

The n.m.r. spectrum showed peaks at δ 0.75 and 1.10 due to three methyl groups attached to saturated carbon, at 2.00 due to one methyl attached to unsaturated carbon, at 3.20 due to the C-3 proton, at *ca.* 3.80 due to four methylenic protons of the acetal, at 4.47 (doublet) due to the acetal proton, and at 9.90 due to the conjugated formyl proton. An analytical sample was prepared by simple distillation, b.p. 140° (bath temp. 0.01 mm.).

Anal. Calcd. for C₁₇H₂₆O₃: C, 73.34; H, 9.41. Found: C, 72.66; H, 9.38.

Acid Hydrolysis of the Ethylene Acetal VII to Helminthosporal (I). To a solution of 600 mg. of the unsaturated aldehyde VII in 45 ml. of tetrahydrofuran was added 28.2 ml. of dilute sulfuric acid (4.4%) with stirring under an argon atmosphere. The reaction mixture was stirred for 24 hr. at 20° under argon. The solvent was concentrated under reduced pressure to a volume of 20 ml. Extraction of the solution with ether followed by washing the extracts with dilute aqueous sodium bicarbonate and water, and then evaporation of the solvent gave 555 mg. of the crude oily product which was chromatographed on 28 g. of neutral alumina (activity 4). Elution with *n*-pentane gave 90 mg. of oily substance. Elution with 1:1 *n*-pentane-benzene mixture gave 395 mg. (66% yield) of the partly crystallized synthetic helminthosporal (I). Recrystallization

from *n*-pentane gave synthetic helminthosporal, m.p. 55–58° (Kofler hot stage), $[\alpha]_D^{18}$ –47.8 (*c* 1.00, chloroform), $\lambda_{\max}^{\text{EtOH}}$ 266 m μ (ϵ 10,800). The infrared and n.m.r. spectra were completely identical with those of the natural substance. In the n.m.r. spectrum signals appeared at δ 0.82, 1.10, and 1.18 due to three methyl groups attached to saturated carbon, at 2.09 due to one methyl attached to unsaturated carbon, at 3.35 (C-3 proton), at 9.43 (doublet) due to nonconjugated formyl, and at 9.90 due to the conjugated formyl proton.

Tetrahydrohelminthosporal Bis-3,5-dinitrobenzoate. Synthetic helminthosporal was reduced with lithium aluminum hydride in ether by the same procedure as reported previously for the natural product to give a diol which was treated directly with 3,5-dinitrobenzoyl chloride in pyridine. Recrystallization from ethanol gave tetrahydrohelminthosporal bis-3,5-dinitrobenzoate, m.p. 148.5–149.5° (capillary), 151–152.5° (Kofler hot stage). A mixture melting point with an authentic tetrahydrohelminthosporal bis-3,5-dinitrobenzoate derived from natural substance showed no depression.

Anal. Calcd. for C₂₉H₃₀N₄O₁₂: C, 55.59; H, 4.83. Found: C, 55.43; H, 4.89.

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The Total Synthesis of α -Caryophyllene Alcohol

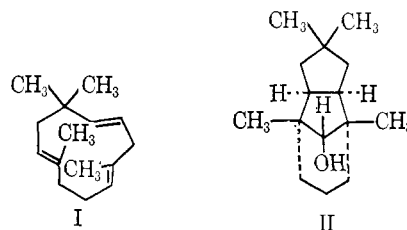
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A three-step synthesis of α -caryophyllene alcohol (II) from two known monocyclic intermediates is described. These structures are joined by a photoaddition process, and the synthesis is completed by carbonyl addition (methylolithium) and 1,2-rearrangement of carbon under acid catalysis.

Acid-catalyzed hydration of humulene (I) or commercial "*caryophyllene*" which contains humulene under various conditions leads to an interesting and long-known saturated tricyclic alcohol which has been designated as α -caryophyllene alcohol in the terpene literature.¹ This substance has recently been assigned structure II both on the basis of an X-ray diffraction study² and chemical investigations,³ and it has been shown that it is formed only from humulene and not from caryophyllene or isocaryophyllene.^{2,3} It appeared to us that this complex molecule ought to be accessible

by a particularly simple synthetic route and so an experimental study was undertaken. This paper records a total synthesis of α -caryophyllene alcohol (II) by a short process consisting of three steps from known compounds.⁴



Slow addition by syringe of a solution of 3-methyl-2-cyclohexenone⁵ in pentane to a solution of 4,4-dimethylcyclopentene⁶ (*ca.* –10°) under ultraviolet irradiation, using the technique previously described^{7,8} for the

(1) See (a) Y. Asahina and T. Tsukamoto, *J. Pharm. Soc. Japan*, **484**, 463 (1922); (b) J. Bell and G. G. Henderson, *J. Chem. Soc.*, 1971 (1930); (c) S. Dev, *Current Sci. (India)*, **20**, 296 (1951); (d) A. Nickon, J. R. Mahajan, and F. J. McGuire, *J. Org. Chem.*, **26**, 3617 (1961).

