2-Chloro-3,5-dimethoxyphenol.[29]—To a solution of 3,5-dimethoxyphenol (20 g.) in 240 cc. of distilled chloroform, 20 g. of sulfuryl chloride (distilled) dissolved in 80 cc. of chloroform was added dropwise in a period of 1 hr., under reflux. The resulting solution was refluxed for 3 hr. more and was then allowed to stand at room temperature for 48 hr. After evaporation to dryness, the residual dark oil was twice extracted with boiling *n*-hexane (first extract, 400 ml.; second, 200 ml.). The combined extracts were allowed to cool. After filtering off 1.1 g. of 4-chloro-3,5-dimethoxyphenol, m.p. 115–130° (reported[23] 132–133°), as the first crop, 10 g. of 2-chloro-3,5-dimethoxyphenol separated as colorless needles, m.p. 58–60°. After recrystallization it melted at 64–65° (reported[23] m.p. 58–59°). In another experiment, the crude mixture was chromatographed over thirty times its weight of alumina (acid-washed). Elution with benzene gave about the same yield as before, m.p. 65°.

2-Hydroxy-3α-dichloro-4,6-dimethoxyacetophenone (XII).[23]—2-Chloro-3,5-dimethoxyphenol (2.62 g.) was dissolved in 3.7 g. of nitrobenzene and to the resulting solution 3.27 g. of chloroacetyl chloride and 3.5 g. of anhydrous aluminum chloride were added successively. The mixture was stirred for 20 hr. at room temperature, then a mixture of 40 ml. of ice-cold water and 10 ml. of concentrated hydrochloric acid was added, and the nitrobenzene was removed by steam distillation. The residual mixture was filtered, and the solid was collected and washed with water, methanol, and ether, successively. The resulting light yellow powder was recrystallized from dioxane, affording 2 g. of XII as yellow needles, m.p. 216° dec. (reported[23] m.p. 211° dec.).

7-Chloro-4,6-dimethoxycoumaran-3-one (II).[23]—A solution of 10 g. of XII in 120 ml. of 95% ethanol containing 11.8 g. of hydrated sodium acetate was refluxed for 2 hr. The solvent was then removed *in vacuo*, and the solid residue was thoroughly washed with water on a filter. The remaining solid was recrystallized from dioxane giving 7.2 g. of 7-chloro-4,6-dimethoxycoumaran-3-one (II) as colorless needles, m.p. 218–225° dec. (reported[23] m.p. 210–220° dec.; t.l.c. silica plate, *n*-butyl acetate: R_f 0.50 (blue fluorescence in ultraviolet light).

Epimerization of Natural (+)-Griseofulvin.—In order to check the ability of the silica plates to separate griseofulvin from epigriseofulvin (XIII), (+)-griseofulvin was partially converted to (+)-epigriseofulvin by the method of Brossi, *et al.*[24a]: Natural (+)-griseofulvin (27 mg.) was dissolved in 2 ml. of 1 *N* methanolic sodium methoxide. The solution was heated at 70° under nitrogen for 3 hr., then cooled to room temperature. This solution was used for t.l.c., silica plate, *n*-butyl acetate, solvent front 11 cm.: two ultraviolet fluorescent (violet) spots (R_f's 0.36 (griseofulvin) and 0.33 (epigriseofulvin); close, but but definite separation). On spraying with 0.2% $KMnO_4$, griseofulvin appears as a bright yellow spot; epigriseofulvin is invisible.

dl-**Griseofulvin (I).**—A solution of potassium *t*-butoxide (prepared by adding 0.048 g. of potassium to 10 ml. of absolute *t*-butyl alcohol) was added to 500 ml. of diglyme (distilled from lithium aluminum hydride under nitrogen). In this mixture 7-chloro-4,6-dimethoxycoumaran-3-one (II) (2.00 g., 0.0088 mole) was dissolved; then 1.00 g. (0.0081 mole) of methoxyethynyl propenyl ketone (freshly distilled) was added at once. The resulting solution was stirred at room temperature for 20 hr. under nitrogen. Glacial acetic acid (2 ml.) was then added and the mixture was poured into water (about 1 l.) and extracted with chloroform (3 times); the combined chloroform extracts were washed with water (3 times), then dried over magnesium sulfate. After evaporating the chloroform, the remaining diglyme was removed by heating to 60° at 0.001 mm. The residual reddish powder was chromatographed over acid-washed alumina (200 g.). Elution with benzene and 5, 10, and 20% ether–benzene, successively, yielded 0.63 g. of the starting material II. Further elution with 20, 50, and 100% ether–benzene gave 0.220 g. of partially crystalline material which was shown to contain *dl*-griseofulvin, as its main component, by t.l.c. analysis. A further 1.2 g. of amorphous solid, which also contained a small amount of griseofulvin according to t.l.c., was eluted with chloroform.

The middle fraction was rechromatographed over 8 g. of Woelm nonalkaline alumina, activity grade I, and the band which gave a blue fluorescence under ultraviolet light was eluted with 50% ether–benzene, giving 100 mg. of *dl*-griseofulvin, m.p. 224–226° (Kofler hot stage), homogeneous by t.l.c. analysis. It was sublimed (150–160° (diffusion pump)) and recrystallized from ethyl acetate–*n*-hexane, giving plates, m.p. 212–213°, then 225–226° (Kofler hot stage) (reported 214–216°,[24a] 228–230°,[24b] 222–224°[24c]); λ_{max}^{MeOH} 318 (ε 5200), 286 (ε 23,000), 245 (sh) (ε 16,000), 230 mμ (ε 21,300) (for comparison with the ultraviolet spectrum of natural (+)-griseofulvin, see Fig. 4, 5); $\lambda_{max}^{CHCl_3}$ 5.93 (s), 6.07 (m), 6.24 (s), 6.33 (s) μ. (For comparison with the infrared spectrum of natural (+) griseofulvin, see Fig. 6, 7.) Analysis by t.l.c., silica plate, *n*-butyl acetate, gave R_f 0.36 (0.2% $KMnO_4$, yellow; ultraviolet, violet fluorescence).

Anal. Calcd. for $C_{17}H_{17}O_6Cl$: C, 57.80; H, 4.86. Found: C, 58.00; H, 4.87.

An additional 43 mg. of *dl*-griseofulvin was obtained by rough rechromatographing of the last fraction from the first chromatography over 30 g. of acid-washed alumina. The combined material from the benzene, 50% ether–benzene, and ether eluates (0.130 g.) was further purified by preparative t.l.c. in two batches, affording 43 mg. of *dl*-griseofulvin, m.p. 224–226°. Thus the total yield of *dl*-griseofulvin was 0.143 g. (5% of the theoretical; 7%, if the recovery of 0.63 g. of II is taken into account).[30,31]

(29) A slight modification of the procedure of J. McMillan, T. P. C. Mulholland, A. W. Dakins, and G. Ward, *J. Chem. Soc.*, 429 (1954).

(30) The over-all yield by this relatively short route does not compare unfavorably with that obtained in the other reported syntheses; *cf.* ref. 24.

(31) This work was supported by grants from the National Institutes of Health and the National Science Foundation.

[CONTRIBUTION FROM THE CONVERSE LABORATORY OF HARVARD UNIVERSITY, CAMBRIDGE 38, MASS.]

Total Synthesis of Longifolene[1]

BY E. J. COREY, MASAJI OHNO, RAJAT B. MITRA, AND PAUL A. VATAKENCHERRY

RECEIVED JULY 12, 1963

An account is given of a total synthesis of longifolene starting from resorcinol by operations which generate structure II unambiguously. The complex bridged-ring system of longifolene was produced by internal cyclization of a homodecalin derivative which in turn was constructed from 1,6-dioxo-8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene (IX) by a novel ring expansion. Resolution was accomplished using L(+)-2,3-butanedithiol which served an additional role in carbonyl protection and reduction.

