Initiated *tert*-Butyl Hydroperoxide-loaded Low-temperature Autoxidation of Alkenes: Alternative Hydroperoxide Syntheses and the Preparation of a Complete Set of Reference Materials[1]

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A complete set of characterization data for the allylic hydroperoxides prepared from 1-methylcyclohexene and the isomeric 4-methyloct-4-enes is presented. The data relies upon the preparation of allylic hydroperoxides by *tert*-butyl hydroperoxide-loaded autoxidations, singlet-ene oxidations and nucleophilic substitution reactions. Appropriate allylic alcohols and relevant scission products have been prepared to support the assignments given.

In the preceding paper[1b] a novel chemoselective method for controlling the autoxidation of simple alkenes to provide allylic hydroperoxides was presented. Here are provided details of both supporting synthetic studies and of some alternative allylic hydroperoxide syntheses.

Results

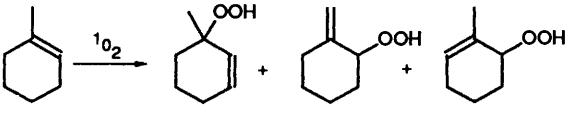
(*a*) *Preparation, Separation and Analysis of Allylic Hydroperoxides.*—(i) *Singlet oxygenation.* Singlet oxygenation of alkenes is presently the most versatile method for clean allylic hydroperoxide preparation.[2] Among the non-photochemical routes to singlet oxygen, we initially used the decomposition of the triphenyl phosphite–ozone complex at subambient temperatures,[3] but this reaction in the presence of 1-methylcyclohexene gave crude alkene-derived products which contained only a small quantity (^{1}H NMR evidence) of at least eight hydroperoxides none of which could be isolated as pure materials.

Photosensitized singlet-oxygenation was then performed using different sensitizers in different solvents. By far the most successful procedure was the photolysis, in an immersion-well photoreactor, of alkenes in dichloromethane (*ca.* 200 cm^3 of 0.2–0.25 mol dm^{-3} solutions) containing 5,10,15,20-tetraphenyl-21*H*,23*H*-porphin (TPP) and protective 2,6-di-*tert*-butyl-4-methylphenol (BHT). As expected, conversion of trisubstituted alkenes was rapid. For 1-methylcyclohexene, for example, the oxygen uptake was typically 1490 cm^3 h^{-1}: analysis of the resultant crude hydroperoxidic product, by 400 MHz ^{1}H NMR spectroscopy, gave a product ratio consistent with the alcohol ratios determined by other workers after reduction of their photolysates (Table 1).

The included BHT perhaps affords some protection in purification of the hydroperoxides during distillation, and it seemed to protect the alkene from competitive autoxidation or the product hydroperoxides from rearrangement during photolysis (judged by the absence of 3-methylcyclohex-2-enyl hydroperoxide, **6** in this product mixture). Flash chromatography allowed isolation of individual hydroperoxides, whose identities were determined both by highfield NMR spectroscopy and by individual reduction to the corresponding allylic alcohols.

Methylenecyclohexane, was, expectedly, a poorer singlet oxygen acceptor.[4] In this instance, extended photolysis was required to obtain a modest level of conversion (uptake rate typically 66 cm^3 h^{-1}), but this regime resulted in isolation, from a host of materials typical of competitive autoxidation/rearrangement and/or photolytic decomposition, eqn. (1), a sample of 1-formylcyclohexene **5** and a mixture of cyclohex-1-enylmethyl hydroperoxide **4** and 2-methylenecyclohexyl hydroperoxide **2**.

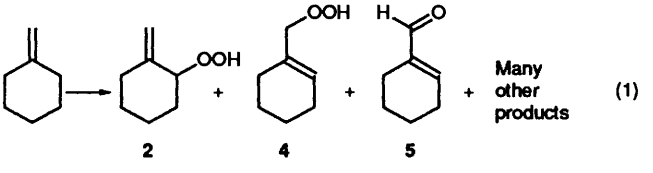
Table 1 Product ratios for singlet oxygenations of 1-methylcyclohexene



	1	2	3
This work (TPP, CH_2Cl_2)	41	43	16
Ref. 4 (RB, MeOH)	36	44	20
Ref. *a* (MB, Pr^{i}OH)	40	45	15
Ref. *b* (MB, MeCN)	45.2	42.6	12.2

RB = Rose Bengal; MB = Methylene Blue.

[a] G. O. Schenk, H. Eggert and W. Denk, *Ann*, 1953, **584**, 177; G. O. Schenk, *Angew. Chem.*, 1952, **64**, 12; K. Gollnick, *Advan. Chem. Ser.*, 1968, **77**, 78. [b] C. W. Jefford and C. G. Rimbault, *Tetrahedron Lett.*, 1981, **22**, 91.

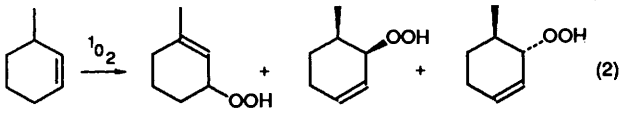


(1)

3-Methylcyclohexene was also a rather poor acceptor (uptake rate typically 129 cm^3 h^{-1}). Photolysis for 4 h (*ca.* 30% conversion) gave a product containing four hydroperoxides. By chromatographic separation and recrystallisation the most mobile of these was found to be 2,6-di-*tert*-butyl-4-hydroperoxy-4-methylcyclohexa-2,5-dienone. This compound, readily prepared[5] by basic autoxidation of BHT, has been shown to be formed[6] during the reaction of BHT as a singlet oxygen acceptor when in the presence of a weakly reacting substrate.

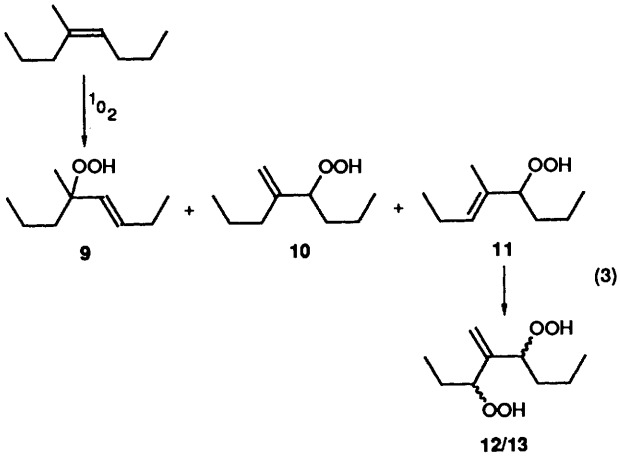
The more polar hydroperoxides could be separated by repetitive chromatography. Although outside the area of interest of this work, we tentatively use ^{1}H NMR data to ascribe to the two epimeric hydroperoxides **7** and **8** the configurations shown in eqn. (2).

The photosensitized method of choice was also applied to an acyclic trisubstituted substrate, *cis*-4-methyloct-4-ene.[7] The reaction was complicated by the fact that, at appreciable substrate conversions, the minor product **11** underwent competitive reaction to provide a mixture of diastereoisomeric bishydroperoxides **12**/**13** [eqn. (3)]. The two major allylic



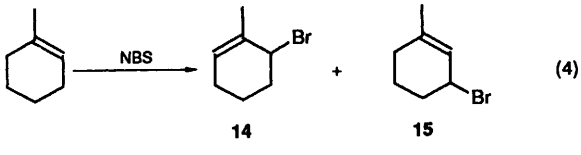
	6	7	8
Mol %	25	25	16

hydroperoxides could, however, be readily separated by a sequence of Kugelrohr distillation and flash liquid chromatography in collected isolated yields of 50–60%.



(ii) *Perhydrolysis of allylic halides and mesylates.* Silver(I) salt-assisted perhydrolysis of alkyl bromides and iodides is a useful route to alkyl hydroperoxides[8] which has found only little use in the preparation of allylic hydroperoxides.[9]

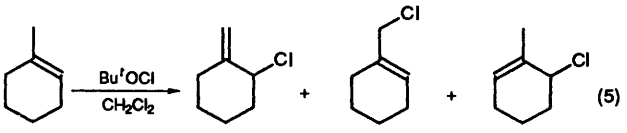
Allylic bromination of 1-methylcyclohexene using *N*-bromosuccinimide (NBS)[10] has been reported[10b] to give an almost equimolar mixture of two secondary bromides [**14** and **15**: eqn. (4)]: a photostimulated reaction is the method of choice for this conversion. This apparent ratio of bromides varied somewhat



according to the method of analysis. A sample, which was stabilised with added BHT after reaction, was concentrated by rotary evaporation at room temperature to give a pungent yellow oil which, by ^{1}H NMR analysis was richer in the isomer **15** (3:1 ratio, relying on the data of Bottini *et al.*[10b]). However, direct ^{1}H NMR analysis of the filtered and BHT-stabilised reaction mixture at the end of a duplicate reaction indicated the presence of an almost equimolar mixture of unchanged alkene and the two bromides **14** and **15**.

