SYNTHESIS OF SESQUITERPENES

By J. M. MELLOR and S. MUNAVALLI
(INSTITUT DE CHEMIE, STRASBOURG, FRANCE)

IN this Review we consider the synthesis of the simpler sesquiterpene skeletons and then in greater detail the synthesis of the more complex skeletons. Much of the earlier synthetic work is described elsewhere.[1,2]

A striking feature of sesquiterpene chemistry is the great variety of different skeletal types. The different modes of cyclisation *in vivo* of *trans-trans*-farnesol* (1a) and of *cis-cis*-farnesol (1b), which give rise to this diversity of structure have been rationalised.[3] The subject has also been discussed in *Quarterly Reviews*.[4] The great variety of structure demands an equal variety of synthetic approaches. Division will be made between the approaches to the synthesis of the non-carbocyclic, the monocyclic, and the bicyclic sesquiterpenes of both naphthalenic and azulenic skeletons. The remaining polycyclic sesquiterpenes of more complex structure will be considered together, although the synthesis of each skeleton within this group poses different problems. This Review will stress the stereochemical control in synthesis, which has permitted the solution of these diverse problems.

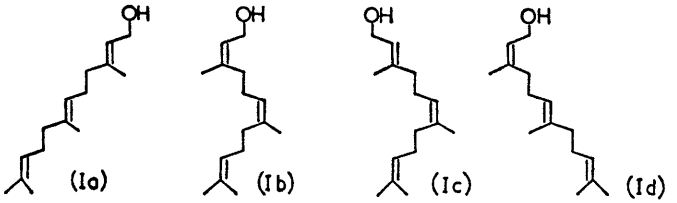
Non-carbocyclic Sesquiterpenes.—The recognition that farnesol is the key intermediate in the biosynthesis of sesquiterpenes has given impetus to the search for better methods of synthesis of the acyclic sesquiterpenes. The greatest difficulties encountered in this work are the preparation of configurational isomers by selective stereospecific reactions and the isolation of the pure configurational forms from mixtures. The latter difficulty has at last been overcome by preparative vapour phase chromatography,[5] but in earlier work tedious and less satisfactory techniques of separation were used.

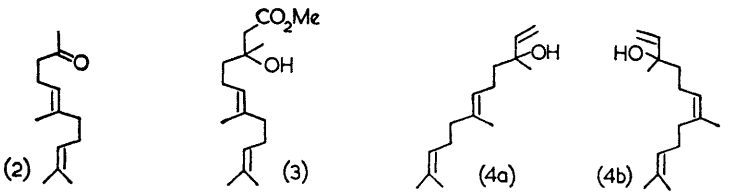
In recent work, undertaken in order to provide labelled compounds for further biosynthetic studies, Cornforth and his co-workers[6] have prepared *trans-trans*-[1-$^2H_2$-2-^{14}C]- and *trans-trans*-[1-$^3H_2$-2-^{14}C]-farnesol. The Reformatsky reaction with *trans*-geranylacetone (2) and methyl bromo-[2-^{14}C]acetate gave methyl 3-hydroxy-3,7,11-trimethyl-[2-^{14}C]dodeca-6,10-dienoate (3), which on dehydration gave an isomeric mixture. This mixture of methyl *cis-trans*- and *trans-trans*-[2-^{14}C]-farnesoate was separ-

*The first configurational designation refers to the 2,3- and the second to the 6,7-double bond.

[1] Simonsen, " The Terpenes," The University Press, Cambridge, 1954, Vol. III.
[2] De Mayo, " Mono and Sesquiterpenoids," Interscience Publ., Inc., New York, 1959.
[3] Ruzicka, *Proc. Chem. Soc.*, 1959, 341; Crabbé and Ourisson, *Ind. Chim. belge*, 1957, **22**, 1309; Hendrickson, *Tetrahedron*, 1959, **7**, 82.
[4] Halsall and Theobald, *Quart. Rev.*, 1962, **16**, 101.
[5] (*a*) Naves and Odermatt, *Bull. Soc. chim. France*, 1958, 377; Naves, *Compt. rend.*, 1960, **251**, 900; Cornforth and Popjak, *J. Chromatog.*, 1960, **4**, 214; (*b*) Bates, Gale, and Gruner, *J. Org. Chem.*, 1963, **28**, 1086.
[6] Cornforth, Cornforth, Goodman, Popjak, and Ryhage, *J. Biol. Chem.*, 1962, **237**, 56.

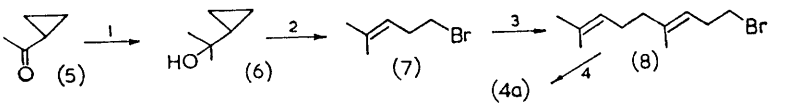
ated by vapour-phase chromatography and subsequent reduction with $^2H_2$- or $^3H_2$-labelled lithium aluminium hydride gave *trans-trans*-[1-$^2H_2$-2-^{14}C]*trans-trans*- or *trans-trans*-[1-$^3H_2$-2-^{14}C]-farnesol, respectively. *trans*-Nerolidol (4a), which is a major constituent of some naturally occurring oils, is now transformed in a commercial process into a mixture of *cis-trans*- (1d) and *trans-trans*-farnesol (1a),[7] whilst in the same conditions of acid catalysis *cis*-nerolidol (4b) gives *trans-cis*- (1c) and *cis-cis*-farnesol (1b).[5b]





Julia and his co-workers[8] have recently devised an elegant synthesis of *trans*-nerolidol (4a) from cyclopropyl methyl ketone (5). Treatment of this ketone with methylmagnesium bromide gave the alcohol (6), which was converted by hydrogen bromide into the bromide (7). Repetition of this sequence gave the bromide (8), which with methyl vinyl ketone gave pure *trans*-nerolidol (4a). Thus in a simple sequence of reactions it is possible to synthesize a number of polyisoprenoids.

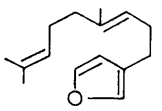
In addition to the group of truly acyclic sesquiterpenes there exists a group of closely related non-carbocyclic sesquiterpenes containing a furan ring. Syntheses of the tetrahydro- and perhydro-derivatives of the optically inactive dendrolasin (9),[9] and the synthesis of a mixture of the naturally occurring optical isomers, ipomeamarone (10) and ngaione,[10] have been

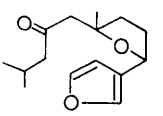


Reagents: 1, MgMeBr. 2, HBr. 3, Grignard reagent from (7). 4, Grignard reagent from (8) and Me·CO·CH:CH_2.

[7] Firmenich and Ruzicka, *Helv. Chim. Acta*, 1939, **22**, 392.
[8] Guegan, Julia, and Julia, *Bull. Soc. chim. France*, 1960, 1072.
[9] Grunanger, Piozzi, and Quilico, *Tetrahedron*, 1957, **1**, 186.
[10] Kubota and Matsuwra, *Chem. and Ind.*, 1956, 521.

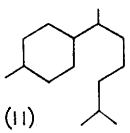
described. The synthetic route involves condensation of a suitable derivative of 3-furoic acid with the appropriate acyclic fragment and subsequent

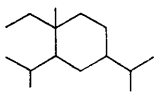

(9)

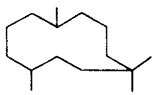

(10)

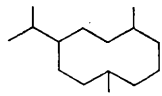
transformation of the oxygenated group.

Monocyclic Sesquiterpenes.—Four different skeletons of monocarbocyclic sesquiterpenes are known. The approaches to the synthesis of the bisabolane (11) and the elemane (12) skeleton will be considered separately, and then the problems encountered in the synthesis of the humulane (13) and the germacrane (14) skeleton will be considered.

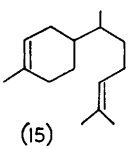

(11)

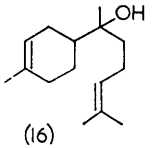

(12)


(13)

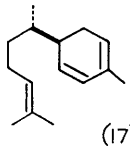

(14)

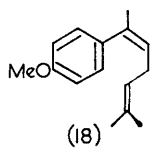
Treatment of nerolidol (4) with acid gives a mixture of acyclic compounds and by cyclisation the monocyclic bisabolene (15) and bisabolol (16).[11] This synthesis is typical of most of the early work, reflecting the great difficulty in separation of the isomeric products. In most of the work concerning the synthesis of compounds containing the bisabolane skeleton it must be considered that any coincidence of the physical constants of the synthetic products and those of the naturally occurring isomers is fortuitous. However, now that chromatographic techniques have facilitated separation of isomeric mixtures, the major synthetic problem has been resolved. Synthesis *via* both alicyclic and aromatic intermediates is possible. Thus the structure of zingiberene (17), a configurational isomer of bisabolene (15), has been confirmed[12] by a synthesis involving Birch reduction


(15)



(16)


(17)

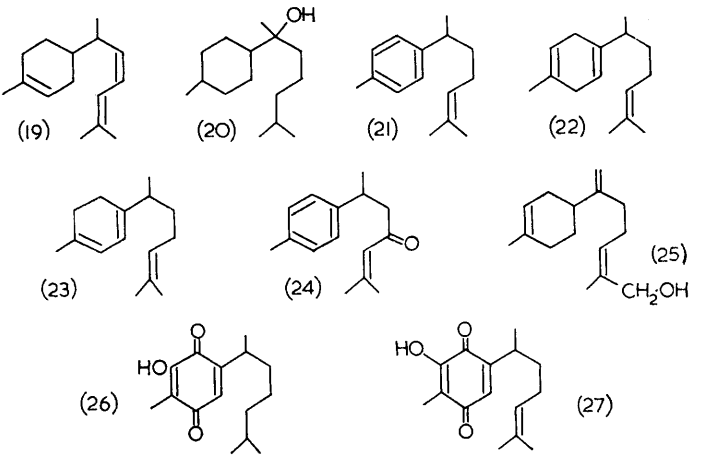


(18)

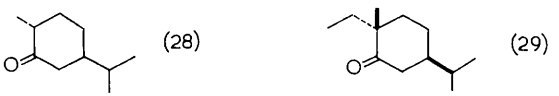
of the aromatic intermediate, 6-*p*-methoxyphenyl-2-methylhepta-2,5-diene (18). This confirmed the structural assignment by Eschenmoser and Schinz,[13] and not the alternative structure (19) proposed by Ruzicka and van Veen.[14]

[11] Capato and Ruzicka, *Helv. Chim. Acta*, 1925, **8**, 259.
[12] Bhattacharyya and Mukherji, *Science and Culture*, 1950, **16**, 268.
[13] Eschenmoser and Schinz, *Helv. Chim. Acta*, 1950, **33**, 171.
[14] Ruzicka and van Veen, *Annalen*, 1929, **468**, 143.