Introduction

The virtuosity of Nature in the construction of intricate molecules is nowhere more evident than in those families which are described broadly as isoprenoids. Within this group an especially concentrated and impressive display of this synthetic expertise can be found in the sesquiterpene class. Here diverse and unusual arrangements of rings and functionality abound notwithstanding a common origin from the same acyclic C_{15}-precursor, as now seems probable. This remarkable variety of design is perhaps the principal reason for the structural chemist's deep interest in this field of natural products, a concern which is out of all proportion to present practical value. At the same time these structures are highly relevant to the study of chemical synthesis since they challenge present principles and methodology, especially in respect to a fundamental element of synthesis, the construction of ring systems and networks of carbon. In this paper and that which follows we report synthetic studies on two of the most interesting sequiterpene structures, longifolene and caryophyllene.[2,3]

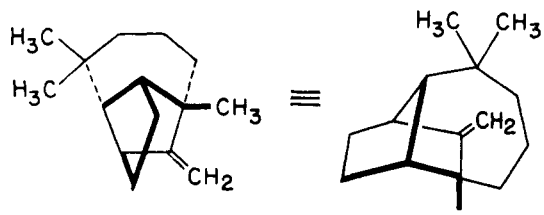
(1) For a preliminary communication on this work see E. J. Corey, M. Ohno, P. A. Vatakencherry, and R. B. Mitra, *J. Am. Chem. Soc.*, **83**, 1251 (1961).

(2) For previous publications from our group on the synthesis of sesquiterpenes in the santalene series see (a) E. J. Corey, S. W. Chow, and R. A. Scherrer, *ibid.*, **79**, 5773 (1957); (b) E. J. Corey, R. Hartmann, and P. A. Vatakencherry, *ibid.*, **84**, 2611 (1962).

(3) A measure of current interest and progress in the synthesis of sesquiterpenes is provided by a partial list of other recently solved problems

The structure of longifolene, long an unsolved and complex chemical problem,[4] was revealed in a dramatic way by an X-ray crystallographic study[5] which presaged the growing importance of this technique in the investigation of complex natural products. This work led to the formulation of the known hydrochloride derivative ($C_{15}H_{25}Cl$) as I and, in combination with chemical results,[6] indicated the structure II for longifolene itself.[7] This assignment is fully supported by subsequent degradative studies which illuminate interesting new aspects of the chemistry of longifolene.[8,9] Apart from the complexity of the molecular structure, several features merit attention: (1) the molecule is related to the simpler camphene–borneol system; (2) the arrangement of carbon in II is such that the system can be constructed from farnesol (or equivalent)

I

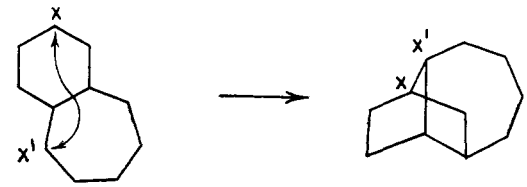


II

by a sequence of cationic addition–elimination processes, in consonance with biosynthetic concepts which presently afford a satisfactory correlation of the known sesquiterpene structures[10]; and (3) the total ring system can be considered in various terms; for example, it can be regarded as a bicyclo[2.2.1]heptane arrangement with a chain of four carbon atoms spanning two of the bridges, or as a bicyclo[5.4.0]undecane fused ring structure with an extra bond joining the six- and seven-membered rings. This last point is important in the planning of a synthesis. Indeed, one of the most important aspects of the synthetic problem in the case of longifolene, and also with other structures having sets of interconnected bridges, is the need to recognize an extraordinary number of very different alternatives for assemblage of the carbon network. The first task in complex molecular synthesis of this sort should be an exhaustive analysis of the topological properties of the carbon network to define the range of possible precursors, both of bridged-ring and fused-ring type, from which the desired skeleton can be produced by the establishment of one or two connecting bonds. The ultimate choice (or choices) may then be made in terms of the considerations which are general to the design of any complex organic synthesis.

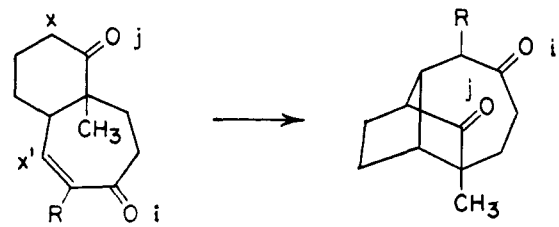
Synthetic Plan.—In this section there follows an abbreviated and general description of the synthetic scheme which was pursued to completion. For simplicity, the consideration of alternative construction patterns is deferred until a later part of this paper; the basis for the choice of plan will be clear in the end.

A special situation exists in the problem of longifolene synthesis, owing to the interconvertibility by rearrangement of longifolene (II) and its hydrochloride (I) which broadens the choice of specific synthetic intermediates. Both, I and II possess the same basic carbocyclic system (mirror images, however!) and so it happens that the plan chosen for construction of the carbon network, specifically the change III → IV, might be used *either* with a substitution pattern which will lead to I *or* one which will produce II. One of the key features of this



III IV

route to the ring system of I and II is the commonplace character of the precursor III, a simple homodecalin type. After the decision to proceed from a starting material of general type III, subordinate details were considered and a definite reaction was marked out for the key step, the conversion of V to VI by intramolecular Michael addition. This represents the choice of a direct route to longifolene rather than an alternative *via* the hydrochloride I. Although the change V → VI



V VI

superficially would seem unusual and perhaps unreasonable, some confidence in its validity seemed indicated from the remarkably smooth transformation of santonin to santonic acid under the influence of alkali,[11,12] the probable course of which is indicated in Fig. 1. Clearly the isomer of V with *cis* ring fusion is required for the cyclization. An advantage of the intermediate V is the possibility of a mobile equilibrium between the *cis* and *trans* isomers, by way of the i-carbonyl enolate, which could serve to remove stereochemical complication in the formation of VI. The utilization of V, R = CH_3, seemed to offer certain advantages over V, R = H. Foremost of these is the possibility of controlling the subsequent methylation α to the i-carbonyl of VI so that the desired *gem*-dimethyl structure is produced. After the methylation step the extra oxygen of the i-carbonyl must be reduced and the j-carbonyl must be converted to C=CH_2 to complete the synthesis.

(a) cedrene, G. Stork and F. H. Clarke, Jr., *J. Am. Chem. Soc.*, **83**, 3114 (1961); (b) cyperone, R. Howe and F. J. McQuillin, *J. Chem. Soc.*, 2423 (1955); (c) maaliol, R. B. Bates, G. Büchi, T. Matsuura, and R. R. Shaffer, *J. Am. Chem. Soc.*, **82**, 2327 (1960); (d) carissone, A. R. Pinder and R. A. Williams, *Chem. Ind.* (London), 1714 (1961); (e) (±)-cuparene, W. Parker, R. Ramage, and R. A. Raphael, *J. Chem. Soc.*, 1558 (1962); (f) (±)-widdrol, C. Enzell, *Tetrahedron Letters*, **No. 5**, 185 (1962); (g) (±)-widdrene, W. G. Dauben and A. C. Ashcraft, *J. Am. Chem. Soc.*, **85**, 3673 (1963); (h) patchouli alcohol, G. Büchi and W. D. MacLeod, Jr., *ibid.*, **84**, 3205 (1962).

(4) For an early discussion of the studies on the constitution of longifolene, see J. S. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, Cambridge University Press, Cambridge, England, 1952, pp. 92–98.

(5) R. H. Moffett and D. Rogers, *Chem. Ind.* (London), 916 (1953).

(6) (a) Naffa and G. Ourisson, *ibid.*, 917 (1953); (b) G. Ourisson, G. Dupont, R. Dulou, and P. Naffa, *Bull. soc. chim. France*, [5] **21**, 1075, 1115, 1410, 1415 (1954).

(7) Absolute configuration: G. Ourisson, *Chem. Ind.* (London), 918 (1953), and *Bull. soc. chim. France*, [6] **22**, 895 (1955).

