# Synthesis of Cedrene. Part 1. Synthesis and Structure of a Key Intermediate

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Photocycloaddition of the dienone (5) leads to a major compound (6b) which is an intermediate in a new synthesis of β-cedrene (8). The structure of its crystalline derivative (12b) has been established by X-ray diffraction. In particular, the relative configuration of the 12-methyl and 11-methylene (cedrene numbering) is the correct one.

PHOTOCYCLOADDITION of olefins onto conjugated cyclo-enones have found an increasing utility in the total synthesis of natural products.[1,2] They usually give strained-ring cyclobutane derivatives which may be converted into rearranged products in high yield and very few steps. Thus (+)-isophyllocladene (1a) can be

(1)

a; R^2 = H
b; R^2 = O

(2)

(3)

Carvone camphor

(4)
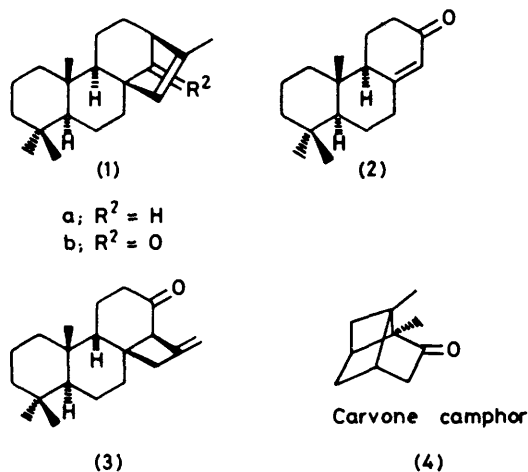
obtained in two steps from the readily available tricyclic ketone (2) and allene. Compound (3) in the presence of toluene-*p*-sulphonic acid rearranges into (+)-isophyllo-cladenone (1b).[3] Related internal cycloadditions are obviously appealing. The synthesis of ' carvone-cam-phor ' (4) in one step from carvone is classical.[4] There-fore we decided to irradiate compound (5). One of the four expected products, (6a), (6b), (7a), and (7b), is a suitable starting material for the synthesis of (±)-β-cedrene (8), based upon a photochemical reaction followed by a molecular rearrangement (see Scheme 1). It turns out that the major compound is indeed the wanted precursor of cedrene (8). Its structure has been elucidated both by n.m.r. spectroscopy and X-ray crystallographic examination.

Synthesis of Dienone (5).—The dienone (5) has been prepared by a method suggested by Corey's synthesis of compound (15).[5] A previously published synthesis [6,7] of 6-chloro-2-methylhept-2-ene (11) gave, as a result of olefinic bond migration, an inseparable (by g.l.c.) mixture. Both ^{1}H and [13]C n.m.r. spectroscopy showed that the expected chloride (11) is contaminated by at least 20% of 6-chloro-2-methylhept-1-ene. The desired

pure compound was, however, readily prepared from the alcohol and triphenylphosphine in CCl$_4$.[8] The corres-ponding lithium derivative reacted with 3-ethoxycyclo-hex-2-en-1-one (14) and hydrolysis of the crude inter-mediate led to the dienone (5) (see Scheme 2).
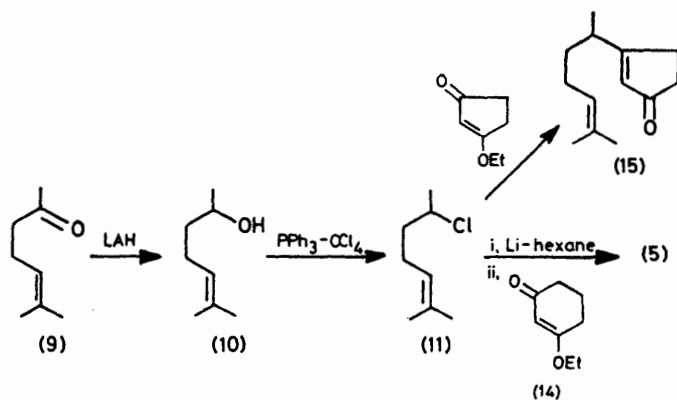
Photoisomerisation of the Dienone (5).—Intramolecular photocycloaddition of the dienone (5) was carried out in dry methylene chloride at −77 °C with a 700-W medium-pressure mercury lamp. The reaction, monitored by t.l.c., proceeds quite rapidly and after 1 h, (5) is totally converted into a substance which seems to be homo-geneous in t.l.c. but was shown to be a mixture of a major and two or three minor compounds by h.p.l.c. (silica gel column; particle diameter 5 μm) with a 5% ether–pentane mixture as eluant. Since no separation on a preparative scale could be achieved at this stage we therefore condensed anisaldehyde with this mixture of ketones. The anisylidene derivative (A) of the major compound crystallised out and could easily be purified (*ca.* 70% of the total). T.l.c. of the pasty residue (silica gel PF$_{254}$; 20% ether–pentane) gave a further oily anisylidene derivative (B) (15% of the total) and an

