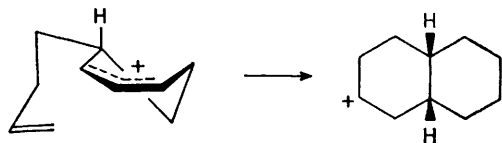


## Diterpene Synthesis. Part 1. Copper(I)-catalysed 1,6-Addition of a Benzyl Grignard Reagent to a Dienone <sup>1</sup>

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Copper(I) salts catalyse the 1,6-conjugate addition reaction of *m*- and *p*-methoxybenzylmagnesium halides to the monocyclic linear dienone (6) at the expense of 1,2- and 1,4-addition. An improved synthesis of the dienone is reported.

THE aromatic ring c diterpenoids and related compounds have been the target of a large number of synthetic studies. In the main, the ring system has been built up either by a Robinson annelation of a tetralone, or by cyclisation of a phenylethylcyclohexanol or congener. The former method normally leads, after hydrogenation, to a product with a *trans* A/B ring junction, while the latter method often produces a mixture of *cis*- and *trans*-isomers.<sup>2</sup> Following our earlier work in this field,<sup>3</sup> we sought a synthetic route that would provide the *cis*-isomer in good yield. Johnson<sup>4</sup> has shown that attack of a double bond on a cyclohexenyl cation produces the desired *cis*-decalin derivative (Scheme 1). In these diterpenoids, this would require attack of an aromatic ring on a suitably substituted cyclohexenyl cation. The first synthetic targets were thus the unsaturated ketones (16a, b), which can be reduced to allylic alcohols, which, in turn, can give the desired cations. Similar functionality in ring A has been produced by nucleophilic attack of the malonate anion on the dienone (5),<sup>5</sup> but no record exists of the conjugate addition of a benzylic group to a linear dienone. Although the conjugate addition of Grignard reagents catalysed by Cu<sup>I</sup> salts or of lithium organocuprates is now a standard reaction, there are no reports of conjugate addition of organocuprates or Grignard reagents to dienones of this type. Recent work has shown that benzyl Grignard reagents undergo predominantly 1,4-addition to enones but the effect of copper catalysts is variable. Danishefsky and Migdalof<sup>6</sup> found that conjugate addition of benzyl- and *m*-methoxybenzyl-magnesium chloride to methyl vinyl ketone showed minor catalysis by copper(I) chloride but the main effect of the copper(I) salts was to inhibit 'abnormal' *ortho*-addition of *m*-methoxybenzylmagnesium chloride. However, Ireland *et al.*<sup>7</sup> showed that the same two Grignard reagents gave high yields of

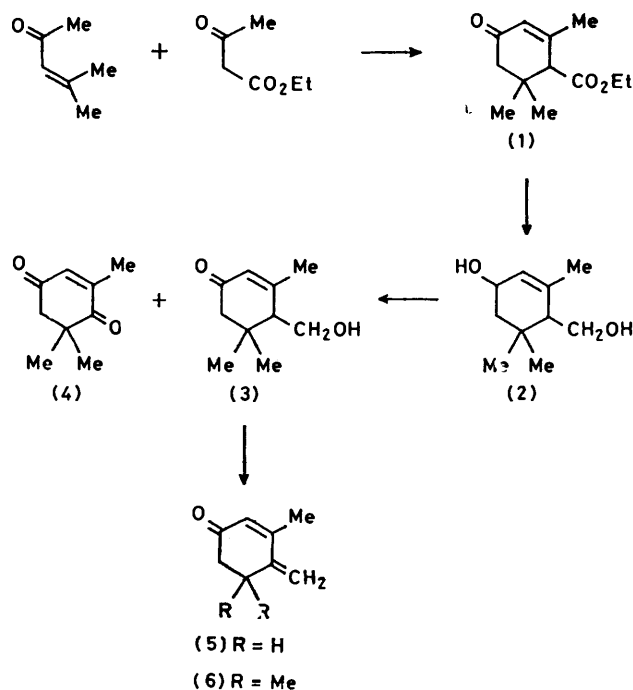


SCHEME 1

conjugate addition to two enones without any copper catalysis. In his review, Posner<sup>8</sup> states that benzyl groups cause organocopper reagents to react most like the corresponding Grignard reagent.

