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The Synthesis of Neoclovene

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Neoclovene, a product from acid-catalysed rearrangement of caryophyllene, has been synthesised in such a manner as to demonstrate the probable intermediacy of a specific carbonium ion derived from (4*S*,7*R*)-3,3,7,11-tetramethyltricyclo[5,4,0,$0^{1,4}$]undecan-11-ol (24) in the formation of neoclovene from caryophyllene. This work also provides additional support for the relative configuration assigned to neoclovene.

THE chemistry of caryophyllene (1), the major hydrocarbon constituent of oil of cloves (*Eugenia caryophyllita*), has been the subject of intense investigation since its first isolation in 1834.[1] Of particular interest is the ease with which caryophyllene undergoes acid-catalysed transannular ring closure to a mixture of clovene (2), caryolan-1-ol (3),[2] and neoclovene (4).[3]

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[1] For leading references see: A. Nickon, *Perfumery Essent. Oil Record*, 1954, **45**, 149; J. L. Simonsen and D. H. R. Barton, 'The Terpenes,' vol. III, Cambridge University Press, London, 1952, p. 39; *ibid.*, vol. V, 1957, p. 517; P. de Mayo, in 'The Chemistry of Natural Products,' ed. K. W. Bentley, vol. II, Interscience, New York, 1959, p. 286.

[2] O. Wallach and W. Walker, *Annalen*, 1892, **271**, 285; Y. Asahina and T. Tsukamoto, *J. Pharm. Soc. Japan*, 1922, **484**, 463; 1929, **491**, 1202.

[3] W. Parker, R. A. Raphael, and J. S. Roberts, *Tetrahedron Letters*, 1965, 2313; *J. Chem. Soc.* (*C*), 1969, 2634.

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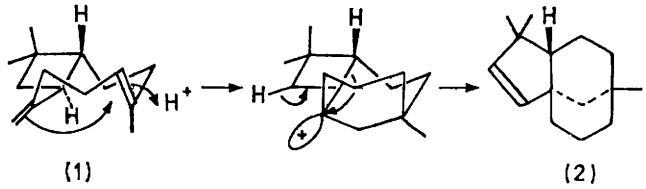
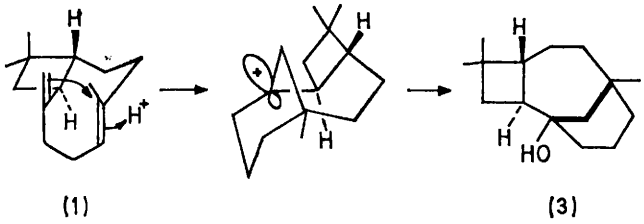
Indeed it was the elucidation of the structures (2) and (3) which led [4] to assignment of the accepted structure



(1) (2)

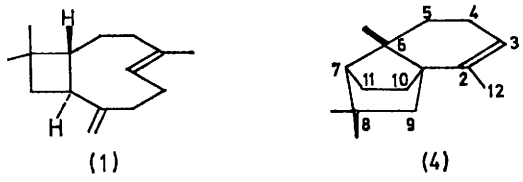
SCHEME 1

(1) for caryophyllene, recently confirmed by total synthesis.[5]



(1) (3)

SCHEME 2

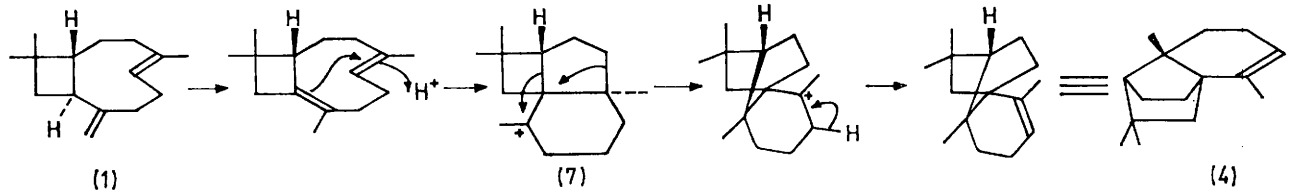


(1) (4)

The formation and final stereochemistry of compounds (2) and (3) have been fully rationalised by Barton [6] (Schemes 1 and 2) and recent deuterium-labelling experiments [7] have confirmed his proposals. It is, however, impossible to accommodate the formation of neoclovene (4) within these mechanisms and so an alternative pathway for this caryophyllene rearrangement was proposed [3] (Scheme 3). In this context, it is significant that isocaryophyllene (5) is not converted into clovene (2) or caryolan-1-ol (3) by mineral acid but instead gives neoclovene (4) and the tricyclic olefin (6) in high yield, presumably by the mechanism illustrated in Scheme 4.[8]

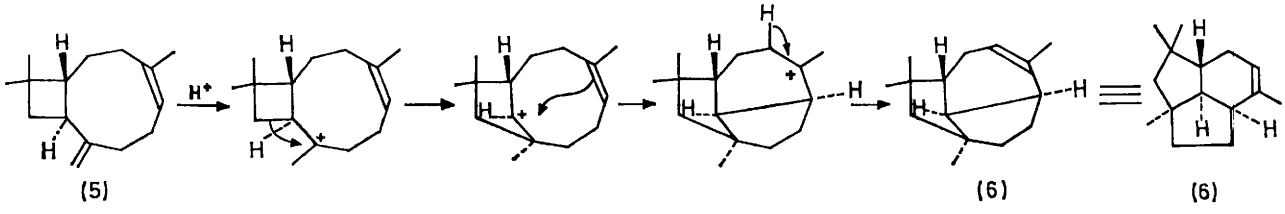
Some approaches to a total synthesis of neoclovene have been reported.[9] We decided to approach the problem by converting caryophyllene into one of the cationic intermediates in Scheme 3 and determining the subsequent behaviour of the cation. The tricyclic carbonium ion (7) was chosen as the primary synthetic goal for several reasons: the carbon framework is well known in caryophyllene chemistry, and since the ion is structurally very different from caryophyllene and neoclovene we felt that its conversion into neoclovene in good yield would lend considerable support to Scheme 3.

The epoxy-ketone (8) is readily available from caryophyllene by epoxidation of the trisubstituted double bond followed by oxidation,[10] and subsequent treatment with potassium hydroxide in methanol brings about an isomerisation to the tricyclic ketol (9). The absolute stereochemistry of (9), as depicted, has been confirmed [11] recently by a modification of the 'asymmetric synthesis' method,[12] and since the postulated cyclisation of caryophyllene to structure (7) involves bond formation between the carbon atoms corresponding to those involved in the transformation (8) → (9), it is reasonable to suppose that the cation (7) will have the same stereochemistry as (9). This is, in fact, the most likely stereochemistry; any other would involve either a *trans*-fused four- and five-membered ring system or a *trans*-indane skeleton. Hence this proposed synthesis



(1) (7) (4)

SCHEME 3



(5) (6) (6)

SCHEME 4

[4] (*a*) D. H. R. Barton and A. S. Lindsey, *J. Chem. Soc.*, 1951, 2988; (*b*) D. H. R. Barton, T. Bruun, and A. S. Lindsey, *J. Chem. Soc.*, 1952, 2210.

[5] E. J. Corey, R. B. Mitra, and H. Uda, *J. Amer. Chem. Soc.*, 1965, **87**, 5733.

