the **13**-d_1 was isolated, the identical nmr spectrum was recorded with the exception that the broadened singlet at δ 4.62 now integrated for only one proton.

Acknowledgment. This research was supported in part through National Cancer Institute Grant No. CA 12115. The authors owe thanks also to Dr. Stanley A. Lang, Jr., for assistance with the 100-MHz nmr spectra.

Total Synthesis of Longifolene

John E. McMurry* and Stephen J. Isser

Contribution from the Department of Chemistry, Natural Science I, University of California, Santa Cruz, California 95060.
Received March 14, 1972

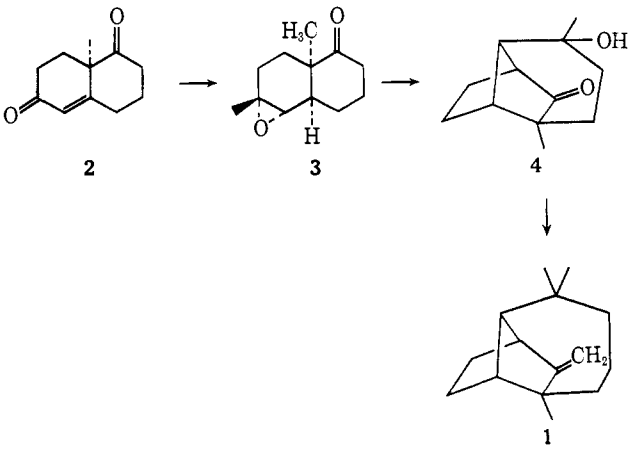
Abstract: A new route to the total synthesis of longifolene (**1**) is reported. Starting from the Wieland–Miescher ketone, the keto epoxide **10** is constructed and then cyclized by base to the tricyclic keto alcohol **11**. Dibromocarbene addition to the olefin derived from **11**, followed by silver ion assisted solvolytic ring enlargement, gives the allylic alcohol **19**. This is oxidized and treated with dimethylcopper lithium to generate ketol **23** by a surprising reductive process. Reduction of **23** to a diol followed by monomesylation and fragmentation gives dehydrolongicamphenilone (**29**) which is easily converted to longifolene.

The tricyclic sesquiterpene longifolene (**1**) is one of nature's more intricate molecular constructions and has attracted a good deal of attention in the past two decades.[1] Much of this attention has dealt with the wide variety of rearrangements which the compact longifolene skeleton undergoes, and much of it has dealt with synthesis. Thus there have been at least four unsuccessful attempts at the total synthesis of longifolene[2] as well as the well-known successful synthesis by Corey.[3] We would like to record a second total synthesis of (±)-longifolene.

Because of experience gained previously in a synthesis of the related sesquiterpene, copacamphene,[4] our attention was drawn to the possibility of forming the tricyclic carbon skeleton of longifolene *via* intramolecular alkylation of a bicyclic keto epoxide.

The Wieland–Miescher ketone (**2**) should serve as a suitable starting material to allow us to construct the necessary keto epoxide **3**. Base treatment should effect cyclization to a tricyclic compound which has sufficient functionality, properly situated, for further elaboration to longifolene.

Analogous to our synthesis of copacamphene, the Wieland–Miescher ketone was selectively monoketalized under carefully controlled conditions,[5] then hydrogenated at atmospheric pressure over a palladium catalyst to give the known[4] cis fused saturated ketone **6**, mp 54–54.5°, in approximately 85% overall yield. Treatment of **6** with methylmagnesium iodide in ether gave a crude carbinol which was dissolved in



2 **3** **4** **1**

cyclohexane and stirred for 45 min at room temperature with 50% aqueous sulfuric acid to effect both dehydration and deketalization. The oily product which was obtained in 96% yield was shown by vpc to be a mixture of two compounds in the ratio 69:31. Separation was readily effected by chromatography on alumina, and the two compounds were identified as the isomeric ketones **8** and **9**. The major isomer was identified as **9** from its nmr spectrum which showed a sharp vinyl singlet at δ 5.07. It is clear from molecular models that the vinyl proton is at a dihedral angle of approximately 80° with its neighbor; thus one would expect small coupling.[6] The minor isomer **8** shows a broad vinyl absorption at δ 5.33. Equilibration experiments aimed at increasing the yield of major isomer by treatment of the mixture with toluenesulfonic acid in refluxing benzene did not change the isomer ratio.

Epoxidation of **9** with 1 equiv of *m*-chloroperbenzoic acid in chloroform at 0° gave a nearly quantitative yield of a single epoxide, mp 73–74°. Presumably this product has the desired stereochemistry as in **10**, based on analogy[4] and on the nmr spectrum which shows a sharp singlet at δ 2.55. The dihedral angle between the

(1) (a) J. S. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, Cambridge University Press, Cambridge, England, 1952, pp 92–98; (b) G. Ourisson, *Proc. Chem. Soc.*, 274 (1964).

(2) (a) R. A. Scherrer, Ph.D. Thesis, University of Illinois, 1958; *Diss. Abstr.*, **19**, 960 (1958); (b) N. J. Hudak, Ph.D. Thesis, Cornell University, 1959; *Diss. Abstr.*, **20**, 79 (1959); (c) R. P. Napier, Ph.D. Thesis, University of Rochester, 1964; *Diss. Abstr.*, **25**, 1577 (1964); (d) J. E. Grant, Jr., Ph.D. Thesis, Pennsylvania State University, 1969; *Diss. Abstr. B*, **29**, 3653 (1969).

(3) E. J. Corey, M. Ohno, R. B. Mitra, and P. A. Vatakencherry, *J. Amer. Chem. Soc.*, **86**, 478 (1964).

(4) J. E. McMurry, *J. Org. Chem.*, **36**, 2826 (1971).