(8) T. Kubota and I. Ogura, *Chem. Ind.* (London), 951 (1958).

(9) R. Mayer and K. Starosta, *J. prakt. Chem.*, [4] **11**, 165 (1960).

(10) See L. Ruzicka, A. Eschenmoser, and H. Heusser, *Experientia*, **9**, 357 (1953), and subsequent elaborations, especially ref. 7 and most recently J. B. Hendrickson, *Tetrahedron*, **7**, 82 (1959).

(11) S. Cannizzaro and F. Sestini, *Gazz. chim. ital.*, **2**, 241 (1873).

(12) R. B. Woodward, F. I. Brutschy, and H. Baer, *J. Am. Chem. Soc.*, **70**, 4216 (1948).

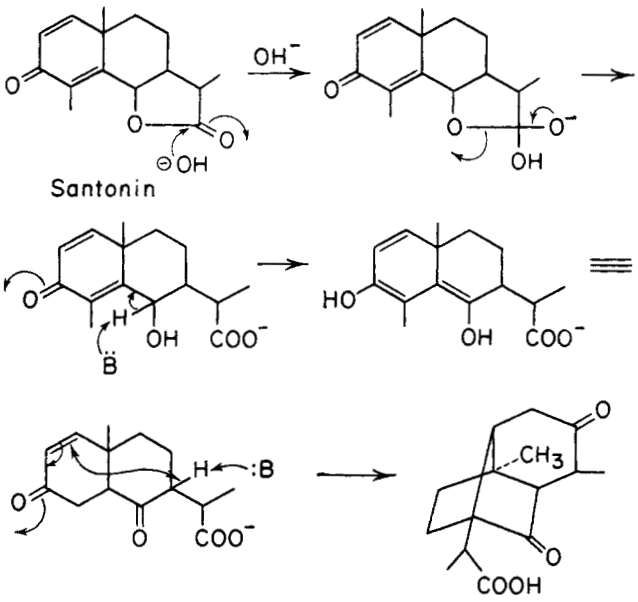
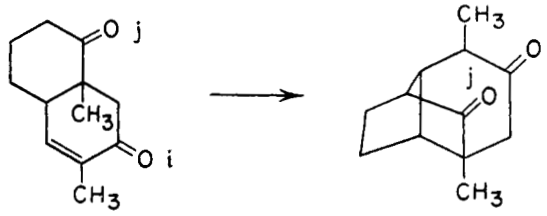


Figure 1.

The most practical methods for the synthesis of the homodecalin V seemed to be those which involve ring expansion of a suitable decalin derivative. This posed certain problems which are delineated below, and also raised the question of a variant of the step V → VI which postpones ring expansion to a later stage of synthesis. This alternative is the process VII → VIII. Conversion of VIII to longifolene would necessitate



VII VIII

ring expansion using the i-carbonyl function after the methylation step. Arbitrarily, the variant with postponed ring expansion was not pursued. However, it remains an attractive and interesting route.

Construction of the Carbon Network.—The Wieland–Miescher ketone[13] IX (Fig. 2) appeared ideally suited as a starting material for the synthesis of the required diketone V (R = H or CH_3) and indeed, the ready availability[14] of this often-used intermediate affected the choice of synthetic plan. A considerable study was made of procedures for ring expansion of IX,[15] and finally the sequence outlined in Fig. 2 was adopted. The ketone IX was converted to the crystalline monoketal X with retention of the α,β-unsaturated carbonyl system (ultraviolet max. 241 mμ, log ϵ 4.0) and thence to the ethylidene derivative XI by treatment with the Wittig reagent ethylidene triphenylphosphorane. This diene was selective hydroxylated to XII (R = H) under carefully controlled conditions with one equivalent of osmium tetroxide in ether–pyridine at 0°. The isolation of the diol XII (as a mixture of diastereomers) from the osmate ester was accomplished satisfactorily using the mild sodium bisulfite–pyridine reductive procedure.[16] The selective hydroxylation of the exocyclic double bond which occurs during the formation of XII

(13) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **33**, 2215 (1950).
(14) See *Org. Syn.*, **41**, 38, 57 (1961).
(15) For a summary (in Japanese) see M. Ohno, *J. Japan. Chem.*, **15**, 716 (1961).
(16) J. S. Baran, *J. Org. Chem.*, **25**, 257 (1960).

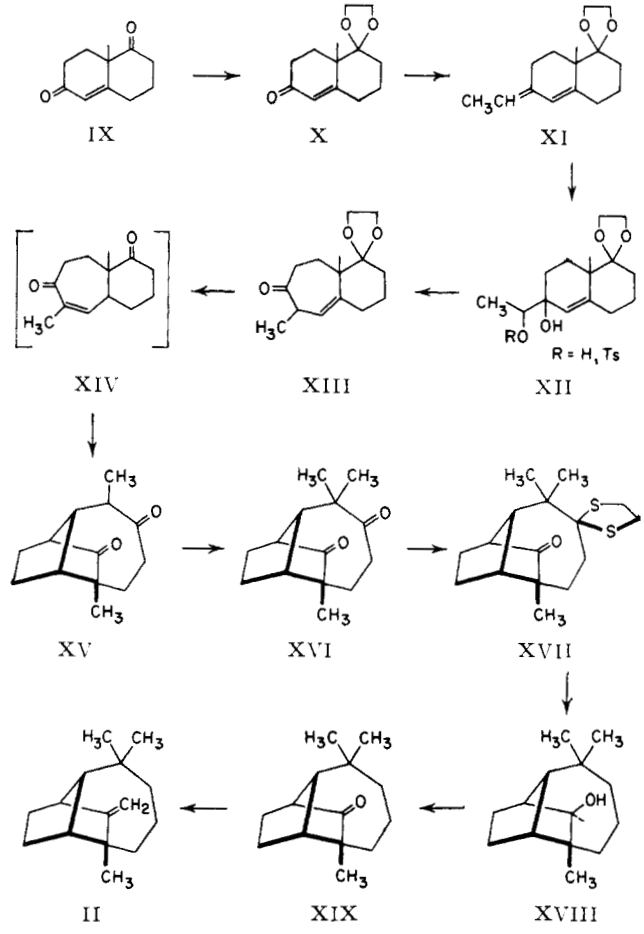


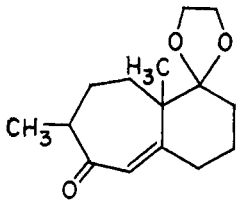
Figure 2.

was expected since this linkage is much more accessible sterically than is the endocyclic olefinic unit.

The secondary mono-*p*-toluenesulfonate derivative XII (R = Ts) was prepared from the diol mixture in order to activate this intermediate for the pinacol rearrangement–ring expansion step. Conditions for this tosylation reaction were critical, but the process was efficient when carefully executed (strictly purified reagents, minimal time, and temperature). Because of the ease of acid-catalyzed elimination of the allylic tertiary hydroxyl group in XII and the presence of the ketal function, the solvolysis ring expansion had to be conducted under essentially nonacidic conditions. The medium chosen for the reaction was tetrahydrofuran containing lithium perchlorate at saturation to facilitate ionization of the *p*-toluenesulfonate[17] and suspended calcium carbonate to ensure neutrality. The reaction of XII in this medium at 50° for 60 hr. led to a mixture of products from which the unconjugated cycloheptenone XIII could be isolated by chromatography (yield 41–48% from XI). The structure of this product is indicated by the lack of ultraviolet absorption, the presence of unconjugated ketone absorption in the infrared spectrum (5.85 μ), the nuclear magnetic resonance spectrum (1 olefinic hydrogen, 4 ketal hydrogens, 1 angular methyl, and 1 methyl attached to –CH–), and other data.

It had been anticipated that the rearrangement of XII toluenesulfonate in the direction of the desired XIII would predominate over the alternative ring expansion to XIIIa because the former pathway involves vinyl rearrangement with π-electron participation (C_4 in XII as the migrating group) whereas the latter re-

(17) S. Winstein, S. Smith, and D. Darwish, *J. Am. Chem. Soc.*, **81**, 5511 (1959).



