The Total Synthesis of Helminthosporal

E. J. Corey and Shigeo Nozoe

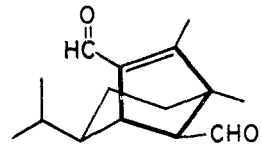
Contribution from the Converse Laboratory of Harvard University, Cambridge, Massachusetts 02138. *Received August 5, 1965*

(−)-Carvomenthone (IIa) has been converted to the naturally occurring toxin helminthosporal (I) by a nine-step synthesis.

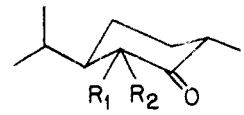
Helminthosporal is a crop destroying toxin which has been isolated[1] from the fungus *Helminthosporium sativum* (recently reclassified as *Bipolaris sorokiniana* (Sacc. in Sorok) Shoemaker). The constitution I (exclusive of absolute configuration) has been assigned to this important natural product on the basis of an interesting degradative study.[2] We report here the total synthesis of helminthosporal by a method which confirms the previous structural conclusions and which additionally allows the designation of absolute configuration.[3]

(−)-Carvomenthone[4,5] (IIa) was converted *via* the known α-hydroxymethylene derivative[6] to the diketoaldehyde IIb using methyl vinyl ketone and triethylamine at room temperature (3 days, 71%).[7] IIb was deformylated by 2% ethanolic potassium carbonate at reflux (16 hr.) to give the diketone IIc in 70% yield. The use of more strongly basic conditions, *e.g.*, sodium methoxide in methanol, proved to be much less satisfactory for this process.

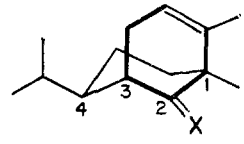
The next objective after the obtention of the diketone IIc was the establishment of a bicyclo[3.3.1]nonene skeleton by an aldol condensation involving the side-chain carbonyl and the distal α carbon of the cyclohexanone unit, the result of which would be formation of the unsaturated, bridged ketone IIIa. However, it will be noted that IIc is a typical 1,5-dicarbonyl intermediate for the Robinson annulation sequence which leads to the generation of a new fused six-membered ring rather than a bridged ring. It would be reasonable to expect that the base-catalyzed intramolecular aldol cyclization of IIc would follow predominantly the Robinson course with the pathway leading to the bridged ring. It would be reasonable to expect that the base-catalyzed intramolecular aldol cyclization of IIc would follow predominantly the Robinson course with the pathway leading to the bridged ring system as a less important accompanying reaction.[8] However, there were a number of indications that under acid



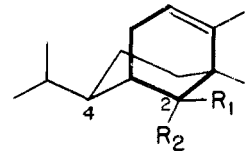
I



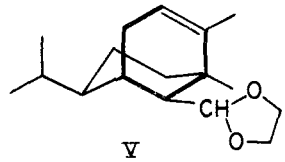
IIa, $R_1 = H; R_2 = H$
IIb, $R_1 = CH_2CH_2COCH_3$; $R_2 =$ CHO
IIc, $R_1 = CH_2CH_2COCH_3$; $R_2 = H$



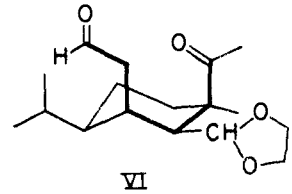
IIIa, X = O
IIIb, X = $CHOCH_3$



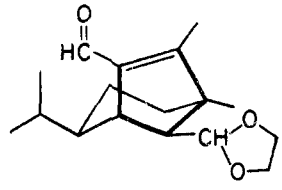
IVa, $R_1 = H$; $R_2 = OH$
IVb, $R_1 = OH$; $R_2 = H$



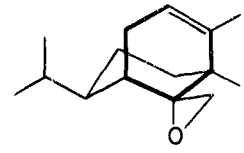
V



VI

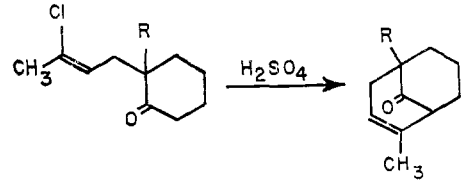


VII



VIII

catalysis the cyclization of IIc to the bridged ring system IIIa might be more favorable than the cyclization to an octalin derivative. The cyclization of substances of type A (*e.g.*, R = CH_3, $COOC_2H_5$) in sulfuric acid as medium produces mainly the bridged ring products of type B, presumably *via* an intermediate 1,5-diketone.[9] Consequently, the experiments which seemed apposite to the conversion of IIc to IIIa were those involving



B

acidic reagents; this approach was effective. Treat-

(1) P. de Mayo, E. Y. Spencer, and R. W. White, *Can. J. Chem.*, **39**, 1608 (1961).

