Diels–Alder Route to Potential Trichothecene Precursors

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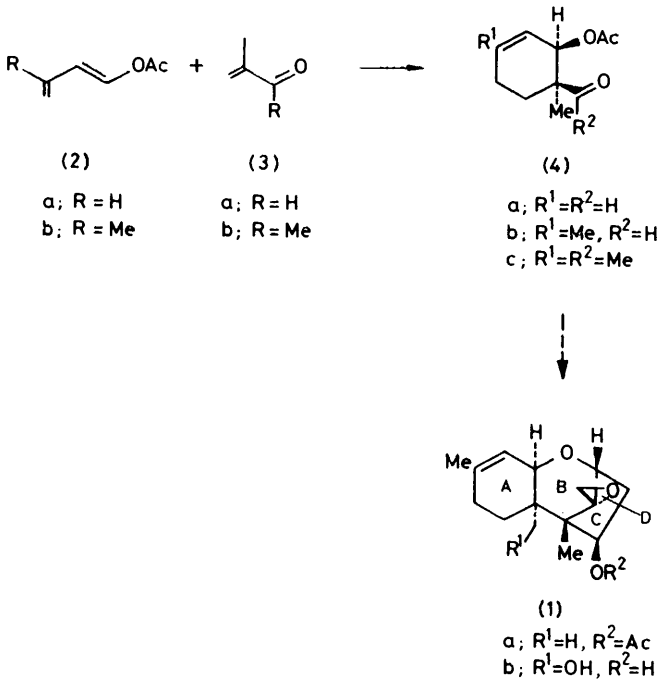
2-Methylbut-3-yn-2-ol (9) is efficiently converted into 6-formyl-3,6-dimethylcyclohex-2-enyl acetate (4b) and into 6-acetyl-3,6-dimethylcyclohex-2-enyl acetate (4c) *via* highly regio- and stereo-selective Diels–Alder cycloadditions of 3-methylbuta-1,3-dienyl acetate (2b). The cycloadduct (4b) is converted by base into 4a,5,6,8a-tetrahydro-4a,7-dimethylcoumarin (13b), whilst the cycloadduct (4c) yields 2,3,4a,5,6,8a-hexahydro-2-hydroxy-2,4a,7-trimethylchroman-4-one (15), the structure of which was confirmed by *X*-ray analysis. Both (13b) and (15) possess a number of structural features of the trichothecenes and may be of value in their total synthesis.

THE unusual combination of structural novelty, cytotoxicity,[1] and potential pharmacological value [1,2] makes the trichothecene fungal metabolites an attractive, yet demanding, synthetic target. To date this total synthetic challenge has only been met by three groups,[3] although promising synthetic intermediates [4] and some aromatic analogues [5] have also been described. Despite

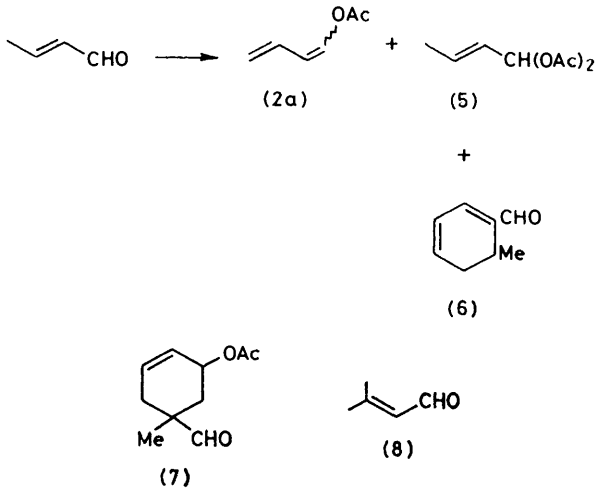


SCHEME 1

these efforts, there remains a need for synthetic approaches which are both short and sufficiently flexible to be applied to a wide range of trichothecene structures or their analogues. This report concerns a short synthesis of two types of trichothecene precursor, by routes which depend on highly selective Diels–Alder reactions.

Our strategy was based on the recognition that the terpenoid moiety of trichothecenes, *e.g.* trichodermin (1a) or verrucarol (1b), could be constructed, as in earlier work,[3a] by an A ⟶ B ⟶ C ⟶ D approach and, moreover, that ring A could be made by a Diels–Alder reaction (see Scheme 1). Not only would this permit suitable functionalisation of ring A, but also it could, in principle, allow control of the geometry at the A–B junction. We thus envisaged that cycloaddition of the buta-1,3-dienyl acetates (2) to the simple αβ-unsaturated carbonyl derivatives (3) would lead to the aldehydes or ketones (4).

Buta-1,3-dienyl acetate (2a) was prepared by a known method [6] from crotonaldehyde and acetic anhydride and found to be an (*E*) : (*Z*)-mixture (65 : 35).[7] The acetates (2a) are always accompanied in the crude product by variable amounts of (*E*)-but-2-enylidene diacetate (5) and 6-methylcyclohexa-1,3-dienecarbaldehyde (6), known by-products [6] of this reaction. Fortunately, the (*E*)-isomer of (2a) is much more reactive than the (*Z*)-isomer under the Diels–Alder conditions used, which led to the formation of essentially one adduct with 2-methylprop-2-enal (3a) as the dienophile. This adduct was assigned structure (4a) on the basis of its proton n.m.r. spectrum, in which the proton on the acetate-bearing carbon appeared as a clean doublet. This pattern would clearly not arise with the alternative, undesired regioisomer (7). A similar conclusion concerning the adduct (4a) has also been reached else-

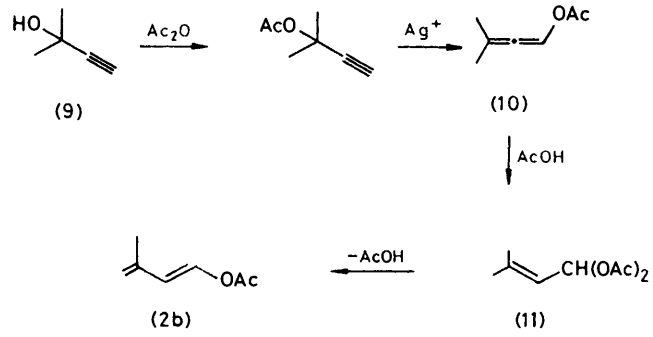


where,[8] although we were unaware of this work when we made our assignments.

