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REGIO- AND STEREO-SPECIFICITY IN THE CYCLISATION OF MEDIUM RING 1,5-DIENES

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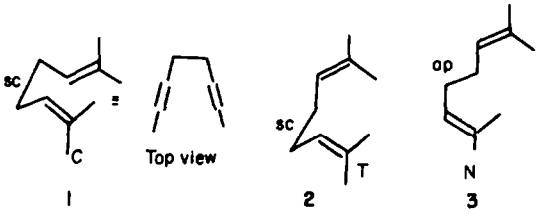
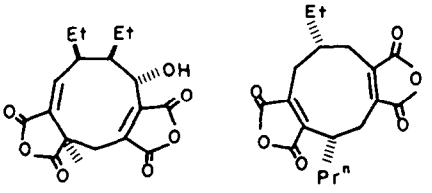
In the past 15 years the chemistry of 9-, 10- and 11-membered cyclic polyenes has been widely investigated; mainly this has been due to the isolation and structure determination of terpenoids containing these features, and the availability of some synthetic compounds. In certain cases the impetus for this work derived from the suggestions of Ruzicka[1] and Barton,[2] elaborated by Hendrickson[3] and Parker, Ramage, and Roberts,[4] that such compounds are involved in biosynthesis of sesquiterpenes. The unravelling of the chemistry of caryophyllene,[5] germacrone,[6] and pyrethrosin[2] showed the diversity of reaction pathways open to these compounds. In the main it has been the chemistry of 1,5-diene derivatives that has been explored and in cases where the double bonds are endocyclic they show remarkable stereoselectivity in their reactions due, primarily, to reaction occurring in a single conformation and to one π-lobe of each double bond being intraannular and unexposed to attack by reagents. There are three distinctive conformational arrangements for a 1,5-diene system within a medium ring as shown in **1**, **2**, and **3**. In a topological sense there are, of course, many more, but they reduce to the three illustrated or their mirror images. From models it appears likely that the C conformation† **1** can be adopted by E,E and Z,E medium ring olefins while the T arrangement **2** is possible for EE, ZE, and Z,Z compounds. The extended conformation **3** would be limited to Z, Z compounds. The reacting comformation is obviously important in determining the stereochemistry of any cyclisation products e.g. formation of a cyclohexane from a Z,Z olefin would give a *trans* ring junction from the C conformation and *cis* from the T.



1 2 3

Fig 1.

In the cyclonona-1,5-diene series there is relatively little firm information regarding preferred conformations. For the Z,Z compounds there are X-ray structure determinations of the nonadrides, glauconic **4**[7] and byssochlamic **5**[8] acids which show the same basic conformation **6** for the ring,



4 **5**

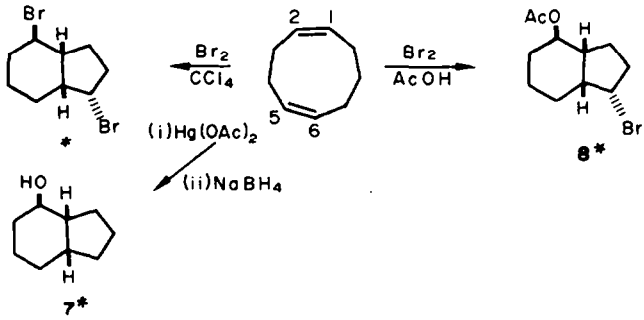
6

despite differing substitution patterns; here the diene unit is in the T arrangement. These compounds undergo a number of interesting pyrolytic and reductive cyclisations but the stereochemistry of the processes has not been unambiquously established. Z,Z-Cyclonona-1,5-diene itself has been cyclised to *cis*-hydrindane derivatives with electrophilic reagents as shown below.‡

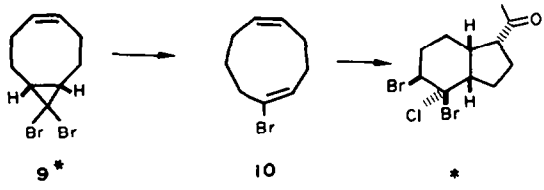
In this study[9] the ring junction stereochemistry has been firmly established as has that of the hydroxyl and acetoxyl in **7** and **8**. These results are in accord with the diene reacting in conformation

†The C and T conformations have been referred to as crossed and parallel. Since the latter is strictly a true description of **2** only when the 2,3,4,5-torsion angle is zero we prefer to use C and T indicating that cyclisation of C–1 to C–6 would give a chair cyclohexane with **1** and a twist (or boat) ring with **2**. N is intended to indicate an extended conformation.

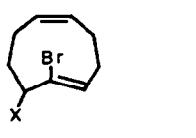
‡Compounds marked with asterisks are racemates, only one enantiomer being illustrated.



