Simple Syntheses of the Atlantones, the Ocimenones, the Tagetones, and Filifolone from Isoprene[1]

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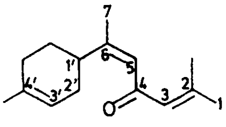
Details of the syntheses of a range of terpenes by stepwise addition of isoprene units are reported. The *cis*- and *trans*-atlantones [2-methyl-6-(4-methylcyclohex-3-enyl)hepta-2.5-dien-4-ones] (1) and (2), *cis*- and *trans*-tagetones (2.6-dimethylocta-5.7-dien-4-ones) (3) and (4), and *cis*- and *trans*-ocimenones (2.6-dimethylocta-2.5.7-trien-4-ones) (5) and (6) have been synthesised by acylation at low temperature and subsequent dehydrochlorination. The atlantones (1) and (2) have also been synthesised from ocimenone by acid-catalysed Diels–Alder addition of isoprene. and filifolone (4,7,7-trimethylbicyclo[3.2.0]hept-3-en-6-one) (8) has been obtained by cyclisation of ocimenone with aluminium chloride.

THE ready availability of isoprene makes it an attractive starting material for the synthesis of terpenes, and the formation of terpenes by stepwise addition of isoprene units has long been an objective of organic synthesis.[2] Synthesis of terpenes from isoprene has relied on routes involving the addition of halogen acids,[3] and though potentially more useful, a practical route involving the direct head-to-tail dimerisation and simultaneous functionalisation of isoprene has not been developed. We describe here an approach to the synthesis of terpenes involving essentially stepwise addition of isoprene units by acylation of olefins and Diels-Alder reactions, both catalysed by Lewis acids. So far, we have concentrated our efforts on the synthesis of the atlantones[4] (1) and (2), the tagetones[5] (3) and (4), and the ocimenones[6] (5) and (6), compounds which are easily accessible by the routes described.



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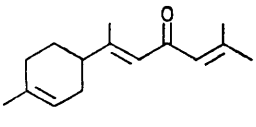

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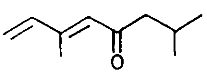

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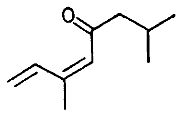

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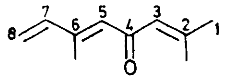

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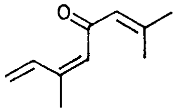

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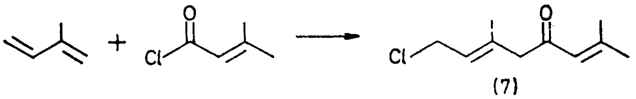
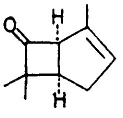
Addition of isoprene in dichloromethane to 3-methylcrotonoyl chloride in dichloromethane containing tin(IV) chloride at −78 °C gave the expected chloro-ketone † (7).



(7)

In a typical run, this was not isolated; the crude chloroketone was treated with lithium fluoride and lithium carbonate in dimethylformamide at 120 °C to give ocimenone in 90% isolated yield, as a mixture of *cis*- and *trans*-isomers (1 : 9), (5) and (6). A similar sequence with isovaleryl chloride as the acid chloride furnished a mixture of *cis*- and *trans*-tagetone (40 : 60), (3) and (4). Atlantone, as a mixture of *cis*- and *trans*-isomers (1: 9), (1) and (2), was obtained by addition of isoprene in dichloromethane to a solution of ocimenone in dichloromethane containing aluminium chloride, at 20 °C, in an overall yield of 85%. Isoprene adds only to the least hindered double bond.

Treatment of ocimenone in methylene chloride with aluminium chloride at 40 °C gave filifolone (8)[7] (80% conversion after 3 h), probably through the intermediate (9) suggested in the rearrangement of chrysanthenone to filifolone.[8]



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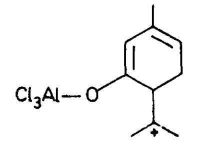

(9)

The *cis*- and *trans*-atlantones (1) and (2) (1 : 9) were also

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† The stereochemistry of this reaction will be discussed later.

[1] Preliminary communication, D. R. Adams, S. P. Bhatnagar, R. C. Cookson, and R. M. Tuddenham, *Tetrahedron Letters*, 1974, 3197.

