

A Model for Olefin Hydration: Intramolecular Nucleophilic Addition of Phenolate Oxygen to the Unactivated Double Bond¹

Christopher M. Evans and Anthony J. Kirby*
University Chemical Laboratory, Cambridge CB2 1EW

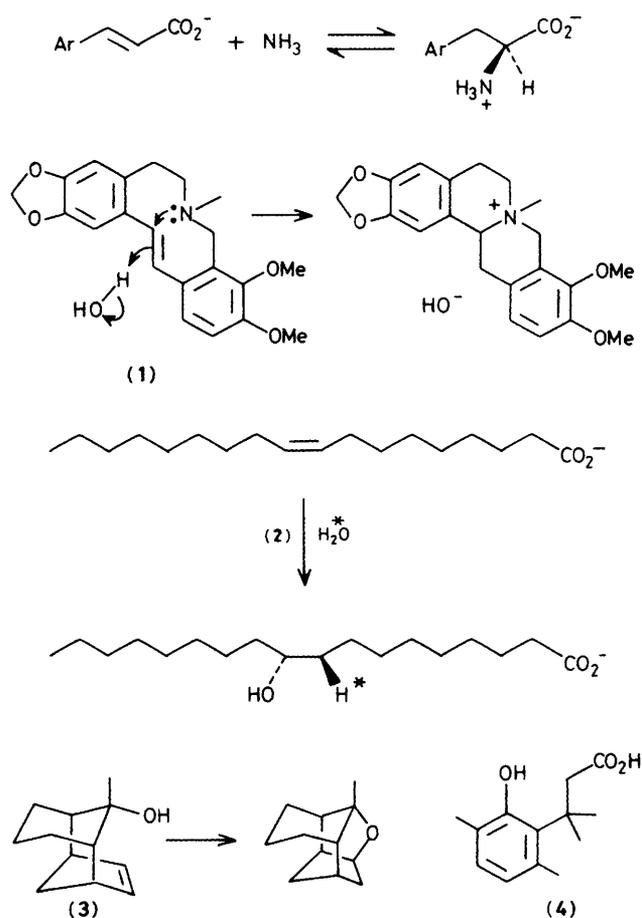
Two series of phenol-olefins with strained ground states cyclise rapidly to ethers at high pH, where the phenol is fully ionised. The reaction involves intramolecular nucleophilic addition of phenolate oxygen to a monoalkylethylene. A primary carbanion is not a full intermediate, but is well developed before proton transfer from a pre-associated water molecule or cationic general acid completes the reaction. The evidence suggests that the special conditions prevailing in enzyme active sites are likely to favour predominantly nucleophilic, rather than the usual electrophilic, attack on most olefins.

We are interested in the mechanisms by which certain enzymes catalyse the addition of weak nucleophiles to unactivated double bonds. The histidine and phenylalanine ammonia lyase reactions, for example, are reversible,² so that these enzymes can catalyse the overall addition of ammonia to the 'wrong' ends of the double bonds of the derived $\alpha\beta$ -unsaturated acids. As an intramolecular model for this process we recently studied the cyclisation of (1).³ This unusual reaction involves the rapid nucleophilic addition of amine nitrogen to the electron-rich transannular stilbene double bond, with assistance at only a relatively late stage from a general acid. Under normal conditions simple alkenes react exclusively with electrophiles, and nucleophilic addition is observed only when strongly electron-withdrawing substituents are present. But our work with (1) suggests that the π -system of even an entirely unactivated double bond can act as an acceptor for a nucleophile brought up to it in appropriate juxtaposition.

From this presumption we have developed an intramolecular model for olefin hydration. The hydro-lyases represent a very large class of enzymes,⁴ many of which react by mechanisms which have familiar *in vitro* counterparts, most commonly the Michael reaction. But at least one enzyme, oleate hydratase (EC 4.2.1.53), catalyses the regio- and stereo-specific hydration (2) of a dialkylethylene, with no assistance from electron withdrawal in the substrate, or apparently from transition metal cations or oxidising systems.⁵

This type of reaction does not occur at all under mild conditions *in vitro*, for what must be kinetic reasons. But the ready cyclisation of (1) suggested that the intramolecular addition of O^- to an unactivated double bond ought to be possible in a comparable system of high effective molarity (EM).⁶ Indeed, since this work was begun Ganter⁷⁻⁹ and Grob¹⁰ and their co-workers have reported that several polycyclic olefin-alcohols do cyclise under basic, as well as the more usual acidic, conditions. In most cases very vigorous conditions are necessary, but compounds such as (3), which are subject to strong steric compression, are cyclised within a few hours at room temperature in *t*-butyl alcohol-*t*-butoxide.⁹

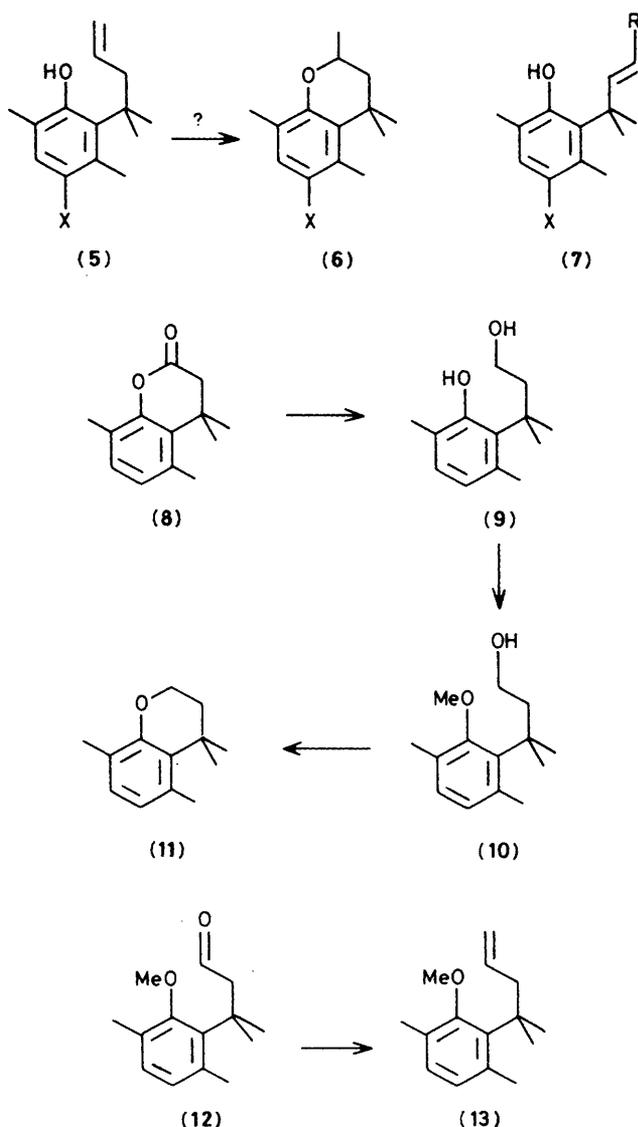
The crucial requirement for an intramolecular model for olefin hydration is clearly that it should have a very high EM for the addition of OH^- to a double bond. The lactonisation of (4)¹¹ has one of the highest recorded EMs⁶ for the addition of OH^- to sp^2 -hybridised carbon: although the reaction has been shown¹² to be much slower than originally supposed, the effective molarity of the OH group is still of the order of 10^{11} .⁶ And a phenolic OH group has the advantage of avoiding mechanistic complications associated with the deprotonation step, since it can readily be fully ionised within the pH-range. So we chose the phenol-olefin (5), expecting that this compound would cyclise at a significant rate under basic conditions to the



chroman (6). We report the synthesis of (5; X = H), and of a series of ring-substituted derivatives; as well as homologues (7; R = H and Me). We also report mechanistic investigations of their cyclisation reactions in an aqueous medium.

Results

Synthesis.—Results with several dimethylallyl ethers showed clearly that the route to the 'trialkyl lock'¹¹ system by way of the Claisen rearrangement is not viable. So we devised syntheses of both systems (5) and (7) based on the readily accessible¹¹ lactone (8) as common precursor. This is easily reduced to the diol (9), which we found after much experimentation (and in contrast to the results of Borchardt and Cohen¹³) could be

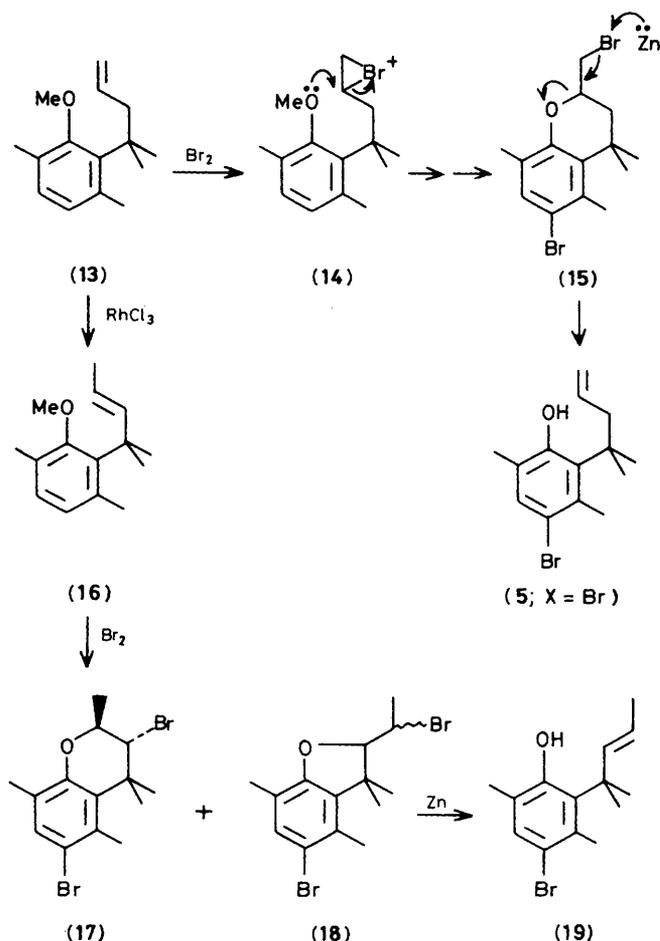


selectively methylated on the phenolic oxygen to give the protected derivative (10).