The instability of the bromide mixture could be retarded by storage over BHT and solid sodium hydrogen carbonate.[11] GLC and normal phase HPLC failed to indicate a method for isomer separation and so the allylic bromides were used as the crude mixture in subsequent reactions.

Allylic chlorides might be expected to be less labile than the corresponding bromides and, accordingly, we examined the reaction of 1-methylcyclohexene with *tert*-butyl hypochlorite [equation (5)]. The photostimulated reaction produced small amounts of what appeared to be dichlorinated products (GLC evidence), whilst silica-gel catalysed reactions produced cleaner monochlorides. The *exo*-methylene chloride **16** initially formed seemed to undergo thermal rearrangement to form isomer **17** during GLC analysis: the three individual chlorides, **16–18**, could be obtained by preparative GLC and their identities determined by highfield ^{1}H NMR along with individual hydrolysis to known allylic alcohols.

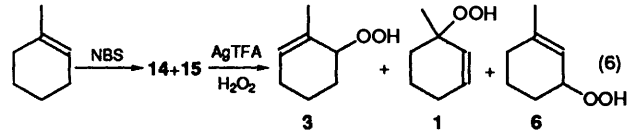


		16	17	18
Photostimulated	*a*	32	0	68
Silica gel	*a*	39	0	61
catalysed	*b*	33	10	55

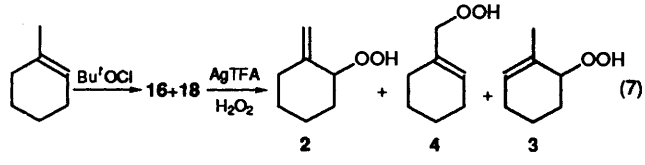
Analysis: *a*, ^{1}H NMR; *b*, GLC (see text)

Bearing in mind the sensitivity of the allylic bromides to apparent acid-induced decomposition, silver(I) oxide was considered as a suitable reagent for assisting their perhydrolysis, since this material has found some success[12] in intramolecular reactions. However, freshly prepared, well-washed silver(I) oxide, when added to a bromide–hydrogen peroxide mixture resulted in rapid hydrogen peroxide decomposition.

Use of silver(I) trifluoroacetate was somewhat more encouraging [eqn. (6)]. The yield of recovered hydroperoxides was, however, poor. One cause might be extensive elimination (*cf.* the perhydrolysis, using *tert*-butyl hydroperoxide, of bromocyclohexane[13]) and the detected occurrence of competitive allylic trifluoroacetate formation. Careful chromatography provided a pure sample of 2-methylcyclohex-2-enyl hydroperoxide **3** but the two other slightly more polar isomers were chromatographically inseparable.



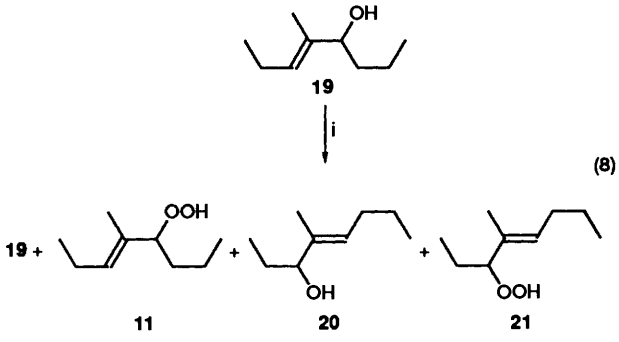
Since the allylic chlorination of 1-methylcyclohexene gave a different regiocollection of allylic halides, the corresponding silver(I) trifluoroacetate-mediated perhydrolysis gave a different selection of allylic hydroperoxides [eqn. (7)]. The reaction was faster and more specific for hydroperoxide formation when carried out in diethyl ether, rather than directly using the crude tetrachloromethane halogenation reaction solution, although (presumably as a result of loss of chlorides during concentration) at the expense of yield (crude yields 86 and 47% respectively).



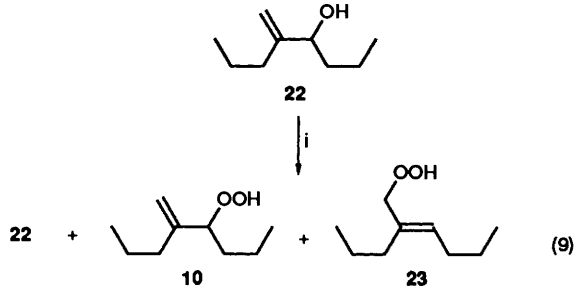
The crude product from the reaction in diethyl ether solvent, when separated by column chromatography gave, after early fractions, which appeared to contain bis-allylic peroxides, later fractions which contained, firstly, a mixture of the primary and secondary hydroperoxides (**4** and **2**) and then a sample of 2-methylcyclohex-2-enyl hydroperoxide, **3**, the three hydroperoxides appearing in almost equimolar ratio.

Displacement of sulfonate esters by alkaline hydrogen peroxide is a classical route to certain alkyl hydroperoxides, but its use for the preparation of allylic hydroperoxides is somewhat unexplored. Guided by the work of Corey[14] and of Frankel[15] and their co-workers crude mesylates were

prepared from the alcohols **19** and **22** and these materials were allowed to react with concentrated hydrogen peroxide in the presence of a small excess of triethylamine [eqns. (8) and (9)].



Reagents: i, sequentially $MeSO_2Cl$, Et_3N, H_2O_2

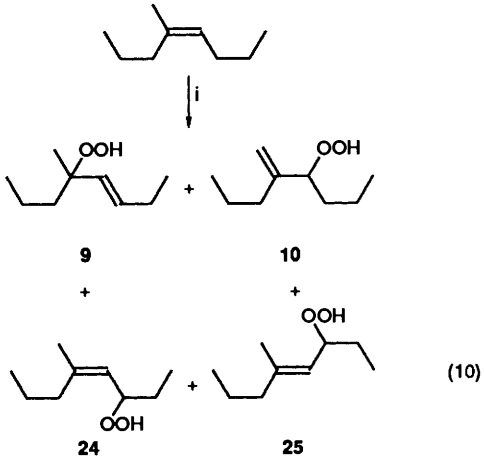


Reagents: i, as eqn. (8)

In each case only small amounts of the desired allylic hydroperoxides were formed and even then as mixtures. Chromatographic separation, however, allowed isolation and identification of these isomers and, by triphenylphosphine reduction, correlation to independently prepared allylic alcohols.

(b) *Synthesis of Reference Materials required for* 4-*Methyl-oct-4-ene Oxidation Studies.*—Apart from hydroperoxide isomers **24** and **25** isolated (along with **9** and **10**) from the *tert*-butyl hydroperoxide loaded autoxidation of *cis*-4-methyl-oct-4-ene [eqn. (10): details in the preceding paper] all isomers were prepared by independent routes.

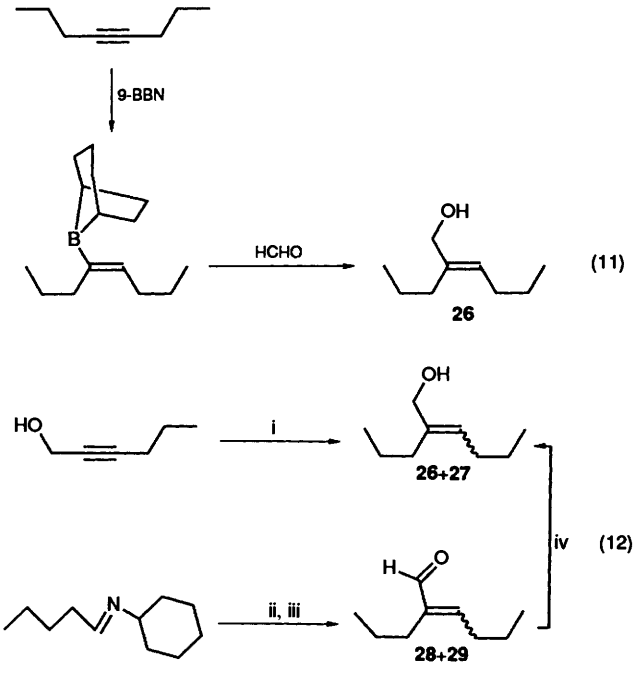
The highfield ^1H and ^{13}C NMR data for these materials are



Reagents and conditions: i, O_2, Bu^t OOH, initiator, 60 °C

available as a Supplementary publication [SUP no. 56879 (10 pp.)].* The routes chosen were those which provide data not only for the allylic alcohols, epoxides and α,β-unsaturated carbonyl compounds required for analysis of the reactions detailed in this work, but also materials which might be expected to be formed in the scission of the allylic hydroperoxides.

The two primary allylic alcohols **26** and **27** and their related α,β-unsaturated aldehydes **28** and **29** proved to be the most challenging targets encountered: the sequences giving the best data are given in eqns. (11) and (12).