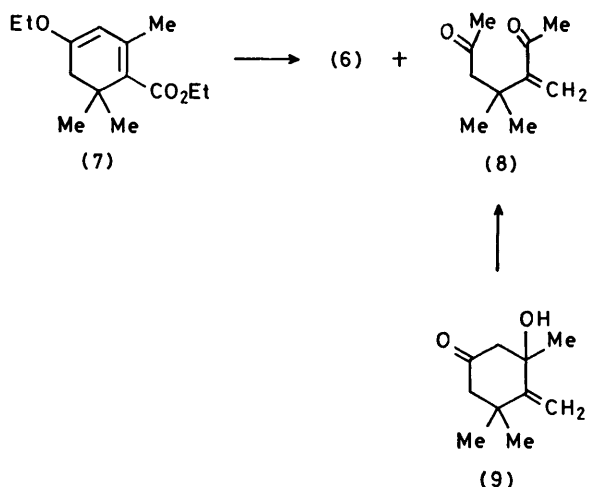
### RESULTS AND DISCUSSION

The desired dienone (6) has been synthesised by Surmatis *et al.*;<sup>9</sup> our modified synthesis is shown in Scheme 2. The keto-ester (1) was reduced to a stereo-



SCHEME 2

isomeric mixture of diols (2), which we found were oxidised to the keto-alcohol (3) in good yield by manganese dioxide; dehydration then occurred readily with sulphuric acid in ether. The known diketone (4)<sup>10</sup> was also isolated in low yield in the oxidation step; it may arise by decomposition of an allylic hydroperoxide. In other experiments seeking to parallel known preparations of related dienones, the keto-ester (1) was converted to the enol ether (7) (Scheme 3) which was then reduced with lithium aluminium hydride. Treatment of the crude reduction product with dilute acid gave the dienone (6) and an unsaturated diketone which was assigned structure (8). The i.r. spectrum showed both conjugated (1 680) and unconjugated (1 715 cm<sup>-1</sup>) ketone groups, while the <sup>1</sup>H n.m.r. spectrum showed six unsplit signals (see Experimental section). The proposed structure is the only one that would not show three- or four-bond



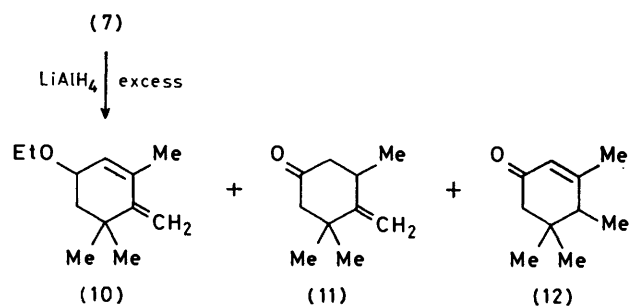
SCHEME 3

coupling of the vinyl protons, and which can be reasonably derived from (7). The diketone arises, presumably, by a reverse aldol reaction from a  $\beta$ -ketol (9) produced during work-up. When an excess of lithium aluminium hydride was used in the reduction of the unsaturated ester (7), significant quantities of over-reduced by-products were isolated (Scheme 4). One product which was not converted to a ketone by treatment with acid was assigned the structure (10) on the basis of elemental analysis, and i.r.,  $^1\text{H}$  and  $^{13}\text{C}$  n.m.r., and mass spectra. The two ketones (11) and (12)<sup>11</sup> were identified similarly.

Having developed a good route to the dienone (6),

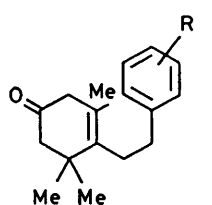
the conjugate addition reaction of *m*- and *p*-methoxybenzylmagnesium chloride was studied. The Grignard reagent was added to the dienone in tetrahydrofuran containing copper(I) chloride, although this salt has limited solubility in that solvent. Even so, it was sufficient to cause almost exclusive 1,6-addition of the *m*-methoxybenzyl Grignard reagent, but the more reactive *para*-isomer still gave significant quantities of the 1,2- and 1,4-addition products. However, by converting the copper salt to its dimethyl sulphide complex, soluble in ether-dimethyl sulphide,<sup>12</sup> the *p*-methoxybenzylmagnesium bromide reagent gave almost exclusive 1,6-addition.