(5)

hν

(6)

a; R^1 = H, R^2 = Me
b; R^1 = Me, R^2 = H

(7)

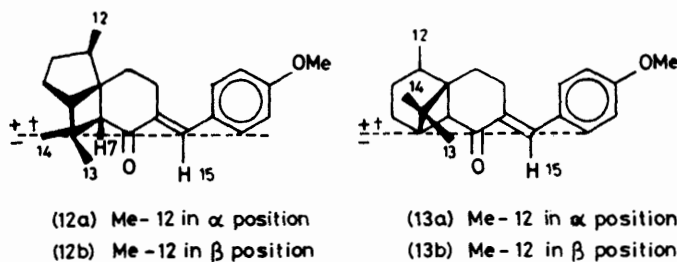a; R^1 = H, R^2 = Me
b; R^1 = Me; R^2 = H

Cedrene (8)
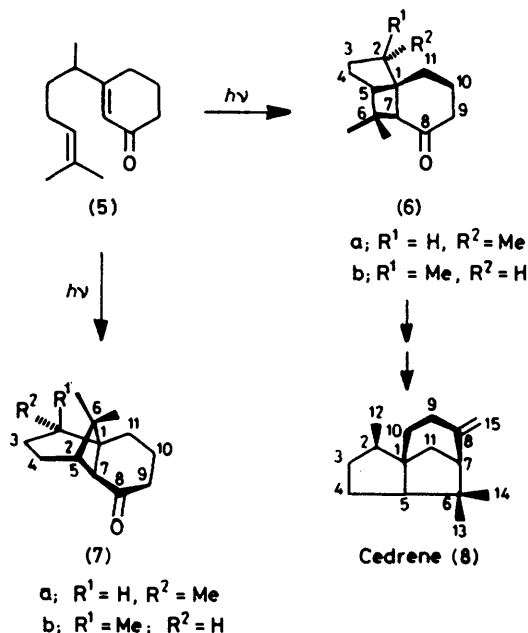
SCHEME 1

apparently intractable mixture which was not further analysed. The [1]H n.m.r. spectral results for compounds (A) and (B) are consistent with their formulation as compounds (12) and (13) respectively. In particular the signal attributed to H-7 (Scheme 3), the only proton α to the carbonyl group, appears as a sharp singlet at 2.25 p.p.m. [compound (A)] and a doublet at 2.53 p.p.m. $J = 1$ Hz [compound (B)]. Such a small ^3J coupling is expected for structures (7a) or (7b) on the basis of the Karplus rule and known data on cyclobutane derivatives. Replacement of $CDCl_3$ by C_6D_6 induces a variation of the

SCHEME 2

(12a) Me-12 in α position
(12b) Me-12 in β position

(13a) Me-12 in α position
(13b) Me-12 in β position

SCHEME 3

different chemical shifts (Table 1) which fit the empirical carbonyl plane rule.[9] In both compounds $\Delta_{C_6D_6}^{CDCl_3} = \delta(CDCl_3) - \delta(C_6D_6)$ should be large and positive for the 12-methyl. In compound (A) $\Delta_{C_6D_6}^{CDCl_3}$ is expected to