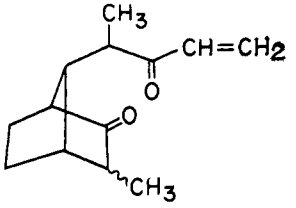
XIII a

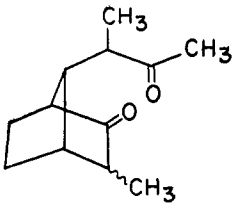
quires a less favorable alkyl rearrangement (C_2 in XII as the migrating group). An oily substance whose properties correspond to XIIIa could, however, be isolated as a minor product of the rearrangement (*ca.* 5%). This and other by-products were not extensively studied.

Attempts to effect ring expansion directly from X using diazomethane or diazoethane in the presence of Lewis acids[18] did not appear profitable. Our experience suggests that the above procedure for the conversion X → XIII is the method of choice at present for ring expansion of α,β-unsaturated ketones such as X and that this procedure may be much more generally useful.[19,20]

Mild acid-catalyzed hydrolysis of the ketal-ketone XIII (25°, 2 *N* hydrochloric acid for 6 hr.) produced the corresponding unconjugated diketone, infrared max. 5.85 μ; more drastic conditions (100°, 2 *N* hydrochloric acid for 24 hr.) led to the conjugated diketone XIV, infrared max. 5.85, 5.99 μ, ultraviolet max. 236 mμ (log ϵ 3.95). The intermediate for the key bridging reaction to form the longifolene nucleus was then readily available.

The intramolecular Michael cyclization reaction of XIV proved to be much less facile than expected from the santonic acid model and the conditions for its operation were far more critical. Strong bases such as potassium *t*-butoxide and even sodium methoxide led to extensive degradation of XIV to complex mixtures. Weaker bases, on the other hand, were without effect on this intermediate at ambient temperature or even at 100°. Nonetheless, the desired bridging reaction was effected starting from either XIV or the nonconjugated isomer (preferably the latter) in ethylene glycol containing triethylamine at 225° for 24 hr. Under conditions which led to transformation of *ca.* 80% of the starting material, the crystalline tricyclic diketone XV was obtained in 10–20% yield along with a number of oily compounds which appear to be degradation products of XV, such as





Isolation of XV was accomplished by chromatography on ethylene glycol–aluminum oxide. The assigned structure of this diketone, m.p. 109–110°, is fully supported by analytical and spectral data. Absorption in the infrared is as expected; there are carbonyl bands at 5.75 and 5.85 μ, but neither hydroxyl nor C=C absorption. The nuclear magnetic resonance spectrum of XV (in $CDCl_3$) exhibits peaks due to an angular methyl group at 1.11 δ[21] (3 protons, sharp) and a methyl attached to –CH– as a sharp doublet at 1.03, 1.15 δ; olefinic proton peaks are absent. Ultraviolet spectral measurement and lack of color with tetranitromethane indicate definitely the absence of carbon–carbon unsaturation. From these data it followed that the transformation XIV to XV had been realized and that the longifolene nucleus had been constructed.

Completion of the Substitution Pattern.—The completion of the synthesis of longifolene from XV requires only the adjustment of substitution pattern along the general lines mentioned earlier. In practice some interesting difficulties were encountered in the removal of the extra carbonyl function i which strongly affected the details of the remaining sequence. The first operation, the α-methylation of the enolate derived from XV, was accomplished without difficulty to afford the crystalline C_{14}-diketone XVI, m.p. 119°, in 60% yield using the trityl sodium–methyl iodide procedure.[22] That the newly introduced methyl group was located at the proper site was clearly indicated by the presence of a *single* sharp peak in the n.m.r. spectrum due to >C-$(CH_3)_2$ at 1.15 δ (6 protons) in addition to an angular methyl peak at 1.32 δ (3 protons). The diketone showed carbonyl absorption in the infrared at 5.75 and 5.87 μ, as anticipated. As a consequence of the success of the direct methylation reaction, it was unnecessary to resort to a more lengthy sequence in which the α-methylene of the cycloheptanone moiety is protected and this option was not explored.

The next task, selective reduction of one carbonyl to methylene, could not be realized in acceptable yield by direct procedures, probably as the result of transannular interaction between the carbonyl centers during the attempted modification. The desired product XIX, longicamphenolone, is a known substance[6b] which could be recognized easily by vapor phase chromatography (v.p.c.). However, it was not possible to detect appreciable amounts of this monoketone in the product from direct Wolff–Kishner reduction of XVI under varying conditions which covered the range of standard procedures. The diketone XVI could be converted to the monoethylene thioketal XVII, a nicely crystalline solid, infrared max. 5.74 μ. Desulfurization experiments with the thioketal XVII were without success and, surprisingly, no more than trace amounts of XIX were formed. The crude products from desulfurization were practically devoid of carbonyl absorption in the infrared, an ominous sign (carbene addition to bridge carbonyl?). Reduction of the carbonyl group by lithium aluminum hydride and subsequent desulfurization with Raney nickel also appeared unpromising. However, the combination of carbonyl reduction by hydride and direct Wolff–Kishner reaction with the hydroxy thioketal by the method of Georgian, *et al.*,[23] did afford the desired product *d,l*-longicamphenylol (XVIII) in good yield. The infrared spectrum and v.p.c. behavior of the synthetic longicamphenylol were identical with those for an authentic sample prepared by lithium aluminum hydride reduction of natural *d*-longicamphenylone.[6b] Oxidation of XVIII with chromic acid afforded *d,l*-longicamphenylone (XIX), m.p. 17–18°, identical spectroscopically (infrared, n.m..r) and vapor chromatographically with authentic *d*-longicamphenylone, m.p. 50–51°.

(18) See (a) W. S. Johnson, M. Neeman, S. P. Birkeland, and N. A. Fedoruk, *J. Am. Chem. Soc.*, **84**, 989 (1962); (b) E. Müller, Z. Bernd, H. Rolf, F. Horst, and S. Harald, *Ann.*, **662**, 38 (1963).

(19) Since the time at which the present experimental work was done a considerably more convenient and efficient procedure for carrying out the Wittig operation in such a sequence has been developed. See R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

(20) A similar method of ring expansion has been developed independently by N. A. Nelson, J. H. Fassnacht, and J. U. Piper, *J. Am. Chem. Soc.*, **83**, 206 (1961).

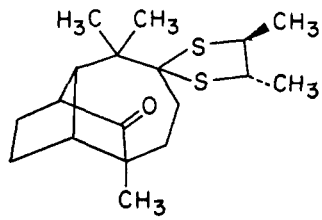
(21) All n.m.r. data are expressed in terms of p.p.m. shift downfield from tetramethylsilane as internal standard.

(22) E. J. Corey and E. W. Cantrall, *J. Am. Chem. Soc.*, **80**, 499 (1958); **81**, 1745 (1959).

(23) V. Georgian, R. Harrisson, and N. Gubitsch, *ibid.*, **81**, 5835 (1959).

The *d,l*-ketone XIX was methylated by reaction with excess methyllithium to the corresponding tertiary alcohol which was dehydrated in the cold by thionyl chloride–pyridine to *d,l*-longifolene (II), obtained as a colorless liquid identical spectroscopically and vapor chromatographically with natural *d*-longifolene (70% over-all yield from XVII).

