Reaction of ' Myrcene–Magnesium ' with Esters, Acetyl Chloride, and Acetic Anhydride: Formation of Cyclopentenols and Cyclopropane Derivatives

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Addition of a series of esters to the' myrcene–magnesium ' complex at room temperature yielded a mixture of ketones [(1) and (2)] and a substituted cyclopentenol (3). The products (1) and (2) were formed by a 1,4-addition across the 1,3-diene system; cyclisation then yielded (3). With ethyl pivalate, the cyclopentenol is >90% of the product mixture, but (3) is almost the only product when the reaction with other esters is conducted at 65 °C. The importance of steric effects in the cyclisation was confirmed by the reaction of ethyl acetate with the magnesium complex of 1,4-diphenylbuta-1,3-diene to give only cyclopentenols. The reaction of the ' myrcene–magnesium ' complex with acetyl chloride or acetic anhydride also yields cyclopropyl acetates, as a result of a 1,2-addition to the diene unit, followed by cyclisation and acetylation.

THE formation of 1,3-diene-magnesium complexes [1] and the reaction of ' isoprene–magnesium ' with carbonyl compounds [2,3] have been reported. In the preceding paper we describe the reactions of ' myrcene–magnesium ' with aldehydes, ketones, epoxides, carbon dioxide, and acetonitrile in which 1,2- or 3,4-addition to the 1,3-diene unit was found.[4] We now report that in the reactions of esters with the ' myrcene–magnesium ' complex a 1,4-addition takes place, followed by cyclisation to form cyclopentenols. Cyclopropane derivatives have been produced as a result of a 1,2- or 3,4-addition of acetyl chloride or acetic anhydride to 'myrcene–magnesium ' followed by cyclisation.

RESULTS AND DISCUSSION

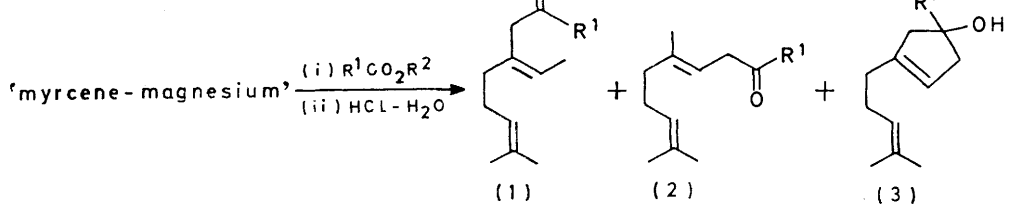
' Myrcene–magnesium ' was prepared by heating myrcene and magnesium in the presence of iron(III) chloride and ethyl bromide in tetrahydrofuran (THF). The ester was added to the solution and, under the conditions summarised in Table 1, the ketones (1) and (2) and the cyclopentenols (3) were formed in varying amounts. The ketones were identified from their i.r. ($\nu_{max.}$ 1 710 cm^{-1}) and n.m.r. spectra [τ 4.9 (2 × :CH), indicating 1,4-addition]. The ketone (1) was distinguished from (2) by means of the n.m.r. signal at τ 7.0 ($CO{\cdot}CH_2{\cdot}CH$:) being a singlet for (1) and a doublet for (2). was unsatisfactory under all conditions. With other esters, at room temperature, a larger amount of (2) was obtained than of (1); the ratio ranged from 3 : 1 for ethyl acetate to 3.5 : 1 for ethyl propionate and 4 : 1 for ethyl butyrate. At 65 °C, (3) was almost the only product and this was also the case with ethyl pivalate at room temperature.