Further reported syntheses in this group are those of bisabolene (15),[15] tetrahydro-α-bisabolol (20),[16] α-curcumene (21),[17] β-curcumene (22),[17] γ-curcumene (23),[17] *ar*-turmerone (24),[18] lanceol (25),[19] and dihydroperezone (26).[20] The last is related to the only known naturally occurring sesquiterpene quinone, perezone (27).



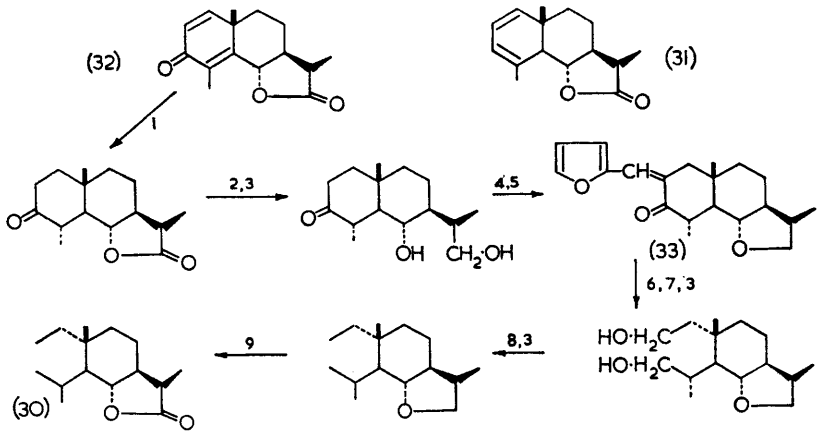
The major obstacle to a successful synthesis of the elemane skeleton is the introduction of the angular methyl group: synthesis by way of aromatic intermediates is thus precluded. This difficulty has been overcome by two methods. The first used to synthesize elemane and thus to confirm the gross skeletal assignment[21] relies upon the alkylation of a suitable ketone to construct the skeleton. Thus carvomenthone (28) was alkylated to give 2-ethyl-5-isopropyl-2-methylcyclohexanone (29). Addition of isopropyllithium followed by dehydration and hydrogenation then gave elemane (12). In the second method use is made of an intermediate in which the



angular methyl group is already incorporated. Tetrahydrosaussurea lactone (30), a member of the elemane group related to the naturally occurring saussurea lactone (31) has been synthesized from santonin (32).[22]

[15] Ligouri and Ruzicka, *Helv. Chim. Acta*, 1932, **15**, 3.
[16] Herout, Šorm, and Zaoral, *Coll. Czech. Chem. Comm.*, 1953, **18**, 122.
[17] Garter, Simonsen, and Williams, *J.*, 1940, 451; Birch and Mukherji, *J.*, 1949, 2531.
[18] Gassman and Rupe, *Helv. Chim. Acta*, 1936, **19**, 569; Rupe and Wieder-Kehr, *ibid.*, 1924, **7**, 654; Colonge and Chambion, *Compt. rend.*, 1946, **227**, 557; Gandhi, Mukherji, and Vig, *Tetrahedron*, 1959, **7**, 236.
[19] Manjarrez, Rio, and Guzman, *Tetrahedron*, 1964, **20**, 333.
[20] Yamaguchi, *J. Pharm. Soc. Japan*, 1942, **62**, 491.
[21] Cerny, Herout, Šorm, and Sykora, *Chem. Listy*, 1954, **48**, 76.
[22] Bhattacharyya, Simonovic, and Rao, *Tetrahedron* 1963, **19**, 1061.

This constitutes a total synthesis of tetrahydrosaussurea lactone as the total synthesis of santonin[23] has been described (see below). The key to the synthesis is the opening of ring A by oxidative degradation whilst the lactone group is protected (see scheme A). This is achieved by ozonolysis of



Scheme A

Reagents: 1, H_2–H^+. 2, $(CH_2{\cdot}OH)_2$–H^+. 3, $LiAlH_4$. 4, H^+. 5, Furfuraldehyde–HO^-. 6, H_2O_2. 7, CH_2N_2. 8, *p*-$C_6H_4Me{\cdot}SO_2Cl$. 9, CrO_3.

the furfurylidene derivative (33) in which the lactone grouping is protected as an ether. Straightforward reduction of the ozonolysis product, followed by regeneration of the lactone group by treatment with chromic acid, gave the desired tetrahydrosaussurea lactone.

The problems encountered in the synthesis of the humulane (13) and the germacrane (14) skeleton are those found in the synthesis of medium-sized ring compounds, which has recently been reviewed.[24] Successful syntheses of germacrane (14)[25] and humulane (13)[26] have been reported in which the critical step of ring formation has been accomplished by the acyloin condensation. Cyclisation of the diester (34) to give the intermediate (35) was followed by straightforward elimination of the hydroxyl groups, to give the fully saturated germacrane. Similarly the diester (36) was cyclized to give the intermediate (37), which was then converted into humulane. These syntheses provided useful confirmation of the gross structure of the parent hydrocarbons of the two groups.

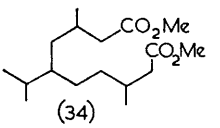
[23] Abe, Harukawa, Ishikawa, Miki, Sumi, and Toga, *J. Amer. Chem. Soc.*, 1956, **78**, 1422.

[24] Šorm, " Progress in the Chemistry of Natural Products, Vol. XIX," ed. Zechmeister, 1961, p. 1.

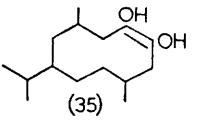
[25] Šorm and Suchy, *Coll. Czech. Chem. Comm.*, 1958, **23**, 2175.

[26] Dolejs, Herout, Jarolim, Novotny, Šorm, and Streibl, *Coll. Czech. Chem. Comm.*, 1954, **19**, 570.

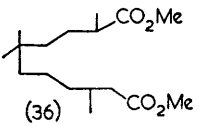
A great difficulty to be overcome in the synthesis of naturally occurring humulane and germacrane derivatives is the introduction of the functional groups. Unsaturated derivatives of humulane or germacrane rearrange with great ease to give bicyclic systems, and stereospecific control in the synthesis of medium-sized ring compounds is, as yet, little explored. In a recent



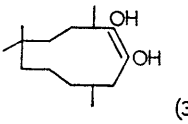
(34)



(35)

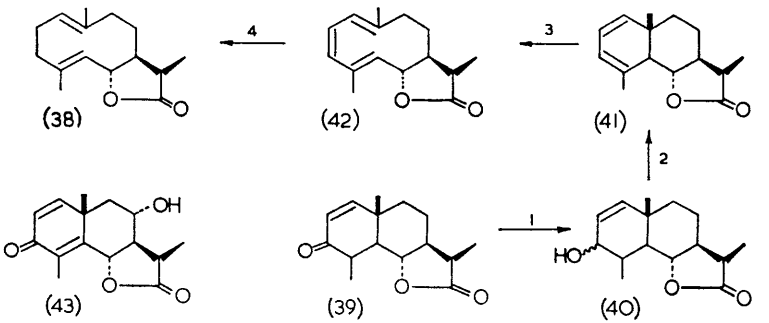


(36)



(37)

synthesis of dihydrocostunolide (38)[27] from the unsaturated ketone (39), which is readily available from santonin (32), these problems have been elegantly overcome. At the start of the synthesis the oxygenated groups of dihydrocostunolide are already in the desired positions and the naphthalenic skeleton must then be transformed into a ten-membered ring. Reduction of the ketone (39) gave an epimeric mixture of alcohols (40), which were carefully dehydrated to the diene (41). Photolysis of this diene gave an intermediate triene (42), which was not isolated but was hydrogenated to dihydrocostunolide (38), the naturally occurring sesquiterpene.



(38) (42) (41) (43) (39) (40)

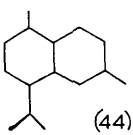
Reagents: 1, $Al(OPr^i)_3$. 2, Al_2O_3. 3, $h\nu$, MeOH. 4, H_2–Raney Ni.

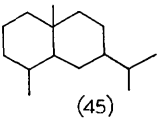
This synthetic route will, no doubt, be further exploited in order to synthesize other members of the germacrane group from naturally occurring sesquiterpenes such as artemisin (43).

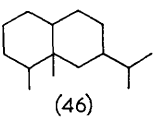
Naphthalenic Sesquiterpenes.—Of the four skeletons incorporating the naphthalenic system, cadinane (44) is the only one in which there is no

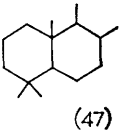
[27] Corey and Hortmann, *J. Amer. Chem. Soc.*, 1963, **85**, 4033.

angular methyl group. In the skeletons of eudalane (45), eremophilane (46), and drimane (47) there is an angular methyl group which thus renders their synthesis more difficult. However, as a result of the important position of santonin (32), a member of the eudalane group, in sesquiterpene chemistry,


(44)

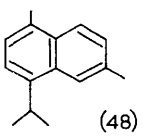

(45)

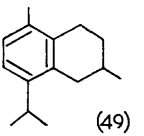

(46)

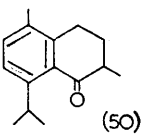

(47)

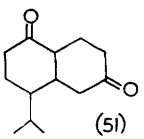
greater efforts have been made towards the syntheses of derivatives of the eudalane skeleton. No members of the eremophilane group has yet been totally synthesized and only recently has synthesis of members of the drimane group been achieved.