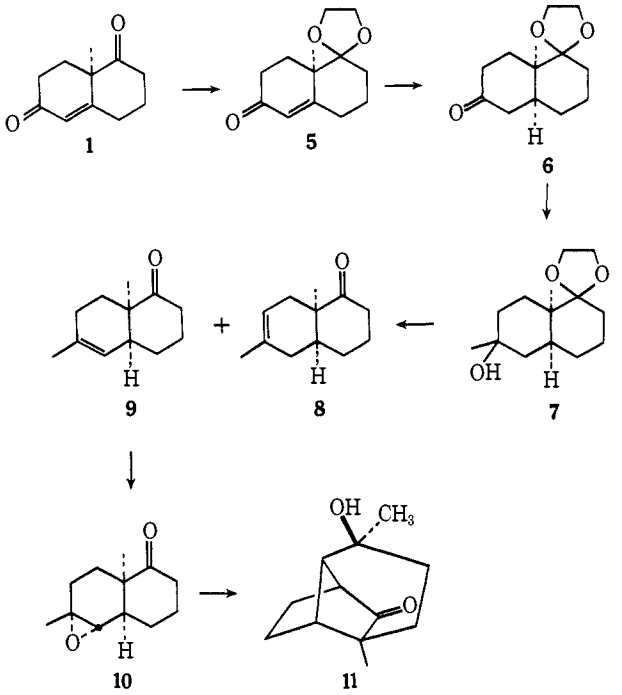
(5) J. E. McMurry, *J. Amer. Chem. Soc.*, **90**, 6821 (1968).

(6) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

epoxy proton and its neighbor at the ring junction is slightly over 90°, so again no coupling is expected. The stereoisomeric epoxide proton should be strongly coupled.

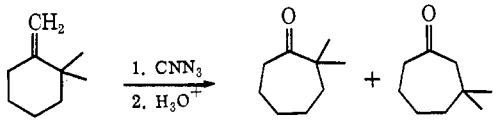
When the keto epoxide **10** was warmed to 60° with 1.75 equiv of dimethylsulfinyl carbanion[7] in DMSO for 5 days, cyclization occurred as expected, and the tricyclic keto alcohol **11** was isolated in a high state of purity in 93% yield, mp 90–91.5°. These transformations are summarized in Scheme I.

Scheme I



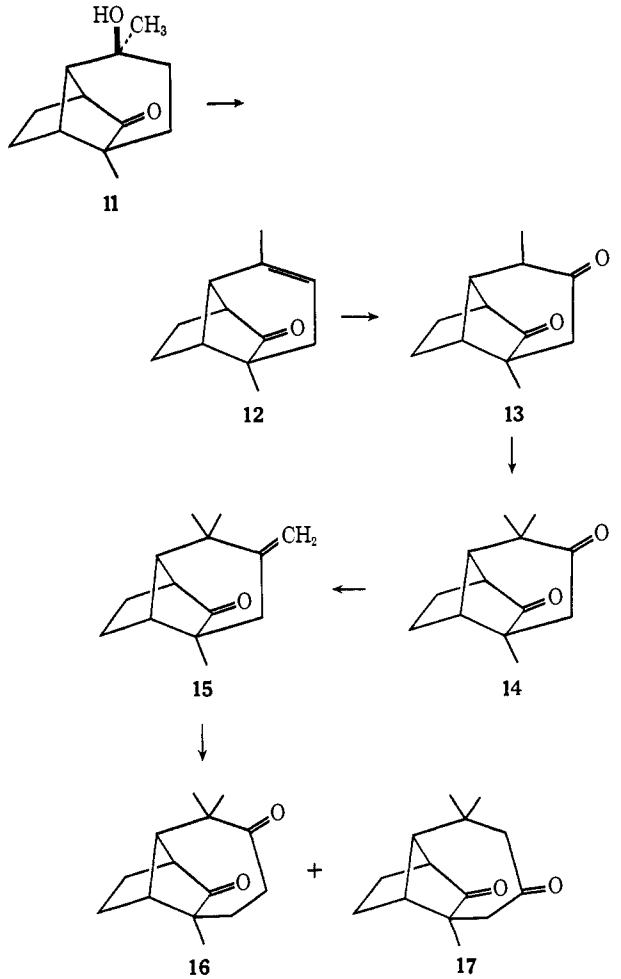
Completion of the synthesis then called for adding a further methyl group followed by ring expansion to form the dimethylcycloheptane ring of the natural product. Therefore, **11** was dehydrated by treatment in hexane solution with 50% aqueous sulfuric acid to give the endocyclic olefin **12** in 90% yield. The hydroboration–chromic acid oxidation sequence occurred normally to give diketone **13** in 75% yield. We planned to take advantage of the cyclohexanone carbonyl to introduce the necessary methyl group and then to ring expand. Thus, according to Corey's directions,[3] treatment of **13** with 1 equiv of tritylllithium in dioxane followed by quenching with excess methyl iodide gave a 6:1 mixture of the desired material **14** plus overmethylated product in 95% yield. Pure **14** could be obtained by careful column chromatography of the mixture.

Ring expansion of **14** by any one of a number of routes should effectively complete the synthesis, but results were discouraging. Thus, treatment of **14** with a large excess of diazomethane,[8] either in the presence[9] or absence of aluminum chloride, resulted in no reaction. We therefore attempted to use a new method of ring enlargement which we introduced several years ago.[10] We had found in a study that when the exocyclic olefin derived from 2,2-dimethylcyclohexanone was treated with cyanogen azide, ring expansion occurred smoothly to give a mixture of dimethylcycloheptanones in good yield.