[6] A. Aebi, D. H. R. Barton, A. W. Burgstahler, and A. S. Lindsey, *J. Chem. Soc.*, 1954, 4659.

[7] A. Nickon, F. Y. Edamura, T. Iwadare, K. Matsuo, F. J. McGuire, and J. S. Roberts, *J. Amer. Chem. Soc.*, 1968, **90**, 4196; F. Y. Edamura and A. Nickon, *J. Org. Chem.*, 1970, **35**, 1509.

[8] K. Gollnick, G. Schade, A. F. Cameron, C. Hannaway, J. S. Roberts, and J. M. Robertson, *Chem. Comm.*, 1970, 248.

[9] H. J. E. Loewenthal, *Israel J. Chem.*, 1966, **4**, 31.

[10] W. Treibs, *Chem. Ber.*, 1947, **80**, 56.

[11] A. Horeau and J. K. Sutherland, *J. Chem. Soc.* (*C*), 1966, 247.

[12] V. Prelog, *Helv. Chim. Acta*, 1953, **36**, 308.

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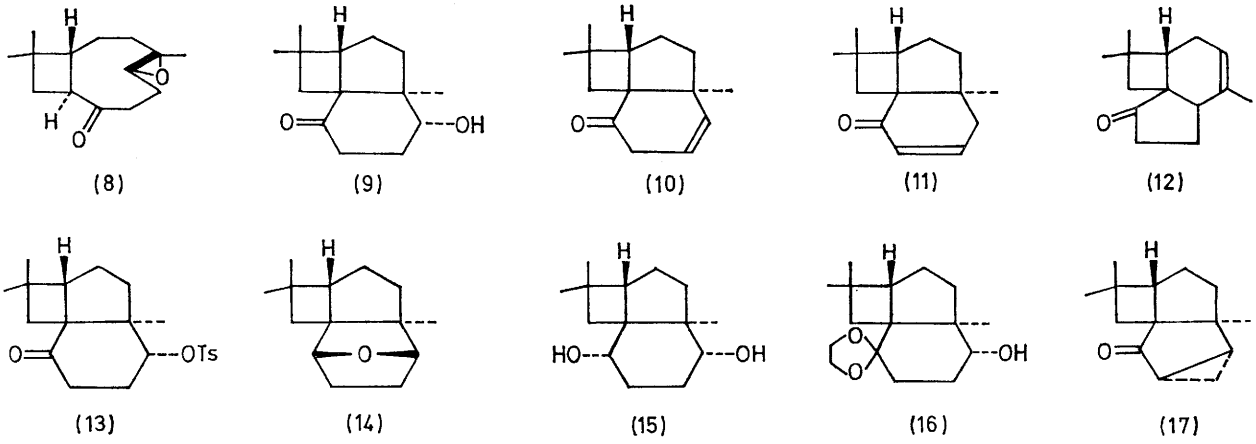
of neoclovene resolved itself into devising an efficient method of converting (9) into the tricyclic ketone (18), to be followed by some methylation procedure to give the tertiary alcohol (24).

Initially, the ketol (9) was prepared by the literature methods,[13] but in our hands, the yields of both caryophyllene epoxide and the epoxy-ketone (8) were lower than those reported. It was then found that epoxidation of caryophyllene could be carried out very efficiently with *m*-chloroperbenzoic acid, and subsequent oxidative cleavage was best achieved with osmium tetroxide–sodium periodate [14] in aqueous dioxan. The resultant epoxy-ketone (8) was then efficiently isomerised by treatment with methanolic potassium hydroxide.

In order to dehydrate (9), phosphoryl chloride and thionyl chloride were both used under a wide variety of conditions but in every case a complex mixture of at least five compounds resulted. Combined gas chromatography–mass spectrometry (g.l.c.–m.s.) showed that two of these compounds contained chlorine, and the parent ions (*m/e* 240) and isotopic distribution indicate that



these corresponded to the chlorides derived from replacement of the hydroxy-group. The crude products were also examined by u.v. spectroscopy; a fairly strong absorption observed at 233 nm might be attributed to the conjugated enone (11). Later, when a mixture of (10) and (11) was obtained free from other impurities, it was shown that two of the olefins formed in minor amounts by the preceding dehydrations corresponded to these olefins in their g.l.c.–m.s. behaviour.

The stereochemistry of structure (9) places the central bond of the indane skeleton exactly *trans*-antiparallel to the hydroxy-group, hence it is not surprising that a complex mixture results on dehydration, since rearrangement would be fairly simple and might well yield an olefin of the type (12). Although almost certainly some of the desired products were obtained, for synthetic purposes such an approach was deemed unsatisfactory, and no further investigations of the mixture were conducted.

It was felt that the foregoing complications resulting from probable skeletal rearrangements could be avoided if the hydroxy-group were removed by hydrogenolysis of the keto-tosylate (13). Treatment of (13) with lithium aluminium hydride in anhydrous ether under reflux for 36 h gave a two-component mixture which was readily separated by column chromatography. The less polar compound (m.p. 31—32°) showed no absorptions due to O–H or C=O in the i.r. spectrum, but did have C–O stretching bands at 1010 and 1030 cm^{-1}, together with some very sharp fine structure. The n.m.r. spectrum showed two highly asymmetric absorptions at τ 5·75 (1H) and 6·05 (1H). The data are consistent with the structure (14), and analysis and mass spectroscopy confirmed the molecular formula. The second product showed strong absorptions at *ca.* 3400 (O–H) and 1000—1100 (C–O) cm^{-1}, and from its m.p. and optical rotation it was assumed to be the diol (15), obtained by Barton [15] from treatment of the ketol (9) with sodium in propanol.

Hydride attack from the α-face on the ketone (13) correctly orients the developing oxy-anion for intramolecular displacement of the tosylate group to give the oxabicyclo[2,2,1]-structure (14), whereas corresponding attack on the β-face cannot readily lead to a transannular reaction, and so one might have expected normal hydrogenolysis of the tosylate to occur. Surprisingly, this was not the case; S–O is preferred to C–O cleavage in this compound. While this is not without precedent,[16] it is uncommon. Accordingly, we felt that the carbonyl group in ketol (9) should be prevented from participating in the hydrogenolysis before a final judgment on this synthetic approach could be made, and so the carbonyl group was protected [17] and the corresponding tosylate was then treated with lithium aluminium hydride in ether. The sole product was identical (i.r. and t.l.c.) with the starting hydroxy-acetal (16). Further, on

[13] See refs. 4*a* and 10; E. W. Warnhoff and V. Srinivasan, *Canad. J. Chem.*, 1966, **44**, 2259.
[14] R. Pappo, D. S. Allen, jun., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, 1956, **21**, 478.
[15] See ref. 4*b*.
[16] H. Schmid and P. Karrer, *Helv. Chim. Acta*, 1949, **32**, 1371.
[17] A. Marquet, M. Dvolaitzky, H. B. Kagan, L. Mamlok, C. Ouannes, and J. Jacques, *Bull. Soc. chim. France*, 1961, 1822.