[2] A. F. Thomas in ' The Total Synthesis of Natural Products,' vol. 2, ed. J. ApSimon, Wiley, New York, 1973.

[3] See for example, B.P. 855,696 (*Chem. Abs.*, 1961, **55**, 23,342).

[4] A. St. Pfau and P. Plattner, *Helv. Chim. Acta*, 1934, **17**, 129; G. S. Krishna Rao, S. Dev, and P. C. Guha, *J. Indian Chem. Soc.*, 1952, **29**, 721; M. I. Golyaev, A. D. Dimbitskii, T. E. Sarkebaeva, and G. I. Krotova, *Izvest. Akad. Nauk Kazakh., S.S.S.R. Ser. khim.*, 1969, **19**, 48 (*Chem. Abs.*, 1969, **71**, 64,019); R. J. Crawford, W. F. Erman, and C. D. Broaddus, *J. Amer. Chem. Soc.*, 1972, **94**, 4298; G. S. Krishna Rao, *Indian J. Chem.*, 1973, **11**, 859.

[5] T. G. H. Jones and F. B. Smith, *J. Chem. Soc.*, 1925, 2530; 1926, 2767; E. E. Boehn, V. Thaller, and M. C. Whiting, *J. Chem. Soc.*, 1963, 2535; P. Teisseire and R. Corbieu, *Recherches*, 1969, **17**, 5.

[6] D. J. J. de Villiers, C. F. Garbers, and R. N. Laurie, *Phytochemistry*, 1971, **10**, 1359.

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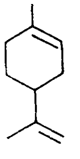
[8] W. F. Erman, R. S. Treptow, P. Bakuzis, and E. Wenkert, *J. Amer. Chem. Soc.*, 1971, **93**. 657.

synthesised by direct acylation and subsequent dehydrochlorination of *p*-mentha-1,8-diene (limonene) (10). 3-Methylcrotonoyl chloride in dichloromethane containing tin(IV) chloride cooled to −78 °C was added to limonene in a mixture of dichloromethane and Freon 12 at −120 °C. The crude chloro-ketones were then treated with lithium fluoride and lithium carbonate in dimethylformamide at 120 °C to afford a mixture of isomers; *cis*- and *trans*-atlantone (1) and (2) constituted *ca.* 60% (g.l.c.) of the reaction mixture. The other major components were the non-conjugated isomer (11) (20%) (g.l.c.) and presumably (not isolated; evidence from g.l.c.–mass spectrometry) the conjugated isomer (12) (9%) (g.l.c.).



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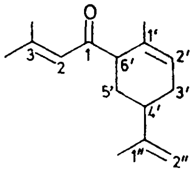

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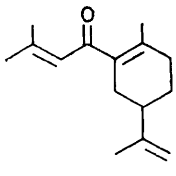

(12)

Electrophilic attack on limonene therefore takes place preferentially on the disubstituted double bond (2 : 1). This preference has also been shown in other electrophilic additions to limonene,[9] presumably as a result of steric hindrance to attack at the ring double bond.

EXPERIMENTAL

N.m.r. (60 MHz) spectra were recorded on a Perkin-Elmer R-12 spectrometer with carbon tetrachloride as solvent and tetramethylsilane as internal reference; 100 MHz spectra were recorded on a Varian HA 100 spectrometer. I.r. spectra were obtained on a Perkin-Elmer 157G spectrometer. Mass spectra were recorded at 70 eV on an A.E.I. MS12 spectrometer. Analytical g.l.c. was performed on a Pye 104 chromatograph [2 m × 4 mm glass columns packed with (*a*) 5% Carbowax 20 M on 80—100 mesh Diatomite C or (*b*) 5% SE 30 on 80—100 mesh Diatomite C]. Preparative g.l.c. was performed on the same chromatograph with 3 m × 6 mm glass columns packed with (*c*) 10% SE 30 on 60—72 mesh Diatomite C or (*d*) 15% Carbowax 20 M on 60—72 mesh Diatomite C. Light petroleum refers to the fraction of b.p. 40—60°. 3-Methylcrotonoyl chloride and isovaleryl chloride were prepared from the corresponding acids with thionyl chloride.