TABLE 1

Product, Δ (in p.p.m.)		Me-12	Me-14	Me-13	H-7	H-15
(12b), $\Delta_{C_6D_6}^{CDCl_3}$	=	+0.16	0.00	−0.12	0.00	−0.38
(13), $\Delta_{C_6D_6}^{CDCl_3}$	=	+0.15	+0.06	−0.02	−0.02	−0.33

be negative for one of the two *gem* methyl groups and quite small for the other. It is the reverse for compound (B): the signal of one of these two methyl groups should be shifted upfield whereas the other should be virtually unaffected. The experimental results are in agreement with these predictions. However, the stereochemistry of the 12-methyl cannot be firmly established on the basis of [1]H n.m.r. results only and thus the structure of the crystalline compound (A) was elucidated by an X-ray diffraction study.

X-Ray Structure of Compound (12b).—Compound (A) crystallizes as thin needles. Suitable crystals for X-ray diffraction were grown in concentrated $CHCl_3$ solutions by a very slow evaporation over a week at room temperature. The largest crystal ($0.4 \times 0.1 \times 0.025$ mm) was selected and mounted on a computer-controlled diffractometer using the Cu-K_α radiation monochromatised by graphite. In order to obtain sufficient data above the background level, each reflection was scanned four times at $0.025°$ s⁻¹. Under these conditions 975 reflections (over a total of 3 255) were greater than 3 σ. The crystals are orthorhombic. The space group deduced from systematic extinctions is *Pbca* with $Z = 8$. Cell parameters are as follows: $a = 9.177(4)$, $b = 15.510(5)$, and $c = 25.474(6)$ Å. The structure was solved by a straightforward application of direct methods using the multisolution technique.[10] The refinements of the atomic positional and isotropic thermal parameters were carried out by a full-matrix least-square procedure (3 cycles) in a first step, followed by four cycles using anisotropic thermal parameters. Hydrogen atoms, except those of the methyl groups, were introduced at their theoretical positions which were not refined. The final R index is 91%. The positional parameters are given in Table 2. The bond lengths (±0.005 Å) and angles ($\pm0.1°$) are listed in Table 3. They do not show special features except the small value for the cyclobutane angles around the spiro-C-1 atom: 88.6°.

TABLE 2

Positional atomic parameters ($\times 10^4$)

Atom	X	Y	Z
C(1)	8 684	5 079	6 515
C(2)	10 333	5 133	6 470
C(3)	10 558	5 305	5 875
C(4)	9 330	5 922	5 730
C(5)	8 023	5 649	6 065
C(6)	7 069	4 880	5 884
C(7)	7 988	4 274	6 248
C(8)	7 226	3 601	6 573
C(9)	7 427	3 631	7 161
C(10)	8 277	4 876	7 386
C(11)	8 038	5 196	7 065
C(12)	10 999	5 859	6 784
C(13)	5 484	4 975	6 040
C(14)	7 128	4 632	5 298
C(15)	6 775	3 008	7 444
C(16)	6 797	2 862	8 013
C(17)	5 585	2 490	8 254
C(18)	5 530	2 362	8 789
C(19)	6 720	2 590	9 096
C(20)	7 955	2 927	8 868
C(21)	7 973	3 072	8 330
C(22)	7 786	2 600	9 966
O(23)	6 513	3 039	6 361
O(24)	6 571	2 434	9 628

