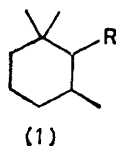


Synthesis of α -Damascone [*trans*-1-(2,6,6-Trimethylcyclohex-2-enyl)but-2-en-1-one] by a Catalysed Diels–Alder Reaction with Inverse Electron Demand¹

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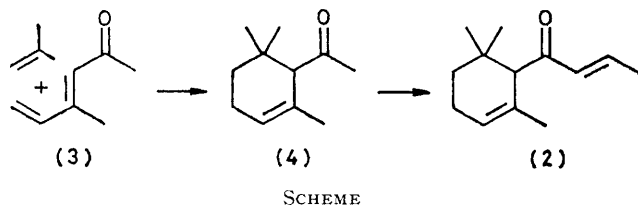
The synthesis of α -damascone from isoprene, acetyl chloride, and 2-methylpropene is described. The catalysed addition of 2-methylpropene to 4-methylhexa-3,5-dien-2-one gave several products including the Diels–Alder adduct (4), which was converted into α -damascone by condensation with acetaldehyde.

THE development of efficient syntheses of β -damascenone and the damascones, natural products with valuable flavour and fragrance properties, has received considerable attention.^{2,3} Most routes to the trisubstituted cyclohexane moiety (1), also characteristic of the ionones and many carotenoids, involve a cationic cyclisation of a preformed hexa-1,5-diene unit. The adjacent carbonyl of the isoionone structure makes direct ring construction by a Diels–Alder reaction an attractive alternative and a synthesis of β -damascenone has recently been



reported⁴ in which the key step is the catalysed Diels–Alder reaction of bromomesityl oxide with penta-1,3-diene. We have investigated a similar approach to α -damascone (2) but involving a novel Diels–Alder reaction with inverse electron demand (Scheme).

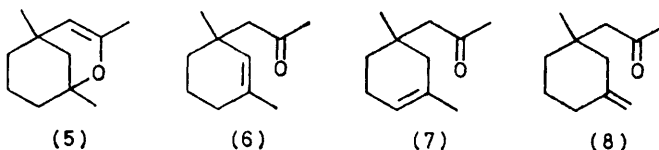
2-Methylpropene was passed through a solution of 4-methylhexa-3,5-dien-2-one⁵ (3), made by acetylation of isoprene [an equilibrium mixture of *cis*- and *trans*-isomers (20 : 80, respectively)], and aluminium chloride (0.9 mol. equiv.) in dichloromethane at room temperature. In 4 h five addition products (4)—(8) were formed in the ratios 20 : 55 : 15 : 6 : 4, respectively, and were isolated in *ca.* 60% yield [based on (3)] after column chromatography. The ketonic products (4) and (6)



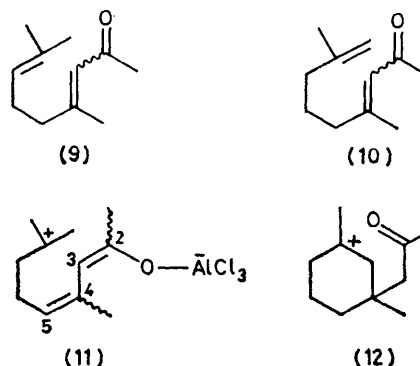
were separated by preparative g.l.c. and the minor components (7) and (8) were identified as a mixture.

No addition products were observed when propene was

passed through a solution of the dienone (3) under similar conditions.



Büchi and Pickenhagen had recently found³ that the vinyl ether (5) is also the major product from the cyclisation of *cis*- and *trans*-4,8-dimethylnona-3,7-dien-2-one (9) in sulphuric acid. Apparently cyclisation to the vinyl ether (5) proceeds through a less sterically crowded transition state which predominates in a protic solvent where the initial double bond rearrangement to the proposed intermediate (10) is fast. We have found that



the dienone (9) polymerises rapidly in the presence of aluminium chloride in dichloromethane, but with boron trifluoride in benzene the ketone (4) is formed preferentially. The ketone (4) and the vinyl ether (5) are unchanged by aluminium chloride in dichloromethane.

There are many conceivable mechanisms for formation of the products (4)—(8). The adduct (4) might be formed directly by a concerted Diels–Alder reaction between the dienone–aluminium chloride complex and 2-methylpropene and the remaining products by competing carbonium ion reactions. It seems more likely,

¹ Preliminary account, R. C. Cookson and R. M. Tuddenham, *J.C.S. Chem. Comm.*, 1973, 742.

