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STEREOSELECTIVE TOTAL SYNTHESIS OF RACEMIC β-EUDESMOL

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β-Eudesmol (13) occupies a central position in the eudesmane group of sesquiterpenes because of its extensive use in structural and stereochemical correlations.[1] For example, it is this substance which provides the configurational link between terpenes and steroids.[2] We delineate in this communication a stereoselective total synthesis of the racemic form of β-eudesmol by a route which, through modification at the terminal stages, could be applied to other members of the eudesmane group.

Our starting material, 10-methyl-1(9)-octal-2-one (1), is readily obtained *via* condensation of 2-methylcyclohexanone with methyl vinyl ketone.[3] This octalone was converted to the ethylene ketal derivative 2 (b.p. 80°/0.2 mm.; m.p. *ca.* -10°) using a toluene azeotrope procedure under conditions which favor double bond migration in steroid analogs.[4] The migration was confirmed in the present case by the n.m.r. spectrum of ketal 2 which revealed absorption at 5.23 p.p.m.

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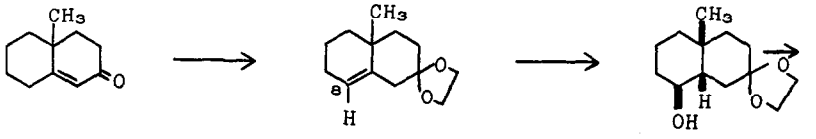
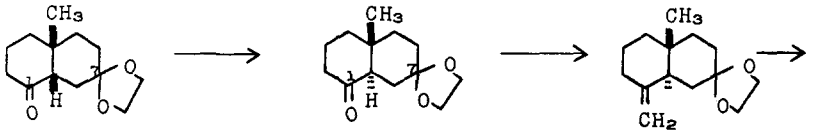
(H-8) as a peak broadened (width at half-height = 7 c.p.s.; unresolved triplet) by coupling of the vinyl proton with the adjacent methylene protons. Hydroboration of the unsaturated ketal 2 followed by oxidation with alkaline hydrogen peroxide[5] afforded hydroxy ketal 3 as the major product. The annexed stereochemistry was initially favored for 3 because of the reported findings for cholestenone ethylene ketal.[6] The following steps demonstrate the validity of this analogy.

Oxidation of hydroxy ketal 3 in acetone at 0° using standard chromic acid reagent[7] gave the cis-decalone ketal 4 [m.p. 77-78°; $\delta^{CCl_4}_{TMS}$ 3.88 ($-OCH_2CH_2O-$), 0.95 p.p.m. (CH_3)]. Equilibration using a catalytic amount of p-toluenesulfonic acid in refluxing benzene for 12 hours afforded a mixture of cis- and trans-decalone ketals 4 and 5 from which the predominant (4:5 = 1:4 evaluated by integration of the n.m.r. spectrum) trans-isomer 5 [m.p. 42.5-43°; $\delta^{CCl_4}_{TMS}$ 3.88 ($-OCH_2CH_2O-$), 0.80 p.p.m. (CH_3)] could be obtained in 65% yield by direct crystallization of the mixture from pentane at -30°. Whereas 10-methyl-1-decalone (4 and 5 with hydrogen replacing the ethylenedioxy grouping) is reported to give nearly a 1:1 equilibrium mixture of cis- and trans-isomers[8], attachment of an ethylenedioxy grouping at C-7 causes the trans-1-decalone derivative 5 to predominate.[9] This trend is expected since molecular models reveal that the concave geometry of the cis-isomer 4 imposes non-

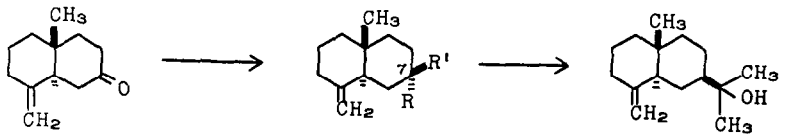
bonded interactions between the cyclohexanone ring and the ketal grouping which are alleviated in the trans-isomer 5. Since equilibration of the keto ketal 4 using methanolic sodium methoxide gave essentially the same result we can dismiss the a priori unlikely possibility that keto ketal 5 is a structural isomer (ketal at C-1) rather than a stereoisomer of 4.