Having established that the required Diels–Alder reaction regiochemistry was favourable, we then turned to the problem of the synthesis of 3-methylbuta-1,3-

† Deceased.

dienyl acetate (2b). Although this diene may be regarded as a derivative of 3-methylbut-2-enal (8), and, indeed, we initially prepared it from (8), the aldehyde was not then conveniently accessible in large amounts.[4e,9] However, earlier work by Saucy *et al.*[10] suggested that a rearrangement of 2-methylbut-3-yn-2-ol (9), originally used to prepare (8), might, under appropriate circumstances, lead instead to the required diene (2b). This turned out to be the case, as shown in Scheme 2. The diene was the major product of a sequence of



SCHEME 2

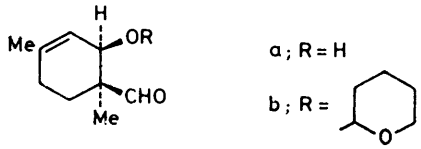
reactions involving at least three intermediates, each of which is observable at the appropriate stage in the sequence. Perhaps the key intermediate is the allene (10), formation of which was anticipated following the preparative work of Benn [11] and the mechanistic work of Schmid and his co-workers,[12] and which adds acetic acid, using our method, to give the diacetate (11). At elevated temperatures, in the presence of acetic acid and sodium chloride, the diacetate readily loses acetic acid to generate the desired diene (2b). Since this work was completed, others [4e,13] have described related, although different, procedures leading from (9) to 3-methylbuta-1,3-dienyl acetate (2b).

In the preparation described herein, the diene (2b) is more than 95% the (*E*)-isomer and it adds smoothly to the dienophiles (3a) and (3b) in refluxing toluene. The regiochemistry was again as desired, with all the evidence indicating that the major products (*ca.* 90%) were (4b) and (4c), respectively. The orientation in these adducts is in accord with the predictions of qualitative, frontier molecular-orbital theory, although the high selectivity of the cycloadditions is noteworthy. For the diene (2b), the acetoxy- and methyl groups each perturb the basic diene HOMO in the same sense [14] and hence high regioselectivity might have been anticipated. However, for the diene (2a), regioselectivity is dependent upon the effect of the acetoxy-group alone and these cycloadditions may be further examples in which secondary overlap is a significant factor.[15]

The stereochemistry of Diels–Alder cycloadditions can usually be anticipated on the basis of the Endo Rule of Alder and Stein.[16] In the case of cycloadditions to (2a) and (2b), it was not possible to confirm the structure of the major adducts from their original spectra or from shift reagent studies. Although the *cis*-relationship of the acetoxy- and carbonyl groups in the major adducts (4) was ultimately confirmed, this was only after *X*-ray and n.m.r. studies on derivatives to be discussed below.

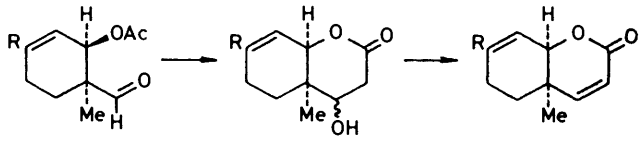
In terms of our projected synthesis, the above preparation and cycloaddition of 3-methylbuta-1,3-dienyl acetate (2b) were most encouraging. Further improvement in these syntheses followed from the observation that the Diels–Alder reaction could be carried out in the acetic anhydride–acetic acid medium used for the propargylic (prop-2-ynyl) rearrangement. This meant that the aldehyde (4b) could be prepared in one flask and we were finally able to isolate it in yields, after distillation, of nearly 70%, based on the allylic alcohol (9).

Thereafter it was intended to chain-extend the formyl group of (4b) and the acetyl group of (4c). Although it was recognised that these carbonyl groups were somewhat hindered, there were a number of favourable omens [17] that this could be achieved by nucleophilic addition. In the event, extensive experimentation with a range of standard methods did not give the desired objectives. Some of these failures were clearly due to the presence of the acetoxy-group in (4b). However, repetition of two of these reactions on the alcohol (12a) or on the corresponding tetrahydropyranyl ether (12b) was no more successful.