6 and allow prediction that the bromine stereochemistry is that shown. 1,6-Bonding would lead to a boat-like transition state for the cyclohexane ring, however, this objection does not hold for 1,5- and 2,6-bonding; why the former is exclusively observed is not clear but if the double bonds were polarised in the sense of C–1 and C–6 being δ^+ this would be understandable. A similar type of cyclisation is observed when the octene **9**[10] is reacted with acetyl chloride and stannic chloride; this reaction has been shown to go *via* the diene **10**. Here the direction of cyclisation is controlled by the bromine which deactivates one double bond, allowing initial attack on the disubstituted double bond but by its mesomeric effect directing cyclisation as shown.



Z,E-Cyclonona-1,5-dienes can be prepared by the cyclopropyl-allyl rearrangement of **9** using silver salts.[11,12] In this way compounds **11–14** were prepared in good yield. On reaction with aqueous N-bromosuccinimide **11**, **12**, and **13** were cyclised to the corresponding *trans*-hydrindane **16**.[13] The stereochemistry of **16** (X = OAc) was firmly established, apart from that of the bromine, by conversion to *trans*-hyrdindan-5-one. Here again initial attack is on the Z-disubstituted double bond but the direction of cyclisation is influenced by the mesomeric effect in the vinyl bromide. Presumably a carbonium ion **18** results from the cyclisation and in an attempt to trap it by C–C bond formation the allyl ether **15** was cyclised; however, only the ketone **16** (X=$OCH_2CH{=}CH_2$) was obtained. These results lead us to postulate that **19** was the reacting conformation and that substituents occupied an equatorial-like position. In the case of **14** Reese[12] has shown that, because of the high energy barrier to ring inversion **19**⇌**20**, the pseudo-equatorial and pseudo-axial diastereomers can be separated; he has also advanced arguments that the pseudo-equatorial isomer is the more stable. The ring inversion requires three distinctive transformations—a flip of the $CH_2CH{=}CHCH_2$ unit, a rotation of the $-CH_2CH_2CHX$-unit, and a rotation of the $-CH{=}CBr$-unit. The latter is likely to be the high energy process since one of the substituents has to pass through the ring. The conformational changes of the three carbon units are difficult to illustrate but are similar to the flexing of a similar unit in a cyclopentane. These three processes lead to a conformational itinerary similar to that for the cyclodecadiene and are discussed later. The conformations **19** and **20** arising from rotation of the double bond units have C diene conformations, while **21** and **22** have T arrangements. The dimethyl



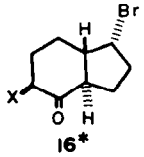
11: X = OAc

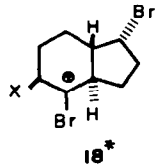
12: X = Br

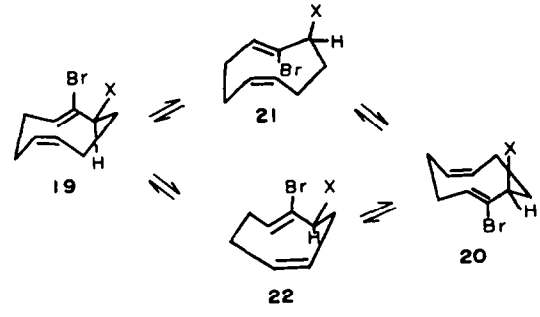
13: X = OH

14: X = OMe

15: X = $OCH_2CH{=}CH_2$

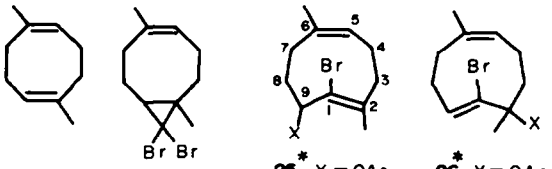






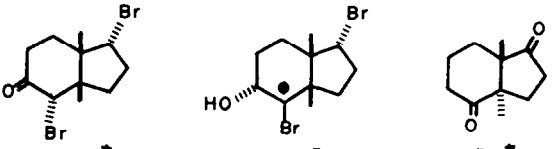
cycloocta-1,5,diene **23** is readily available from the dimerisation of isoprene[14] and gives a monodibromocarbene adduct **24**, which on cyclopropyl-allyl rearrangement with silver acetate and aqueous silver perchlorate gives mixtures of **25** and **26** and

27 and 28 respectively. We[16] cyclised the alcohol 27 with aqueous N-bromosuccinimide to 30, presumably *via* the cation 31 which then undergoes a 1,2-hydride shift to form 30. The stereochemistry of 30 was determined by degradation to the parent hydrocarbon whose constitution was firmly estab-