1 2 3



4 5 6



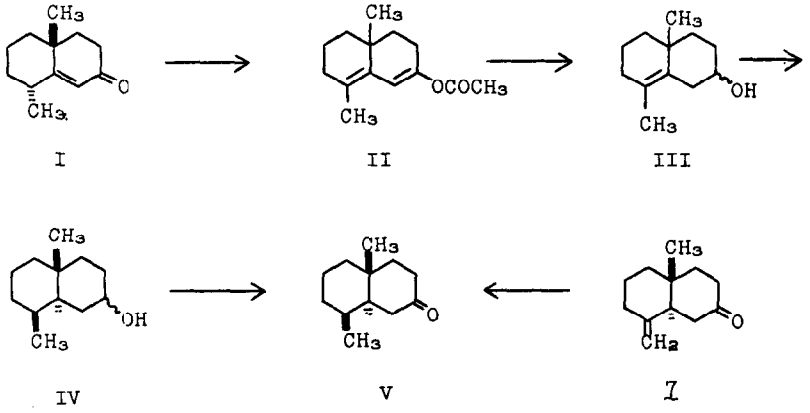
7

8; R=H, R'=OH
9; R=H, R'=p-CH3-C6H4-SO3
10; R=CN, R'=H
11; R=H, R'=CO2H
12; R=H, R'=CO2CH3

13

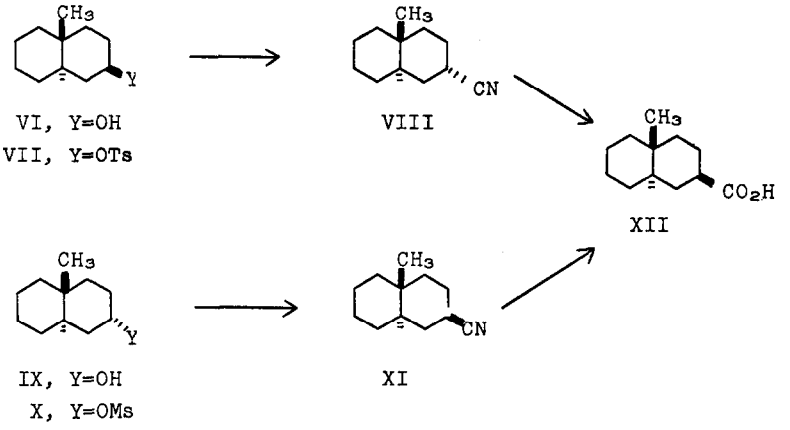
Ketone ketal 5 condensed readily with triphenylphosphonium methylide in dimethyl sulfoxide[10] to give methylene ketal 6 which, after hydrolysis in aqueous acetone containing dilute hydrochloric acid, yielded the methylene decalone 7 [m.p. 50-51°; λ_{max}^{KBr} 3.24 (C=CH$_2$), 5.85 (CO), 6.07 (C=C), 7.84, 8.54, 11.09, 11.23 μ; $\delta_{TMS}^{CCl_4}$ 4.87, 4.52 (C=CH$_2$), 0.95 p.p.m. (CH$_3$)]. The sequence described above is most conveniently effected without purification of the intermediates 2-6. In this manner crystalline ketone 7 can be prepared from octalone 1 in 25% overall yield. Preliminary studies indicate that cis-decalone ketal 4 condenses less readily with triphenylphosphonium methylide than the trans-isomer 5.