² E. Demole, P. Enggist, U. Sauberli, M. Stoll, and E. Sz. Kovats, *Helv. Chim. Acta*, 1970, **53**, 541; G.P. 1,807,568; G. Ohloff and G. Uhde, *Helv. Chim. Acta*, 1970, **53**, 531; G. Büchi and H. Wuest, *ibid.*, 1971, **54**, 1767; G. Büchi and J. Vederas, *J. Amer. Chem. Soc.*, 1972, **94**, 9128.

³ G. Büchi and W. Pickenhagen, *J. Org. Chem.*, 1973, **38**, 894.

⁴ K. S. Ayyar, R. C. Cookson, and D. A. Kagi, *J.C.S. Perkin I*, 1975, 1727.

⁵ D. R. Adams, S. P. Bhatnagar, and R. C. Cookson, *J.C.S. Perkin I*, 1975, 1502; D. R. Adams, S. P. Bhatnagar, R. C. Cookson, and R. M. Tuddenham, *ibid.*, p. 1741.

however, that all the products arise from initial addition of 2-methylpropene to the terminal carbon atom of the dienone (3), which must be strongly electrophilic in the aluminium chloride complex. Eight stereoisomers of the intermediate dipolar ion (11) can exist if the diene unit is approximately planar, differing in configuration about the 2,3- and 4,5-double bonds and the 3,4-single bond: only the four with *Z*-stereochemistry about the 4,5-double bond could cyclise to the aluminium chloride complex of the adduct (4). Compound (11) can also rearrange by intra- or inter-molecular proton transfer to give (10), in equilibrium with its aluminium chloride complex. The latter can then cyclise to (12) [just as (3) attacks 2-methylpropene to form (11)] which loses a proton to generate (6), (7), and (8) or cyclises further to give (5). Again, there is the possibility, perhaps less likely, that the appropriate conformation of (10) gives (5) directly in an intramolecular Diels-Alder reaction,⁶ while (8) might be formed in an intramolecular ene reaction.⁷ Since Lewis acids catalyse carbonium ion reactions and proton transfers, cycloadditions, and ene reactions, the detailed routes by which the various products arise must remain speculative.

The adduct (4) was treated with *N*-methylanilino-magnesium bromide⁸ and then with acetaldehyde. Elimination of water from the intermediate aldol with sodium acetate in acetic anhydride gave α -damascone, albeit in low overall yield from the dienone (3).

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer 157G spectrophotometer. N.m.r. spectra (60 MHz) on a Perkin-Elmer R12 spectrometer with carbon tetrachloride as solvent and tetramethylsilane as internal reference, and mass spectra on an A.E.I. MS12 spectrometer at 70 eV. Analytical g.l.c. was performed on a Pye Series 104 and preparative g.l.c. on a Pye Series 105 chromatograph. The following columns were used: (A) 2 m \times 4 mm 5% Carbowax 20M on 80–100 mesh Diatomite C, (B) 2 m \times 4 mm 5% SE 30 on 80–100 mesh Diatomite C, (C) 3 m \times 6 mm 10% Carbowax 20M on 60–72 mesh Diatomite C, and (D) 3 m \times 6 mm 15% PPGA on 60–72 mesh Diatomite C. Silica gel used for column chromatography was 100–200 mesh (Grace). Light petroleum refers to the fraction of b.p. 40–60 °C.

4-Methylhexa-3,5-dien-2-one (3) was prepared by the method recently developed for the acylation of isoprene.⁵ Purification of the dienone (3) by distillation or column chromatography resulted in some polymerisation. In the presence of aluminium chloride an equilibrium mixture of *cis*- and *trans*-isomers was obtained (20 : 80 respectively)⁹

Addition of 2-Methylpropene to 4-Methylhexa-3,5-dien-2-one (3).—To anhydrous powdered aluminium chloride (1.2 g, 9 mmol) in dry dichloromethane (75 ml) stirred under nitrogen was added 4-methylhexa-3,5-dien-2-one (3) (1.1 g, 10 mmol) in dichloromethane (50 ml) over 30 min. In 30 min the aluminium chloride dissolved and more dichloromethane (100 ml) was added. 2-Methylpropene gas was