When the Grignard addition mixtures were worked up



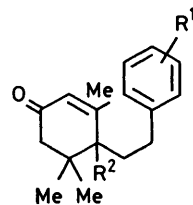
SCHEME 4

in near-neutral (ammonium chloride) or dilute acid conditions, the  $\beta\gamma$ -unsaturated ketones (13a, b) could be isolated, but because of the ease with which they underwent oxidation and conjugation, they could not be puri-



(13a)  $R = p\text{-OMe}$

(13b)  $R = m\text{-OMe}$



(14a)  $R^1 = p\text{-OMe}, R^2 = \text{OOH}$

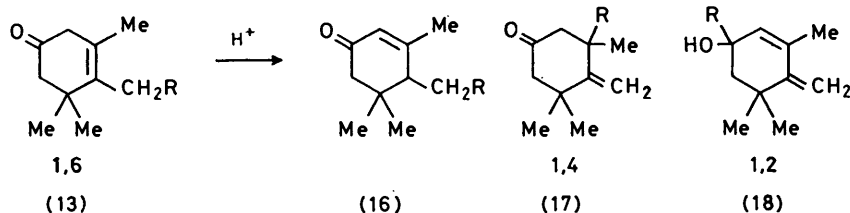
(14b)  $R^1 = m\text{-OMe}, R^2 = \text{OOH}$

(15a)  $R^1 = p\text{-OMe}, R^2 = \text{OH}$

(15b)  $R^1 = m\text{-OMe}, R^2 = \text{OH}$

(16a)  $R^1 = p\text{-OMe}, R^2 = \text{H}$

(16b)  $R^1 = m\text{-OMe}, R^2 = \text{H}$



a;  $R = p\text{-MeO-benzyl}$

b;  $R = m\text{-MeO-benzyl}$

SCHEME 5

fied for elemental analysis. On standing in air, the unconjugated ketones produced the hydroperoxides (14a, b). Treatment with alcoholic potassium iodide gave iodine and the corresponding alcohols (15a, b). The  $\beta\gamma$ -unsaturated ketones produced the desired  $\alpha\beta$ -unsaturated isomers (16a, b) by treatment with dilute acid; for synthetic purposes the conjugated enones were obtained directly from the Grignard reaction mixture, by heating it under reflux with hydrochloric acid in tetrahydrofuran for 1 h.

In the absence of copper(I) salts, the 1,4- and 1,2-addition products were obtained from the Grignard reaction. These unstable compounds were separated by preparative t.l.c. and identified by spectral methods. The relative amounts of the three addition products (in the crude mixture) were estimated from the integral of the vinyl protons in the  $^1\text{H}$  n.m.r. spectra (Scheme 5), both before and after treatment with acid. The results are shown in the Table.

Clearly, the copper(I) salts are having a marked effect in catalysing the 1,6-addition of the benzyl Grignard reagent.

	Mode of addition (relative to 1,4 = 1)		
	1,2	1,4	1,6
<i>m</i> -MeO-Benzyl reagent			
Without CuBr in THF	3.5	1	3
With CuBr in THF	3	1	20—40
<i>p</i> -MeO-Benzyl reagent			
Without CuBr in THF	4	1	3
With CuBr in THF	4	1	15
With $\text{Cu}(\text{Me}_2\text{S})\text{Br}$ in $\text{Et}_2\text{O}-\text{Me}_2\text{S}$	3	1	20—40

## EXPERIMENTAL

M.p.s were determined with a Reichert-Kofler hot-stage apparatus. I.r. spectra were recorded with a Perkin-Elmer 237 spectrometer,  $^1\text{H}$  n.m.r. spectra with a Varian T60 spectrometer, and  $^{13}\text{C}$  n.m.r. spectra with a JEOL JNM-FX60 Fourier-transform spectrometer. Low-resolution mass spectra were obtained with a Varian MAT CH-7 spectrometer. Microanalyses were performed by Professor A. D. Campbell, University of Otago.

**4-Hydroxymethyl-3,5,5-trimethylcyclohex-2-enone (3).**—The diol (2) (3.8 g) in dichloromethane (170 ml) was shaken with active manganese dioxide (38 g) for 6 h. Removal of oxidant and solvent gave the keto-alcohol (3) (2.5 g, 65%), m.p. 63—65 °C (lit.,<sup>9</sup> 63—65 °C), from hexane-ether. In addition, 2,6,6-trimethylcyclohex-2-ene-1,4-dione (4)<sup>10</sup> was isolated (<5%) (Found:  $M^+$ , 152. Calc. for  $\text{C}_9\text{H}_{12}\text{O}_2$ :  $M$ , 152);  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 6.44 (1 H, m, 3-H), 2.62 (2 H, s, 5- $\text{H}_2$ ), 1.98 (3 H, d,  $J$  2 Hz, 2-Me), and 1.20 (6 H, s, 6- $\text{Me}_2$ ) (lit.,<sup>10</sup>  $\delta_{\text{H}}$  6.49, 2.63, 1.98, and 1.22; same integration and multiplicity).