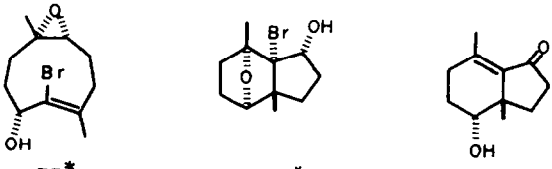
23 24* 25*: X = OAc 26*: X = OAc 27*: X = OH 28*: X = OH 29*: X = Br

lished and which is not identical to the *trans*-hydrindane prepared from 32.[17] This implies that 27, unlike 13, is reacting in a T conformation 21. In support of this it has been shown that when the 2-Me of the bromide 29 is irradiated an n.O.e. of 17% is observed on the 5–H and one of 15% on 9–H; the latter also establishes that the double bond



30* 31* 32*

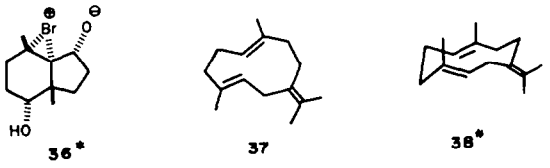
has Z stereochemistry. A most unusual cyclisation of the oxide 33 is observed[15] when it crystallises. The oxide of the corresponding acetate is stable in the solid state and 33 is stable in dilute solution; however after crystallisation the oxide decomposes in a short time to a mixture of 34 and 35. The constitution of 34 and 35 were established unam-



33* 34* 35*

biguously but the stereochemistry is assumed on the basis of a T reacting conformation. From the stability of the acetate of 33 in the solid state it appears that intermolecular H-bonding between hydroxyl and epoxide must initiate this reaction leading to the zwitter-ion 36 which cyclises to 34 (with retention of configuration) or eliminates hydrogen bromide to form 35 after initial hydride migration. It is notable that the oxide of the bisnormethyl alcohol corresponding to 33 does not react in a similar manner. From the preceeding work it is clear that a conformational inversion has occurred in going to the dimethyl series and it is reasonable to ascribe this to the transannular Me–Br interaction in the C conformation being greater than the Me–Me interaction in the T arrangement.

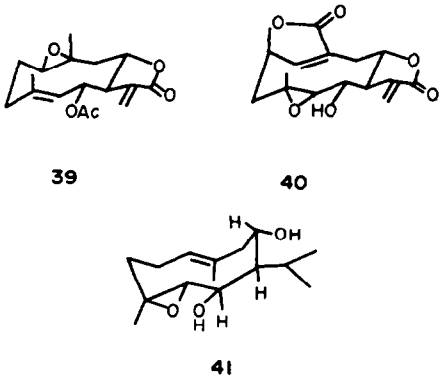
A much greater volume of work has been published on cyclodecadienes chiefly because of the availability of numerous sesquiterpenes containing this system and the mono-oxides derived from it. To our knowledge the first sesquiterpenoid E,E-cyclodeca-1,5-diene whose stereochemistry was unambiguously established by X-ray analysis[18] was germacrene 37. From this study the crown conformation 38 with a C conformation of the 1,5-diene



36* 37 38*

emerged and, since then the oxide pyrethrosin 39[19] and the lactone, elephantol 40[20] have been shown to have similar conformations.

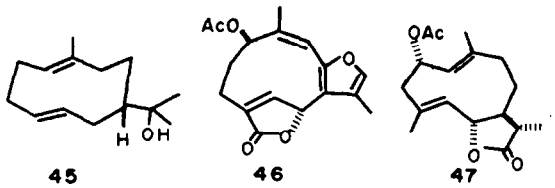
Slight variants (but still containing the C diene conformation) are found in the conformations of pregeigerene[20] and shiromodiol 41[20] where there has been a rotation of the C–8,9 unit. However, in other cases spectral evidence has been put forward



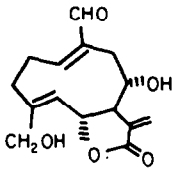
39 40 41

for the existence of two conformers in solution and Halsall's group has shown that two readily interconvertible compounds, urospermals A and B 42,[21] can be isolated; there is good evidence that there are conformational isomers and it has been suggested that A has the crown conformation stabilised by H-bonding between the primary hydroxyl and aldehyde, while B has a T conformation stabilised by H-bonding between the primary and secondary hydroxyl groups; however such H-bonding could also occur in a C′ conformation where both E units have been rotated to give a shiromodiol 41 type of conformation.