Reagents: i, PrMgCl, CuI; ii, LDA; iii, PrCHO; iv, $LiAlH_4$

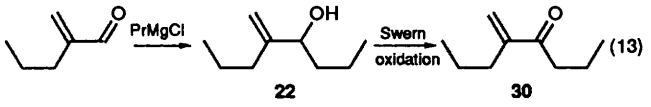
cis-Hydroboration of oct-4-yne (*cf.* work by Jacob and Brown[16]) followed by reaction with gaseous formaldehyde[17] gave, in low conversion (judged, by the isolation after the oxidative work-up, of a substantial quantity of octan-4-one) a small sample of the *trans*-alcohol **26**. The same alcohol was the principal product from the reaction shown in the upper portion of eqn. (12). Thus, by following the method described by Duboudin and Jousseaume,[18] a mixture of hex-2-yn-1-ol and copper(I) iodide in diethyl ether was treated with an excess of propylmagnesium chloride. Even after extensive reaction times, only modest conversion (*ca.* 20%) of substrate alcohol to product was achieved, but by sequential Kugelrohr distillation and flash chromatography, a sample of *trans*-alcohol **26** was obtained.

The lower part of eqn. (12) depicts an alternative route to the two primary alcohols *via* the α,β-unsaturated aldehydes **28** and **29** based upon the method of Wittig and co-workers.[19] Thus, reaction between butanal and the α-lithiated cyclohexyl imine of pentanal gave a very modest yield of the mixed α,β-unsaturated aldehydes **28** and **29**. These rather sensitive materials were characterised spectroscopically as a mixture before being reduced to a mixture of the primary allylic alcohols **26** and **27**.

The preparation of the isoallylic secondary alcohol isomer **22** was more straightforward [eqn. (13)].

Thus, 2-propylbut-2-enal (obtained by Mannich reaction of pentanal[20]) was added to ethereal propylmagnesium chloride.

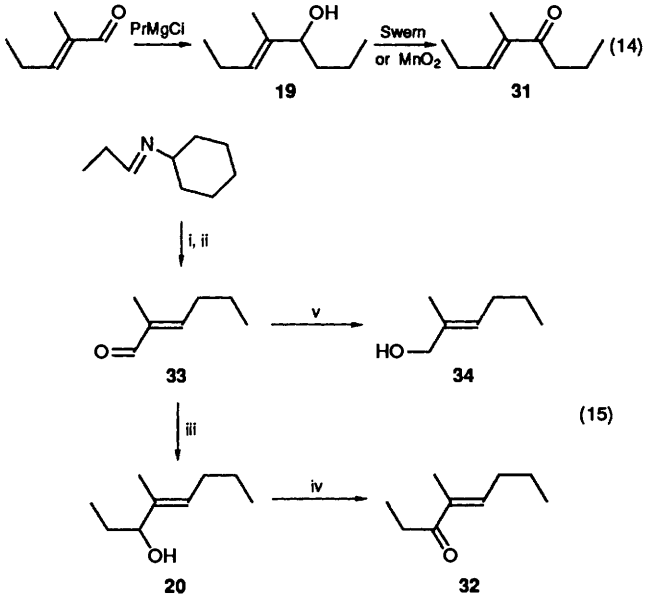
* For details of the Supplementary publications scheme, see Instructions for Authors (1992), *J. Chem. Soc., Perkin Trans. 1*, 1992, Issue 1.



(13)

Work-up gave an essentially quantitative yield of analytically pure material, a portion of which was cleanly oxidized, using the Swern procedure,[21] to the α,β-unsaturated ketone **30**.

The isoallylic set of secondary alcohols shown in eqns. (14) and (15) were prepared using similar reactions.



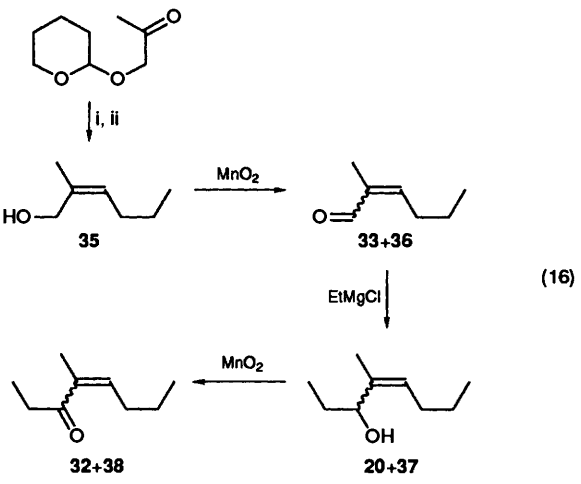
(14)
(15)

Reagents: i, LDA; ii, PrCHO; iii, EtMgCl; iv, Swern; v, $LiAlH_4$

Thus, the alcohol **19** was prepared according to a published procedure[22] as a single isomer in good yield. The oxidation step under Swern conditions, however, resulted in a low level of isomerization to give α,β-unsaturated ketone **31** contaminated with *ca.* 10% of isomer **32** (by GLC analysis of this rather volatile material after flash chromatography). Oxidation overnight at ambient temperature, of a deuteriochloroform solution of the alcohol **19** using a mixture of manganese(IV) oxide and powdered 4 Å molecular sieves resulted in cleaner oxidation to the ketone **31** (contaminated with 4% of isomer **32** and 12% of unchanged and unisomerised alcohol **19**).

trans-α,β-Unsaturated aldehyde **33** was prepared by analogy with the Wittig procedure described for **28** and **29** above: the volatile and sensitive product was most conveniently obtained in good yield by isolation of the intermediate unsaturated imine, followed by its hydrolysis (aqueous oxalic acid in the presence of protective BHT) and direct steam distillation. The spectroscopic data for the product accord with reported lowfield ^1H NMR data[23] for material prepared by a less convenient route. Simple reduction of this product gave the *trans*-allylic alcohol **34**, while treatment with ethylmagnesium chloride gave the secondary allylic alcohol **20**. Swern oxidation gave α,β-unsaturated ketone **32**, again contaminated with positional isomer **31**.

The *cis*-series of isomers was approached by the sequence shown in eqn. (16): *cis*-selective Wittig olefination of the tetrahydropyran adduct of 1-hydroxypropan-2-one[24] using the general procedure of Still[25] and of Sato[26] and their co-workers, gave the primary alcohol **35**, contaminated with only 1% of the *trans* isomer **34**, which was, in the familiar sequence, converted, using manganese(IV) oxide, into a mixture of the aldehydes **33** and **36**, and then, using ethylmagnesium chloride, to the secondary alcohols **20** and **37**.

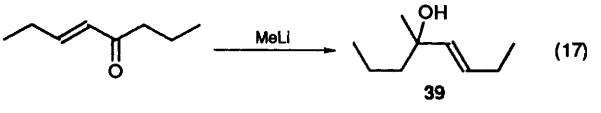


(16)

Reagents: i, KHMDS then $PrPh_3P^+Br^-$; ii, PPTS/MeOH

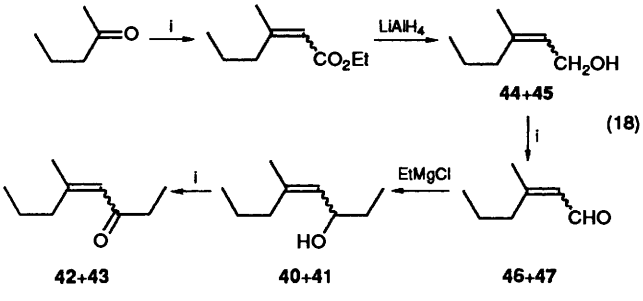
The oxidation of **35** was attended with variable amounts of isomerisation to the apparently more stable *trans* aldehyde **33**. This loss of stereocontrol was exacerbated in the final oxidation of the mixture of **20**/**37**: the initial ^1H NMR spectrum of the product enabled assignment of the signals due to *cis*-α,β-unsaturated ketone **38** to be made, but complete isomerisation to the *trans*-isomer **32** occurred during the time required for acquisition of the ^{13}C NMR spectrum. It was noteworthy, however, that isomerisation to the isoallylic *trans* isomer **31** was not detected under these oxidation conditions.

The *trans*-tertiary allylic alcohol **39** was readily prepared by the addition of *trans*-oct-5-en-4-one (available from earlier work) to an ethereal solution of methyl-lithium [eqn. (17) *cf.* of the procedures of Pearce *et al.*[27]].



(17)

The isoallylic secondary alcohols **40** and **41** and the ketones **42**/**43** were prepared using a route [eqn. (18)] *via* known[28] alcohols **44**/**45** and aldehydes **46**/**47**.