**3,5,5-Trimethyl-4-methylenecyclohex-2-enone (6).**—The keto-alcohol (3) (4.1 g) in ether (80 ml) was stirred at 0 °C and concentrated sulphuric acid (4.5 g) was added dropwise. Stirring was continued for 3 h and the mixture was rapidly diluted with cold water (100 ml) to yield the dienone (6) (2.7 g, 74%), b.p. 50—52 °C at 0.2 mmHg (lit.,<sup>9</sup> 64—66 °C at 0.75 mmHg);  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ) 5.92 (1 H, m, 2-H), 5.44 and 5.36 (2 H, s and d respectively,  $^5J$  1.8 Hz, = $\text{CH}_2$ ), 2.35 (2 H, s, 6- $\text{H}_2$ ), 2.06 (3 H, d,  $J$  1 Hz, 3-Me), and 1.22 (6 H, s, 5- $\text{Me}_2$ );  $\delta_{\text{C}}$  208.9 (C-1), 153.2 (C-4), 151.5 (C-3), 126.9 (C-2),

114.2 (4= $\text{CH}_2$ ), 51.9 (C-6), 39.2 (C-5), 28.6 (5- $\text{Me}_2$ ), and 20.8 (3-Me).

**Lithium Aluminium Hydride Reduction of the Enol Ether Ester (7).**—The enol ether ester (7) (10 g) in dry ether (40 ml) was added slowly to lithium aluminium hydride (2 g) in dry ether (40 ml) at 15 °C. The mixture was stirred at room temperature under nitrogen for 4 h and hydrolysed with water (10 ml). Removal of salts and solvent gave a residue which was stirred with 1 : 1 tetrahydrofuran-5% aqueous hydrochloric acid (150 ml) for 3 h. A portion (250 mg) of the residual oil (7.7 g) was separated by p.l.c. [hexane-ether (4 : 1)] into the dienone (6) (100 mg) and 4,4-dimethyl-3-methyleneheptane-2,6-dione (8) (60 mg),  $m/e$  168 ( $M^+$ ) (Calc. for  $\text{C}_{10}\text{H}_{16}\text{O}_2$ :  $M$ , 168);  $\nu_{\text{max}}$ . 1715 (C=O) and 1680  $\text{cm}^{-1}$  (conjugated C=O);  $\delta_{\text{H}}$  ( $\text{CCl}_4$ ) 5.94 and 5.86 (2 H, 2 s, = $\text{CH}_2$ ), 2.90 (2 H, s, 5- $\text{H}_2$ ), 2.34 (3 H, s, 1- $\text{H}_3$ ), 2.03 (3 H, s, 7- $\text{H}_3$ ), 1.20 (6 H, s, 4- $\text{Me}_2$ ).

