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MONOTERPENOIDS — V[†]

(+)-CARVONE FROM (+)-CAR-3-ENE[#]

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Abstract - A stereoselective conversion of the readily available (+)-car-3-ene into (+)-carvone by two different routes is described. This is the first report on synthesis of carvone from car-3-ene.

(+)-Carvone (9) is valued as a flavouring component for its warm-herbaceous, breadlike, spicy and slightly floral odour.[1] Its commercial production is essentially based on its isolation from caraway seed oil[2] (Carum carvi L.) or dill seed oil[2] (Anethum graveolens L.), though occasionally some synthetic (+)-carvone is reportedly[3] manufactured from the rather scarce (-)-limonene. Synthesis of (+)-carvone from (-)-limonene[4] as well as from (-)-carvone[5] have been described. We now report its preparation from the abundantly available (+)-car-3-ene (1) by two different routes, which are shown in Fig. 1. The key reaction in each case is the well-established[6] stereospecific (1,5) sigmatropic rearrangement[7] (Fig. 2) of a car-2-ene derivative under thermal treatment.

(+)-3α,4α-Epoxycarane (2), readily obtainable[8,9] from (+)-car-3-ene is the starting point for both the schemes. The conversion of this oxide to the desired car-2-en-4-ol (3)[10], under the influence of KOBu-t in pyridine has been reported earlier,[11] and 3 has been claimed as the only product of this reaction. However, in our hands, both the desired alcohol 3 and the allylic tertiary alcohol (10)[10] were obtained in an approximate ratio of 1:1.3; changing the amount of base relative to the epoxide (0.2-4.4 mol. equiv. of base per one mol. equiv. of epoxide) had little effect on the product composition, though rate of isomerisation decreased significantly with lower proportions of base. These results are

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[†] Part III: J. Indian Chem. Soc. 38, 674 (1961). The publication: R. Sobti and Sukh Dev, Tetrahedron 30, 2927 (1974), is to be considered Part IV of this Series.

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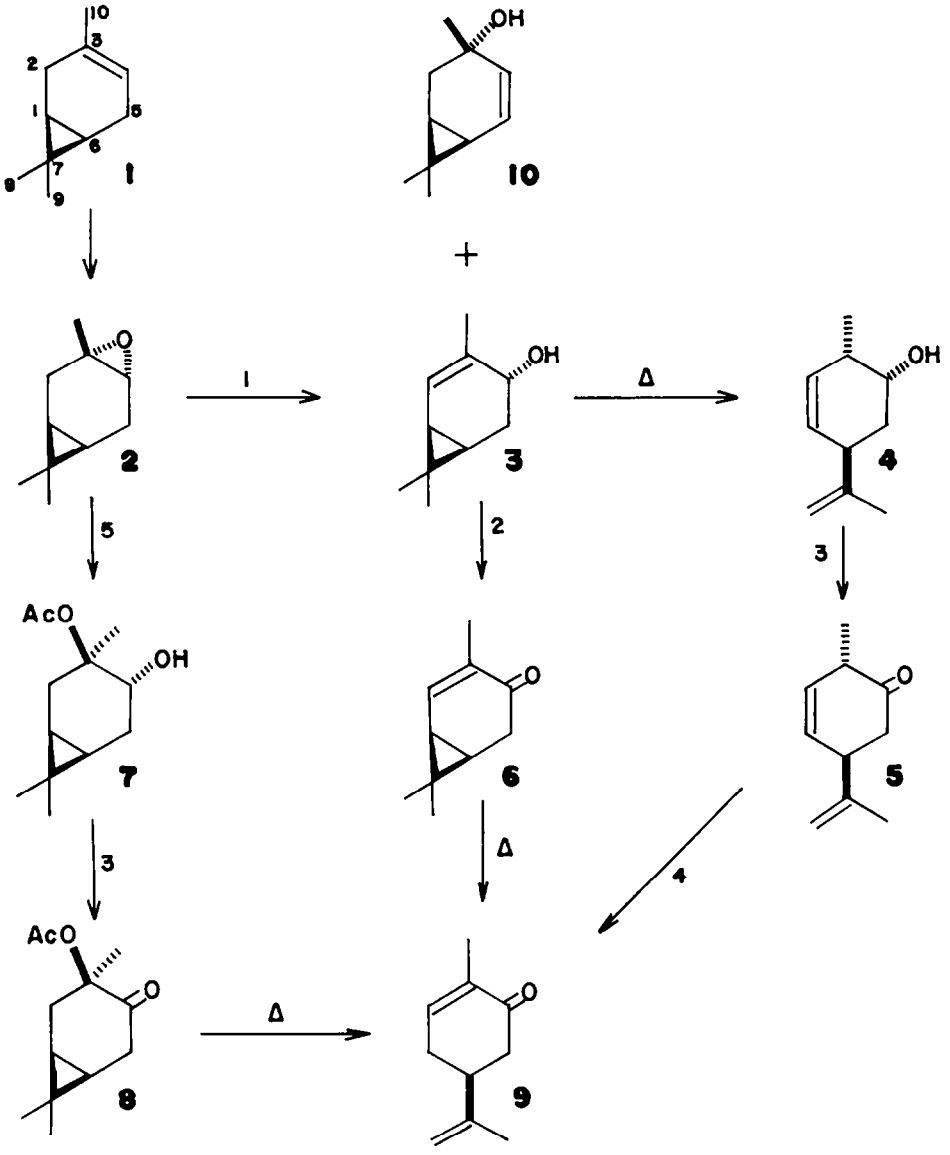