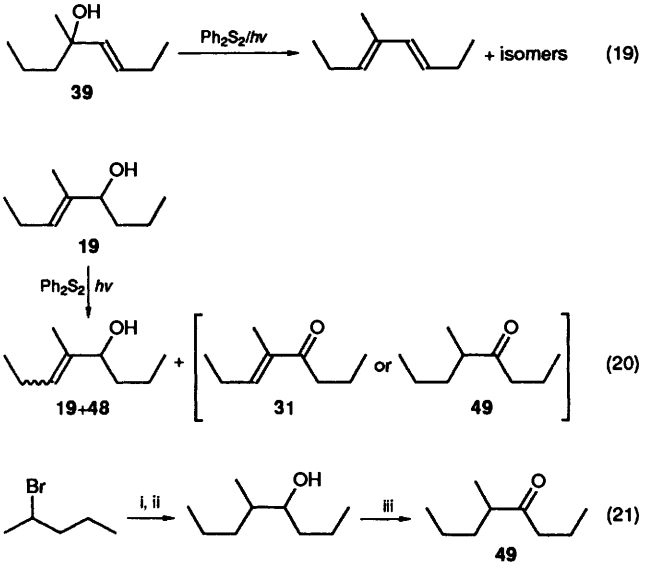
(18)

Reagents: i, see text

The initial Wadworth–Emmons olefination step gave a mixture of esters enriched in the *trans* ester (*ca.* 75%) when either the classical (sodium hydride)[29] or Masamune/Roush (LiCl/DBU)[30] routes were followed. This isomeric ratio was carried through the reduction (lithium aluminium hydride) and oxidation steps [Swern or manganese(IV) oxide or Fetizon's Reagent[28]] to **44**/**45** and **46**/**47** respectively. The mixture of these rather labile aldehydes was promptly converted into the alcohols **40**/**41** by reaction with ethylmagnesium chloride. It was noticed, however, that regardless of the care with which the work-up was performed, the product was always contaminated

with the isoallylic tertiary alcohol **39** (ratio **39**:**40**:**41** = 27:31:42). This contaminant could be removed by flash chromatography but the secondary isomers were inseparable and so were characterised spectroscopically as a mixture. The crude mixture of alcohols was oxidised using manganese(IV) oxide to give the very volatile α,β-unsaturated ketones **42** and **43**, easily removed by chromatography, as a mixture, from the unconverted tertiary alcohol **39**.

Attempts were made to isomerise the double bonds present in alcohols **19** and **39** using UV irradiation of light petroleum solutions of these substrates mixed with catalytic quantities of diphenyl disulfide: a procedure that is effective for the isomerisation of simple alkenes.[31] In both cases, other products were formed: the *tertiary* isomer **39** was dehydrated to a selection of conjugated dienes [eqn. (19)], while the secondary isomer **19** was converted in an irreproducible way into a mixture of isomeric allylic alcohols containing either some of the desired *cis*-allylic alcohol **48** and either α,β-unsaturated ketone **31** or saturated ketone **49** [eqn. (20)]. A reference sample of the latter compound was prepared[32] by addition of butanal to ice-cold pentan-2-ylmagnesium bromide followed by direct oxidation of the crude product in diethyl ether with acidified aqueous sodium dichromate[33] [eqn. (21)].



Reagents: i, Mg; ii, PrCHO; iii, $Na_2Cr_2O_7$

These products are indicative of the involvement of (perhaps photolytically generated) acids. Some photochemical reactions of this kind have been carried out in solvents that contain added pyridine[34] but when the reaction depicted in eqn. (20) was carried out in a medium containing 10 vol% pyridine the same set of materials were detected, unconverted **19** and saturated ketone **49** being the principal components.

Conclusions.—Of the preparative methods chosen for allylic hydroperoxide synthesis, the *tert*-butyl hydroperoxide-loaded autoxidation method provides clean samples of free-radical derived hydroperoxides, albeit with the expected regio- and stereo-isomeric complexity. Singlet oxygenation also cleanly provide allylic hydroperoxides, although the requirement of an electron-rich substrate can be a limiting factor and isomeric mixtures also usually result. The inclusion of BHT in such ene oxidations appears to suppress concomitant autoxidation or rearrangement, but the action of this antioxidant as a competitor for singlet oxygen can give rise to problems of separation.

Experimental

HAZARD NOTE

Workers new to the manipulation of organic peroxides should heed the Hazard Note in the preceding paper.

General Methods.—For spectroscopic and general experimental methods, consult the appropriate sections in the preceding paper. Preparative GLC (for allylic chlorides **16**–**18**) was performed using a Perkin-Elmer F30 chromatograph (SE30 column, 100 °C for 20 min and then 4 °C/min to 120 °C). Melting points were determined using a Metler MP2 instrument and are uncorrected.

Materials.—The following data adds to that contained in the preceding paper.

Commercial materials were obtained from the Aldrich Chemical Company except where stated and were used, except where noted, as received. Ozone was generated using a Pennwalt Wallace and Tiernan Type BA.023012 apparatus. *N*-Bromosuccinimide was recrystallised from hot water (fume cupboard) and dried to constant weight over phosphorus pentoxide. *tert*-Butyl hypochlorite was prepared according to the method of Mintz and Walling[35] (a safer alternative to the method of Teeter and Bell[36]) and was stored in the refrigerator over calcium chloride.

Silver(I) oxide was prepared according to a published procedure[37] and was well washed to neutrality. Silver trifluoroacetate was prepared by completing the same procedure[37] and, after drying over solid potassium hydroxide in a desiccator, was stored in the dark.

2-Methylcyclohex-2-enol was prepared by Treibs oxidation of 1-methylcyclohexene following a published procedure.[38] The crude alcohol (62% overall) was purified by Kugelrohr distillation (pot to 155 °C, *ca.* 15 mmHg: lit., 35% overall, b.p. 86–87 °C/40 mmHg) and characterised by NMR; δ_H 5.543 (br s, 1 H, 3-H), 3.986 (br t, 1-H) 1.773 (s, 3 H, 2-Me) and 2.08–1.52 (m, 6 H, 4–6-H_2);[38] δ_C 135.25 (C-2), 125.51 (C-3), 68.44 (C-1), 32.18, 25.43 and 18.13 (C-4, C-5, C-6) and 20.69 (Me).

cis- and *trans*-1-Methyl-1,2-dipropyloxiranes as individual isomers were prepared as fragrant liquids by epoxidation of the individual alkenes using 3-chloroperoxybenzoic acid in dichloromethane in the usual manner (*cf.* the reported procedure used for a mixture of the alkenes).[39] The crude products, after concentration (ice-bath; 60 mmHg) were examined spectroscopically to give the data reported in the Supplementary publication.

Experimental Procedures (*Peroxide Syntheses*)

(a) *Triphenyl Phosphite Ozonide Mediated Singlet Oxygenation.*—A 3-necked, 250 cm^3 round-bottomed flask, cooled to −78 °C (well-lagged solid CO_2–methanol bath) and fitted with a fritted gas introduction tube, was charged with triphenyl phosphite (6.55 cm^3, 25 mmol) in dichloromethane (62.5 cm^3). An ozone mixture from an ozonator (air flow 200 cm^3 min^{-1}, 200 V) was then passed into the solution. After treatment for *ca.* 8 h at −78 °C, the solution began to develop a green tint and so the ozone supply was replaced by one of dry nitrogen. After a further 1 h, 1-methylcyclohexene (3.0 cm^3, 25 mmol) in dichloromethane (5 cm^3) was slowly added. The flask and contents were then set aside in a well-insulated cold bath overnight.

The next morning, the mixture having warmed to room temperature, rotary evaporation gave a pale yellow oil, comprising triphenylphosphate and the reaction products. A solution of the oil in methanol (17 cm^3) was diluted with water (8 cm^3): the precipitated oil crystallised when the mixture was kept in an ice–methanol bath (*ca.* −10 °C). The decanted mother liquors, combined with washings of the crystalline

triphenyl phosphate [MeOH–water (2:1); 15 cm^3] were diluted with water (100 cm^3) and extracted with dichloromethane (2 × 100 cm^3). The combined extracts were dried ($MgSO_4$) and, after addition of a trace of BHT, rotary evaporation (room temp., *ca.* 10 mmHg) gave a pale yellow oil (0.97 g).

(b) *Photoassisted Singlet Oxygenation of Alkenes.*—Wine-red solutions (*ca.* 200 cm^3) of the alkene (*ca.* 0.2–0.25 mol dm^{-3}), BHT (*ca.* 0.01 mol dm^{-3}) and TPP (99+%, *ca.* 2.5 × 10^{-4} mol dm^{-3}) in dichloromethane were loaded in an immersion-well reactor. Under comparable conditions, the photooxygenation of 1-methylcyclohexene was complete in *ca.* 1 h, while 3-methylcyclohexene and methylenecyclohexane were only slowly converted. In the latter cases the reaction was only allowed to run for 5–6 h: extended photolysis (methylenecyclohexane) resulted in extensive product decompositions. The deep-green product solutions were concentrated (rotary-evaporation, ice or cold water bath, $p \simeq 25$ mmHg), before being treated as described, individually, below.