All our attempts to dehydrate (10), by a wide range of methods, gave the chroman (11), but it could be oxidised to the aldehyde (12), which was converted into the olefin (13) by a Wittig synthesis.

It proved impossible to demethylate (13) by conventional methods, but deprotection was eventually achieved by harnessing the powerful driving force for cyclisation intrinsic to this system. Treatment of (13) with bromine gave in good yield the bromoether (15), no doubt by way of intramolecular attack by the methoxy-group on the intermediate bromonium ion (14), a reaction with close literature precedent.¹⁴ The bromoether (15) was then converted efficiently into the phenol-olefin (5; X = Br) with zinc in refluxing ethanol. [Compound (5; X = H) was prepared by using the more selective *N*-bromosuccinimide for the bromodemethylation of (13).] Isomerisation of (13) using RhCl_3 as catalyst gave only *trans*-olefin (16). On treatment with bromine as before this gave a 7:1 mixture of isomeric bromoethers (17) and (18), both of which gave the phenol-olefin (19) on treatment with zinc in ethanol.

The preparation of (7; R = H) also started from the lactone (8), and ended with zinc-mediated elimination, but the bromination step, which now involves an enol ether (21), could



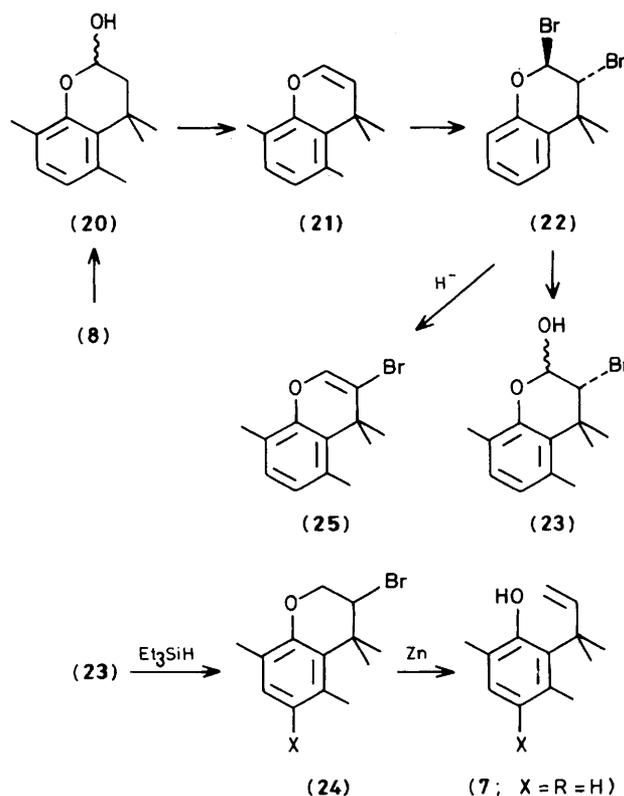
be carried out selectively in this case. [Attempts to reduce (22) directly to (24; X = H) using hydride reducing agents failed: when reaction did occur the major product was usually (25).]

Substituted derivatives (7; R = H, X = Br, CHO, COCH₃) were readily prepared by aromatic electrophilic substitution of (24; X = H) followed by the usual zinc-mediated elimination reaction.

Kinetic Methods and Results.—Inorganic buffers salts were of AnalaR grade, and used without further purification, save for drying at 110 °C for 2 h where necessary. Amines were distilled from NaOH pellets or from calcium hydride. Acetonitrile was distilled from P₂O₅, then CaH₂, and stored under nitrogen. Water for kinetic runs was thrice distilled from all-glass apparatus.

Ionic strength was maintained with KCl. Buffers routinely contained 10⁻³M-EDTA to sequester traces of metal ions, which otherwise catalyse radical oxidation of phenolate anions, (observed as rapid random spectral changes). For solubility reasons reactions were run in 1:1 (v/v) aqueous acetonitrile, limiting the ionic strength to a maximum of 0.2M. No hydrolysis of acetonitrile could be detected, by its effect on the measured pH of solutions, after 2 weeks under reaction conditions.

Phenol pK_a values were measured by the usual spectrophotometric method¹⁵ under reaction conditions, extrapolating readings back to zero time where necessary. The cyclisation of the phenol-olefins to ethers was followed by monitoring the disappearance of the phenolate chromophore at its absorption maximum (λ_{max} and ϵ_{max} are recorded for each compound in the Experimental section) in the thermostatted cell-holder of a Zeiss PMQ II or PMQ III single-beam spectrometer with M4Q III or



MQ3 monochromator. Faster reactions ($t_{1/2} < 10$ min) were followed continuously using a chart recorder. Chart speeds and timer accuracy were correct to better than 1%.

Kinetic runs were started by injecting a small sample of a stock solution of substrate (usually *ca.* 20 mg ml⁻¹ in dioxane or absolute ethanol) into buffer solution (2 ml) in the preheated cuvette. Buffer concentrations were never less than 100 times substrate concentrations, so that pseudo-first-order conditions were maintained. Cyclisations of phenols at pH values more than 1 pH unit below the pK_a were followed by injecting aliquot portions of reaction mixture into 0.2M-KOH in 1:1 aqueous acetonitrile, and extrapolating back to zero time. Standard conditions were 1:1 (v/v) aqueous acetonitrile at 39.0 °C and ionic strength 0.2M (KCl).

The first phenol-olefin we made (**5**; X = Br) showed unexpectedly complex behaviour in solution, which was eventually ascribed to specific salt effects on the activity of the phenolate anion in the mixed solvent. The apparent ϵ_{max} decreases in hydroxide solutions as K⁺ is replaced by Na⁺, but a normal ionisation curve is obtained if only K⁺ salts are used.

The cyclisation reaction proved considerably more complex. Reaction was readily followed, by the disappearance of the phenolate chromophore, in the region of the pK_a . But at higher base concentrations, where the rate of cyclisation is expected to level out as the compound becomes fully ionised, the reaction actually slows down. Reaction in 0.2M-KOH is over five times slower than at 0.02M-base (Table 1). It was thought at first that this must be a specific anion effect on hydroxide activity: it persisted, qualitatively unchanged, when K⁺ was changed for Na⁺ for tetra-*n*-butylammonium, and in aqueous methanol, dioxane, and dimethyl sulphoxide, and the one change we cannot avoid at constant ionic strength is in the relative concentrations of hydroxide and chloride. But using fluoride (closer in size and solvation requirements to hydroxide) to maintain the ionic strength still did not reduce the effect significantly.

Table 1. Rate constants for the cyclisation of (**5**; X = Br) at 39 °C and ionic strength 0.2M (KCl), in 1:1 (v/v) aqueous acetonitrile

[KOH]/M	Runs	10 ⁴ Mean rate constant (s ⁻¹)
0.002	2	2.01 ± 0.00
0.003	2	3.39 ± 0.08
0.005	3	4.67 ± 0.03
0.01	2	5.10 ± 0.05
0.02	3	5.38 ± 0.24
0.03	4	4.48 ± 0.13
0.05	3	4.11 ± 0.13
0.10	1	2.27
0.20	1	1.00

From rate constants at low base concentrations and the measured pK_a (12.68 ± 0.09) under these conditions an estimate of $1.4 \pm 0.2 \times 10^{-3}$ s⁻¹ can be made for the rate constant for the pH-independent cyclisation of the phenolate anion.

Table 2. Rate constants for the cyclisation of (**7**; X = Br, R = H), at 39 °C and ionic strength 0.2M (KCl) in 1:1 (v/v) aqueous acetonitrile.