passed through the stirred solution and the course of reaction was monitored by g.l.c. analysis [column (A), 110 °C]. After 4 h the mixture was washed with cold 10% hydrochloric acid (1 \times 50 ml) and saturated sodium chloride solution (1 \times 50 ml) and dried (K_2CO_3). The bulk of the solvent was evaporated off under reduced pressure and the residue was combined with the aqueous washes and extracted with light petroleum (5 \times 30 ml). The combined extracts were washed with 10% hydrochloric acid (1 \times 50 ml), saturated sodium hydrogen carbonate solution (2 \times 50 ml), and saturated sodium chloride solution (1 \times 50 ml), and dried ($MgSO_4$). The solvent was evaporated off under reduced pressure to afford a yellow liquid (1.6 g) which was chromatographed on a column of silica gel (100 g). Elution with 1% diethyl ether–light petroleum gave 1,3,5-trimethyl-2-oxabicyclo[3.3.1]non-3-ene (5) (480 mg, 3 mmol); *m/e* 166 (M^+ , 18%), 151(26), 123(100), 108(15), 98(11), 95(11), 93(11), 83(15), 43(37), and 41(11); τ 9.05 (3 H, s, 5-Me), 8.82 (3 H, s, 1-Me), 8.31 (3 H, s, 3-Me), 7.70–8.70 (8 H, m, 6-, 7-, 8-, and 9-H), and 6.00 (1 H, s, 4-H); ν_{max} (film) 2940s, 1668m, and 1445 cm^{-1} .

Elution with 8% diethyl ether–light petroleum gave a mixture of four ketonic compounds (4), (6), (7), and (8). The major compound, isolated by preparative g.l.c. [column (C), 140 °C], was 3-acetyl-2,4,4-trimethylcyclohexene (4); *m/e* 166 (M^+ , 16%), 123(55), 81(26), 69(8), 67(8), 57(8), 55(10), 43(100), and 42(26); τ 9.10 (6 H, s, 4-Me), 8.40 (3 H, s, 2-Me), 7.94 (3 H, s, Ac), 7.41 (1 H, s, 3-H), 7.90–8.90 (4 H, m, 5- and 6-H), and 4.55 (1 H, s, 1-H); ν_{max} (CCl_4) 1710s, 1365m, and 1355 cm^{-1} .

The ketone (6), isolated by preparative g.l.c. [column (C), 170 °C], was 1-(1,3-dimethylcyclohex-2-enyl)propan-2-one; *m/e* 166 (M^+ , 4%), 151(3), 123(7), 109(100), 108(70), 93(21), 67(18), and 43(70); τ 8.98 (3 H, s, 1-Me), 8.38 (3 H, s, 3-Me), 7.99 (3 H, s, MeCO), 7.83 (2 H, s, CH_2COMe), 8.00–8.70 (6 H, m, 4-, 5-, and 6-H), and 4.73br (1 H, s, 2-H); ν_{max} (CCl_4) 1705s, 1620m, and 1360 cm^{-1} .

Minor products (7) and (8) were obtained as a mixture after preparative g.l.c. [column (D), 170 °C] and were only separated by analytical g.l.c. [column (B), 100 °C]. 1-(1,3-Dimethylcyclohex-3-enyl)propan-2-one (7) showed *m/e* 166 (M^+ , 2%), 151(2), 123(4), 109(34), 108(100), 93(92), 79(30), 43(100), 41(40), and 39(28); τ 9.01 (3 H, s, 1-Me), 8.38 (3 H, s, 3-Me), 8.00–8.70 (6 H, m, 2-, 5-, and 6-H), 7.98 (3 H, s, COMe), 7.75 (2 H, s, CH_2COMe), and 4.73br (1 H, s, 4-H); ν_{max} (CCl_4) 1703s, 1650w, 1362s, and 908 cm^{-1} .

1-(1-Methyl-3-methylenecyclohexyl)propan-2-one (8) showed *m/e* 166 (M^+ , 2%), 151(2), 123(4), 109(40), 108(100), 93(100), 67(57), 55(59), 41(68), and 39(68); τ 9.01 (3 H, s, 1-Me), 8.00–8.70 (8 H, m, 2-, 4-, 5-, and 6-H), 7.98 (3 H, s, COMe), 7.75 (2 H, s, CH_2COMe), and 5.40br (2 H, d, :CH_2); ν_{max} (CCl_4) 1703s, 1650w, 1362s, and 908 cm^{-1} .

Further elution with 15–20% diethyl ether–light petroleum gave unchanged dienone (3) (93 mg).