(i) 1-*Methylcyclohexene.* The crude products could be purified directly by flash chromatography or, better, after Kugelrohr distillation. Thus, the photooxidation product from 1-methylcyclohexene, upon concentration (rotary-evaporation, ice–water bath, $p \simeq 25$ mmHg) gave the crude hydroperoxides as a brown oil (10.1 g). Direct chromatography of a portion (1.8 g) of the crude hydroperoxides over silica (150 g) gave, in fractions 7–41, the hydroperoxides eluting in the order **2**, **3**, **1**. Fractions 23–41 contained the tertiary isomer **1** which was recovered by solvent evaporation (0.583 g, equivalent to 50% isolated yield). This isomer had NMR spectroscopic properties similar to those of a sample previously isolated from a Methylene Blue-sensitised oxidation: 1-methylcyclohex-2-enyl hydroperoxide **1**;[40] δ_H 7.516 (s, 1 H, OOH), 5.956 (dt, 1 H, 3-H, $J_{2,3}$ 10.00, $J_{3,4}$ 3.60), 5.596 (br d, 1 H, 2-H) 2.08, 1.96, 1.78 and 1.60 (all m, 4–6-H_2) and 1.327 (s, 3 H, 1-Me); δ_C 132.95, 129.11 (C-2, C-3) 80.10 (C-1), 31.89, 25.18 and 24.61 (C-4, C-5, C-6) and 19.22 (Me). A portion of this isomer was reduced in deuteriochloroform solution with triphenylphosphine (1 equiv.). ^1H NMR spectral results for the product corresponded to reported lowfield NMR data:[41] highfield data for 1-methylcyclohex-2-enol: δ_H 5.736 (ddd, 1 H, 3-H, $J_{2,3}$ 9.88, $J_{3,4}$ 3.24 and 4.08), 5.628 (br d, 1 H, 2-H) 2.22 (br, 1 H, OH) 2.08–1.88 (2 H) and 1.80–1.60 (4 H) (4–6-H_2) and 1.281 (s, 3 H, Me); δ_C 133.826, 133.060 (C-2, C-3), 67.891 (C-1), 37.891, 29.446, 19.534 (C-4, C-5, C-6) and 25.072 (Me).

The secondary, *exo*-methylene isomer, also isolated from the earlier preparation had characteristic NMR data. 2-Methylenecyclohexyl hydroperoxide, **2**: δ_H 7.923 (s, 1 H, OOH) 4.943 (s) and 4.931 (s) (each 1 H, *exo* CH_2), 4.422 (br dd, 1 H, J_{sum} 8.8) 2.32 (m, 1 H) 2.15 (m, 1 H) 1.88 (m, 1 H) 1.77 (m, 1 H) 1.69 (m, 2 H) and 1.47 (m, 2 H); δ_C 146.42 (C-2) 111.11 (*exo*-CH_2), 85.48 (C-1), 31.85, 31.18, 27.52 and 21.62 (C-3, C-4, C-5, C-6). The reduced hydroperoxide (triphenylphosphine–deuteriochloroform or lithium aluminium hydride–ether) had NMR spectral results which corresponded to published ^{13}C [42a] and lowfield[42] ^1H NMR data for 2-methylenecyclohexanol δ_H 4.886 (s) and 4.743, (s) (each 1 H, *exo*-CH_2) 4.069 (br dd, 1 H, 1-H), 2.41 (m) (1 H), 2.00 (m, 2 H), 1.81 (m, 1 H), 1.65 [m, 2 H (inc. OH)] and 1.43 (3 H).

(ii) 3-*Methylcyclohexene.* The photooxygenation of 3-methylcyclohexene for 4 h resulted in *ca.* 30% conversion (crude product, green oil, 7.39 g). A portion of this crude product (1 g) applied directly to a flash chromatography column gave peroxide materials in fractions 12–36. Fractions 12–16 contained the singlet oxygen adduct of BHT which after recrystallisation from light petroleum (b.p. 40–60 °C) had m.p. 116.4–117.4 °C (lit.,[5] 115–116 °C) and IR results compatible with literature values. The later fractions (fractions 27–36) contained pure 3-methylcyclohex-2-enyl hydroperoxide, **6** δ_H 8.026 (s, 1 H, OOH), 5.487 (br m, 1 H, 2-H), 4.476 (m, 1 H, 1-H) and 1.719 (s, 3 H, 3-Me); δ_C 143.31 (C-3), 118.16 (C-2), 79.02 (C-1), 30.89 and 25.96 (C-4, C-6), 23.94 (Me) and 18.44 (C-5).

This isomer, upon triphenylphosphine reduction in deuteriochloroform gave 3-methylcyclohex-2-enol whose ^1H NMR (90 MHz) spectrum accorded with that of commercial material (Aldrich: selected experimental data δ 5.56, 4.21 and 1.71).

Rechromatography of those intermediate fractions free from the above-mentioned hydroperoxides gave small samples of the configurational isomers of 6-*methylcyclohex-2-enyl hydroperoxide*, **7**, then **8**, whose identities were inferred from their ^1H NMR (90 MHz) spectra: less polar isomer, presumed to be *cis* [δ 7.77 (1 H, s, OOH), 6.1–5.5 (2 H, 2-H + 3-H), 4.41 (m, 1 H, $w_{\frac{1}{2}}$ 10, 1-H), 2.05 (m) and 1.62 (m) (4 H, 4-H_2 + 5-H_2) and 1.10 (d, 3 H, 6-Me, J 7)]; and the more polar presumed to be *trans* [7.76 (1 H, s, OOH), 5.9–5.5 (2 H, 2-H, 3-H), 4.01 (m, 1 H, $w_{\frac{1}{2}}$ 12, 1-H), 2.15–1.20 (m, 4 H, 4-H + 5-H_2), 1.02 (d, 3 H, 6-Me, J 7.0)]. The combined substrate-derived hydroperoxides collectively represented about 58% recovery of alkene as products.

(iii) *Methylenecyclohexane.* Photolysis for 27 h results in oxygen uptake appropriate to *ca.* 45% conversion. Preliminary ^1H NMR examination showed the crude product (after solvent and unchanged alkene evaporation) to be a very complicated mixture. The whole crude product was, therefore, subjected to Kugelrohr distillation (bath to 70 °C, $p \simeq 0.01$ mmHg), using a trap maintained at −78 °C. Flash chromatography (150 g silica) upon the trap contents (1.15 g) gave fractions containing eight distinct products in small yields (10–50 mg of each as pure materials by TLC). A middle fraction (R_f 0.23) contained 1-*formylcyclohexene*, **5** [δ_H(90 MHz)[43] 9.54 (s, 1 H, CHO), 6.86 (br s, $w_{\frac{1}{2}}$ 8.3, 1 H, 2-H), 2.23 and 1.63 (m, 6 H, 3–5-H_2); 2,4-DNP[44] m.p. 210–220 °C (phase change), 220.7–221.5 °C]. A later fraction (R_f 0.21) contained a 13:87 mol% mixture of 2-methylenecyclohexyl hydroperoxide **2** and 1-cyclohexenylmethyl hydroperoxide **4** for which NMR data for this mixture are: δ_H 7.800 (s, 1 H, OOH), 5.806 (br s, $w_{\frac{1}{2}}$ 7.1, 1 H, 2-H), 4.366 [s, $w_{\frac{1}{2}}$ 2.8, 2 H, CH_2(OOH)], 2.058 (m, 4 H, 3-H_2 + 6-H_2) 1.70–1.58 (m, 4 H, 4-H_2 + 5-H_2); δ_C 132.94 (C-1), 128.60 (C-2) and 82.13 [CH_2(OOH)].

Triphenylphosphine reduction of the mixed hydroperoxides provided the expected alcohols in 16:84 mol % ratio. The ^1H NMR spectrum of the mixture was assigned by comparison with literature data: for cyclohexenylmethanol:[45] δ 5.681 (s, $w_{\frac{1}{2}}$ 8.4, 1 H, 2-H) 3.981 (s, $w_{\frac{1}{2}}$ 4.2, 2 H, CH_2OH), 2.035 (m, 4 H, 3-H_2 + 6-H_2), 1.70–1.50 (m, 4 H, 4-H_2 + 5-H_2).