Conditions (pH)	Runs	k_o/s^{-1}	$k_B/dm^3 mol^{-1} s^{-1}$
KOH, 0.2M	6	$8.37 \pm 0.17 \times 10^{-3}$	
KOD, 0.2M in D ₂ O	3	$4.92 \pm 0.15 \times 10^{-3}$	
KOH, 0.1M	6	$8.28 \pm 0.17 \times 10^{-3}$	
KOD, 0.1M in D ₂ O	4	$4.76 \pm 0.09 \times 10^{-3}$	
KOH, 0.05M	4	$8.36 \pm 0.54 \times 10^{-3}$	
KOD, 0.05M in D ₂ O	4	$4.95 \pm 0.11 \times 10^{-3}$	
KOH, 0.03M	4	$8.36 \pm 0.09 \times 10^{-3}$	
KOH, 0.02M	3	$8.26 \pm 0.07 \times 10^{-3}$	
KOH, 0.01M	4	$7.36 \pm 0.08 \times 10^{-3}$	
KOH, 0.005M	2	$5.61 \pm 0.04 \times 10^{-3}$	
KOH, 0.003M	4	$4.12 \pm 0.18 \times 10^{-3}$	
KOH, 0.002M	3	$2.16 \pm 0.15 \times 10^{-3}$	
KOH, 0.001M (11.70)	2	$1.44 \pm 0.27 \times 10^{-3}$	
Piperidine, 80% FB (11.25)	5	$3.00 \pm 0.01 \times 10^{-4}$	$1.21 \pm 0.01 \times 10^{-3}$
Piperidine 80% FB in D ₂ O	4	$1.37 \pm 0.08 \times 10^{-4}$	$7.34 \pm 0.10 \times 10^{-4}$
Piperidine, 67% FB (10.86)	5	$9.80 \pm 1.30 \times 10^{-5}$	$1.42 \pm 0.07 \times 10^{-3}$
Piperidine, 50% FB (10.56)	4	$4.87 \pm 0.52 \times 10^{-5}$	$8.40 \pm 0.70 \times 10^{-4}$
Piperidine, 33% FB (10.30)	4	$3.34 \pm 0.76 \times 10^{-5}$	$5.57 \pm 0.08 \times 10^{-4}$
Piperidine, 20% FB (9.92)	4	$1.77 \pm 0.05 \times 10^{-5}$	$2.52 \pm 0.06 \times 10^{-4}$
<i>n</i> -Butylamine, 50% FB (10.12)	6	$1.80 \pm 0.10 \times 10^{-5}$	$2.99 \pm 0.02 \times 10^{-4}$
Ethylenediamine, 50% FB (9.74)	4	$1.20 \pm 0.05 \times 10^{-5}$	$1.31 \pm 0.07 \times 10^{-4}$
Ethanolamine, 50% FB (9.36)	4	$5.02 \pm 0.90 \times 10^{-6}$	$3.65 \pm 0.08 \times 10^{-5}$
TRIS, 50% FB (8.08)	4	$1.65 \pm 0.07 \times 10^{-6}$	$1.14 \pm 0.11 \times 10^{-5}$
Acetate, 50% FB (5.94)	3	$1.79 \pm 0.09 \times 10^{-6}$	
HCl, 0.01M	1	$1.88 \pm 0.08 \times 10^{-6}$	
HCl, 0.10M	2	$1.12 \pm 0.08 \times 10^{-5}$	
HCl, 0.20M	1	$6.25 \pm 0.10 \times 10^{-5}$	
KOH, 0.2M, at 25.4 °C	4	$2.06 \pm 0.05 \times 10^{-3}$	
KOH, 0.2M, at 31.2 °C	4	$3.81 \pm 0.08 \times 10^{-3}$	
KOH, 0.2M, at 45.0 °C	5	$1.46 \pm 0.05 \times 10^{-2}$	
KOH, 0.2M, at 51.1 °C	5	$2.71 \pm 0.06 \times 10^{-2}$	
KOH, 0.2M, at 59.6 °C	4	$6.12 \pm 0.04 \times 10^{-2}$	

Eventually it was found that this unusual behaviour is specific to the substrates (5; X = H and Br). First we made the sulphonic acid derivative (5; X = SO₃⁻), which is much more water soluble, and found that it behaved normally. Furthermore, and at about the same time, the homologue (7; R = H, X = Br) became available, and it too behaved normally, showing a plateau in the pH-rate profile at high base concentrations, as did all the substrates we have studied since. So our detailed results concern primarily the reactions of this latter system (7).

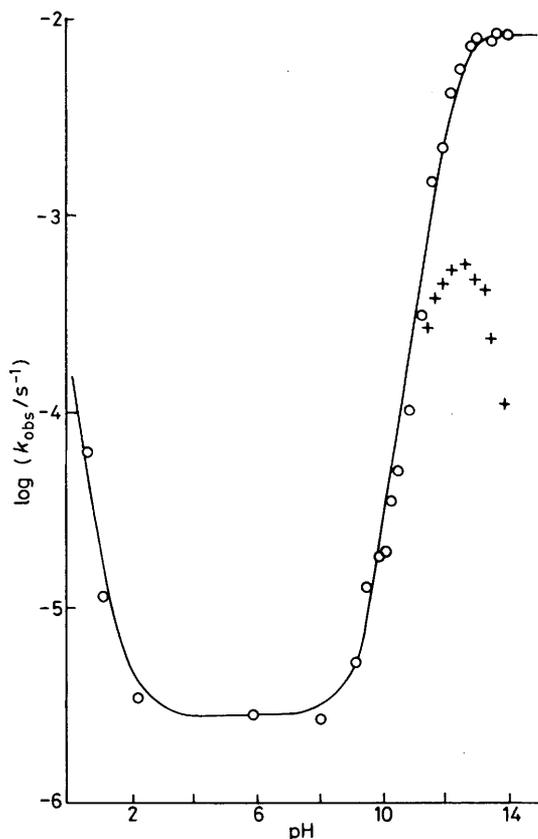


Figure. pH-rate profile for the cyclisation of (7; X = Br, R = H) (circles) and, over a limited range, for the same reaction of (5; X = Br) (crosses). The points are experimental, the curve that calculated for the cyclisation of (7; X = Br) using the rate and dissociation constants give in Table 3 (where conditions are specified)

The cyclisation of (7; R = H, X = Br), to give a five-membered ring, is significantly faster than that of its homologue (5; X = Br). A summary of the data for the reaction of the former bromo-compound is given in Table 2. The reaction is catalysed by cationic (amine) buffers, but not by acetate-acetic acid, carbonate-hydrogencarbonate, or trifluoroethanol-oxide, all of which cause apparent inhibition. Thus all points on the pH-rate profile below pH 11.5 (Figure) represent extrapolations to zero buffer concentrations.

Below pH 2 the pH-rate profile is a straight line with a slope of -1 . Between pH 2–8 reaction is pH-independent; and above pH 8 the curve follows the dissociation of the phenol group. Here the data were fitted to the equation $k_{\text{obs}} = k_p - k_{\text{obs}}a_{\text{H}}/K_a$, where k_p is the rate constant for the cyclisation of the phenolate anion.

Catalysis by amine buffers was measured mostly more than 2 pH units below the pK_a of the substrate, and was (from plots of k_B versus fraction of free base) exclusively general base catalysis of the reaction of the phenol. Data for pH values closer than this to the pK_a were corrected for the degree of ionisation of the substrate according to this interpretation. Buffer catalysis constants are given in Table 2.

Solvent deuterium isotope effects were measured on the plateau, in 0.2M-KOD, and in 50% free base piperidine, where the substrate is largely protonated. Under the latter conditions values for the isotope effect on both k_o and k_B could be measured. The apparent value of the effect on the reaction at zero buffer concentration ($k_{\text{H}}/k_{\text{D}}$ 2.19 \pm 0.01) is higher than that measured for the anion in 0.2M-KOH, where it is fully ionised, no doubt because under the conditions the substrate is ionised to a different extent in D₂O than in H₂O. We can correct for this factor very simply, using the correct figure known from the measurements at high base concentration, and the factor obtained (2.19/1.72) was used to correct the value of $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ (uncorrected 2.06) measured for the piperidine-catalysed reaction.

These data, and other derived kinetic parameters for the cyclisation of (7; X = Br), are summarised in Table 3, together with rate constants, measured at high KOH concentrations, for three substituted derivatives (7; X = H, COCH₃, and CHO).

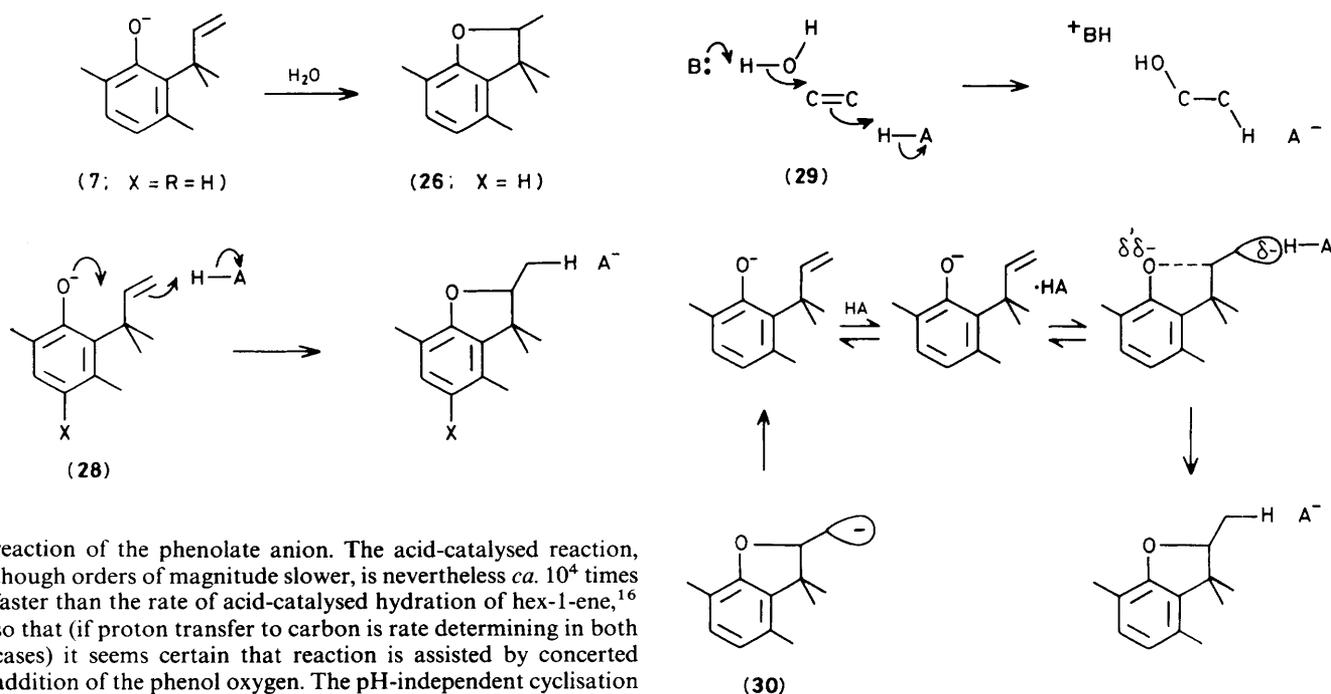
Discussion

Both series of phenol-olefins (5) and (7) undergo ready cyclisation to the corresponding ethers (6) and (26). Reaction is relatively slow for the neutral substrates, but rapid for the phenolate anions [$t_{1/2}$ for the 5-*exo-trig* cyclisation of (7; R = X = H) is 50 s at 39°C]. We will discuss almost exclusively this