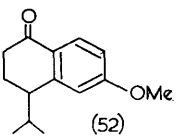
The structure of the cadinane skeleton has been confirmed by synthesis of cadalene (48),[28] the fully aromatic dehydrogenation product of cadinane derivatives. Calamenene (49), a further dehydrogenation product, has been synthesized[29] from γ-(5-isopropyl-2-methylphenyl)-α-methylbutyric acid by ring closure and subsequent transformation of the ketone (50). A key intermediate for more ambitious synthesis in the cadinane group is the diketone (51). Control of the stereochemistry of the ring junction and of the configuration of the substituents is now a problem, absent in the synthesis of the dehydrogenation products. This intermediate (51), available synthetically as the racemate[30] prepared from 4-isopropyl-6-methoxy-1-tetralone (52), or as the (−)-isomer prepared[31] from (−)-cryptone (53) offers the possibility of elaboration to other members of the cadinane group. It has already been converted into (±)-cadinene hydrochloride (54).[30]


(48)

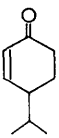

(49)

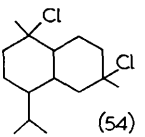

(50)


(51)



(52)


(53)

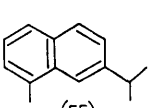


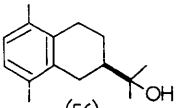
(54)

Dehydrogenation of members of the eudalane group gives eudalene (55).[32] Synthesis of this hydrocarbon establishes the position of fourteen of

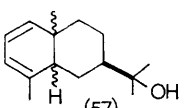
[28] Ruzicka and Siedel, *Helv. Chim. Acta*, 1922, **5**, 369.
[29] Herout, Šorm, and Veres, *Coll. Czech. Chem. Comm.*, 1953, **18**, 106.
[30] Dev, Rao, and Rao, *Tetrahedron Letters*, 1960, No. 27, p. 27.
[31] Adams, Gunay, Karman, and Soffer, *Tetrahedron Letters*, 1963, 389.
[32] Ruzicka and Stoll, *Helv. Chim. Acta*, 1922, **5**, 923.

the fifteen carbon atoms of the eudalane skeleton. Occidol (56), closely related to the naturally occurring occidentol (57), has been synthesized in a


(55)

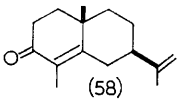


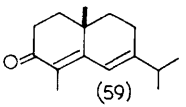
(56)

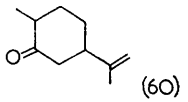


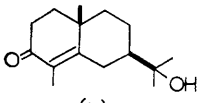
(57)

straightforward manner,[33] but all other synthetic work in this group of sesquiterpenes has been confronted with the problem encountered for other sesquiterpene, diterpene, triterpene, and steroid systems—the problem of the stereospecific introduction of an angular methyl group. The approach to this task has been similar to that found in the construction of the A/B-*trans*-fused ring system of the steroids. In all the totally synthetic work to be described, annelation of a methylcyclohexanone is the key to success.

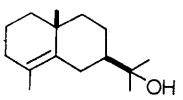

(58)


(59)

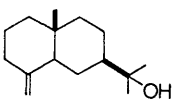

(60)



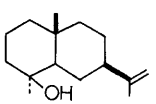
(61)



(62)



(63)



(64)

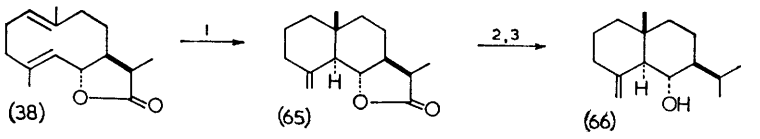
A monoterpene may be a convenient starting material. Thus impure α- (58) and β-cyperone (59) have been obtained by alkylation of dihydrocarvone (60) with methyl β-chloropropionate and subsequent cyclisation.[34]

In later work refinements have been made to afford pure optical isomers of α-cyperone (58)[35] or β-cyperone (59)[36] from dihydrocarvone by annelation with diethylmethyl-3-oxopentylammonium bromide. α-Cyperone has been elaborated[37] to the closely related alcohols, carissone (61) and γ-eudesmol (62). An isomer of γ-eudesmol, β-eudesmol (63), has recently been converted into the naturally occurring alcohol, neointermedeol (64).[38]

It has already been noted that dihydrocostunolide (38) has been synthesized from santonin by photochemical formation of the ten-membered ring.[27] The reverse reaction of acid-catalysed cyclisation of dihydrocostunolide (38) has been used to give the lactone (65), which was then readily transformed into (+)-juneol (66),[39] the antipode of the naturally

[33] Hirose and Nakatsuka, *Bull Agric. Chem. Soc. Japan*, 1959, **23**, 253.
[34] Adamson, McQuillan, Robinson, and Simonsen, *J.*, 1937, 1576.
[35] Howe and McQuillan, *J.*, 1955, 2423.
[36] Roy, *Chem. and Ind.*, 1954, 1393.
[37] Pinder and Williams, *J.*, 1963, 2775.
[38] Shaligram, Zalkow, and Zalkow, *Chem. and Ind.*, 1964, 194.
[39] Bhattacharyya, Rao, and Shaligram, *Tetrahedron*, 1962, **18**, 969.

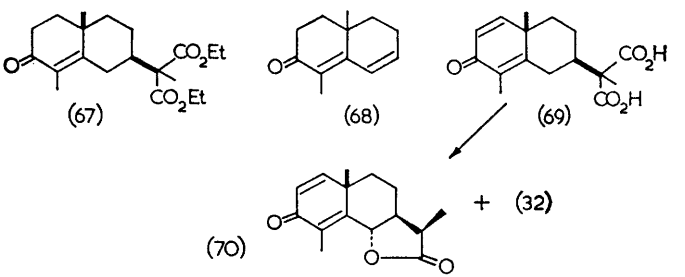
occurring alcohol. These interconversions again illustrate the focal position of santonin (32) in the chemistry of the sesquiterpene lactones. Already the



Reagents: 1, H^+. 2, $LiAlH_4$. 3, $NH_2{\cdot}NH_2$–HO^-.

transformation of santonin into dihydrocostunolide has been indicated, and the latter lactone has been used to synthesize juneol, a member of the eudesmane group, and saussurea lactone (31),[40] a member of the elemane group.

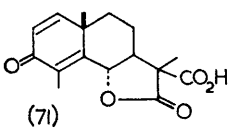
The important position of santonin in this field has stimulated attempted syntheses of santonin. There are four asymmetric centres in the santonin molecule and hence eight possible racemic pairs might exist, of which two pairs may be discarded because the lactone ring would be impossibly fused diaxially. It is thus evident that, in addition to the problems of the construction of the basic skeleton, a high degree of stereochemical control is demanded in a successful synthesis. An early report[41] of the synthesis of optically active santonin from optically inactive starting materials without a resolution has now been discredited[42] and the first satisfactory synthesis was only achieved much later.[23] The critical stereochemical control was lacking until Abe and his co-workers developed a successful synthesis from the keto-ester (67). This compound was prepared from the dienone (68) by Michael addition of diethyl methylmalonate.[23] Dehydrogenation of the

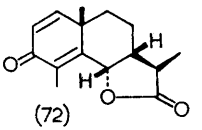


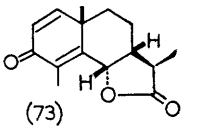
keto-ester (67), followed by hydrolysis, gave the acid (69), which was resolved. Subsequent decarboxylation gave, from the dextrorotatory acid, a mixture of two lactones, the antipode of natural (—)-α-santonin (32), and (+)-β-santonin (70). The lævorotatory acid gave impure natural (—)-α-santonin and (—)-β-santonin (70). In similar work which largely

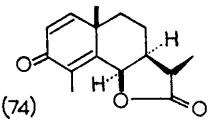
[40] Bhattacharyya, Paul, Rao, and Sadgopal, *Tetrahedron*, 1961, **13**, 319.
[41] Bhide, Nargund, Paranjape, and Phalinikar, *Rasayanam*, 1943, **1**, 233; *Nature*, 1944, **153**, 141.
[42] Cornforth, Cornforth, and Dewar, *Nature*, 1944, **153**, 317.

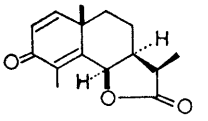
followed the same route, the acid (71) was obtained and resolved. A relatively stereospecific decarboxylation then gave pure (−)-α-santonin. By similar methods santonin A (72), B (73), C (74), and D (75) have been synthesized.[43]


(71)

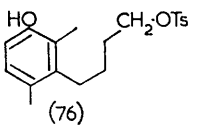

(72)

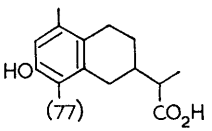

(73)

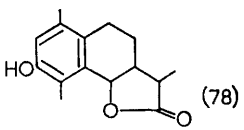

(74)


(75)

A recent interesting method of construction of the santonin skeleton is by aryl participation in the solvolysis of 4-(3-hydroxy-2,6-dimethylphenyl)-butyl toluene-*p*-sulphonate (76), which leads to the formation of dienones of the santonin type and also to the ψ-santonin ring system.[44] Syntheses of (±)-santanous acid (77)[45] and (±)-desmotroposantonin (78),[46] acid-catalysed rearrangement products of santonin, and the synthesis of the stereoisomers of artemisin (43), a hydroxysantonin,[47] have been reported.


(76)


(77)

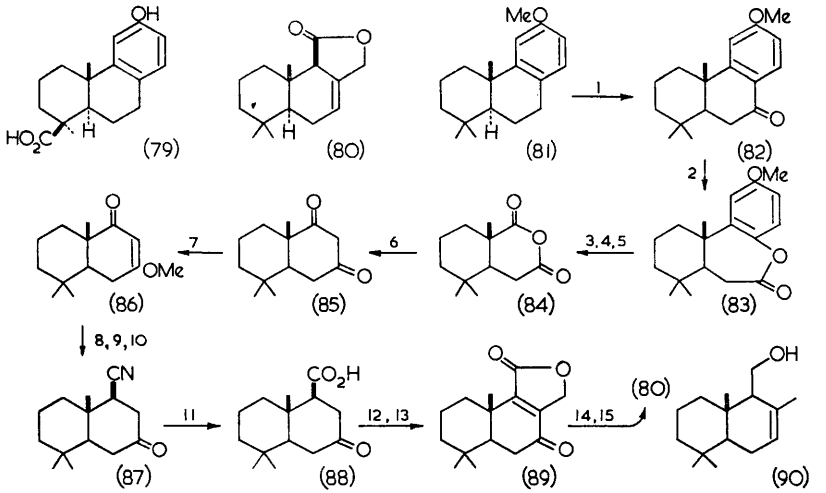

(78)

Ts = p-$C_6H_4Me{\cdot}SO_2$.