(12)

We therefore resorted to one of our original options; that of controlled ring-closure of the acetates (4a), (4b), and (4c). This was achieved under basic conditions and the best for the aldehyde (4b) was found to be treatment with sodium hydride in dimethyl sulphoxide.[18] With this reagent, the major product was the unsaturated δ-lactone (13b), presumably formed *via* the β-hydroxylactone (14b), as shown in Scheme 3. Unfortunately,



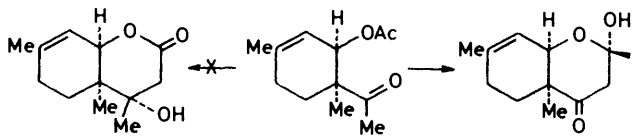
(4) (14) (13)

a; R = H a; R = H a; R = H
b; R = Me b; R = Me b; R = Me

SCHEME 3

this conversion was somewhat capricious and yields above 40% could not be relied upon. The structures of the lactones (13) were indicated, in the first instance, by proton n.m.r. and i.r. data. Particularly pertinent for (13b) were the n.m.r. evidence for the AB-system (δ 6.7 and 5.85, dd, *J* 10 Hz) on the lactone ring, the =CH–CH–O–C(O) unit in the alicyclic ring (δ 5.47, d and 4.58, d, *J* 1.5 Hz), and the carbonyl stretch (1 710 cm^{-1}) of the

lactone.[19] The related lactone (13a), derived from the aldehyde (4a), also showed the same general spectral features. The *cis*-fusion of these lactones (13) was inferred by the nuclear Overhauser enhancement [20]



(14c) (4c) (15)

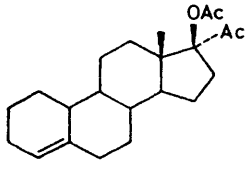
SCHEME 4

observed with the signals for the 4a-methyl hydrogen, when the 8a-hydrogen of (13a) was irradiated, and *vice-versa*.

Application of the same reaction conditions to the ketone (4c) did not lead to an αβ-unsaturated carbonyl compound. Instead, the lactol (15) was formed as the major product. Clearly, this results from attack of the ketone-enolate ion of (4c) on the pendant acetoxy-group, without subsequent dehydration, as outlined in Scheme 4. It transpired to be difficult to distinguish (15) from its isomer, the β-hydroxy-lactone (14c), by standard methods; each would be expected to show diastereo-isotopic methylene protons and two quaternary methyl groups in the n.m.r., as well as hydroxy-group and H-bonded carbonyl absorptions in the i.r. spectrum.

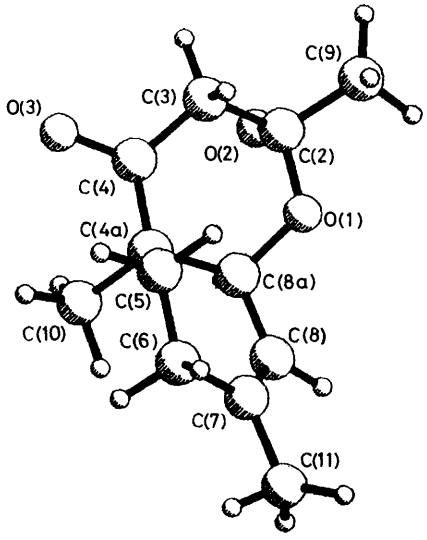
This problem was solved by a single crystal *X*-ray structure determination of the lactol (15). Although the crystals were of poor quality, the *X*-ray data did confirm the presence of the β-hydroxy-ketone unit and that the ring fusion was clearly *cis*- and hence that the original Diels–Alder reaction had occurred *via* an *endo*-mode. This confirmed the nuclear Overhauser result on the lactone (13a) and was in keeping with 250 MHz n.m.r. work on the aldehyde (4a), reported by Gounesard *et al.*[8] The hydroxy-group in (15) is placed axially on the chair-shaped heterocyclic ring and is hydrogen bonded to the carbonyl group in an adjacent molecule, as shown in the Figure.

The formation of the lactones (13) from the aldehyde precursors (4a) and (4b) and of the lactol (15) from the ketone (4c), was not foreseen. While this may be related to the relative acidity of acetyl and acetate groups, as in (4c), it is not clear why the ketonic product (15) retains the β-hydroxy-group, whereas the presumed β-hydroxy-lactone (14b) intermediate is dehydrated under the conditions used. Similar observations have been reported for the steroidal acetoxy-ketone (16) [21] and the earlier work of Lehmann [18] also records the formation of a β-hydroxy-lactone under basic conditions for related steroids.



(16)

In conclusion, the conversion of 2-methylbut-3-yn-2-ol (9) into the lactone (13b) and the lactol (15) has been achieved. These fused structures have reactive functionality in the heterocyclic rings and should allow a number of approaches to selected trichothecenes, by addition of rings C and D in turn.



FIGURE

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer 137 spectrophotometer and are for liquid films, unless otherwise stated. U.v. spectra were recorded with a Pye-Unicam SP 800 spectrophotometer, using solutions in ethanol. Mass spectra were determined with an A.E.I. MS 9 spectrometer. ^{1}H N.m.r. spectra were recorded either on a Perkin-Elmer R 10 (60 MHz) or on a Bruker HX 90 (90 MHz), using solutions in carbon tetrachloride with tetramethylsilane as internal standard, unless otherwise indicated.

Buta-1,3-dienyl Acetate (2a).—This was prepared by modified versions of literature routes.[6] Crotonaldehyde (70 g, 1 mol), acetic anhydride (163 g, 1.6 mol), and sodium acetate (50 g, 0.6 mol) were thoroughly mixed and then heated (oil bath 150 °C) under nitrogen for 10 h. Fractional distillation at reduced pressure from the same flask yielded buta-1,3-dienyl acetate (60 g, 54%), b.p. 42—45 °C/10 mmHg (lit.,[6a] 38 °C/10.5 mmHg); *m/e* 112 (M^+), 70 (base); $\nu_{max.}$ 3 005, 1 835, 1 775, 1 675, 1 225, 1 112, 1 050, 1 000, 895, and 790 cm^{-1}; δ 2.15 (s) and 2.19 (s) (ratio 2 : 1, 3 H, Ac), and 5.0—7.60 (5 H, m, diene). Analysis of the ^{1}H n.m.r. spectrum showed that the protons at lowest field were due to the C(1) protons of the (*E*)-acetate (δ 7.46 d, *J* 12 Hz) and the (*Z*)-acetate (δ 7.18, d, *J* 7 Hz) and that the (*E*)-acetate was predominant (65%). This mixture was used directly in the Diels–Alder reactions described below.