(2) P. de Mayo, E. Y. Spencer, and R. W. White, *ibid.*, **41**, 2996 (1963); *J. Am. Chem. Soc.*, **84**, 494 (1962).

(3) For a preliminary account of this work see E. J. Corey and S. Nozoe, *ibid.*, **85**, 3527 (1963).

(4) Prepared by hydrogenation of (+)-carvone over palladium–alumina catalyst: see E. S. Rothman and A. R. Day, *ibid.*, **76**, 111 (1954).

(5) Formal total syntheses of both (−)- and (+)-carvomenthone are provided by the terpene literature. For example, a route for the (−)-isomer appears in the series: (a) W. H. Perkin, Jr., *J. Chem. Soc.*, **85**, 654 (1904); K. Alder and W. Vogt, *Ann.*, 564, 109 (1949); (b) A. T. Fuller and J. Kenyon, *J. Chem. Soc.*, 125, 2304 (1924); (c) K. Fujita and T. Matsuura, *J. Sci. Hiroshima Univ.*, **A18**, 455 (1955); *Chem. Abstr.*, **50**, 10682 (1956); (d) M. G. Vavon, *Compt. rend.*, **153**, 70 (1911).

(6) V. Sýkora, J. Černy, V. Herout, and F. Šorm., *Collection Czech. Chem. Commun.*, **19**, 566 (1954).

(7) See R. B. Turner, D. E. Nettleton, Jr., and R. Ferebee, *J. Am. Chem. Soc.*, **78**, 5923 (1956), for an analogous procedure.

(8) The formation of bridged-ring products such as IIIa, as a side reaction in the Robinson annulation process, has been discussed recently by W. S. Johnson, J. J. Korst, R. A. Clement, and J. Dutta, *ibid.*, **82**, 614 (1960).

(9) See S. Julia, *Bull. soc. chim. France*, **21**, 780 (1954), and references cited therein, and also Y.-L. Chow, *Tetrahedron Letters*, **21**, 1337 (1964).

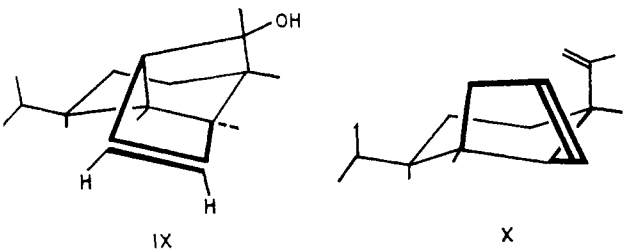
ment of the diketone IIc with boron trifluoride in methylene chloride solution at 25° (16 hr.) afforded in 40% yield two bridged keto olefins (ratio 4:1) which are considered to be IIIa and its C-4 epimer. The mixture of liquid epimers was resolved by vapor phase chromatography (v.p.c.) and both isomers were obtained in pure condition in this way. The major epimer, regarded as IIIa, was readily purified on a larger scale *via* the crystalline semicarbazone derivative by recrystallization; the infrared, ultraviolet, and nuclear magnetic resonance (n.m.r.) spectra of this substance are consistent with the assigned structure and clearly exclude the alternative octalone system, *i.e.*, the conjugated enone. The assignment of configuration at C-4 in the major epimer as shown in IIIa (equatorial isopropyl) rests on chemical and physical data. The reduction of the major epimer with lithium aluminum hydride produces a mixture of epimeric secondary alcohols in a ratio 4:1, whereas the reduction under the same conditions of the minor bridged unsaturated ketone mentioned above leads to a single secondary alcohol. The reasonable assumption that the axial isopropyl group in the C-4 epimer of IIIa would strongly inhibit a *cis* approach of the aluminum hydride anion leads to the conclusion that the ketone which gives a single alcohol by reduction is the 4-epimer of IIIa, *i.e.*, that the major ketone is IIIa. As is required by this argument the predominating course of reduction of both IIIa and its C-4 epimer is that which produces an hydroxyl with axial orientation of the cyclohexane ring (IVa and the C-4 epimer) as is indicated by n.m.r. data. The n.m.r. peak due to the CHO proton is at δ 3.54 for IVa and at 3.48 for the C-4 epimer; the corresponding proton in the spectrum of the minor alcohol from IIIa (IVb) shows a peak at 3.10.[10]

It is interesting to note that the proportion of the two unsaturated bridged ring ketones, IIIa and its C-4 epimer, produced from IIc varied with the acidic reagent and the reaction conditions (see the Experimental Section). In view of the assignment of IIIa to the predominating epimeric bridged ring ketone and the formulation I for helminthosporal the remaining synthetic transformations were carried out with the major epimer which, in fact, must certainly be IIIa since it led eventually to I.