Reduction of (7) with 2 mol equiv. of lithium aluminium hydride in ether at reflux temperatures for 4 h gave (6) and (8) as major products, along with three products separated by p.l.c. [hexane-ether (4 : 1)] in ca. 10, 2, and 2% yield, respectively, and identified as (i) 1-ethoxy-3,5,5-trimethyl-4-methylenecyclohex-2-ene (10) (Found: C, 80.3; H, 11.1%;  $M^+$ , 180.  $\text{C}_{12}\text{H}_{20}\text{O}$  requires C, 79.9; H, 11.2%;  $M$ , 180);  $\delta_{\text{H}}$  ( $\text{CCl}_4$ ) 5.66 (1 H, m, 2-H), 4.96 (2 H, s, = $\text{CH}_2$ ), 3.88 (1 H, br t,  $J$  7 Hz, 1-H), 3.46 (2 H, q,  $J$  7 Hz,  $\text{OCH}_2\text{CH}_3$ ), 1.82 (3 H, m, 3-Me), 1.14 (3 H, s, 5-Me), 1.12 (3 H, t,  $J$  7 Hz,  $\text{OCH}_2\text{CH}_3$ ), and 1.02 (3 H, s, 5-Me);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 152.5 (C-4), 133.6 (C-3), 127.4 (C-2), 107.3 (=  $\text{CH}_2$ ), 63.3 ( $\text{OCH}_2\text{CH}_3$ ), 43.2 (C-6), 35.6 (C-5), 29.5 (5-Me), 28.3 (5-Me), 20.3 (3-Me), 15.7 ( $\text{OCH}_2\text{CH}_3$ ); (ii) 3,3,5-trimethyl-4-methylenecyclohexanone (11) (Found:  $M^+$ , 152.1159. Calc. for  $\text{C}_{10}\text{H}_{16}\text{O}$ :  $M$ , 152.1197;  $\nu_{\text{max}}$ . 1730 (C=O) and 1610  $\text{cm}^{-1}$  (C=C),  $\delta_{\text{H}}$  ( $\text{CCl}_4$ ) 4.96 (1 H, d,  $J$  1 Hz, = $\text{CHH}$ ), 4.84 (1 H, d,  $J$  2 Hz, = $\text{CHH}$ ), 3.0—1.5 (5 H, m, ring protons), 1.18 (3 H, s, 3-Me), 1.10 (3 H, d,  $J$  6 Hz, 5-Me), 1.02 (3 H, s, 3-Me);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ ) 210.0 (C-1), 156.3 (C-4), 105.8 (=  $\text{CH}_2$ ), 55.9 (C-2), 49.3 (C-6), 39.3 (C-3), 33.3 (C-5), 29.3 (Me), 28.5 (Me), and 18.9 (3-Me); and (iii) 3,4,5,5-tetramethylcyclohex-2-enone (12),  $m/e$  152 ( $M^+$ ) (Calc. for  $\text{C}_{10}\text{H}_{16}\text{O}$ :  $M$ , 152);  $m/e$  137, 109, and 93 (base peak);  $\nu_{\text{max}}$ . 1665 (C=O) and 1625  $\text{cm}^{-1}$  (C=C);  $^1\text{H}$  n.m.r. spectrum identical with published spectrum.<sup>11</sup>

**Copper(I)-catalysed Conjugate Addition of Benzyl Grignard Reagents to the Dienone (6).**—Standard procedure for the preparation of Grignard reagents. Magnesium was placed in a 25-ml triple-necked flask equipped with a magnetic stirrer, reflux condenser, addition funnel, and rubber septum. The flask was flushed with dry nitrogen, and was subsequently maintained under positive nitrogen pressure. The magnesium was covered with dry ether and several drops of organic halide and a small iodine crystal were added to initiate the reaction. When the reaction had begun, the mixture was stirred and the remaining organic halide in dry ether was added to maintain gentle reflux (20—30 min). The mixture was then heated under reflux for an additional 30 min and allowed to cool to room temperature.

**Standard procedure for the addition of Grignard reagents to the dienone (6).** A solution of the dienone (6) in dry solvent was mixed with a copper(I) salt in a 25-ml flask equipped with a magnetic stirrer and a pressure-equalising funnel stoppered with a rubber septum. The flask was flushed with dry nitrogen, and was subsequently maintained under positive nitrogen pressure. The Grignard reagent, prepared

as above, was transferred to the funnel through a length of 1-mm i.d. stainless-steel tubing by nitrogen pressure and was slowly added to the stirred and cooled (0 °C) dienone solution, producing initially a transient purple colour which persisted when the Grignard reagent was present in excess. When addition was complete, the reaction mixture was stirred at room temperature for 30 min and worked up. When near-neutral work-up conditions were required, the reaction mixture was poured into 10% aqueous ammonium chloride (200 ml) and extracted with ether. When acid work-up was required, the reaction mixture was poured into 1:1 tetrahydrofuran–10% hydrochloric acid (200 ml) and heated under nitrogen for 1 h. The ether was allowed to escape so that the reflux temperature rose to approximately 60 °C. The cooled mixture was extracted with ether. When required, the product was purified by p.l.c. [chloroform–ether (15:1) or hexane–ether (5:1)].

**4-(2-*m*-Methoxyphenylethyl)-3,5,5-trimethylcyclohex-2-enone (16b).**—The reagents were *m*-methoxybenzyl bromide (2.68 g,  $1.3 \times 10^{-2}$  mol) in ether (8 ml), magnesium (0.42 g,  $1.7 \times 10^{-2}$  mol) in ether (2 ml), the dienone (6) (1.00 g,  $6.6 \times 10^{-3}$  mol) in tetrahydrofuran (8 ml), and  $\text{Cu}^{\text{I}}\text{Br}$  (0.10 g,  $6.9 \times 10^{-4}$  mol).