The above fractional distillation also yielded a fraction, 18 g, b.p. 55—58 °C/10 mmHg (lit.,[22] 92—93 °C/10 mmHg), which was found to be identical to (*E*)-but-2-enylidene diacetate (5); δ 1.75 (3 H, d, *J* 7 Hz, *Me*CH=C), 2.04 (6 H, s, Ac), 5.6 (1 H, d and d, *J* 6 and 16 Hz), 6.1 (1 H, d and q, *J*

7 and 16 Hz), and 7.14 [1 H, d, J 6 Hz, CH(OAc)$_2$]. A further fraction (13.5 g), b.p. 65—68 °C/10 mmHg, was found to be 6-methylcyclohexa-1,3-dienecarbaldehyde (6) (lit.,[6a] 84 °C/16 mmHg); $\lambda_{max.}$ 302 nm; δ 0.95 (3 H, d, J 7 Hz, Me), 2.3—3.2 (3 H, m, CH–CH$_2$), 6.3 (2 H, m) and 6.85 (1 H, m) (HC=CH–CH=), and 9.64 (1 H, S, CHO). The proportion of these higher-boiling fractions was noticeably dependent upon the rate and length of heating and upon the reagent ratios used.

3-Methylbuta-1,3-dienyl Acetate (2b).—(a) *From 3-methylbut-2-enal* (8). A crystal of hydroquinone was added to a mixture of 3-methylbut-2-enal (11 g, 0.13 mol), acetic anhydride (24.5 g, 0.24 mol), and sodium acetate (10.7 g, 0.13 mol) and the mixture refluxed under nitrogen for 8 h. After cooling, the mixture was poured into a saturated solution containing equal weights of sodium acetate and sodium chloride, and then an ether extract taken. This was washed successively with saturated sodium hydrogencarbonate and then water, and then dried. Filtration, evaporation of solvent, and then distillation yielded (*E*)-3-methylbuta-1,3-dienyl acetate (2b), (7.7 g, 47%), b.p. 86—90 °C/28 mmHg (lit.,[4e] 60—62 °C/20 mmHg) (Found: M 126.068. $C_7H_{10}O_2$ requires 126.068); $\nu_{max.}$ 2 925, 1 760, 1 650, 1 225, 1 112, 937, and 828 cm^{-1}; δ 1.88 (3 H, d, J 1.5 Hz, MeC=C), 2.15 (3 H, s, AcO), 4.99 (2 H, m; =CH$_2$), 6.17 (1 H, d, J 12 Hz), and 7.42 (1 H, d, J 12 Hz) (*E*-CH=CH). The ^{1}H n.m.r. spectrum of (2b) also revealed about 5% of the (*Z*)-isomer; δ 5.35 (1 H, d, J 7 Hz) and 7.00 (1 H, d, J 7 Hz).

(b) *From 2-methylbut-3-yn-2-ol* (9). The alcohol (9) (84 g, 1 mol) was heated at 120 °C for 10 h under nitrogen with acetic anhydride (204 g, 2.0 mol), by which time ^{1}H n.m.r. spectra of aliquots indicated complete conversion of (9) into its acetate. The temperature was lowered to 90 °C, silver acetate (1 g) added, and heating continued at 90 °C for 3 h. At this stage, ^{1}H n.m.r. spectrum of the mixture showed the allenic acetate (10) and 3-methylbut-2-enylidene diacetate (11) to be present, the latter being predominant (65—90%). In addition to overlapping AcO signals, the allene (10) showed δ 1.63 (6 H, m, J 2 Hz) and 7.30 (1 H, m, HC=C=C), whereas the 1,1-diacetate (11) showed δ 1.80 (6 H, m, MeC=C), 5.32 (1 H, d br, J 8 Hz, CH–CH=C), and 7.46 (1 H, d, J 8 Hz, CH–CH=).

Sodium chloride (30 g, 0.5 mol) was then added to the mixture, once it had cooled, and heating at 120 °C was continued for 6 h. The cooled mixture was poured into a water–petroleum (b.p. 40—60 °C) mixture (750 ml each) and the petroleum extract dried over a mixture of anhydrous magnesium sulphate and anhydrous potassium carbonate. After removal of the solvent, the residue was distilled to give (*E*)-3-methylbuta-1,3-dienyl acetate (2b), (97 g, 76%), b.p. 55—58 °C/18 mmHg (lit.,[4e] 60—62 °C/20 mmHg). Spectral data were identical to that described above, except that the (*Z*)-isomer was estimated to comprise *ca.* 3% of (2b).

Diels–Alder Reaction of Buta-1,3-dienyl Acetate (2a) *with 2-Methylprop-2-enal* (3a).—Buta-1,3-dienyl acetate (2a) (37 g, 0.33 mol) and 2-methylprop-2-enal (3a) (20 g, 0.285 mol) were dissolved in toluene (100 ml) containing a few crystals of hydroquinone. The solution was heated at 120 °C under nitrogen for 10 h. Volatile material was removed by rotary evaporation from a bath at 55—60 °C and the residue fractionally distilled to give 6-formyl-6-methylcyclohex-2-enyl acetate (4a) (39 g, 70%), b.p. 78—80 °C/1.0 mmHg (lit.,[8] 90 °C/0.3 mmHg) (Found: C, 66.0; H, 7.9. $C_{10}H_{14}O_3$ requires C, 65.92; H, 7.7%); $\nu_{max.}$ 3 030, 2 930, 2 700, 1 745—1 730d,s, 1 675w, 1 240vs, 1 060, 1 025s, 968, 947, and 728 cm^{-1}; δ 1.09 (3 H, s, Me–C), 2.05 (s, OAc) and 1.5—2.2 (m, CH$_2$CH$_2$) overlapped (total integral 7 H), 5.4 (1 H, d br, J 3 Hz), 6.0 (2 H, m, HC=CH). and 9.86 (1 H, s, CHO). The ^{1}H n.m.r. spectrum also showed that a second aldehyde (δ 9.6) was present and that it constituted *ca.* 5% of the mixture with (4a).