Table 3. Kinetic parameters for the cyclisation of the anion of (7; X = H), and its derivatives, at 39°C and ionic strength 0.2M in 1:1 (v/v) aqueous acetonitrile

Compound (7) X =	H	Br	COCH ₃	CHO
k_p^a/s^{-1}	$1.38 \pm 0.08 \times 10^{-2}$	$8.34 \pm 0.04 \times 10^{-3}$	$8.90 \pm 0.03 \times 10^{-4}$	$3.53 \pm 0.13 \times 10^{-4}$
$(k_o^b)/s^{-1}$		1.8×10^{-6}		
$(k_{\text{H}^+}^b)/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$		2.2×10^{-4}		
pK_a		12.48 ± 0.14		
$k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$		1.72 ± 0.02		
$\Delta H^\ddagger/\text{kcal mol}^{-1}$ (kJ mol ⁻¹)		18.8 ± 0.04		
$\Delta S^\ddagger/\text{cal mol}^{-1} \text{ K}^{-1}$		(78.4 ± 0.3)		
(J mol ⁻¹ K ⁻¹)		-7.7 ± 0.3		
Buffer catalysis, β		(32.1 ± 1.3)		
$k_B(\text{H}_2\text{O})/k_B(\text{D}_2\text{O})$, piperidine		0.94 ± 0.05		
Hammett ρ (based on σ^-)	1.43 ± 0.03	1.60 ± 0.03	1.43 ± 0.03	

^a k_p is the pseudo-first order rate constant for the cyclisation of the ionised phenol, observed as the plateau at high pH. ^b k_o^b and $k_{\text{H}^+}^b$ are the rate constants for the pH-independent and specific-acid-catalysed cyclisations of the neutral (7; X = Br), observed at pH 2–8, and pH 2, respectively.



Scheme.

reaction of the phenolate anion. The acid-catalysed reaction, though orders of magnitude slower, is nevertheless *ca.* 10^4 times faster than the rate of acid-catalysed hydration of hex-1-ene,¹⁶ so that (if proton transfer to carbon is rate determining in both cases) it seems certain that reaction is assisted by concerted addition of the phenol oxygen. The pH-independent cyclisation observed between pH 2 and 8 is also an interesting reaction, clearly too fast to be the H_3O^+ -catalysed addition of phenolate anion, so it may be the H_2O -catalysed addition of neutral OH. But it is very slow even for our highly reactive substrates, and inconveniently slow in particular for accurate reproducible measurements; so we have not investigated it in detail.

It appears that in these systems (5) and (7), where the OH group is brought into very close proximity to the π -system of a monoalkylalkene, the favoured mode of addition is primarily nucleophilic. This is an unusual, or at any rate unfamiliar, pattern of reactivity for a simple alkene, elicited by precisely the sort of factors likely to be encountered in an enzyme active site. So it is of interest to define the mechanism in some detail. This we do in the present paper. In the following paper we discuss regio- and stereo-selectivity in these reactions, and compare nucleophilic additions of this unusual type to similar reactions of alkynes.

The evidence shows very clearly that phenolate addition is concerted with proton transfer from a general acid. What we actually observe is general base catalysis of the cyclisation of the phenol (Brønsted coefficient β 0.94 ± 0.05); but this does not make good sense mechanistically, under conditions where significant amounts of phenolate anion may be present; so we interpret buffer catalysis in terms of the kinetically equivalent general-acid-catalysed cyclisation of the phenolate anion (28).

All the other kinetic parameters (Table 3) are consistent with this mechanism; and similar in detail to those measured³ for the related cyclisation of the amino-olefin (1), which also involves the addition of a weak nucleophile to an unactivated olefin. The only exception is the entropy of activation, which is more positive (-7.7 compared with -18.8 cal mol⁻¹ K⁻¹) for the spontaneous reaction (28; HA = H₂O) than for the cyclisation of (1).³ This presumably reflects the different charge distributions in the two reactions. The cyclisation of (1) generates charge, whereas the negative charge which must be solvated in the transition state for the cyclisation of (28) is already present in the ground state.

The concerted mechanism represents a formal solution to the problem of the lack of activating substituents on an alkene like (5) and (7), or oleate. In principle it would appear possible for an enzyme to catalyse a 'perfectly concerted' reaction (29) involving smooth transition of electron density through the π -

system, from the nucleophile, or even from a general base (B), to a general acid (HA), without any accumulation of charge at either end of the double bond. In such a process there could be no substituent effect, and the direction of addition would be determined entirely by the geometry of the system. Whether or not such a process is possible, it is quite clear that our reactions are not like this at all.

The evidence comes from the Hammett and Brønsted coefficients. The Hammett ρ^- value for -1.43 may be compared with a value of -2.1 for the neutralisation of phenolate anions,¹⁷ and indicates that the negative charge on the oxygen nucleophile is largely neutralised in the transition state for cyclisation. But the observed Brønsted β (Table 1) is very close to unity, corresponding to an α value near zero for general acid catalysis (28). Proton transfer to carbon has thus scarcely begun, so the negative charge which has disappeared from the phenolate oxygen must be localised on the alkene.

The simplest picture consistent with all the facts involves pre-association¹⁸ of phenolate anion and general acid (Scheme). Addition of O^- to the alkene will in principle give the primary carbanion (30), but this is expected to be a prohibitively high-energy species. [Recent calculations¹⁹ indicate that a primary β -fluoroalkyl carbanion will break down to fluoride anion and alkene with zero activation energy. This may well be true for (30) and related intermediates also, since they, or something very much like them, are generated in ethanol during the final step of our phenol-olefin synthesis, without significant competition from protonation by the solvent.] So (30), even if formed, is expected to revert instantaneously to starting materials. It can, however, go on to products, if a proton source is already in position, in an encounter complex,* as the primary carbanion centre develops.

* It is presumably the more favourable equilibrium constant for the formation of an ion pair encounter complex, $\text{ArO}^- \text{H}^+ \text{NR}_3$, which accounts for the reaction being catalysed exclusively by protonated amines, and not by neutral or anionic general acids. The same phenomenon is apparent in the general-acid-catalysed ring-opening of the anion of 1-phenylcyclopropanol, which has also been explained in terms of a pre-association mechanism.¹⁹

Proton transfer evidently begins only at a point where a substantial amount of negative charge has developed on the terminal methylene group, and leads to almost immediate stabilisation of the system. Thus the transition state is reached almost as soon as proton transfer begins. The bond to the general acid is thus very weak in the transition state, accounting for the almost complete insensitivity to its pK_a , and the low solvent deuterium isotope effect (Table 3).

Conclusions.—This work has defined the basic requirements for the addition of a weak nucleophile like water to an unactivated double bond. Furthermore, the similarity of the reactions for the addition of oxygen and nitrogen nucleophiles suggests that these requirements may be of some general applicability. The key factors are the way the nucleophile is brought up to the double bond, and the presence of a general acid already in position to neutralise the developing anion. There is a strong presumption, and rather good evidence, that this mode of attack, in which the alkene acts as an electrophile, may be intrinsically more favourable than the more usual electrophilic mechanism under the special conditions of an enzyme active site. An enzyme can readily arrange for a general acid to be in position to protonate a developing carbanion; but the low effective molarities characteristic of intramolecular general acid catalysis⁶ make it difficult to imagine that protonation of a double bond by a weak general acid could initiate reaction. Bringing together heavy atom centres, on the other hand, can be achieved very efficiently in both intramolecular⁶ and enzyme reactions.

The EM of the phenolate oxygen in our systems (5) and (7) is particularly high because cyclisation is accompanied by the relief of ground-state strain, and we do not suppose that substrate binding can subject molecules in active sites to strain of this sort. But of the observed EM of $ca. 10^{11}$ for the cyclisation of (7), no more than about three powers of ten need come from this factor, since EMs as high as $10^8 M$ can be observed in conformationally flexible systems.⁶ And the dependence of reactivity in our system (7) on the basicity of the nucleophile suggests that hydroxide, which is more basic than phenolate by more than 5 pK units, could be more reactive by 3–4 orders of magnitude. A problem of some interest is of course how an enzyme could immobilise water, or incipient hydroxide, so effectively that it acts as a nucleophile with such high efficiency. But the rapid hydrolysis reactions of many acyl- and phosphoryl-enzyme intermediates leave no doubt that this is possible.

Experimental

N.m.r. spectra were recorded on Varian EM360A or EM390 instruments, i.r. spectra on a Perkin-Elmer 297 spectrophotometer, high-resolution mass spectra on an AEI MS30 mass spectrometer, and u.v. spectra on a Pye-Unicam SP8-100 spectrophotometer. M.p.s were recorded on a Köfler hot-stage apparatus, and are uncorrected.

M.p.c. refers to a medium-pressure chromatographic technique using fine (t.l.c. grade) silica. All chromatographic solvents were distilled before use. Petrol refers to light petroleum, the fraction boiling at 40–60 °C. Tetrahydrofuran was distilled from lithium aluminium hydride directly before use. All extracts were dried over anhydrous magnesium sulphate.

Materials.—4,4,5,8-Tetramethyl-3,4-dihydro-2H-1-benzopyran-2-one (8). This was prepared in 20% yield according to Colonge *et al.*,²⁰ m.p. 103–104 °C (lit.,¹¹ 97–99 °C), from hexane; ν_{max} (CCl₄) 1 775 cm^{-1} (C=O); δ_H (CDCl₃; 60 MHz) 6.97 (1 H, d, J 9 Hz, ArH), 6.73 (1 H, d, J 9 Hz, ArH), 2.60 (2 H, s, CH₂), 2.40 (3 H, s, ArCH₃), 2.25 (3 H, s, ArCH₃), and 1.45 (6 H,

s, CH₃) (Found: M^+ , 204.1156. C₁₃H₁₆O₂ requires M , 204.1157); m/z 204 (M^+ , 100%), 189 (72), 162 (45), 147 (30), and 145 (60).