(2) K. W. Gemmell, W. Parker, J. S. Roberts, and G. A. Sim, *J. Am. Chem. Soc.*, **86**, 1438 (1964).

(3) A. Nickon, F. J. McGuire, J. R. Mahajan, B. Umezawa, and S. A. Narang, *ibid.*, **86**, 1437 (1964).

(4) For a preliminary announcement see E. J. Corey and S. Nozoe, *ibid.*, **86**, 1652 (1964).

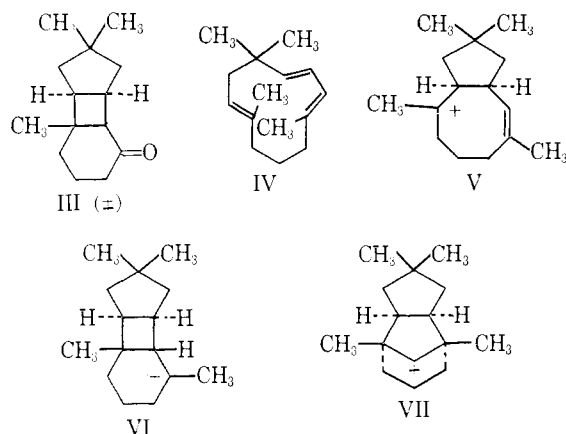
(5) See G. F. Woods, P. H. Griswald, Jr., B. H. Armbrrecht, D. I. Blumenthal, and R. Plapinger, *ibid.*, **71**, 2028 (1949).

(6) See H. Kwart and J. A. Ford, Jr., *J. Org. Chem.*, **24**, 2060 (1959).

(7) E. J. Corey, R. B. Mitra, and H. Uda, *J. Am. Chem. Soc.*, **86**, 485 (1964).

(8) E. J. Corey, J. D. Bass, R. LeMahieu, and R. B. Mitra, *ibid.*, **86**, 5770 (1964).

photoaddition of cyclohexenones to olefins, led to the formation of three isomeric 1:1 adducts of structures IIIa, b, and c, in the ratio 74:12:14, respectively, as the only volatile products. Passage of this mixture in ether through a column of neutral alumina (Woelm, activity I) caused isomerization of c to b and, hence,



these ketones differ in configuration at the methine carbon α to the carbonyl group; isomer c possesses a *trans* 4-6 fusion and b a *cis* 4-6 fusion.^{7,8} Isomer a was not changed by this treatment and is assigned a *cis* 4-6 fusion. Since isomer a predominates threefold over b plus c, this was taken to be the *cis-anti-cis* adduct and was used for the synthesis of II. The ketone IIIa was purified by preparative vapor phase chromatography and characterized by infrared and nuclear magnetic resonance (n.m.r.) measurements which are in agreement with the assigned structure (see the Experimental Section). Reaction of the pure ketone IIIa with methyllithium produced the corresponding methylated tertiary alcohol having the expected n.m.r. and infrared spectra; the same compound was obtained more conveniently from the mixture of *cis*-fused isomers IIIa and IIIb by methylation and subsequent recrystallization from pentane.

Treatment of the tertiary alcohol from IIIa in tetrahydrofuran with 40% aqueous sulfuric acid at 0 to -5° for 15 min., and further at 25° for 2 hr., gave synthetic α -caryophyllene alcohol (approximately 50% yield), m.p. 118–118.5°, undepressed upon admixture with authentic material.⁹ The n.m.r. and infrared spectra of the synthetic and naturally derived α -caryophyllene alcohol were identical. The former showed peaks due to methyl groups at 0.82 (two CH_3), 0.90 (one CH_3), and 1.03 p.p.m. (one CH_3).

An especially simple mechanistic explanation for the formation of II from humulene by an acid-catalyzed process involves prototropic rearrangement of humulene to the isomeric conjugated triene IV and protonation of IV with subsequent formation of the carbonium ions V, VI, and VII. On the basis of this hypothesis, it is to be expected that the tertiary alcohol obtained by methylation of the ketone III would give rise to α -caryophyllene alcohol under acidic conditions, as is indeed the case.