Reagents. 1: KOBu-t, pyr. 2: Pyridinium dichromate, CH_2Cl_2
3: $Na_2Cr_2O_7$-H_2SO_4 aq 4: NaOH-MeOH 5: AcOH

Fig.1 Transformation of (+)-car-3-ene into (+)-carvone

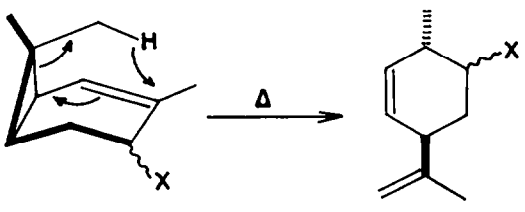

Fig.2 Thermal rearrangement of car-2-ene and its derivatives

not surprising if one concedes that the C-5 methylene protons, being next to the cyclopropane ring can effectively[12] compete with the C-10 methyl hydrogens for reaction with the base, notwithstanding the greater propensity of a methyl group for carbanion formation in such reactions.[13] The two alcohols, 3 and 10, were readily separated by precise fractionation under vacuum.

Oxidation of car-2-en-4-ol (3) was best carried out by pyridinium dichromate[14] in CH_2Cl_2 to furnish car-2-en-4-one (6), earlier described[15] as a minor oxidation product of car-3-ene with permanganate. When this ketone was heated to ~ 200° (N_2) for some 5 hr, it smoothly got transferred into the required (+)-carvone (9); ^{1}H-NMR monitoring of the reaction clearly established the intermediacy of p-mentha-5,8-dien-2-one (5). The overall yield of 9 from 3 was 50%. Alternatively, car-2-en-4-ol (3) was thermally rearranged to the known[6b] p-mentha-5,8-dien-2-ol (4). Oxidation of 4 with $Na_2Cr_2O_7$-H_2SO_4 aq in a two-phase system, furnished in 60% yield the corresponding ketone (5).[16] Exposure of 5 to methanolic NaOH (1 hr, reflux) resulted in its isomerisation to the desired (+)-carvone (9). In another variant of this sequence, p-mentha-5,8-dien-2-ol (4) was converted to (+)-carvone in over 80% yield by one-pot oxidation and *in situ* isomerisation with N-chlorosuccinimide-dimethyl sulphide[17] with triethylamine as base.