Diels–Alder Reactions of 3-Methylbuta-1,3-dienyl Acetate (2b).—(a) *With 2-methylprop-2-enal* (3a). The aldehyde (3a) (3.5 g, 0.05 mol) and the diene (2b) (6.1 g, 0.048 mol) were dissolved in anhydrous toluene (10 ml) to which one crystal of hydroquinone had been added. The solution was refluxed under nitrogen for 18 h. Evaporation of the solvent and other volatile material on a rotary evaporator gave a residual oil, which was fractionally distilled to give 6-formyl-3,6-dimethylcyclohex-2-enyl acetate (4b) (4.4 g, 46%), b.p. 82—84 °C/0.2 mmHg (Found: C, 67.1; H, 8.2. $C_{11}H_{16}O_3$ requires C, 67.3; H, 8.2%); $\nu_{max.}$ 2 930, 2 700w, 1 720s, 1 670w, 1 235vs, 1 020s, 960, 935, and 755 cm^{-1}; δ 1.04 (3 H, s, Me–C), 1.74 (3 H, s br, MeC=C), 2.00 (s, OAc) and 1.9—2.2 (m, CH$_2$CH$_2$) overlapped (total integral 7 H), 5.31 (1 H, s br, CH–OAc), 5.54 (1 H, m, CH=C), and 9.75 (1 H, s, CHO). The ^{1}H n.m.r. spectrum also revealed another aldehyde, *ca.* 5% (δ 9.58). This minor product was not detected by g.l.c. on Apiezon L at 150 °C, but was revealed using a 15% polyethylene glycol column at 195 °C; the aldehyde (4b) had the lower retention time.

(b) *With 3-methylbut-3-en-2-one* (3b). A mixture of the ketone (3b) (13.0 g, 0.155 mol) and the diene (2b) (19.0 g, 0.15 mol) in toluene (50 ml) was refluxed for 8 h and the volatiles removed as above. Fractional distillation gave 6-acetyl-3,6-dimethylcyclohex-2-enyl acetate (4c) (17.2 g, 54%), b.p. 86—89 °C/0.07 mmHg (Found: C, 68.2; H, 8.4. $C_{12}H_{18}O_3$ requires C, 68.53; H, 8.63%); $\nu_{max.}$ 2 925, 1 737 and 1 712 (both vs), 1 675w, 1 230bs, 1 020s, 960m, and 910m cm^{-1}; δ 1.07 (3 H, s, Me–C), 1.74 (3 H, br s, MeC=C), 1.94(s) and 2.10(s) and 1.9—2.2 (m, CH$_2$CH$_2$) overlapped (total integral 10 H), 5.2 (1 H, d, J 5 Hz, CH–OAc), and 5.64 (1 H, m, CH=C). A very weak absorption (δ 1.15) suggested that another ketone was present, *ca.* 10%.

Direct Conversion of 2-Methylbut-3-yn-2-ol (9) *into the Diels–Alder Adduct* (4b).—2-Methylbut-3-yn-2-ol (9) (42 g, 0.5 mol) and acetic anhydride (102 g, 1 mol) were converted into 3-methylbuta-1,3-dienyl acetate (2b) as described above. A solution of 2-methylprop-2-enal (3a) (35 g, 0.5 mol) in acetic anhydride (500 g) was then added and the solution heated at 120 °C (bath temperature) under nitrogen for 17 h. Volatile material was then removed on a rotary evaporator and the residual oil fractionally distilled to give 6-formyl-3,6-dimethylcyclohex-2-enyl acetate (4b) (60.2 g, 66%), identical in spectra with the samples prepared as above.

2-Hydroxy-1,4-dimethylcyclohex-3-enecarbaldehyde (12a).—The acetate (4b) (2 g, 13 mmol) was added to a stirred solution of potassium hydroxide (0.8 g) in methanol (20 ml) at 20 °C. After 10 min the mixture was poured into an ether–water mixture and the ether phase washed successively with saturated brine and water. Drying of the ether solution and removal of solvent, followed by distillation, yielded 2-hydroxy-1,4-dimethylcyclohex-3-enecarbaldehyde (12a) (1.0 g, 63.6%), b.p. 90 °C/0.8 mmHg (Found: C, 69.9; H, 8.95. $C_9H_{14}O_2$ requires C, 70.10; H, 9.15%); $\nu_{max.}$ 3 425br s, 2 920, 2 700, 1 730s, 1 675w,

and 1 012s cm^{-1}; δ 1.09 (3 H, s, Me–C), 1.74 (3 H, br s, MeC=C), 1.8—2.1 (4 H, m, CH_2CH_2), 3.07 (1 H, br s, OH, lost in D_2O), 4.07 (1 H, br s, C*H*–OH), 5.54 (1 H, br m, CH=), and 9.67 (1 H, s, CHO). A small peak (δ 0.43) indicated that about 5% of an isomeric aldehyde was present.