It is interesting to note that although the intermediate ketone IIIa and the tertiary alcohol derived from it by methylation have four and five asymmetric centers, respectively, and are racemates, the final prod-

(9) We are indebted to Drs. A. Nickon and J. B. DiGiorgio for providing an authentic sample of naturally derived α -caryophyllene alcohol.

uct of the above synthesis, α -caryophyllene alcohol (II), is a symmetric molecule which is classically described as a *meso* form.

Experimental Section¹⁰

Photoaddition of 4,4-Dimethylcyclopentene to 3-Methyl-2-cyclohexen-1-one. 4,4-Dimethylcyclopentene was prepared by the procedure of Kwart and Ford⁶ from dimethyl 3,3-dimethylglutarate. The product had b.p. $75.5\text{--}77^\circ$; n.m.r. peaks at δ 1.04 (six protons; methyl), 2.07 (four protons; methylene), and 5.44 (two olefinic protons). V.p.c. analysis of this compound showed a single peak at retention time 26 min. using a 10-ft. column of 35% of a saturated solution of silver nitrate in $\text{CH}_3\text{O}(\text{CH}_2\text{CH}_2\text{O})_4\text{CH}_3$ on chromosorb P at 45° (He flow 30 ml./min.). The apparatus used for the photoaddition reaction³ consisted of an irradiation vessel fitted with a water-cooled quartz immersion well, a rubber stopple in one side neck for addition, a Dry Ice condenser connected to a mercury U-tube seal on the other side neck, and an argon inlet tube fitted with a glass frit at the bottom of the reaction vessel. The reactor was swept for 30 min. with a current of argon from the bottom inlet, surrounded by aluminum foil, and fully immersed in an outer Dry Ice-ethanol bath (-20°). A solution of 8 g. of 4,4-dimethylcyclopentene⁶ in 25 ml. of purified *n*-pentane was injected by syringe through a rubber stopple, and argon was bubbled constantly through the pentane solution during irradiation with a Type L, 450-w. Hanovia mercury arc and a Corex filter. At the same time, a solution of 2 g. of 3-methyl-2-cyclohexen-1-one⁵ in 5 ml. of purified *n*-pentane was injected slowly by a syringe fitted with a long needle over a period of 3 hr. After completion of addition, irradiation was continued for 1 additional hr. at -20° . The crude photoproduct, obtained by removal of pentane and 4,4-dimethylcyclopentene on a water bath, showed in the infrared spectrum total absence of the unsaturated carbonyl band of the starting cyclohexenone and two peaks assignable to nonconjugated carbonyl at 5.81 (μ , weak) and 5.88 μ . The crude oily product was distilled through a Holtzmann column and after a forerun of 31 mg., b.p. $<70^\circ$ (0.08 mm.), the main fraction (1.6 g.) was obtained, b.p. $70\text{--}78^\circ$ (0.08 mm.); 1.3 g. of a gummy orange residue remained in the flask. The infrared spectrum of this main fraction showed carbonyl peaks at 5.88 (main peak) and at 5.81 μ (shoulder), and the n.m.r. spectrum showed five peaks in the region of δ 0.8–1.25 (δ 0.80, 1.01, 1.07 (small), 1.12, and 1.25 (small)) and no olefinic proton peaks. V.p.c. analysis of this material on a column of 10% fluorosilicone on Diatoport at 185° (He flow 50 ml./min.) showed mainly one peak at a retention time of 23 min. (IIIa) accompanied by two minor peaks of retention time 20.3 (IIIb) and 25.5 (IIIc) min. The ratio of amounts of the photo ketones IIIa, IIIb, and IIIc was 74:12:14, respectively. This mixture of photoproducts was subjected to isomerization under the mild conditions used previously^{7,8} to effect *trans* \rightarrow *cis* conversion in the bicyclo[4.2.0]-octanone-2 series.

The photo ketone mixture (960 mg.) was placed on a column of 50 g. of grade I neutral alumina for 30 min.

(10) Infrared and n.m.r. spectra were determined using carbon tetrachloride as solvent unless otherwise stated and with Perkin-Elmer Infra-Record and Varian A-60 instruments, respectively.