With the successful completion of the synthesis of racemic longifolene, it became of interest to determine whether the synthetic scheme could be adapted to the preparation of the optically active natural product. Indeed, this was readily accomplished on a small scale starting with synthetic, racemic diketone XVI. This intermediate was treated with L(+)-2,3-butanedithiol, a reagent developed in these laboratories specifically for this application,[24] to give an oily mixture of diastereomeric monothioketals, infrared max. 5.74 μ. The separation of the mixture was accomplished by column chromatography, first using neutral alumina (Woelm Grade III) as adsorbent and then a partition system with alumina (Woelm Grade I) containing 5% dimethyl sulfoxide as stationary phase. One diastereoisomer was obtained as a crystalline substance, unchanged by further chromatography. This turned out to be the desired isomer XX. Reduction of this substance with lithium aluminum hydride, further direct Wolff–Kishner–Georgian reduction[23]



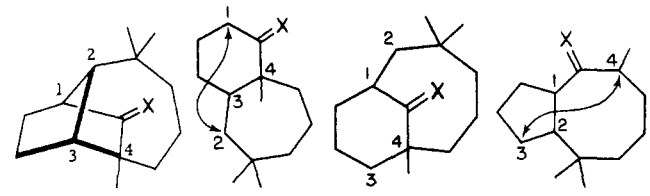
XX

of the hydroxy thioketal, and subsequent oxidation with ruthenium tetroxide–Freon 11[25] gave (+)-longicamphenylone identical with natural material by infrared and vapor chromatographic analyses. The optical rotation of this sample was +587° at 296.6 mμ and +495° at 302 mμ, and that found for authentic (+)-longicamphenylone from natural longifolene was found to be +610° at 296.6 mμ and +500° at 302 mμ under the same conditions.[26] The conversion of (+)-longicamphenylone to (+)-longifolene completed the total synthesis of the natural product.

General Discussion

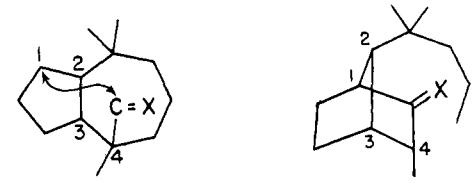
Because of the diversity and the number of pathways by which the longifolene system can, in theory, be constructed, some consideration of the approaches which were *not* investigated experimentally is in order. It is interesting that the choice of a synthetic plan from a broad range of possibilities is very much a function of the methodology of synthetic chemistry available at a given time, of certain practical considerations such as the availability of the necessary materials and reagents, and of certain subjective judgments relating to the feasibility of key reactions or the existence of alternatives. Hence, it is entirely reasonable that attention be given to those designs which, though not reduced to practice, appear to be at least possible in light of present knowledge.

A simple analysis of the carbon network of longifolene, for the purpose of designing possible syntheses, was made in the following way. (Obviously, a similar study can be made for the longifolene hydrochloride system (I) or for similar complex bridged-ring structures.) First the "common atoms" are designated; these are defined as ring-member atoms which are bonded to *three* or *four* other ring members (but not two). In expression XXI the common atoms are numbered 1–4. A less complex ring system is then derived by removing one of the bonds joining two



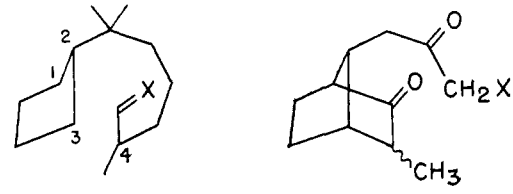
XXI XXII XXIII XXIV

common atoms, and the full series of such simplified structures is developed by operating on each bond between two common atoms. Thus XXI affords the series XXII–XXIV. Similarly, a series can be evolved by forming structures from XXI in which one bond connecting a common atom and a noncommon atom is broken. Two members of this series are XXV and XXVI. The next stage is the generation of a series of structures by breaking *two* bonds of the original



XXV XXVI

network XXI, especially those which join two adjacent atoms to one or more common atoms as in XXVII. These series so generated will probably contain the



XXVII XXVIII

simplest possibilities for intermediate structures in synthesis; however, in certain circumstances it may be profitable to consider further series.[27] Next comes an evaluation of the synthetic routes to these simpler intermediates and a consideration of the specific reactions for forming the bond(s) leading to the desired network. Many reactions need to be considered, *e.g.*, intramolecular carbanion alkylation, cation–olefin addition, Michael addition, Diels–Alder addition, carbene and photochemical reactions depending on favorable proximity effects—in essence the gamut of ring closure methods. It can be shown that a number of rational routes can be devised which utilize some of the intermediates XXII–XXVII.

A point made earlier in this paper needs emphasis here: schemes with smaller or larger rings than those shown for the above intermediates may be used advantageously with subsequent modification of ring size in a later phase of synthesis. For example, using the idea of intermediate XXVI, a superior approach

(24) E. J. Corey and R. B. Mitra, *J. Am. Chem. Soc.*, **84**, 2938 (1962).

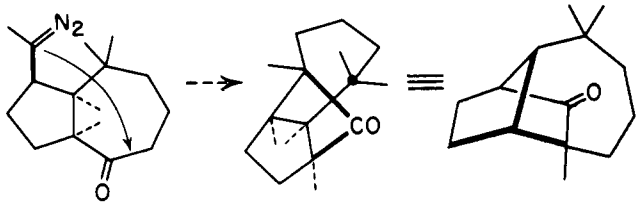
(25) See E. J. Corey, J. Casanova, Jr., P. A. Vatakencherry, and R. Winter, *ibid.*, **85**, 169 (1963).

(26) *Cf.* G. Jacob, G. Ourisson, and A. Rassat, *Bull. soc. chim. France*, 1374 (1959).

(27) A particularly simple and interesting synthetic problem for which this analytical approach is illuminating can be seen in the case of the "twistane" molecule. One synthesis of this structure has recently been described by H. W. Whitlock, Jr., *J. Am. Chem. Soc.*, **84**, 3412 (1962).

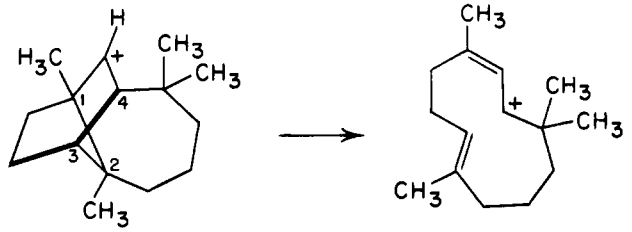
might be internal alkylation using XXVIII followed by methylation and ring expansion at the tricyclic stage.

An allowance must also be made for the possible application of rearrangements in synthesis, *e.g.*, XXIX → XXX.



XXIX XXX

The type of network analysis described above may also be of value in the consideration of possible *biosynthetic* routes. For example, rupture of single bonds 1,2 and 3,4 in the cation XXXI (related to the longifolene hydrochloride structure) produces the cation XXXII, a monocyclofarnesyl cation which is a reasonable biosynthetic intermediate (*cf.* ref. 10). A number of plausible biosyntheses can be arrived at in this way.



XXXI XXXII

Experimental

Δ^4-9-Methyloctalin-3,8-dion-8-ethylene Ketal (X).—A mixture of benzene (400 ml.) and ethylene glycol (70 g., 10 mole equiv.) was refluxed with stirring and the moisture in this mixture was removed using a water collector. To this mixture was added a solution of anhydrous *p*-toluenesulfonic acid (0.197 g., 1.124 mmoles) and Δ^4-9-methyl-3,8-octalindione[14] (IX, 20.12 g., 0.1124 mole) in benzene (120 ml.). The reactants were heated to reflux until 2 ml. of water was collected in the water collector. The reaction mixture was then cooled, washed with sodium bicarbonate solution, brine, and distilled water, dried over anhydrous sodium sulfate, and concentrated to give 23.8 g. of crude ketal. This was chromatographed on alumina (300 g., Merck) using petroleum ether–benzene mixture (4:1) and ether as eluents. By this procedure 16.5 g. (66% of theory) of pure ketal, m.p. 62–63°, was obtained, infrared max. 6.0, 9.0–9.5 μ (ketal) and ultraviolet max. 241 mμ (log ϵ, 4.0).[28] An analytical sample of X, m.p. 66–67°, was prepared by recrystallization from ethyl acetate and drying at 0.05 mm., 25°, for 24 hr.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.33; H, 8.09.