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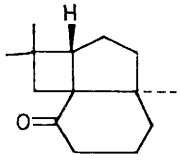
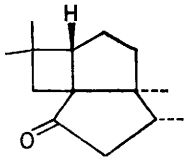
warming with 4N-hydrochloric acid for 10 min, the ketol (9) was recovered. Thus, in this case, it is apparent that hydrogenolysis of the tosylate does not proceed normally, with cleavage of the S–O bond being totally preferred to the more usual C–O cleavage.

In an alternative attempt to remove the hydroxy-group from compound (9), the keto-tosylate (13) was treated with sodium ethoxide in ethanol. The resultant product (m.p. 66—67°) showed a band at 1717 cm^{-1} but no hydroxy-, tosylate, or olefinic absorption in its i.r. spectrum. Elemental analysis and mass and ^1H n.m.r. spectra showed this compound to be the novel cyclopropyl ketone (17) resulting from tosylate elimination by the enolate anion.

Since the hydroxy-group had been removed in high yield, it was expected that the ketone (17) might be of use if the cyclopropane ring could be hydrogenolysed to give structure (18) rather than (19) or (20). The tetracyclic ketone (17) was hydrogenated in acetic acid [18] over palladium–charcoal until uptake ceased (1 equiv. absorbed). The n.m.r. and i.r. ($\nu_{C=O}$ 1725 cm^{-1}) spectra confirmed that hydrogenolysis of the 2-oxobicyclo[3,1,0]hexane fragment of (17) had led to a cyclopentanone (three tertiary methyl resonances and a doublet centred at τ 9·03). Of the two possible products, the β-methyl ketone (19) * is favoured on the basis of the reported preference [19] for carbon–carbon bond cleavage between the carbon atom activated by the ketone group and the carbon atom bearing the least number of substituents. Evidence in support of structure (19) was obtained from ^1H n.m.r. solvent shift studies.



(18)



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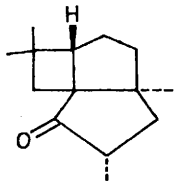
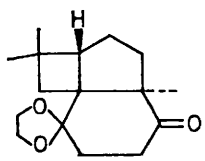


(20)



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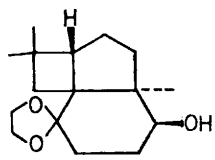
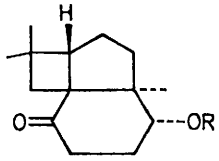


(22)

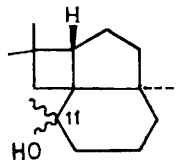
At this stage it was felt that the hydroxy-acetal (16) could be oxidised to the oxo-acetal (21) prior to a Wolff–Kishner reduction of the ketone function; hydrolysis of the resultant tricyclic acetal should then yield the elusive ketone (18). Snatzke's oxidation method [20] was most convenient for the conversion of (16) into (21), but unfortunately, Wolff–Kishner reduction of (21) gave a mixture of products from which only 9% of the desired acetal was isolated by preparative t.l.c. The two other major products were hydroxy-acetals, and since one of them was identical with (16), the other was taken to be its epimer (22) from the similarity of their i.r. spectra.

Although the keto-acetate (23; R = Ac) did not undergo thermal decomposition even at 450°, the corresponding carbonate (23; R = CO_2Et) was smoothly decomposed at 350° to a mixture of the conjugated and non-conjugated ketones (11) and (10) in a ratio of 1 : 3, which was not altered [21] by treatment with either acid or base. Hydrogenation of this mixture in ethyl acetate over 10% palladium–charcoal then gave (18), identical with the ketone obtained from Wolff–Kishner reduction of (21). Treatment of the tricyclic ketone (18) with methylmagnesium iodide then gave a poor yield of a single tertiary alcohol (24) whose stereochemistry at C-11 is as yet undetermined.

When this alcohol was treated in ether with concentrated sulphuric acid under conditions identical to those employed in the rearrangement of caryophyllene, a three-component mixture was obtained. The major product (96%) was a hydrocarbon whose mass spectrum was identical to that of neoclovene. A second hydrocarbon, *M*, 204 (1% yield), had a retention time on g.l.c. very close to that of neoclovene but exhibited a completely different mass spectral fragmentation pattern. The third component, unchanged alcohol (24), was separated from the hydrocarbons by column chromatography and although the small amount of the second



(23)



(24)

hydrocarbon could not be removed from the synthetic neoclovene, it did not interfere to any extent with a comparison of the synthetic and authentic hydrocarbons. Thus, the n.m.r. and i.r. spectra were identical and g.l.c. analysis by co-injection on four different stationary phases (including two 50-m capillary columns) demonstrated the identity of the two samples. The synthetic neoclovene also exhibited $[\alpha]_D^{25}$ −69° (*c* 0·40 in $CHCl_3$) which compares reasonably well with that of authentic material, $[\alpha]_D^{25}$ −72° (*c* 1·78 in $CHCl_3$).

The fact that the tertiary alcohol (24) can be converted into neoclovene *in high yield* is strong support for Scheme 3 as the mechanism whereby caryophyllene rearranges into neoclovene, since an alternative ring

* β Refers to the location and not the stereochemistry. From solvent shift data and the mechanism of formation, the methyl group is taken to be α in configuration.

[18] A. Windaus and O. Dalmer, *Ber.*, 1919, **52**, 162; C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 1952, 3361.

[19] R. L. Augustine, 'Catalytic Hydrogenation,' Arnold, London, 1965, p. 133.

[20] G. Snatzke, *Chem. Ber.*, 1961, **94**, 729.

[21] K. G. Lewis and G. J. Williams, *Tetrahedron Letters*, 1965, 4573.

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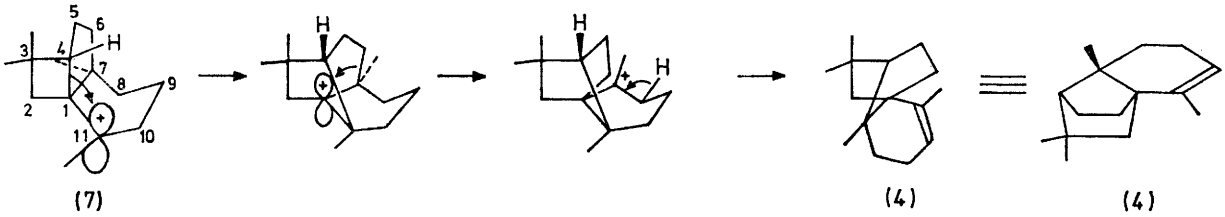
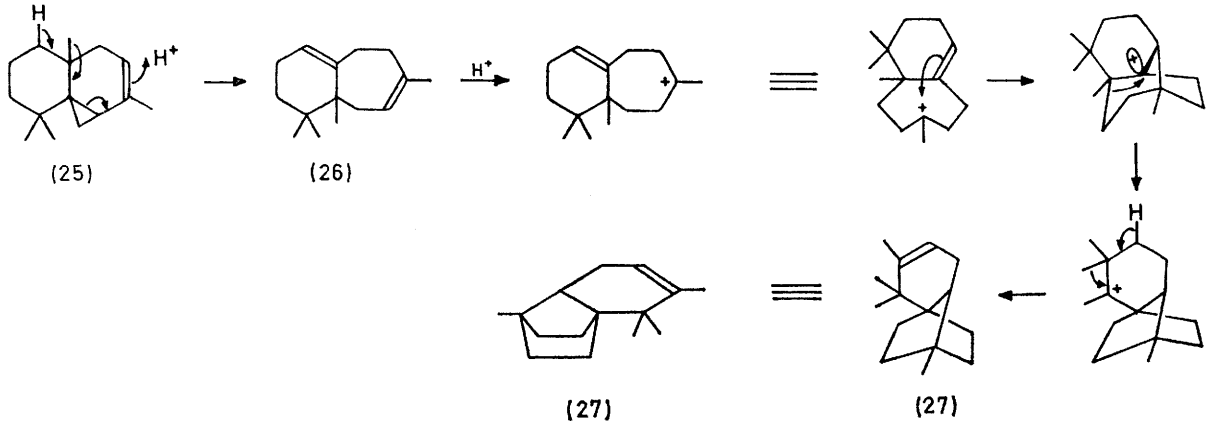
opening of the cation (7) to a protonated form of caryophyllene (1) or isocaryophyllene (5) would be expected to give caryolan-1-ol, clovene, and the tricyclic olefin (6) in addition to neoclovene.