Reaction of the unsaturated ketone IIIa with methoxymethylene triphenylphosphorane in dimethyl sulfoxide[11] gave a 90% yield of the Wittig product IIIb which was further transformed into the ethylene acetal V (together with smaller amounts of the C-2 epimer) with ethylene glycol–benzene–*p*-toluenesulfonic acid at reflux (1 hr., 86% yield). Hydroxylation of V with osmium tetroxide followed by oxidation of the diol with lead tetraacetate lead to the keto aldehyde VI (80%), infrared maxima at 5.78 and 5.87 μ as expected for aldehydic and ketonic carbonyl functions. Treatment of VI with dilute ethanolic base resulted in the formation of the unsaturated aldehyde VII, the monoethylene acetal of helminthosporal, and this was converted to helminthosporal by acid-catalyzed hydrolysis under mild conditions. The properties of the synthetic product were completely identical with those of naturally derived helminthosporal (I) (see the Experimental Section), including the optical rotation. Since the absolute configuration of the starting material for the synthesis, (−)-carvomenthone, is as shown in IIa, it follows that formula I correctly depicts the absolute configuration of natural, levorotatory, helminthosporal. The orientation of the formyl group at C-2 in helminthosporal as shown in I is indicated by n.m.r. data. It is noteworthy that the formyl group at C-2 appears to be in the more stable orientation in helminthosporal since this substance resists isomerization under the influence of an acid catalyst. The occurrence of both C-2 epimers of the intermediate V–VII in the synthesis is consequently not a problem.

An alternative route to helminthosporal consists of the reaction of the ketone IIIa with the methylene transfer agent dimethylsulfonium methylide[12] to give the oxirane VIII (95% yield, configuration at C-2 unspecified, subsequent treatment with zinc bromide–benzene (30% yield) to form a mixture of C-2 epimeric aldehydes, and conversion to V (and the C-2 epimer) with ethylene glycol under acid catalysis.

The method employed in the present synthetic approach to helminthosporal is but one of several interesting possibilities. Another which appears to be attractive is of relevance to the suggested[13,13a] biosynthesis of helminthosporal from tricyclic, farnesol derived intermediates as IX. Helminthosporal ought to be readily derivable from IX by oxidative fission of the unsaturated linkage followed by elimination of water from the resulting β-hydroxy dialdehyde. A related scheme which is simpler in some respects, but nonbiogenetic, involves the oxidation of both double bonds in the bicyclic diene X.



IX X

Experimental Section[14]

Condensation of Hydroxymethylenecarvomenthone with Methyl Vinyl Ketone. Hydroxymethylenecarvomenthone was prepared by the procedure of Šorm and co-workers[6] from (−)-carvomenthone.[4] To a mixture of 9.1 g. of hydroxymethylenecarvomenthone and 10.5 g. of freshly distilled methyl vinyl ketone was added 6.5 g. of triethylamine with swirling and cooling.[7] The reaction mixture was cooled in an ice bath for 1 hr. and then allowed to stand at 25° for 3 days after which time the unreacted methyl vinyl ketone and triethylamine were removed by distillation under reduced pressure,

(10) The carbinyl proton resonance in IV (R_1 = OH, R_2 = H) can be expected to occur at higher field than that in the epimeric IV (R_1 = H, R_2 = OH) by *ca.* 0.5 p.p.m. See, *e.g.*, A. H. Lewin and S. Winstein, *J. Am. Chem. Soc.*, **84**, 2464 (1962); R. R. Fraser, *Can. J. Chem.*, **40**, 78 (1962).

(11) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

(12) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 867 (1962).

(13) P. de Mayo, J. R. Robinson, E. Y. Spencer, and R. W. White, *Experientia*, **18**, 359 (1962).

