Intramolecular Nucleophilic Addition of Phenolate to Unactivated Double and Triple Bonds. Relative Reactivity, Regiospecificity, Stereochemistry, and Mechanism

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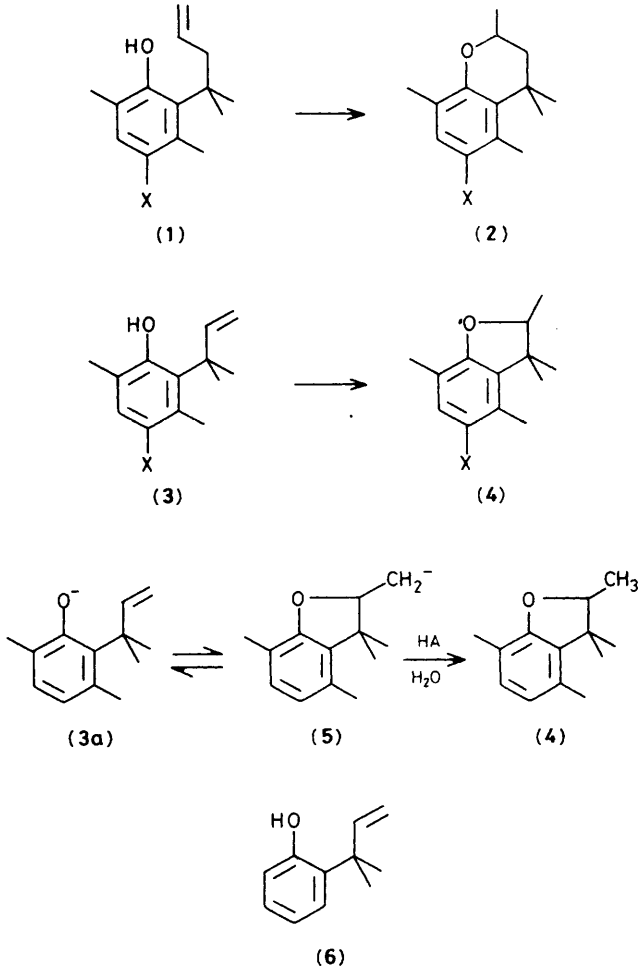
The intramolecular nucleophilic addition of phenolate oxygen to the unactivated triple bond of a series of terminal acetylenes (**11**) is a two-step process, involving rate-determining formation of a vinyl carbanion. Reaction is almost 10^4 times faster than the cyclisation of the corresponding alkene (a factor already reduced by the change in mechanism). The cyclisation of the corresponding methyl acetylene (**18**) is over 10^3 times slower, and is general acid-catalysed, presumably because the methyl-substituted vinyl carbanion is a prohibitively high-energy species. It is clear that the much greater reactivity of alkynes, compared with the alkenes, towards nucleophilic attack is primarily a transition-state property, reflecting the greater stability of the sp^2 (compared with sp^3)-hybridised carbanions produced. Antiperiplanar addition is probably involved in all these reactions. There is little difference in intrinsic reactivity between 5-*exo*, 6-*exo*, and 6-*endo-trig* olefin cyclisations, but a stronger preference for the 5-*exo* over the 6-*endo-dig* mode for the acetylene reaction.

We have described the synthesis of two systems (**1**) and (**3**) in which the phenolate oxygen adds readily to a neighbouring monoalkylethylene, with assistance from solvent water, or a protonated amine, acting as a general acid.[1] In this paper we compare these remarkable reactions of unactivated alkenes with similar intramolecular additions to triple bonds. Nucleophilic addition to acetylenes is a more familiar process,[2–4] and the Reppe vinylation[5] of alcohols with acetylene itself proceeds smoothly under basic conditions at high temperatures. So acetylenes are evidently more reactive towards nucleophiles than are the corresponding olefins. However, no simple comparison of reactivity is available.

The mechanism of cyclisation of (**3**) to (**4**) appears to be very simple.[1] The nucleophilic phenolate oxygen adds to the double bond, up to the point where bond formation, and hence development of the primary carbanion (**5**) is well advanced. Ion (**5**) generally reverts to starting materials, but in the presence of a molecule of general acid, preassociated in an encounter complex, it can be protonated rapidly enough to trap it as stable product (**4**).[1] Thus we have nucleophilic addition to an alkene in a system of well defined geometry, uncomplicated by the stereoelectronic requirements of electron-withdrawing groups—what appears, in fact, to be an ideal system for the study of such basic questions as intrinsic reactivity, the stereochemistry of the addition process, and regiospecificity in the framework of Baldwin's rules.[6]