In the second approach, carene epoxide (2) was exposed to AcOH (25°, 72 hr) to get a complex reaction product from which the known[18] hydroxy acetate (7) could be isolated in 83% purity[19] in a yield of ~40%. Its oxidation to the acetoxy ketone (8) could be successfully manipulated by oxidation with Brown's reagent[20] at 0-5°, using the inverse addition technique. Pure 8 on pyrolysis (~200°) yielded a complex mixture of products from which pure (+)-carvone was isolated by chromatography (SiO_2 gel) in a yield of ~25%. ^{1}H-NMR monitoring of the reaction showed that the conversion proceeds by way of car-3(10)-en-4-one to 6 → 5 → 9.

EXPERIMENTAL

All b.ps are uncorrected. Light petroleum refers to fractions b.p. 60-80°. All solvent extracts were finally washed with brine and dried (Na_2SO_4). Silica gel for chromatography (-100, +200 mesh) was washed with hot water, till sulphate-free, dried and activated at 125-130° for 6 hr and standardised.[21] TLC was carried out on silica gel layers (0.25 mm) containing 15% gypsum and activated at 110-115° (2 hr.); spray reagent, 1% vanillin in 50% H_3PO_4 aq.

The following instruments were used for spectral/analytical data: Schmidt + Haensch electronic polarimeter model Polatronic 1; Perkin-Elmer model 402 Ultraviolet Spectrophotometer; Perkin-Elmer model 267 Infrared Spectrophotometer;

Perkin-Elmer model R32 (90 MHz) NMR Spectrometer; Varian Mat CH7 Mass spectrometer (70 eV, direct inlet system); Hewlett-Packard 5712A and 7624A Gas Chromatographs (Al columns, 180 cm x 0.6 cm, unless stated otherwise; support 60-80 mesh Chromosorb W; carrier gas, H_2). All ^{1}H-NMR spectra were recorded with 15-20% soln in CCl_4 with TMS as internal reference; signals are reported in ppm (δ); while citing ^{1}H-NMR data, following abbreviations have been used: s(singlet), t (triplet), q (quartet), m(multiplet), b(broad). While summarising mass spectral data, besides the molecular ion, nine most abundant ions (m/z) are reported with their relative intensities.

(+)-Car-2-en-4α-ol (3) and (-)-car-4-en-3α-ol (10)

To t-BuOK (from 41 g of K, 1.052 g atom) prepared in the usual manner, anhydrous pyridine (300 ml) was added, under dry inert gas (N_2) conditions. After stirring for ∿20 min to dissolve t-BuOK, 3α,4α-epoxycarane (304 g, 2.0 moles) was introduced and the reaction mixture refluxed (bath temp. 125-130°) with stirring for 2.5 hr, when TLC (solvent: 15% EtOAc in light pet.) indicated essentially complete conversion. During the next 3 hr, bulk of pyridine and t-BuOH were collected by distillation, and the residue cooled, diluted with ice water (500 ml) and the product taken up in light pet. (150 ml x 4). After usual work-up, 285 g of a liquid product, shown by GLC (glass column, 5% Carbowax 20M, 110°) to consist of 3 (40%, RRT = 2.26) and 10 (52%, RRT = 1.00) with some other products (not investigated) was obtained. Fractionation of this material (166 g), using a spinning-band column (45 theoretical plates) furnished car-4-en-3α-ol (10; 75.3g, b.p. 82-83/7 mm, > 95% pure by GLC) and car-2-en-4α-ol (3; 55 g, b.p. 92-95°/6 mm, ∿90% pure by GLC).