Diketone **14** was therefore subjected to Wittig olefination with methylenetriphenylphosphorane in DMSO[11] and keto olefin **15** was obtained in 57% yield. The cyclopentanone carbonyl is extremely unreactive and resists even the forcing conditions used on **14** (10 equiv, 60°, 2 days). Cyanogen azide ring expansion was attempted under a variety of conditions which worked well on model systems, but the results were not encouraging. Under our most vigorous conditions, two isomeric products totaling 10% yield were spectrally identified as being the desired ring expanded diketones (**16** and **17**), but because of the low yield and because we anticipated possible trouble removing the unwanted cycloheptanone carbonyls in any event,[12] we decided to shelve this approach (Scheme II).

Scheme II



(7) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1345 (1965).

(8) See C. D. Gutsche and D. R. Redmore, "Carbocyclic Ring Expansion Reactions," Academic Press, New York, N. Y., 1968, Chapter IV.

(9) E. Müller, B. Zeeh, R. Heischkeil, F. Fricke, and H. Suhr, *Justus Liebigs Ann. Chem.*, **662**, 38 (1963).

(10) J. E. McMurry, *J. Amer. Chem. Soc.*, **91**, 3676 (1969).

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

(12) Corey, for example (ref 3), had great difficulty at this stage for his synthesis.

In addition to those methods already mentioned, another good method of ring enlargement involves addition of a dihalocarbene to an olefin followed by silver ion assisted rearrangement[13] and oxidation. Employment of this method in the present case looks quite attractive, because the product of the sequence is an enone which might allow introduction of the necessary methyl group by conjugate addition.

Olefin **12** was therefore treated with bromoform and potassium *tert*-butoxide in pentane at 0° and the crystalline adduct **18**, mp 128–129°, was isolated in 43% yield. Not unexpectedly, only one isomer was found, presumably that resulting from attack from the less hindered side. Solvolysis of **18** with 3 equiv of silver perchlorate in 95/5 (v/v) acetone–water for 17 hr at 45° led to a quantitative yield of allylic alcohol which was immediately oxidized with Collins reagent[14] to enedione **21** in 95% yield. Interestingly, if the allylic alcohol was allowed to stand for periods of time, the cyclopentanone carbonyl absorption slowly disappeared from the ir, indicating that intramolecular hemiketal formation was occurring to give **20**, thus defining the stereochemistry of the allylic alcohol as in **19**. The hemiketal could also be oxidized to enedione **21** with Collins reagent and so did not interfere with the synthesis.

At this point we planned to introduce the necessary methyl group by conjugate addition with dimethylcopper lithium. Although there did not appear to be any examples in the literature of conjugate addition to an α-bromoenone, we expected the desired reaction to occur since conjugate additions are known[15] to be very fast relative to replacement reactions on halides,[16] a possible competing reaction pathway. When bromoenedione **21** was treated with 3 equiv of dimethylcopper lithium at −40° in ether followed by slow warming of the mixture to room temperature, a 3:1 mixture of products was isolated in 92% yield. The minor product was tentatively identified by spectral methods as the product of bromide substitution, **22**. The major product, however, was considerably more interesting since it showed ir absorptions at 1730 (C=O) and 3430 cm^{-1} (O–H), its nmr showed a six-proton singlet at δ 1.15 and another quaternary CH_3 at 0.99, and its mass spectrum showed a molecular ion at *m/e* 220. This molecular weight corresponds to loss of bromine and addition of CH_4, *i.e.*, a net reduction had taken place. These spectral data are best accommodated by the tetracyclic ketol structure **23**. The transformations are shown in Scheme III.

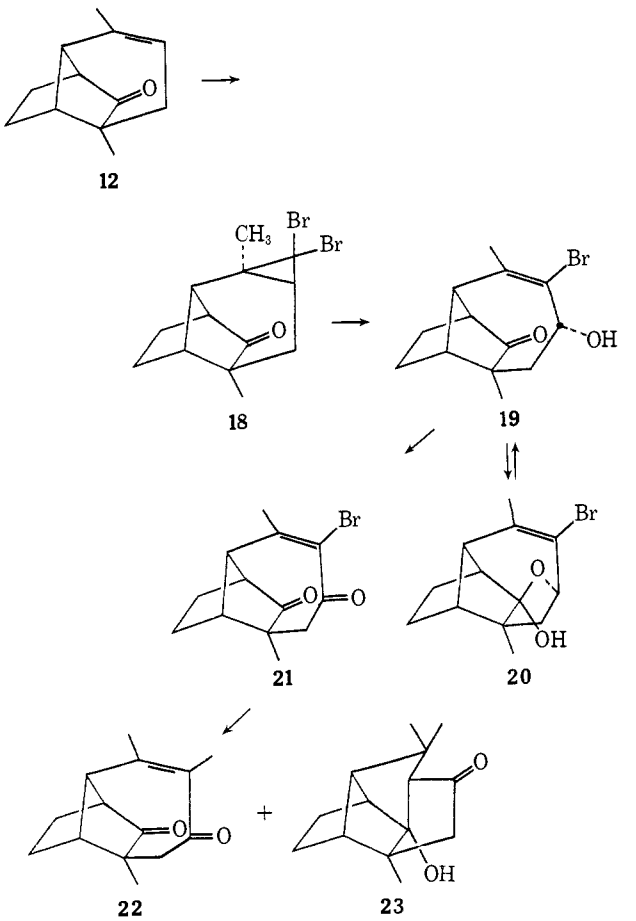
The reductive elimination of the bromine atom is without precedent to our knowledge, and a satisfactory mechanistic explanation is difficult to arrive at without further experimentation.

Ketol **23** could also be obtained by a more logical route. Treatment of the allylic alcohol **19** obtained from ring expansion, with excess sodium in 10% methanol–liquid NH_3, gave, in 62% yield, a crystalline diol, mp 165–166° (**24**). Collins oxidation of **24** gave enedione **25** in 95% yield and conjugate addition of a methyl group by treatment of **25** with dimethylcopper lithium again gave ketol **23** in 96% yield, thus verifying the proposed structure. Once again, however, the propensity of the compact longifolene skeleton to internal rearrangements was noted, for if enedione **25** was allowed to stand for prolonged periods, or if slowly chromatographed on alumina, an isomeric product was obtained which was spectrally identified as the internal aldol product **26**.