(iv) cis-4-*Methyloct-4-ene.* Under the standard conditions (200 cm^3 solution, 0.2 mol alkene) reaction was rapid resulting in absorption of *ca.* 1 equiv. of oxygen (*ca.* 885 cm^3) in 1 h. Concentration gave a dark green oil (6.96 g) 102% crude yield), a portion of which (1.05 g) was purified by Kugelrohr distillation (oven 55–65 °C; p 0.05 mmHg) to give a colourless liquid (0.579 g) which was analysed (^1H NMR) and shown to be a simple mixture of the *tertiary* and *exo*-methylene hydroperoxides **9** and **10** in a 3.3:1 ratio, a recovery which represents a 61% yield of alkene as monohydroperoxides. The product from an earlier distillation was further purified by flash chromatography ($R_{f,DCM}$ 0.39) to give samples of these two materials, spectroscopic data for which are included in the Supplementary publication. The later-eluted fraction, containing the tertiary isomer, when stored as a deuteriochloroform solution, underwent equilibrium to an inseparable mixture characterised as *tertiary* isomer **9** (34%), *cis*-secondary isomer **24** (22%) and *trans*-secondary isomer **25** (44%): spectroscopic data for which are also included in the Supplementary publication. The pot residue from the earlier distillation was fractionated by flash chromatography (15 g silica; initial column using dichloromethane as eluent followed by stripping with diethyl ether;

followed by a second column on stripped out polar materials using 2.5 vol % methanol in dichloromethane) to give, in elution order, mono-hydroperoxides (traces), the singlet-oxygen adduct of BHT[5,6] (trace, $R_{f,DCM}$ 0.35) and an inseparable mixture containing only the diastereoisomeric bis-hydroperoxides **12** and **13** (124 mg, 0.65 mmol, $R_{f,DCM}$ 0.07) which was examined by highfield NMR before and after triphenylphosphine reduction. Data for bis-3,5-hydroperoxy-4-methyleneoctanes: *major isomer* δ_H 8.876 (br s, 2 H, 2 × OOH), 5.445 (br s, 1 H) and 5.432 (br s, 1 H) (together C(4)=CH_2); 4.522 (dd, 1 H, 7.9 and 2.4) and 4.431 (t, 1 H, 8.4) (3-H and 5-H), 1.3–1.8 (overlapping signals, 3 × CH_2), 0.945 and 0.938 (both t, $J \simeq 7.5$, 1-Me and 8-Me); δ_C 146.02 (C-4), 118.60 (4-C = CH_2) 87.08, 87.80 (C-3, C-5), 34.15, 25.04, 19.17 (C-2, C-6, C-7) 13.96, 10.38 (C-1, C-8).

Minor isomer δ_H 8.306 (br s, 2 H), 5.415 and 5.400 [both br t, 1 H, J 0.9, C(4)=CH_2], 4.444 (ddd, 1 H, 8.1, 1.8, 0.9) and 4.357 (ddd, J 7.8, 5.8 and 0.9) 3-H_2 and 5-H_2, 1.3–1.8 (overlapping signals, 3 × CH_2), 0.992 and 0.964 (both t, $J \simeq 7.5$, 1-Me and 8-Me); δ_C 146.35 (C-4), 116.62 [C(4)=CH_2] 86.36 and 85.52 (C-3, C-5) 34.27, 25.17 and 19.25 (C-2, C-6, C-7) 14.00 and 10.42 (C-1, C-8). Data for 4-methyleneoctane-3,5-diols: δ_H 5.053 [apparent triplet, 2 H, C(4)=CH_2, both isomers superimposed), 4.204 and 4.113 (major isomer), 4.181 and 4.131 (minor isomer) (all triplets, $J \simeq 7$, together 2 H, 3-H and 5-H), 1.56–1.74 (6 H, 3 × CH_2), 0.933 and 0.913 (major isomer), 0.927 and 0.909 (minor isomer) (all triplets, $J \simeq 7.5$, together 6 H, 1-Me and 8-Me); δ_C(major isomer/minor isomer) 110.88/111.52 [C(4)=CH_2] 74.99, 73.39/74.60, 72.88 (C-3, C-5) 38.84, 29.45, 19.39/38.16, 28.77, 19.25 (C-2, C-6, C-7) 14.20, 10.55/14.21, 10.46 (C-1, C-8) [C-4 signals obscured by $Ph_3P(O)$].

(c) *Allylic Halogenation of Alkenes.*—(i) N-*Bromosuccinimide (NBS)-mediated bromination of* 1-*methylcyclohexene.* Thermal or photochemically induced reaction gave similar isomer ratios but the latter is preferred. Thus, suspension of NBS (2.97 g, 17 mmol) in carbon tetrachloride (25 cm^3) was degassed with a flow of nitrogen. To this suspension was added 1-methylcyclohexene (2.96 cm^3, 25 mmol) and a small quantity of benzoyl peroxide. The mixture was magnetically stirred (this was found to be important) whilst under irradiation from a 100 W tungsten filament bulb. The reaction flask was cooled with cold water and aluminium foil was used as a rudimentary reflector to concentrate the light onto the flask. After illumination for 5 h, the reaction mixture was left overnight. The floating succinimide was then filtered off and the filtrate (a pale yellow solution) was stabilized by addition of a trace of BHT.

(ii) tert-*Butyl hypochlorite-mediated chlorination of* 1-*methylcyclohexene.* A round-bottomed flask, equipped with a magnetic stirrer bar was charged with silica gel (8 g, Merck 9385), dichloromethane (80 cm^3) and 1-methylcyclohexene (2.83 cm^3, 24 mmol). To this stirred mixture at room temperature was added *tert*-butyl hypochlorite (3.27 cm^3, 30 mmol), the colour of which discharged immediately upon addition. After 30 min, the mixture was filtered and the filtrate washed with freshly prepared aqueous sodium sulfite (5%; 20 cm^3) and water (20 cm^3) and then dried ($MgSO_4$). The solvent was removed by distillation at atmospheric pressure through an efficient column.

The individual allylic chlorides were collected by preparative GLC. The products, reported in order of elution were identified by NMR: 1-*chloro*-2-*methylenecyclohexane* **16**,[46] δ_H 4.983 (s, $w_{\frac{1}{2}}$ 3.4 Hz, 1 H) and 4.805 (s, $w_{\frac{1}{2}}$ 3.9, 1 H, *exo*-CH_2) 4.661 (dd, 1 H, J_{sum} 8.16, 1-H_{ax}) 2.515 (dddt, 1 H, 3-H_{ax}, J_{gem} 13.76, $J_{ax,ax}$ 10.79, $J_{ax,eq}$ 4.47), 2.137 (dt, 1 H, 3-H_{eq}, $J_{eq,ax} = J_{eq,eq}$ 4.64), 2.04–1.82 (m, 3 H), 1.725 (m, 1 H), 1.561 (m, 1 H) and 1.441 (m, 1 H) (4–6-H); δ_C 147.64 (C-2), 110.30 (C-7), 63.54 (C-1), 36.74, 31.07, 27.28 and 21.45 (3–6-C). 6-*Chloro*-1-*methylcyclohexene* **18**,[47] δ_H 5.602 (br m, $w_{\frac{1}{2}}$ 9.6, 1 H, 2-H), 4.428 (br m, $w_{\frac{1}{2}}$ 8.0, 1 H, 6-H) 1.790 (s, 3 H, Me), 2.12 (m, 2 H), 1.85 (m, 1 H), 1.64 (m, 1 H) and 1.19 (m, 2 H, 3–5-H); δ_C 133.41 (C-1), 127.16 (C-3), 60.25 (C-6), 32.58, 25.12, 21.54 (C-3–5), 16.98 (Me). 1-*Chloromethylcyclohexene* **17**,[46,48] δ_H 5.815 (m, $w_{\frac{1}{2}}$ 8, 1 H, 2-H), 3.995 (s, 2 H, CH_2Cl), 2.07 (m, 4 H, 3-H_2 + 6-H_2), 1.67 (m, 2 H) and 1.59 (m, 2 H, 4-H_2 + 5-H_2); δ_C 134.37 (C-1), 127.55 (C-2), 50.79 (CH_2Cl), 25.87, 25.21 (C-3, C-6), 22.35 and 21.90 (C-4, C-5). Stereochemical assignments were made on the basis of hydrolysis products (2 mol dm^{-3} NaOH, reflux, 1 h, ^1H NMR analysis). The three chlorides noted above gave, respectively, 2-methylenecyclohexanol, 2-methylcyclohex-2-enol, and a 45:55 mol % mixture of cyclohex-1-enylmethanol and 2-methylenecyclohexanol (along in this instance with, solely, residual, unrearranged chloride).

(d) *Silver Salt-assisted Perhydrolysis of* 1-*Methylcyclohexene-derived Allylic Halides.*—(i) *Silver(I) oxide, 50% hydrogen peroxide reaction of bromides.* When wet, fresh, neutral silver(I) oxide was added to a stirred mixture of the crude bromides (from NBS, 17 mmol) in dichloromethane (25 cm^3) and 50% hydrogen peroxide (3.4 cm^3), vigorous oxygen evolution occurred. After stirring the mixture for 4 days at room temperature, the oxide was unchanged and the recovered product, after work-up appeared, by ^1H NMR (90 MHz) analysis to contain little of the desired hydroperoxides.