cis- *and* trans-*Ocimenone* [(5) *and* (6)].—(i) 8-*Chloro*-2,6-*dimethylocta*-2,6-*dien*-4-*one* (7). 3-Methylcrotonoyl chloride (12.0 g, 0.1 mol) in dichloromethane (50 ml) was added to tin(IV) chloride (24.0 g, 0.09 mol) in dichloromethane (50 ml), stirred under anhydrous conditions in a nitrogen atmosphere, and the solution was cooled to −78 °C. To this solution was then added isoprene (8.8 g, 0.13 mol) in dichloromethane (120 ml), dropwise over 1.5 h. The mixture was stirred for a further 0.5 h at −78 °C and then pyridine (30 ml) was added. The resultant mixture was poured into ether (500 ml) and filtered, and the filtrate was washed successively with water (5 × 100 ml) and saturated sodium chloride solution (5 × 100 ml), then dried (Na_2SO_4), filtered, and evaporated to afford an oil (21.0 g). G.l.c. analysis on column (*b*) at 145 °C showed the residue to be mainly one compound, which was used as such in the subsequent dehydrochlorination. The mass spectrum (g.l.c., crude material) showed no M^+ and a fragmentation pattern identical with that of ocimenone. The n.m.r. spectrum (60 MHz) showed τ 3.95br (1H, s, H-3), 4.49 (1H, t, *J* 8 Hz, H-7), 5.95 (2H, d, H-8), 6.95 (2H, s, H-5), 7.90 (3H, s, 6-Me), and 8.14(s) and 8.30(s) (6H, CMe_2); $\nu_{max.}$ (film) 1690 (C=O), and 1665 and 1610 cm^{-1} (C=C).

(ii) *Dehydrochlorination.* The crude chloro-ketone (7) (21.0 g) in dimethylformamide (25 ml) was added to dimethylformamide (100 ml) containing lithium fluoride (7.8 g, 0.3 mol) and lithium carbonate (22.2 g, 0.3 mol) and heated at 120 °C in a nitrogen atmosphere. After being stirred at 120 °C for 1.25 h the mixture was cooled and filtered, the residue washed with light petroleum (4 × 50 ml), and the filtrate poured into ice-cold water (500 ml). The aqueous layer was separated and extracted with light petroleum (5 × 100 ml). The combined extracts were washed with saturated sodium chloride solution (5 × 100 ml), dried (Na_2SO_4), filtered, and evaporated to yield an oil (16.8 g). This material was chromatographed on silica gel (500 g; 60—120 mesh; benzene as eluant) to afford a mixture of *cis*- and *trans*-ocimenone [(5) and (6)] (1 : 9) [g.l.c. column (*b*), 145 °C] (13.5 g, 90%); b.p. 80—82° at 3.0 Torr; *m/e* 150 (M^+, 77%), 135 (100%), 107 (58), 95 (43), 91 (55), 83 (51), 67 (58), 55 (60), and 41 (83); τ (60 MHz) 3.65 (1H, q, *J* 10 and 17 Hz, H-7), 4.18 [1H, d, *J* 17 Hz, also fine coupling *ca.* 1 Hz, H-8 (*trans*)], 4.69 [1H, d, *J* 10 Hz, also fine coupling <1 Hz, H-8(*cis*)], 7.78br (3H, s, 6-Me), 7.85br [3H, s, 2-Me(*trans*)], and 8.13br [3H, s, 2-Me (*cis*)] [definitive evidence for the presence of the *cis*-isomer (5) was given by τ 2.16 (H-7, *J* 10 and 17 Hz)]; $\nu_{max.}$ (film) 1668 (C=O), 1620 and 1590 (C=C), 1452 and 1390 (*gem*-dimethyl), and 1365, 1223, 1115, and 1042 cm^{-1}.