3-(3,6-Dimethyl-2-hydroxyphenyl)-3-methylbutan-1-ol (9). A solution of the coumarin (8) (3.4 g, 17 mmol) in dry tetrahydrofuran (25 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0.64 g) in dry THF (25 ml), at 0 °C under nitrogen. The mixture was refluxed for 2 h, then water (1 ml) added cautiously, followed by 2N-HCl, until the precipitate dissolved. The mixture was extracted with ether, then the extract washed with water, dried, and evaporated *in vacuo* to give the alcohol (9) (3.0 g, 80%) as needles, m.p. 79–81 °C (from petrol), ν_{max} (CCl₄) 3 330 cm^{-1} (OH), δ_H (CDCl₃; 60 MHz) 6.83 (1 H, d, J 8 Hz, ArH), 6.52 (1 H, d, J 8 Hz, ArH), 5.35 (1 H, s, exchangeable, OH), 3.55 (2 H, t, J 6 Hz, CH₂O), 2.45 (3 H, s, ArCH₃), 2.20 (2 H, t, J 6 Hz, CH₂), 2.15 (3 H, s, ArCH₃), and 1.60 (6 H, s, CH₃) (Found: M^+ , 208.1458. C₁₃H₂₀O₂ requires M , 208.1453); m/z 208 (M^+ , 47%), 175 (46), 163 (100), 135 (68), and 122 (30).

3-(3,6-Dimethyl-2-methoxyphenyl)-3-methylbutan-1-ol (10). The diol (9) (3.50 g, 17 mmol), anhydrous potassium carbonate (3.70 g, 17 mmol), and methyl iodide (10 ml) were refluxed in acetone (75 ml) for 24 h. The suspension was filtered and the acetone solution concentrated *in vacuo*, the residue partitioned between water and ether, and the aqueous phase extracted with ether. The extract was dried and concentrated *in vacuo*, to give the crude (95% by n.m.r.) methyl phenyl ether (10) (3.50 g, 90%). This oil was generally used without further purification, but could be purified by m.p.c. (eluant 5% methanol–dichloromethane) if desired, ν_{max} (CCl₄) 3 330 cm^{-1} (OH); δ_H (CDCl₃; 90 MHz) 6.94 (1 H, d, J 7 Hz, ArH), 6.73 (1 H, d, J 7 Hz, ArH), 3.65 (3 H, s, OCH₃), 3.55 (2 H, t, J 6 Hz, OCH₂), 2.45 (3 H, s, ArCH₃), 2.25 (2 H, s, ArCH₃), 2.20br (1 H, exchangeable, OH), 2.15 (2 H, t, J 6 Hz, CH₂), and 1.55 (6 H, s, CH₃) (Found: M^+ 222.1637. C₁₄H₂₂O₂ requires M , 222.1635); m/z 222 (M^+ , 34%), 117 (100), 162 (25), and 119 (35).

Attempted dehydration of (10) with *o*-nitrophenyl selenocyanate–tri-*n*-butylphosphine. According to the method of Majetich and his co-workers,²¹ tri-*n*-butylphosphine (0.35 ml, 1.4 mmol) was added to a solution of alcohol (10) (0.27 g, 1.2 mmol) and *o*-nitrophenyl selenocyanate (0.32 g, 1.4 mmol) in dry THF (5 ml) under nitrogen at room temperature. The solution was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue separated into components by p.t.l.c. (eluant ether) to give chroman (11) as the major product, δ_H (CDCl₃; 60 MHz) 6.85 (1 H, d, J 8 Hz, ArH), 6.52 (1 H, d, J 8 Hz, ArH), 4.15 (2 H, m, OCH₂), 2.55 (3 H, s, ArCH₃), 2.20 (3 H, s, ArCH₃), 1.80 (2 H, m, CH₂), and 1.50 (6 H, s, CH₃) (Found: M^+ , 190.1352. C₁₃H₁₈O requires M , 190.1353); m/z 190 (M^+ , 50%), 175 (100), 135 (25), 107 (15), and 91 (11).

3-(3,6-Dimethyl-2-methoxyphenyl)-3-methylbutanal (12). The alcohol (10) (12 g, 54 mmol) and pyridinium dichromate²² (22 g, 60 mmol) were stirred in dry dichloromethane (50 ml) under nitrogen for 20 h. Ether (200 ml) was added and the suspension stirred for 15 min before filtering through silica gel. The solid residue was extracted several times with warm ether, the combined filtrate was evaporated *in vacuo* to give a brown oil which was purified by m.p.c. (30 g silica, eluant petrol), to give the aldehyde (12) (9.11 g, 77%) as an oil, ν_{max} (liquid film) 1 715 cm^{-1} (C=O); δ_H (CDCl₃; 60 MHz) 9.55 (1 H, t, J 3 Hz, CHO), 6.99 (1 H, d, J 8 Hz, ArH), 6.78 (1 H, d, J 8 Hz, ArH), 3.65 (3 H, s, OCH₃), 2.85 (2 H, d, J 3 Hz, CH₂), 2.50 (3 H, s, ArCH₃), 2.25 (3 H, s, ArCH₃), and 1.55 (6 H, s, CH₃) (Found: M^+ , 220.1464. C₁₄H₂₀O₂ requires M , 220.1464); m/z 220 (M^+ , 24%), 117 (45), 162 (30), 136 (100), and 119 (50).

4-(3,6-Dimethyl-2-methoxyphenyl)-4-methylpent-1-ene (13). *n*-Butyl-lithium (21 ml of a 1.2M solution in hexane) was added dropwise to a stirred suspension of methyltriphenyl-

phosphonium bromide (10.21 g, 25 mmol) in dry THF (75 ml) under nitrogen at 0 °C. The resulting orange solution was stirred at 0 °C for 30 min, and then a solution of aldehyde (**12**) (5.70 g, 25 mmol) in dry THF (15 ml) was added dropwise. The mixture was warmed to room temperature over 90 min before quenching with saturated ammonium chloride solution (25 ml). Further water (25 ml) was added and the phases separated; the aqueous phase was extracted with ether. The combined extract was dried and concentrated *in vacuo*, the bulk of the triphenylphosphine oxide impurity was removed by a cycle of trituration with petrol and evaporation of the resulting mother liquors. Final purification by m.p.c. (25 g silica, eluant petrol) gave the olefin (**13**) (5.00 g, 92%) as an oil, v_{\max} (liquid film) 1 620 cm^{-1} (C=C); δ_{H} (CDCl₃; 60 MHz) 6.90 (1 H, d, *J* 8 Hz, ArH), 6.71 (1 H, d, *J* 8 Hz, ArH), 5.65 (1 H, ddt, *J* 18, 10, 6 Hz, CH=CH₂), 4.95 (1 H, dd, *J* 10, 1 Hz, CH=CHH), 4.70 (1 H, dd, *J* 18, 1 Hz, CH=CHH), (3 H, s, OCH₃), 2.65 (2 H, d, *J* 6 Hz, CH₂), 2.50 (3 H, s, Ar), 2.30 (3 H, s, ArCH₃), and 1.60 (6 H, s, CH₃) (Found: M^+ , 218.1651. C₁₅H₂₂O requires M , 218.1653); m/z 218 (M^+ , 0.5%), 201 (32), 183 (45), 177 (100), 162 (20), and 119 (35).

Attempted deprotection of (13) with iodotrimethylsilane (TMSI). The ether-olefin (**13**) (0.11 g, 0.5 mmol), TMSI (0.09 ml, 0.6 mmol), and AnalaR tetrachloromethane (0.3 ml) were sealed in an n.m.r. tube under nitrogen and heated to 100 °C in an oil-bath. The reaction was followed by n.m.r. at 24 h intervals. After 5 days the contents of the tube were separated by p.t.l.c. (eluant petrol) to give several products. The major product (50 mg) was identified as 2,4,4,5,8-pentamethyl-3,4-dihydro-2H-1-benzopyran (**11**) on the basis of its n.m.r. spectrum: δ_{H} (CDCl₃; 60 MHz) 6.78 (1 H, d, *J* 8 Hz, Ar), 6.42 (1 H, d, *J* 8 Hz, Ar), 4.50 (1 H, m, OCH), 2.50 (3 H, s, ArCH₃), 2.20 (3 H, s, ArCH₃), 2.00 (2 H, d, *J* 7 Hz, Hz, CH₂), 1.60 (3 H, d, *J* 6 Hz, CH₃CH), and 1.50 (6 H, 2 × s, CH₃). When this experiment was repeated on a larger scale the pentamethylchroman (**11**) was the sole product.