The Figure shows an ORTEP diagram of the molecule. Evidently, the methyl group at C-2 is β with respect to the six-membered ring. The cyclobutane ring has an unexpected flat conformation, the torsional angle being only 12°. The cyclopentane ring is in a twist conformation (ring parameters $\Delta = 16.4$ and $\phi_m = 39.5$ [11]) while the six-membered ring led to a ‘ sofa ’ mean conformation. The calculated and the observed structural
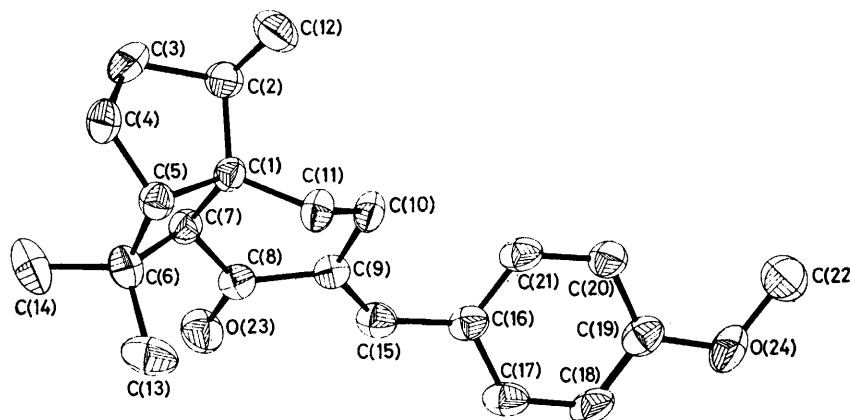
TABLE 3

Bond distances and angles of compound (12b)

(a) Distances (Å)

C(1)–C(2)	1.520		C(8)–O(23)	1.217
C(1)–C(5)	1.570		C(9)–C(10)	1.508
C(1)–C(7)	1.557		C(9)–C(15)	1.346
C(1)–C(11)	1.532		C(10)–C(11)	1.529
C(2)–C(3)	1.551		C(15)–C(16)	1.465
C(2)–C(12)	1.510		C(16)–C(17)	1.396
C(3)–C(4)	1.524		C(16)–C(21)	1.387
C(4)–C(5)	1.531		C(17)–C(18)	1.378
C(5)–C(6)	1.549		C(18)–C(19)	1.390
C(6)–C(7)	1.568		C(19)–C(20)	1.376
C(6)–C(13)	1.541		C(19)–O(24)	1.383
C(6)–C(14)	1.516		C(20)–C(21)	1.389
C(7)–C(8)	1.505		C(22)–O(24)	1.432
C(8)–C(9)	1.509			

(b) Angles (°)

C(2)–C(1)–C(5)	107.4		C(7)–C(8)–O(23)	120.1
C(2)–C(1)–C(11)	116.6		C(9)–C(8)–O(23)	121.9
C(5)–C(1)–C(7)	88.6		C(8)–C(9)–C(10)	117.7
C(7)–C(1)–C(11)	109.6		C(8)–C(9)–C(15)	125.2
C(1)–C(2)–C(3)	102.4		C(10)–C(9)–C(15)	117.1
C(1)–C(2)–C(12)	113.9		C(9)–C(10)–C(11)	111.1
C(3)–C(2)–C(12)	109.6		C(1)–C(11)–C(10)	109.6
C(2)–C(3)–C(4)	104.3		C(9)–C(15)–C(16)	129.3
C(3)–C(4)–C(5)	105.7		C(15)–C(16)–C(17)	119.2
C(1)–C(5)–C(4)	105.1		C(15)–C(16)–C(21)	123.4
C(1)–C(5)–C(6)	90.1		C(17)–C(16)–C(21)	117.4
C(4)–C(5)–C(6)	119.3		C(16)–C(17)–C(18)	121.6
C(5)–C(6)–C(7)	88.9		C(17)–C(18)–C(19)	119.6
C(5)–C(6)–C(14)	112.8		C(18)–C(19)–C(20)	120.4
C(7)–C(6)–C(13)	113.9		C(18)–C(19)–O(24)	115.3
C(13)–C(6)–C(14)	108.2		C(20)–C(19)–O(24)	124.2
C(1)–C(7)–C(6)	89.9		C(19)–C(20)–C(21)	119.2
C(1)–C(7)–C(8)	120.5		C(16)–C(21)–C(20)	121.9
C(6)–C(7)–C(8)	119.6		C(19)–O(24)–C(22)	118.7
C(7)–C(8)–C(b)	117.9			

factors are listed in the supplementary publication No. 22485 (16 pp.).*

there is no evidence of thermodynamic control on these reactions.