The group of sesquiterpenes with the drimane skeleton is of particular interest in that the bicyclic system incorporates the same *trans*-ring junction found in rings A and B of many diterpenes, triterpenes, and steroids. This suggests that synthesis from a diterpene might be possible, and recently podocarpic acid (79), which has been totally synthesized,[48] has been converted into drimenin (80).[49] The synthetic route demands transformation of the carboxyl group in podocarpic acid (79) into a methyl group, and this was effected by conversion into the known *O*-methylpodocarpane (81). Degradation of the tricyclic skeleton was initiated by oxidation of ring B of

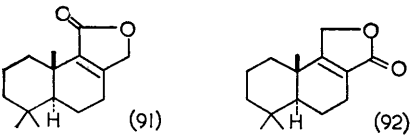
[43] Abe, Harukawa, Ishikawa, Miki, Sumi, and Toga, *J. Amer. Chem. Soc.*, 1956, **78**, 1416.
[44] Caine, Kilpatrik, and Mandell, *J. Amer. Chem. Soc.*, 1961, **83**, 4457.
[45] Clemo, Haworth, and Walton, *J.*, 1929, 2363.
[46] Clemo, Haworth, and Walton, *J.*, 1930, 1110, 2579.
[47] Abe and Sumi, *Proc. Japan Acad.*, 1955, **31**, 309.
[48] King, King, and Topliss, *Chem. and Ind.*, 1956, 133.
[49] Wenkert and Strike, personal communication.

O-methylpodocarpane to give 7-oxo-*O*-methylpodocarpane (82), which was further oxidized by the method of Baeyer–Villiger to give the lactone (83). Oxidative degradation of the lactone led to the anhydride (84) which was converted in a number of steps into the diketone (85). At this stage of the



Reagents: 1, CrO_3. 2, R·CO_3H. 3, HO^-. 4, O_3. 5, Ac_2O. 6, $CdMe_2$; CH_2N_2; Bu^tOK–Bu^tOH. 7, MeOH–*p*-$C_6H_4Me·SO_3H$. 8, $LiAlH_4$. 9, H^+. 10, KCN–NH_4Cl in H·CO·NMe_2. 11, $(CH_2·OH)_2$–H^+; HO^-; H^+. 12, H·CO_2Et–Bu^tOK–Bu^tOH. 13, Ac_2O–NaOAc. 14, Zn–AcOH; $NaBH_4$. 15, *p*-$C_6H_4Me·SO_2Cl$ in pyridine and Me_2SO.

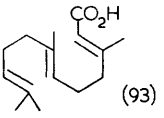
synthesis, with degradation to the bicyclic system now complete, it was necessary to differentiate the two carbonyl groups. This was achieved by preparation of the monomethyl ether of the enolic form (86) of the diketone. This ether was transformed into the cyano-ketone (87), which was subsequently hydrolysed to the keto-acid (88). Base-catalysed condensation with diethyl formate gave the lactone (89), which was converted in several steps into drimenin (80). The synthesis of other members of the group,



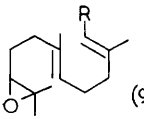
drimenol (90), isodrimenin (91), and confertifolin (92) was then achieved from drimenin. This synthesis illustrates how a naturally occurring substance may be used as a relay in the synthesis of other naturally occurring compounds.

A second route to the drimane skeleton is by acid-catalysed cyclisation of

derivatives of farnesol (1).[50,51] Racemic drimenol (90) has been prepared by acid-catalysed cyclisation of farnesic acid (93).[50] More recently the acid-catalysed opening of epoxides (94; R = CH_2·OAc or CO_2Me) prepared[51] by selective oxidation of the terminal double bond of farnesol derivatives,



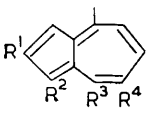
(93)



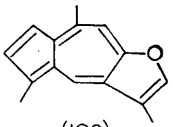
(94)

has been shown to lead to cyclisation and formation of the drimane skeleton. In this manner racemic drimenol and the 9-epimer, epidrimenol, were synthesized.[51] This synthetic route is of particular interest as its pattern is that of the supposed biosynthetic route from farnesol to the drimane skeleton.

Azulenic Sesquiterpenes.—All the above work in the field of bicyclic sesquiterpenes has been directed towards the construction of a naphthalenic skeleton. Although many syntheses of aromatic dehydrogenation products of sesquiterpenes with an azulenic skeleton have been reported,[52] there has been no synthesis of the more fully saturated, naturally occurring sesquiterpenes of this type. The synthesis of dehydrogenation products, a classical method used in the determination of the gross structure of terpenes, has proved of immense value in the field of sesquiterpene chemistry, and in particular Šorm and his co-workers have demonstrated the power of this technique in the successful determination of the structures of both lactonic and non-lactonic sesquiterpenes having an azulene skeleton.[52,53]



(95 → 101)



(102)

No.	R^1	R^2	R^3	R^4
95	H	Me	M	Pr^i
97	Me	H	Pr^i	H
99	H	Me	H	Et
101	H	Me	H	Pr^i

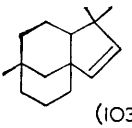
No.	R^1	R^2	R^3	R^4
96	Pr^i	H	Me	H
98	Me	H	H	Pr^i
100	H	Me	H	$CMe{:}CH_2$

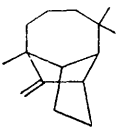
The following syntheses will here be merely recorded: guaiazulene (95),[54] vetivazulene (96),[55] zierazulene (97),[56] *Se*-guaiazulene (98),[57] chamazulene

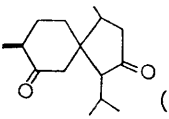
[50] Eschenmoser, Schinz, Stadler, and Stork, *Helv. Chim. Acta*, 1957, **40**, 2191.
[51] Hessler, Schwartz, Storni, and Van Tamelen, *J. Amer. Chem. Soc.*, 1963, **85**, 3296.
[52] Šorm, *Record Chem. Progress* 1960, **21**, 73.
[53] De Mayo and Schmid, *Perfumery Essential Oil Record*, 1957, **48**, 18, 68.
[54] Furst, Marte, and Plattner, *Helv. Chim. Acta*, 1949, **32**, 2137; 2452.
[55] Pfau and Plattner, *Helv. Chim. Acta*, 1939, **22**, 202.
[56] Birch, Collins, and Penfold, *Chem. and Ind.*, 1955, 1773.
[57] Gut, Kucera, and Šorm, *Coll. Czech. Chem. Comm.*, 1951, **16**, 184.

(99),[58] lactarazulene (100),[59] *S*-guaiazulene (101),[60] and linderazulene (102),[61] The syntheses of a number of more fully saturated degradation products of azulenic sesquiterpenes have also been described.[62]

Other Polycyclic Sesquiterpenes.—There remains to be discussed much recent work directed towards the synthesis of a group of sesquiterpenes of diverse skeletal types. The necessity for the synthesis of an unusual skeleton, often sterically strained, is the only factor uniting the synthetic approaches to these sesquiterpenes. Thus the difficulties encountered in the synthesis of clovene (103) are entirely different from those found in the synthesis of longifolene (104) or in the synthesis of acorone (105). However, a number of points of general significance may be made.

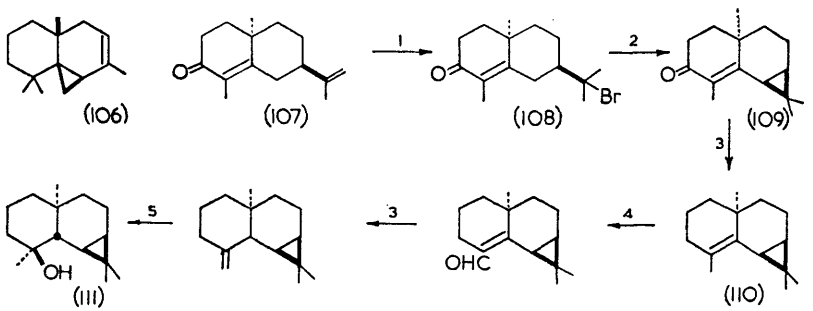

(103)


(104)


(105)

Many of the skeletons to be discussed are sterically strained and under equilibrating conditions would rearrange to thermodynamically more stable skeletons. It is evident that such equilibrating conditions, in particular acid-treatment which permits carbonium-ion rearrangements, must be avoided. Stereospecificity, as always with carbocyclic systems, is of vital importance. A combination of the theoretical development of an understanding of conformational analysis and of dynamic stereochemistry with the practical development of reagents of greater stereospecificity has permitted the following syntheses.

The syntheses of maaliol (111) (see scheme B) and thujopsene (106) will



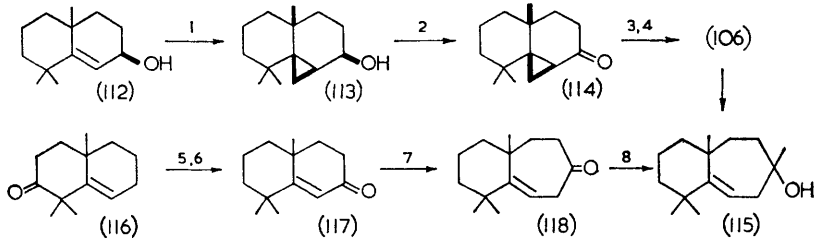
Scheme B

Reagents: 1, HBr–AcOH. 2, HO^-–MeOH. 3, $NH_2{\cdot}NH_2$–HO^-. 4, SeO_2. 5, OsO_4–*p*-$C_6H_4Me{\cdot}SO_2Cl$; $LiAlH_4$.