One distinctive conformational itinerary for **43** has been discussed in detail by Wharton.[22] This is summarised in the Fig 2, using a notation different from his and which is based on the conformation of the cyclohexane rings obtained by notionally cyclising the cyclodecadiene to a decalin by joining C–1 and C–6. C indicates that cyclisation generates a chair conformation, T that



45 46 47



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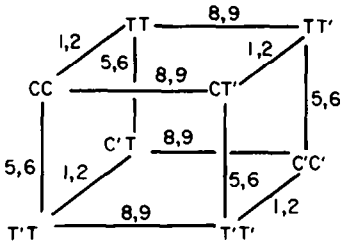
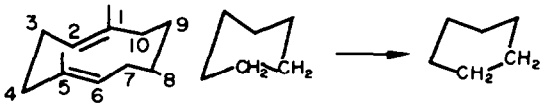


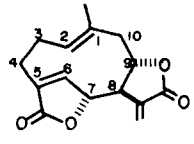
Fig 2. Conformational itinerary of E,E-cyclodeca-1,5-dienes. Numbers indicate the bond systems which are rotated.

it is a twist-boat or boat and C' and T' are conformations enantiomeric to C and T. The first letter is the conformation of the diene unit C–1 to C–6, the second that of C–6 to C–1. Wharton has pointed out that the conversion of **43** in the crown C,C, conformation to its enantiomer C'C' requires three distinctive conformational changes *viz* rotation of the 1,2 and 5,6 double bond units through 180° and a flipping of the C–8 and C–9 methylenes analogous to the change of a methylene pair in going from chair to boat cyclohexane **44**. Elegant use of deuterium labelling and variable temperature NMR spectroscopy demonstrated that the CC, TT, TT' conformers and their enantiomers



43* 44

were present with C,C predominating at lower temperatures; the CT' conformation, i.e. the shiromodiol type could not be detected. The assignment of C or T diene conformations was based on the expectation that in the C arrangement the C–1 methyl (τ 8·68) and the C–6 hydrogen (τ 5·70) would be shielded relative to C–5 methyl (τ 8·52) and C–2 hydrogen (τ 5·20) and also to the corresponding absorptions of the T conformation (τ 5·0, 8·55, 8·60). A similar investigation of hedycaryol **45** showed that the major conformers were TT and T'T. Only in exceptional cases can conventional NMR spectroscopy do other than indicate the number of conformers present in these ten-ring compounds; a more powerful tool is the observation of transannular nuclear Overhauser effects first used in this area by Takeda *et al.* to establish the conformations of the Z,E-cyclodeca-1,6-diene derivatives zeylanine **46**[23] and its oxide, zeylanane and later, by Bhacca, to demonstrate the crown conformation for dihydrotamaulipin-A-acetate **47**.[24] There have been a number of applications of this technique since then. The first observation of two interconvertible conformations in solution was made by Maybury on isabellin **48**;[25] later it was shown that the major one was C'T.[26]



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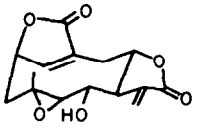

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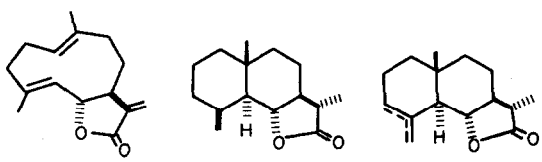
Many of the terpenoid compounds in this series contain *trans*-fused γ-lactone rings which introduce constraints to conformational mobility; thus such a lactone ring at 8,9 prevents the T→T' conversion. A 5,7 γ-lactone as in isabellin or a 1,3-lactone as in elephantol **49** prevents that double bond rotating which, since they have the same absolute configuration at C–8, leads to a CC conformation for elephantol and a C'T for the major conformer of isabellin. To summarise it appears that the C conformation for the 1,5 diene unit is the favoured one but that in certain circumstances appreciable amounts of the T isomers can be present.

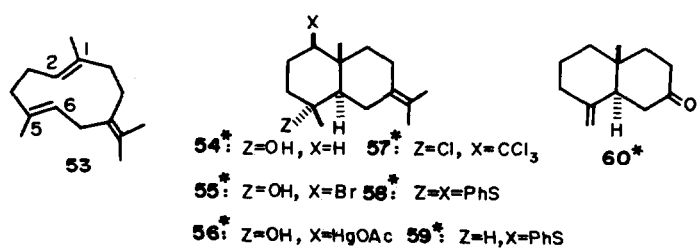
The proton and Lewis acid induced cyclisation of germacrenes and their derivatives was an early feature of their chemistry and this led to renewed

speculation regarding their role in the biosynthesis of bicyclic sesquiterpenes; Ruzicka[1] had made the original proposal before any of these types had been discovered. It was in 1957 that Barton and de Mayo[2] proposed the cyclodecane structure for pyrethrosin and Sorm[6] and his collaborators that for germacrone. Since then a large number of compounds with this ring system have been discovered.[27] In the early work on costunolide **50** it was converted to **51** by hydrogenation under acidic conditions;[28] similar results were obtained in other cases but there was the doubt as to whether the ring junction stereochemistry was produced by cyclisation or hydrogenation. This was clarified by Bhattacharyya[29] *et al.* who showed that dihydrocostunolide cyclised to a mixture of olefins **52**.