6-Bromo-2-bromomethyl-4,4,5,8-tetramethyl-3,4-dihydro-2H-1-benzopyran (15). Bromine (9.2 ml of 1M solution in tetrachloromethane) was added dropwise over 2 h to a solution of the olefin-ether (**13**) (1.0 g, 4.6 mmol) in tetrachloromethane (10 ml) at 0 °C. After stirring at room temperature for a further 2 h the solution was diluted with dichloromethane (20 ml), washed with sodium thiosulphate solution and with brine, dried, and concentrated *in vacuo*. The resulting oil was purified by m.p.c. (10 g silica, eluant petrol) to give the bromo-ether (**15**) (1.23 g, 74%) as an oil; i.r. (CCl₄) no diagnostic peaks; δ_{H} (CDCl₃; 90 MHz) 7.23 (1 H, s, ArH), 4.15 (1 H, m, OCH), 3.55 (2 H, m, CH₂Br), 2.55 (3 H, s, ArCH₃), 2.17 (3 H, s, ArCH₃), 1.80 (2 H, m, CH₂), and 1.50 (6 H, s, CH₃) (Found: M^+ , 360.9785. C₁₄H₁₈Br₂O requires M , 360.9767); m/z 364 (M^+ , 50%), 362 (M^+ , 100), 360 (M^+ , 50), 349 (30), 347 (62), 345 (32), 268 (19), 266 (15), 257 (15), 255 (20), 216 (10), 214 (10), 187 (20), 186 (10), 173 (20), and 146 (25).

trans-4-(3,6-Dimethyl-2-methoxyphenyl)-4-methylpent-2-ene (16). The ether-olefin (**13**) (0.49 g, 2.2 mmol), RhCl₃ (15 mg), and water (0.3 ml) were stirred in ethanol (5 ml) at 70 °C for 18 h. The brown solution was poured into water (30 ml) and extracted with petrol. The extract was dried, concentrated *in vacuo*, and purified by chromatography over silica (eluant petrol), to give the *trans*-olefin (**16**) (0.42 g, 86%) as an oil, v_{\max} (CCl₄) 1 620 (C=C), 1 580 (Ar), and 970 cm^{-1} (*trans* C=C); δ_{H} (CCl₄; 90 MHz) 6.95 (1 H, d, *J* 8 Hz, ArH), 6.76 (1 H, d, *J* 8 Hz, ArH), 5.80 (1 H, dt, *J* 16, 2 Hz, CH=), 5.20 (1 H, dt, *J* 16, 8 Hz, =CHCH₃), 3.60 (3 H, s, OCH₃), 2.30 (3 H, s, ArCH₃), 2.20 (3 H, s, ArCH₃), 1.72 (3 H, dd, *J* 8, 2 Hz, =CHCH₃), and 1.50 (6 H, s, CH₃) (Found: M^+ , 218.1674. C₁₅H₂₂O requires M , 218.1674); m/z 218 (M^+ , 100%), 204 (31), 203 (80), 189 (76), 187 (25), 177 (63), 175 (31), 174 (25), 173 (50), and 84 (90).

Bromination of (16). Treatment of the *trans*-olefin (**16**) using

two equivalents of bromine as described above in the synthesis of (**15**) gave two products (85% overall yield) in a 7:1 ratio (by n.m.r. of the crude reaction mixture). Chromatography over silica gel (eluant hexane) gave one isomer (R_{F} 0.4) as needles, m.p. 75–76.5 °C, and the other (R_{F} 0.3) also as needles, m.p. 69–73 °C, but containing *ca.* 10% for the first isomer. These were assigned the following structures for reasons described below.

3,6-Dibromo-2,4,4,5,8-pentamethyl-3,4-dihydro-2H-1-benzopyran (17). This has R_{F} 0.4 (hexane); δ_{H} (CDCl₃; 90 MHz) 7.15 (1 H, s, ArH), 4.45–4.10 (2 H, m, CHBr + OCH), 2.35 (3 H, s, ArCH₃), 2.10 (3 H, s, ArCH₃), 1.89 (3 H, d, *J* 6 Hz, CH₃CO), 1.65 (3 H, s, CH₃), and 1.34 (3 H, s, CH₃) (Found: M^+ , 363.9686. C₁₄H₁₈Br₂O requires M , 363.9686); m/z 364 (M^+ , 30%), 362 (M^+ , 62), 360 (M^+ , 32), 349 (12), 347 (24), 345 (12), 284 (18), 282 (20), 269 (10), 267 (20), 188 (65), 187 (100), 174 (80), and 160 (40).

5-Bromo-2-(1-bromoethyl)-3,3,4,7-tetramethyl-2,3-dihydro-benzofuran (18). This had R_{F} 0.3 (hexane); δ_{H} (CDCl₃; 90 MHz) 7.10 (1 H, s, ArH), 4.30 (1 H, m) + 3.95 (1 H, m) (CHBr + OCH), 2.32 (3 H, s, ArCH₃), 2.10 (3 H, s, ArCH₃), 1.75 (3 H, d, *J* 5 Hz, CH₃CBr), 1.32 (3 H, s, CH₃), and 1.10 (3 H, s, CH₃) (Found: M^+ , 363.9678. C₁₄H₁₈Br₂O requires M , 363.9686); m/z 364 (M^+ , 6%), 362 (M^+ , 12), 360 (M^+ , 6), 394 (2), 347 (5), 345 (2), 284 (30), 282 (32), 269 (20), 267 (20), 188 (100), and 174 (30).

Assignment of structures (17) and (18). The methine protons of the two isomeric bromo-ethers obtained from the bromination of (**16**) were not resolved at 90 MHz, and initial, tentative, structural assignments were based on the chemical shifts of the *gem*-dimethyl groups. The minor isomer showed a singlet at δ 1.10, and these signals appear at such high field only for the benzofurans prepared in this work. Stronger evidence was obtained from 250 MHz spectra, where the methine signals were (just) resolved. Irradiation of the methyl doublet of the major isomer caused the collapse of the complex methine signal to a pair of doublets at δ 4.23 and 4.13 (*J* 10 Hz). Similar irradiation of the methyl doublet of the minor isomer caused the 1 H multiplet at δ 3.96 to collapse to a broad singlet, indicating only weak coupling to the other methine proton (hidden under impurity peaks δ 4.3). *trans*-Addition would result in the stereochemistry shown for (**17**), with the methine protons both axial, and a relatively large coupling constant expected. The small coupling observed for the methine protons of the minor isomer is consistent with the conformationally flexible structure (**18**).

2-Hydroxy-4,4,5,8-tetramethyl-3,4-dihydro-2H-1-benzopyran (20). Di-isobutylaluminium hydride (12 ml of a 1M solution in hexane) was added dropwise to a solution of the lactone (**8**) (2.0 g, 9.8 mmol) in dry dichloromethane (20 ml) under nitrogen at –78 °C. The mixture was stirred at –78 °C for 2 h, then quenched by the addition of methanol (15 ml) and allowed to warm to room temperature. The suspension was filtered through Celite and the mother liquors concentrated *in vacuo*. The residue was partitioned between dichloromethane and 3N-sulphuric acid, the aqueous phase extracted with dichloromethane, and the combined extracts washed with 3N-sulphuric acid and with water, dried, and concentrated *in vacuo* to give the lactol (**20**) (1.5 g, 74%) as prisms, m.p. 68–69 °C (from *n*-hexane); v_{\max} (CCl₄) 3 600 cm^{-1} (OH); δ_{H} (CDCl₃; 90 MHz) 6.88 (1 H, d, *J* 9 Hz, ArH), 6.60 (1 H, d, *J* 8 Hz, ArH), 5.60 (1 H, m, OCH), 3.05br (1 H, s, exchangeable, OH), 2.45 (3 H, s, ArCH₃), 2.15 (3 H, s, ArCH₃), 1.85 (2 H, m, CH₂), 1.45 (3 H, s, CH₃), and 1.40 (3 H, s, CH₃) (Found: M^+ , 206.1309. C₁₃H₁₈O₂ requires M , 206.1311); m/z 206 (M^+ , 3%), 188 (5), 173 (100), and 85 (25).

4,4,5,8-Tetramethyl-4H-1-benzopyran (21). Lactol (**20**) (1.96 g, 9.5 mmol) and anhydrous oxalic acid (0.2 g) were refluxed in dry toluene (50 ml) for 48 h, using a Dean–Stark trap. The solvent was then removed *in vacuo* and the residue purified by m.p.c.

(eluant petrol) to give the *vinyl ether* (**21**) (1.40 g, 78%) as an oil, $\nu_{\max}(\text{CCl}_4)$ 1 690 cm^{-1} (C=C); $\delta_{\text{H}}(\text{CDCl}_3; 60 \text{ MHz})$ 6.84 (1 H, d, *J* 8 Hz, ArH), 6.65 (1 H, d, *J* 8 Hz, ArH), 6.40 (1 H, d, *J* 6 Hz, =CHO-), 4.55 (1 H, d, *J* 6 Hz, CH=), 2.40 (3 H, s, ArCH₃), 2.15 (3 H, s, ArCH₃), and 1.45 (6 H, s, CH₃) (Found: M^+ , 188.1199. $\text{C}_{13}\text{H}_{16}\text{O}$ requires M , 188.1197; m/z 188 (M^+ 10%), 173 (100), and 86 (15).

2,3-Dibromo-4,4,5,8-tetramethyl-3,4-dihydro-2H-1-benzopyran (22). Bromine (ca. 2 ml of 0.5M solution in tetrachloromethane) was added dropwise with stirring to a solution of the vinyl ether (**21**) (0.19 g, 1 mmol) in AnalaR tetrachloromethane (1 ml) at 0 °C. The solvent was removed *in vacuo* to give the *dibromide* (**22**) (0.35 g, 100%) as a pale yellow oil. Any attempt at purification resulted in decomposition (see text), $\delta_{\text{H}}(\text{CDCl}_3; 60 \text{ MHz})$ 6.84 (1 H, d, *J* 8 Hz, ArH), 6.64 (1 H, d, *J* 8 Hz, ArH), 6.60 (1H, d, *J* 6 Hz, OCHBr), 4.35 (1H, d, *J* 6 Hz, CHBr), 2.45 (3 H, s, ArCH₃), 2.20 (3 H, s, ArCH₃), 1.72 (3 H, s, CH₃), and 1.40 (3 H, s, CH₃).