The interesting feature is that the major cyclisation compound has precisely the right stereochemistry for its conversion into cedrene (8). However, the simplest method which was successful in the case of less-strained substrates, namely the treatment of ketone (6b) in boiling benzene with toluene-p-sulphonic acid, was not encouraging (Scheme 4): ketone (6b) undergoes a retro-cycloaddition giving back the dienone (5) in good yield (80%). An entirely different approach, using transition metals is being investigated.

(6b) p-MeC$_6$H$_4$SO$_3$H   →   →   (5)
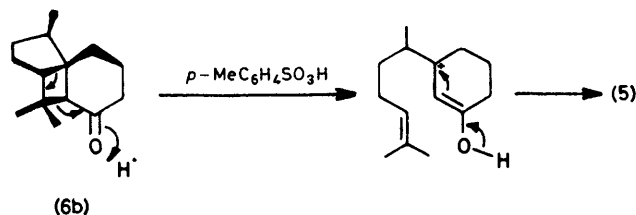
EXPERIMENTAL

General.—M.p.s were determined on a Reichert Kofler block and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer Model 577 spectrophotometer. N.m.r. spectra were recorded on a Varian NV 14 NMR spectrometer or a Varian XL 100 FT NMR spectrometer for the 100 MHz spectra. Chemical shifts are expressed in p.p.m. downfield from the signal of SiMe$_4$, which was used as an internal standard.

6-Hydroxy-2-methylhept-2-ene (10).—A solution of commercial 6-methylhept-5-en-2-one (7 g) in diethyl ether (5 ml) was added slowly in a suspension of lithium alu-

ORTEP diagram of (12b); the thermal ellipsoids are drawn at the 50% probability level

DISCUSSION

The net result of the photocycloaddition of the precursor (5) is the preferred formation of one of the four possible isomers. This cannot be predicted with the aid of Dreiding models. A more refined approach, the calculation of the steric energy of the various candidates with a force-field method [12] is obviously questionable:

* For details of the Supplementary publications scheme see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1978, Index issue.

minium hydride (2 g). After being stirred at room temperature for 2 h the mixture was successively treated with water (3 g), a 2N-solution of NaOH (3 g), and water (3 g). The solution was then filtered, dried, and the solvent was removed under reduced pressure to give the alcohol (10) (6.9 g) as an oily product; i.r. (film) 3 300 (OH) and 1 650 cm^{-1} (weak, C=C); n.m.r. (CCl$_4$) 1.16 (d, 3 H, J = 6 Hz, Me-1), 1.62br (s, 6 H, Me-7 and Me-8), 3.72 (sext, 1 H, J = 6 Hz, H *gem* with OH), and 5.1br (t, 1 H, J = 6.5 Hz, olefinic H).

6-*Chloro-2-methylhept-2-ene* (11).—A mixture of the alcohol (10) (10 g), triphenylephosphine (25 g), and CCl_4 (100 ml) was refluxed for 24 h. The course of the reaction was monitored by t.l.c. The cooled solution was filtered and the solvent removed. The obtained mixture was separated with a Kugelrohr distillation apparatus; 8.5 g of the pure chloro-derivative (11) was obtained as an oily product; i.r. (film) 1 670 (C=C) and 670 cm⁻¹ (CCl); n.m.r. (CCl_4) 1.47 (d, 3 H, $J = 6.5$ Hz, Me-1), 1.63br and 1.67br (each s, 3 H, Me-7 and Me-8), 3.85 (sext, 1 H, $J = 6.5$ Hz, H *gem* with Cl), and 5.01br (t, 1 H, $I = 6.5$ Hz, olefinic H).