When the rearrangement of cation (7) into neoclovene is examined with molecular models (Scheme 5), it can be seen that the carbon–carbon bonds involved (1,4- and 6,7-) are *cis*-oriented and are therefore necessarily eclipsed because of lack of conformational mobility in (7). Hence this rearrangement could be cited as an exception to the normal antiperiplanar arrangement of



SCHEME 5



SCHEME 6

σ-bonds in multiple Wagner–Meerwein rearrangements,[22] and probably involves discrete intermediates proceeding *via* stereospecific solvation of the incipient carbonium ion at C-1 during migration of C-4 to C-11, followed by displacement of the solvating species by C-6 in the more usual *trans*-antiparallel fashion.[23]

Dauben and Friedrich have recently examined the acid-catalysed rearrangements of thujopsene (25) to structure (26) in $HClO_4$–acetone [24] and to structure (27) in $HClO_4$–HOAc.[25] It is significant that they propose a mechanism (Scheme 6) which involves a Wagner–Meerwein shift with ring-contraction to a bridgehead bicyclo[3,2,1]octane carbonium ion as the means of forming the bicyclo[2,2,1]heptane part of structure (27), *cf.* Scheme 5. An interesting feature of Scheme 5 is the final *syn*-configuration of the methyl group at C-6 in neoclovene with respect to the *gem*-dimethyl group at C-8. The successful synthesis of neoclovene from (18) would imply that the relative configuration of these two centres must also be *syn* in the authentic material, a configurational assignment which has recently been obtained from o.r.d. studies on a degradation product of neoclovene.[3]

EXPERIMENTAL

M.p.s were recorded on a Kofler hot-stage apparatus and are corrected; b.p.s are not corrected. The adsorbents used in column chromatography were commercial Woelm alumina, Mallinckrodt silicic acid, and 25% silver nitrate on 140—200 mesh silica gel (Applied Science Laboratories). Thin (0·25 mm) and thick (1·00 mm) layer chromatographic plates were prepared from Merck Kieselgel G and were developed with either cerium(IV) ammonium sulphate or iodine. Analytical g.l.c. was carried out on a Pye-Argon Chromatogram with 4 ft × 4 mm i.d. packed glass columns; analytical capillary columns were used with a Perkin-Elmer F11 instrument. Preparative g.l.c. separations were effected with an Aerograph Autoprep A-700 instrument.

When necessary, solvents were purified and dried in the recommended manner, and reagents were either distilled or recrystallised. Light petroleum refers to the fraction of b.p. 40—60° and all organic extracts were dried over anhydrous $MgSO_4$ unless otherwise stated.

I.r. spectra were recorded on a Unicam SP 200 instrument and high resolution spectra were obtained with the Unicam

[22] For a review, see *inter al.* J. F. King and P. de Mayo in 'Molecular Rearrangements,' ed. P. de Mayo, Interscience, New York, 1963, part II, ch. 13; J. A. Berson, *Angew. Chem. Internat. Edn.*, 1968, **7**, 779.

[23] J. W. Cornforth, R. H. Cornforth, G. Popjak, and L. Yengoyan, *J. Biol. Chem.*, 1966, **241**, 3970.

[24] W. G. Dauben and L. E. Friedrich, *Tetrahedron Letters*, 1967, 1735.

[25] W. G. Dauben and L. E. Friedrich, Abstracts of 5th International Symposium on the Chemistry of Natural Products, London, 1968, F.13, p. 296.

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SP 100 double-beam spectrophotometer equipped with an SP 130 sodium chloride prism-grating double monochromator, operated under vacuum. U.v. absorption spectra were measured with an automatic Unicam SP 800 spectrometer.

N.m.r. spectra were measured with tetramethylsilane as internal reference for solutions in deuteriochloroform. Benzene was also used during the studies on solvent shifts and the spectra obtained with this solvent are indicated in the text. Spin-decoupling experiments were performed on a Varian 100 MHz instrument; all other spectra were recorded with a Perkin-Elmer 60 MHz spectrometer. Mass spectra were determined on a G.E.C.-A.E.I. MS 9 instrument; volatile mixtures were normally examined by means of the L.K.B. 9000 g.l.c.–m.s. machine.

Purification of Caryophyllene (1).—Commercial grade caryophyllene (Koch-Light) was shown (g.l.c.) to contain considerable amounts of phenols (mostly 4-allyl-2-methoxyphenol) and 2,6,6,9-tetramethylcycloundeca-1,4,8-triene (humulene). The following purification procedure gives >99% pure caryophyllene.

Crude caryophyllene (150 g), dissolved in light petroleum (500 ml), was washed several times with dilute aqueous sodium hydroxide and then water until the aqueous layer was neutral. The organic layer was then washed (3×) with silver nitrate solution (50%) to remove the humulene, and finally with water. The petroleum extract was dried and evaporated and the residual, colourless oil was adsorbed on alumina (1 kg, grade II) and eluted with light petroleum. Evaporation of the eluate and distillation afforded pure caryophyllene (1), n_D^{20} 1·4986, b.p. 75—76° at 0·14 mmHg, $\nu_{max.}$ (film) 3070, 1670, 1635, 890, 825, and 815 cm^{-1}.

Caryophyllene Epoxide.—To a stirred solution of caryophyllene (11·00 g, 0·054 mol) in chloroform (75 ml) was added *m*-chloroperbenzoic acid (11·00 g, estimated 85% active, 0·0542 mol) in chloroform (120 ml) during 10 min with the temperature kept at 25°. The mixture was stirred for 12 h, after which a white crystalline solid (*m*-chlorobenzoic acid) had precipitated. Any excess of peroxy-acid (starch–iodide paper) was destroyed by the slow addition of sodium sulphite solution (10%). The chloroform solution was then washed with saturated sodium hydrogen carbonate solution and brine, and dried; the chloroform was removed to give an oily, semi-solid mass (12·10 g, 96%), distillation of which gave a small amount of caryophyllene in addition to the desired epoxide (11·00 g; b.p. 79—81° at 0·1 mmHg). Although the epoxide solidified in the receiver during distillation, it was recrystallised from ethanol at low temperature to give white crystals, m.p. 62—63°.