and then eluted with ether. After elution of 91 mg. of a nonpolar impurity, 730 mg. of the equilibrated photomixture was obtained having a single peak in the carbonyl stretching region of the infrared spectrum at 5.88μ . A comparison of n.m.r. spectra showed that the two peaks at 1.07 and 1.25μ had increased in intensity. V.p.c. analysis indicated that the major peak at retention time 23 min. remained, but that the peak at 25.5 min. had completely disappeared, and that at 20.3 min. had increased in intensity; the ratio of the peaks at 23 and 20.3 min. (IIIa:IIIb) was 75:25, respectively. These results indicate that the photo ketone IIIc is a *trans*-fused 6-4 ring system and that IIIb is the corresponding 6-4 *cis*-fused isomer. After equilibration of the photoproduct mixture, the compounds IIIa and IIIb corresponding to the major and minor peaks were isolated by preparative v.p.c. with a 12-ft., 20% fluoro-silicone on Diatoport column at 195° (He flow 190 ml./min.) using an Aerograph "Autoprep" instrument; the retention times were 31 and 27 min., respectively. The infrared spectrum of each isomer showed a strong carbonyl band at 5.88μ . The major isomer showed the *gem*-dimethyl grouping as two equally intense peaks at δ 1.00 and 1.10 in the n.m.r. spectrum and the minor isomer showed the *gem*-dimethyl as peaks at δ 1.07 and 1.24 (equal intensity). The n.m.r. spectrum of each isomer contained a sharp three-proton singlet at δ 0.79 due to the methyl group attached to the 6-4 ring junction.

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found for IIIa: C, 81.15; H, 10.69. Found for IIIb: C, 81.08; H, 10.70.

Methylation of IIIa with Methylolithium. A solution of 40 mg. of the pure ketone IIIa, isolated by v.p.c., in 2 ml. of ether was injected through a rubber stopple by syringe to a stirred solution of methylolithium in ether (2 ml. of 1.99 M solution) under nitrogen with ice cooling. Then the reaction mixture was heated at reflux for 24 hr. under nitrogen. After cooling, the excess methylolithium was decomposed by ice-water and the resulting ethereal solution was separated, washed with saturated salt solution, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 45 mg. of semi-solid product, which was dissolved in a minimum amount of pentane and refrigerated. Filtration of the crystals and washing with cold pentane afforded 28 mg. (65%) of crystalline tertiary alcohol. Recrystallization from pentane gave the analytical sample as needles, m.p. $97-98^\circ$, showing hydroxyl absorption in the infrared at 2.67 and 2.84μ and no carbonyl absorption. The n.m.r. spectrum exhibited two equally intense peaks at δ 0.81 and 0.90 due to the *gem*-dimethyl groups, a sharp peak at 1.09 due to the carbinyl methyl group, and a sharp peak due to the methyl group attached to the 4-6 junction at 1.09

(shifted because of the 1,3-diaxial interaction with the hydroxyl group).

Anal. Calcd. for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.01; H, 11.85.

Methylation of the Photoproduct Mixture (IIIa and IIIb) with Methylolithium. A solution of 206 mg. of photoproduct mixture⁴ IIIa and IIIb in 5 ml. of ether was treated with a solution of methylolithium in ether as described above to give 240 mg. of crude product. Recrystallization from pentane gave 83 mg. of tertiary alcohol, m.p. $97-98^\circ$, which was identical with the above-described sample prepared from pure ketone IIIa. The oily filtrate was chromatographed over 7.5 g. of silica gel (Davison). Benzene-ether mixture (95:5) eluted first 37 mg. of oily, nonhydroxylic material, then 64 mg. of an oily mixture of alcohols which appears to be produced from IIIb, and finally 48 mg. of crystalline material which was recrystallized from pentane to give 36 mg. of tertiary alcohol from IIIa, m.p. $97-98^\circ$.

α -Caryophyllene Alcohol. To a solution of 80 mg. of the above tertiary alcohol from IIIa in 5 ml. of tetrahydrofuran was added dropwise 1 ml. of 40% sulfuric acid (v./v.) with cooling in an ice-salt bath (-5°) over a period of 5 min. The reaction mixture was stirred for 15 min. at 0° , then for 2 hr. with the bath removed. After concentration at 20 mm. to remove most of the tetrahydrofuran, the acidic aqueous suspension was diluted with saturated salt solution and the product was extracted with ether. The ethereal solution was washed with saturated salt solution and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 67 mg. of crude product which was chromatographed on 2 g. of Davison silica gel with benzene as eluting solvent. After elution of 14 mg. of oily material which appeared to be olefinic (infrared), 40 mg. of crystalline α -caryophyllene alcohol was obtained (50% yield). Recrystallization from pentane gave 28 mg. of pure α -caryophyllene alcohol as prisms, m.p. $117.5-118.5^\circ$ (micro hot stage), m.p. $118-118.5^\circ$ (capillary tube). A mixture melting point with an authentic sample⁹ derived from natural humulene showed no depression. The infrared spectrum of the synthetic alcohol was absolutely identical with that of the authentic sample ($CHCl_3$ and CS_2). The n.m.r. spectra of synthetic and naturally derived materials were identical and included a peak due to two methyl groups at δ 0.82 (6 H) and the two peaks of equal intensity due to the *gem*-dimethyl groups at 0.90 and 1.03.

Anal. Calcd. for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.14; H, 11.77.

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