[58] Novak, Šorm, and Sicher, *Coll. Czech. Chem. Comm.*, 1954, **19**, 1264.
[59] Benesova, Herout, and Šorm, *Coll. Czech. Chem. Comm.*, 1954, **19**, 357.
[60] Gut, Hlavnicka, Kucera, Sedivy, and Šorm, *Coll. Czech. Chem. Comm.*, 1951, **16**, 168.
[61] Ishikawa, Minato, and Takeda, *Tetrahedron Letters*, 1963, 121.
[62] Naito, *J. Pharm. Soc. Japan*, 1955, **75**, 325.

first be considered. The chief obstacle to the total synthesis of these naturally occurring sesquiterpenes is the construction of the cyclopropane ring. In the two syntheses entirely different methods are used for the formation of the three-membered ring. Buchi and his co-workers,[63] in the synthesis of maaliol (111), used (−)-epi-α-cyperone[35] (107) as the starting material. Epi-α-cyperone was brominated and dehydrobrominated, to give the ketone (109) by way of the bromo-ketone (108), with construction of the cyclopropane ring. Wolff–Kishner reduction eliminated the carbonyl group, and maaliol (111) was obtained by a number of elegant transpositions from the hydrocarbon (110). Other syntheses of the maaliane skeleton, both partial and total, are described in this and in earlier work.[64]

Dauben and Ashcraft,[65] in the synthesis of thujopsene (106) used the addition of carbene to cyclic allylic alcohols, to give a cyclopropane compound in which the cyclopropane ring and the hydroxyl group have a *cis*-arrangement. Thus the allylic alcohol (112), on treatment with methylene iodide in the presence of a zinc–copper couple, gave the alcohol (113).



Reagents: 1, CH_2I_2–Zn-Cu. 2, CrO_3. 3, MeMg Br; NH_4Cl. 4, H^+. 5, $NH_2{\cdot}NH_2$–HO^-. 6, $Na_2Cr_2O_7$. 7, CH_2N_2–$AlCl_3$. 8, MeLi.

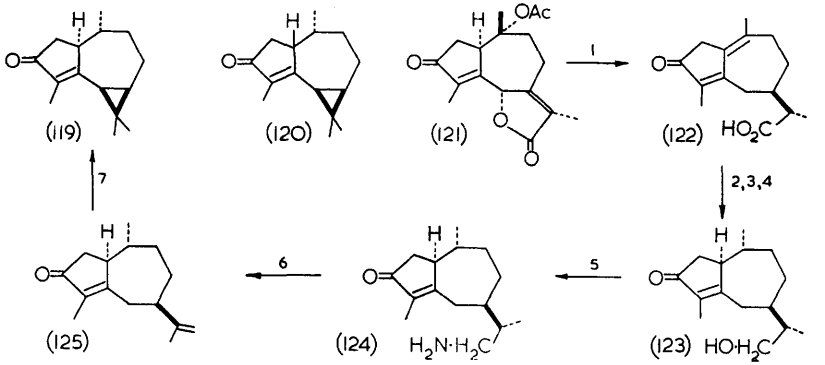
Subsequent oxidation to the cyclopropane ketone (114), treatment with methylmagnesium bromide, and dehydration, gave thujopsene (106).

Rearrangement of thujopsene under acid conditions gives the naturally occurring alcohol, widdrol (115). Dauben and Ashcraft completed the total synthesis of widdrol by such a route, but the racemic alcohol had already been synthesized by Enzell.[66] Enzell's route involved expansion of a six-membered to a seven-membered ring. The ketone (116), a well-known intermediate in synthetic approaches to triterpenes, was converted by reduction and then allylic oxidation into the conjugated ketone (117), which on acid catalysed addition of diazomethane gave the ketone (118), subsequently converted by treatment with methyl-lithium into widdrol.

It is at this point relevant to consider the total synthesis of epicyclocolorenone (119).[67] This constitutes a total synthesis of an isomer of another

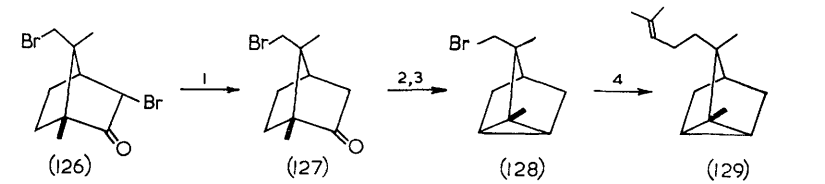
[63] Bates, Buchi, Matsuura, and Shaffer, *J. Amer. Chem. Soc.*, 1960, **82**, 2327.
[64] Buchi, Wittenau, and White, *J. Amer. Chem. Soc.*, 1959, **81**, 1968.
[65] Dauben and Ashcraft, *J. Amer. Chem. Soc.*, in the press.
[66] Enzell, *Tetrahedron Letters*, 1962, 185.
[67] Buchi and Lowenthal, *Proc. Chem. Soc.*, 1962, 280.

sesquiterpene cyclocolorenone (120) with a skeleton incorporating the structural feature of a cyclopropane ring. This cyclopropane ring is constructed in the same manner as in the synthesis[63] of maaliol (111). The starting point of the synthesis is *O*-acetylisophotosantonic acid lactone (121),[68,69] previously obtained from santonin, which was converted by standard reactions into the acid (122). Reduction of the acid with lithium aluminium hydride, followed by partial oxidation of the product with 2,3-dichloro-5,6-dicyanobenzoquinone, gave the primary alcohol (123). Treatment of the *p*-bromobenzenesulphonate of this primary alcohol



Reagents: 1, $CrCl_2$–AcOH. 2, H_2. 3, $LiAlH_4$. 4, 2,3-Dichloro-5,6-dicyanobenzoquinone. 5, p-$BrC_6H_4SO_2Cl$; $NHMe_2$; MeCN. 6, H_2O_2; heat. 7, HBr–AcOH; HO^-–MeOH.

with dimethylamine, and then pyrolysis of the *N*-oxide of the amine (124), gave the olefin (125). The cyclopropane ring was then constructed by treatment of the olefin with hydrogen bromide, followed by dehydrobromination of the product with base to give epicyclocolorenone (119). This differs from naturally occurring cyclocolorenone (120) only in the stereochemistry of the ring junction.



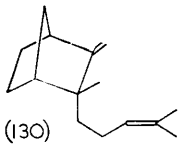
Reagents: 1, Zn–HBr. 2, $NH_2·NH_2$. 3, HgO. 4, Mg; $CMe_2{:}CH·CH_2·O·CO·C_9H_{11}$.

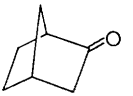
[68] Barton, De Mayo, and Shafig, *J.*, 1957, 929.
[69] Arrigoni, Bosshard, Bruderer, Buchi, Jeger, and Krebaum, *Helv. Chim. Acta*, 1957, **40**, 1732.

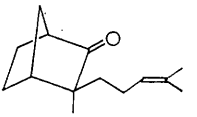
In the above syntheses the cyclopropane ring was constructed either by an elimination or by addition of carbene to a double bond. A third method is used in the synthesis of α-santalene (129).[70]

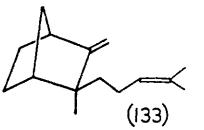
Bromocamphor was brominated and the resultant dibromide (126) was selectively reduced to give the monobromo-ketone (127). The carbonyl group serves as the key to the construction of the cyclopropane ring, and oxidation of the hydrazone gave the tricyclic bromide (128). The synthesis was then completed by treatment of the magnesium derivative of the bromotricyclene (128) with α,α-dimethylallyl mesitoate, to give α-santalene (129) as the sole product.

A structure closely related to that of α-santalene is that of β-santalene (133). It is now well known that the sterically favoured direction of attack


(130)

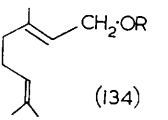

(131)


(132)

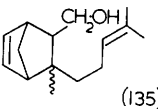

(133)

of the norbornane skeleton is *exo* to the bridge-methylene group and this was used as the basis of a synthesis of β-santalene from norcamphor (131).[71] First methylation and then alkylation with a 4-methylpent-3-enyl halide gave β-santalene (133), after routine conversion of the carbonyl group of (132) into an exocyclic methylene group. A reversal in the order of alkylation gave an isomeric ketone, and thence epi-β-santalene. This synthetic work thus confirms the stereochemical assignment of β-santalene (133) and epi-β-santalene (130).[72]

Recently, both racemic β-santalene and racemic epi-β-santalene have been synthesized by an entirely different route.[73] The Diels–Alder addition



(134)



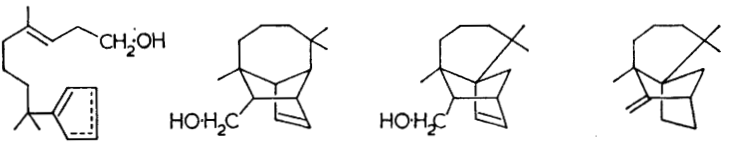
(135)

of geranyl alcohol (134; R=H) to cyclopentadiene gave a very low yield of the alcohol (135). Hydrogenation, followed by pyrolysis of the corresponding acetate, gave β-santalene (133) and epi-β-santalene in a ratio of 3:2. The mixture was satisfactorily separated by vapour-phase chromatography.

A less successful application of the Diels–Alder cyclisation was in an attempted synthesis of longifolene (104).[74] The reaction of cyclopentadienylmagnesium bromide with the monohydrochloride of geranyl acetate (134; R = Ac) gave the alcohol (136). It was hoped that heating

[70] Corey, Chow, and Scherrer, *J. Amer. Chem. Soc.*, 1957, **79**, 5773.
[71] Corey, Hartmann, and Vatakencherry, *J. Amer. Chem. Soc.*, 1962, **84**, 2611.
[72] Ourisson, *Bull. Soc. chim. France*, 1955, 895.
[73] Brieger, *Tetrahedron Letters*, 1963, 1949.
[74] Brieger, *J. Amer. Chem. Soc.*, 1963, **85**, 3783.