(ii) *Silver trifluoroacetate, 85% hydrogen peroxide reaction of bromides.* To an ice-cooled, magnetically stirred mixture of the crude bromides (from NBS, 8.5 mmol) in a mixture of diethyl ether (25 cm^3) and hydrogen peroxide (85%; 1.0 g. **CARE!**) was added silver(I) trifluoroacetate (2.76 g, 12.5 mmol). After 15 min, water (25 cm^3) was added and the mixture was filtered, under vacuum, through Hiflow Supercell. The organic layer was retained, washed with water (× 5) to remove all traces of residual hydrogen peroxide, dried ($MgSO_4$) and concentrated. [A duplicate reaction using carbon tetrachloride as reaction solvent (the crude NBS reaction solution) gave only slow conversion of the bromides into product.]

Flash column chromatography of the product provided, in early fractions ($R_{f,DCM}$ 0.6–0.8) samples of what appeared to be bis(allylic) peroxides (ADADH positive) and trifluoroacetates (by IR, 1770 cm^{-1}). Later fractions almost contained pure hydroperoxide. Of these, one contained solely 2-*methylcyclohex*-2-*enyl hydroperoxide* **3** alone; δ_H 7.804 (s, 1 H, OOH), 5.729 (br s, 1 H, 3-H), 4.311 (br s, 1 H, 1-H), 1.782 (dd, 3 H, J 3.60 and 1.60 Me) 2.204 (m, 1 H), 2.10–1.84 (m, 2 H) and 1.70–1.52 (m, 3 H, 4–6-H_2); δ_C 130.18 (C-2), 129.88 (C-3), 82.02 (C-1), 26.47, 25.45 and 21.29 (C-4–6) and 17.49 (Me). Reduction using triphenylphosphine in deuteriochloroform converted this hydroperoxide into 2-methylcyclohex-2-enol.

(iii) *Reaction of chlorides in the presence of silver trifluoroacetate and 85% hydrogen peroxide.* To a cold, stirred solution of the crude chlorides in diethyl ether (20 cm^3) [prepared from 1-methylcyclohexene (0.71 cm^3, 6 mmol) and *tert*-butyl hypochlorite in the presence of silica gel] was added hydrogen peroxide (85%; 1 cm^3) and then silver(I) trifluoroacetate (1.63 g, 7.4 mmol). After 15 min, the cloudy mixture was worked up and subjected to flash column chromatography in the manner described in part (ii) directly above. Early fractions appeared to contain bisallylic peroxides (ADADH spray evidence), whilst the hydroperoxides were collected in later fractions. Fractions 31–35 ($R_{f,DCM}$ 0.24), upon rotary evaporation, gave an almost equimolar mixture of cyclohex-1-enylmethyl hydroperoxide **4** and 2-methylenecyclohexyl hydroperoxide **2** (total 73 mg, 9.5% isolated yield) whilst from fractions 37–43, 2-methylcyclo-2-hexenyl hydroperoxide **3** (26 mg, 3% yield) was obtained.

(e) *Displacements of Allylic Methanesulfonates.*—A magnetically stirred solution of *trans*-5-methyloct-5-en-4-ol **19** (1.42 g,

10 mmol) in anhydrous diethyl ether (10 cm^3) was cooled, under nitrogen, to −60 °C (bath temperature) and then treated first with methanesulfonyl chloride (0.774 cm^3, 10 mmol) and then, dropwise, with triethylamine (1.39 cm^3, 10 mmol). The latter addend gave, instantaneously, a white precipitate. After the mixture had briefly warmed to room temperature and then recooled over Drikold, BHT (a few crystals) and a solution of hydrogen peroxide (90% w/v by titration, 2 cm^3, 53 mmol) in diethyl ether (2 cm^3) were added. The mixture was allowed to warm to room temperature (by which time a homogeneous solution had formed) and was maintained at that temperature for 30 min before being quenched with water (50 cm^3). The crude hydroperoxide (1.712 g, 108% as pure hydroperoxide, but see below) was isolated by diethyl ether extraction, washing (2 mol dm^{-3} HCl, 5% $NaHCO_3$), drying ($MgSO_4$) and rotary evaporation (ice-bath; $p \simeq 80$ mmHg). The crude product, to which extra BHT (0.5 g) had been added was purified initially by Kugelrohr distillation (oven to a *maximum* of 70 °C; $p \simeq 0.01$ mmHg) and subsequent flash chromatography. Spectroscopic examination of the distillate, of the hydroperoxidic fractions from the chromatography ($R_{f,DCM}$ 0.39 and 0.38) and triphenylphosphine-treated peroxides enabled the data for the hydroperoxides **11** and **21** (see Supplementary publication) to be deduced and, furthermore, for the molar ratio of compounds in the distillate to be obtained (**19**:**11**:**20**:**21** = 2.2:5.1:1.6:6.5).

The same procedure, on the same scale applied to the *exo*-methylene alcohol **22** gave no hydroperoxides and an essentially quantitative recovery of unchanged starting material. In a second run, the quantity of triethylamine used, prior to hydrogen peroxide addition, was doubled. Under these conditions, the crude product gave a 57% recovery of unchanged alcohol ($R_{f,DCM}$ 0.27), small quantities of rearranged and unrearranged mesylates ($R_{f,DCM}$ 0.62, ^1H NMR data for unrearranged mesylate, δ 5.04, 4.92, 4.21, 3.64 *etc.*), contaminated with a trace of α,β-unsaturated ketone **30** ($R_{f,DCM}$ 0.45), and a small quantity (*ca.* 2% isolated yield) of a mixture of the *trans*-primary hydroperoxide isomer **23** and the *exo*-secondary hydroperoxide isomer **10**. Triphenylphosphine reduction of this mixture provided correlation of structures to allylic alcohols **26** and **22**.

Experimental Methods (*Alcohol, Ketone, Aldehyde Synthesis*).—(i) *General.* Familiar methods were used for the majority of the reactions described in 'Results' and spectroscopic data for products are given in the Supplementary publication. Additions of Grignard reagents and methyllithium were carried out under nitrogen and with efficient ice-cooling. Reductions using commercial ether solutions of lithium aluminium hydride were quenched using the Mihilovic[49] procedure. Manganese(IV) oxidation of allylic alcohols (typically 0.05 mol dm^{-3}) in light petroleum, dichloromethane or deuteriochloroform were conducted using Attenburrow[50a] or commercial material (typically 10–11-fold excess of oxidant). Inclusion of powdered 4 Å molecular sieves sometimes appeared to drive these oxidations to completion. Manganese(IV) oxide on charcoal[50b] was not found especially advantageous. Swern oxidations (10 mmol scale or higher) were performed as described:[21] poor control of the exotherm during reagent preparation was not found deleterious. Excellent yields were obtained if careful attention during solvent evaporation was made. However, in certain cases, this reaction appeared to result in modest levels of product isomerisation (see Results section).

Spectroscopic data are given in the Supplementary publication, and combustion data (C and H) for the isomeric allylic alcohols (C_{calc} = 76.06%; H_{calc} = 12.68%) were obtained as follows: **20**, 75.8; 12.6; **22**, 75.6, 12.5; **26**/**27**, 76.0, 12.9; **37**, 75.1, 13.0; **39**, 76.3, 12.2; **40**/**41**, 76.5, 12.5.

(ii) trans-2-*Methylhex*-2-*enal.* The cyclohexylimine of propanal was prepared (0.2 mol scale) by slow combination of the neat reactants[51] with stirring, under nitrogen at −10 to +5 °C (internal), followed by dilution with light petroleum (25 cm^3), drying ($MgSO_4$) and rotary evaporation (ice-bath; p 60 mmHg) to give a pale yellow liquid (97%) characterised by ^1H NMR (300 MHz) 7.58 (t, 1 H, J 1.3, iminyl H), 2.88 [br, 1 H, CH(N)] 2.19 (dq, 2 H, α-CH_2) and 0.8–1.8 (remaining H).

A solution of the above dry, nitrogen-purged imine (*ca.* 0.2 mol) in anhydrous diethyl ether (Aldrich; 40 cm^3) was added to a nitrogen protected, ice-cooled, stirred solution of lithium diisopropylamide–THF complex in cyclohexane (Aldrich; 100 cm^3, nominally 1.5 mol dm^{-3}, *i.e. ca.* 0.15 mol). After 15 min on ice, the mixture was cooled to an internal temperature of −50 to −55 °C, whereupon over a period of 30 min, a solution of butanal (molecular sieves dried, nitrogen-purged, 10.8 cm^3, 0.15 mol) in anhydrous diethyl ether (10 cm^3) was added. The mixture was allowed to warm to room temperature and then left, overnight, before being quenched (iced water with included BHT). Acidification (2 mol dm^{-3} HCl), followed rapidly by extraction (cyclohexane), washing (5% $NaHCO_3$) and drying ($MgSO_4$) gave a crude product which was purified by distillation (8 in Tantalum spiral, under nitrogen, atmospheric pressure), to remove solvents, traces of unchanged aldehydes, and ethylbenzene (an impurity in the LDA complex).