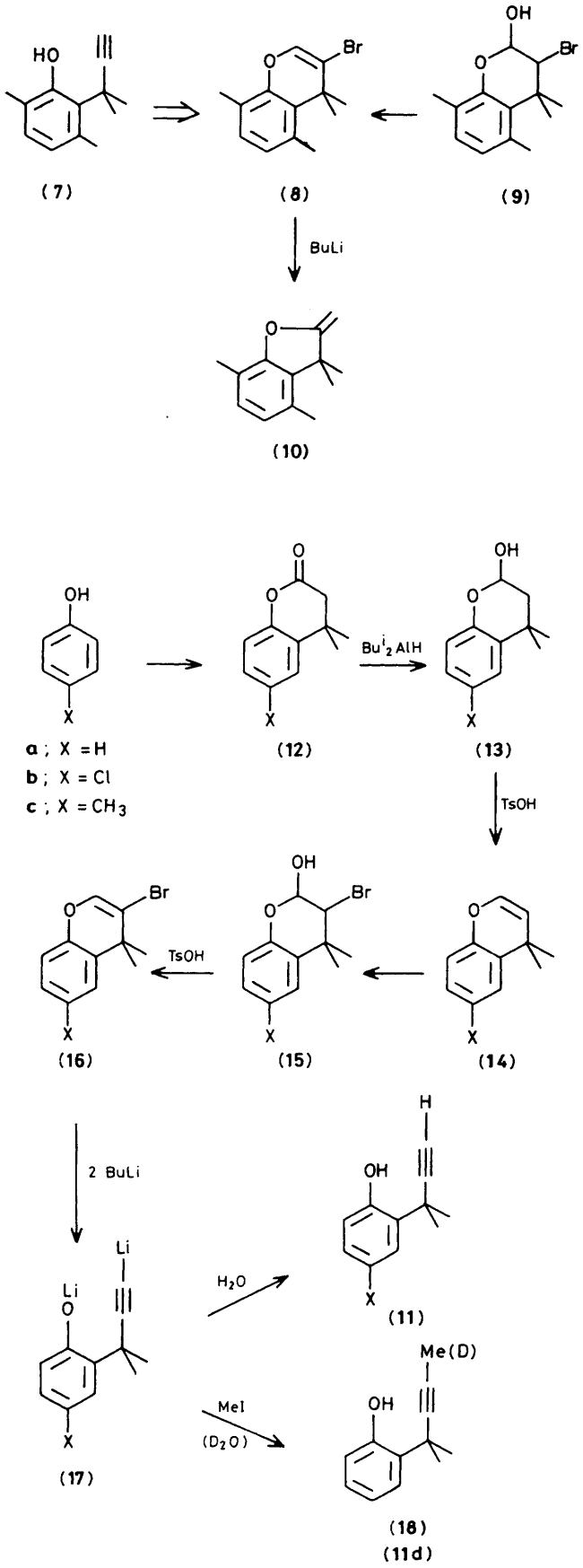
Results

For this work we prepared a series of phenol-acetylenes (Scheme 1) corresponding to (**3**), and for comparison the phenol-olefin (**6**).[7] Our initial target molecule was the alkyne (**7**), which we hoped to prepare from the vinyl bromide (**8**) (a compound we had already prepared inadvertently[1]) by our zinc-mediated elimination reaction. We devised an efficient synthesis of (**8**), by dehydration of the lactone (**9**), but (**8**) was recovered unchanged from Zn in 95% ethanol under our usual conditions.[1] Metallation with n-butyl-lithium gave a reaction, but the only product was the vinyl ether (**10**), presumably the result of premature cyclisation of the desired alkyne (**7**). The use of two equivalents of Bu^nLi, which should generate the less electrophilic acetylide anion, gave no improvement, so we decided to prepare an alkyne (**11**) which was expected to be less rapidly cyclised.



The route chosen (Scheme 1) was analogous to that which failed only at the last stage for the preparation of (**7**).

As part of a proposed synthesis of an analogue of olefin (**1**) we also prepared the protected alkyne (**21**) by the route shown.



Scheme 1.

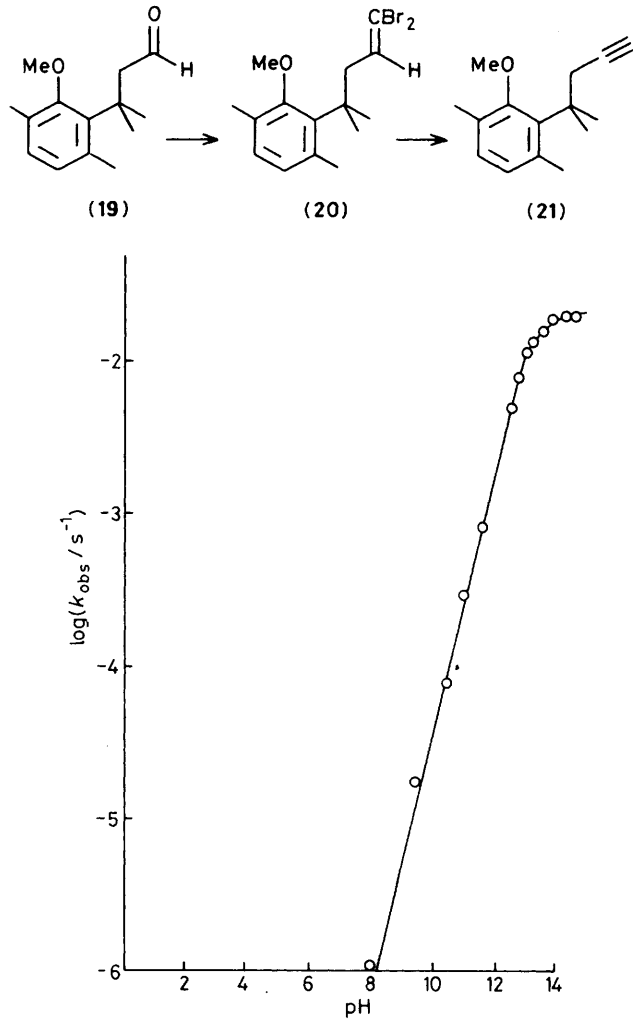


Figure. pH–rate profile for the cyclisation of (**11a**) in 1:1 aqueous acetonitrile at 39 °C and ionic strength 0.2M (KCl). Open circles are experimental points, the curve is calculated (for constants see Tables 1 and 2), assuming that only the phenolate anion is reactive

This compound was used in the equilibrium isotope effect study described later.

Product Characterisation.—Preparative-scale cyclisations were carried out as described in the preceding paper,[1] on both (**11a**) and its methyl derivative (**18**). In both cases only a single product was detected.

Alkyne (**11a**) gave 2,3-*dihydro*-3,3-*dimethyl*-2-*methylenebenzofuran* (**22**), $\nu_{max.}(CCl_4)$ 1 640 cm^{-1} (OC=C); δ ($CDCl_3$; 60 MHz) 7.25—6.70 (4 H, m, Ar), 4.64 (1 H, d, *J* 3 Hz, =CH), 4.21 (1 H, d, *J* 3 Hz, =CH), and 1.45 (6 H, s, CH_3) (Found: M^+, 160.0890. $C_{11}H_{12}O$ requires *M*, 160.0890); *m/z* 161 (*M* + 1, 100%), 160 (M^+, 5), 145 (15), 135 (30), 121 (8), and 107 (5).

Methylalkyne (**18**) gave (Z)-3,3-*dimethyl*-2-*ethylidene*-2,3-*dihydrobenzofuran* (**23**), $\nu_{max.}(CCl_4)$ 1 700 cm^{-1} (C=C); δ ($CDCl_3$; 90 MHz) 7.30—6.75 (4 H, m, Ar), 4.52 (1 H, q, *J* 7 Hz, =CH), 2.72 (3 H, d, *J* 7 Hz, =CHCH_3), and 1.36 (6 H, s, CH_3).

Product Isotope Effects.—These were measured by high-resolution mass spectrometry, on samples prepared in the same way, in 1:1 (v/v) aqueous acetonitrile made up with 1:1 (molar ratio) H_2O and D_2O.

The cyclisation of the alkene (**3**; X = Br) gave (**4**; X = Br).

Table 1. Rate constants for the cyclisation of phenol-acetylene (**11a**), at 39 °C and ionic strength 0.2M (KCl) in 1:1 (v/v) aqueous acetonitrile

Conditions (pH)	Runs	k_{obs}/s^{-1}
0.20M-KOH	6	$1.87 \pm 0.09 \times 10^{-2}$
0.20M-KOD in D_2O	6	$1.88 \pm 0.03 \times 10^{-2}$
0.10M-KOH	4	$1.83 \pm 0.03 \times 10^{-2}$
0.03M-KOH	3	$1.76 \pm 0.05 \times 10^{-2}$
0.02M-KOH	3	$1.49 \pm 0.07 \times 10^{-2}$
0.01M-KOH	3	$1.16 \pm 0.06 \times 10^{-2}$
0.005M-KOH	3	$1.08 \pm 0.05 \times 10^{-2}$
0.003M-KOH	3	$7.34 \pm 0.15 \times 10^{-3}$
0.002M-KOH	3	$4.61 \pm 0.09 \times 10^{-3}$
Piperidine, 80% FB (11.25)	2	$7.50 \pm 0.21 \times 10^{-4}$
Piperidine, 50% FB (10.56)	3	$2.59 \pm 0.08 \times 10^{-4}$
n-Butylamine, 50% FB (10.12)	2	$6.80 \pm 0.07 \times 10^{-5}$
Ethanolamine, 50% FB (9.35)	2	$1.52 \pm 0.15 \times 10^{-5}$
TRIS, 50% FB (8.08)	2	$1.05 \pm 0.04 \times 10^{-6}$
0.20M-KOH, 25.9 °C	3	$5.03 \pm 0.06 \times 10^{-3}$
0.20M-KOH, 31.4 °C	3	$9.18 \pm 0.09 \times 10^{-3}$
0.20M-KOH, 45.0 °C	3	$3.73 \pm 0.02 \times 10^{-2}$
0.20M-KOH, 51.0 °C	3	$6.89 \pm 0.01 \times 10^{-2}$
0.20M-KOH, 59.4 °C	3	$1.44 \pm 0.11 \times 10^{-1}$
$\Delta H^{\ddagger}$/kcal mol^{-1}		19.0 ± 1.0
$\Delta H^{\ddagger}$/kJ mol^{-1}		79 ± 4
$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}		-4.4 ± 0.1
$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}		-18.3 ± 0.5
pK_a		12.6 ± 0.2