The spectral properties of compounds (4)–(6) have been published elsewhere.³

α -Damascone [*trans*-1-(2,6,6-Trimethylcyclohex-2-enyl)but-2-en-1-one] (2).—To a stirred, cooled solution of ethylmagnesium bromide [from magnesium turnings (50 mg, 2.2 mmol) and bromoethane (230 mg, 2.2 mmol) in dry ether (5 ml)] was added *N*-methylaniline (151 mg, 1.5 mmol) in

⁶ W. Oppolzer, *Angew. Chem. Internat. Edn.*, 1977, **16**, 10.

⁷ W. Oppolzer and V. Snieckus, *Angew. Chem. Internat. Edn.*, 1978, **17**, in the press.

⁸ A. T. Nielsen, C. Gibbons, and C. A. Zimmerman, *J. Amer. Chem. Soc.*, 1951, **73**, 4696.

⁹ Cf. E. E. Boehm and M. C. Whiting, *J. Chem. Soc.*, 1963, 1541.

dry benzene (5 ml). After 15 min at 0 °C, 3-acetyl-2,4,4-trimethylcyclohexene (4) (200 mg, 1.2 mmol) in benzene (3 ml) was added. The mixture was stirred at room temperature for 30 min and cooled (ice-bath), before acetaldehyde (120 mg, 2.7 mmol) in benzene (3 ml) was added over 5 min. The mixture was stirred for a further 30 min and then poured into cold 10% hydrochloric acid (20 ml). The mixture was extracted with light petroleum (5 × 30 ml) and the combined extracts were washed with 10% hydrochloric acid (5 × 30 ml), saturated sodium hydrogen carbonate solution (2 × 30 ml), and saturated sodium chloride solution (1 × 30 ml), and dried (MgSO₄). Evaporation under reduced pressure left an oil (280 mg), 3-hydroxy-1-(2,6,6-trimethylcyclohex-2-enyl)butan-1-one; τ 9.10 (6 H, s, 6-Me), 8.93 [3 H, d, J 6.5 Hz, CH₃CH(OH)], 8.43 (3 H, s, 2-H), 7.80–8.20 (4 H, m, 4- and 5-H), 7.50 (2 H, m, CO·CH₂:CH), 7.39 (1 H, m, 1-H), 6.91br (1 H, s, exchanges with D₂O, OH), 5.98 (1 H, m, CHOH), and 4.48 (1 H, m, 3-H).

Without purification the aldol was added to a stirred suspension of anhydrous sodium acetate (150 mg, 1.8 mmol) in acetic anhydride (1.5 g) and the mixture was kept at 100 °C over 1.5 h. Water (5 ml) was then added and the mixture was stirred at 100 °C for a further 10 min before pouring into water (20 ml) and extracting with light petroleum (4 × 20 ml). The combined extracts were washed with saturated sodium hydrogen carbonate solution

(3 × 30 ml), and saturated sodium chloride solution (1 × 30 ml) and dried (MgSO₄). Evaporation under reduced pressure left α -damascone (180 mg, 0.9 mmol, 78%) [one component on g.l.c. analysis, column (A), 140 °C], showing spectral properties identical with those published for α -damascone.

Cyclisation of 4,8-Dimethylnona-3,7-dien-2-one (9).—4,8-Dimethylnona-3,7-dien-2-one was prepared from citral¹⁰ as a mixture of *cis*- and *trans*-isomers in the ratio 40 : 60, respectively [n.m.r. and g.l.c. analysis, column (A), 125 °C].

4,8-Dimethylnona-3,7-dien-2-one (664 mg, 4 mmol) in dry benzene (5 ml) was added to a solution of boron trifluoride-diethyl ether complex (284 mg, 2 mmol) in benzene (5 ml) over 5 min. The mixture was kept at 55 °C for 1 h and then poured into ice-water. The resulting mixture was extracted with diethyl ether (3 × 25 ml) and the combined extracts were washed with saturated sodium hydrogen carbonate solution (2 × 50 ml) and saturated sodium chloride solution (1 × 50 ml) and dried (MgSO₄). The solvent was removed under reduced pressure to give a yellow liquid (550 mg, 83%). Analysis of this material by g.l.c. [column (B), 110 °C] and n.m.r. showed two products: the vinyl ether (5) and 3-acetyl-2,4,4-trimethylcyclohexene (4) in the ratio 25 : 75, respectively.

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¹⁰ N. A. Mirza, Ph.D. Thesis. Southampton University, 1966.