3-(1,6-*Dimethylhex-4-enyl*)*cyclohex*-2-*enone* (5).—Compound (11) (5.0 g) was added to a suspension of a 10% Na in lithium alloy in dry hexane. The mixture was refluxed for 2 h. The solution was then assayed (Gilman's method [13]) and an equivalent amount of the commercial product (14) (*ca.* 2 g) was carefully added. The mixture was treated with water and extracted with diethyl ether. The olefinic ketone (5) was separated by chromatography on a column of silica gel with a pentane–diethyl ether mixture (8 : 1) as eluant as an oily product; i.r. (film) 3 020 (olefinic CH) and 1 620 cm⁻¹ (C=C); n.m.r. 1.09 (d, 3 H, $J = 6.5$ Hz, Me), 5.02br (tr, 1 H, $J = 7$ Hz, olefinic proton), and 5.72 (s, 1 H, olefinic proton); ¹³C n.m.r., C-1 199.9, C-2 125.1, C-3 170.8, C-4 26.5, C-5 25.9, C-6 34.8, C-7 41.2, C-8 37.7, C-9 27.0, C-10 123.8, C-11 132.0, C-12 25.7, C-13 17.7, and C-14 18.9.

Photoisomerisation.—A solution of compound (5) (3 g) in CH_2Cl_2 (500 ml) was irradiated through a Pyrex filter with a 700-W medium-pressure mercury lamp for 1 h. The mixture of photoisomers was homogeneous by t.l.c. with a R_F quite different from that of the starting material. The products were not separated but converted directly into their anisylidene derivatives.

Anisylidene Derivatives (12b) *and* (13).—The mixture of photoisomers (750 mg), anisaldehyde (1.5 g), and a 33% NaOH solution in methanol (3 ml) was stirred overnight at room temperature under nitrogen. The major product (12b), which crystallized *in situ*, was filtered off and washed with water and cold methanol. After a recrystallization from methanol compound (12b) (650 mg) was obtained. The mother liquors (300 mg) were separated by t.l.c. on silica gel with a pentane–diethyl ether mixture (8 : 2) as eluant. Two groups of products were separated. The first one (R_F 0.6; 140 mg) consisted of 90% of compound (12b) contaminated with 10% of compound (13). The second group (R_F 0.55; 140 mg) was a complex mixture of anisylidene derivatives whose structures were not elucidated.

Compound (12b) had m.p. 114—115 °C; u.v. (EtOH) $\lambda_{max.} = 325$ (ε 22 300) and 231 nm (10 800); i.r. (CS_2) 1 665 cm⁻¹ ($\nu_{C=O}$); n.m.r. ($CDCl_3$) 0.87 (d, 3 H, $J = 6.5$ Hz, Me-14), 1.08 (s, 3 H, Me-12), 1.13 (s, 3 H, Me-13), 2.25 (s, 1 H, H-7), 3.81 (s, 3 H, OMe), and 7.50br (s, 1 H, olefinic H). (Found: C, 81.3; H, 8.9; O, 9.8. $C_{22}H_{29}O_2$ requires C, 81.23; H, 8.92; O, 9.84%).

Compound (13) was an oil; u.v. (ethanol) $\lambda_{max.}$ 325 nm (ε 18 500); i.r. (film) 1 665 cm⁻¹ ($\nu_{C=O}$); n.m.r. ($CDCl_3$) 0.95 (d, 3 H, $J = 6$ Hz, Me-14), 1.10 (s, 6 H, Me-12 and -13), 2.50 (d, 1 H, $J = 1$ Hz, H-7), 3.83 (s, 3 H, OMe), and 7.55br (s, 1 H, olefinic H).

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[12] D. H. Wertz, N. L. Allinger, *Tetrahedron*, 1974, **30**, 1579, the computed steric energies after minimisation are (in kcal) (6a) = 22.0; (6b) = 22.6; (7a) = 30.8; (7b) = 30.9.
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