Use of the standard procedure with acid work-up and p.l.c. gave the *enone* (16b) (0.89 g, 51%), b.p. 170 °C at 0.2 mmHg (Found: C, 79.5; H, 9.1%;  $M^+$ , 272.  $\text{C}_{18}\text{H}_{24}\text{O}_2$  requires C, 79.4; H, 8.9%;  $M$ , 272);  $\nu_{\text{max}}$ . 1660 (C=O), and 1600 and 1585  $\text{cm}^{-1}$  (C=C);  $\delta_{\text{H}}(\text{CDCl}_3)$  7.20–6.60 (4 H, m, aromatic H), 5.80 (1 H, m, 2-H), 3.76 (3 H, s, OMe), 2.66 (2 H, m, 2'-H<sub>2</sub>), 1.97 (3 H, d,  $J$  1.5 Hz, 3-Me), 1.14 (3 H, s, 5-Me), and 1.04 (3 H, s, 5-Me);  $\delta_{\text{C}}(\text{CDCl}_3)$  198.8 (C-1), 165.1 (C-3), 159.6 (C-1''), 143.2 (C-3''), 129.3 (C-5''), 124.9 (C-2), 120.6 (C-4''), 114.2 (C-2''), 111.1 (C-6''), 55.0 (OMe), 50.5 (C-4), 47.1 (C-6), 36.3 (C-5), 35.7 (C-2), 32.0 (C-1'), 28.6 (5-Me), 27.1 (5-Me), and 24.3 (3-Me).

When near-neutral work-up conditions were used, the main product was 4-(2-*m*-methoxyphenylethyl)cyclohex-3-enone (13b);  $\nu_{\text{max}}$ . 1700  $\text{cm}^{-1}$  (C=O);  $\delta_{\text{H}}(\text{CDCl}_3)$  7.20–6.60 (4 H, m, aromatic H), 3.76 (3 H, s, OMe), 2.78 (2 H, br s,  $W_{\frac{1}{2}}$  4 Hz, 2-H<sub>2</sub>), 2.52 (4 H, m,  $W_{\frac{1}{2}}$  16 Hz, 1'-H<sub>2</sub> and 2-H<sub>2</sub>), 2.36 (2 H, s, 6-H<sub>2</sub>), 1.70 (3 H, s, 3-Me), and 1.12 (6 H, s, 5-Me<sub>2</sub>). When set aside in air for several days, the  $\beta\gamma$ -unsaturated ketone (13b) was oxidised to yield (p.l.c.) 4-hydroperoxy-4-(2-*m*-methoxyphenylethyl)-3,5,5-trimethylcyclohex-2-enone (14b);  $\nu_{\text{max}}$ . 3230 (OH) and 1650  $\text{cm}^{-1}$  (C=O);  $\delta_{\text{H}}(\text{CDCl}_3)$  8.2br (1 H, s, exchanges on deuteration, 4-OOH), 7.20–6.60 (4 H, m, aromatic H), 5.99 (1 H, m, 2-H), 3.78 (3 H, s, OMe), 2.14 (3 H, d,  $J$  2 Hz, 3-Me), 1.14 (3 H, s, 5-Me), and 1.10 (3 H, s, 5-Me);  $\delta_{\text{C}}(\text{CDCl}_3)$  199.0 (C-1), 164.3 (C-3), 159.6 (C-1''), 143.6 (C-3''), 129.5 (C-5''), 127.6 (C-2), 120.6 (C-4''), 114.2 (C-2''), 111.2 (C-6''), 88.6 (C-4), 55.1 (OMe), 51.4 (C-6), 42.0 (C-5), 35.6 (C-2), 31.6 (C-1'), 25.6 (5-Me), 24.5 (5-Me), and 21.8 (3-Me). The hydroperoxide (14b) slowly decomposed to a mixture of products which yielded (p.l.c.) 4-hydroxy-4-(2-*m*-methoxyphenylethyl)-3,5,5-trimethylcyclohex-2-enone (15b), m.p. 155–156 °C (hexane–ether) (Found: C, 75.0; H, 8.5%;  $M^+$ , 288.  $\text{C}_{18}\text{H}_{24}\text{O}_3$  requires C, 74.95; H, 8.4%;  $M$ , 288);  $\nu_{\text{max}}$ . (KBr) 3440 (O-H) and 1645  $\text{cm}^{-1}$  (C=O);  $\delta_{\text{H}}(\text{CDCl}_3)$  7.20–6.60 (4 H, m, aromatic H), 5.92 (1 H, m, 2-H), 3.78 (3 H, s, OMe), 2.08 (3 H, d,  $J$  1.5 Hz, 3-Me), 1.80 (1 H, s, exchanges on deuteration, 4-OH), and 1.08 (6 H, s, 5-Me<sub>2</sub>).