1,4-*Dimethyl*-2-(*perhydropyran*-2-*yloxy*)*cyclohex*-3-*enecarbaldehyde* (12b).—Dihydropyran (0.6 g, 7.5 mmol) and toluene-*p*-sulphonic acid (0.059 g, 0.31 mmol) in anhydrous ether (5 ml) were added to a stirred solution of 2-hydroxy-1,4-dimethylcyclohex-3-enecarbaldehyde (12a) (0.75 g, mmol) in anhydrous ether (5 ml) at room temperature. After 1.5 h the mixture was diluted with saturated sodium hydrogencarbonate and the aqueous phase extracted with ether. After washing with water, the ether extract was dried and the solvent was evaporated to give a viscous oil (1.15 g), the perhydropyranyl ether (12b); M^+ 238; $\nu_{max.}$ 2 930, 2 700, 1 730s, and 1 672w cm^{-1}; δ 0.95 (3 H, s, Me–C), 4.35 (1 H, d, *J* 3 Hz, =C–CH–O), 4.60 (1 H, m, OCH–O), 5.54 (1 H, m, CH=C), and 9.70 (1 H, s, CHO). Attempted distillation or column chromatography of (12b) resulted in considerable decomposition and the crude material, when free from OH absorption, was used in subsequent experiments.

Experiments with the N.M.R. Shift-reagent $Eu(dpm)_3$.—The shift reagent, trispivaloylmethanatoeuropium(III) [$Eu(dpm)_3$] was added in aliquots to solutions of the aldehydes (4b) and (12a) in carbon tetrachloride. The molar ratio of the shift reagent to substrate was increased from 1 : 20 to 1 : 2 over six aliquots and the resultant shifts in the protons of the substrate plotted against this ratio. With 6-formyl-3,6-dimethylcyclohex-2-enyl acetate (4b) as the substrate, good straight lines were obtained. However, the acetoxy-protons and the formyl proton were shifted to the same extent (within experimental error) and it was concluded that the shift reagent was not complexing selectively at one site in (4b). With the corresponding alcohol (12a) as substrate, additional peaks appeared in the spectrum after addition of only two portions of $Eu(dpm)_3$. It seemed that the reagent had catalysed dehydration of the allylic alcohol.

Attempted Chain Extension Reactions of 6-*Formyl*-3,6-*dimethylcyclohex*-2-*enyl Acetate* (4b).—The following reactions resulted in recovery of (4b). (a) Darzen's reaction,[23] using ethyl chloroacetate and potassium t-butoxide in t-butyl alcohol. (b) Wittig reaction, using methoxymethylenetriphenylphosphorane (generated with n-butyllithium in ether).[24]

The following reactions resulted in considerable loss of (4b) and i.r. and ^1H n.m.r. spectra of the crude product revealed loss of the acetoxy-group and gain of the hydroxy-group absorptions in the i.r. spectrum. (a) Reaction with ethoxymethyl-lithium, generated in dimethoxymethane using lithium and chloromethyl ethyl ether.[25] (b) Reaction with dimethyl sulphoxonium methylide in dimethyl sulphoxide.[26] (c) Reaction with dimethyl sulphonium methylide in dimethyl sulphoxide.[26]

In none of these reactions was there any evidence (i.r. or n.m.r.) that the desired reaction had occurred at the formyl group of (4b). The quality of reagents and the rigour of our procedures was checked in each case by their success with simple carbonyl compounds, such as benzaldehyde and acetophenone.

Attempted Chain Extension Reactions with 2-*Hydroxy*-1,4-*dimethylcyclohex*-3-*enecarbaldehyde* (12a) *and its Perhydropyranyl Ether* (12b).—The alcohol (12a) was subjected to standard Wittig reaction conditions using methoxymethyltriphenylphosphorane, as above. The product was extremely complex (t.l.c. evidence), but displayed both C=O and H–O absorption in the i.r., but no formyl proton in the n.m.r. The region around δ 1.0 showed several singlets. Under the same conditions, the ether (12b) was unreactive. A similar pattern of reactivity for (4b) and (12b) was also observed with dimethylsulphonium methylide.

4a,5,6,8a-*Tetrahydro*-4a-*methylcoumarin* (13a).—A solution of lithium di-isopropylamide (0.032 mol) in tetrahydrofuran (THF) (50 ml) was prepared at −10 °C in anhydrous conditions under nitrogen. After cooling to −78 °C, dry hexamethylphosphoric triamide (6.3 g, 0.035 mol) was added and the mixture stirred for 30 min. 6-Formyl-6-methylcyclohex-2-enyl acetate (4a) (4.74 g, 0.026 mol) in THF (15 ml) was then added, and the mixture stirred for a further 30 min at −78 °C. Thereafter, the mixture was allowed to come to room temperature over a period of 3 h and then most of the solvent removed by evaporation. The residue was poured into water (200 ml) and extracted with ether. After drying, the ether extract yielded an oily residue (3.5 g), which was chromatographed on a short column of neutral alumina. Elution with 2% ethanol in toluene gave 4a,5,6,8a-tetrahydro-4a-methylcoumarin (13a) (2.01 g, 37%) (Found: M^+ 164.083 6. $C_{10}H_{12}O_2$ requires 164.083 7); $\nu_{max.}$ 3 020, 2 850, 1 710, 1 645, 1 248, 1 005, 992, 834, 790, and 725 cm^{-1}, δ 1.17 (3 H, s, Me), 1.4—1.85 (2 H, m, CH_2), 2,0—2.35 (2 H, m, CH_2–C=C), 4.68 (1 H, d, *J* 3 Hz, CH–O), 5.86 (3 H, m, C=C–H), and 6.71 (1 H, d, *J* 10 Hz, C*H*=CH–C=O). Attempts to distil (13a) were not successful, but it was obtained pure by t.l.c. in two different solvent systems. Irradiation of the ^1H n.m.r. sample of (13a) at the 4a-Me frequency resulted in a 14% increase in the intensity of the 8a-proton. Corresponding irradiation at the 8a-proton frequency resulted in an n.O.e. of 15% in the integral for the 4a-Me group. No other signals were affected by irradiation at these values.