(13a) Note Added in Proof. See also P. de Mayo and R. E. Williams, *J. Am. Chem. Soc.*, **87**, 3275 (1965), for the isolation of sativene, a hypothetical percursor of helminthosporal.

(14) Infrared and n.m.r. spectra were determined using carbon tetrachloride as solvent unless otherwise indicated.

and the residue was dissolved in ether. The ethereal solution was washed successively with dilute hydrochloric acid, dilute aqueous sodium hydroxide, and water, and dried over sodium sulfate. Evaporation of the solvent gave 8.9 g. (71% yield) of the diketoaldehyde IIb. The infrared spectrum showed absorption at 3.69 (aldehyde) and at 5.84 and 5.92 μ (aldehyde and ketone). In the n.m.r. spectrum peaks appeared at δ 0.82, 0.93, and 1.04 due to three methyl groups attached to saturated carbon, at 2.10 due to C-acetyl protons, and at 9.82 due to a formyl proton. This product was satisfactory for the subsequent reaction.

Deformylation of the Diketoaldehyde IIb. To a solution of 46.5 g. of the diketoaldehyde IIb in 1000 ml. of ethanol was added a solution of 3.2 g. of potassium carbonate in 20 ml. of water. The reaction mixture was heated at reflux for 20 hr. under nitrogen. The solvent was evaporated under reduced pressure and the residue was dissolved in ether. The ethereal solution was washed with water, dried, and evaporated to give crude product which was purified by passage through an alumina column (120 g. of neutral alumina, activity 3) with elution by pentane. Distillation through a short-path apparatus gave 28.7 g. (70%) of the diketo compound IIc, b.p. 130–136° (bath temp.) (0.03 mm.), as a pale yellow oil. The infrared spectrum showed carbonyl absorption at 5.82 μ. The n.m.r. spectrum exhibited six peaks at δ 0.87 to 1.02 (doublet) due to three methyl groups attached to saturated carbon and at 2.05 due to C-acetyl protons, and showed no formyl proton.

Anal. Calcd. for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.93; H, 10.83.

Cyclization of Diketone IIc. Boron trifluoride gas was passed into a cold solution of 35 g. of diketone IIc in 2.5 l. of methylene chloride until the solution (kept at 0°) became turbid (at saturation). The reaction flask was stoppered tightly and allowed to stand for 16 hr. at 25°. The color of the solution turned to a reddish brown, and a small amount of oily substance separated. The methylene chloride solution was washed with water, dried over sodium sulfate, and evaporated to give 30 g. of brown crude oily product, which was passed through 175 g. of neutral alumina (activity 3) using *n*-pentane for elution. Evaporation of the solvent and distillation of the residue gave 13 g. (40% yield) of bridged keto olefin III, b.p. 69–71°, (0.05 mm.), showing no high-intensity absorption in the ultraviolet above 210 mμ. The infrared spectrum showed nonconjugated carbonyl absorption at 5.82 μ.

This product was found to consist of two isomeric bridged keto olefins, III and the C-4 epimer, in a ratio of about 4:1. This composition was determined by vapor phase chromatography on an 8-ft. 20% fluorosilicone column (column temp. 210° and He flow rate 40 ml./min.); two peaks appeared, one at a retention time of 20 min. (major isomer IIIa) and the other at 16 min. (minor isomer 4-epi IIIa). A pure sample of the major isomer IIIa was collected by v.p.c. using the same column and under the same conditions as described above. This compound had infrared maximum 5.83 μ (C=O) and peaks in the n.m.r. at δ 0.80, 0.90, and 1.01 due to three methyl groups attached to saturated carbon, at 1.60 (doublet) due to a methyl attached to unsaturated carbon, and at 5.60 due to an olefinic proton.

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.54; H, 10.77.

To obtain a pure sample of the minor isomer 4-epi IIIa, the isomeric mixture (2.5 g.) was chromatographed on 96 g. of florisil using for elution a benzene–*n*-pentane mixture (5:95). The first eluted fractions were enriched in 4-epi IIIa and these fractions were purified further by v.p.c. using an 11-ft. 10% fluorosilicone column (180°, retention time, 16.6 min., He flow 50 ml./min.).

The n.m.r. spectrum of the minor isomer 4-epi IIIa so obtained was similar to that of the major isomer IIIa, but the infrared spectrum was clearly different in the finger-print region; infrared maximum 5.82 μ (C=O). The n.m.r. spectrum was characterized by peaks at δ 0.82, 0.91, and 1.00 due to three methyl groups attached to saturated carbon, at 1.63 (doublet) due to one methyl group attached to unsaturated carbon, and at 5.60 due to one olefinic proton.