At this point, we only needed to dealdolize and remove the cycloheptanone carbonyl to reach longicamphenilone (**30**), an intermediate which is easily transformed into longifolene. Several variations of Wolff–Kishner type reductions[17] were attempted in the hope that dealdolization–reduction would occur in one step, but these attempts resulted in failure.

Reduction of ketol **23** with sodium borohydride gave a single crystalline diol, mp 146–147°, in 97% yield. Assuming attack from the less hindered side, this diol must have the stereochemistry indicated in **27**, a stereochemistry which is admirably suited for a fragmentation reaction. Treatment of **27** with 1 equiv of methanesulfonyl chloride in triethylamine–methylene chloride[18] selectively gave the secondary monomesylate **28** which fragmented in 100% yield when treated with potassium *tert*-butoxide at 45° for 1 hr. The enone

Scheme III



(13) (a) C. W. Jefford, *Chimia*, 24, 357 (1970); (b) R. A. Moss and R. Gerstl, *Tetrahedron*, 23, 2549 (1967); (c) A. Baylouny, K. Hankovsky, D. Kates, and J. P. Sibilia, *Tetrahedron Lett.*, 2093 (1970); (d) M. S. Baird, D. G. Lindsay, and C. B. Reese, *J. Chem. Soc. C*, 1173 (1969); (e) W. E. Doering and W. A. Henderson, *J. Amer. Chem. Soc.*, 80, 5274 (1958).

(14) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, 35, 4000 (1970).

(15) H. O. House, W. L. Respess, and G. M. Whitesides, *ibid.*, 31, 3128 (1966).

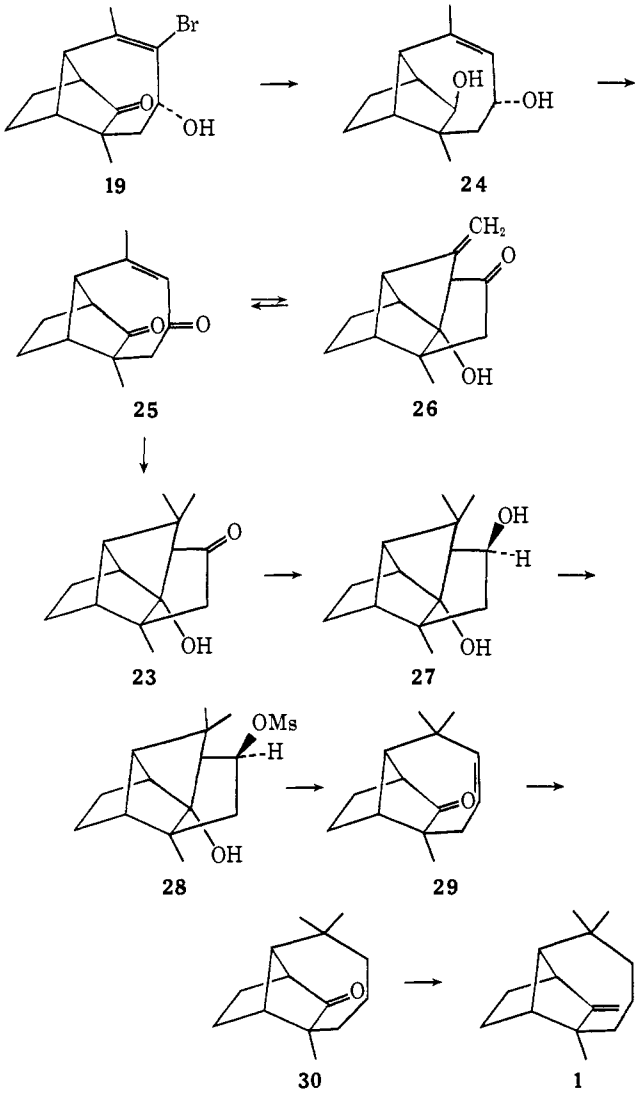
(16) E. J. Corey and G. H. Posner, *J. Amer. Chem. Soc.*, 89, 3911 (1967).

(17) (a) Huang-Minlon, *ibid.*, 71, 3301 (1949); (b) M. Gates and G. Tschudi, *ibid.*, 78, 1380 (1956); (c) W. Nagata and H. Itazaki, *Chem. Ind. (London)*, 1194 (1964).

(18) R. K. Crossland and K. L. Servis, *J. Org. Chem.*, 35, 3195 (1970).

29 thus obtained was hydrogenated without incident over the Wilkinson catalyst[19] to provide (±)-longicamphenilone (**30**). Transformation to longifolene occurred smoothly upon treatment of **30** with methyllithium followed by dehydration ($SOCl_2$–pyridine) (80% from **30**) (Scheme IV). The longifolene obtained

Scheme IV



was identical with the natural product by direct comparison of vpc behavior and spectral properties.

A second total synthesis of longifolene has therefore been completed. All of the steps proceed in quite acceptable yields and the method should be of some generality for the synthesis of related systems.

Experimental Section

Microanalyses were performed by the Microanalytical Laboratories, University of California, Berkeley. Nmr spectra were run in the solvents indicated (TMS internal standard) on a Varian A-56/60A instrument. Mass spectra were measured on a Hitachi-Perkin-Elmer RMU6E instrument. Melting points are uncorrected.