Kugelrohr distillation of the residues gave a mixture of the *trans*-aldehyde contaminated with ethyl benzene (oven to 90 °C; 1.98 g colourless liquid, mol ratio *ca.* 6:1) and then a sample believed to be the *trans*-α,β-unsaturated imine (oven 100 °C, p 0.88 mmHg; 3.82 g, 12%; δ_H 7.91 (s, 1 H), 5.82 (dt, 1 H), 1.5 (J 7.2), 2.99 (m, 1 H), 2.20 (q, 2 H, J 7.1), 1.87 (s) and 1.2–1.7 (m) (total 8 H) and 0.95 (t, 3 H, J 7.5). This material, mixed with oxalic acid (40 g) and a little BHT was subjected to steam distillation to provide a clean sample of the titled aldehyde (2.12 g, 88%).

(iii) cis-2-*Methylhex*-2-*en*-1-*ol.* THP-protected 1-hydroxypropan-2-one (2-oxopropyl tetrahydropyran-2-yl ether) could be equally well used as prepared[24] or after distillation (b.p. 73 °C, p 3 mmHg; δ_H 4.68 (m, 1 H, $w_{\frac{1}{2}}$ 7), 4.21 (AB dd, 2 H, J_{gem} 18, m, w 25) and 3.54 (m, w 20) (both 1 H), 2.20 (s, 3 H) and 1.50–1.95 (m, 6 H).

In dry apparatus under nitrogen a sample of potassium hydride (35 wt % in mineral oil; 11.3 g, 0.085 mol) under THF (Aldrich; anhydrous, 30 cm^3) was treated dropwise, at room temperature with fresh hexamethyldisilazane (HMDS; 17.9 cm^3, 0.085 mol). Once the steady hydrogen evolution had subsided, the resultant cloudy solution was added to a stirred, nitrogen protected suspension of butyl(triphenyl)phosphonium bromide (35.3 g, 0.088 mol, 1.04 equiv.) in THF (150 cm^3). A weakly exothermic reaction resulted in the formation of a tomato-coloured suspension which, after cooling to *ca.* −70 °C (internal), was slowly treated with 1-hydroxypropyl tetrahydropyran-2-yl ether (13.42 g, 0.085 mol). The internal temperature rose to −42 °C and a pale yellow suspension resulted. The mixture was allowed to reach room temperature overnight, before addition of water (250 cm^3) and light petroleum (redistilled; b.p. 30–40 °C; 100 cm^3). The lower, viscous red phase was rejected while the other two layers were separated, light petroleum extracts of the aqueous phase being added to the upper organic layer. This resulted in precipitation of a white solid which was removed by decantation before drying ($MgSO_4$) and concentration (ambient; p 25 mmHg) to leave a pale yellow liquid (64.49 g) which deposited a further crop of white solid upon refrigeration.

The material, by ^1H NMR spectroscopy was seen to be a mixture of oil from the potassium hydride, HMDS and the product alcohol as its THP ether δ 5.38 (t, 1 H, J 7.5), 4.58

(t, 1 H); 4.12 (d, 2 H, $J < 1$), 3.88 (m, *w* 23) and 3.52 (m, *w* 20), 2.05 (q, 2 H, *J ca.* 7), 1.78 (d, 3 H, $J < 1.0$), 1.5–2.0 (m, 6 H), 1.37 (sextet, 2 H, *J* ca. 7) and 0.86 (t, 3 H, *J* 7.5).

Various deprotection procedures were inefficient (*e.g.* aqueous acetic acid,[25] THF–acetic acid, aqueous or methanolic hydrochloric acid, equilibration with ethane-1,2-diol), the best being equilibration with an excess of methanol using pyridinium toluene-*p*-sulfonate (PPTS) catalysis,[24b] once the excess of HMDS had been removed using a hydrochloric acid wash. Thus, 10% of the crude material, mixed with methanol (75 cm^3) and PPTS (0.25 g) was set aside at room temperature (4 h) and then in the refrigerator (5 days). Partition between brine and diethyl ether gave a residue (3.42 g) which was found to be a mixture of 2-methoxytetrahydropyran [MeOTHP: ^1H NMR data: δ 4.51 (t, 1 H), 3.5, 3.76 and 3.52 (both dt), 3.40 (s) and 1.5–2.0 (6 H)], unchanged starting material and the titled alcohol: the key finding was the fact that, although MeOTHP had about the same TLC polarity as the product alcohol ($R_{f,DCM}$ 0.15 and 0.16 respectively), the latter gave a sky-blue colour reaction when sprayed and then gently warmed with acidic vanillin, while the former gave a purple–pink colour reaction. The titled alcohol co-distilled with MeOTHP during Kugelrohr distillation (oven 70 °C; *p* 20 mmHg) and co-eluted during flash chromatography. Both materials so obtained were freed from the contaminant by brief washing with dilute hydrochloric acid to give the titled alcohol (*ca.* 99% *cis* using NMR data in the Supplementary publication). An alternative equilibration using butanol gave a slightly less polar, less volatile exchange product (2-butoxytetrahydropyran; $R_{f,DCM}$ 0.27) which, however, tailed during chromatography into the desired alcohol, while the excess of butanol co-distilled with the product during Kugelrohr distillation.

(iv) trans-2-*Propylhex*-2-*en*-1-*ol* **26**. (a) To a magnetically stirred, ice-cooled and nitrogen protected mixture of hex-2-yn-1-ol (Lancaster Synthesis, molecular sieves dried, nitrogen flushed; 4.3 g, 0.044 mol) and copper(I) iodide (Aldrich 99.999%; 0.971 g, 0.0044 mol) in anhydrous diethyl ether (50 cm^3) was added, dropwise, propylmagnesium chloride (2 mol dm^{-3} in diethyl ether; 50 cm^3, 0.1 mol). The initial addition resulted in colour changes of the suspension (pale fawn, to pale pink then to yellow) and, once *ca.* 1 mol equiv. had been added, gas evolution from the viscous mixture was noted followed, suddenly, by reduction in the viscosity of the mixture and the development of a chocolate brown colour. The resulting mixture, once the addition was complete, was stirred at ambient temperature for a total of 60 h, before being quenched by the addition of a little saturated aqueous ammonium chloride. Filtration through Celite (the pad of which was well washed) and concentration (ice-bath, *p* 60 mmHg) gave a pale brown liquid (3.28 g), which, by ^1H NMR spectroscopic analysis, was seen to be a mixture (*ca.* 4:1) of the starting alcohol and the desired product. Kugelrohr distillation failed to give adequate separation, but an enriched portion, gave, upon flash chromatography a sample of the titled alcohol (2% isolated yield; $R_{f,DCM}$ 0.22).

(b) In a second method a small, long-necked flask and a larger three-necked reaction flask were arranged in series with a nitrogen supply, the reaction flask being connected to the smaller by a short length of Tygon tubing ending in a fritted gas inlet. The reaction flask was fitted with a narrow-bore tap adaptor and a reflux condenser. The top of the condenser was connected to the nitrogen supply and a bubbler. The nitrogen supply was arranged so that, using a clip, it could be directed through the small flask and into the reaction flask, or so that it could by-pass the small flask. Oct-4-yne (25 g, 0.23 mol, probably an unnecessary excess) was then added to a magnetically stirred, nitrogen-protected solution of 9-borabicyclo-[3.3.1]nonane (9-BBN) in THF (0.5 mol dm^{-3}; 100 cm^3, 0.05 mol) in the reaction flask at ambient temperature. This mixture was left at room temperature overnight and, the next morning, the small flask was charged with paraformaldehyde (dried overnight *in vacuo* over phosphorus pentoxide; 4.5 g, 0.15 mol) before being lowered into a pre-heated oil-bath (150 °C), the nitrogen flow being adjusted so that the gaseous formaldehyde so produced was blown into the reaction flask. As this flow was being generated, the contents of the reaction flask were warmed slowly to reflux, *ca.* half of the addition being complete once reflux started. The next day, the reflux having been continued overnight, the mixture was cooled and then treated sequentially with aqueous sodium hydroxide (2 mol dm^{-3}; 45 cm^3, 0.09 mol) and, slowly, with hydrogen peroxide (30%; 30 cm^3). The resulting warm mixture was cooled, added to water (1 dm^3) and separated, the organic layer then being washed with water (2 × 250 cm^3), dried ($MgSO_4$) and concentrated by Kugelrohr distillation (oven 50–70 °C; *p* 0.1 mmHg; ice-cooled receiver, volatiles to Drikold trap). The distillate (0.87 g, oil) was purified by flash chromatography [20 g silica, 2:1 (v/v) light petroleum (b.p. 40–60 °C)–dichloromethane (200 cm^3), then gradually to neat dichloromethane], to give a mixture of octan-4-one ($R_{f,DCM}$ 0.47–0.40 g) which contained a little of the *trans*-α,β-unsaturated aldehyde **28** and then the *trans*-alcohol **26** (171 mg, 2% isolated yield; $R_{f,DCM}$ 0.16).

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