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.22, H, 10.71.

A large-scale separation of the major isomer IIIa (equatorial isopropyl group at C-4, see Discussion) which was used for this total synthesis was accomplished *via* the crystalline semicarbazone. Two different melting points were observed for the semicarbazone prepared in the usual manner and recrystallized from ethanol, m.p. 156–158° and 177–179°, but each of these was hydrolyzed with 12 *N* hydrochloric acid to generate identical samples of pure IIIa (90% yield of the theoretical amount), b.p. 66–68° (0.06 mm.). The infrared spectrum was identical with that of the sample collected by v.p.c. The unsaturated ketone IIIa is a liquid at room temperature but becomes crystalline on refrigeration at −20°. The semicarbazone of the minor isomer 4-epi IIIa was not isolated from the mixture.

It was found that the diketoaldehyde IIb also underwent cyclization in the same manner to give the bridged keto olefin mixture directly with boron trifluoride in methylene chloride solution. However, the yield was very poor (5–10%).

Cyclization of the Diketo Compound IIc with Stannic Chloride. The ratio of the bridged keto olefins IIIa and 4-epi IIIa could be altered by changing reaction conditions. A mixture of 4.4 g. of diketone IIc and 5.2 g. of stannic chloride in 50 ml. of benzene was heated at reflux for 45 min. The product was isolated in the usual way and purified by chromatography on alumina and distillation to give 2.4 g. of the bridged keto olefin mixture. The ratio of the two epimers in this product was determined by v.p.c. using an 8 ft. 20% fluorosilicone column, and was approximately 1:1 (210°, He flow 50 ml./min.). This product contained a less polar impurity with a retention time of 7 min. (*ca.* 5–10%).

Lithium Aluminum Hydride Reduction of the Bridged Keto Olefin IIIa and the 4-Epimer. To a solution of 200 mg. of the bridged keto olefin IIIa, purified *via* the semicarbazone in 2 ml. of ether was added a solution of 30 mg. of lithium aluminum hydride in 2 ml. of ether with stirring. The mixture was stirred for 6 hr. at 25°, after which the excess hydride was decomposed with

ice water and the product was isolated in the usual way. The alcohol (160 mg.) was obtained as a colorless oil showing no CO absorption in the infrared spectrum.

Vapor phase chromatography showed the presence of two isomeric alcohols (IVa and IVb) in a ratio of about 4:1 with retention times of 17.3 (major alcohol) and 21 min. (minor alcohol) on an 11-ft. 10% fluorosilicone column (180° and He flow rate 50 ml./min.). The mixture in *n*-pentane was chromatographed on Florisil (30-fold by weight) and eluted with increasing amounts of benzene in *n*-pentane. Elution with benzene–*n*-pentane in the range 4:96 to 8:92 gave 77 mg. of the major alcohol IVa as a colorless oil. Analysis by v.p.c. using the same column described above indicated that this material was essentially pure (single peak at retention time of 12.6 min., 190°, He flow rate 55 ml./min.). The infrared spectrum showed hydroxyl absorption at 2.68 and 2.83 μ ($CHCl_3$). The n.m.r. spectrum exhibited peaks at δ 0.79, 0.87, and 0.95 due to two methyls of the isopropyl group, at 0.99 due to an angular methyl, at 1.52 due to a methyl attached to unsaturated carbon, at 3.54 (doublet), a proton of type CHO, and at 5.30, one olefinic proton. The doublet in the n.m.r. spectrum due to the CHO group was shifted to δ 3.83 in pyridine solution. Acetylation of this alcohol with acetic anhydride and pyridine at 40° gave an acetate which showed the doublet due to the CHO proton at δ 4.77; the other features in the n.m.r. spectrum were as expected. Further elution of the column with benzene–*n*-pentane mixture in the range 1:4 to 2:3 gave 24 mg. of the minor alcohol IVb which showed a single peak at a retention time of 15 min. by v.p.c. analysis (same column and same condition as for IVa); infrared maxima ($CHCl_3$) 2.87 and 2.86 μ (OH); n.m.r. peaks at δ 0.82 and 0.93 (pair of doublets) due to methyls of the isopropyl group, at 1.06 due to one angular methyl, at 1.55 (doublet) due to one methyl attached to unsaturated carbon, at 3.10 (doublet) due to the CHO proton, and at 5.47 due to an olefinic proton. The peak due to the CHO proton was moved to δ 3.41 in pyridine solution and occurred at 4.50 in the spectrum of the corresponding acetate from IVb.