cis- *and* trans-*Atlantone* [(1) *and* (2)].—(i) *From ocimenone.* To dichloromethane (50 ml) containing aluminium chloride (0.6 g, 0.0043 mol) stirred under anhydrous conditions in a nitrogen atmosphere, was added a solution of ocimenone (0.9 g, 0.006 mol) in dichloromethane (50 ml) at room temperature and the solution was stirred for 1 h. Isoprene (1.63 g, 0.024 mol) in dichloromethane (50 ml) was then added dropwise over 4 h, and the mixture stirred for a further 24 h at room temperature. This solution was poured into ice-cold 10% hydrochloric acid (100 ml) and extracted with ether (1 × 200 ml; 3 × 50 ml); the combined extracts were washed successively with 10% hydrochloric acid (2 × 100 ml), saturated sodium hydrogen carbonate solution (2 × 100 ml), and saturated sodium chloride solution (4 × 100 ml), dried (Na_2SO_4), filtered, and evaporated to yield an oil (2.0 g). This was chromatographed on silica gel (100 g; 100—200 mesh; eluant chloroform–ether, 95 : 5) to afford a mixture of *cis*- and *trans*-atlantone [(1) and (2)] (1 : 9) [g.l.c. column (*b*); 180 °C] (1.1 g, 85%). This mixture was then re-chromatographed on silica gel (50 g; 100—200 mesh); elution with light petroleum–chloroform (9 : 1) afforded successively *trans*-atlantone (2) (0.3 g), *m/e* 218 (M^+, 14%), 203 (9%), 163 (9), 135 (45), 123 (32), 107 (27), 105 (19), 95 (25), 93 (17), 91 (27), 83 (100), 79 (25), 67 (27), 55 (23), and 41 (42), τ (100 MHz) 4.1 (2H, m, H-3 and -5), 4.87br (1H, s, H-3′), 7.90br [6H, s, 6-Me and 2-Me(*cis*)], 8.17 [3H, s, 2-Me(*trans*)], and 8.38 (3H, s, 4′-Me); $\nu_{max.}$ (film) 1670 (C=O), and 1630 and 1610 cm^{-1} (C=C); and *cis*-atlantone (1) (0.05 g), *m/e* 218 (M^+, 9%), 203 (9%), 175 (17), 163 (7), 135 (24), 120 (24), 119 (29), 107 (19), 105 (43), 91 (31), 83 (100),

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[9] See, for example, M. Bambagiotti A., F. F. Vincieri, and S. A. Coran, *J. Org. Chem.*, 1974, **39**, 680.

79 (24), 55 (48), and 41 (37); τ (100 MHz) 4.12 (2H, m, H-3 and -5), 4.67br (1H, m, H-3′), 7.89 [3H, d, J 1 Hz, 2-Me(*cis*)], 8.16(d) and 8.23(d) (6H, J 2 Hz, 6-Me and 2-Me(*trans*)], and 8.36br (3H, s, 4′-Me); $\nu_{max.}$ (film) 1670 (C=O), and 1630 and 1610 cm^{-1} (C=C).

The spectroscopic properties and g.l.c. retention times of these two products were identical with those of samples of *cis*- and *trans*-atlantone isolated from the essential oil of *Cedrus atlantica*.

(ii) *From* p-*mentha*-1,8-*diene* (*limonene*). 3-Methylcrotonyl chloride (5.9 g, 0.05 mol) was added to dichloromethane (50 ml) containing tin(IV) chloride (11.7 g, 0.045 mol). This solution was stirred for 15 min, cooled to −78 °C and then added dropwise over 1 h to (+)-*p*-mentha-1,8-diene {$[\alpha]_D$ + 110° (in $CHCl_3$); 6.8 g, 0.05 mol} in a mixture of dichloromethane (50 ml) and Freon 12 (20 ml) cooled to −120 °C. The solution was stirred at −120 °C for a further 0.5 h, pyridine (15 ml) in ether (50 ml) was added, and the resultant mixture was poured into ether (400 ml) and filtered. The filtrate was washed successively with 10% hydrochloric acid (5 × 100 ml), saturated sodium hydrogen carbonate solution (2 × 100 ml), and saturated brine (4 × 100 ml), dried ($MgSO_4$), filtered, and evaporated to yield an oil (12.0 g).