**4-(2-*p*-Methoxyphenylethyl)-3,5,5-trimethylcyclohex-2-enone (16a).**—(a) The reagents were *p*-methoxybenzyl

chloride (0.75 g,  $4.8 \times 10^{-3}$  mol) in ether (4.5 ml), magnesium (2.3 g,  $9.6 \times 10^{-2}$  mol) in ether (15 ml), the dienone (6) (0.43 g,  $2.9 \times 10^{-3}$  mol) in tetrahydrofuran (6 ml), and  $\text{Cu}^{\text{I}}\text{Br}$  (0.05 g,  $3.5 \times 10^{-4}$  mol). The standard procedure, with acid work-up and purification by p.l.c., yielded the *enone* (16a) (0.37 g, 48%).

(b) The reagents were *p*-methoxybenzyl chloride (0.75 g,  $4.8 \times 10^{-3}$  mol) in ether (4.5 ml), magnesium (2.3 g,  $9.6 \times 10^{-2}$  mol) in ether (15 ml), the dienone (6) (0.45 g,  $3.0 \times 10^{-3}$  mol) in ether (8 ml), and  $\text{Cu}^{\text{I}}(\text{Me}_2\text{S})\text{Br}$  (0.06 g,  $3.0 \times 10^{-4}$  mol) in dimethyl sulphide (2 ml). The standard procedure with acid work-up yielded (p.l.c.) the *enone* (16a) (0.54 g, 66%), b.p. 170 °C at 0.2 mmHg (Found: C, 79.2; H, 9.0%;  $M^+$ , 272.  $\text{C}_{18}\text{H}_{24}\text{O}_2$  requires C, 79.4; H, 8.9%;  $M$ , 272);  $\nu_{\text{max}}$ . 1660 (C=O), 1600, and 1585  $\text{cm}^{-1}$  (C=C);  $^1\text{H}$  n.m.r. spectrum identical to that of (16b) except for aromatic protons,  $\delta_{\text{H}}$  7.10–6.90 (4 H, 2 d,  $J$  8 Hz);  $\delta_{\text{C}}(\text{CDCl}_3)$  199.1 (C-1), 165.4 (C-3), 158.0 (C-1''), 133.7 (C-4''), 129.1 (C-2''), 6''), 125.0 (C-2), 113.8 (C-3''), 5''), 55.2 (OMe), 50.6 (C-4), 47.1 (C-6), 36.4 (C-5), 34.9 (C-2), 32.5 (C-1'), 28.7 (5-Me), 27.1 (5-Me), and 24.5 (3-Me).

If near-neutral work-up was employed, the main product was 4-(2-*p*-methoxyphenylethyl)-3,5,5-trimethylcyclohex-3-enone (13a);  $\nu_{\text{max}}$ . 1700  $\text{cm}^{-1}$  (C=O);  $^1\text{H}$  n.m.r. spectrum identical to that of (13b) except for the aromatic region. The  $\beta\gamma$ -unsaturated ketone (13a) slowly oxidised to form 4-hydroperoxy-4-(2-*p*-methoxyphenylethyl)-3,5,5-trimethylcyclohex-2-enone (14a);  $\nu_{\text{max}}$ . 3230 (O-H), and 1650  $\text{cm}^{-1}$  (C=O);  $^1\text{H}$  n.m.r. spectrum identical to that of (14b) except in the aromatic region. Treatment of the hydroperoxide with potassium iodide in methanol gave iodine and 4-hydroxy-4-(2-*p*-methoxyphenylethyl)-3,5,5-trimethylcyclohex-2-enone (15a), m.p. 155–156 °C (hexane–ether) (Found: C, 74.65; H, 8.6%;  $M^+$ , 288.  $\text{C}_{18}\text{H}_{24}\text{O}_3$  requires C, 74.95; H, 8.4%;  $M$ , 288);  $\nu_{\text{max}}$ . (Nujol) 3380 (O-H) and 1640  $\text{cm}^{-1}$  (C=O);  $^1\text{H}$  n.m.r. spectrum identical to that of (15b) except in the aromatic region;  $\delta_{\text{C}}(\text{CDCl}_3)$  197.6 (C-1), 167.3 (C-3), 158.2 (C-1''), 133.9 (C-4''), 129.1 (C-2''), 6''), 126.6 (C-2), 114.1 (C-3''), 5''), 78.4 (C-4), 55.3 (OMe), 50.1 (C-6), 41.8 (C-5), 41.0 (C-1'), 30.4 (C-2'), 24.0 (5-Me), 23.6 (5-Me), 21.4 (3-Me).