Ketone 7 represents a key intermediate for synthetic studies involving the eudesmane sesquiterpenes. Therefore, before proceeding further we sought additional evidence to corroborate our structural assignment. The following interconversions provided this confirmatory evidence.



trans-8,10-Dimethyl-1(9)-octal-2-one (I)[11] was converted to octalol III[11] [b.p. 96-103°/0.3 mm.; $\delta^{CCl_4}_{TMS}$ 4.15 (OH), 3.0-2.5 (CHOH), 1.63 (C-4 CH_3), 1.07 p.p.m. (C-10 CH_3), no absorption between 5 and 7 p.p.m. (vinyl H)] by reduction of the enol acetate derivative II.[12] Hydrogenation of this unsaturated alcohol over platinum in acetic acid[13] followed by oxidation of the resulting decalol IV yielded cis-8,10-dimethyl-trans-2-decalone [V, b.p. 95° (bath)/0.3 mm.; λ^{film}_{max} 5.85 (CO), 7.21, 8.10, 8.47, 8.69, 9.02, 9.44, 10.62 μ; $\delta^{CCl_4}_{TMS}$ 1.13 (C-10 CH_3), 0.95 p.p.m. (C-4 CH_3; doublet, J=7 c.p.s.); 95% pure according to gas chromatography]. The same decalone was obtained by hydrogenation of unsaturated ketone 7 over platinum in ethanol. The identity of the decalone samples obtained from IV and 7 was established by infrared and n.m.r. spectra comparison and gas chromatography (peak enhancement).

Ketone 7 was reduced (lithium aluminum hydride) to alcohol 8, m.p. 67-67.5°, which was subsequently converted to the p-toluenesulfonate derivative 9, m.p. 81-82°, with p-toluenesulfonyl chloride in pyridine (25°, 48 hr.). The toluenesulfonate grouping of 9 was displaced using potassium cyanide in N-methylpyrrolidone[14] and the resulting nitrile 10, m.p. 63-65°, was saponified with ethylene glycolic potassium hydroxide (150°, 12 hr.) to give the acid 11, m.p. 116-117°. In order to confirm the stereochemistry of acid 11 the following study was conducted on the known trans-10-methyl-2-decalol epimers[15] VI and IX.



VI, Y=OH
VII, Y=OTs

VIII

XII

IX, Y=OH
X, Y=OMs

XI

The equatorial alcohol VI gave the p-toluenesulfonate VII, m.p. 55-56.5°,[15] which upon treatment with potassium cyanide in N-methylpyrrolidone[14] yielded nitrile VIII [m.p. 60.5-61.5°; $\delta^{CCl_4}_{TMS}$ 2.98 (>CHCN, symmetrical envelope, width at half-height = 9 c.p.s.), 0.87 p.p.m. (CH_3)]. An isomeric oily nitrile XI [$\delta^{CCl_4}_{TMS}$ 0.90 p.p.m. (CH_3)] was obtained from the methanesulfonate derivative X (oil) of axial alcohol IX.[15] The non-identity of nitriles VIII and XI was determined by infrared and n.m.r. spectra comparison. Saponification of either nitrile VIII or XI using ethylene glycolic potassium hydroxide at 150° for 12 hours afforded the same crystalline carboxylic acid XII (m.p. 107.5-108.5; $\delta^{CCl_4}_{TMS}$ 12.16 (CO_2H), 0.88 p.p.m. (CH_3)]. Therefore, the conditions employed for saponification of nitrile 10 appear sufficient to effect epimerization at C-7. Furthermore, a cis-

relationship between the angular methyl and the carboxylic acid groupings of XII (and therefore 11) must result whether epimerization preceeds or follows saponification since an equatorial nitrile or carboxamide grouping should saponify much more rapidly and enjoy greater stability than the axial isomer.[16]

Esterification of acid 11 (diazomethane) followed by addition of excess ethereal methyllithium to the methyl ester 12[17] afforded racemic β-eudesmol [m.p. 68-69°; λ_{max}^{KBr} 3.02 (OH), 3.25 ($C=CH_2$), 6.09 (C=C), 7.25, 7.95, 8.22, 8.42, 8.82, 10.15, 10.45, 10.91, 11.12, 11.32, 11.71 μ.] The identity of the natural and racemic material was established by the exact correspondence of their richly detailed infrared spectra and their gas chromatographic and t.l.c. mobilities.*

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