Pure samples had the following characteristics. Car-4-en-3α-ol (10): n_D^{25} 1.4818, $[\alpha]_D$ -287.3° (C_6H_6, c 5.4%). (Lit.[10], n_D^{20} 1.4853, $[\alpha]_D^{26}$ -289° in C_6H_6, c 3.6%). IR (liq.): 3400, 1645, 1224, 1173, 1115, 1076, 995, 943, 912, 860, and 742 cm^{-1}. ^{1}H-NMR: Me-C (3H singlets at 0.88 and 1.15 ppm), Me-C-O (3H,s, 1.15 ppm), CH=CH (2H, s, 5.77 ppm). Car-2-en-4α-ol (3): n_D^{25} 1.4958, $[\alpha]_D$ + 190.0° (C_6H_6, c 5.0%). (Lit.[10], n_D^{20} 1.4978, $[\alpha]_D^{22}$ + 203.8° in C_6H_6, c 3.2%). IR (liq.): 3360, 1650, 1200, 1140, 1070, 1040, 1000, 875 and 845 cm^{-1}. ^{1}H-NMR: Me-C (3H singlets at 0.82 and 1.10 ppm), Me-C=C (3H, s, 1.78 ppm), CHOH (1H, t, 3.62 ppm, J = 5 Hz), C=CH (1H, bs, 5.53 ppm).

(+)-Car-2-en-4-one (6)

To a soln of 3 (10 g, 0.066 mole) in CH_2Cl_2 (100 ml), powdered pyridinium dichromate[14] (30 g, 0.08 mole) was added with stirring during 10 min and the mixture stirred at room temp (∿30°) till TLC (solvent, 10% EtOAc in light pet.)

showed absence of the starting alcohol (~7 hr). At this stage the reaction mixture was filtered through a short column of neutral Al_2O_3 (grade III; 120 g), the column washed with EtOAc (100 ml x 3), and the combined filtrate and washings washed with 10% $NaHCO_3$ aq (70 ml x 1), brine (70 ml x 1) and dried. Removal of solvent furnished a residue (9.5 g), which was distilled to get a pale yellow product (8.3 g), b.p. 60-70°/2.5 mm. This product (68.0 g) which was only 75% pure by GLC (10% Carbowax 20M, 170°) was further purified by fractional distillation on a high-performance spinning-band column (80 theoretical plates)[22] to get over 90% pure (GLC) carenone (6) as a colourless liquid, b.p. 95°/10 mm, n_D^{27} 1.5270. $[\alpha]_D$ + 5.24°(neat). IR (liq.): 1660, 1640(sh), 1456, 1409,1380, 1312, 1259, 1140, 1084, 1048, 1010, 927, 850 cm^{-1}. ^{1}H-NMR: Me-C (3H, singlets at 0.83 and 1.20 ppm), Me-C=C (3H, s, 1.75 ppm), CH_2CO (2H, m, 2.48 ppm), C=CH (1H, m, 6.69 ppm). Mass: m/z 150(M^+, 60%), 107 (100%), 108 (75%), 91 (46%), 79 (38%), 77 (26%), 135 (25%), 93 (24%). (Found: C, 79.48; H, 9.65. $C_{10}H_{14}O$ requires: C, 79.95; H, 9.39%).

(+)-trans-p-Mentha-5,8-dien-2-ol (4)

Car-2-en-4α-ol (3; 53.72g, 0.354 mole) and pyridine (0.6 ml) were refluxed (bath temp. 215-220°) under N_2 for a total of 11½ hr, when TLC (10% $AgNO_3$-SiO_2 gel G; solvent, 15% EtOAc in toluene) established disappearance of 3. The reaction mixture was distilled to get the required p-menthadienol 4: b.p. 84-86°/5 mm, 51.4 g (GLC purity 95%; GLC: 360 cm x 0.6 cm Al column, 10% Carbowax 20M, 170°). An analytically pure sample was obtained by Inverse-Dry-Column-Chromatography[23] using 15% $AgNO_3$-SiO_2 gel (28.5 cm x 7.5 cm; solvent, 25% EtOAc in toluene; 4 charged, 3.9 g); b.p. 86°/5 mm, n_D^{25}1.4911, $[\alpha]_D^{25}$+ 242.2° ($CHCl_3$, 4.3%) (Lit.[6b], $[\alpha]_D^{20}$+ 232.4°). IR (liq.): 3400, 1649, 1070, 1050, 1000, 897, 790 cm^{-1}. ^{1}H-NMR: Me-CH (3H, d, 1.03 ppm, J = 7Hz), Me-C=CH_2 (3H, s, 1.75 ppm), CHOH (1H, b sig., 3.88 ppm, W_H = 11Hz), Me-C=CH_2 (2H, s, 4.74 ppm), CH-CH=CH-CH (2H, bs, 5.5 ppm).

