-iodo-2-phenyl-1,3-dioxane, **23** and (*Z*)-5-chloro-5-iodomethyl-2-phenyl-1,3-dioxane, **21**.

(*Z*)-5-Chloro-5-iodomethyl-2-phenyl-1,3-dioxane, 21. δ_H(100 MHz, $CDCl_3$) 3.46 (s, 2H), 4.17 (s, 4H), 5.48 (s, 1H), 7.4 (m, 5H); δ_C(25.18 MHz, $CDCl_3$) 8.3, 62.6, 75.2, 101.6, 126.4, 128.5, 129.4, 136.9; *m*/*z* 337–340 (M^+).

(*E*)-5-Chloro-5-iodomethyl-2-phenyl-1,3-dioxane, 22. δ_H(100 MHz, $CDCl_3$) 3.87 (s, 2H), 3.91 (d, *J* 10.5, 2H), 4.26 (d, *J* 10.5, 2H), 5.32 (s, 1H), 7.3 (m, 5H); δ_C(25.18 MHz, $CDCl_3$) 13.8, 60.4, 74.1, 101.8, 125.7, 128.1, 129.0, 136.5; *m*/*z* 337–340 (M^+).

(*Z*)-5-Chloromethyl-5-iodo-2-phenyl-1,3-dioxane, 23. ν/cm^{-1} 3015, 2865, 1462, 1271, 1173, 1110, 995, 706; δ_H(100 MHz, $CDCl_3$) 4.05 (d, *J* 12, 2H), 4.09 (s, 2H), 4.24 (d, *J* 12, 2H), 5.52 (s, 1H), 7.4 (m, 5H); δ_C(25.18 MHz, $CDCl_3$) 45.3, 49.4, 75.8, 101.9, 128.5, 129.4, 137.1; *m*/*z* 337.97 (calc. for $C_{11}H_{12}{}^{35}ClIO_2^+$: 337.96).

(*E*)-5-Chloromethyl-5-iodo-2-phenyl-1,3-dioxane, 24. δ_H(100 MHz, $CDCl_3$) 4.12 (s, 2H), 4.25 (d, *J* 11, 2H), 4.38 (d, *J* 11, 2H), 5.43 (s, 1H), 7.3 (m, 5H); δ_C(25.18 MHz, $CDCl_3$) 44.2, 50.8, 75.0, 101.8, 125.7, 128.1, 129.0, 136.7; *m*/*z* 339.95, 337.96 (calc. for $C_{11}H_{12}{}^{37}ClIO_2^+$: 339.95, and for $C_{11}H_{12}{}^{35}ClIO_2^+$: 337.96).

Iodochlorination of 5-methylene-2-phenyl-1,3-dioxane in carbon tetrachloride with propylene oxide

Compound **1** (115 mg, 0.65 mmol) and iodine monochloride (0.77 mmol) were reacted together in carbon tetrachloride (10 ml) with propylene oxide added (20 mg) and gave iodochloride **23** only (>91%). No decomposition products were noted.

Iodochlorination of 1-*tert*-butyl-4-methylenecyclohexane

Compound **2** (0.337 g, 2.19 mmol) and iodine monochloride [2.19 mmol in CCl_4 (11 ml)] were reacted together for 10 min. Work up yielded an oil (548 mg, 80%). The two predominant products were separated using flash column chromatography to afford two unstable oils identified as 1-chloro-1-iodomethyl-4-*tert*-butylcyclohexane, **29**, and 1-chloro-1-chloromethyl-4-*tert*-butylcyclohexane, **30**. Repetition of the experiment with the addition of propylene oxide (75 mg) gave an identical yield and product ratio.

1-Chloro-1-iodomethyl-4-*tert*-butylcyclohexane, 29. ν/cm^{-1} 2860, 1480, 1374, 1098, 1017, 888; δ_H(100 MHz, $CDCl_3$) 0.89 (s, 9H), 1.2 (m, 5H), 1.7 (m, 2H), 2.3 (m, 2H), 3.70 (s, 2H); δ_C(25.18 MHz, $CDCl_3$) 17.5, 24.8, 27.5, 32.2, 40.7, 46.9, 70.0; *m*/*z* 187 ($M^+ - I$).

1-Chloro-1-chloromethyl-4-*tert*-butylcyclohexane, 30. ν/cm^{-1} 2960, 1448, 1373, 1098, 983, 690, 618; δ_H(100 MHz, $CDCl_3$) 0.89 (s, 9H), 1.2 (m, 5H), 1.5 (m, 4H), 1.9 (m, 4H), 4.175 (s, 2H); δ_C(25.18 MHz, $CDCl_3$) 27.2, 27.5, 32.3, 39.7, 46.9, 57.4, 62.0.

Iodochlorination of 3-methoxy-2-methoxymethylprop-1-ene

Iodochlorination of **3** (0.31 g, 2.58 mmol) with ICl (0.95 equiv.) in CCl_4 (20 ml) for 80 min yielded, after work up, an oil (600 mg, 84%). The two predominant components were separated by flash column chromatography (silica, CH_2Cl_2–CCl_4) to afford 2-chloro-2-iodomethyl-1,3-dimethoxypropane, **25**, and 2-chloromethyl-1,3-dimethoxy-2-iodopropane, **26**, as colourless oils. Repetition of the experiment with propylene oxide (150 mg) added made no difference to the final isomer ratio.

2-Chloro-2-iodomethyl-1,3-dimethoxypropane, 25. ν/cm^{-1} 2995, 2925, 2895, 2720, 1452, 1111; δ_H(100 MHz, $CDCl_3$) 3.45 (s, 6H), 3.64 (s, 2H), 3.68 (s, 4H); δ_C(25.18 MHz, $CDCl_3$) 10.7, 59.5, 69.6, 75.7; *m*/*z* (CI with isobutane) 278.968 (calc. for $C_6H_{12}{}^{35}ClIO_3^+$: 278.965).

2-Chloromethyl-1,3-dimethoxy-2-iodopropane, 26. ν/cm^{-1} 3000, 2930, 2895, 2735, 1467, 1450, 1114, 700; δ_H(100 MHz, $CDCl_3$) 3.46 (s, 6H), 3.60 (s, 2H), 3.99 (s, 2H); δ_C(25.18 MHz, $CDCl_3$) 49.5, 52.1, 59.3, 76.4; *m*/*z* (CI with NH_3) 279 ($M^+ - 1$).

Acknowledgements

I am heavily indebted to Dr Ian D. R. Stevens of the Department of Chemistry, The University of Southampton, for the major part he played in the preparation of this manuscript and for the helpful guidance he was able to give. This he did gladly for the sake of the memory of my supervisor, his good friend and greatly missed colleague Dr John Hudec. Very sadly Ian died suddenly shortly before this manuscript went to press. We thank the SERC for the award of a maintenance grant (J. W. L.).

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Paper 8/01001C
Received 4*th February* 1998
Accepted 13*th February* 1998