TABLE 1

Reaction of esters with ' myrcene–magnesium '

Ester	Conditions	Yield (%) of products [a] (1)	(2)	(3)
HCO_2Et	−10 °C (2 h) or 65 °C (½ h)			
	Room temp. (2 h)		9.7	
$MeCO_2Et$	−10 °C (2 h)	7.7	16	6.4
	Room temp. (2 h)	5.6	17	11
	Room temp. (18 h)	2.3	7.2	5.9
	65 °C (½ h)	Trace	Trace	30
$MeCO_2Me$	65 °C (½ h)	Trace	Trace	26
$MeCO_2Bu^s$	65 °C (½ h)		2.4	23
$EtCO_2Et$	Room temp. (½ h)	4.5	17	9
	65 °C (½ h)		1.4	28
Pr^nCO_2Et	Room temp. (½ h)	4.9	20	5.9
	65 °C (½ h)		1.1	27
Bu^tCO_2Et	Room temp. (½ h)		1.5	26

[a] Based on ' myrcene–magnesium,' which was formed to the extent of *ca.* 90%



The product (3) was also identified from its i.r. ($\nu_{max.}$ 3 400 cm^{-1}) and n.m.r. spectra [τ 4.9 (2 × CH:) and 7.7 (4 H)]. Higher-boiling products consisting of two or more myrcene units were not analysed.

Addition of ethyl formate to ' myrcene–magnesium '

No detailed examination has been made of the structure of the magnesium complex, but previous reactions could be explained on the basis of an intermediate such as (4).[4] A preference for attack at C-4 rather than C-1 of the 1,3-diene system is consistent with some steric control by interaction with the alk-2-enyl

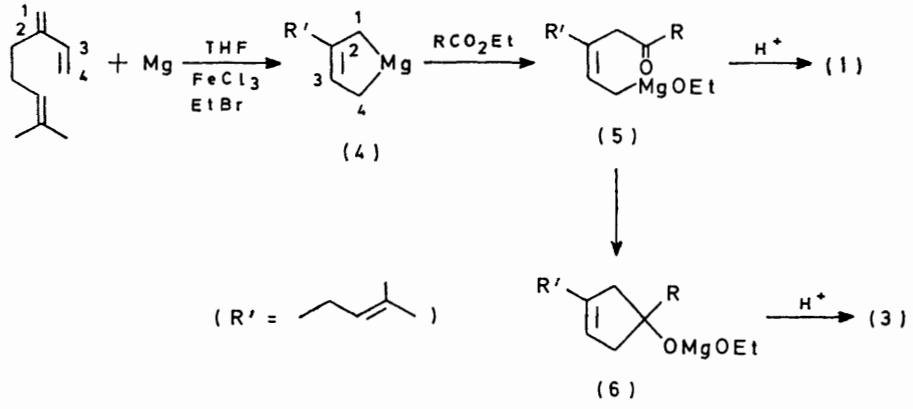
[1] H. E. Ramsden, U.S.P., 3,354,190/1967; 3,388,179/1968; 3,711,560/1973; 3,642,845/1972; S. Akutagawa, T. Sakaguchi, and A. Komatsu, Jap.P., 3,770/1971; 15,941/1972; 20,005/1972; 42,824/1972.

[2] M. Yang, K. Yamamoto, N. Otake, M. Ando, and K. Takase, *Tetrahedron Letters*, 1970, 3843.