(+)-trans-p-Mentha-5,8-dien-2-one (5)

To a soln of above alcohol (50.53 g, 0.33 mole) in EtOAc (150 ml) cooled to 10 ± 2°, Brown's reagent[20] (495 ml, 0.33 mole; 100 g $Na_2Cr_2O_7.2H_2O$ + 300 ml H_2O + 136 g 97% H_2SO_4 → made to 500 ml) was added (1½ hr) while stirring at 25 ± 3°. Stirring was continued at this temp. for an additional 4 hr 20 min, when absence of starting alcohol was indicated by TLC (solvent,5% EtOAc in toluene). EtOAc layer was separated, aq. part extracted with EtOAc (150 ml x 4). The combined EtOAc extract was washed with 10% $NaHCO_3$ aq (25 ml x 5), water (25 ml), brine (25 ml x 2) and dried. Removal of solvent and fractionation of residue furnished 5 as a colourless liquid (28-32 g), b.p. 80-85°/5 mm (GLC purity >95%), n_D^{25} 1.4830, $[\alpha]_D^{25°}$ + 192° (neat). IR (liq.): 1725, 1650, 1320, 1230, 1150, 905, 805 cm^{-1}.

^{1}H-NMR: Me-CH (3H, d, 1.15 ppm, J = 7.5 Hz), Me-C=CH$_2$ (3H, s, 1.75 ppm), Me-C=CH$_2$ (2H, s, 4.78 ppm), CH-CH=CH-CH (2H, s, 5.72 ppm).

3β-Acetoxycaran-4-one (8)

3α,4α-Epoxycaran (62 g, 0.41 mole) was mixed with gl.AcOH (250 ml) and the soln. left aside at room temp. (∿25°) for 72 hr, when TLC (solvent, 15% EtOAc in toluene) showed only traces of epoxide. The reaction mixture was diluted with water (250 ml) and the product taken up in light pet. (100 ml x 4). The combined extracts were washed with 10% $NaHCO_3$ aq (30 ml x 3), water (30 ml) and brine (30 ml). Solvent was flashed off and the residue distilled to collect a fraction (28.0 g), b.p. 100-103°/1 mm containing 83% of the rqd. 3β-acetoxycaran-4α-ol (7) (GLC; 10% Carbowax 20M, 360 cm x 0.6 cm, 200°). Structure 7 was clear from comparison of its IR and ^{1}H-NMR spectra with the values reported in the literature.[18]

To Brown's reagent[20] (225 ml ≡ 0.15 mole $Na_2Cr_2O_7.2H_2O$) and EtOAc (50 ml), cooled to 0°, the above product (27.0 g, 83% GLC purity) in EtOAc (40 ml) was slowly introduced, with stirring, during 1 hr at 0-5°. Stirring was continued at 10 ± 5° for additional 1.5 hr with TLC monitoring (solvent, 10% EtOAc in light pet.). Usual work-up furnished a product (26 g), which was distilled to get a material (19.7 g), b.p. 122-123°/3-4 mm, containing ∿72% required ketone 8 by GLC (10% SE-30, 150°). This was purified by column chromatography over SiO_2 gel/IIA (2.5 cm x 110.7 cm); 5% EtOAc in light pet. (100 ml x 3) eluted GLC pure ketone 8 (14.5 g): b.p. 122-123°/3.5 mm, n_D^{25} 1.4690, $[\alpha]_D$ + 222.8° (neat). IR (liq.): 1740, 1725, 1460, 1370, 1255, 1145, 1095, 1065, 1024, 970, 870, 820 and 750 cm^{-1}. ^{1}H-NMR: Me-C (6H, s, 1.12 ppm), Me-C-O (3H, s, 1.44 ppm), CH_3COO (3H, s, 1.95 ppm), CH_2CO (2H, m, 2.40 ppm). Mass: m/z 210 (M^+, 0.5%), 43 (100%), 107 (40%), 150 (30%), 108 (30%), 82 (30%), 67 (22%), 135 (13%). (Found: C, 69.05; H, 8.24. $C_{12}H_{18}O_3$ requires: C, 68.54; H, 8.63%).