The minor epimeric bridged keto olefin, the 4-epimer of IIIa, purified by v.p.c., was reduced with lithium aluminum hydride by the same procedure as described for IIIa to give 36 mg. of oily alcohol, the 4-epimer of IVa. Vapor phase chromatography showed only one peak at a retention time of 15.3 min. on an 11-ft. 10% fluorosilicone column at 180° (He flow rate 50 ml./min., 11.4 min. at 190°); infrared maxima ($CHCl_3$) 2.64 and 2.82 μ (OH); n.m.r. peaks at δ 0.79, 0.89, and 0.99 due to methyls of the isopropyl group, at 0.97 due to one methyl, at 1.53 due to one methyl attached to unsaturated carbon, at 3.48 (doublet) due to the CHO proton, and at 5.33 due to an olefinic proton. The peak due to the CHO proton occurred at δ 3.77 in pyridine solution and at 4.67 in the spectrum of the acetate derivative of the 4-epimer of IVa.

Formation of the Methoxymethylene Compound IIIb by the Wittig Reaction. To a solution of methylsulfinyl carbanion prepared by heating a mixture of 2.40 g. of powdered sodium hydride (0.1 ml.) and 50 ml. of dimethyl sulfoxide at 75° with stirring for 45 min. and cooling to 20° was added a solution of 34.25 g. (0.1 ml.) of methoxymethylene triphenyl phosphonium chloride in 100 ml. of dimethyl sulfoxide with cooling.[11] The resulting solution of the ylide was stirred (room temp.) for 10 min. A solution of 4.12 g. of bridged keto olefin IIIa (0.02 ml.) in 20 ml. of dimethyl sulfoxide was added to the ylide solution and the reaction mixture was stirred at 40° for 12 hr. The entire operation was carried out under a nitrogen atmosphere. The reaction mixture was cooled and poured into 170 ml. of water and the aqueous layer was extracted with *n*-pentane. The pentane layer was washed with 1:1 water–dimethyl sulfoxide solution, and then with saturated sodium chloride solution and dried over sodium sulfate. Evaporation of the solvent gave a crude product containing crystals of triphenylphosphine. The crystals were removed by filtration and washed thoroughly with cold *n*-pentane. The filtrate was evaporated and the residual oil was dissolved in 100 ml. of ether and treated with 2 ml. of 30% hydrogen peroxide dropwise with stirring, and at room temperature for 30 min. This solution was washed successively with water, aqueous sodium bisulfite, and water, dried, and evaporated. The triphenylphosphine oxide in the reaction product was removed by passing a solution of the product in *n*-pentane through 20 g. of neutral alumina (activity 3). Elution with *n*-pentane followed by evaporation of the solvent and distillation of the residue afforded 4.4 g. (90% yield) of methoxymethylene compound, b.p. 95–100° (bath temp.) (0.05 mm.), as a colorless oil. The infrared spectrum showed no carbonyl absorption, a double-bond stretching band at 5.96, and C–O stretching absorption at 8.90 μ. The n.m.r. spectrum exhibits four peaks due to isopropyl methyls at δ 0.83 to 0.94, another due to one methyl attached to saturated carbon at 1.02, a doublet due to one methyl attached to unsaturated carbon at 1.52, one olefinic proton at 5.39 (broad), and one peak due to the vinyl proton of the enol ether group at 5.60 (sharp). The signal due to methoxy methyl was split into two peaks at δ 3.42 and 3.48 which indicates the probable presence of *cis* and *trans* forms of the enol ether function. This was also evident from v.p.c. analysis (12-ft. 10% fluorosilicone column at 180°, He flow rate 60 ml./min.) which showed an unresolved double peak of retention times 10.4 and 11.4 min. (intensity ratio of about 5:3).