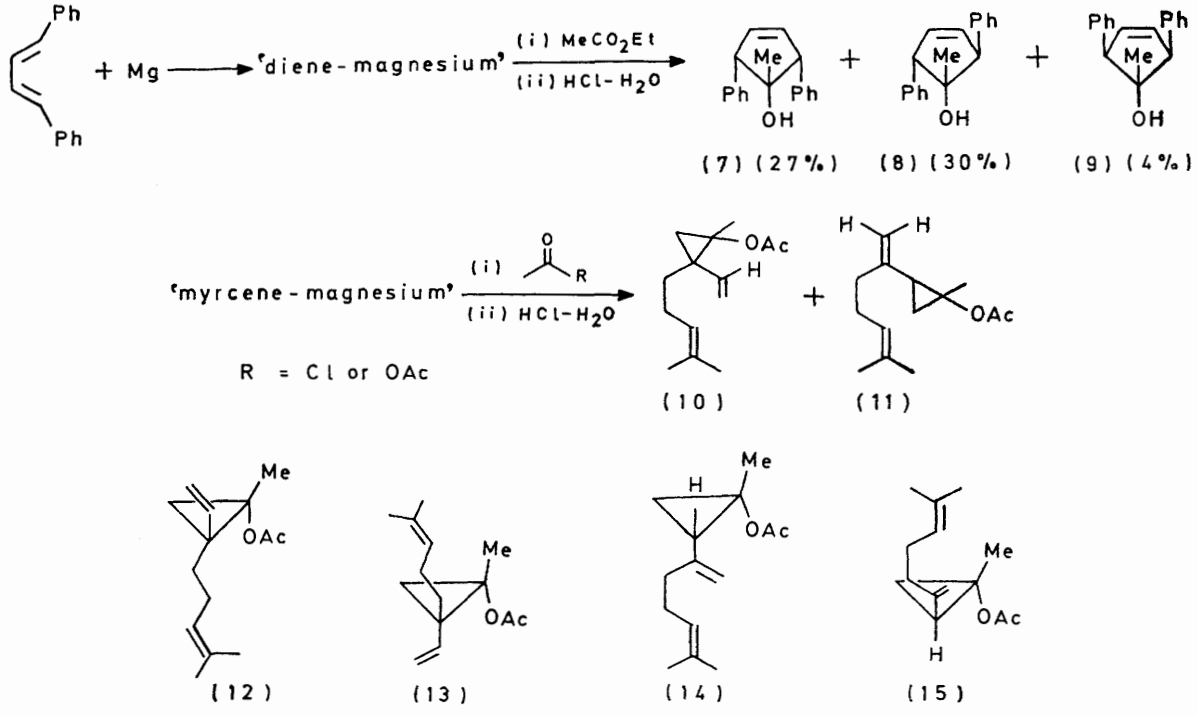
[3] M. Yang, M. Ando, and K. Takase, *Tetrahedron Letters*, 1971, 3529.

[4] R. Baker, R. C. Cookson, and A. D. Saunders, preceding paper.

group in the myrcene intermediate. Formation of the ketone can then be followed by cyclisation to (6) (Scheme 1); this second step does not occur to any extent at room temperature (except for the reaction with ethyl pivalate) and requires a temperature of 65 °C. The ready formation of (6) from ethyl pivalate at room temperature must be associated with the steric bulk of the pivaloyl group, but the origin of the steric effect is with ethyl acetate. Complete cyclisation occurred to form the three 1-methyl-2,5-diphenylcyclopent-3-enols (7) (27%), (8) (30%), and (9) (4%); in addition, the reaction demonstrated the loss of stereochemistry at C-1 and C-4, adding further support to an intermediate of structure analogous to (4). The products (7)—(9) were distinguished by means of the chemical shifts of the methyl groups in their n.m.r. spectra [τ 8.7 for (7),



SCHEME 1



not readily apparent. A similar effect has been observed in the reactions of ' isoprene–magnesium ' with esters.[3]

The ketones (1) and (2) are the result of 1,4-addition to the 1,3-diene moiety; this contrasts with the 1,2- and 3,4-addition observed with aldehydes, ketones, epoxides, carbon dioxide, and acetonitrile.[4]

The importance of steric effects in the formation of cyclopentene derivatives is confirmed by the reaction of ' *trans,trans*-1,4-diphenylbuta-1,3-diene–magnesium 9.22 for (8), and 9.75 for (9)]. The changes are due to the ring current effect of the phenyl groups. In structure (7) the phenyl groups have no effect, but in (8) the methyl group is under the influence of one phenyl group, and in (9) both phenyl groups are involved. The stereochemical assignment is corroborated by the non-equivalence of the two benzylic protons of (8).

A distinctive course was observed in the reaction of ' myrcene–magnesium ' with acetyl chloride and acetic anhydride: 1,2- or 3,4-addition was followed by cyclis-

ation. With both reagents a mixture of the cyclopropyl derivatives (10) and (11) was obtained. Both products were formed as mixtures of geometrical isomers, (12)—(15). Separation and identification of these compounds was difficult, and the suggested structures are based on n.m.r. spectra: (12) and (13) were distinguished by means of the chemical shifts of their methyl groups [τ 8.67 for (12) and 8.5 for (13), owing to shielding by the double bond]. Compounds (14) and (15) were identified similarly (τ 8.5 and 8.7). Yields of (12)—(15) depended upon the reagent and the temperature of addition (Table 2).