50 **51** **52**

However, interpretation of these cyclisations was a problem since it was extremely difficult to establish beyond doubt the stereochemistry of cyclodecadiene double bonds by chemical methods. X-ray crystallography solved this problem and Allen and Rodgers[18] demonstrated that in the silver nitrate complex of germacrene **53** the double bonds were E,E. Concurrently with this work we investigated[30] the cyclisation of germacrene with electrophilic reagents (H^+, BrOH, and HgOAc) and showed that the sole or major products were *trans*-decalins **54**,† **55**, and **56** the stereochemistry of which were established by interrelations and degradation to the ketone **60** of established structure and

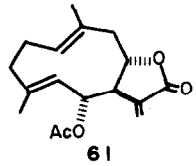


stereochemistry.[31] We were unable to detect any *cis*-decalins or guiane derivatives. A similar series of reactions with similar results has been carried out on costunolide and its derivatives.[32] This then established that germacrene was reacting in a C conformation and there was *trans* addition to the double bonds. We obtained similar stereochemical results[33] using reagents which react *via* radical intermediates; addition to **53** of CCL_4, $(PhS)_2$, and PhSH yielding **57**, **58** and **59**. In order to explain the apparent absence of products derived by attack on the 5,6-double bond [e.g. **54** is produced quantitatively] we have postulated that C–C bond formation is synchronous with C–X bond formation since electrophilic reagents which do not lead to cyclisation show similar affinities for the two endocyclic double bonds, indeed in epoxidation with one mole of reagent the ratio of 5,6- to 1,2-epoxide is 7:3. The slight difference in reactivity of the two double bonds is explicable[34] if it is accepted that the conformation found for germacrene in the solid silver nitrate complex is close to that found in solution. The similarity of the torsion angles of the 2,3 and 6,7 and 1,10 and 4,5 bonds makes it clear that each double bond is equally hindered to approach by a reagent, however both double bonds are torsionally twisted (1,2 by 13°, 5,6 by 20°); how much of this is induced by metal complexing is unclear since, to date, no structure determination has been carried out on a torsionally twisted olefin in both the free and complexed state. In the case of the unstrained Z,Z,Z-1,4,7-cyclononatriene there are no differences in structural parameters between the free olefin and its silver complex. In addition there are now a number of well-established cases where torsionally twisted double bonds have been observed with uncomplexed olefins. Even if the silver ion induces an increase in torsion it is likely that the relative amount of torsion of the two double bonds will be similar in the free and complexed state. Clearly one would expect greater relief of steric strain in the transition state for the epoxidation of the more highly torsionally strained double bond, so leading to the observed preferential attack. Rough calculations support this view.

With the simple E,E-germacrenes and germacranolides one can summarise the present situation by saying that in concerted cycloadditions reaction should occur at the torsionally most strained bond whereas cation or radical mediated reactions should lead to *trans*-decalin derivatives. So far the cyclisation of compounds with established TT conformers has only been studied in one case but even here, since the Curtin–Hammett principle should hold, the more favourable chair-like transition-state

†Professor G. Büchi kindly informed us that he had isolated germacrene from natural sources and cyclised it to **54**.

from the C conformer could lead to *trans*-decalins. Indeed the only reported cyclisation product of laurenobiolide **61** is a *trans*-decalin obtained in 25% yield.[35]



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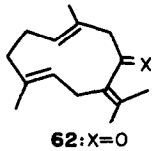
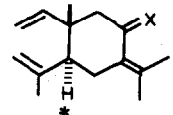
Another question which remains to be answered is whether cyclisation of compounds with C'T conformation like isabellin would lead to santonins with the ring system enantiomeric to the natural series.