Formation of the Oxirane VIII. A mixture of 1.44 g. of powdered sodium hydride and 20 ml. of dimethyl sulfoxide was heated under nitrogen with stirring at 75° until the evolution of hydrogen ceased. The solution was cooled to room temperature, diluted with 20 ml. of dry tetrahydrofuran, and cooled in a salt–ice bath. A solution of 12.2 g. of trimethylsulfonium iodide in 40 ml. of dimethyl sulfoxide was added rapidly and the mixture was stirred for 5 min.[12] A solution of 3.09 g. of the bridged keto olefin IIIa in 5 ml. of tetrahydrofuran was added and the reaction mixture was stirred for 10 min. at 0°, then for 30 min. with the bath removed. The entire operation was carried out under nitrogen. The reaction mixture was diluted with water and the product was extracted with ether. The ether layer was washed with water and dried over potassium carbonate.

Evaporation of the solvent and distillation of the residue afforded 3.14 g. (95% yield) of the oxirane VIII, b.p. 88–90° (bath temp.) (0.05 mm.), as a colorless oil. The infrared spectrum showed no carbonyl ab-

sorption; the n.m.r. spectrum was characterized by peaks at δ 0.75 due to an angular methyl group, four peaks centered at 0.88 due to two methyls of the isopropyl group, at 1.56 due to one methyl attached to unsaturated carbon, at 2.25, 2.32, 2.67, and 2.74 (quartet) due to methylene protons of the epoxide, and at 5.48 due to an olefinic proton.

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.61; H, 10.65.

Formation of the Ethylene Acetal V. A. From the Wittig Product. A mixture of 4.44 g. of methoxymethylene compound IIIb, 6.00 g. of ethylene glycol, and 10 mg. of *p*-toluenesulfonic acid in 80 ml. of benzene was refluxed under nitrogen using a Dean–Stark trap for 1 hr. The reaction mixture was cooled and diluted with *n*-pentane. The pentane–benzene layer was washed successively with dilute sodium bicarbonate solution and water and then dried over sodium sulfate. Evaporation of the solvent and distillation of the residue gave 4.29 g. (86% yield) of the ethylene acetal V, b.p. 115° (bath temp.) (0.03 mm.), which showed strong absorption characteristic of an acetal at 8.80, 8.93, 9.40, and 9.57 μ in the infrared spectrum. In the n.m.r. spectrum peaks due to the OCHO proton appeared at δ 4.70 and 4.97 (both doublets with approximately the same splitting) in a ratio about 1:2. This indicated that the reaction product consisted of the acetals of both epimers of V (at C–2), a point which was also shown by v.p.c. analysis on a 12-ft. 10% fluorosilicone column. Two peaks were observed, one at a retention time of 20.2 min. (major epimer) and the other at 22.2 min. (minor epimer) in a ratio of about 70:30 (180°, and He flow rate 60 ml./min.). The n.m.r. spectrum of the product also showed peaks at δ 0.83, 0.92, and 1.01 due to one methyl and two methyls of isopropyl group, at 1.52 (doublet) due to one methyl attached to unsaturated carbon, at *ca.* 3.79 (multiplet) due to four ethylenic protons of the ethylenedioxy grouping, and at 5.43 due to one olefinic proton.

Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.48; H, 10.66.

B. From the Oxirane VIII. A mixture of 300 mg. of the oxirane VIII and 30 mg. of zinc bromide in 8 ml. of benzene was heated at reflux for 2 hr. under nitrogen. After evaporation of benzene *in vacuo*, the residue was extracted with *n*-pentane. The pentane layer was washed with water, dried, and evaporated to leave 240 mg. of crude aldehyde, which was chromatographed on neutral alumina column (activity 4, 40-fold by weight) and eluted with *n*-pentane. After elution of 104 mg. of unidentified components, 92 mg. of the aldehyde was obtained by elution with the same solvent. The infrared spectrum showed characteristic absorption of an aldehyde at 3.70 and 5.88 mμ. In the n.m.r. spectrum peaks due to a formyl proton occur at δ 9.68 and 9.88 (both doublets). Analysis by v.p.c. using a 12-ft. 10% fluorosilicone column at 210° showed two peaks at retention times of 11.6 min. (minor) and at 13.3 min. (major) in a ratio of about 30:70 (He flow rate 54 ml./min.). Treatment of this product with a 0.5% solution of hydrogen chloride in benzene containing 5% acetic acid, for 18 hr., changed the ratio of the epimeric aldehydes from the 30:70 original value to 20:80. Additional treatment produced no further change; this is evidently the equilibrium mixture. A mixture of 22 mg. of the aldehyde, 30 mg. of ethylene glycol, and a trace of *p*-toluenesulfonic acid in 2 ml. of benzene was subjected to the same procedure as used for the above-described enol methyl ether to give 20 mg. of the corresponding ethylene acetal V. The infrared spectrum of this acetal was indistinguishable from that of the acetal derived from Wittig product IIIb. V.p.c. analysis also showed two peaks at the same retention time (20.2 and 22.2 min.; a small peak due to an impurity at a retention time of 24.8 min. was also observed).