This preparation was repeated a number of times with slight alterations in the above conditions. In the absence of hexamethylphosphoric triamide, the major product was the alcohol (12a), and the δ-lactone (13a) was a minor product. As the molar proportion of the triamide was increased to 1 : 1, the yield of the lactone (13a) improved, but further increases in the ratio did not result in better yields of (13a). Likewise, changes in the temperature of mixing of the aldehyde (4a) with lithium di-isopropylamide produced no reproducible improvement in lactone yield.

4a,5,6,8a-*Tetrahydro*-4a,7-*dimethylcoumarin* (13b).—(a) Via *Lithium di-isopropylamide*. This was prepared from 6-formyl-3,6-dimethylcyclohex-2-enyl acetate (4b) in exactly the same way as for (13a). After chromatography, an oily sample of (13b) was obtained (variable yield, 12—37%). This was then re-chromatographed on neutral alumina to give the coumarin (13b), m.p. 29—32 °C (Found: C, 74.2; H, 7.9. $C_{11}H_{14}O_2$ requires C, 74.13; H, 7.92%); $\nu_{max.}$ 2 955, 2 910, 1 730—1 710, 1 670, 1 242, 1 219, 1 005, 990, and 822 cm^{-1}; δ 1.11 (3 H, s, Me–C), 1.5—2.3 (br m, CH_2–CH_2–C=) and 1.70 (br s, MeC=C) overlapped (with total integral 7 H), 4.58 (1 H, d, *J* 1.5 Hz, CH–O), 5.47 (1 H, d, *J* 1.5 Hz, =C*H*–CH–O), 5.84 (1 H, d, *J* 10 Hz, CH=C*H*–C=O), and 6.76 (1 H, d, *J* 10 Hz, C*H*=CH–CO).

(b) Via *Sodium methylsulphinylmethanide*. A solution of sodium methylsulphinylmethanide (0.011 mol) in anhy-

drous dimethyl sulphoxide (20 ml) was prepared at 65 °C. To this solution, at 20 °C under nitrogen, was added 6-formyl-3,6-dimethylcyclohex-2-enyl acetate (4b) (1.96 g, 0.01 mol) in dry dimethyl sulphoxide (5 ml). The mixture was stirred successively for 14 h at 20 °C and 4 h at 60 °C before being poured into dilute acetic acid (0.01 M; 50 ml). Extraction with light petroleum (b.p. 40—60 °C) (4 × 50 ml) and then with a mixture of ether and light petroleum (b.p. 40—60 °C) (2 × 50 ml), yielded an oil which was chromatographed on silica. Elution with petroleum–ethyl acetate (20 : 1) yielded the lactone (13b) (0.7 g, 39%), identified as above.

2,3,4a,5,6,8a-*Hexahydro*-2-*hydroxy*-2,4a,7-*trimethylchroman*-4-*one* (15).—6-Acetyl-3,6-dimethylcyclohex-2-enyl acetate (4c) (3.15 g, 0.015 mol) in dry dimethyl sulphoxide (10 ml) was added at 20 °C to a stirred solution of sodium methylsulphinylmethanide (1.05 mol equiv.) in dimethyl sulphoxide (20 ml) under nitrogen. Stirring was continued for 2 h at 20 °C and then for 12 h at 50 °C. Ice-cold, aqueous acetic acid was added to the mixture and a crystalline precipitate formed. This was separated by filtration and recrystallized from acetone to give 2,3,4a,5,6,8a-hexahydro-2-hydroxy-2,4a,7-trimethylchroman-4-one (15) (1.6 g, 51%), m.p. 78—80 °C (Found: C, 68.6; H, 8.52. $C_{12}H_{18}O_3$ requires C, 68.53; H, 8.63%); $\nu_{max.}$ (Nujol) 3 420 s, sharp (O–H), 1 696s, 1 395, 1 298, 1 230, 1 060, 1 032, and 896 cm^{-1}; δ(CD_3OD) 0.87 (3 H, s, Me–C), 1.36 (3 H, s, MeC–OH), 1.70 (3 H, s br, MeC=C), 1.96 (4 H, br s, CH_2 CH_2–C=C), 2.35 and 2.62 [2 H, dd, *J* 14 Hz, –C(:O)–C_AH_BH], 4.15 (1 H, d, *J* 5.5 Hz, C=CHC*H*–O), and 5.40 (1 H, d, *J* 5.5 Hz, C=C*H*–CH–O–).

Crystal Data.—$C_{12}H_{18}O_3$, *M* = 216, monoclinic, *a* = 33.14(5), *b* = 6.440(11), *c* = 10.77(2) Å, β = 101.2(1)°, *V* = 2 255 Å^3, *Z* = 8, D_c = 1.27 g cm^{-3}, *F*(000) = 912. Cu-K_α radiation (λ = 1.541 8 Å), μ = 6.3 cm^{-1}. Space group *Cc* or *C2/c* from systematic absences, *C2/c* from structure determination.