Measurements of the relative intensities of both 270—271 and 268—269 peaks for four separate scans gave the product isotope effect (p.i.e.) as $M/(M+1) = 1.9 \pm 0.2$

The cyclisation of the alkyne (**11a**) under these conditions gave *three* molecular ion peaks, M, $M+1$, and $M+2$, at m/z 160, 161, and 162, in the ratios 4.0:4.1:1.0, indicating that exchange of the acetylenic proton had occurred. This was confirmed by two ^{1}H n.m.r. experiments.

The cyclisation of alkyne (**11a**) in deuteriated solvent (0.2M-KOD in 1:1 D_2O–MeCN) gave exclusively (^{1}H n.m.r.) the doubly deuteriated vinyl ether (see Scheme 2), $\nu_{max.}(CCl_4)$ 1 650 cm^{-1} (C=C); δ ($CDCl_3$; 60 MHz) 7.25—6.50 (4 H, m, ArH) and 1.45 (6 H, s, CH_3) (Found: M^+, 162.1049. $C_{11}H_{10}D_2O$ requires M, 162.1049); m/z 162 (M^+, 41%), 135 (100), 121 (20), 117 (15), 107 (50), and 91 (25).

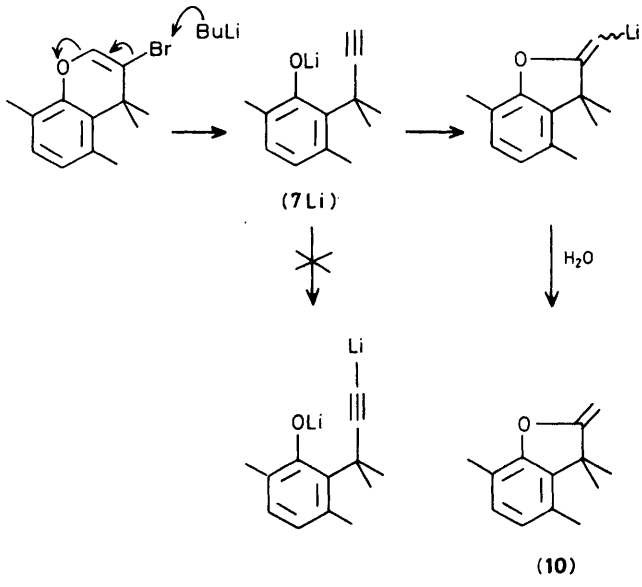
The cyclisation in H_2O of the deuteriated alkyne (**11d**) similarly gave only protiovinyl ether (**22**).

Rate Measurements.—Phenol-acetylene (**11a**) cyclised to the enol ether (**22**) at a significant rate only at high pH. The pH–rate profile (Figure) follows the dissociation curve of the phenol (pK_a 12.6), and no measurable reaction of the neutral compound was observed. The data are given in Table 1. In contrast to results with the corresponding phenol-olefin (**3**), the reaction is not buffer catalysed, and shows no solvent deuterium isotope effect.

Two ring-substituted derivatives (**11b** and **c**) were also cyclised under the same conditions, allowing the construction of a three-point Hammett plot, enough to define the reaction constant, ρ 1.4 ± 0.1, identical, within experimental error, to the value obtained for the cyclisation of the phenol-olefins (**3**) under the same conditions. These data, and rate constants for the cyclisation of the disubstituted acetylene (**18**), and the olefins (**6**), (**3**; X = H), and (**25**) for comparison, are listed in Table 2.

Table 2. Effects of substituents on rate constants for cyclisation of phenol-acetylene (**11a**) and the corresponding olefin, at 39 °C in 0.20M-KOH in 1:1 (v/v) aqueous acetonitrile

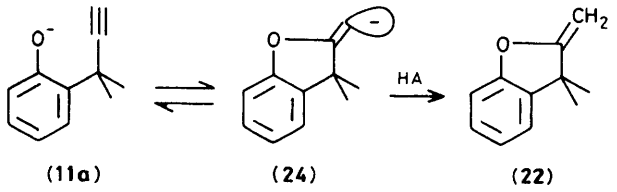
Compound	Runs	k_{obs}/s^{-1}
(**11a**)	6	$1.87 \pm 0.09 \times 10^{-2}$
(**11b**)	3	$7.66 \pm 0.03 \times 10^{-3}$
(**11c**)	6	$2.72 \pm 0.18 \times 10^{-2}$
Hammett ρ		1.4 ± 0.1
(**18a**)	3	$1.36 \pm 0.03 \times 10^{-5}$
(**18a**) (in D_2O)	2	$1.00 \pm 0.12 \times 10^{-5}$
k_{H_2O}/k_{D_2O}		1.4 ± 0.1
(**18a**), piperidine buffer, 80% FB, pH 11.25		
0.125M	1	9.20×10^{-7}
0.25M	1	1.03×10^{-6}
0.375M	1	1.13×10^{-6}
0.50M	1	1.30×10^{-6} dm^3 mol^{-1} s^{-1}
(**6**)	2	$2.08 \pm 0.04 \times 10^{-6}$
(**3**)	1	$8.34 \pm 0.04 \times 10^{-3}$
(**25**)	3	$2.03 \pm 0.08 \times 10^{-3}$



Discussion

There is a very substantial difference in reactivity towards the intramolecular nucleophile between the acetylenic and olefinic systems. Our attempted preparation of (**7**), for example, gave only the enol ether (**10**), suggesting that the phenol-acetylene anion cyclises faster than it can be deprotonated to dianion. Our mechanistic investigation therefore involved the less reactive system (**11**). For comparison we measured the rate of cyclisation of the corresponding phenol-olefin (**6**), and found that the acetylene is more reactive towards intramolecular nucleophilic attack by a factor of almost 10^4. This figure compares well with the factor of at least 10^3 which may be deduced from the incomplete data of Miller for the addition of methoxide ion to phenylacetylene and styrene.[8]