**Determination of the Effect of Copper(I) on Conjugate Addition of Benzyl Grignard Reagents.**—Experiments were performed by the standard procedure, in which *m*- and *p*-methoxybenzyl Grignard reagents were added to the dienone (6), both in the presence and in the absence of copper(I) salts. The product mixtures were worked-up under near-neutral conditions, analysed by  $^1\text{H}$  n.m.r. spectroscopy, treated with aqueous acid as described for the acid work-up procedure, and re-analysed by  $^1\text{H}$  n.m.r. spectroscopy. The ratio of 1,2 to 1,4 addition was determined by comparison of the area of the peak at  $\delta$  5.04 (=CH<sub>2</sub>, 2 protons) with that at  $\delta$  5.16 (1 proton of =CH<sub>2</sub>) before the acid treatment of the product mixtures. The ratio of 1,4 to 1,6 addition was determined after the acid treatment by comparison of the peak area at  $\delta$  5.16 with that at  $\delta$  5.80 (CMe=CH–CO, 1 proton).

The 1,2 and 1,4 addition products could be isolated from the product mixtures from additions in the absence of copper(I). The 1,2 addition products were obtained from bands with slightly lower  $R_{\text{F}}$  than those of the 1,4 and 1,6 addition products. The *m*- and *p*-methoxybenzyl Grignard reagents gave respectively 1-*m*-methoxybenzyl-3,5,5-trimethyl-4-methylenecyclohex-2-en-1-ol (18b);  $\nu_{\text{max}}$ . 3400  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}(\text{CDCl}_3)$  7.20–6.60 (4 H, m, aromatic H), 5.48

(1 H, m, 2-H), 5.04 (2 H, d,  $J$  1.5 Hz, =CH<sub>2</sub>), 3.78 (3 H, s, OMe), 2.78 (2 H, s, -CH<sub>2</sub>-), 1.88 (3 H, d,  $J$  2 Hz, 3-Me), 1.66 (3 H, m, 1 H exchanges on deuteration, 6-H<sub>2</sub> and 1-OH), and 1.20 (6 H, s, 5-Me<sub>2</sub>): and 1-*p*-methoxybenzyl-3,5,5-trimethyl-4-methylenecyclohex-2-en-1-ol (18a);  $\nu_{\max}$ . 3 400 cm<sup>-1</sup> (O-H); <sup>1</sup>H n.m.r. spectrum identical to that of (18a) except in the aromatic region.

Treatment of the addition products with acid destroyed the 1,2-addition products (18) and rearranged the 1,6-addition products (13) to the conjugated ketones (16). P.l.c. of the acid-treated products gave the 1,4-addition products with slightly greater  $R_F$  values than the conjugated ketones and identified as (i) 3-*m*-methoxybenzyl-3,5,5-trimethyl-4-methylenecyclohexanone (17b) (Found:  $M^+$ , 272. Calc. for C<sub>18</sub>H<sub>24</sub>O<sub>2</sub>:  $M$ , 272);  $\nu_{\max}$ . 1 715 cm<sup>-1</sup> (C=O);  $\delta_H$ (CDCl<sub>3</sub>) 7.20—6.60 (4 H, m, aromatic H), 5.32 and 5.16 (2 H, 2 s, =CH<sub>2</sub>), 3.78 (3 H, s, OMe), 3.0—2.0 (6 H, multiple peaks, 2-H<sub>2</sub>, 6-H<sub>2</sub>, 3-H<sub>2</sub>), 1.20 (6 H, s, Me<sub>2</sub>), and 1.06 (3 H, s, Me): and (ii) 3-*p*-methoxybenzyl-3,5,5-trimethyl-4-methylenecyclohexanone (17a) (Found:  $M^+$ , 272. Calc. for C<sub>18</sub>H<sub>24</sub>O<sub>2</sub>:  $M$ , 272);  $\nu_{\max}$ . 1 715 cm<sup>-1</sup> (C=O); <sup>1</sup>H n.m.r. spectrum identical to that of (17a) except in the aromatic region.

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