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# THE STEREOSELECTIVE SYNTHESIS OF L-VALERANONE

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The nonisoprenoid sesquiterpene, D-valeranone, has held international interest from the time of its announced isolation by Stoll and co-workers in 1957.[1] The unusual carbon skeleton of this terpene caused several erroneous structure proposals and only recently, through the combined efforts of several schools, has the entire structure problem received satisfactory clarification.[2] The present report describes a stereoselective synthesis of L-valeranone (13) by a method which fully supports the most recently assigned formula[1b,1e,1f,2] and removes any doubt concerning the structure of this uncommon sesquiterpene.

Octalone 4 [$\lambda_{max}^{film}$ 6.00 (conj. CO), 6.20 (C=C), 7.93, 8.03, 8.30, 8.39, 10.19, 11.66, 12.98 μ] of known stereochemistry[3] was prepared from methyl vinyl ketone (1) and

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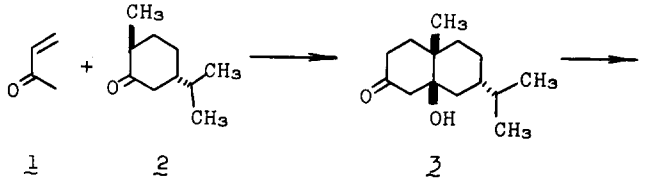
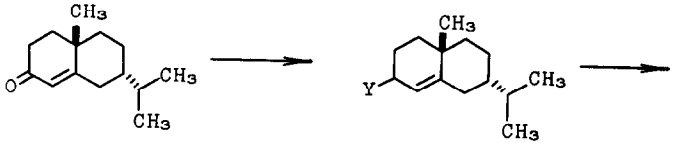
(-)-carvomenthone (2) via the crystalline ketol 3 [m.p. 58-59°, $\lambda_{max}^{CCl_4}$ 2.89 (OH), 5.87 (CO), 9.62, 9.96, 10.67 μ] according to a modified Robinson annelation procedure.[4] The alcohol 5 [$\lambda_{max}^{film}$ 3.00 (OH), 9.30, 9.46, 9.66 μ], obtained by reducing octalone 4 with lithium aluminum hydride, was converted to the corresponding acetate 6 [$\lambda_{max}^{film}$ 5.78 (CO), 6.03 (C=C), 8.07, 9.77, 10.20 μ] which, in turn, gave octalin 7 [$\lambda_{max}^{film}$ 6.02 (C=C), 9.24, 9.88, 10.04, 11.57 μ; $\delta_{TMS}^{CCl_4}$ 5.27 (C=CH) 1H, 1.08 (angular $CH_3$) 3H, 0.86 p.p.m. (doublet, J = 7 c.p.s.) 6H] upon hydrogenolysis with lithium in ethylamine.[5] The hydroboration-oxidation method of Brown and co-workers,[6] when applied to octalin 7, stereoselectively afforded the expected 1-decalol [$\lambda_{max}^{film}$ 2.98 (OH), 8.60, 8.95, 10.22, 10.58 μ] in high yield. Dreiding models show that the isopropyl group of octalin 7, because of its axial orientation, more effectively blocks approach to the carbon-carbon double bond than the angular methyl group. Hence formula 8 most likely depicts the stereochemistry of the decalol obtained from octalin 7.

Additional evidence regarding this point was secured through oxidation of decalol 8 with chromic acid under mild (nonepimerizing) conditions.[7] The decalone 9, thus obtained, yielded a nearly 1:1 mixture of enol acetates II and IV[8] as evidenced by the infrared [$\lambda_{max}^{film}$ 5.70 (CO), 8.19 μ] and integrated n.m.r. spectra [$\delta_{TMS}^{CCl_4}$ 5.08-5.25



1 2 3



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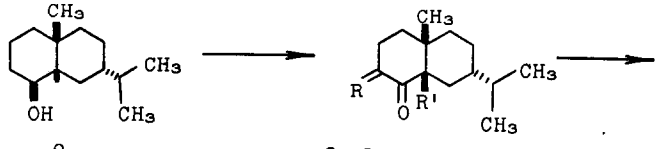
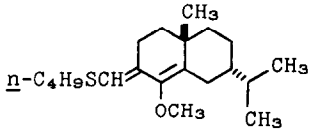
5, Y = OH
6, Y = OAc
7, Y = H



8

9, R = $H_2$; R' = H
10, R = n-$C_4H_9SCH$; R' = H
11, R = n-$C_4H_9SCH$; R' = $CH_3$



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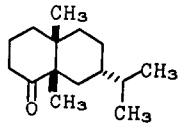

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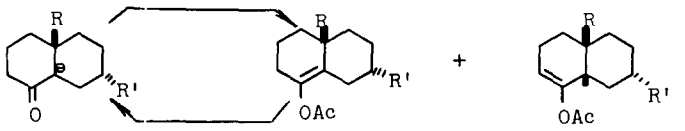
(C=C-H) 0.5H, 2.02 ($CH_3CO$) 3H, 0.99 and 1.13 (angular $CH_3$ of II and IV) 3H]. Hydrolysis of this enol acetate mixture