(+)-Carvone (9)

(a) From (+)-car-2-en-4-one (6). Ketone 6 (7.76 g; 85% pure) was heated at 205±2° (bath temp. 220 ± 5°), under reflux (N_2), for 5 hr. At this stage GLC (10% Carbowax 20M, 170°) showed absence of both 6 or 5. Distillation of the product furnished a distillate (6.52 g) containing ∿80% carvone (GLC; 10% Carbowax 20M, 170°). A part (2.0 g) of this product was chromatographed (SiO_2 gel/IIA 1.5 cm x 40 cm) to get pure carvone (1.3 g, eluted with 5% EtOAc in light pet.): colourless liquid with a clean caraway odour, b.p. 95°/7 mm, n_D^{25} 1.4955, $[\alpha]_D^{25}$ + 62.21°. λ_{max}^{EtOH} 235 nm (ε, 10630). IR (liq): 1675, 1645, 1250, 1110, 895 cm^{-1}. ^{1}H-NMR: Me-C=C (6H, bs, 1.76 ppm), C=CH$_2$ (2H, bs, 4.76 ppm), C=CH (1H, b sig., 6.67 ppm, W_H = 10 Hz). (Lit.[24]: $[\alpha]_D$ + 62.3°, UV, IR, ^{1}H-NMR).

(b) From (+)-trans-p-mentha-5,8-dien-2-one (5). Exposure of this ketone (22.5 g, 0.15 mole) to NaOH (0.9 g, 0.022 mole)dissolved in MeOH (90 ml) at reflux for 1 hr (N_2) effected its smooth, essentially quantitative isomerisation to (+)-carvone, which was recovered, after usual work-up followed by distillation, b.p. 92-95°/7mm, yield 20.52 g (GLC purity, 97%).

(c) From (+)-trans-p-mentha-5,8-dien-2-ol(4). To a suspension of N-chlorosuccinimide (6.95 g, 0.052 mole) in dry dichloroethane (40 ml), cooled to 0°, anhydrous dimethylsulphide (4 ml, 0.054 mole) was introduced with stirring under strictly anhydrous conditions (N_2). To the complex, thus obtained, alcohol 4 (5.0 g, 0.032 mole) dissolved in dichloroethane (10 ml) was added slowly (10 min) while stirring and maintaining temp. at -10 to -8°. After stirring at this temp. for 2.5 hr, dry triethylamine (8.0 ml, 0.057 mole) was slowly introduced. The reaction mixture was stirred for another 5 min, cold bath removed to permit the reaction mixture to attain room temp. when it was heated at 70° for 1 hr. The reaction mixture was made acidic(H_2SO_4 aq),the solvent layer separated, washed with water (20 ml x 2),5% Na_2CO_3 aq(5 ml), water (20 ml x 2), brine (20 ml) and dried. Usual work-up, furnished after distillation, a product (4.13 g), b.p. 75-88°/5 mm, containing 97% carvone (GLC), but having an undesirable odour.

(d) From (+)-3β-acetoxycaran-4-one (8). Pure 8 (2.86 g) was heated under reflux (N_2; bath temp. 240 ± 5°, pot temp. 180-190°) for 4 hr and worked up with EtOAc (50 ml), which was washed with 10% Na_2CO_3 aq (5 ml x 2), water and brine and dried. Removal of solvent gave a product (1.95 g), which was now free from AcOH. This material (0.7 g) was again heated as before (bath temp. 240 ± 5°, pot temp. 210 ± 5°) for 3 hr and worked up. The product was chromatographed on SiO_2-gel/IIA (1.5 cm x 24.0 cm), when 5% EtOAc in light pet (10 ml x 2) eluted 0.2 g of pure (+)-carvone (GLC, PMR).