6,8a-Dimethyl-3,4,4a,7,8,8a-hexahydronaphthalen-1(2*H*)-one (9). Ketal **6** (36 g, 0.161 mol) in 400 ml of dry distilled ether was added dropwise over 3.5 hr to an ether solution of 3.35 *M* methyl magnesium iodide (101 ml, 0.338 mol) at room temperature. After another hour at room temperature, excess Grignard reagent was destroyed by dropwise addition of 10% sulfuric acid. The product was isolated in the usual way.[20] The crude carbinol residue was dissolved in 350 ml of cyclohexane; 100 ml of 50% aqueous sulfuric acid was added, and the two-phase system was stirred 45 min at room temperature (longer stirring times gave reduced yields of olefin). Work-up[20] gave 29.5 g of crude brown oil. Rapid chromatography of the crude material over basic alumina with ether gave 29.4 g (96%) of yellow oil. Glc analysis indicated the oil to be a 69:31 mixture of **9** and **8**, respectively. The components were separated by careful chromatography on acidic alumina using cyclohexane–ether solvent mixtures. The desired Δ^5 isomer **9** was eluted first, followed by the Δ^6 isomer **8**. Δ^5-Olefin (**9**) showed the following: ir (film) 3030 and 1710 cm^{-1} (C=O); nmr (CCl_4) δ 5.07 (br s, 1 H, vinyl proton), 1.63 (br s, 3 H, olefinic methyl), and 1.11 (s, 3 H).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.78; H, 10.29.

Δ^6-Olefin (**8**) showed the following: ir (film) 3030 and 1710 cm^{-1} (C=O); nmr (CCl_4) δ 5.33 (br s, 1 H, vinyl proton), 1.63 (br s, 3 H, olefinic methyl), and 0.98 (s, 3 H).

Keto Epoxide 10. Keto olefin **9** (15 g, 85.5 mmol) in 150 ml of chloroform was treated dropwise with a chloroform solution of 85% *m*-chloroperbenzoic acid (18.3 g, 90 mmol), maintaining the reaction temperature at 0°. After addition was complete, the solution was allowed to warm to room temperature and stirred overnight. The chloroform solution was washed six times with 10% sodium hydroxide and the basic extracts were washed once with chloroform. The combined organic fractions were worked up[20] to give 16.8 g (100%) of white crystalline epoxide. This material was recrystallized from cyclohexane to give the analytical sample: mp 73–74°; ir (film) 1710 cm^{-1} (C=O); nmr (CCl_4) δ 2.55 (s, 1 H, epoxide proton), 1.18 (s, 7 H, contains epoxide methyl), and 1.08 (s, 3 H).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.24; H, 9.34.

Tricyclic Ketol 11. A 1 *M* solution of methyl sulfinyl carbanion was prepared.[7] Sodium hydride (60%, 5 g, 125 mmol) was placed in a flame-dried three-necked flask fitted with stirring bar and nitrogen inlet tube, and washed several times with hexane to remove the mineral oil. Dimethyl sulfoxide (125 ml) was added and the mixture stirred at 70° for 2.5 hr until hydrogen evolution had ceased and the color of the anion solution had turned dark.

Crystalline keto epoxide **10** (13.8 g, 71 mmol) in 70 ml of DMSO was added to the solution of 1.75 equiv of sulfinyl carbanion at room temperature and a slight evolution of heat was noted. The mixture was stirred under nitrogen at 60° and the reaction progress followed by glc (20% SE-30, 200°). The peak with a retention time of 2.65 min reached a maximum after 5.5 days. The dark mixture was diluted with 200 ml of water and worked up[20] to give 12.8 g (92.5%) of dark oil suitable for further use. An analytical sample was obtained by crystallization from isopropyl ether: mp 90–91.5°; ir (film) 3450 (O–H) and 1740 cm^{-1} (cyclopentanone C=O); nmr ($CDCl_3$) δ 1.26 (s, 3 H, hydroxy methyl) and 1.01 (s, 3 H, angular methyl).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.28; H, 9.54.

Tricyclic Keto Olefin 12. Tricyclic ketol **11** (24.2 g, 125 mmol) in 300 ml of 1:1 cyclohexane–methylene chloride was stirred for 15 min with 75 ml of 50% aqueous sulfuric acid. Longer stirring times give considerably lower yields. The two layers were separated and the reaction worked up[20] to give 20.0 g (91%) of brown oil judged quite pure by spectral analysis. For purer material the crude product was rapidly chromatographed over acidic alumina with ether to give 18.7 g (85%) of yellow oil. The analytical sample was isolated by glc (20% SE-30; 190°): ir (film) 3030 and 1745 cm^{-1} (cyclopentanone C=O); nmr (CCl_4) δ 5.11 (br s, 1 H, vinyl proton), 2.60 (s, 1 H, allylic methine bridgehead proton), 1.68 (d, 3 H, J = 2 Hz, olefinic methyl), and 0.99 (s, 3 H).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.75; H, 9.21.

Dibromocarbene Adduct 18. Potassium *tert*-butoxide (16.9 g, 151 mmol) was placed in a flame-dried 500-ml three-necked flask fitted with a nitrogen inlet tube and dropping funnel. The flask was cooled to 0° in an ice bath and enough pentane was added to make an easily stirred suspension. Tricyclic keto olefin **12** (4.43 g,

(19) J. F. Young, J. A. Osborn, F. H. Jardine, and G. Wilkinson, *Chem. Commun.*, 131 (1965).

(20) The "usual" work-up consists of diluting the reaction mixture with water, extracting several times with ether, combining the ether extracts, drying the extracts over $MgSO_4$, filtering, and removing the solvent at the rotary evaporator.