Being 1,5-dienes germacrenes and germacranolides readily undergo Cope rearrangement to form elemenes. Germacrone **62** on heating forms **64**[36] while germacrene gives **65**;[30] in the latter case the stereochemistry could be related to that of the selinane series by reaction of **65** with HOBr to form

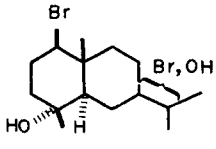


62: X=O
63: X=H_2



64*: X=O
65*: X=H_2

66 which on reduction with zinc in acetic acid yields the cyclisation product **55** from germacrene. A similar cyclisation has been effected with the Cope rearrangement product of costunolide[32] and saussurea lactone **67** undergoes a proton initiated cyclisation to **68**.[29] The position of equilibrium between



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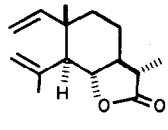

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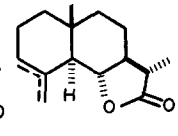
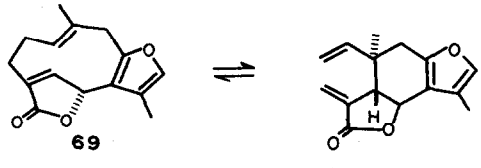


68

the 10- and 6-ring compounds varies with structure but usually favours the latter. Some notable exceptions are dihydrotamaulipin-B-acetate **47** where two parts of it are in equilibrium with three parts of the divinylcyclohexane[38] and linderalactone[39] **69** where the ratio was 3:2. It is notable that in the latter case stereochemistry enantiomeric to the



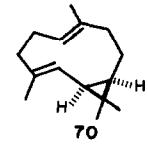
69

†The *transoid* allylic cation must isomerise to the *cisoid* intermediate before cyclisation.

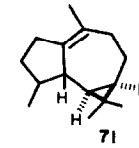
natural series at the ring junction is found because of the lactone ring preventing any rotation of the double bond unit. The Cope rearrangements of these systems occur at $>100°$, however, as first noted with Z,E-cyclodeca-1,5-diene[37] and later shown with germacrene, treatment with $PdCl_2.(PhCN)_2$ in DMSO brings about a facile isomerisation to the divinylcyclohexene complexes at room temperature.[33]

In all cases so far examined the expected preference for reaction *via* C diene conformations is observed. The Cope rearrangements will not be discussed further since they are the subject of another review in this Volume.

When perturbing groups are present near the 1,5-diene system the cyclisation of germacrenes can take a different course. The bicyclogermacrene **70**,[40] which has a C'C' conformation,[41] on treatment with acid yields the hydrocarbons **71** and **72**. Clearly the cyclopropane ring by its ability to stabilise a carbonium ion centre **73** and to be cleaved **74**† can give rise to intermediates which could be the precursors of the cyclised hydrocarbons. It would be of interest to see if **70** could be converted directly to the maliol derivative[42] **75**



70



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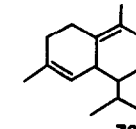

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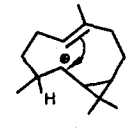

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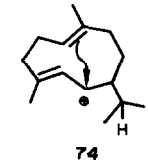

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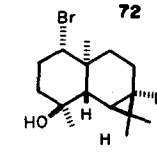
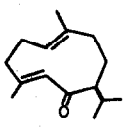
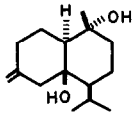


75

which has been prepared from the Cope rearrangement product using our N-bromosuccinimide/acetone/water method.[30] Acoragermacrene **76** gives a variety of cyclisation products; with hot acetic acid a complex mixture is obtained including **77** which is apparently formed by a Prins reaction of the deconjugated ketone.[43] In formic acid the *cis*- and *trans*-isomers of **78** were obtained[44] as well as **77**; the formation of the two isomers was interpreted as being due to two possible modes of cyclisation of the intermediate enol but it is not clear if the possibility of acid catalysed equilibration of the *trans*-isomer as the source of the *cis*-compound was tested. With formic acid in thiophenol the thioether **79** was formed.[44] This reaction has been formulated as an ionic addition but a radical mechanism would be more in accord with the structure. While the cyclisation of **80** to **81**[45] is not strictly within the terms of this review it is an interesting example of different stereoselectivity in this area.

Many germacrenes and germacranolides exist as


76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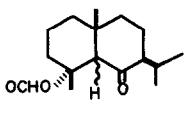
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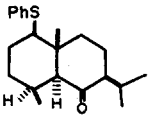
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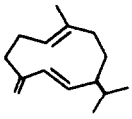
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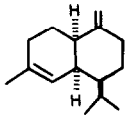
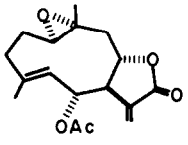

81

their 1,2- or 5,6-oxides, indeed the key reaction in the determination of the constitution of pyrethrosin **82** was its cyclisation to the acetates **83**[2] with *p*-toluene sulphonic acid in acetic anhydride the stereochemistry of which were established later.[46]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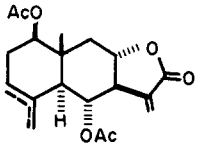
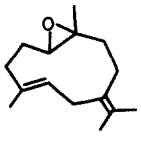
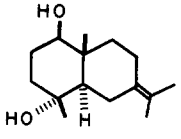
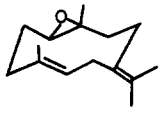