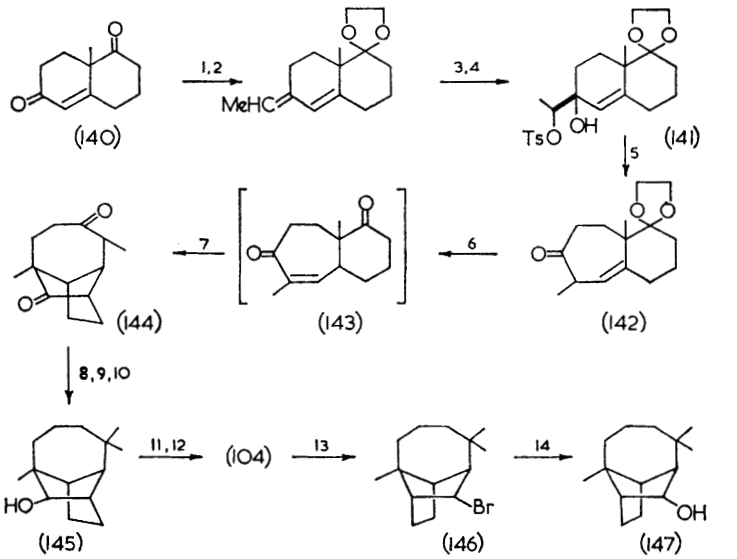
this alcohol would, by an internal Diels–Alder cyclisation, give the alcohol (137), which could then be simply transformed into longifolene. An internal cyclisation did occur, but the product is probably the alcohol (138),



(136) (137) (138) (139)

which on hydrogenation and pyrolysis of the acetate of the hydrogenation product gave an olefin, that was different from longifolene and was considered to have structure (139).

In the only successful synthesis of longifolene the tricyclic system is obtained[75] from a bicyclic system by an internal condensation. In this well-conceived key stage the cycloheptenone (142) gave, by acid-catalysed hydrolysis, the intermediate dione (143), which under the reaction condi-



(140) (141) (142) (143) (144) (104) (145) (146) (147)

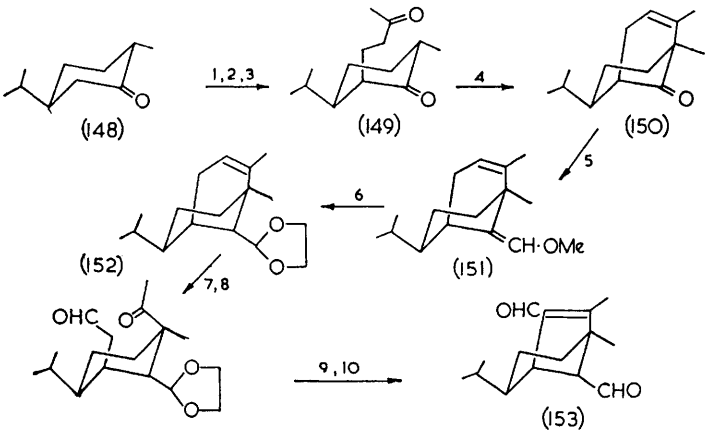
Reagents: 1, $(CH_2{\cdot}OH)_2$–H^+. 2, PPh_3:CHMe. 3, OsO_4. 4, *p*-$C_6H_4Me{\cdot}SO_2Cl$. 5, $LiClO_4$–$CaCO_3$. 6, H^+. 7, NEt_3. 8, MeI–NaH. 9, $(CH_2{\cdot}SH)_2$. 10, $LiAlH_4$. 11, CrO_3. 12, MeLi; $SOCl_2$. 13, HBr. 14, Mg; O_2–Et_2O.

tions cyclized to the tricyclic dione (144). The cycloheptenone (142) had been prepared from the dione (140) by a route in which the key stage was pinacol rearrangement of the monotoluene-*p*-sulphonate (141) by lithium

[75] Corey, Mitra, Ohno, and Vatakencherry, *J. Amer. Chem. Soc.*, 1964, **86**, 478.

perchlorate in tetrahydrofuran, to give the cycloheptenone (142). The tricyclic dione (144) was then converted into longifolene in a series of reactions which well illustrate the art of stereospecific synthesis. Alkylation of the dione (144) specifically introduced a methyl group, and then the less hindered ketonic oxygen atom was selectively removed, to give the ketone (145). Treatment of this ketone with methyl-lithium, followed by dehydration, gave longifolene (104). Longifolene has been converted into longibornyl bromide (146), which was transformed into longiborneol (147).[76] This alcohol was later shown to be identical with the naturally occurring alcohol, juniperol.[77]

The structure of the toxin, helminthosporal (153), is closely related to that of longifolene, and it is reasonable to suppose that biogenetically helminthosporal is derived from a precursor of longifolene type. A total synthesis[78] of the naturally occurring isomer has recently been reported from (—)-carvomenthone (148). Formylation, followed by the Michael addition of methyl vinyl ketone and deformylation, gave the diketone (149). Cyclisation catalysed by boron trifluoride then yielded a separable mixture of bicyclic ketone (150) and the 4-epimer in a ratio of 4:1. Acid-catalysed cyclisation gives the bicyclo[3,3,1]-skeleton, whereas a base-catalysed cyclisation would lead to a naphthalene skeleton because of the



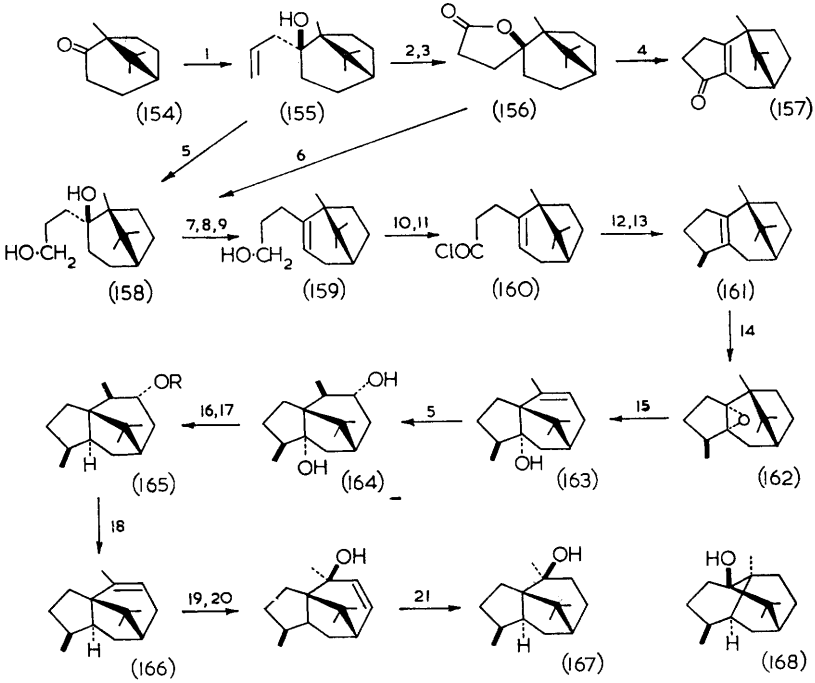
Reagents: 1, NaOMe–H·CO_2Et. 2, CH_2:CH·COMe–$NHEt_2$. 3, 2% K_2CO_3–EtOH 4, BF_3. 5, PPh_3:CH·OMe. 6, $(CH_2·OH)_2$–H^+. 7, OsO_4. 8, $Pb(OAc)_4$. 9, HO^-. 10, 1·5% H_2SO_4.

relative stabilities of the enols and carbanions derived from the two ketone groups. Reaction of the bicyclic ketone (150), with a Wittig reagent gave the ether (151), readily converted into the ketal (152). Oxidative fission of

[76] Naffa and Ourisson, *Bull. Soc. chim. France*, 1954, 1410.
[77] Akiyoshi, Erdtman, and Kubota, *Tetrahedron*, 1960, **9**, 237.
[78] Corey and Nozoe, *J. Amer. Chem. Soc.*, 1963, **85**, 3527.

the double bond in this, followed by recyclisation and careful hydrolysis, gave helminthosporal (153).

An attempt to synthesize patchouli alcohol (168)—an attempt which until very recently was considered to have been successful—has been reported.[79] The bicyclo[3,2,1]octane skeleton of homocamphor (154) is incorporated in α-patchoulene (166) and it was considered that patchouli alcohol had the closely related structure (167). This synthesis is concerned with the elaboration of homocamphor to give α-patchoulene (166) and the resultant transformation of the olefin into an alcohol which was presumed to have the structure (167). Treatment of (−)-homocamphor (154) with allylmagnesium chloride gave the unsaturated alcohol (155).