25.2 mmol) in 125 ml of pentane was added to the suspension in one portion. Bromoform (38.2 g, 151 mmol) was added dropwise to the light brown suspension over 30 min maintaining the temperature at 0°. After addition was complete the reaction mixture was stirred for 2 hr more as it slowly warmed to room temperature. Work-up[20] gave a crude yield of 8.42 g of brown oil. This crude adduct was purified by rapid chromatography over basic alumina with ether to give 7.47 g (85%) of brown crystalline material. Recrystallization from cyclohexane–isopropyl ether gave 3.77 g (43%) of light brown crystals. The analytical sample was obtained by repeated crystallization: white crystals; mp 128–129°; ir (film) 1745 (C=O) and 655 cm^{-1} (C—Br); nmr (CCl_4) δ 1.48 (s, 3 H), and 0.90 (s, 3 H).

Anal. Calcd for $C_{13}H_{16}OBr_2$: C, 44.86; H, 4.63. Found: C, 44.85; H, 4.61.

Ring Expansion Product 19. Crystalline *gem*-dibromocyclopropyl adduct **18** (2.30 g, 6.6 mmol) and silver perchlorate (4.1 g, 19.8 mmol) were placed in a dry flask and 30 ml of a 95:5 v/v mixture of acetone and water was added. The mixture, which darkened rapidly, was stirred under nitrogen at 45° for 17 hr. The reaction mixture was first evaporated to remove the acetone and the residue was worked up[20] to give 1.88 g (100%) of yellow oil. Nmr analysis of the oil indicated that it was a mixture of the two isomers **19** and **20**. The composition of the mixture varied with reaction time or storage, longer times giving more of the crystalline hemiketal form **20**. Pure **19** was isolated by recrystallization from isopropyl ether: mp 159–160°; ir (film) 3430 (O–H), 1740 (C=O), and 1650 cm^{-1} (C=C); nmr (CCl_4) δ 4.53 (quintuplet, 1 H, J = 2 Hz), 3.50 (s, 1 H, O–H), 1.87 (s, 3 H, olefinic methyl), and 0.99 (s, 3 H).

Hemiketal **20** showed the following: ir ($CHCl_3$) 3710, 3650, and 3610 (free O–H), 3415 (intermolecularly hydrogen bonded O–H), 3085 (olefinic C–H stretch), 1745 (trace C=O), 1665 cm^{-1} (C=C); nmr (CCl_4) δ 4.69 (t, 1 H, J = 4 Hz), 3.49 (br s, 1 H, O–H), 1.93 (s, 7 H, olefinic methyl, C-5 methylene, and two unidentified protons), and 1.09 (s, 3 H).

Anal. Calcd for $C_{13}H_{17}O_2Br$: C, 54.75; H, 6.01. Found: C, 54.61; H, 6.17.

α-Bromoenone (21). Collins reagent (3.28 mmol, 8 equiv) was prepared *in situ* by dissolving dry pyridine (518 mg, 6.56 mmol) in 4 ml of dry methylene chloride.[14] Chromium trioxide (328 mg, 3.28 mmol) was added and the dark red suspension stirred 15 min at room temperature under nitrogen. Hemiketal **20** or the mixture of ring expansion products could be oxidized with equal efficiency. In this example, pure **19** (117 mg, 0.41 mmol) in 4 ml of methylene chloride was added all at once to the stirring $CrO_3 \cdot 2Py$ complex. The reaction turned dark brown immediately and was allowed to stir at room temperature for 15 min. The flask contents were transferred to a separatory funnel with the aid of a little methylene chloride and worked up.[20] An orange oil was obtained (110 mg, 95%) which showed satisfactory spectral data for structure **21**: ir (film) 1750 (C=O) and 1675 cm^{-1} (C=C); nmr (CCl_4) δ 2.89 (s, 1 H, allylic bridgehead proton), 2.64 (s, 1 H, proton α to the carbonyl), 2.08 (s, 5 H, enone methyl and methylene protons next to carbonyl), and 1.09 (s, 3 H).

Tricyclic Diol 24. Liquid ammonia (100 ml) was distilled over sodium into a large three-necked flask equipped with a stirring bar, nitrogen inlet tube, and Dry Ice condenser. Compound **19** (954 mg, 3.36 mmol) in 10 ml of absolute methanol was dissolved in the liquid ammonia and sodium (772 mg, 33.6 mmol, 10 equiv) was added to the stirring solution in small pieces, and the blue color disappeared instantaneously. A small amount of sodium nitrite was added to decompose any excess sodium and the ammonia was evaporated with the aid of a hot water bath. The residue was worked up[20] to give 695 mg of a white solid. Glc analysis (20% SE-30, 200°) showed a major and minor peak, the major one consisting of two overlapping peaks. Trituration of the crude product with isopropyl ether removed the minor component and gave white crystals of **24** soluble only in acetone and dimethyl sulfoxide: mp 165–166°; yield 432 mg (62%); ir (KBr) 3360 (O–H), 1665 (C=C), and 1050 cm^{-1} (C–O stretch); nmr ($CDCl_3$, slurry) δ 5.26 (br s, 1 H) and 0.88 (s, 3 H).

Ketoenone (25). Collins reagent (26.4 mmol, 13 equiv) was prepared *in situ*[14] by dissolving pyridine (4.17 g, 52.8 mmol) in 50 ml of methylene chloride, adding chromium trioxide (2.64 g, 26.4 mmol), and stirring the mixture for 15 min. Diol **24** (418 mg, 2.03 mmol) in 75 ml of methylene chloride was added all at once and the dark brown reaction mixture stirred 15 min at room temperature. The contents of the flask were transferred to a separatory funnel with the aid of methylene chloride and worked up.[20] An orange oil was obtained (410 mg, 100%) which was homogeneous by glc (20% SE-30, 210°). The oil solidified on standing and an analytical sample was obtained by crystallization from ether: mp 86–87°; ir (film) 1750 (saturated C=O) and 1645 cm^{-1} (enone); nmr (CCl_4) δ 5.63 (s, 1 H, vinyl proton), 2.59 (br s, 2 H, methylene next to carbonyl), 1.87 (d, 3 H, J = 1.5 Hz), and 1.02 (s, 3 H).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.44; H, 8.06.