83

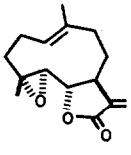
Sorm showed that the oxide of dihydrocostunolide behaved similarly and we converted **84** into the diol **85** and the corresponding olefins.[48] These findings are in accord with the epoxide reacting in a CC conformation. Clearly epoxidation locks one of the units such that it cannot rotate, however, fewer conformational studies have been conducted on

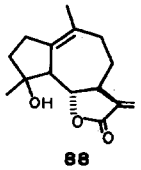

84*


85*


86*

these compounds though the crown appears to be the favoured one. Govindachari *et al* have cyclised parthenolide **87** to the guiane **88**[49] and the stereochemistry of the cyclisation followed from our conversion of germacrene-5,6-oxide to the diol **89** the stereochemistry of which was related to **85**.


87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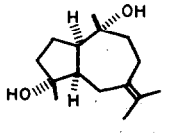
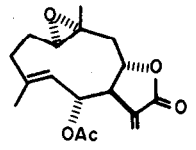

89*

Again these results are in complete agreement with cyclisation in a CC conformation. An unusual type of rearrangement is observed on pyrolysis of the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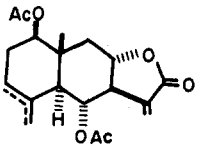
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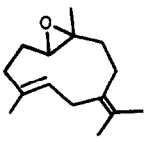
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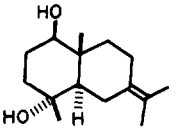
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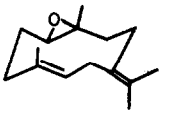
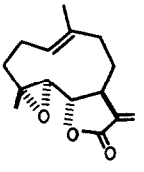
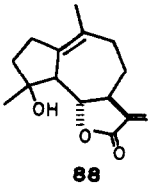
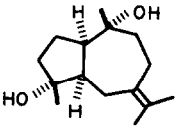

86*

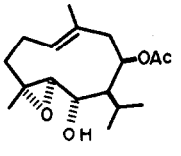
5,6-oxides; shiromodiol acetate **117** being converted to the cyclopropane **90** and the guianes


87


88


89*

91.[50] Analogous results are found with the germacrene oxide.[51] This reaction has been formulated as a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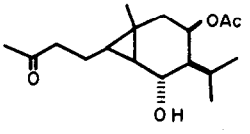
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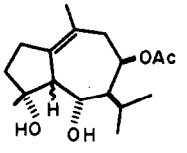
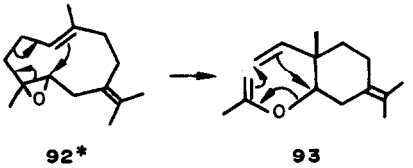
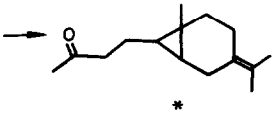

91

radical process but two consecutive electrocyclic reactions **92** and **93** could also account for the


92* 93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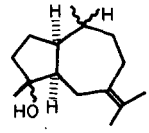
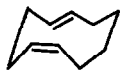
cyclopropane products as could a chelotropic reaction. The 5,6-oxide of germacrene has also been cyclised reductively using lithium in ammonia to give **94** of unestablished stereochemistry.[33]

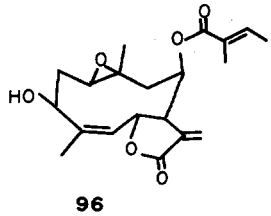


94*

Cyclonona-1E,5Z-dienes have also been studied. Wilke has shown that the parent compound is readily available from the Ni(O) catalysed condensation of butadiene and ethylene.[52] As with the E,E-dienes, there are four distinctive conformers and their enantiomers which are interconvertible by C-8,9 flipping, rotation of the E unit, and rotation of the Z unit, which should be a lower energy process than that for the E unit. A CT conformation **95** was demonstrated by X-ray analysis[53] for the silver nitrate complex of the parent diene. A different conformation, TT, is found for the oxide heliangine **96**[54] but here the conformation is locked since the