There is also an important qualitative difference between these two reactions. The cyclisation of the acetylene (**11a**) is not general base-catalysed by amine buffers,[1] and shows no solvent deuterium isotope effect. We presume that this is a consequence of the increased stability expected for a vinyl carbanion *vis à vis* a primary alkyl carbanion.[9] If the vinyl carbanion (**24**) is stable enough to be a full intermediate, either its formation or its



(11a) (24) (22)

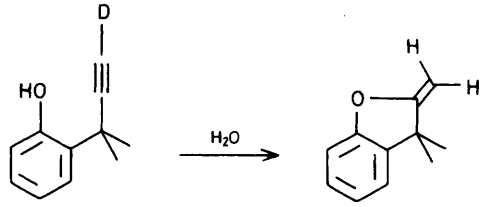
protonation can be rate determining. Apparently the formation step is rate determining in this case, as shown most clearly by the evidence that a proton is not being transferred in the transition state. The near-zero entropy of activation and Hammett ρ value (1.4 ± 0.1) are consistent with this mechanistic formulation, but do not specifically require it (being numerically very close to the values observed for the corresponding reaction of the olefin (**3**; X = Br).[1] In particular, the negative charge on the phenolate oxygen has been neutralised to almost the same extent in the transition states for both reactions.

It seems that the acetylene cyclisation lies close to the dividing line between these two mechanisms, because the introduction of the C-Me group, in (**18**), results in the appearance of general acid catalysis and a small, but significant, solvent deuterium isotope effect (Table 2). Presumably the *C*-methyl group destabilises the vinyl carbanion to the point where it is again no longer viable as a full intermediate, and general acid catalysis is enforced, as it appears to be in the olefin cyclisation.[1] This is consistent with the remarkably large effect of this *C*-methyl group on the rate of the reaction: (**18**) is cyclised over 10^3 times more slowly than the ≡CH compound (**11a**), whereas the introduction of a *C*-methyl substituent on the terminal CH_2 group decreases the rate of the olefin cyclisation [(**3**; X = H) compared with (**25**)] by a factor of only four. This indicates that the general acid involved in the olefin cyclisation has a substantial stabilising effect on the developing primary carbanion, even though the actual degree of proton transfer in the transition state is small.[1] It also sheds important light on the general problem of the relative reactivity of alkynes and alkenes towards nucleophiles.

Calculations show, not expectedly, that electron densities are higher in the region of *sp*- compared with sp^2-hydridised carbon;[4] so simple frontier orbital considerations[10] would predict that nucleophiles would attack *alkenes* more readily. Dickstein and Miller[4] conclude therefore that reactivity must be controlled largely by transition state stabilities, and our results provide strong support for this interpretation, at least for the simple nucleophilic addition processes we have studied. In both cases, of addition to double and triple bonds, the transition state, as measured by the degree of neutralisation of the phenolate oxygen (Hammett ρ value) is late, indicating a substantial build-up of negative charge in the region of the terminal carbon atom of the π-bond under attack. This can clearly be accommodated more effectively on an sp^2 than on a less electronegative sp^3-hybridised carbon.

Stereochemistry of Addition.—The intramolecular addition of phenolate oxygen to the double bonds of compounds (**1**) and (**3**) is a concerted process, albeit a loose one, and might be expected to be stereospecific. We presume that this is the case, and expect addition to be specifically antiperiplanar, on the following grounds.* (1) The reaction is concerted (general acid-catalysed),[1] and the kinetic isotope effect[1] is identical with the product isotope effect (k_{H_2O}/k_{D_2O} 1.9 ± 0.2); so the proton being transferred to the terminal CH_2 group in the transition state is present in the product. (2) The reaction is mechanistically closely similar to the transannular addition of amine nitrogen to an unactivated double bond which we studied previously, and showed involves antiperiplanar addition.[11] (3) The reverse reaction, though not observable under mild conditions, would be a concerted *E*2 reaction, and certainly expected to involve antiperiplanar stereochemistry.

The cyclisation of the phenol-acetylenes (**11**), on the other hand, is not a concerted process, and the stereochemistry of addition will reflect the configurational stability of the vinyl carbanion intermediate (**24**). Our first results showed only that the cyclisation is slower than the exchange of the acetylenic proton in 0.2M-KOH. Even in buffers near pH 9 the cyclisation of (**11d**) in H_2O gave exclusively the protio-product (**22**). [Conversely, the reaction of (**11a**) in D_2O gave the $=CD_2$ product.]



(11d) (22)

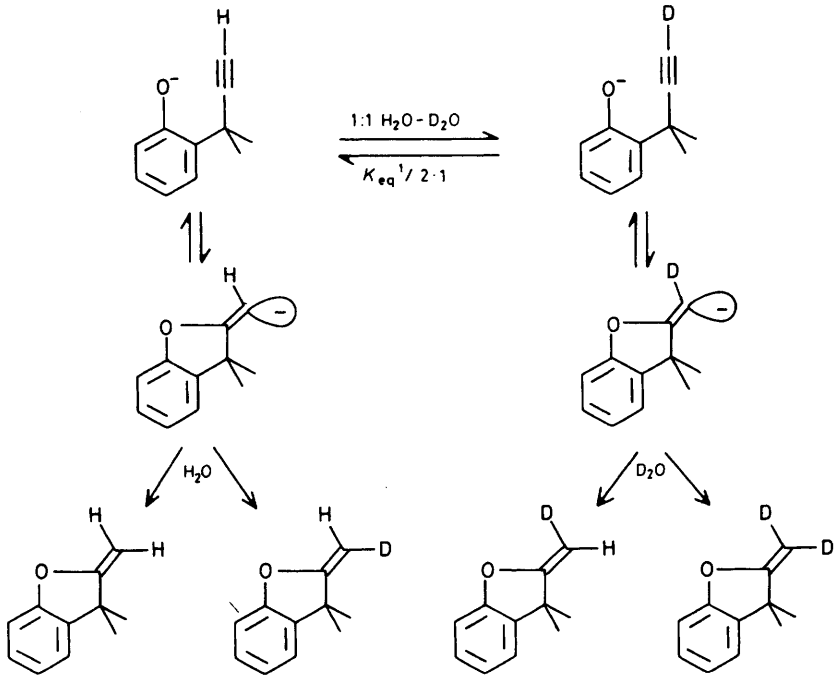
On reaction in a 1:1 (mole ratio) mixture of H_2O and D_2O a mixture of all four possible deuteriated derivatives of (**10**) was obtained, comprising CH_2, CD_2 and *E*- and *Z*-CHD compounds (Scheme 2). From high-resolution mass spectrometry the CH_2:CD_2 ratio was determined as 4.0:1. In the 400 MHz ^{1}H n.m.r. spectrum the signals from the vinyl protons of the CH_2 and *E*- and *Z*-CHD compounds are cleanly resolved, and can be integrated to give ratios of 2:1:1. Thus the product ratio CH_2:CHD:CDH:CD_2 is 4:2:2:1; and the equal amounts of isomeric monodeuterio-products in particular are consistent with an intermediate carbanion of rapidly equilibrating configuration.