Caryophyllene Epoxy-ketone (8).—(*a*) Potassium permanganate (10 g, 0·057 mol) was added in small portions during 48 h to a stirred solution of caryophyllene epoxide (4·2 g, 0·019 mol) in acetone (50 ml) containing water (0·5 ml). The dark red solution was filtered through Celite 535; evaporation of the dried filtrate gave a crude red oil, which was dissolved in ether, washed with water, and dried. Removal of the ether gave a thick, yellow oil from which crystalline material was obtained by trituration with light petroleum. Recrystallisation from methanol and thorough drying gave colourless crystals (1·3 g, 30%), m.p. 63—64°.

(*b*) A stream of ozonised oxygen was passed through a solution of the epoxide (440 mg, 2 mmol) in ethyl acetate (4·0 ml) and pyridine (500 mg) at −80°, until a pale blue colour persisted (*ca.* 2 h). The mixture warmed to room temperature very slowly, and was then treated with dilute hydrochloric acid and ether; the ethereal layer was separated, washed with sodium hydrogen carbonate solution and then brine, and dried. Evaporation gave a yellow oil (390 mg), chromatography of which on neutral alumina (15 gm, grade II) with light petroleum (b.p. 60—80°) gave pure epoxy-ketone (8) (280 mg, 63%). *N.B.* On a larger scale, attempted distillation of the crude products before chromatography resulted in polymerisation to a brown tar, which contained no epoxy-ketone.

(*c*) Osmium tetroxide (137·5 mg, 5·4 mmol) in ether (5 ml) was added to a stirred solution of caryophyllene epoxide (11 g, 0·05 mol) in water (50 ml) and peroxide-free dioxan (150 ml). After 10 min, the black solution was treated with sodium periodate (22·47 g, 0·105 mol) in small portions during 30 min and then stirred at room temperature for 12 h. To ensure completion of the reaction more osmium tetroxide (69 mg, 2·5 mmol) and sodium periodate (5·49 g, 0·026 mol) were added and stirring was continued for a further 20 h. Sodium hydrogen sulphite solution (50 ml; saturated) was added, together with ether (150 ml); the mixture was stirred for 1 h and then thoroughly extracted with ether. The combined extracts were washed with brine, dried, and evaporated to leave a brown semi-solid mass (9·5 g) which was chromatographed on neutral alumina (250 g, grade III) with light petroleum (b.p. 60—80°). The first fractions (2 g) contained the epoxy-ketone (8) contaminated with starting material, and further fractions gave the pure epoxy-ketone (8) (6·6 g, 60%), m.p. 63—64°.

An alternative work-up procedure, on a small-scale, involving hydrogen sulphide decomposition of the osmate ester gave cleaner products.

The Ketol (9).—The ketol (9) was prepared from caryophyllene epoxy-ketone (8) as described previously.[4a]

Attempted Dehydrations of the Ketol (9).—(a) *Phosphoryl chloride in pyridine under reflux.* Redistilled phosphoryl chloride (0·2 ml, 2·18 mmol) was added to an ice-cold solution of the ketol (9) (100 mg, 0·45 mmol) in anhydrous pyridine (5 ml) and heated under reflux for 30 min. The cooled mixture was diluted with water and thoroughly extracted with ether, and the combined extracts were washed with 4N-hydrochloric acid and brine and then dried. Removal of the solvent *in vacuo* yielded a crude, brown oil (95 mg), which separated into at least three spots on t.l.c. with 10% ethyl acetate–light petroleum, but was seen to contain five compounds on g.l.c. A detailed g.l.c.–m.s. examination of the products confirmed the presence of a mixture of olefins and chloro-compounds.

(b) *Phosphoryl chloride in pyridine at room temperature.* Redistilled phosphoryl chloride (0·1 ml, 1·09 mmol) was added to a solution of the ketol (9) (10 mg, 0·045 mmol) in anhydrous pyridine, and the flask was kept at room temperature for 3 days. A work-up procedure as in (a) yielded a similarly complex mixture of products.

(c) *Thionyl chloride in pyridine under reflux.* A solution of the ketol (9) (100 mg, 0·45 mmol) and thionyl chloride (1 ml, 14·0 mmol) in anhydrous pyridine (5 ml) was heated under reflux under a nitrogen atmosphere for 10 min and then poured into ice–water. The same work-up yielded an equally complex mixture of products but in different proportions from (a) and (b).

(d) *Thionyl chloride in benzene under reflux.* A stirred solution of the ketol (9) (350 mg, 1·58 mmol) in anhydrous benzene (12 ml) cooled to 0°, was treated with redistilled

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thionyl chloride (2 ml, 28·0 mmol) under nitrogen and heated under reflux. T.l.c. showed that almost all of the starting material had been consumed after 2 h, but the principal products were the corresponding chlorides which did not seem to undergo dehydrohalogenation.

Keto-tosylate (13).—Recrystallised toluene-*p*-sulphonyl chloride (476 mg, 0·25 mmol) was added to a solution of the hydroxy-ketone (9) (500 mg, 2·25 mmol) in anhydrous pyridine (3 ml) and the mixture was set aside at 0° overnight. Ether and water were added and the ethereal layer was washed twice each with 0·25N-hydrochloric acid and brine, then dried and evaporated *in vacuo* at room temperature to give the *tosylate* (13) as needles (760 mg, 90%), m.p. 144—146° (from ether–light petroleum), $\nu_{max.}$ (Nujol) 1690, 1600, 1185, and 1175 cm^{-1}.

Reduction with Lithium Aluminium Hydride of Keto-tosylate (13).—A solution of the foregoing keto-tosylate (760 mg, 2·02 mmol) in anhydrous ether (15 ml) was heated under reflux with lithium aluminium hydride (152 mg, 4·0 mmol) for 36 h. Excess of the reducing agent was destroyed by dropwise addition of water, and then the ethereal layer was filtered and evaporated to give an oil (400 mg). This was chromatographed on neutral alumina (20 g, grade III) with light petroleum to give an oil which slowly crystallised to give the *ether* (14) (320 mg, 86%) and sublimed to form fine needles, m.p. 31—32°, $[\alpha]_D^{25}$ −36° (*c* 1·825), $\lambda_{max.}$ (molten film) 1465, 1445, 1380, 1370, 1030, 1010, 950, and 900 cm^{-1}, τ 5·75 (1H, m), 6·05 (1H, m), 8·8 (3H, s), 9·09 (3H, s), and 9·18 (3H, s) (Found: C, 81·3; H, 10·75. $C_{14}H_{22}O$ requires C, 81·5; H 10·75%).

Further elution with 10% ether–light petroleum gave the diol (15) as small prisms (50 mg, 12%), m.p. 160—161° (from chloroform–light petroleum), $[\alpha]_D^{25}$ −72° (*c* 0·535) {lit.,[15] m.p. 159—159·5°, $[\alpha]_D$ −69° (*c* 1·24)}, $\nu_{max.}$ (Nujol) 3400, 1110, 1070, 1045, 1020, and 990 cm^{-1} (Found: C, 74·95; H, 10·8. Calc. for $C_{14}H_{24}O_2$: C, 74·9; H, 10·95%).