Reagents: 1, CH_2:CH·CH_2·MgCl. 2, B_2H_6. 3, Jones's reagent. 4, 1% $ZnCl_2$–AcOH–Ac_2O. 5, B_2H_6–H_2O_2. 6, $LiAlH_4$. 7, Ac_2O. 8, $POCl_3$–pyridine. 9, $LiAlH_4$. 10, CrO_3. 11, $SOCl_2$–$AlCl_3$. 12, PPh_3:CH_2. 13, H_2–Raney Ni. 14, AcO_2H. 15, BF_3. 16, Ac_2O–pyridine. 17, $HClO_4$–H_2. 18, Heat. 19, Peracids. 20, Ac_2O; heat. 21, H_2–Pt.

which on hydroxylation by the Brown method, followed by oxidation with Jones's reagent, gave the lactone (156). The cyclopentane ring was then formed under acid conditions, acylium attack affording the tricyclic pentenone (157). However, in this dehydration, racemisation of the product occurred and a slightly different route to the cyclopentenone (157) was

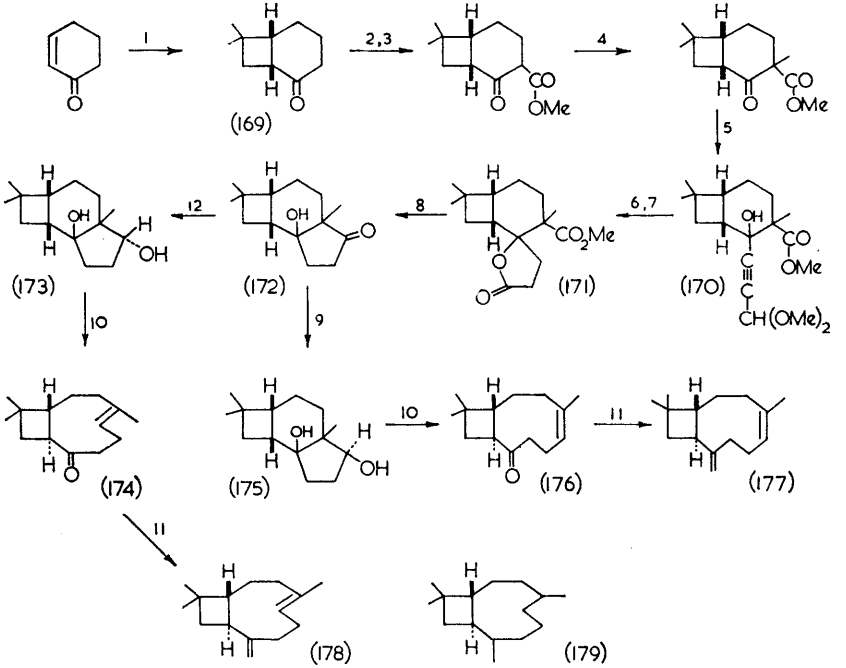
[79] Buchi, Macleod, and Padilla O, in the press.

necessary to avoid this. Selective dehydration of the readily obtainable diol (158) gave the primary alcohol (159). Oxidation, followed by cyclisation of the acid chloride (160), gave the desired cyclopentenone (157) without racemisation. β-Patchoulene (161) was then prepared from the ketone (157) by the Wittig reaction. Synthesis of α-patchoulene (166) was much more difficult. The acid-catalysed equilibrium between β-patchoulene (161) and α-patchoulene (166) favours the former. However, acid-catalysed rearrangement of the epoxide (162) of β-patchoulene gave the unsaturated alcohol (163) with formation of the skeleton of α-patchoulene, and it then remained to eliminate the hydroxyl group without simultaneous return to the skeleton of β-patchoulene. This was achieved[80] by selective catalytic reduction of the diol (164) to the alcohol (165; R=H), and pyrolysis of the acetate (165; R = Ac) gave α-patchoulene (166). As α-patchoulene had earlier been reconverted into patchouli alcohol it was considered that this work represented a final proof of the structure of the alcohol which was formulated as (167). However, a subsequent determination of the structure of patchouli alcohol by *X*-ray crystallography[81] demonstrated that the correct structure is (168). Dehydration of patchouli alcohol to give α-patchoulene is thus due to a skeletal rearrangement, and, more surprisingly, the hydration of patchoulene to give the alcohol proceeds with the reverse skeletal rearrangement.

It is not always possible to choose a synthetic route in which the starting material and the desired product have a closely related skeleton. This is clearly illustrated in the oustanding synthesis of caryophyllene (178).[82] Corey and his co-workers developed a synthesis in which the four-membered ring was first constructed by photolytic addition of isobutene to cyclohexenone. The resultant ketone (169) was then elaborated by standard reactions, to give the acetylene (170) and then the lactone (171). The key intermediate in the synthesis, the hydroxy-ketone (172), was obtained by treatment of the lactone with base and later removal of the methoxycarbonyl group. Reduction of the key hydroxy-ketone (172) under different conditions gave either the alcohol (173) or the epimer (175). Construction of the nine-membered ring system was then accomplished by solvolysis of the monotoluene-*p*-sulphonates of the alcohols (173) and (175). The former gave the ketone (174) with the caryophyllene skeleton, and the latter gave the ketone (176) with the isocaryophyllene skeleton. The solvolysis is accompanied by isomerisation of the ring junction from the *cis*- to the *trans*-configuration. A Wittig reaction then gave caryophyllene (178) and isocaryophyllene (177) from the respective ketones. The critical points of this synthesis are the initial construction of the four-membered ring by the novel photochemical addition, the transposition of the lactone (171) into the ketone (172), thus potentially forming the nine-membered ring, and the

[80] Buchi and Macleod, *J. Amer. Chem. Soc.*, 1962, **84,** 3205.
[81] Buchi, Dobler, Dunitz, Gubler, Padilla O, and Weber, *Proc. Chem. Soc.*, 1963, 383.
[82] Corey, Mitra, and Uda, *J. Amer. Chem. Soc.*, 1964, **86,** 485.

final realisation of the nine-membered ring by decomposition of the monotoluene-*p*-sulphonate. In earlier work[83] the gross structure of caryophyllene had been demonstrated by total synthesis of tetrahydrocaryophyllene (179).



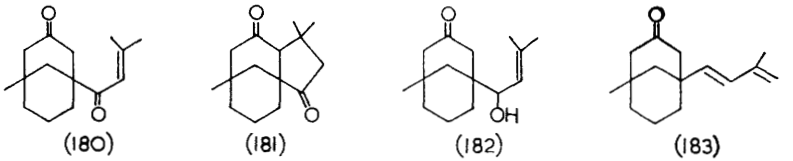
Reagents: 1, $CMe_2{:}CH_2$, *hν*. 2, $(CO_2Et)_2$. 3, Heat. 4, NaH–MeI. 5, $Li{\cdot}C{\equiv}C{\cdot}CH(OMe)_2$. 6, H_2–Pd–C. 7, CrO_3–AcOH. 8, Sodium-methylsulphinyl carbanion in Me_2SO; hydrolysis. 9, H_2–Raney Ni. 10, p-$C_6H_4Me{\cdot}SO_2Cl$; sodium-methylsulphinyl carbanion in Me_2SO; Bu^tOH. 11, $PPh_3{:}CH_2$. 12, $LiAlH_4$.

Attention may be drawn here to the utility of such syntheses as that of caryophyllene. The importance of such an elegant synthesis is far greater than the mere successful synthesis of yet another sesquiterpene. First, reactions—either previously unknown or little appreciated—are developed and generalised to enrich all fields of synthetic chemistry. Secondly, the brilliant solution of a specific problem of synthesis encourages others to consider the improbable to be within the realms of the possible.

Acid-catalysed rearrangement of caryophyllene (178) gives the hydrocarbon clovene (103). The structure of clovene has been known for sometime, but only recently has this sesquiterpene been synthesized,[84] after a number of unsuccessful attempts[85] in which the critical steps of ring

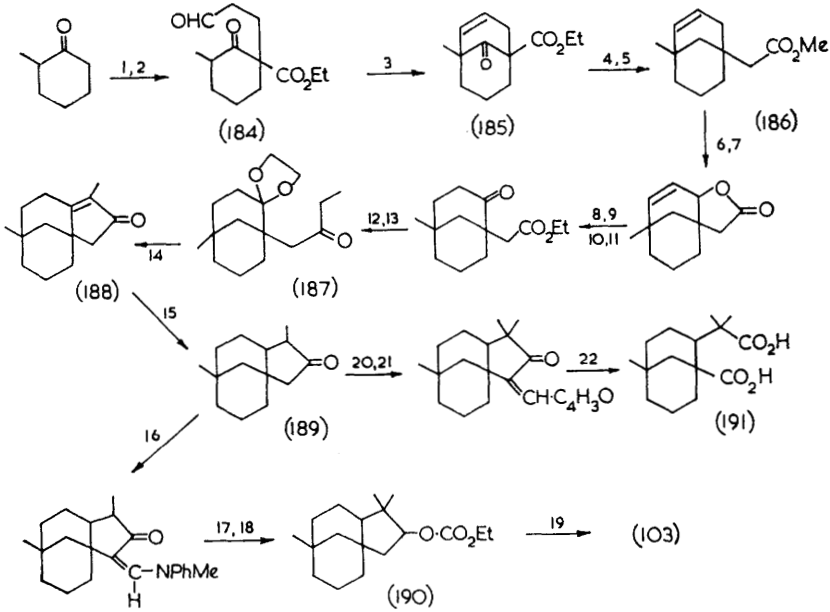
[83] Dolejs, Jarolim, Šorm, and Streibl, *Coll. Czech. Chem. Comm.*, 1957, **22**, 1277.
[84] Doyle, Maclean, Parker, and Raphael, *Proc. Chem. Soc.*, 1963, 239.
[85] Murray, Parker, and Raphael, *Tetrahedron*, 1961, **16**, 74.

formation were by internal condensations. Thus internal Michael condensation of compound (180) failed to give the desired tricyclic diketone (181). An attempt was made to obtain this skeleton by hydrolysis of the *p*-bromobenzenesulphonate of the alcohol (182); however, the product was the bicyclic dienone (183) and not the desired cyclisation product.[85]



(180) (181) (182) (183)

In the successful synthesis[84] of racemic clovene (103) the tricyclic system was obtained by cyclisation of the ketone (187) to the conjugated ketone (188). This ketone was converted by standard methods into the carbonate (190), whose pyrolysis gave the desired racemic clovene (103). The bicyclic

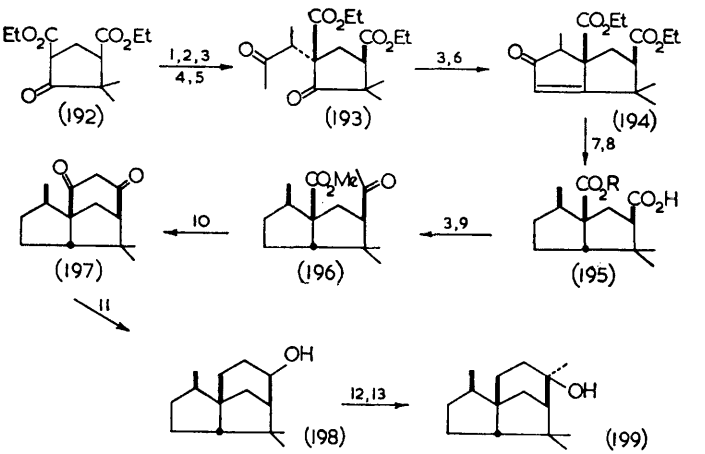


Reagents: 1, $(CO_2Et)_2$–NaOEt; heat; −CO. 2, CH_2:CH·CHO–NaOEt. 3, H_2SO_4. 4, Zn–Hg–HCl. 5, Arndt–Eistert. 6, CH_2N_2. 7, SeO_2–AcOH. 8, $LiAlH_4$. 9, MnO_2. 10, CrO_3–H_2SO_4. 11, H_2; CH_2N_2. 12, $(CH_2{\cdot}OH)_2$–H^+; HO^-. 13, EtLi. 14, H^+; KOH. 15, H_2. 16, H·CO·NPhMe. 17, Alkylation and removal of protecting group. 18, $LiAlH_4$. 19, Heat. 20, Furfuraldehyde–HO^-. 21, Alkylation. 22, O_3–H_2O_2.

ketone (187) was prepared by a route in which addition of acraldehyde to 2-ethoxycarbonylcyclohexanone yielded the keto-aldehyde (184). Cyclisation of this compound to the bicyclic keto-ester (185) was followed by routine transformations into the ester (186) and the ketone (187). Raphael and his colleagues also used the ketone (189) to permit a synthesis

of an oxidative degradation product of clovene, namely, clovenic acid (191).