Tetracyclic Ketol 23 from α-Bromoenone (21). A solution containing 1 mmol (5 equiv) of dimethylcopper lithium was prepared by suspending cuprous iodide (190 mg, 1 mmol) in a dry three-necked round-bottomed flask, fitted with a dropping funnel and rubber septum, with 1 ml of dry ether. The reaction vessel was cooled to 0° and 1.6 ml of 1.22 *M* methyllithium solution (1.9 mmol) was injected through the serum cap; the contents in the flask turned a brown color. The dimethylcopper lithium solution was stirred at 0° for 15 min and the flask was then cooled to −40°. Bromoenone **21** (56 mg, 0.198 mmol) in 2 ml of ether was added dropwise at this temperature. The temperature of the reaction mixture was allowed to warm to 0° and remain there 15 min, after which the reaction contents were quenched with 20% ammonium chloride solution. The reaction mixture was transferred to a separatory funnel, and worked up[20] to give a crude oil weighing 51 mg. Glc analysis (20% SE-30, 195°) indicated the oil to be a mixture of two major peaks. These were isolated from the gas chromatograph and found to be tetracyclic ketol **23** (61%), and substitution product **22** (24% assigned on the basis of its mass spectrum alone).

Enone **22** showed the following characteristics: mass spectrum (80 eV) *m/e* (rel intensity) 218 ($5M^+$), 203 (4), 190 (42), 175 (6), 162 (29), 147 (69), 134 (41), 120 (43), 95 (42), 91 (43), 41 (100).

Tetracyclic Ketol 23 from Enone 25. To an ether solution of 2.5 equiv of dimethylcopper lithium prepared at −20° from cuprous iodide (1.1 g, 5.78 mmol) and 1.6 *M* methyllithium (7.23 ml, 11.56 mmol) was added ketoenone **25** (471 mg, 2.31 mmol) in 15 ml of ether dropwise over 10 min. The mixture was stirred at −20° for 30 min more, then quenched with 20% ammonium chloride. Work-up[20] gave 487 mg (96%) of orange oil. The material was homogeneous on glc (20% SE-30, 195°) and identical in its retention time with the major product of dimethylcopper lithium treatment of bromoenone **20**. An analytical sample was obtained on recrystallization from isopropyl ether: mp 118–118.5°; ir (film) 3430 (O–H) and 1730 cm^{-1} (br cyclopentanone); nmr (CCl_4) δ 3.3 (s, 1 H, O–H identified by its disappearance upon addition of D_2O), 2.18 (s, 1 H, methine bridgehead proton next to carbonyl), 2.06 (s, 2 H, methylene protons next to carbonyl), 1.17 (s, 3 H), and 1.13 (s, 3 H, *gem*-dimethyl group), and 0.96 (s, 3 H, angular methyl).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.27; H, 9.19.

Diol 27. Sodium borohydride (3.8 g, 100 mmol) was dissolved in 80 ml of methanol to which one-half of a sodium hydroxide pellet had been added. The solution was cooled to 0° and ketol **23** (450 mg, 2.05 mmol) in a small amount of methanol was added dropwise rapidly, maintaining the temperature at 0°. The reaction mixture was allowed to stir at 0° for 30 min, then warmed to room temperature and stirred overnight. The slightly yellow solution was acidified to pH 6 with acetic acid and the methanol was evaporated. The residue was worked up[20] to give 440 mg (97%) of white solid. The diol was homogeneous by glc (20% SE-30, 210°). An analytical sample was obtained by crystallization from isopropyl ether: mp 146–147°; ir ($CHCl_3$) 3615 (free O–H) and 3440 cm^{-1} (intermolecularly hydrogen bonded O–H); nmr ($CDCl_3$) δ 4.42 (sextuplet, 1 H, J = 5 Hz, exo proton α to the secondary hydroxyl function), 1.28 (s, 3 H) and 1.10 (s, 3 H) (*gem*-dimethyl group), and 0.94 (s, 3 H).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.66; H, 10.27.

Hydroxy Mesylate (28). Diol **27** (351 mg, 1.58 mmol) in 25 ml of methylene chloride was stirred at −20° in a three-necked flask fitted with a rubber septum and nitrogen inlet tube. Triethylamine (330 μl, 2.37 mmol) was injected through the septum and then methanesulfonyl chloride (134 μl, 1.74 mmol, 1.1 equiv) was injected and the resulting solution stirred at −10° for 15 min. Work-up[20] gave 474 mg (100%) of light green oil which solidified on standing. The structure of the product was confirmed spectrally: ir (film) 3530 (O–H) and 1170 cm^{-1}; nmr ($CDCl_3$) δ 3.59 (sextuplet, 1 H, J = 7 Hz, proton α to the mesylate function), 2.98 (s, 3 H, sulfonate methyl), 1.25 (s, 3 H) and 1.14 (s, 3 H) (*gem*-dimethyl group), and 0.99 (s, 3 H).

Dehydrolongicamphenilone (29). Hydroxy mesylate (**28**) (452 mg, 1.5 mmol) in 15 ml of dry *tert*-butyl alcohol was mixed with a slurry of potassium *tert*-butoxide (420 mg, 3.75 mmol) in 15 ml of *tert*-butyl alcohol and warmed at 35° under nitrogen for 1 hr. The reaction mixture was worked up[20] and an orange oil was obtained in quantitative yield (306 mg). The material was homogeneous on glc (20% SE-30, 190°) and possessed appropriate spectral properties: ir (film) 3030 (olefinic C–H), 1745 (C=O), and 725 cm^{-1} (cis olefinic C–H bend); nmr (CCl_4) δ 4.93 (m, 2 H), 1.05 (s, 3 H), 1.00 (s, 3 H), and 0.95 (s, 3 H).