Hydroxy-acetal (16).—(*a*) Freshly distilled boron trifluoride–ether complex (2 ml) was added to a solution of the ketol (9) (100 mg, 0·45 mmol) in ethane-1,2-diol (20 ml) and the mixture was set aside for 2 days at room temperature. Normal work-up with chloroform and water gave only unchanged starting material.

(*b*) A solution of the ketol (9) (80 mg, 0·36 mmol), ethane-1,2-diol (300 mg, 4·84 mmol) and toluene-*p*-sulphonic acid (50 mg, 0·263 mmol) in anhydrous benzene (15 ml) was heated under reflux under a Soxhlet thimble containing calcium hydride for 16 h. The cooled mixture was diluted with water and extracted with ether, and the combined extracts were washed repeatedly with brine and dried. Evaporation left a semi-solid oil (65 mg), which was shown by t.l.c. to contain a considerable amount of starting material in addition to material later identified as the desired hydroxy-acetal (16).

(*c*) A mixture of the ketol (9) (2·04 g, 9·18 mmol), ethane-1,2-diol (3 ml, 53·6 mmol), toluene-*p*-sulphonic acid (150 mg, 0·789 mmol), and ethyl orthoformate (6 ml) was heated slowly in an oil-bath to 150° and the ethanol and ethyl formate produced were distilled off during 3 h. The mixture was cooled, poured into sodium hydrogen carbonate solution (100 ml), and extracted with ether (100 ml); the extract was washed with brine, dried, and evaporated. The residual yellow oil (2·1 g) was adsorbed on basic alumina (80 g; grade V) from ether; elution with 25% ether–light petroleum gave the *hydroxy-acetal* (16) as a crystalline solid (1·8 g, 72%), which sublimed to form needles, m.p. 100—101°, $\nu_{max.}$ (Nujol) 3400, 1140, 1080, 1030, 1020, 980, 950, and 920 cm^{-1}, τ 6·1 (4H, s), 8·9 (3H, s), and 9·2 (6H, s) (Found: C, 72·0; H, 9·75%; *M*, 266. $C_{16}H_{26}O_3$ requires C, 72·15; H, 9·85%; M, 266).

Acetal-tosylate.—The hydroxy-acetal (16) (30 mg, 0·113 mmol) and toluene-*p*-sulphonyl chloride (30 mg, 0·157 mmol) were dissolved in the minimum amount of dry pyridine and kept at 0° overnight. Normal work-up (omitting the mineral-acid wash) gave a white, crystalline solid (35 mg), $\nu_{max.}$ (Nujol) 1600, 1180, 1170, 1080, 960, 940, 920, 880, 860, and 680 cm^{-1}. Without further purification this product was reduced as follows.

Reduction with Lithium Aluminium Hydride of the Acetal-tosylate.—The solid tosylate (35 mg, 0·083 mmol) dissolved in ether was added dropwise to a stirred, ice-cold solution of lithium aluminium hydride (200 mg) in ether (15 ml) and heated under reflux for 24 h. Water was added dropwise to the cooled solution until no more hydrogen was evolved, and the solvent was removed *in vacuo* from the filtered solution yielding a semi-solid (22 mg). Comparison (t.l.c. and i.r.) showed that the product was the hydroxy-acetal (16). This was confirmed by warming the product with 4N-hydrochloric acid for 10 min, ether extraction affording crystalline ketol (9) (17 mg, 90%).

Cyclopropyl Ketone (17).—A solution of the keto-tosylate (13) (300 mg, 0·78 mmol) in 10% sodium ethoxide in ethanol (12 ml) was heated under reflux for 1·5 h, then diluted with water and extracted with ether. The combined extracts were washed with water, dried, and evaporated to give the crystalline *cyclopropyl ketone* (17) (120 mg, 75%), which sublimed to form needles, m.p. 66·5—67°, $\nu_{max.}$ (CCl_4) 3069, 3016, 2994, 1717, 1033, 1020, and 1006 cm^{-1}, τ 7·61 (1H, t, *J* 7 Hz), 8·00—8·45br (8H, m), 8·77 (3H, s), 8·85 (3H, s), 9·05 (3H, s), and 9·55 (1H, q, *J* 4 Hz) (Found: C, 82·5; H, 9·7%. $C_{14}H_{20}O$ requires C, 82·3; H, 9·85%).

Hydrogenation of the Cyclopropyl Ketone (17).—The cyclopropyl ketone was recovered unchanged from attempted hydrogenation with either pre-reduced platinum oxide in methanol or 10% palladium–charcoal in ethyl acetate; both reactions were conducted at room temperature and under 1 atm of hydrogen.

(*a*) A solution of the cyclopropyl ketone (17) (200 mg, 0·98 mmol) in glacial acetic acid (75 ml) was shaken with 10% palladium–charcoal in the presence of hydrogen. After 10 h, 1 mol. equiv. of hydrogen had been consumed. The filtered solution was diluted with water, neutralised with dilute sodium hydroxide solution, and extracted with ether. The combined extracts were washed with water, dried, and evaporated to give a mobile oil (201 mg, 100%). G.l.c. (10% Apiezon L, 150°; flow rate 43 ml min^{-1}) showed the material to be a single compound (R_t 18·0; *cf.* starting material R_t 22·0 min). Small-scale distillation in a sublimation tube gave an oil, shown to be the *cyclopentanone* (19), b.p. (block temp.) 100—110° at 10 mmHg, $\nu_{max.}$ (liquid) 2980, 1725, 1460, 1430, 1410, 1380, 1364, and 1275 cm^{-1} (Found: C, 81·7; H, 10·85. $C_{14}H_{22}O$ requires C, 81·5; H, 10·75%).

(*b*) The cyclopropyl ketone (17) (70 mg, 0·343 mmol) was added to pre-reduced Adams catalyst (50 mg) in glacial acetic acid (15 ml) and shaken vigorously under hydrogen for 10 h (uptake *ca.* 2 mol. equiv.). Normal work-up produced a liquid (72 mg), ν_{O-H} *ca.* 3500s cm^{-1}, shown (g.l.c.) to consist of at least three alcohols [R_t (10% Apiezon

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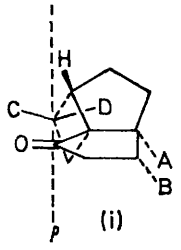
L, 150°; flow rate 43 ml min^{-1}) 24·5, 21·0, and 19·3 min]. The crude alcohols were dissolved in AnalaR acetone (5 ml) and 8N-Jones reagent was added dropwise until an orange colour persisted in the supernatant liquid. Normal ether–water work-up yielded a yellow oil (65 mg, 90% overall), $\nu_{max.}$ 1725 and 1710sh cm^{-1}. G.l.c. of this oil showed it to contain the ketones (19) and (17) in the ratio of 9 : 1.

The empirical rule [26] most commonly used in correlating solvent shifts may be stated as follows. If a plane (*P*) is drawn through the carbon atom of a carbonyl group and at right angles to the C–O bond, then protons in the environment of *P* show distinct changes in chemical shift on alteration of solvent. The magnitude and sign of these changes depend critically on the stereorelationship between *P* and the proton being considered. Hence, if one defines $\Delta\tau = \tau(C_6H_6) - \tau(CDCl_3)$, then protons on that side of *P* nearest the oxygen atom show negative $\Delta\tau$ values; the effect is small at very small distances from *P*, increasing to a maximum at *ca.* 3 Å, and then decreasing almost immediately. Protons on the other side of *P* show positive values of $\Delta\tau$ which also increase as one moves away from *P* to a maximum and then decrease rapidly.