TABLE 2

Reactions of acetyl chloride and acetic anhydride with ' myrcene–magnesium '

		Yields (%) of products [a]			
Reagent	Conditions	(12)	(13)	(14)	(15)
MeCOCl	65 °C (0.5 h)	3.8	3.8	9.1	13
	Room temp. (0.5 h)	4.1	1.6	2.6	22
	−15 °C (2 h)	3.2	1.6	8.8	17
$(MeCO)_2O$	−10 °C (2 h)	1.5	2.1	8.4	13

[a] Based on ' myrcene-magnesium.'

The reaction can again be interpreted as involving an intermediate such as (4) (Scheme 2), in which preferential attack by the reagent is at the 3-position of the 1,3-diene, owing to steric approach control. Under these conditions acetylation of a tertiary alcohol does not normally occur, but in this case the presence of the magnesium might facilitate the process.

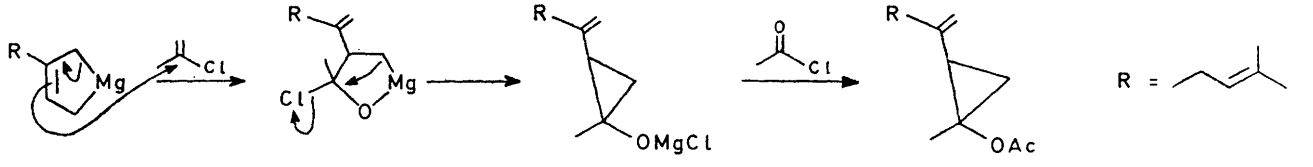
' Isoprene–magnesium ' reacted with acetyl chloride in a similar way to form *cis*- and *trans*-1,2-dimethyl-2-vinylcyclopropyl acetates (16) (trace) and (17) (6.6%), *cis*- and *trans*-2-isopropylidene-1-methylcyclopropyl acetates (18) (3.8%) and (19) (11%), and 2 : 2 adducts (12%). The assignments of stereochemistry were similar to those previously described, but the higher molecular weight adducts were not analysed.

EXPERIMENTAL

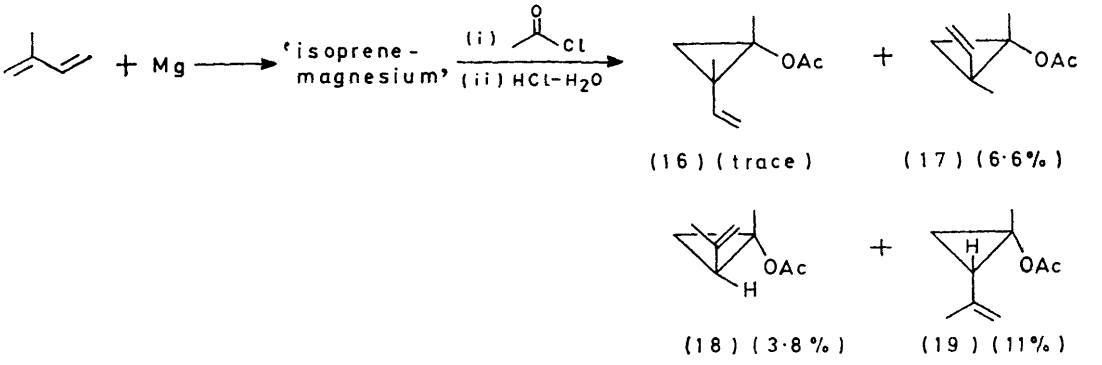
Myrcene–magnesium was prepared as described previously.[4]

Reactions with Esters.—An equimolar amount of the ester was added to a solution of ' myrcene–magnesium ' in tetrahydrofuran, and the reaction was carried out under the conditions described in Table 1. A stoicheiometric quantity of dilute hydrochloric acid was added and the products were extracted with ether. The dried extract was evaporated and the residue distilled under reduced pressure to yield a small amount of unchanged myrcene and a fraction containing the products. This fraction was analysed by g.l.c. (Pye 104; carrier gas N_2 at 60 ml min^{-1}; 10 ft 15% PPGA; 170 °C) and three products were detected in each case except for the reaction with ethyl formate. Part of this fraction (*ca.* 1 g) was chromatographed on silica gel (60 g) (ether–petroleum as eluant). Increasing the proportion of ether in the eluant from 1 to 5% gave the ketone (1) followed by (2), and the cyclopentenol (3) was obtained with 10% ether.