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.39; H, 9.78.

Alternatively, **29** could be prepared by stirring the mesylate (119 mg, 0.4 mmol) with a suspension of 60% sodium hydride (80 mg, 2 mmol washed free of mineral oil with hexane) in 4 ml of dry tetrahydrofuran for 1 hr at room temperature. The solvent was evaporated and the residue taken up in water and extracted with ether. Usual work-up[20] gave 67 mg (83%) of oily **29**.

(±)-Longicamphenilone (30). Tristriphenylphosphinerhodium chloride (75 mg) was dissolved in 20 ml of 3:1 benzene–methanol in a three-necked flask fitted with a stirring bar and rubber septum. The catalyst was equilibrated with hydrogen at atmospheric pressure for 45 min. To this solution was added, *via* the septum, keto olefin **29** (115 mg, 0.565 mmol) in 4 ml of benzene–methanol, and the orange solution was stirred in a hydrogen atmosphere for 4.5 days. After 2.5 days the solvent was evaporated, and the residue was taken up in ether and percolated through basic alumina to give, after evaporation, longicamphenilone (**30**) (101 mg, 87%) as a light red-brown oil. An analytical sample was obtained by preparative glc: ir (film) 1750 cm^{-1} (C=O); nmr (CCl_4) δ 1.01 (s, 3 H, endo bridge methyl) and 0.91 (s, 6 H, exo and angular methyls).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.29; H, 10.83.

(±)-Longifolene (1). To longicamphenilone (**30**) (87 mg, 0.422 mmol) in 10 ml of anhydrous ether was added 10 ml of 1.3 *M* methyllithium, and the resulting solution heated for 3 hr at 48°. Shorter reaction times gave incomplete reaction. The excess methyllithium was destroyed by dropwise addition of water, and the reaction was worked up[20] to give 89 mg of carbinol as an oily solid: ir (film) 3470 cm^{-1} (OH).

The crude carbinol (89 mg, 0.401 mmol) in 7 ml of pyridine was treated with thionyl chloride (251 mg, 2.11 mmol) for 10 min at 0°. The reaction mixture was worked up[20] to give 79 mg (85%) of a colorless oil whose spectral properties were identical with those of (+)-longifolene. An analytical sample was obtained by preparative glc: ir (film) 3080, 1655, and 868 cm^{-1}; nmr (CCl_4) exocyclic methylene protons δ 4.72 (s, 1 H) and 4.46 (s, 1 H), endo methyl 0.99 (s, 3 H), exo methyl 0.95 (s, 3 H), and angular methyl 0.90 (s, 3 H).

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.09; H, 11.70.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their support of this work.

A Direct Determination of the Spatial Geometry of Molecules in Solution. I. Conformation of Chloroquine, an Antimalarial[1]

Neil S. Angerman,[2a] Steven S. Danyluk,*[2a] and Thomas A. Victor[2b]

Contribution from the Division of Biological and Medical Research, Argonne National Laboratory, Argonne, Illinois 60439, and the Department of Molecular Biology, Walter Reed Army Institute of Research, Washington, D. C. 20012.
Received February 11, 1972

Abstract: A three-dimensional structural determination is reported for the important antimalarial chloroquine (CQ) in acetone solution. The spatial structure was deduced from the results of detailed proton magnetic resonance studies employing a paramagnetic ion probe, tris(2,2,6,6-tetramethylheptane-3,5-dionato)praseodymium-(III), ($Pr(tmh)_3$). Pseudocontact shifts induced by $Pr(tmh)_3$ were measured at 220 MHz for all of the CQ protons up to a 1:1 CQ:$Pr(tmh)_3$ concentration ratio at 20 and 48°. Both the shift data and independent optical measurements were consistent with the formation of a 1:1 complex between CQ and $Pr(tmh)_3$ with equilibrium constants of 63 and 13 M^{-1} at 20 and 48°, respectively. An extensive analysis of the pseudocontact shift data was then carried out to obtain a set of coordinates for a time-averaged CQ structure which gives the best overall least-squares fit between calculated and observed chemical shifts for all protons in the molecule. A stereoscopic representation of the time-averaged CQ structure was constructed from the final sets of coordinates at each temperature. The three-dimensional structure of CQ, as found in the CQ·$Pr(tmh)_3$ complex in solution, is quite compact with the side chain curled over the plane of the quinoline ring. The indication of the compactness is given by the rather short distance of 7.4 Å between the N-1 and N-3 positions at 20°. The structure is opened up somewhat at the higher temperature but the essential features are not altered drastically. The solution structure differs markedly from the structure reported for diprotonated CQ in the crystalline state. Possible reasons for these differences are discussed as are the implications of the solution structure for the binding interaction of CQ with deoxyribonucleic acid. Finally, the present work illustrates the feasibility and merits of paramagnetic ion probes and shift agents in structure studies of biomolecules.

Recent detailed pmr studies show that a wide variety of aliphatic and aromatic compounds interact weakly with tris-β-diketone complexes of the lanthanide ions to produce dramatic chemical-shift changes in the proton resonances.[3] These chemical-shift variations have been used to resolve severe overlap of proton resonances,[4a] simplify complex spectra,[4b] and in some cases assign proton resonances from the relative magnitude

(1) Work supported in part by the U. S. Atomic Energy Commission.
(2) (a) Argonne National Laboratory; (b) Walter Reed Army Institute of Research; this paper is contribution no. 1025 from the Army Malaria Research Program.

(3) J. K. M. Sanders and D. H. Williams, *J. Amer. Chem. Soc.*, **93**, 641 (1971).
(4) (a) C. C. Hinckley, *ibid.*, **91**, 5160 (1969); (b) P. V. Demarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, *ibid.*, **92**, 5734 (1970).