3-Bromo-2-hydroxy-4,4,5,8-tetramethyl-3,4-dihydro-2H-1-benzopyran (23). Dibromide (**22**) (0.35 g, 1 mmol) was stirred vigorously in a mixture of THF (5 ml) and water (5 ml) for 18 h. The mixture was extracted with dichloromethane; the extract was dried, concentrated *in vacuo*, and purified by chromatography over silica gel (eluant dichloromethane) to give the *trans-bromo-lactol* (**23**) (0.25 g, 88%) as an oil, $\nu_{\max}(\text{CCl}_4)$ 3 550 and 3 300 cm^{-1} (OH); $\delta(\text{CDCl}_3; 90 \text{ MHz})$ 6.88 (1 H, d, *J* 7 Hz, ArH), 6.65 (1 H, d, *J* 7 Hz, ArH), 5.45 (1 H, d, *J* 9 Hz, OCHOH), 4.10 (1 H, d, *J* 9 Hz, CHBr), 3.80br (1 H, exchangeable, OH), 2.45 (3 H, s, ArCH₃), 2.15 (3 H, s, ArCH₃), 1.60 (3 H, s, CH₃), and 1.50 (3 H, s, CH₃) (Found: M^+ , 284.0414. $\text{C}_{13}\text{H}_{17}\text{BrO}_2$ requires M , 284.0414; m/z 286 (M^+ , 36%), 284 (M^+ , 35), 271 (10), 269 (10), 175 (100), 161 (60), and 149 (20). A small amount (30 mg) of the *cis-bromo-lactol* was also recovered from the column; this compound had the following n.m.r. spectrum: $\delta_{\text{H}}(\text{CDCl}_3; 60 \text{ MHz})$ 6.88 (1 H, d, *J* 7 Hz, ArH), 6.65 (1 H, d, *J* 7 Hz, ArH), 5.20br (1 H, s, OHCO), 4.15br (1 H, s, CHBr), 3.80br (1 H, exchangeable, OH), 2.45 (3 H, s, ArCH₃), 2.15 (3 H, s, ArCH₃), 1.70 (3 H, s, CH₃), and 1.60 (3 H, s, CH₃). I.r. and low-resolution mass spectrum were identical with those obtained for the *trans*-isomer.

3-Bromo-4,4,5,8-tetramethyl-3,4-dihydro-2H-1-benzopyran (24; X = H). Boron trifluoride-ether (0.2 ml of a 48% solution) was added to a stirred solution of bromo-lactol (**23**) (0.18 g, 0.6 mmol) and triethylsilane (0.2 ml) in dry dichloromethane (2 ml) under nitrogen. After stirring at room temperature for 90 min the mixture was quenched by addition of potassium carbonate (0.1 g) and water (5 ml), and extracted with dichloromethane. The extract was dried and concentrated *in vacuo*, before final purification by m.p.c. (8 g silica, eluant hexane) to give the pure *bromo-ether* (**24; X = H**) (0.12 g, 73%) as an oil, $\nu_{\max}(\text{CCl}_4)$ no diagnostic peaks; $\delta_{\text{H}}(\text{CDCl}_3; 90 \text{ MHz})$ 6.85 (1 H, d, *J* 8 Hz, ArH), 6.60 (1 H, d, *J* 8 Hz, ArH), 4.50–4.15 (3 H, m, OCH₂ + CHBr), 2.45 (3 H, s, ArCH₃), 2.15 (3 H, s, ArCH₃), 1.55 (3 H, s, CH₃), and 1.50 (3 H, s, CH₃) (Found: M^+ , 268.0465. $\text{C}_{13}\text{H}_{17}\text{BrO}$ requires M , 268.0465; m/z 270 (M^+ , 28%), 268 (M^+ , 25), 253 (15), 173 (100), and 159 (40).

3,6-Dibromo-4,4,5,8-tetramethyl-3,4-dihydro-2H-1-benzopyran (24; X = Br). Bromine solution (2.0 ml of a 0.5M solution in tetrachloromethane) was added to a solution of the bromo-ether (**24; X = H**) (0.27 g, 1 mmol) in tetrachloromethane (1 ml), and the solution stirred at room temperature for 2 h. The solution was diluted with dichloromethane, washed with sodium thiosulphate solution and with brine, dried, and concentrated *in vacuo*. The residue was purified by m.p.c. (eluant petrol) to give the *dibromide* (**24; X = Br**) (0.31 g, 89%) as an oil, $\delta_{\text{H}}(\text{CDCl}_3; 90 \text{ MHz})$ 7.25 (1 H, s, ArH), 4.45–4.15 (3 H, m, OCH₂ + CHBr), 2.50 (3 H, s, ArCH₃), 2.10 (3 H, s, ArCH₃), 1.55 (3 H, s, CH₃), and 1.53 (3 H, s, CH₃) (Found: M^+ ,

347.9546. $\text{C}_{13}\text{H}_{16}\text{Br}_2\text{O}$ requires M , 347.9546; m/z 350 (M^+ , 48%), 348 (M^+ , 90), 346 (M^+ , 46), 317 (15), 315 (30), 313 (17), 254 (22), 253 (25), 252 (22), 251 (19), 239 (10), 237 (10), and 173 (100).

6-Acetyl-3-bromo-4,4,5,8-tetramethyl-3,4-dihydro-2H-1-benzopyran (24; X = COCH₃). Aluminium trichloride (0.07 g, 0.5 mmol) was added to a solution of distilled acetyl chloride (0.05 g, 0.5 mmol) in dry dichloromethane (0.5 ml) at 0 °C. When all the solid had dissolved a solution of the phenylether (**24; X = H**) (0.14 g, 0.5 mmol) in dry dichloromethane (0.5 ml) was added dropwise. The mixture was stirred at 0 °C for 30 min, and then quenched with ice-concentrated hydrochloric acid. The organic phase was separated and the aqueous phase extracted with dichloromethane. The extracts were dried, concentrated *in vacuo*, and purified by m.p.c. (8 g silica, eluant 5% methanol-hexane) to give the *6-acetyl compound* (0.15 g, 91%) as crystals, m.p. 79–81 °C (from hexane), $\nu_{\max}(\text{CCl}_4)$ 1 690 (C=O) and 1 600 (Ar) cm^{-1} ; $\delta_{\text{H}}(\text{CDCl}_3; 90 \text{ MHz})$ 7.30 (1 H, s, ArH), 4.65–4.15 (3 H, m, OCH₂ + CHBr), 2.55 (6 H, s, CH₃CO + ArCH₃), 2.20 (3 H, s, ArCH₃), and 1.60 (6 H, s, CH₃) (Found: M^+ , 310.0563. $\text{C}_{15}\text{H}_{19}\text{BrO}_2$ requires M , 310.0564; m/z 312 (M^+ , 40%), 310 (M^+ , 36), 297 (100), 295 (100), 245 (5), 231 (28), 215 (32), 201 (19), and 173 (60).

3-Bromo-6-formyl-4,4,5,8-tetramethyl-3,4-dihydro-2H-1-benzopyran (24; X = CHO). Following the general procedure of Rieche *et al.*²³ titanium tetrachloride (0.1 ml, 0.9 mmol) was added to a stirred solution of the phenyl ether (**24; X = H**) (0.14 g, 0.5 mmol) in dry dichloromethane (1 ml) under nitrogen at –23 °C; dichloromethyl methyl ether (0.1 ml, 1 mmol) was then added and the red solution stirred at –23 °C for 1 h before pouring onto ice. The organic phase was separated, dried, and concentrated *in vacuo* to give the aldehyde (0.11 g, 74%) as prisms, m.p. 95–97 °C (from hexane), $\nu_{\max}(\text{CCl}_4)$ 2 730, 2 800 (CHO), 1 700 (C=O), and 1 600 (Ar) cm^{-1} ; $\delta_{\text{H}}(\text{CDCl}_3; 60 \text{ MHz})$ 10.03 (1 H, s, CHO), 7.35 (1 H, s, ArH), 4.70–4.05 (3 H, s, CH₂O + CHBr), 2.74 (3 H, s, ArCH₃), 2.20 (3 H, s, ArCH₃), and 1.65 (6 H, s, CH₃) (Found: M^+ , 296.0416. $\text{C}_{14}\text{H}_{17}\text{BrO}_2$ requires M , 296.0415; m/z 298 (M^+ , 58), 296 (M^+ , 58), 283 (14), 281 (14), 217 (100), 202 (28), 201 (43), 187 (30), and 173 (52).

Preparation of phenol-olefins. The zinc dust used in the following reactions must be activated before use by stirring for 5 min with dilute HCl. The acid is removed by filtration, and the zinc then washed with water, acetone, and ether before drying *in vacuo* at 50 °C. It is also essential that 95% ethanol is used as solvent.

4-(5-Bromo-3,6-dimethyl-2-hydroxyphenyl)-4-methylpent-1-ene (5; X = Br). Bromo-ether (**15**) (0.51 g, 1.4 mmol) and freshly activated zinc dust (0.2 g) were refluxed in 95% ethanol (10 ml) with efficient stirring under nitrogen for 4 h. The suspension was filtered through Celite and concentrated *in vacuo*. The residue was dissolved in dichloromethane, dried, and concentrated *in vacuo* to give the *olefin* (**5; X = Br**) (0.04 g, 100%) as an oil. Further purification by p.t.l.c. (eluant petrol) was sometimes needed to obtain an absolutely pure sample, λ_{\max} . (0.2M-KOH, 1:1 H₂O-MeCN) 312 nm (ϵ_{\max} , 17 000); $\nu_{\max}(\text{CCl}_4)$ 3 620 (HO) and 1 640 (C=C) cm^{-1} ; $\delta_{\text{H}}(\text{CDCl}_3; 60 \text{ MHz})$ 7.10 (1 H, s, ArH), 5.60 (1 H, ddt, *J* 18, 10, 8 Hz, CH=CH₂), 4.90 (1 H, dd, *J* 18, 1 Hz, CH=CHH), 4.85 (1 H, dd, *J* 10, 1 Hz, CH=CHH), 4.70br (1 H, s, exchangeable, OH), 2.65 (2 H, d, *J* 8 Hz, CH₂), 2.48 (3 H, s, ArCH₃), 2.10 (3 H, s, ArCH₃), and 1.50 (6 H, s, CH₃) (Found: M^+ , 282.0605. $\text{C}_{14}\text{H}_{19}\text{BrO}$ requires M , 282.0604; m/z 284 (M^+ , 20%), 282 (M^+ , 16), 269 (20), 267 (20), and 174 (100).