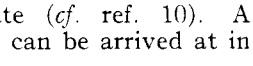
From some runs the diketal of IX was isolated, m.p. 91–92°, no carbonyl absorption in the infrared. An analytical sample was prepared by recrystallization from ether.

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 68.08; H, 8.26.

Diene XI by Reaction of Ketone-Ketal X with Ethylidene Triphenylphosphorane.—A suspension of 54.4 g. of powdered and dried ethyl triphenylphosphonium bromide[29] in 100 ml. of anhydrous ether in a 1-l. three-necked flask kept under nitrogen was treated with 100 ml. of 1.4 *N* *n*-butyllithium solution in ether gradually with efficient stirring. A beautiful orange colored solution was formed which was stirred for 2–4 hr. at room temperature (25°). To this was added gradually a solution of 8.15 g. (0.035 mole) of Δ^4-methyloctalin-3,8-dion-8-ethylene ketal in 70 ml. of ether (white precipitate formed). The mixture was stirred for 12 hr. at room temperature and then the ether was removed using a water pump and heating (bath at 40–50°) and replaced by 100 ml. of dry tetrahydrofuran, part of which also was removed under reduced pressure at 60°. Then 300 ml. of dry tetrahydrofuran was added, and the reactants (still under nitrogen) were refluxed with stirring for 36 hr. (bath temperature at 85°). At this point most of the tetrahydrofuran was distilled and the excess Wittig reagent was decomposed by gradual addition of ice water with stirring *after cooling the flask in an ice bath.* The resulting mixture was extracted with ether (3 × 150 ml.), washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was triturated with petroleum ether–ether mixture to remove the product from phosphine oxide. The solution was concentrated and chromatographed on a column (2.5 × 40 cm.) of alumina (Merck, 200 g.), transferring the substance only with petroleum ether (200 ml.) and eluting first with petroleum ether and then with mixture of petroleum ether–ether (1:1). The first two fractions (1 l.) gave 8.159 g. (95.8%) of the desired product XI as a liquid (probably a mixture of geometrical isomers); ultraviolet max. (ethanol) 235, 243 mμ (log ϵ, 4.34, 4.38); no carbonyl or hydroxyl absorption in the infrared.

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.99; H, 9.33.

Hydroxylation of XI to the Diol XII.—A solution of 10 g. of osmium tetroxide in 100 cc. of dry ether was added dropwise during 0.5 hr. to a stirred solution of 9.2 g. of XI in 30 cc. of dry pyridine and 60 cc. of dry ether, cooled to −20°. The reaction mixture was allowed to warm up to room temperature during 1 hr. and stirred 24 hr. at room temperature. The mixture was then cooled to 5–10° and the brown complex which had separated was decomposed by the addition of 570 cc. of pyridine and a solution of 18 g. of sodium bisulfite in 430 cc. of water.[16] Stirring for 0.5 hr. at room temperature gave a deep red solution which was extracted thoroughly with chloroform. The combined organic extract was washed twice with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate. Removal of solvents at room temperature *in vacuo* gave 10.9 g. of a pale brown oily residue which solidified on standing. The infrared spectrum of this product showed absorption at 2.76–3.0 μ for hydroxyl and 6.04 μ for isolated C=C. The ultraviolet absorption of the starting diene XI was completely absent. This material is probably a mixture of diastereoisomers since the m.p. was gradually raised by successive recrystallization from ether or acetone–water to 110–111°. The infrared spectrum of the purified material was very similar to that of the crude product. The n.m.r. spectrum of recrystallized material displayed a single olefinic proton (unsplit) and the peaks expected for angular methyl, $-CHCH_3$ methyl, and ketal hydrogens. The crude reaction product XII was suitable for the next step in the synthesis.



Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 66.94; H, 8.97.

Conversion of the Diol XII to the Ketal-Ketone XIII.—A solution of 10.7 g. of freshly recrystallized *p*-toluenesulfonyl chloride in 3 cc. of dry pyridine and 25 cc. of dry methylene chloride, cooled to 0°, was added dropwise during 0.5 hr. to a stirred solution of 10.9 g. of crude glycol XII in 15 cc. of dry pyridine and 25 cc. of dry methylene chloride, cooled to 0°. The mixture was stirred further for 0.5 hr. at 0°, and then kept at 3° for 22 hr. Excess of *p*-toluenesulfonyl chloride in the reaction mixture was hydrolyzed by the addition of 25 g. of crushed ice to the cooled and vigorously stirred mixture. After stirring for 0.5 hr. the mixture was extracted with chloroform. The chloroform extract was washed thoroughly with water and dried briefly over anhydrous sodium sulfate. Removal of solvents at room temperature *in vacuo* gave a viscous brown oil which was immediately solvolyzed as described below. The infrared spectrum of the crude tosylate showed weak hydroxyl absorption and arene sulfonate bands at 7.4 and 8.65 μ.

A solution of the crude tosylate XII (R = Ts), obtained above, in 125 cc. of freshly distilled dry tetrahydrofuran was added dropwise during 0.5 hr. under an atmosphere of dry nitrogen to a stirred suspension of 150 g. of lithium perchlorate[17] and 25 g. of calcium carbonate in 300 cc. of dry tetrahydrofuran, at room temperature. The mixture was stirred for 2.5 days at 50° under a nitrogen atmosphere, cooled, diluted with 200 cc. of ether, and filtered to remove insoluble solids. The filtrate was concentrated to 350 cc. *in vacuo*, diluted with 500 cc. of water and extracted with a 1:2 mixture of methylene chloride and ether. The combined extract was washed with water, 5% aqueous sodium bicarbonate, water, and a saturated aqueous solution of sodium chloride, and dried over anhydrous sodium sulfate. Removal of solvents gave a viscous oil which was chromatographed over 110 g. of Woelm neutral alumina, Grade IV. Petroleum ether eluted first 4.73 g. (48%) of XIII (over-all from XI), infrared max. 5.85 μ, as a clean viscous pale yellow oil. An analytical sample was prepared by evaporative distillation at 0.05 mm., bath temperature of 125–135°. The n.m.r. spectrum was consistent with structure XIII and indicated the probable occurrence of two stereoisomers having different orientations of methyl α to the carbonyl group. The ultraviolet spectrum of this material showed no absorption between 210 and 290 mμ, ruling out the

(28) This compound had been reported previously as a liquid: J. Kalvoda and H. Loeffel, *Helv. Chim. Acta*, **40**, 2340 (1957).

(29) G. Wittig and D. Wittenberg, *Ann.*, **606**, 1 (1957).

presence of a conjugated ketone function. With tetranitromethane a yellow color was produced.

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 71.97; H, 8.86. Found: C, 71.98; H, 8.87.

Later fractions from the chromatographic separation of the total reaction mixture (eluted with 1:1 petroleum ether–benzene) afforded *ca.* 500 mg. of an oily conjugated ketone showing infrared absorption at 6.0 and 6.19 μ (carbonyl and C=C) and at 9.0–10.0 μ (ketal) and ultraviolet absorption max. at 240 mμ (ϵ *ca.* 7000). The fact that the unconjugated ketone obtained above did not isomerize to a conjugated isomer during even lengthy chromatographic treatment and the fact that the two keto-ketals gave different acid-hydrolysis products make it seem probable that this conjugated ketone is the substance XIIIa, formed by the alternative mode of rearrangement. Benzene and ether eluted further oily materials from the chromatographic column, but these were not investigated.

Acid-Catalyzed Hydrolysis of the Keto-Ketal XIIIa to Unconjugated Diketone and to Conjugated Diketone XIV.—(a) A solution of 8 cc. of 6 *N* hydrochloric acid was added to a solution of 3.70 g. of XIII in 25 cc. of 95% ethanol and the mixture was stored at room temperature under nitrogen for 4 hr. The solution was then concentrated to 15 cc., diluted with water, and extracted thoroughly with a 2:1 mixture of pentane and methylene chloride. The organic layer was washed with water and saturated sodium chloride solution and dried over anhydrous sodium sulfate. Removal of solvents gave 3.1 g. (100%) of diketone corresponding to XII as a yellow viscous oil, infrared max. 5.85 μ. The characteristic strong band due to ketal (9–10 μ) was absent from the infrared spectrum. An analytical specimen was not obtained because some decomposition occurred invariably on high-vacuum distillation.