Conversion into the ' myrcene–magnesium ' was *ca.* 87% and yields are summarised in Table 1; n.m.r. data are detailed in Table 3, and i.r. and mass spectral data are available as Supplementary Publication No. SUP 12802 (2 pp.).†



SCHEME 2



The b.p. ranges of the adducts and analytical g.l.c. details are as follows: from ethyl acetate, 100—130° at 5 mmHg (t_R 8.1, 10.2, and 11.1 min); from ethyl propionate, 120—150° at 5 mmHg (9.0, 12.0, and 14.4 min); from ethyl butyrate, 130—160° at 5 mmHg (12.0, 15.0, and 19.5 min); from ethyl pivalate, 120—150° at 5 mmHg (14.6 and 21.6 min).

Reactions with Acetyl Chloride and Acetic Anhydride.—' Myrcene–magnesium ' was cooled to room temperature and an equimolar amount of acetyl chloride or acetic anhydride was added dropwise. The complex was stirred for 0.5 h before decomposition. The dried ethereal extract

† For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S Perkin I*, 1975, Index issue.

was evaporated and the residue distilled at reduced pressure to give two fractions: unchanged myrcene (b.p. 40—60° at 5 mmHg) and a second fraction, b.p. 100—130° at 5 mmHg, which showed four peaks (t_R 7.5, 8.4, 9.0, and 9.6 min) on analysis by g.l.c. (10 ft 15% PPGA; 170 °C). The products (13)—(15) were isolated pure by preparative g.l.c. (30 ft 15% PPGA; 170 °C) and (12) was obtained by column chromatography. Part of the second fraction (1.04 g) was chromatographed on silica gel (50 g) with 1% ether–petroleum as eluant. Increasing the ether composition to 3% gave compound (12), followed by (13), (14), and (15). All the products were oils and the n.m.r. data are recorded in Table 3 (i.r. and mass spectral data are in the Supplementary Publication).

2 850, 1 605, 1 500, 1 460, 1 380, 1 170, 1 100, 1 040, and 880 cm^{-1}; τ (CCl_4) 9.22 (3 H, s), 7.28 (1 H, t, J 9.0 Hz), 6.90 (1 H, t, J 9.0 Hz), 4.0 (2 H, m), 3.15 (5 H, m), and 2.9 (5 H, m); (9) *m/e* 250, 232, 207, 132, 131, 117, 104, 102, 91, and 77; $\nu_{max.}$ (CCl_4) 3 600, 3 050, 3 020, 2 960, 2 850, 1 605, 1 500, 1 460, 1 390, 1 360, 1 160, 1 130, and 1 090 cm^{-1}; τ (CCl_4) 9.75 (3 H, s), 5.97br (2 H, s), 4.03br (2 H, s), and 2.84 (10 H, s).

Reaction of ' Isoprene–Magnesium ' with Acetyl Chloride.—' Isoprene–magnesium ' (0.1 mol), prepared by the method of Takase *et al.*,[3] was cooled to room temperature, and acetyl chloride (0.1 mol) was added at such a rate that the solution did not boil. The solution was stirred for 0.5 h before decomposition. The dried ethereal extract was

TABLE 3

^1H N.m.r. data of products from reactions of ' myrcene–magnesium '