This seems most unlikely, in view of the high barriers to inversion, in the region of 30—40 kcal mol^{-1}, estimated for vinyl carbanions.[12–15] The key to the isotopic distribution in the product turns out to be a substantial *equilibrium* isotope effect on the starting acetylenes. We have measured (by high-resolution mass spectrometry) ≡CH/≡CD ratios for both phenylacetylene and for the protected substrate analogue (**21**), after equilibration in 1:1 (v/v) aqueous acetonitrile made up with 1:1 (molar ratio) H_2O:D_2O, as used in the product isotope effect experiments, and find ratios of 2.1 ± 0.1 in both cases. This equilibrium isotope effect is, coincidentally, identical within experimental error with the *kinetic* isotope effect on the protonation of the vinyl carbanion.† The observed isotope distribution can then be explained in terms of stereospecific (presumed *trans*) addition, as shown in Scheme 2; though the coincidence of kinetic and equilibrium isotope effects means that we cannot formally rule out the possibility that addition is non-stereospecific.

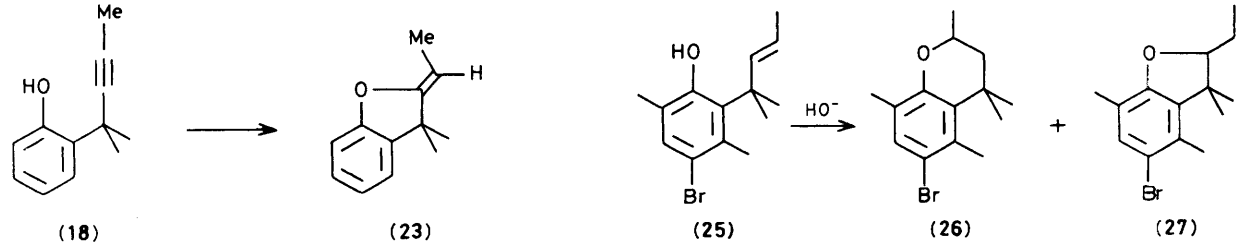
The preparative-scale cyclisation of the methylacetylene (**18**) did give a single product, identified on the basis of n.m.r. chemical shift arguments as (**23**), so stereospecific *anti*-addition does occur in this case. But since the cyclisation of (**18**) is general acid-catalysed, no discrete vinyl carbanion is involved in this reaction, and no conclusions about configurational stability can be drawn.

* It is a non-trivial matter to demonstrate stereospecific addition when one of the groups generated is CH_3. We had intended to do the necessary experiments using *cis*- and *trans*-isomers of the =CHMe olefin (**25**), but we were unable to prepare the *cis*-isomer: all reactions involving electrophilic reagents led to premature cyclisation of the protected (OMe) phenol,[1] and attempted photoisomerisation failed.

† *Observed* only as a product isotope effect, because this step is not rate determining.



Scheme 2.

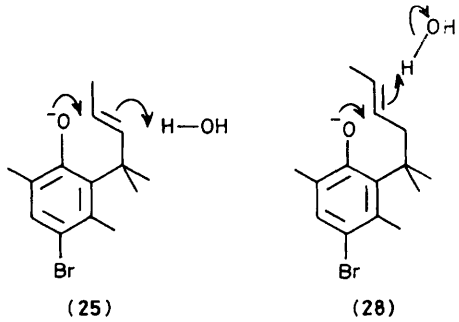


(18) (23) (25) (26) (27)

Regioselectivity.—The cyclisations of the terminal alkenes (**1**) and (**3**),[1] and of the terminal acetylenes (**11**), all give single products (**2**), (**4**), and (**22**), respectively, resulting from regiospecific 5- or 6-*exo* addition of oxygen to the substituted end of the multiple bond. This is to be expected, especially in view of the large substituent effects of a methyl group on the rate of the acetylene reaction, because *endo*-addition would lead to a more heavily alkyl-substituted, and thus less stable, carbanionoid intermediate or transition state.

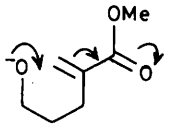
We therefore prepared the electronically symmetrical compounds (**25**)[1] and (**18**), and examined the products of cyclisation under our standard conditions (0.2M-KOH in 50% aqueous acetonitrile). Products of both 5-*exo* and 6-*endo-trig* addition were isolated from the cyclisation of the alkene (**25**),[1] in a ratio (**27**):(**26**) of 18:1. This is consistent with Baldwin's rules,[6] according to which both processes are deemed favourable, and with the general observation that five-membered rings are formed more rapidly than six. It is not possible to put a figure on this ring-size effect, since it varies a great deal from system to system,[16] but any strictly geometrical preference for 5-*exo versus* 6-*endo-trig* addition must be small.

We can also compare, rather more accurately, a 6-*endo versus* a 6-*exo-trig* addition, since we have measured rate constants for both processes. Dissecting the rate constant (Table 2) for the disappearance of (**25**) using the measured product ratio gives a rate constant for the 6-*endo-trig* cyclisation of 1.13×10^{-4} s^{-1}. The rate of the 6-*exo-trig* cyclisation of (**1**; X = Br) was measured previously:[1] allowing a factor of 4.35 for the



(25) (28)

retarding effect of a terminal methyl group [as measured for the 5-*exo-trig* reaction of (**25**) compared with that of (**3**; X = Br)] allows an estimate of 3.2×10^{-4} s^{-1} for the rate constant for cyclisation (6-*exo-trig*) of the dialkylethylene (**28**). This is less than three times faster than the 6-*endo-trig* cyclisation of (**25**), so that there appears to be no important difference in intrinsic reactivity between the *endo* and *exo* modes of cyclisation at trigonal centres to form six-membered rings. This is consistent with Baldwin's rules as originally formulated,[6] which classify both 6-*exo* and 6-*endo-trig* processes as favourable. A later experiment,[17] which showed that the 6-*endo-trig* cyclisation of (**29**) is much (10^2—10^3 times) slower than the similar 6-*exo-trig* reaction of (**30**), is not a satisfactory measure of relative reactivity in the two modes, because the two reactions give a



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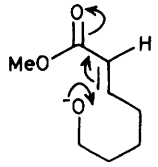

(30)

tertiary and a secondary carbanion, respectively. The effect of an extra alkyl substituent on the stability of a carbanion (expected to be a full intermediate in a Michael addition) can be large, as shown for example by the 10^3-fold slower cyclisation of the phenol-alkyne (**18**) studied in this work, and could account for much if not all the observed difference in reactivity.