REFERENCES & NOTES

1 S. Arctander, Perfume and Flavor Chemicals, Vol. I, monograph 579. Published by the Author, Montclair, N.J. (1969).

2 W. Treibs and K. Bournot, E. Gildemeister/Fr. Hoffmann, Die Atherischen Ole, Vol. VI, pp. 393, 450. Akademie-Verlag, Berlin (1961).

3 Takasago (Japan), private communication.

4 See e.g.: B. Singaram and J. Verghese, Perfumer and Flavorist 2 (June/July), 47 (1977).

5 [a]E. Klein and G. Ohloff, Tetrahedron 19, 1091 (1963); [b]V.K. Honwad, E. Siscovic and A.S. Rao, Indian J. Chem. 5, 234 (1967); [c] L. Friedman and J.G. Miller, Science 172, 1044 (1971).

6 [a]G. Ohloff, Chem. Ber. 93, 2673 (1960); [b]G. Ohloff, Tetrahedron Letters 3795 (1965); K. Gollnick and G. Schade, Tetrahedron 22, 123 (1966).

7 See e.g.: C.W. Spangler, Chem. Rev. 76, 187 (1976).

8 [a]P.J. Kropp, J. Amer. Chem. Soc. 88, 4926 (1966); [b]A. Suzuki, M. Miki and M. Itoh, Tetrahedron 23, 3621 (1967).

9 R. Sobti and Sukh Dev, Tetrahedron 30, 2927 (1974).

10 K. Gollnick, S. Schroeter, G. Ohloff, G. Schade and G.O. Schenck, Liebig's Ann. 687, 14 (1965).

11 Z. Rykowski and K. Burak, Roczniki Chemii 50, 1709 (1976).

12 Cyclopropyl group stabilisation of carbanions has been established recently, though the effect has been found to be rather small: M.J. Perkins, N.B. Peynircioglu and B.V. Smith, J. Chem. Soc. Perkin II, 1025 (1978).

13 B. Rickborn and R.P. Thummel, J. Org. Chem. 34, 3583 (1969).

14 E.J. Corey and G. Schmidt, Tetrahedron Letters 399 (1979).

15 W.D.P. Burns, M.S. Carson, W. Cocker and P.V.R. Shannon, J. Chem. Soc.(C) 3073 (1968).

16 The laevo- compound has been described in a patent: A.B. Booth, U.S. 2,918,495 (Dec. 1959). Also see: S. Arctander, Perfume and Flavour Chemicals, Vol. II, monograph 2861. Published by the Author, Montclair, N.J. (1969).

17 E.J. Corey and C.U. Kim, J. Am. Chem. Soc. 94, 7586 (1972).

18 [a]W. Cocker and D.H. Grayson, J. Chem. Soc. Perkin I 1217 (1975); [b]W. Cocker and D.H. Grayson, ibid. 155 (1978). These authors used AcOH buffered with NaOAc or H_2O_2-Ac_2O in AcOH for conversion of 2 to 7. In our hands these reagents gave poorer results.

19 This compound is quite labile and undergoes rather facile acetyl migration to 3β-hydroxy-4α-acetoxycarane (^{1}H-NMR).

20 H.C.Brown, C.P. Garg and K-T. Liu, J. Org. Chem. 36, 387 (1971).

21 R. Hernandez, R. Hernandez, Jr. and L. R. Axelrod, Analyt. Chem. 33, 370(1961).

22 Adiabatic Annular Teflon Spinning-band distillation unit, Nester/Faust Manufacturing Corporation, Newark, USA.

23 V.K. Bhalla, U.R. Nayak and Sukh Dev, J. Chromatog. 26, 54 (1967).

24 Sukh Dev, A.P.S. Narula and J.S. Yadav, Handbook of Terpenoids: Monoterpenoids, Vol. II, p. 276. CRC Press, Boca Raton (1982).