Reagent	Products	τ(CCl_4)(J in Hz)
$MeCO_2Et$	4-Ethylidene-8-methylnon-7-en-2-one (1)	8.4 (9 H, d),* 8.0 (7 H, br), 7.0 (2 H, s), 4.9 (2 H, br)
	(4*E*)-5,9-Dimethyldeca-4,8-dien-2-one (2)	8.4 (9 H, d),* 8.0 (7 H, br), 7.0 (2 H, d, J 6.7), 4.9 (1 H, br), 4.7 (1 H, t, J 6.7)
	1-Methyl-3-(4-methylpent-3-enyl)cyclopent-3-enol (3)	8.66 (3 H, s), 8.35 (6 H, d),* 7.96 (4 H, br), 7.7 (4 H, d), 4.99 (1 H, br), 4.84 (1 H, s), 6.9 (OH)
$EtCO_2Et$	5-Ethylidene-9-methyldec-8-en-3-one (1)	9.1 (3 H, t, J 7.3), 8.45 (9 H, d), 8.0 (4 H, br), 7.7 (2 H, q, J 7.3), 7.05 (2 H, s), 5.15 (1 H, br), 4.9 (1 H, s)
	(5*E*)-6,10-Dimethylundeca-5,9-dien-3-one (2)	9.0 (3 H, t, J 7.3), 8.4 (9 H, d),* 8.0 (4 H, br), 7.65 (2 H, q, J 7.3), 7.0 (2 H, d, J 7.3), 5.0 (1 H, br), 4.8 (1 H, t, J 7.3)
	1-Ethyl-3-(4-methylpent-3-enyl)cyclopent-3-enol (3)	9.15 (3 H, t, J 7.0), 8.5 (2 H, q, J 7.0), 8.4 (6 H, d),* 8.03 (4 H, br), 7.27 (4 H, br), 5.05 (1 H, br), 4.89 (1 H, s), 8.81 (OH)
Pr^nCO_2Et	6-Ethylidene-10-methylundec-9-en-4-one (1)	9.1 (3 H, t, J 7.3), 8.55 (2 H, m), 8.35 (9 H, d),* 8.0 (4 H, br), 7.7 (2 H, t, J 6.0), 7.0 (2 H, s), 4.95 (2 H, br)
	(6*E*)-7,11-Dimethyldodeca-6,10-dien-4-one (2)	9.1 (3 H, t, J 7.3), 8.5 (2 H, m), 8.35 (9 H, d),* 7.95 (4 H, br), 7.7 (2 H, t, J 6.0), 7.0 (2 H, t, J 6.7), 4.9 (2 H, m)
	3-(4-Methylpent-3-enyl)-1-propylcyclopent-3-enol (3)	9.14 (3 H, t, J 6.0), 8.5 (2 H, m), 8.35 (8 H, d on m),* 8.03 (4 H, br), 7.79 (4 H, br), 5.03 (1 H, br), 4.89 (1 H, br), 7.57 (OH)
Bu^tCO_2Et	(5*E*)-2,2,6,10-Tetramethylundeca-5,9-dien-3-one (2)	8.98 (9 H, s), 8.4 (9 H, d),* 8.0 (4 H, br), 7.95 (2 H, d, J 7.0), 5.0 (2 H, br)
	3-(4-Methylpent-3-enyl)-1-t-butylcyclopent-3-enol (3)	9.06 (9 H, s), 8.4 (6 H, d),* 8.0 (4 H, br), 7.6 (4 H, br), 5.0 (1 H, br), 4.84 (1 H, br)
MeCOCl or $(MeCO)_2O$	1-Methyl-*cis*-2-(4-methylpent-3-enyl)-2-vinylcyclopropyl acetate (12)	9.3 (1 H, d, J 6.0), 9.2 (1 H, d, J 6.0), 8.67 (3 H, s), 8.4 (6 H, d),* 8.1 (3 H, s), 8.06 (4 H, br), 5.0 (3 H, m), 4.2 (1 H, dd, J_{cis} 10.0, J_{trans} 16.0)
	1-Methyl-*trans*-2-(4-methylpent-3-enyl)-2-vinylcyclopropyl acetate (13)	9.5 (1 H, d, J 6.7), 9.1 (11, d, J 6.7), 8.5 (3 H, s), 8.4 (6 H, d),* 8.15 (3 H, s), 8.0 (4 H, br), 5.0 (3 H, m), 4.4 (1 H, dd, J_{cis} 7.0, J_{trans} 19.0)
	1-Methyl-*cis*-2-(5-methyl-1-methylenehex-4-enyl)cyclopropyl acetate (14)	9.1 (3 H, m), 8.5 (3 H, s), 8.4 (6 H, d),* 8.15 (3 H, s), 7.9 (4 H, br), 5.45 (1 H, br), 5.25 (1 H, br), 4.9 (1 H, br)
	1-Methyl-*trans*-2-(5-methyl-1-methylenehex-4-enyl)cyclopropyl acetate (15)	8.7 (3 H, s), 8.4 (6 H, d),* 8.1 (3 H, s), 7.85 (4 H, br), 5.5 (1 H, br), 5.3 (1 H, br), 4.95 (1 H, br), 9.1 (3 H, m)