The cyclisation of the electronically symmetrical acetylene (**18**) gives a single product, identified as the *Z*-alkene (**23**). In this case, therefore, 5-*exo-dig* addition is favoured more decisively over the 6-*endo* mode. (The difference is not necessarily large: experimentally we can say only that the difference is at least 100:1 for the alkyne, compared with 18:1 for the alkene.) Baldwin's rules, as originally formulated, suggested that *endo-dig* addition was favoured for the formation of five- and six-membered rings.[6] This is clearly not the case for the cyclisation of (**18**), and this preference for the *exo* mode at *sp*-hybridised centres is probably general.[4]

Experimental

Coumarins (**12**) were prepared as described in the previous paper.[1] 4,4-*Dimethyl*-3,4-*dihydro*-2H-1-*benzopyran*-2-*one* (**12a**) had b.p. 80—85 °C at 0.1 mmHg (lit.,[18] 81—83 °C at 0.15 mmHg), $\nu_{max.}(CCl_4)$ 1 780 (C=O) and 1 600 (Ar) cm^{-1}; δ ($CDCl_3$; 60 MHz) 7.45—6.90 (4 H, m, ArH), 2.60 (2 H, s, CH_2), and 1.45 (6 H, s, CH_3) (Found: M^+, 176.0841. Calc. for $C_{11}H_{12}O_2$: *M*, 176.0841); *m/z* 176 (M^+, 15%), 161 (28), 101 (32), and 59 (100). 6-*Chloro*-4,4-*dimethyl*-3,4-*dihydro*-2H-1-*benzopyran*-2-*one* (**12b**) had m.p. 91—93 °C (lit.,[18] 90—91 °C), $\nu_{max.}(CCl_4)$ 1 780 (C=O) and 1 500 (Ar) cm^{-1}; δ ($CDCl_3$; 60 MHz) 7.30—6.80 (4 H, m, ArH), 2.61 (2 H, s, CH_2), and 1.34 (6 H, s, CH_3) (Found: M^+, 210.0440. Calc. for $C_{11}H_{11}ClO_2$: *M*, 210.0441); *m/z* 212 (M^+, 32%), 210 (M^+, 100), 197 (33), 195 (98), 170 (22), 168 (65), and 153 (28). 4,4,6-*Trimethyl*-3,4-*dihydro*-2H-1-*benzopyran*-2-*one* (**12c**) had b.p. 98—100 °C at 0.1 mmHg, $\nu_{max.}(CCl_4)$ 1 775 (C=O), 1 600, and 1 500 (Ar) cm^{-1}; δ ($CDCl_3$; 60 MHz) 7.15—6.70 (3 H, m, ArH), 2.50 (2 H, s, CH_2), 2.25 (3 H, s, $ArCH_3$), and 1.25 (6 H, s, CH_3) (Found: M^+, 190.0983. $C_{12}H_{14}O_2$ requires *M*, 190.0984); *m/z* 190 (M^+, 95%), 175 (100), 149 (11), 148 (58), 147 (12), 133 (23), 119 (10), 91 (15), and 73 (18).

These lactones were then reduced with di-isobutylaluminium hydride to the lactols (**13**). 4,4-*Dimethyl*-3,4-*dihydro*-2-*hydroxy*-2H-1-*benzopyran* (**13a**) had $\nu_{max.}(CCl_4)$ 3 600 cm^{-1} (OH); δ ($CDCl_3$; 60 MHz) 7.20—6.60 (4 H, m, ArH), 5.40 (1 H, m), 4.80br (1 H, exchangeable), 1.80 (2 H, m), 1.40 (3 H, s), and 1.35 (3 H, s) (Found: M^+, 178.0991. $C_{11}H_{14}O_2$ requires *M*, 178.0991); *m/z* 178 (M^+, 100%), 163 (62), 161 (20), 145 (52), 135 (70), 134 (36), 119 (28), 107 (50), and 91 (48). 6-*Chloro*-4,4-*dimethyl*-3,4-*dihydro*-2-*hydroxy*-2H-1-*benzopyran* (**13b**) had m.p. 93—94 °C, $\nu_{max.}(CCl_4)$ 3 600 and 3 450 cm^{-1} (OH); δ ($CDCl_3$; 60 MHz) 7.30—6.60 (3 H, m, ArH), 5.54 (1 H, m), 4.30 (1 H, d, *J* 6 Hz, exchangeable), 1.87 (2 H, m), 1.35 (3 H, s), and 1.30 (3 H, s) (Found: M^+, 212.0603. $C_{11}H_{13}ClO_2$ requires *M*, 212.0603); *m/z* 214 (M^+, 31%), 212 (M^+, 100), 199 (20), 197 (50), 181 (12), 179 (47), 171 (21), 170 (40), 169 (61), 168 (83), 153 (27), 143 (28), and 141 (65). 4,4,6-*Trimethyl*-3,4-*dihydro*-2-*hydroxy*-2H-1-*benzopyran* (**13c**) had $\nu_{max.}(CCl_4)$ 3 600 and 3 450 cm^{-1} (OH); δ ($CDCl_3$; 60 MHz) 7.05—6.55 (3 H, m, ArH), 5.50 (1 H, m), 4.46br (1 H, exchangeable), 2.20 (3 H, s, $ArCH_3$), 1.85 (2 H, m), 1.35 (3 H, s), and 1.25 (3 H, s) (Found: M^+, 192.1131. $C_{12}H_{16}O_2$ requires *M*, 192.1133); *m/z* 192 (M^+, 100%), 177 (48), 159 (30), 149 (68), 148 (50), 130 (27), and 121 (46).

3-*Bromo*-4,4,5,8-*tetramethyl*-4H-1-*benzopyran* (**8**).—Bromolactol (**9**) (0.6 g, 2.1 mmol)[1] and toluene-*p*-sulphonic acid (trace) were refluxed in dry benzene (35 ml) (using a Soxhlet extractor filled with 4A molecular sieves to remove water) for 24 h. The solvent was removed *in vacuo* and the residue purified by m.p.c. (10 g silica, eluant petrol) to give the *vinyl ether* (**8**) (0.50 g, 89%) as an oil, $\nu_{max.}(CCl_4)$ 3 200 (OCH=) and 1 635 (OC=C) cm^{-1}; δ ($CDCl_3$; 60 MHz) 6.92 (1 H, d, *J* 8 Hz, ArH), 6.75 (1 H, d, *J* 8 Hz, ArH), 6.72 (1 H, s, OCH=), 2.50 (3 H, s, $ArCH_3$), 2.19 (3 H, s, $ArCH_3$), and 1.65 (6 H, s, CH_3) (Found: M^+, 266.0316. $C_{13}H_{15}BrO$ requires *M*, 266.0315); *m/z* 268 (M^+, 10%), 266 (M^+, 10), 253 (98), 251 (100), and 128 (18).

Prepared by a similar method was 4,4-*dimethyl*-4H-1-*benzopyran* (**14a**), $\nu_{max.}(CCl_4)$ 3 070, 3 040 (=CH), and 1 670 (C=C) cm^{-1}; δ ($CDCl_3$; 60 MHz) 7.35—6.80 (4 H, m, Ar), 6.42 (1 H, d, *J* 6 Hz, OCH=), 4.68 (1 H, d, *J* 6 Hz, =CH), 2.30 (3 H, s, $ArCH_3$), and 1.38 (5 H, s, CH_3) (Found: M^+, 174.1036. $C_{12}H_{14}O$ requires *M*, 174.1037); *m/z* 174 (M^+, 15%), 159 (100), 149 (39), 145 (20), 143 (40), and 117 (20).