(b) To 300 mg. of the keto-ketal XIII in 10 ml. of 95% ethanol was added 2 ml. of 12 *N* hydrochloric acid; the mixture was heated to reflux under nitrogen for 24 hr., concentrated under reduced pressure to remove ethanol, and extracted with methylene chloride. The diketone XIV (222 mg.) was obtained as a pale yellow oil after washing and removal of solvent, infrared max. 5.85 and 5.99 μ, ultraviolet absorption (in ethanol) at 236 mμ (ϵ *ca.* 8500).

Formation of the Tricyclic Diketone XV by Intramolecular Michael Reaction.—A mixture of 1.0 g. of the unconjugated diketone, prepared as described under section a above, 2.42 g. of triethylamine, and 40 cc. of redistilled, dry ethylene glycol was heated in a sealed tube under an atmosphere of nitrogen for 24 hr. at 225°. The homogeneous pale yellow solution was cooled, diluted with water, and thoroughly extracted with a 2:1 mixture of pentane–methylene chloride. The organic layer was washed with a saturated solution of sodium chloride, dried over anhydrous sodium sulfate, and freed from solvents to give 1.09 g. of viscous oil which was chromatographed over 270 g. of Woelm neutral alumina containing 20% by weight of ethylene glycol. Petroleum ether (20 ml. fractions) eluted first starting material (*ca.* 200 mg., fractions 10–15), then an oily mixture (80 mg., fractions 18–22), a mixture of ketones which would seem to be methyl and vinyl ketones from infrared and n.m.r. (120 mg., fractions 25–32), and in fractions 55–65, 75–120 mg. (variation from run to run) of crystalline diketone XV, m.p. 109–110°. Later fractions were semisolid and possibly a mixture of diastereoisomers of XV having different orientations of the methyl group α to the cycloheptanone carbonyl. The crystalline fraction was further purified by recrystallization from ether and sublimation at 90° (0.1 mm.); colorless crystals, m.p. 110°, infrared max. 5.75 and 5.85 μ (both intense, no hydroxyl or C=C), no color with tetranitromethane. The n.m.r. spectrum revealed methyl peaks at 1.11 δ (3 protons, sharp), 1.03, 1.15 doublet (3 protons), and no peaks in the olefin proton region.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.58; H, 8.73.

Methylation of XV to XVI.—A small excess of triphenylmethyl sodium in ether was added under dry nitrogen to a stirred solution of 219 mg. of XV in 7 cc. of dry dioxane to give a pale red solution. After 3 min., a 12-fold excess of freshly distilled dry methyl iodide was quickly added after which the red color was immediately discharged. After stirring for 36 hr. under nitrogen at 30°, the reaction mixture was freed from solvents *in vacuo* and the residue was diluted with water and extracted with a 2:1 mixture of pentane and methylene chloride. The organic layer was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and freed from solvents to give a semisolid mixture which was chromatographed over 60 g. of Woelm neutral alumina, Grade III. Petroleum ether eluted first triphenylmethane. An oily product was eluted next with 5% ether–petroleum ether mixture and then crystalline product was eluted with 20% ether–petroleum ether. Sublimation of the solid at 95–110° (0.05 mm.) gave 137 mg., m.p. 117–119°. The infrared spectrum of purified product showed carbonyl bands at 5.75 and 5.87 μ and methyl peaks at 7.21, 7.28, and 7.85 μ. Methyl peaks appear in the n.m.r. spectrum at 1.32 δ (3 protons) and 1.5 δ (6 protons). A mixture m.p. with starting material, m.p. 110°, was in the range 85–105°.

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.68; H, 9.06.

Thioketal XVII from the Diketone XVI.—A mixture of 136 mg. of XVI and 0.8 cc. of ethanedithiol was treated with 0.5 cc. of boron trifluoride etherate at room temperature for 1.5 hr. This homogeneous reaction mixture was then poured into an excess of chilled 10% NaOH solution and extracted with a 2:1 mixture of pentane–methylene chloride. The organic layer was washed with water and then with saturated sodium chloride solution, dried over anhydrous Na_2SO_4, and freed from solvents to give a solid residue which after trituration with chilled ether gave 131 mg. (72%) of VIII as a crystalline solid, m.p. 167–168°, infrared max. 5.74 μ.

Anal. Calcd. for $C_{16}H_{24}OS_2$: C, 64.81; H, 8.16. Found: C, 64.63; H, 8.16.

Conversion of the Thioketal XVII to *d,l*-Longicamphenylone XIX.—A solution of *ca.* 200 mg. of lithium aluminum hydride in 10 cc. of dry ether was added to a solution of 131 mg. of thioketal XVII in 15 ml. of dry ether and the mixture was refluxed under a nitrogen atmosphere for 5 hr. The reaction mixture was then cautiously decomposed with water and thoroughly extracted with ether. The ether extract was washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate, and freed from ether to give 137 mg. (quantitative) of hydroxy thioketal as a crude viscous oil; infrared max. 2.7 μ, no absorption in the C=O region.

A mixture of this product (137 mg.), 1.2 cc. of hydrazine (95 + %), and a solution of 225 mg. of sodium in 6 cc. of dry ethylene glycol was heated at 190–195° for 16 hr. under an atmosphere of nitrogen.[23] Evolution of gas was observed during the first 6 hr. The reaction mixture was then cooled, diluted with 25 ml. of water, and extracted with Freon 11 (b.p. 22°).

The Freon extract, on removal of solvent, gave 96 mg. (100%) of *d,l*-longicamphenylol (XVII), identical in infrared spectrum and vapor chromatographically with *d*-longicamphenylol obtained by the hydride reduction of *d*-longicamphenylone,[6b] m.p. 50–51°; retention time of each sample, 7 min., 0 sec. on a 4-ft., 25% silicone rubber column, programmed from 150 to 250° at 4.6°/min. with helium flow 72 ml./min.

A solution of 96 mg. of this product in 3 cc. of acetic acid was treated with a solution of *ca.* 80 mg. of chromium trioxide in 0.5 ml. of acetic acid and 0.5 ml. of water and the mixture was kept at room temperature for 1 hr. A solution of 80 mg. of manganous sulfate in 0.5 cc. of water was then added and the reaction mixture was heated at 55° for 0.5 hr. After destroying the excess of chromium trioxide with methanol, the mixture was diluted to 20 cc. with water and extracted with Freon 11. The Freon extract was washed with 10% sodium hydroxide solution, and water, then dried and freed from solvent to give 78 mg. (82%) of *d,l*-longicamphenylone, m.p. 17–18°, identical spectroscopically (infrared, n.m.r.) and vapor chromatographically with *d*-longicamphenylone[6b]; retention time: 5 min., 40 sec. on a 4-ft., 25% silicone rubber column, programmed from 150–250° at 4.6°/min. with a helium flow of 72 ml./min.

The sample for analysis was collected by vapor chromatography.

Anal. Calcd. for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.72; H, 10.71.

Conversion of *d,l*-Longicamphenylone XIX to *d,l*-Longifolene.—A solution of 95 mg. of synthetic *d,l*-longicamphenylone in 3 ml. of ether was added to 22 ml. of a 1.8 *N* solution of methyllithium and the reactants were heated to reflux for 3 days under nitrogen. After this time the solution was cooled and treated dropwise with water. The ether layer was separated, washed, and concentrated to give 95 mg. of tertiary alcohol (93%), m.p. *ca.* 40°, which showed hydroxyl but no carbonyl absorption in the infrared.