Prepared in a similar manner were (n.m.r. assignments are given only when they differ from those above); 3-(5-bromo-3,6-dimethyl-2-hydroxyphenyl)-3-methylbut-1-ene (**7; R = H, X = Br**) from (**24; X = Br**), λ_{\max} . (0.2M-KOH, 1:1 H₂O-MeCN) 312 nm (ϵ_{\max} , 15 000); $\nu_{\max}(\text{CCl}_4)$ 3 480 (OH) and 1 625 (C=C) cm^{-1} ; $\delta_{\text{H}}(\text{CDCl}_3; 90 \text{ MHz})$ 7.10 (1 H, s, ArH), 6.90 (1 H, s,

exchangeable), 6.25 (1 H, dd, J 18, 10 Hz), 5.25 (1 H, dd, J 18, 1 Hz), 5.15 (1 H, dd, J 10, 1 Hz), 2.50 (3 H, s), 2.20 (3 H, s), and 1.55 (6 H, s) (Found: M^+ , 270.0439. $C_{13}H_{17}BrO$ requires M , 270.0439); m/z 270 (M^+ , 10%), 268 (M^+ , 10), 253 (20), 251 (20), 174 (100), 160 (40), and 159 (20); 3-(3,6-dimethyl-2-hydroxyphenyl)-3-methylbut-1-ene (7; $R = X = H$) from (24; $X = H$), $\lambda_{max.}$ (0.2M-KOH, 1:1 H_2O -MeCN) 301 nm (ϵ 15 000); $\nu_{max.}$ (CCl_4) 3 480 (OH) and 1 620 (C=C) cm^{-1} ; δ_H ($CDCl_3$; 60 MHz) 6.74 (1 H, d, J 8 Hz, ArH), 6.42 (1 H, d, J 8 Hz, ArH), 6.25 (1 H, dd, J 18, 10 Hz), 6.15 (1 H, s, exchangeable), 5.25 (1 H, dd, J 18, 1 Hz), 5.15 (1 H, dd, J 10, 1 Hz), 2.50 (3 H, s), 2.20 (3 H, s), and 1.60 (6 H, s) (Found: M^+ , 190.1358. $C_{13}H_{18}O$ requires M , 190.1358); m/z 190 (M^+ , 35%), 175 (100), 161 (25), 160 (22), 147 (29), and 123 (25); 3-(5-acetyl-3,6-dimethyl-2-hydroxyphenyl)-3-methylbut-1-ene (7; $R = H$, $X = COCH_3$) from (24; $X = COCH_3$); $\lambda_{max.}$ (0.2M-KOH, 1:1 H_2O -MeCN) 350 nm (ϵ 17 000); $\nu_{max.}$ (CCl_4) 3 460 (OH), 1 690 (C=O), and 1 620 (C=C) cm^{-1} ; δ_H ($CDCl_3$; 60 MHz) 7.40 (1 H, s, ArH), 7.00 (1 H, s, exchangeable), 6.34 (1 H, dd, J 18, 10 Hz), 5.25 (1 H, dd, J 18, 1 Hz), 5.20 (1 H, dd, J 10, 1 Hz), 2.70 (3 H, s, $COCH_3$), 2.50 (3 H, s), 2.15 (3 H, s), and 1.52 (6 H, s) (Found: M^+ , 232.1452. $C_{15}H_{20}O_2$ requires M , 232.1453); m/z 232 (M^+ , 48%), 217 (100), 175 (42), 173 (20), 159 (20), 119 (30), 117 (30), and 91 (45); 3-(3,6-dimethyl-5-formyl-2-hydroxyphenyl)-3-methylbut-1-ene (7; $R = H$, $X = CHO$) from (24; $X = CHO$), $\lambda_{max.}$ (0.2M-KOH, 1:1 H_2O -MeCN) 360 nm (ϵ 17 500); $\nu_{max.}$ (CCl_4) 3 450 (OH), 2 880 (CHO), 1 690 (C=O), 1 620 (C=C), and 1 600 (Ar) cm^{-1} ; δ_H ($CDCl_3$; 60 MHz) 10.10 (1 H, s, CHO), 7.70 (1 H, s, exchangeable), 7.50 (1 H, s, ArH), 6.40 (1 H, dd, J 18, 10 Hz), 5.35 (1 H, dd, J 18, 1 Hz), 5.30 (1 H, dd, J 10, 1 Hz), 2.80 (3 H, s), 2.20 (3 H, s), and 1.65 (6 H, s) (Found: M^+ , 218.1310. $C_{14}H_{18}O_2$ requires M , 218.1310); m/z 218 (M^+ , 77%), 217 (11), 203 (50), 189 (25), 175 (100), 160 (21), 147 (43), and 91 (38); trans-4-(5-bromo-3,6-dimethyl-2-hydroxyphenyl)-4-methylpent-1-ene (7; $R = CH_3$, $X = Br$) from (17), $\lambda_{max.}$ (0.2M-KOH, 1:1 H_2O -MeCN) 312 nm (ϵ 15 000); $\nu_{max.}$ (CCl_4) 3 440 cm^{-1} (OH); δ_H ($CDCl_3$; 90 MHz) 7.28 (1 H, s, ArH), 6.70 (1 H, s, exchangeable, OH), 6.00 (1 H, d, J 15 Hz, =CH), 5.57 (1 H, dq, J 15, 5 Hz, =CHCH₃), 2.35 (3 H, s, ArCH₃), 2.15 (3 H, s, ArCH₃), 1.79 (3 H, d, J 5 Hz, =CCH₃), and 1.50 (6 H, s, CH₃) (Found: M^+ , 282.0606. $C_{14}H_{19}BrO$ requires M , 282.0604); m/z 284 (M^+ , 30%), 282 (M^+ , 30), 269 (20), 267 (20), 254 (40), 252 (40), and 174 (100).

Product Characterisation.—The procedure used in preparative-scale cyclisations was as follows. The olefin (typically 30 mg) was dissolved in a suitable buffer (10 ml; made up in the same way as for the kinetic experiments) and this was incubated at 39 °C for 10 half-lives. The solution was then poured into brine and extracted with dichloromethane. The extract was dried and concentrated *in vacuo*, before purification by p.t.l.c. if necessary. Thus phenol-olefin (5; $X = Br$) gave 6-bromo-2,4,4,5,8-pentamethyl-3,4-dihydro-2H-1-benzopyran (6; $X = Br$), $\nu_{max.}$ (CCl_4) no diagnostic peaks, δ_H ($CDCl_3$; 90 MHz) 7.28 (1 H, s, ArH), 4.20 (1 H, m, OCH), 2.57 (3 H, s, ArCH₃), 2.19 (3 H, s, ArCH₃), 1.67 (2 H, m, CH₂), 1.47 (3 H, s, CH₃), 1.44 (3 H, s, CH₃), and 1.38 (3 H, d, J 7 Hz, CH₃CHO) (Found: M^+ , 284.0609. $C_{14}H_{19}BrO$ requires M , 284.0608); m/z 284 (M^+ , 50%), 282 (M^+ , 50), 170 (22), 168 (40), 178 (12), 176 (15), 175 (45), 173 (25), 135 (100), 105 (25), and 69 (22).

Alkene (7; $R = H$, $X = Br$) gave 5-bromo-2,3,3,4,7-pentamethyl-2,3-dihydrobenzofuran (26), δ_H ($CDCl_3$; 90 MHz) 7.15 (1

H, s, ArH), 4.21 (1 H, q, J 5 Hz, OCH), 2.32 (3 H, s, ArCH₃), 2.09 (3 H, s, ArCH₃), 1.30 (3 H, d, J 5 Hz, OCHCH₃), 1.30 (3 H, s, CH₃), and 1.04 (3 H, s, CH₃) (Found: M^+ , 270.0432. $C_{13}H_{17}BrO$ requires M , 270.0433); m/z 270 (M^+ , 32%), 268 (M^+ , 32), 255 (11), 253 (15), 174 (100), 159 (11), 146 (16), and 135 (12).

A similar experiment with the *trans*-alkene (19) gave two products. These were separated by p.t.l.c. (eluant hexane). The faster running isomer (R_F 0.40) was assigned the structure 5-bromo-2-ethyl-3,3,4,7-tetramethyl-2,3-dihydrobenzofuran (27) on this basis of its spectra, δ_H ($CDCl_3$; 90 MHz) 7.15 (1 H, s, ArH), 3.39 (1 H, m, OCH), 2.33 (3 H, s, ArCH₃), 2.11 (3 H, s, ArCH₃), 1.55 (2 H, m, CH₂), 1.35 (3 H, s, CH₃), 1.15 (3 H, t, J 5 Hz, CH₂CH₃), and 1.12 (3 H, s, CH₃) (Found: M^+ , 282.0621. $C_{14}H_{19}BrO$ requires M , 282.0621); m/z 284 (M^+ , 15%), 282 (M^+ , 20), 270 (28), 268 (28), 218 (25), 188 (62), 176 (100), 160 (18), 159 (18), 135 (30), and 101 (15). The second compound (R_F 0.35) had spectra identical to those obtained previously for (6; $X = Br$).

G.l.c. analysis of the crude reaction mixture (Carbowax 20 M column, oven temperature 200 °C, zone temperature 250 °C, carrier flow 37.5 lb in⁻²) showed (21) and (19) (retention times 11.2 and 14.6 min, respectively) had been formed in a 18:1 ratio.

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