Prepared in the same way from the corresponding 2-hydroxy-3-bromo-compounds [(**15**), below] were 3-*bromo*-4,4-*dimethyl*-4H-1-*benzopyran* (**16a**), $\nu_{max.}(CCl_4)$ 3 090, 3 050 (=CH), 1 660 (C=C), 1 600, and 1 580 (Ar) cm^{-1}; δ ($CDCl_3$; 60 MHz) 7.30—6.60 (4 H, m, ArH), 6.63 (1 H, s, =CH), and 1.61 (6 H, s, CH_3) (Found: M^+, 238.0008. $C_{11}H_{11}BrO$ requires *M*, 238.0007); *m/z* 240 (M^+, 11%), 238 (M^+, 11), 225 (98), 223 (100), 174 (18), 158 (22), 145 (15), 144 (30), and 115 (90); 3-*bromo*-6-*chloro*-4,4-*dimethyl*-4H-1-*benzopyran* (**16b**), $\nu_{max.}(CCl_4)$ 1 665 cm^{-1} (C=C); δ ($CDCl_3$; 60 MHz) 7.38—6.62 (3 H, m, ArH), 6.71 (1 H, s, OCH=), and 1.52 (6 H, s, CH_3) (Found: M^+, 273.9577. $C_{11}H_{10}BrClO$ requires *M*, 273.9578); *m/z* 276 (M^+, 4%), 274 (M^+, 14), 272 (M^+, 12), 261 (23), 259 (100), 257 (77), 135 (32), and 118 (32); 3-*bromo*-4,4,6-*trimethyl*-4H-1-*benzopyran* (**16c**), $\nu_{max.}(CCl_4)$ 1 665 (C=C) and 1 500 (Ar) cm^{-1}; δ ($CDCl_3$; 60 MHz) 7.10—6.50 (3 H, m, ArH), 6.62 (1 H, s, =CH), 2.25 (3 H, s, $ArCH_3$), and 1.50 (6 H, s, CH_3) (Found: M^+, 252.0164. $C_{12}H_{13}BrO$ requires *M*, 252.0162); *m/z* 254 (M^+, 7%), 252 (M^+, 7), 239 (90), 237 (100), 137 (20), 135 (70), 121 (20), 96 (11), and 81 (30).

The 2-hydroxy-3-bromo-compounds (**15**) were prepared by treatment of the chromenes (**14**) with Br_2 followed by aqueous tetrahydrofuran, as described for the preparation of (**9**) in the preceding paper.[1] 3-*Bromo*-3,4-*dihydro*-2-*hydroxy*-4,4-*dimethyl*-2H-1-*benzofuran* (**15a**) had $\nu_{max.}(CCl_4)$ 3 565, 3 650 (OH), 1 600, and 1 580 (Ar) cm^{-1}; δ ($CDCl_3$; 90 MHz) 7.45—6.75 (4 H, m, ArH), 5.59 (d, *J* 8 Hz) + 5.40 (m) (1 H, OCHO), 4.30 (d, *J* 2 Hz) + 4.15 (d, *J* 8 Hz) (1 H, CHBr), 3.70br (1 H, exchangeable, OH), and 1.55 (s) + 1.50 (s) + 1.35 (s) (total 6 H, CH_3) (Found: M^+, 256.0092. $C_{11}H_{13}BrO_2$ requires *M*, 256.0091); *m/z* 258 (M^+, 41%), 256 (M^+, 41), 243 (10), 241 (10), 161 (35), 160 (20), 147 (85), 145 (40), 136 (50), 135 (100), 134 (30), 119 (30), 107 (20), and 91 (20). 3-*Bromo*-6-*chloro*-3,4-*dihydro*-2-*hydroxy*-4,4-*dimethyl*-2H-1-*benzopyran* (**15b**) had $\nu_{max.}(CCl_4)$ 3 620 and 3 500 cm^{-1} (OH); δ ($CDCl_3$; 60 MHz) 7.20—6.60 (3 H, m, ArH), 5.55 (d, *J* 8 Hz) + 5.35 (m) (1 H, OCHO), 4.40br (1 H, exchangeable, OH), 4.25 (d, *J* 2 Hz) + 4.05 (d, *J* 8 Hz) (1 H, CHBr), and 1.55 (s) + 1.48 (s) (total 6 H, CH_3) (Found: M^+, 293.9659. $C_{11}H_{12}BrClO_2$ requires *M*, 293.9659); *m/z* 294 (M^+, 14%), 292 (M^+, 60), 290 (M^+, 50), 210 (21), 183 (28), 181 (90), 171 (15), 169 (100), 168 (38), 167 (20), 153 (20), 141 (30), and 135 (30). 3-*Bromo*-3,4-*dihydro*-2-*hydroxy*-4,4,6-*trimethyl*-2H-1-*benzopyran* (**15c**) had $\nu_{max.}(CCl_4)$ 3 600, 3 450 (OH), and 1 600 (Ar) cm^{-1}; δ ($CDCl_3$; 60 MHz) 7.05—6.60 (3 H, m, Ar), 5.60—

5.20 (1 H, m, OCHO), 4.25 (d, *J* 2 Hz) + 4.10 (d, *J* 8 Hz) (1 H, CHBr), 4.20br (1 H, exchangeable, OH), 2.25 (3 H, s, $ArCH_3$), and 1.55 (s) + 1.45 (s) + 1.35 (s) (total 6 H, CH_3) (Found: M^+, 272.0237. $C_{12}H_{15}BrO_2$ requires *M*, 272.0237); *m/z* 272 (M^+, 54%), 270 (M^+, 48), 190 (28), 175 (45), 161 (60), 150 (21), 149 (100), 148 (25), 147 (30), 135 (70), 121 (25), 105 (25), and 91 (20).

3-(2-*Hydroxyphenyl*)-3-*methylbutyne* (**11a**).—n-Butyl-lithium (0.5 ml of a 1.6M solution in hexane) was added dropwise to a cooled (−78 °C) solution of the bromovinyl ether (**16a**) (100 mg, 0.4 mmol) in dry THF (1 ml) under nitrogen. The resulting solution was stirred at −78 °C for 1 h and then at room temperature for 1 h, before quenching by pouring into saturated ammonium chloride solution (5 ml). This mixture was extracted and purified by p.t.l.c. (eluant petrol) to give the *alkyne* (**11a**) (30 mg, 50%) as an oil, $\lambda_{max.}$ (0.2M-KOH, 1:1 H_2O–MeCN) 295 nm (ε 15 000); $\nu_{max.}(CCl_4)$ 3 500 (OH), 3 310 (≡CH), and 2 105 (C≡C) cm^{-1}; δ ($CDCl_3$; 90 MHz) 7.30—6.68 (4 H, m, ArH), 6.50 (1 H, s, exchangeable, OH), 2.45 (1 H, s, ≡CH), and 1.65 (6 H, s, CH_3) (Found: M^+, 160.0885. $C_{11}H_{12}O$ requires *M*, 160.0885); *m/z* 160 (M^+, 22%), 145 (100), 135 (46), 127 (15), 116 (38), 102 (25), and 91 (30).