* Two peaks, separation *ca.* 4 Hz.

Reaction of ' trans,trans-1,4-Diphenylbuta-1,3-diene–Magnesium ' with Ethyl Acetate.—The 1,3-diene (8.6 g) in tetrahydrofuran (100 ml) was added to magnesium (1.0 g), iron(III) chloride (0.34 g), and ethyl bromide (0.2 ml) and the mixture was heated at 65 °C for 0.5 h. After cooling to room temperature, ethyl acetate (3.66 g) was added and the solution further refluxed for 0.5 h before decomposition with dilute acid. The dried ethereal extract was evaporated and the products were separated by chromatography. Part of the product (2.0 g) was eluted from silica gel (75 g) with 5% ether–petroleum. Unchanged diene separated and the proportion of ether in the eluant was increased to 10 and then to 15%. *cis,cis*-1-Methyl-2,5-diphenylcyclopent-3-enol (7) separated, followed by the *trans,cis*- (8), and *trans,trans*- (9) isomers; all were oils with the following characteristics: (7) *m/e* 250, 232, 207, 130, 117, 91, and 77; $\nu_{max.}$ (CCl_4) 3 600, 3 050, 3 020, 2 950, 2 850, 1 605, 1 505, 1 460, 1 380, 1 260, 1 240, 1 170, 1 110, 1 090, and 1 040 cm^{-1}; τ (CCl_4) 8.7 (3 H, s), 6.24 (2 H, d, J 1.0 Hz), 4.08 (2 H, d, J 1.0 Hz), and 2.81 (10 H, s); (8) *m/e* 250, 207, 132, 131, 117, 91, and 77; $\nu_{max.}$ (CCl_4) 3 600, 3 050, 3 020, evaporated and distilled at reduced pressure. A fraction of boiling range 50—70° at 5 mmHg (21% yield) was separated by preparative g.l.c. (30 ft 15% PPGA; 150 °C) into two components. The first contained mainly the cyclopropane (17), *m/e* 154, 112, 111, 97, 79, 69, 67, 53, and 43; $\nu_{max.}$ (CCl_4) 3 080, 2 970, 2 940, 2 880, 1 745, 1 630, 1 440, 1 375, 1 185, 1 160, 1 085, 1 020, and 905 cm^{-1}; τ (CCl_4) 9.23 (2 H, dd, J_{cis} 6.0 Hz), 8.85 (3 H, s), 8.56 (3 H, s), 8.07 (3 H, s), 5.0 (2 H, m), 4.25 (1 H, dd, J_{cis} 9.0, J_{trans} 18.0 Hz), with trace of (16) [τ 8.47 (CH_3) and 8.15 (OAc)]. The second component contained mainly (19), *m/e* 154, 112, 111, 97, 96, 79, 69, 67, 53, and 43; $\nu_{max.}$ (CCl_4) 3 050, 2 970, 2 930, 2 850, 1 745, 1 650, 1 440, 1 380, 1 370, 1 220, 1 190, 1 040, 1 020, and 890 cm^{-1}; τ (CCl_4) 9.2 (3 H, m), 8.69 (3 H, s), 8.15 (3 H, s), 8.11 (3 H, s), 5.51br (1 H), and 5.25br (1 H) and a trace of (18) [τ 8.50 (CH_3) and 8.79 (CH_3)].

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