This crude product in dimethylformamide (50 ml) was added to dimethylformamide (50 ml) containing lithium fluoride (3.9 g, 0.15 mol) and lithium carbonate (11.1 g, 0.15 mol) stirred at 120 °C in a nitrogen atmosphere. After stirring for 2 h at 120 °C and at room temperature for 10 h the mixture was filtered; the residue was washed with light petroleum (3 × 50 ml) and the two layers were separated. The dimethylformamide layer was acidified with 10% hydrochloric acid (200 ml) and extracted with light petroleum (4 × 100 ml). The combined extracts were washed successively with 10% hydrochloric acid (4 × 100 ml), saturated sodium hydrogen carbonate solution (2 × 100 ml), and saturated brine (4 × 100 ml) and then dried ($MgSO_4$), filtered, and evaporated to yield an oil (10.0 g). G.l.c. analysis of this residue on column (*b*) at 150 °C showed the presence of four major components in the ratio 20 : 9 : 6 : 54, in order of increasing retention time. G.l.c.–mass spectrometry of this mixture showed that they were isomers (M^+ 218) and that the 6% and 54% components were *cis*- and *trans*-atlantone, (1) and (2), respectively. Pure samples of the 20% component and *trans*-atlantone (2) were obtained by preparative g.l.c. on column (*c*) at 180 °C. The *trans*-atlantone (2), $[\alpha]_D^{20}$ +25° (in $CHCl_3$), had mass, n.m.r., and i.r. spectral data identical with those previously reported. The 20% component was shown to be 1-(5-isopropenyl-2-methylcyclohex-2-enyl)-3-methylbut-2-en-1-one (11), $[\alpha]_D^{20}$ +33° (in $CHCl_3$); *m/e* 218 (M^+, 1%), 134 (10%), 119 (4), 107 (4), 93 (8), 91 (8), 84 (8), 83 (100), 55 (21), and 41 (8); τ (100 MHz) 3.95 (1H, m, H-2), 4.46br (1H, s, H-3′), 5.39br (2H, s, H-2″), 7.11br (1H, d, H-1′), 7.89 [3H, s, 3-Me, (*cis*)], 8.12 [3H, s, 3-Me(*trans*)], 8.31 (3H, d, 1″-Me), and 8.41br (3H, s, 2′-Me); $\nu_{max.}$ (CCl_4) 1690 (C=O), and 1650 and 1620 cm^{-1} (C=C).

The 9% component, *m/e* 218 (M^+, 9%), 203 (9%), 173 (3), 135 (16), 119 (14), 107 (14), 105 (12), 93 (14), 91 (14), 83 (100), 79 (13), 77 (12), 55 (40), 53 (12), and 41 (23), is presumably the conjugated isomer (12).

(±)-*Filifolone* (8).—A solution of ocimenone (0.6 g, 0.004 mol) in dichloromethane (60 ml) was added to dichloromethane (100 ml) containing aluminium chloride (0.4 g, 0.003 mol) stirred under anhydrous conditions in a nitrogen atmosphere. After the aluminium chloride had dissolved (1 h) the solution was boiled at reflux, and after 3.25 h g.l.c. analysis on column (*a*) temperature programmed from 120 to 160 °C showed starting material (20%) and a new component (80%). A pure sample of this new component was obtained by preparative g.l.c. on column (*d*) temperature programmed from 120 to 160 °C, and was shown to be (±)-filifolone (8), *m/e* 150 (M^+, 18%), 122 (34%), 107 (65), 91 (30), 80 (100), and 70 (27); τ (60 MHz) 4.62br (1H, s, H-3), 6.05 (1H, m, H-1), 7.5 (3H, m, H-2 and -5), 8.25 (3H, s, 4-Me), 8.83 (3H, s, 7-Me), and 8.93 (3H, s, 7-Me); $\nu_{max.}$ (CCl_4) 1778, 1653, 1456, 1378, 1368, and 1064 cm^{-1}.

Tagetones [(3) *and* (4)].—A similar sequence to that for the ocimenones (5) and (6), but with isovaleryl chloride (10.0 g, 0.083 mol) and tin(IV) chloride (20.0 g, 0.077 mol) in dichloromethane (80 ml), and isoprene (7.0 g, 0.1 mol) in dichloromethane (40 ml), furnished a mixture of *cis*- and *trans*-tagetone (3) and (4) (40 : 60) [g.l.c. column (*a*) at 130 °C] in 40% overall yield. In this case, the final product was purified by distillation; b.p. 64—66° at 1.5—2.0 Torr. The tagetones (3) and (4) had spectral properties identical with those previously reported.[5]

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