Quenching of a solution of the dianion with a dilute solution of DCl in D_2O (*ca.* 2%) instead of ammonium chloride solution, followed by a similar work-up, gave 1-*deuterio*-3-(2-*hydroxyphenyl*)-3-*methylbutyne* (**11d**), $\nu_{max.}(CCl_4)$ 3 500 (OH) and 2 600 (CD) cm^{-1}; δ ($CDCl_3$; 90 MHz) 7.30—6.68 (4 H, m, ArH), 6.50 (1 H, s, exchangeable, OH), and 1.65 (6 H, s, CH_3) (Found: M^+, 161.0996. $C_{11}H_{11}DO$ requires *M*, 191.0996); *m/z* 161 (M^+, 20%), 146 (100), 135 (30), 128 (15), and 116 (30).

Also prepared by the above method were 3-(5-*chloro*-2-*hydroxyphenyl*)-3-*methylbutyne* (**11b**), $\lambda_{max.}$ (0.2M-KOH, 1:1 H_2O–MeCN) 309 nm (ε 6 000); $\nu_{max.}(CCl_4)$ 3 500 (OH), 3 310 (≡CH), and 2 100 (C≡C) cm^{-1}; δ ($CDCl_3$; 90 MHz) 7.30—6.75 (3 H, m, ArH), 6.61 (1 H, s, exchangeable, OH), 2.52 (1 H, s, ≡CH), and 1.60 (6 H, s, CH_3) (Found: M^+, 194.0485. $C_{11}H_{11}ClO$ requires *M*, 194.0486); *m/z* 196 (M^+, 9%), 194 (M^+, 27), 181 (30), 179 (100), 159 (38), 144 (22), and 115 (22), and 3-(2-*hydroxy*-5-*methylphenyl*)-3-*methylbutyne* (**11c**), $\lambda_{max.}$ (0.2M-KOH, 1:1 H_2O–MeCN) 303 nm (ε 12 000); $\nu_{max.}(CCl_4)$ 3 500 (OH), 3 310 (≡CH), and 2 100 (C≡C) cm^{-1}; δ ($CDCl_3$; 90 MHz) 7.15—6.75 (3 H, m, ArH), 6.49 (1 H, s, exchangeable, OH), 2.51 (1 H, s, ≡CH), 2.30 (3 H, s, $ArCH_3$), and 1.65 (6 H, s, CH_3) (Found: M^+, 174.1037. $C_{12}H_{14}O$ requires *M*, 174.1038); *m/z* 174 (M^+, 24%), 159 (100), 139 (12), 125 (20), and 59 (22).

4-(2-*Hydroxyphenyl*)-4-*methylpent*-2-*yne* (**18**).—A solution of the dianion of alkyne (**11a**) was prepared as described above. After stirring at room temperature for 1 h, dry methyl iodide (1 ml) was added and the mixture stirred at room temperature for a further 1 h. Work-up as described above gave the *methylalkyne* (**18**) (40 mg, 60%), $\lambda_{max.}$ (0.2M-KOH, 1:1 H_2O–MeCN) 294 nm (ε 14 000); $\nu_{max.}(CCl_4)$ 3 450 (OH) and 1 500 (Ar) cm^{-1}; δ ($CDCl_3$; 90 MHz) 7.50—6.70 (5 H, decreases to 4 H on addition of D_2O, m, ArH + OH), 1.80 (3 H, s, $\equiv CCH_3$), and 1.55 (6 H, s, CH_3) (Found: M^+, 174.1037. $C_{12}H_{14}O$ requires *M*, 174.1038); *m/z* 174 (M^+, 11%) 159 (42), 145 (100), 115 (22), 110 (22), 86 (50), and 84 (80).

1,1-*Dibromo*-4-(3,6-*dimethyl*-2-*methoxyphenyl*)-4-*methylpent*-1-*ene* (**20**).—Triphenylphosphine (0.26 g, 1 mmol) was added to a cooled solution of carbon tetrabromide (0.17 g, 0.5 mmol) in dry methylene dichloride (2.5 ml). The orange solution was cooled to 0 °C and a solution of aldehyde (**19**)[1] (0.11 g, 0.5 mmol) in dry methylene dichloride (0.5 ml) was added dropwise, under nitrogen. Stirring was continued for 10 min before warming the solution to room temperature. The mixture was washed with water, dried, and evaporated to dryness *in vacuo*. The residue was extracted with hexane, the extract filtered and concentrated before purifying by p.t.l.c. (eluant chloroform) to give the *dibromo-olefin* (**20**) (0.14 g, 73%) as an oil, $\nu_{max.}(CCl_4)$ 1 615 cm^{-1} (C=C); δ ($CDCl_3$; 60 MHz) 6.90 (1 H, d, *J* 8 Hz, Ar), 6.70 (1 H, d, *J* 8 Hz, Ar), 6.15 (1 H, t, *J* 7 Hz, CH=C), 3.60 (3 H, s, OCH_3), 2.64 (2 H, d, *J* 7 Hz, CH_2), 2.45 (3 H, s, $ArCH_3$), 2.20 (3 H, s, $ArCH_3$), and 1.50 (6 H, s, CH_3) (Found: M^+, 377.9825. $C_{15}H_{20}Br_2O$ requires *M*, 377.9823); *m/z* 378 (M^+, 10%), 376 (M^+, 20), 374 (M^+, 10), 177 (100), and 162 (17).

4-(3,6-*Dimethyl*-2-*methoxyphenyl*)-4-*methylpent*-1-*yne* (**21**).—Following the method of Corey and Fuchs, n-butyl-lithium (1.5 ml of a *ca.* 1.3M solution in hexane) was added dropwise to a solution of the dibromo-olefin (**20**) (0.19 g, 0.5 mmol) in dry THF (2 ml) under nitrogen at −78 °C. The mixture was stirred at −78 °C for 45 min, and then at room temperature for a further 45 min; it was quenched by the dropwise addition of water (2 ml), and the phases separated. The aqueous phase was extracted with methylene dichloride. The combined extracts were dried and concentrated *in vacuo*: purification of the resulting oil by m.p.c. (8 g silica, eluant petrol) afforded the *alkyne* (0.11 g, 100%) as a pale yellow oil, $\nu_{max.}(CCl_4)$ 3 310 (≡CH) and 2 110 (C≡C) cm^{-1}; δ ($CDCl_3$; 60 MHz) 6.85 (1 H, d, *J* 8 Hz, Ar), 6.65 (1 H, d, *J* 8 Hz, Ar), 3.60 (3 H, s, OCH_3), 2.75 (2 H, d, *J* 3 Hz, CH_2), 2.47 (3 H, s, $ArCH_3$), 2.25 (3 H, s, $ArCH_3$), 1.82 (1 H, t, *J* 3 Hz, ≡CH), and 1.55 (6 H, s, CH_3) (Found: M^+, 216.1524. $C_{15}H_{20}O$ requires *M*, 216.1525); *m/z* 218 (M^+, 8%), 178 (10), 177 (100), 175 (12), 162 (23), and 119 (48).

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