Hydroxylation of the Ethylene Acetal V with Osmium Tetroxide and Cleavage to VI. A mixture of 3.168 g. of the ethylene acetal V and 3.051 g. of osmium tetroxide in 22 ml. of dry pyridine was stirred for 2 hr. under nitrogen (room temp.). To the resulting dark brown solution was added with stirring a solution of 5.4 g. of sodium bisulfite in 90 ml. of water and 54 ml. of pyridine; the mixture was stirred for 2 hr.[15] The product was extracted with ether, and the ethereal layer was washed successively with water, copper sulfate solution, and water, and dried over sodium sulfate. Evaporation of the ether afforded 3.26 g. (91% yield) of the crude glycol as a yellow oil. This crude material was used for the next step of the reaction sequence without further purification. The infrared spectrum showed strong hydroxyl absorption at 2.81 and an acetal band at 9.70 μ ($CHCl_3$).

To a solution of 3.338 g. of the 1,2-glycol in 60 ml. of benzene was added with stirring a suspension of 5.4 g. of lead tetraacetate in 60 ml. of benzene containing 3 ml. of acetic acid over a period of 10 min. The reaction mixture was stirred for 30 min. (room temp.). and then diluted with 120 ml. of *n*-pentane to promote the precipitation of salts. After filtration, the filtrate and washings were concentrated to a volume of 20 ml. under reduced pressure. The pentane solution was washed with aqueous sodium bicarbonate and water and dried over sodium sulfate. Evaporation of the solvent gave 3.26 g. of the crude ketoaldehyde VI which was passed through a neutral alumina column (activity 5, 16 g.), using pentane for elution to give 2.99 g. (90% yield) of the ketoaldehyde VI; the infrared spectrum showed absorption at 3.68 (aldehyde), at 5.78 and 5.87 (aldehyde and ketone), and at 8.84 μ (acetal).

Anal. Calcd. for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.80; H, 8.97.

Cyclization of the Ketoaldehyde VI with Base. A solution of 2.50 g. of the ketoaldehyde VI and 100 mg. of sodium hydroxide in 100 ml. of anhydrous ethanol was allowed to stand for 30 min. under nitrogen at room temperature. The ethanol was evaporated under reduced pressure and the residue was extracted with ether. The ethereal solution was washed with water, dried, and evaporated to give 2.315 g. of crude oily product. The crude material was chromatographed on 30 g. of neutral alumina (activity 3) using pentane for elution to give 1.24 g. (50% yield) of the unsaturated aldehyde VII as a pale yellow oil. This product was satisfactory for the subsequent reaction. The infrared spectrum showed absorption at 3.67 (aldehyde), 5.98 (unsaturated aldehyde), 8.60–9.00 (acetal), 6.17 and μ (double bond). Ultraviolet absorption (ethanol) showed: λ_{max} 266 mμ (ε 9900).

(15) J. S. Baran, *J. Org. Chem.*, **25**, 257 (1960).

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 $C_{17}H_{26}O_3$: 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), $[\alpha]^{18}D$ −47.8 (*c* 1.00, chloroform), λ_{max}^{EtOH} 266 mμ (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 $C_{29}H_{30}N_4O_{12}$: C, 55.59; H, 4.83. Found: C, 55.43; H, 4.89.

Acknowledgment. This work was supported by the National Institutes of Health and the National Science Foundation.

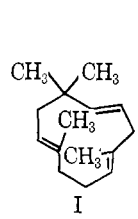
The Total Synthesis of α-Caryophyllene Alcohol

E. J. Corey and Shigeo Nozoe

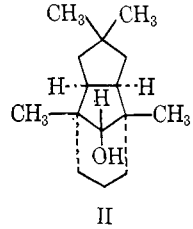
Contribution from the Converse Laboratory of Harvard University, Cambridge, Massachusetts 02138. *Received August 5, 1965*

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 (methyllithium) 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 study[2] 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]



I



II

Slow addition by syringe of a solution of 3-methyl-2-cyclohexenone[5] in pentane to a solution of 4,4-dimethylcyclopentene[6] (*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. Armbrecht, 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).