TABLE 1



(i)

Methyl group	$\tau(C_6H_6)$	$\tau(CDCl_3)$	$\Delta\tau$
A(s)	9·46	9·21	+0·25
B(d)	9·30	9·03	+0·27
C(s)	8·70	8·83	−0·13
D(s)	9·21	9·09	+0·12

Consideration of the data in Table 1 together with a molecular model (i) supports the proposal that the compound formed by cyclopropane opening is the β-methyl cyclopentanone. If the methyl signals are properly assigned in both solvents, it can be seen that the shifts for the two methyl groups on the cyclopentane ring are almost the same, which would require two β-methyl groups to be *cis* to one another. (An α-methyl group would give a shift of only *ca.* 0·1 p.p.m.) The *gem*-dimethyl system in the four-membered ring is bisected by the plane (*P*), so that one methyl group suffers a downfield shift of almost the same magnitude as the other undergoes in the upfield direction. No deuteriation studies were carried out to check the correctness of the methyl assignments; hence structure (19) is not a definitive assignment.

Reduction with Lithium Aluminium Hydride of the Cyclopropyl Ketone.—A solution of the ketone (17) (160 mg, 0·784 mmol) in anhydrous ether (25 ml) was treated with an excess of lithium aluminium hydride (100 mg) and stirred for 24 h. Work-up as for previous reductions gave an oil (153 mg), ν_{O-H} (liquid) 3500 cm^{-1}, which was shown by g.l.c. to contain two of the alcohols already obtained by reduction of the ketone (17) with platinum oxide in acetic acid, these having R_t 24·5 and 21·0 min (10% Apiezon L, 150°; flow rate 43 ml min^{-1}).

Oxidation of the mixture with Jones reagent gave back only the starting ketone (17) as a crystalline solid.

The Oxo-acetal (21).—(*a*) 8N-Jones reagent was added dropwise to a stirred, ice-cold solution of the hydroxy-acetal (16) (18 mg, 0·0676 mmol) in AnalaR acetone (5 ml) until an orange colour persisted. Water was added and the mixture was extracted with light petroleum; the extracts were washed with brine, dried and evaporated to furnish an oil (17 mg), $\nu_{max.}$ (liquid) 1720—1680 cm^{-1}, which also showed acetal absorptions at 1000—900 cm^{-1} which were less intense than would be expected. T.l.c. confirmed that partial hydrolysis of the protecting acetal group had occurred, two distinct spots being evident.

(*b*) The Sarett reagent was prepared by adding chromium trioxide (35 mg) in small portions with stirring to anhydrous pyridine (1 ml), and to this was added a solution of hydroxy-acetal (30 mg, 0·1128 mmol) in anhydrous pyridine (1 ml). The mixture was left at room temperature for 5 h, then poured into ice–water, extracted with light petroleum. The extract was washed with water and brine, dried, and evaporated leaving an oil (25 mg). T.l.c. again showed two components, the oxo-acetal (21) and unchanged starting material (very small amount). The i.r. spectrum (film) confirmed this analysis, showing a strong absorption 1705 (C=O) cm^{-1}, but also a much smaller one at 3400 (O–H) cm^{-1}.

(*c*) Chromium trioxide (1·4 g) was added with swirling to a solution of hydroxy-acetal (16) (1·0 g, 3·76 mmol) in dry dimethylformamide (50 ml) and concentrated sulphuric acid (2 drops). The mixture was kept at room temperature for 20 h, then poured into ice–water and ether. The ethereal layer was washed repeatedly with brine, dried, and evaporated. The residual oil (950 mg) was chromatographed on neutral alumina (40 g; grade III) with light petroleum–ether to give the crystalline *oxo-acetal* (21) (800 mg, 80%) which sublimed to form *needles*, m.p. 65—66°, $\nu_{max.}$ (Nujol) 1705, 1190, 1135, 1115, 1075, 1020, 990, 960, 938, and 915 cm^{-1}, τ 5·92 (4H, s), 6·8—7·8 (4H, m), 7·9—8·7 (7H, m), 8·79 (3H, s), 8·89 (3H, s), and 9·10 (3H, s) (Found: C, 72·45; H, 9·15. $C_{16}H_{24}O_3$ requires C, 72·7; H, 9·15%).

The Ethylene Acetal of (18).—A mixture of metallic sodium (50 mg) [dissolved in redistilled bis-(2-hydroxyethyl) ether (2 ml)], oxo-acetal (21) (100 mg, 0·369 mmol), and hydrazine hydrate (2 ml) was heated under reflux for 1 h and the excess of hydrazine hydrate and the water formed were then distilled off. After a further 3 h at 200°, water was added to the cooled solution and the mixture was extracted thoroughly with ether. The combined extracts were washed with brine, dried, and evaporated, leaving a yellow oil (65 mg). T.l.c. showed three main products, which were separated (1 mm preparative chromatoplate) with 40% ether–light petroleum. Of the two slow-running compounds, one was identical with the hydroxy-acetal (16); the other, with a similar i.r. spectrum, is assumed to be the epimeric hydroxy-acetal. The fast-running material, believed to be the desired acetal, was obtained as an oil (9 mg, 9%) with no C=O or O–H absorptions but still containing the characteristic acetal bands in its i.r. spectrum.

Tricyclic Ketone (18).—An ethereal solution of the foregoing acetal (9 mg, 0·0338 mmol) was shaken for 30 min with 4N-hydrochloric acid (10 ml), then washed with sodium hydrogen carbonate solution and brine, dried, and evaporated. The residual oil (7 mg) showed $\nu_{max.}$ (liquid) 2980, 1695, 1470, 1430, 1385, 1370, 1325, and 1290 cm^{-1} *m/e* 206 (M^+). The mass spectral fragmentation pattern was consistent with the tricyclic ketone structure (18),

[26] N. S. Bhacca and D. H. Williams, *Tetrahedron Letters*, 1964, 3127; J. D. Connolly and R. McCrindle, *Chem. and Ind.*, 1965, 379.

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showing an intense peak corresponding to loss of 55 m.u. (*i.e.* $^{+}O{=}C{\cdot}CH{=}CH_2$).

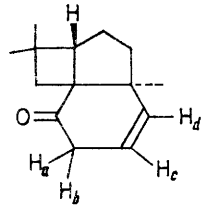
This compound was identical (g.l.c.–m.s. and i.r.) with the ketone (18) obtained by pyrolysis.

Carbonate Ester (23; R = CO_2Et).—Redistilled ethyl chloroformate (3·5 ml, 36·8 mmol) was added dropwise to a stirred solution of the ketol (9) (4·5 g, 20·2 mmol) in anhydrous pyridine; the temperature was maintained at *ca.* −10 °C by an ice–salt bath. A vigorous reaction occurred during addition giving a pink solution and a heavy white precipitate of pyridine hydrochloride. The mixture was stirred for 1 h more, left at 0° overnight, and then poured into ether and water. The ethereal layer was washed with dilute mineral acid, sodium hydrogen carbonate solution and brine, dried, and evaporated leaving a yellow, viscous oil (5·5 g), which was chromatographed on neutral alumina (200 g; grade IV) with 25% ether–light petroleum. This procedure gave the crystalline, white *carbonate ester* (23; R = CO_2Et) (4·8 g, 80%), which crystallised from light petroleum at low temperature as prisms, m.p. 53—55°, $\nu_{max.}$ (Nujol) 1740, 1695, 1275, 1015, 960, and 800 cm^{-1} (Found: C, 69·35; H, 8·75. $C_{17}H_{26}O_4$ requires C, 69·35; H, 8·9%).