Data Collection.—Preliminary photographs showed that most crystals of suitable size were split or twinned and that fragments cut from larger crystals were warped. In addition, few high-angle reflections were apparent. A data set adequate for resolution of the structure was finally obtained from one crystal of dimensions 0.07 × 0.31 × 0.31 mm mounted, in turn, on the *b* and on the *c* axis. Equi-inclination Weissenberg photographs of levels *h*0—3*l* and *hk*0—7 were scanned by the S.R.C. Microdensitometer Service; 932 unique reflections out of *ca.* 1800 scanned were above background.

Structure Analysis.—The structure was solved by direct methods in space group *Cc*. For this purpose 545 unobserved reflections were added to the data set. Some initial difficulty resulted from the preponderance of *ggg* and *uuu* reflections amongst those of larger |*E*|. This subsequently proved to be because 10 of the 15 non-hydrogen atoms in each molecule lie close to the *n* glide-plane at *y* = 1/4. When a sufficient number of mixed-parity reflections were assigned initial phases (512 phase combinations), the *E*-map of highest figure-of-merit showed all the non-hydrogen atoms of the two molecules in the asymmetric unit. After two cycles of Fourier refinement it was clear that these molecules were related by a diad axis and this was confirmed from an *E*-map generated in space-group *C2/c*. During full-matrix least-squares refinement in *C2/c* (observed reflections only) *R* fell to 0.19 with isotropic, and to 0.14 with anisotropic, thermal parameters for all carbon and oxygen atoms. A difference map then showed peaks near the expected positions of 11 of the 18 hydrogen atoms, but as the stronger 'noise' peaks were of similar height the hydrogen atoms were included at calculated positions (d_{C-H} 1.07 Å, U_H 0.05) in the last cycles of refinement. After 10 low-angle reflections with $|F_o| < 0.5|F_c|$ had been removed, refinement converged at *R* 0.121 (922 data, 145 parameters, unit weights). A final difference map showed no unexpected features. The rather high value of the final residual and standard deviation seem inevitable in view of the crystal quality and the large proportion of reflections that were unobserved.

All calculations were performed on the Dundee University DEC10 computer by use of the SHELX76 program.[27] Bond lengths and angles are recorded in Table 1 and atomic co-ordinates in Table 2. Details of thermal parameters and observed and calculated structure factors may be found in Supplementary Publication No. SUP 23000 (9 pp).*

TABLE 1

Bond lengths (Å) and interbond angles (°) for 2,3,4a,5,6,8a-hexahydro-2-hydroxy-2,4a,7-trimethylchroman-4-one (15).

O(1)–C(2)	1.428(11)	C(4a)–C(5)	1.564(16)
O(1)–C(8a)	1.444(11)	C(4a)–C(8a)	1.560(13)
C(2)–O(2)	1.404(12)	C(4a)–C(10)	1.516(15)
C(2)–C(3)	1.521(15)	C(5)–C(6)	1.502(15)
C(2)–C(9)	1.503(14)	C(6)–C(7)	1.533(16)
C(3)–C(4)	1.472(16)	C(7)–C(8)	1.306(15)
C(4)–C(4a)	1.482)5)	C(7)–C(11)	1.564(15)
C(4)–O(3)	1.267(13)	C(8)–C(8a)	1.477(14)
C(2)–O(1)–C(8a)	114.5(7)	C(4)–C(4a)–C(10)	112.2(1.0)
O(1)–C(2)–O(2)	111.0(8)	C(8a)–C(4a)–C(10)	108.3(9)
C(3)–C(2)–O(1)	109.1(9)	C(4a)–C(5)–C(6)	111.9(9)
C(3)–C(2)–C(9)	113.2(1.0)	C(5)–C(6)–C(7)	112.2(1.0)
O(2)–C(2)–C(9)	111.2(9)	C(6)–C(7)–C(8)	122.8(1.0)
C(2)–C(3)–C(4)	109.5(9)	C(6)–C(7)–C(11)	114.8(1.1)
C(3)–C(4)–C(4a)	120.9(1.0)	C(8)–C(7)–C(11)	122.4(1.1)
O(3)–C(4)–C(4a)	120.5(1.1)	C(7)–C(8)–C(8a)	124.3(1.0)
C(3)–C(4)–O(3)	118.5(1.0)	O(1)–C(8a)–C(4a)	111.0(8)
C(4)–C(4a)–C(5)	105.8(9)	O(1)–C(8a)–C(8)	106.4(8)
C(4)–C(4a)–C(8a)	111.0(1.0)	C(4a)–C(8a)–C(8)	113.7(9)

TABLE 2

Atomic co-ordinates (× 10^4) for 2,3,4a,5,6,8a-hexahydro-2-hydroxy-2,4a,7-trimethylchroman-4-one (15)

Atom	*x*	*y*	*z*
O(1)	3 965(2)	2 501(11)	4 787(6)
C(2)	4 373(3)	1 872(17)	4 724(10)
C(3)	4 524(3)	3 140(19)	3 712(12)
C(4)	4 226(3)	2 967(19)	2 510(13)
C(4a)	3 643(3)	3 113(17)	2 477(10)
C(5)	3 683(3)	5 484(19)	2 552(11)
C(6)	3 236(3)	5 877(19)	2 556(11)
C(7)	3 067(3)	4 409(21)	3 451(11)
C(8)	3 262(3)	2 742(18)	3 928(10)
C(8a)	3 662(3)	2 056(18)	3 663(9)
C(9)	4 626(3)	2 200(22)	6 027(10)
C(10)	3 527(4)	2 106(21)	1 303(10)
C(11)	2 637(3)	5 032(23)	3 727(13)
O(2)	4 383(2)	−214(12)	4 352(6)
O(3)	4 361(3)	2 664(13)	1 501(8)

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