The utility of internal condensations, the key to the successful synthesis of clovene (103), is further exemplified by the synthesis of cedrol (199) and acorone (105). Norcedrenedicarboxylic acid (195; R=H) was used as a relay in the synthesis of cedrol.[86] Thus the two critical stages of the synthesis are formation of the skeleton of norcedrenedicarboxylic acid and transformation of the acid into the tricyclic cedrol skeleton. The cyclopentenone diester (192) was used as the starting material and elaboration by standard methods gave the diester (193). An internal Claisen condensation afforded

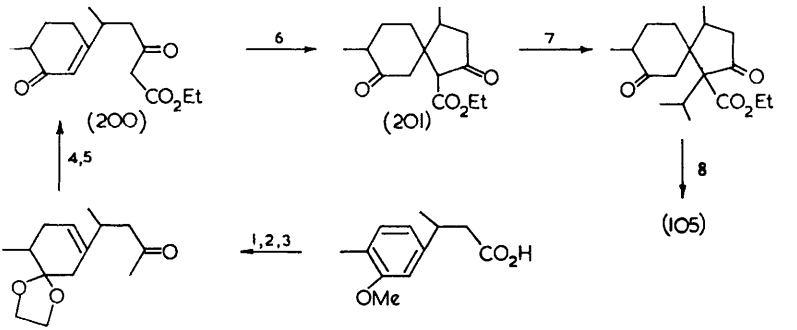


Reagents: 1, NaH–CHMeBr·CO_2·CH_2Ph in Me_2SO. 2, H_2–Pd–C. 3, $(COCl)_2$. 4, CH_2N_2–dry HCl. 5, Zn–AcOH. 6, Bu^tOK–Bu^tOH–H^+. 7, Li–liquid NH_3 or H_2–Pd–C. 8, $(CH_2·SH)_2$; Raney Ni; partial hydrolysis. 9, $CdMe_2$. 10, Bu^tOK–Bu^tOH. 11, $LiAlH_4$. 12, CrO_3–pyridine. 13, MeLi.

the bicyclic skeleton, giving compound (194) which was then converted into norcedrenedicarboxylic acid to complete the first part of the synthesis. The keto-ester (196) obtained from this acid was readily cyclised by base to the tricyclic β-diketone (197), to effect the second important cyclisation. Either direct reduction with lithium aluminium hydride or reduction of the enol ether mixture from the diketone (197) gave the alcohol (198), which was converted into cedrol (199) in two further steps. This synthesis is characterized by the high degree of stereospecificity in the varied alkylations and condensations.

Acorone (105) is a member of a group of spiran sesquiterpenes, the only known spiran terpenes. An internal condensation was the key to the major synthetic problem, the construction of the spiran system. Base-catalysed condensation of the diketo-ester (200), synthesized from the readily available 3-methoxy-4-methylacetophenone, gave the spiran diketo-ester (201).

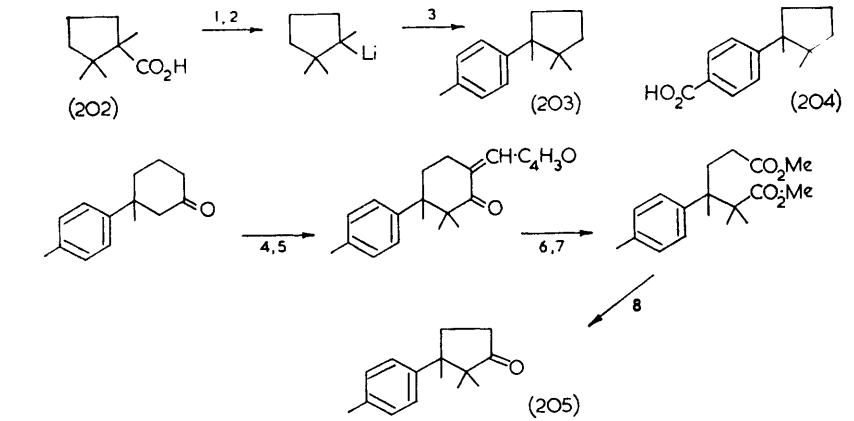
[86] Clarke and Stork, *J. Amer. Chem. Soc.*, 1961, **83**, 3114.



Reagents: 1, Li–liquid NH_3. 2, $(CH_2{\cdot}OH)_2$–H^+. 3, MeLi. 4, Et_2CO_3–NaH in Me_2SO. 5, H^+. 6, Base. 7, Alkylation. 8, HO^-; $-CO_2$.

Subsequent alkylation and hydrolytic decarboxylation gave acorone (105).[87]

Cuparene (203), a naturally occurring sesquiterpene, has been synthesized by a number of routes,[88,89] and was also the target of earlier unsuccessful synthetic work.[89] A simple three-step synthesis[88] from camphonanic acid (202) has been described. 1,2,2-Trimethylcyclopentyl bromide, pre-

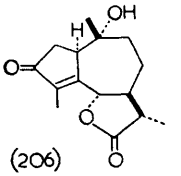


Reagents: 1, Hunsdiecker reaction. 2, Li. 3, *p*-C_6H_4MeBr. 4, furfuraldehyhe–HO^-. 5, MeI–NaH. 6, O_3. 7, CH_2N_2. 8, Dieckmann condn.; HO^-; $-CO_2$.

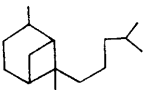
pared from camphonanic acid by the Hunsdiecker reaction, was converted into the lithio-compound and condensed with *p*-bromotoluene to give (±)-cuparene. Cuparenic acid (204), another naturally occurring compound, was prepared by ready oxidation of cuparene (203). A second, more lengthy synthesis[89] of cuparene has been reported in which 2,2,3-trimethyl-3-*p*-tolylcyclopentanone (205) was used as an intermediate. This ketone has recently been shown to be of natural occurrence.[90]

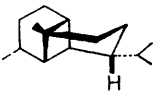
[87] Parker, Ramage, and Raphael, personal communication.
[88] Nozoe and Takashita, *Tetrahedron Letters*, 1960, No. 23, p. 14.
[89] Parker, Ramage, and Raphael, *J.*, 1962, 1558.
[90] Chetty and Dev, *Tetrahedron Letters*, 1964, 73.

Conclusions.—The Reviewers consider that as the tools of chemical synthesis become more precise, permitting reactions of greater specificity, more attention will be paid, not to total synthesis, but to the study *in vitro* of the intricate cyclisations and rearrangements which *in vivo* give rise to the many diverse sesquiterpenoid structures. Classically a total synthesis is the last stage in the proof of a structural determination. However, an example[81] has already been cited where this final proof of structure fails, and today with the advent of *X*-ray crystallography it is frequently preferred to confirm a structural elucidation by the use of this physical technique. As further synthetic advances are made, formal total syntheses may be made more readily by correlation of a specific compound with others, previously totally synthesized. Thus, now that santonin (32),[23] dihydrocostunolide (38),[27] and isophotosantonic acid lactone (206)[68,69] have all been synthesized, synthesis of other sesquiterpene lactones is facilitated.



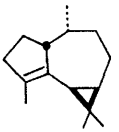
(206)

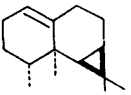

(207)



(208)


(209)


(210)


(211)

However, many problems of total synthesis remain to be solved. No syntheses have been reported of members of the eremophilane (46) or the bergomotane[91] (207) group. The recent structural elucidations of hydrocarbons of the complexity of copaene (208),[92] the tetracyclic longicyclene (209),[93] α-gurjunene (210),[94] and calarene (211),[95] and of oxygenated sesquiterpenes pose fresh problems.

The authors thank Professor G. Ourisson for his helpful comments and Professors G. Buchi, W. G. Dauben, R. A. Raphael, and E. Wenkert for communications before their publication. The work was supported by a NATO post-doctoral fellowship (to J.M.M.) and a CNRS post-doctoral fellowship (to S.M.).

[91] Bates, Bhattacharyya, Kulkarni, Paknikar, Kelkar, and Vaidya, *Tetrahedron Letters*, 1963, 505; Bapat, Bhattacharyya, Kanthamani, Kelkar, Kulkarni, Kulkarni, Lakshimikumari, Narayanan, Paknikar, and Vaidya, *Tetrahedron*, 1964, 963.

[92] Buchi, Fearrhellar, de Mayo, and Williams, *Proc. Chem. Soc.*, 1963, 214; Dev, Kapadia, Nagasmpagi, and Naik, *Tetrahedron Letters*, 1963, 1933.

[93] Dev and Nayak, *Tetrahedron Letters*, 1963, 243.

[94] Ourisson, Palmade, Pesnelle, and Streith, *Bull. Soc. chim. France*, 1963, 14.

[95] Ourisson, Pesnelle, and Streith, *Bull. Soc. chim. France*, 1963, 518; Herout, Krepinsky, Šorm, and Viitol, *Tetrahedron Letters*, 1963, 225.