The tertiary alcohol was dehydrated to *d,l*-longifolene by dissolving in 3 ml. of Freon 11 and 0.23 ml. of pyridine and treating this solution at 0° with 0.10 ml. of redistilled, purified thionyl chloride in 1 ml. of Freon 11. After 12 min. at 0° the reaction mixture was washed with dilute hydrochloric acid, then with water; the resulting Freon solution was filtered through cotton and concentrated to give *d,l*-longifolene, 83 mg., as a colorless liquid having completely identical infrared and n.m.r. spectra with the natural product. The natural and synthetic samples exhibited identical behavior on two v.p.c. columns, silicone rubber and tri-β-cyanoethoxypropane. An analytical sample was prepared by v.p.c.

Anal. Calcd. for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.18; H, 11.72.

Resolution of the Diketone XVI *via* the Thioketal XX with L(+)-Butane-2,3-dithiol.—To 110 mg. of the diketone XVI was added 273 mg. (4.5 equiv.) of the optically active dithiol[24] and 265 mg. of boron trifluoride etherate and the mixture was kept

at room temperature for 12 hr. It was then cooled, treated with excess of cold 10% sodium hydroxide solution, and extracted four times with a 3:1 mixture of pentane–methylene chloride. The organic layer was dried over anhydrous sodium sulfate and freed from solvents to give 135 mg. of thioketal isomer mixture as a clean viscous gum, infrared max. 5.74 μ.

The above material was then chromatographed over 10 g. of Woelm neutral Grade III alumina and eluted with a mixture of 5% methylene chloride and 95% of petroleum ether. A total of 150 fractions of 3 ml. each was collected. Fractions 22–40 gave 40 mg. of solid, m.p. 70–86°, $[\alpha]_D$ +3° (*c* 1.815, $CHCl_3$).

Rechromatography of the above 40 mg. of solid under the same conditions as above gave no further separation. It was, therefore, subjected to partition chromatography over 16 g. of Woelm neutral alumina Grade I containing 5% by weight of dimethyl sulfoxide. The column was eluted with petroleum ether and 3-ml. fractions were collected; 11 mg. of solid XX, m.p. 97–101°, was obtained, together with 21 mg., m.p. 75–85°. The 21 mg. of solid was then rechromatographed by the partition method as given above and 6 mg. of solid, m.p. 97–101°, was obtained. Thus, a total of 17 mg. of solid XX, m.p. 97–101°, was obtained and was carried through the subsequent steps.

Conversion of XX to (+)-Longicamphenylone.—A mixture of 17 mg. of XX, m.p. 97–101°, and 50 mg. of lithium aluminum hydride in 5 ml. of dry ether was refluxed under nitrogen for 5 hr., then cooled and decomposed dropwise with water till a slightly moist precipitate of alumina was obtained. The clear ether solution was decanted and the solid residue extracted thoroughly with ether. Drying and evaporation of the ether solution gave 17 mg. (quantitative) of hydroxy thioketal. Infrared showed the presence of hydroxyl at 3.0–3.3 μ and no C=O band.

A solution of 28 mg. of sodium metal in 1 ml. of dry ethylene glycol was added to a mixture of 17 mg. of this product and 0.2 ml. of 95% hydrazine, and the mixture was heated under nitrogen at bath temperature of 190–195° for 16 hr. The mixture was cooled, diluted with 2 ml. of water, and extracted with Freon 11. Drying and evaporation of the Freon gave 9 mg. (78%) of crude longicamphenylol.

A solution of the longicamphenylol (9 mg.) in Freon was tr eated in the cold with excess of a solution of ruthenium tetrox ide in Freon[25] for 3 min. The excess oxidizing agent was destroyed by adding a few drops of ether. Filtration through cotton and concentration to remove Freon gave 8 mg. of longicamphenylone, m.p. 43–46°. This product was identical with authentic material prepared from natural *d*-longifolene by infrared and v.p.c. analyses on a 20% silicone rubber column (retention times 8 min., 10 sec., at 175° with a helium flow 85 ml./min.). A sample was purified for rotation measurement by v.p.c. The rotation was measured on a Rudolph spectropolarimeter and at the same time measurements were made on an authentic sample of (+)-longicamphenylone. (We are indebted to Mr. G. Holzwarth for assistance with these measurements.) Rotation was determined at two wave lengths, 296.6 and 302 mμ (where the values are large), with solutions of the ketones in cyclohexane; found for natural ketone (0.971 mg. in 1.50 ml. of cyclohexane): at 296.6 mμ, observed rotation +0.395°, $[\alpha]$ +610°; at 302 mμ, observed rotation +0.324°, $[\alpha]$ +500°; found for synthetic ketone (1.39 mg. in 1.35 ml. cyclohexane): at 296.6 mμ, observed rotation +0.600°, $[\alpha]$ +587°; at 302 mμ, observed rotation +0.511°, $[\alpha]$ +495°.

Conversion of *d*-Longicamphenylone to *d*-Longifolene.—A sample of natural *d*-longicamphenylone (500 mg.) was treated with methyllithium (excess) in ether at reflux for 3 days and worked up as described above to give the corresponding methylated tertiary alcohol as a solid, m.p. approximately 40°. Dehydration of this alcohol as described above using thionyl chloride–pyridine in Freon 11 gave *d*-longifolene, spectroscopically and vapor chromatographically identical with the pure natural product.

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[CONTRIBUTION FROM THE CONVERSE LABORATORY OF HARVARD UNIVERSITY, CAMBRIDGE 38, MASS.]

Total Synthesis of *d,l*-Caryophyllene and *d,l*-Isocaryophyllene[1]

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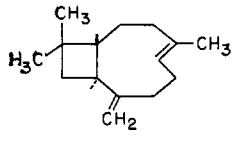
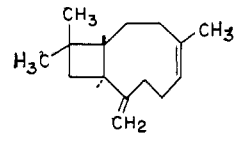
The caryophyllenes (I and II) have been synthesized starting with 2-cyclohexenone by way of a tricarbocyclic intermediate with fused four-, five-, and six-membered rings. The four-membered ring was added to the six by a photochemical cycloaddition process which formed 7,7-dimethylbicyclo[4.2.0]octanone-2 in one step; then the five-membered cycle was appended by a sequence involving methoxycarbonylation, alkylation, carbonyl addition, and Dieckmann condensation. The nine-membered ring of the caryophyllenes was then generated simply by removing the carbon-to-carbon span which served as the common bond of the six- and five-membered rings. The intermediates were selected to permit control of the 4–9 fusion (*trans*) and of the geometry of the endocyclic double bond *either* as in caryophyllene (I) *or* as in isocaryophyllene (II).

Introduction

Inspection of the molecular formulas of the sesquiterpenes caryophyllene (I) and isocaryophyllene (II) provides no more than a hint of the unusual and difficult problems which the study of these companions has entailed through successive stages over more than a century. Confronted with the complication that the reactions of these substances often lead to remarkable entanglements of the original structure, and with the fact that mixtures of isomers occur at every turn, the classical approaches, even in the hands of the most redoubtable practitioners, were for many years hopelessly inadequate.[2] Only during the past decade or so, with the help of recent improvements in reaction theory, a clearer understanding of the chemistry of large- and small-ring compounds and the application of physical methods has this quite singular puzzle been unraveled. Noteworthy



I



II

chapters include the following: structure and synthesis of the cyclobutane derivatives, norcaryophyllenic acid[3] and caryophyllenic acid,[4,5] recognition of a nine-membered ring in the caryophyllenes,[6,7] proposal of the currently accepted formulation exclusive of stereochemistry,[8] X-ray determination of the structure of caryolanyl chloride (caryophyllene hydrochloride) (III) and the

(1) This research was supported by the National Science Foundation (GP-221).

(2) See (a) J. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, Cambridge University Press, Cambridge, England, 1952, pp. 39–75; (b) P. de Mayo, "Mono- and Sesquiterpenoids," Interscience Publishers Inc., New York, N. Y., 1959, pp. 286–302.

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