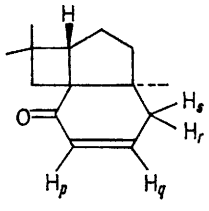
Pyrolysis of Carbonate (23; R = CO_2Et).—The carbonate ester (4·0 g, 13·6 mmol) was heated under reflux in a nitrogen atmosphere at 340—350 °C for 1 h. The resultant yellow oil consisted of (t.l.c. and i.r.) starting material and a considerable amount of material identical (R_F) with the ketol (9), in addition to the expected keto-olefins (10) and (11). The oil was fractionally distilled to give a pure keto-olefin fraction (1 g, 40%), b.p. 58—60° at 0·25 mmHg; the higher-boiling fractions were combined, treated with ethyl chloroformate, and repyrolysed. This procedure afforded pure keto-olefins in an overall yield of 65%.

TABLE 2 [a]

Decoupling experiments on the n.m.r. spectra of the non-conjugated enone (10)



(10)



(11)

Proton irradiated	Effect on H_a	H_b	H_c	H_d
None	6·85, td, J_{ab} 20, $J_{ac}J_{ad}$ 3	7·36, dd, J_{ba} 20, J_{bc} 3	4·47, td, J_{cd} 10, $J_{ca}J_{cb}$ 3	4·68, dd, J_{dc} 10, J_{da} 3
H_a↑			dd, J_{cd} 10, J_{cb} 3	d, J_{dc} 10
H_b↑			dd, J_{cd} 10, J_{ca} 3,	dd, J_{dc} 10, J_{da} 3
H_a↑ and H_b↑			d, J_{cd} 10	d, J_{dc} 10
H_c↑ and H_d↑	d, J_{ab} 20	d, J_{ba} 20		

[a] Coupling constants (J/Hz) are observed values; H_a↑, H_p,↑ *etc.*, mean that the spins corresponding to protons *a*, *b*, *etc.*, are irradiated.

G.l.c. showed the formation of two compounds [R_t (1% S.E. 30, 75°; flow rate 60 ml min^{-1}) 11·5 and 16·6 min], g.l.c.–m.s. showed both to have M, 204. Unfortunately the complexity of the systems did not allow complete assignments of the fragmentation patterns. The n.m.r. data are given in Tables 2 and 3.

Separation of the keto-olefins being impossible, the recorded physical data are for a mixture of the two components, $\nu_{max.}$ (liquid) 3050, 2980, 1705, 1690sh, 1660, 1450, 1310, 1290, 750, and 730 cm^{-1} (Found: C, 82·05; H, 10·1. Calc. for $C_{14}H_{20}O$: C, 82·3; H, 9·9%).

Tricyclic Ketone (18).—Catalytic reduction of the foregoing olefinic mixture (400 mg, 1·96 mmol) with 10% palladium–charcoal proceeded with uptake of 48 ml of hydrogen in 1·5 h (*ca.* 1 mol. equiv.). The mixture was then filtered through Celite 535 and evaporated to give a mobile *liquid* (402 mg, 99%) which was identical with the ketone (18) obtained from Wolff–Kishner reduction of the oxo-acetal (21), R_t (1% SE 30, 75 °C; flow rate 60 ml min^{-1}) 24·0 min, $\nu_{max.}$ (liquid) 2980, 1695, 1470, 1430, 1385, 1370, 1325, and 1290 cm^{-1}, $[\alpha]_D^{20}$ −42·9° (*c* 0·746 in $CHCl_3$)

TABLE 3 [a]

Decoupling experiments on the n.m.r. spectra of the conjugated enone (11)

Proton irradiated	Effect on H_p	H_q	H_r	H_s
None	4·11, dd, J_{pq} 10, $J_{pr(s)}$ 3·5	3·34 m	*b*	*b*
H_r↑ and H_s↑	d(broad), J_{pq} 10	d(distorted), J_{qp} 10		

[a] See footnote *a* to Table 2. [b] Unassignable, but centred at *ca.* τ 8·4.

[Found: C, 81·25; H, 10·5%; M (mass spec.), 206. $C_{14}H_{22}O$ requires C, 81·5; H, 10·75%; M, 206].

Tricyclic Tertiary Alcohol (24).—An ethereal solution of the ketone (18) (400 mg, 1·96 mmol) was added to a stirred solution of methylmagnesium iodide [prepared from magnesium turnings (280 mg) and methyl iodide (0·75 ml)] in anhydrous ether (10 ml) at 0° C under dry nitrogen. The mixture was then heated under reflux for 2·5 h and stirred at room temperature during a further 48 h. Ammonium sulphate solution (20%) was added dropwise until no further gas was evolved, and, after normal ether–water work-up, removal of the solvent gave a red oil (400 mg) which was adsorbed on neutral alumina (15 g, grade IV) from ethereal solution. Elution with 25% ether–light petroleum gave material contaminated with starting ketone (80 mg) in addition to the desired *tricyclic tertiary alcohol* (24) (210 mg, 47%) as an oil, b.p. 50—52° at 0·015 mmHg, $\nu_{max.}$ (liquid) 3480, 1465, 1380, and 1085 cm^{-1}, $[\alpha]_D^{20}$ −56·5° (*c* 0·443 in $CHCl_3$), τ 8·65 (1H, s, exchangeable with D_2O), 8·80 (3H, s), 8·88 (3H, s), and 9·10 (6H, s) (Found: C, 80·8; H, 11·65. $C_{15}H_{26}O$ requires C, 81·0; H, 11·8%).

Neoclovene.—A solution of the tertiary alcohol (24) (95 mg, 0·482 mmol) in anhydrous ether (1 ml) was added with stirring to a solution of concentrated sulphuric acid (2 ml) in dry ether (7 ml) at 0°. The mixture was then stirred for 30 min at 0 °C and 30 min at room temperature, diluted with ice–water, and was slowly neutralised with 4N-sodium hydroxide solution. Thorough extraction with ether and washing with brine of these extracts gave, after drying and removal of solvent, a mobile liquid (65 mg, 75%). Apart from a small amount of starting material (2%) which was removed by chromatography on neutral alumina with light

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petroleum elution, the products were all hydrocarbons. Extensive g.l.c. examination (50-m capillary columns) showed the product to be 99% pure neoclovene (4), identical with authentic neoclovene, b.p. 58—60° at 0·1 mmHg, $[\alpha]_D^{20}$ −69° (*c* 0·40 in $CHCl_3$), $\nu_{max.}$ (liquid) 3023, 1657, 1383, 1376, 1362, 838, 812, 788, and 771 cm^{-1}, τ 4·91br (1H, m), 8·80 (3H, s), and 8·99 (6H, s).

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