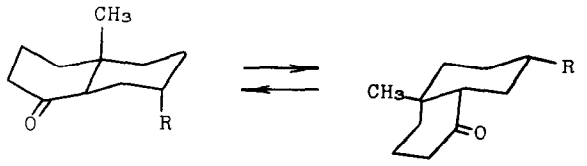



9, R = $CH_3$; R' = i-Pr
I, R = R' = H

II, R = $CH_3$; R' = i-Pr
III, R = R' = H

IV, R = $CH_3$; R = i-Pr
V, R = R' = H

regenerated the starting decalone 9 and not a stereoisomer (at C-9). Therefore, decalone 9 possesses the more stable ring fusion. In the all-chair conformation of trans-decalone VI, the isopropyl group must adopt an axial orientation whereas the nonsteroid conformation of the cis isomer 9, allows this group to attain the preferred equatorial orientation. Equilibration of 10-methyl-1-decalone yields a nearly 1:1 mixture of the cis and trans isomers VIII and VII.[9] Therefore, we can safely assume that the equatorial vs axial orientation of an isopropyl side chain provides sufficient driving force to ensure a substantial predominance of the cis-decalone 9 at equilibrium.[10] Since decalone 9 is obtained from decalol 8 under nonequilibrating conditions, this alcohol likewise possesses a cis ring fusion (QED).




VI, R = i-Pr
VII, R = H

9, R = i-Pr
VIII, R = H

Treatment with methanesulfonic acid in acetic anhydride (97 hr.) failed to alter the composition (ca. 1:1) of the enol acetate mixture II and IV thus indicating equilibrium had been reached during the preparation of these isomers. In contrast, 1-decalone (I), under comparable conditions,[11] affords a mixture of enol acetates III and V with the more substituted isomer predominating (94:6). The discrepancy must arise because the axial orientation required of the isopropyl group in the more substituted enol acetate II destabilizes this isomer relative to the cis isomer IV. The latter can adopt the favorable nonsteroid conformation, mentioned above (e.g. 9), in which the isopropyl group becomes equatorial.

Decalone 9 possesses all the features of valeranone except the most interesting one, the second angular methyl group. We planned to elaborate this remaining point through methylation of the bridgehead enolate derived from 9. Once formed, this enolate should undergo a highly stereoselective reaction to give the desired cis-decalone derivative because of intrinsic steric factors[12] augmented

by the axial (in the enolate) isopropyl group which blocks the pathway leading to the trans product (cf. 7 → 8). Our experience with enol acetates II and IV, along with the findings of others with 1-decalone itself,[13] suggested that direct angular methylation of decalone 9 would not be feasible. We therefore considered indirect means for accomplishing this conversion (9 → 13).

House and Trost[12] have recently devised a potentially useful method for generating enolates from enol acetates using methyllithium. We have not yet explored this possibility because of difficulties encountered in purifying the requisite enol acetate II. Meanwhile, we have investigated less direct approaches employing blocking groups to direct the methylation reaction. Neither the hydroxymethylene[14] nor the standard n-butylthiomethylene[15] alkylation procedures proved effective; only unchanged starting material was recovered. The latter derivative 10 [$\lambda_{max}^{film}$ 6.01 (C=C), 6.50 (CO), 7.70, 7.82, 8.30, 11.11, 11.50, 11.69 μ], prepared by the reported technique,[15] formed the enolate in dimethyl sulfoxide (DMSO) with sodium hydride (probably via sodium methylsulfinylcarbanion),[16] but treatment with methyl iodide afforded the enol ether 12 [$\lambda_{max}^{film}$ 6.18, 6.36 (C=C), 8.03, 8.18, 8.30, 8.90, 9.18, 9.42, 9.70, 9.88, 10.05 μ; $\delta_{TMS}^{CCl_4}$ 5.92 (C=C-H), 3.40 ($OCH_3$), 1.08 p.p.m. (angular $CH_3$)] as the sole isolable product. However, when this same procedure was modified by replacing the DMSO with benzene before the

methyl iodide was added, a 3:1 mixture of the enol ether and the desired C-methylated product 11 was obtained.[17] These two compounds were readily separated by elution chromatography on Silica, and the enol ether thus purified was converted to the starting n-butylthiomethylene ketone 10 through hydrolysis.[18]

The C-methylated ketone 11 afforded L-valeranone (13) upon alkaline hydrolysis under the standard conditions.[15] The identity of this substance was confirmed through comparison of the infrared spectrum[1a] [$\lambda_{max}^{film}$ 5.88 (CO), 7.60, 7.78, 7.89, 8.02, 8.93, 9.43, 10.65, 12.06 μ], refractive index ($n_D^{30}$ = 1.4918), and optical rotatory dispersion curve ($\underline{a}$ = + 120°) with the corresponding properties reported for D-valeranone.[19,2a] In addition, the synthetic material gave a 2,4-dinitrophenylhydrazone, m.p. 104-105°, in close agreement with that reported (m.p. 101°) for the corresponding derivative of the ketone derived from natural sources.[19]

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