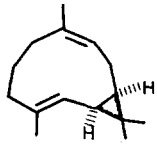


95*

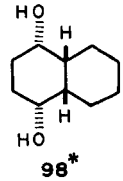


96

presence of the γ-lactone prevents rotation of the Z-unit, and the epoxide any flipping of the E one. It is interesting to note that this is the conformation expected if its immediate precursor were the E,E compound in a C′C′ conformation. Isobicyclogermacrene **97** has been shown by n.O.e. experiments to have a conformation similar to **95**[35] and most of the cyclisations carried out in this series can be interpreted in terms of **95** being the reacting conformation. In general electrophilic reagents attack the torsionally strained E-double bond preferentially. Thus mono epoxidation[55] of **95** gave the E-oxide (which cyclised on boiling in water to the diol **98**) and reaction with the electrophilic dibromocarbene[56] took place preferentially at the E double bond while diimide reduction gave exclusively Z-cyclodecene. Here, as with germacrene,

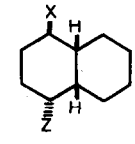


97



98*

concerted molecular additions do not lead to cyclisation. Traynham and his group[57] have investigated the cyclisation of the diene with trifluoroacetic acid, lead tetraacetate, bromine, mercuric acetate (followed by borohydride reduction), methane sulphenyl chloride, and chlorine and obtained as the major or sole products the *cis*-decalins **99–104** respectively. It appears that in all cases attack of the electrophilic part of the addend and ring formation are stereospecific but that addition of the nucleophile may not be totally specific. Radical induced cyclisation with bromoform and bromotrichloromethane appears to be anomalous in that **105** and **106** are formed, implying that initial attack is on the Z-double bond. However in this case there is no definitive evidence that the compound is *cis* or even a decalin. The Z,E-germacrone oxide **107** on treatment with formic acid gives the diol **109** and the *cis*-decalin **110**[58] in accord with



99*: X=H, Z=OCOCF$_3$

100*: X=Z=OAc

101*: X=Z=Br

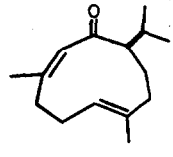
102*: X=H, Z=OAc

103*: X=SCH$_3$, Z=Cl

104*: X=Z=Cl

105*: X=Br, Z=CHBr$_2$

106*: X=Br; Z=CCl$_3$



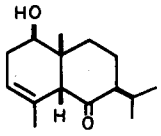
107: a oxide at 5,6

108:

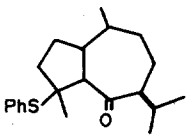
109: diol at 5,6

the previous results; this is one of the few cases in which monocyclic derivatives are isolated and is probably caused by the reduced nucleophilicity of the conjugated double bond. The Z,Z-isomer of the parent germacrone was cyclised by formic acid in thiophenol to a *trans*-decalin **79**. In contrast the Z,E compound **108** is cyclised to the guiane **111** of undefined stereochemistry; again this has been interpreted as an ionic reaction but a radical mechanism would be in accord with Traynham's observation of initial radical attack at the Z-double bond. Cope rearrangements have been more widely studied than cyclisation reactions amongst the natural products of this stereochemical series[59] and most results fit in with the original observation that cyclonona-1E,5Z-diene gives *cis*-divinylcyclohexane.[60]

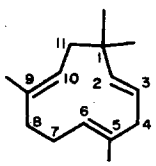
The final example of these cyclisations is the reaction of humulene **112** with N-bromosuccinimide-aqueous acetone where we obtain equal parts



110

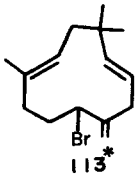


111

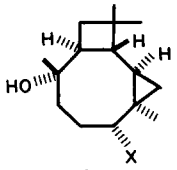


112

of **113** and **114**[61]—in the latter compound six contiguous chiral centres are formed in one step with very high stereoselectivity. There is a close correspondence between the conformation found



113*

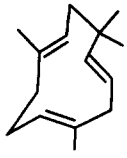


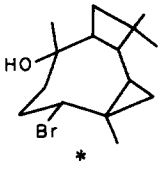
114*: X=Br

115*: X=OH

116*: X=H

for the silver nitrate-humulene complex[62] and that of the tricycle[63] and indeed the humulene conformation is that required to generate the stereochemistry illustrated. Humulene has two 1,5-diene units—the C–4 to C–10 which is in a C conformation and C–3





*

to C–8 which is T. From an inspection of models it is not clear why both should not be C. The 7,8-monooxide of humulene has been cyclised to the diol **115**.[64] Interestingly the high stereoselectivity of these reactions is retained in the decyclisation of **116** to humulene which is brought about by silica gel.

It is clear that the cyclisation of medium ring dienes often leads to high regio- and stereoselectivity and, if simple stereospecific methods for their synthesis from aliphatic compounds can be developed, it can become a powerful synthetic method. The present understanding of medium-ring 1,5-diene chemistry may be summarised by saying that C conformations appear to be the more stable in most cases and are highly favoured as reacting ones due to the chair-like transition state. In addition it is likely that the principle that pseudo-equatorial substituents are more stable than pseudoaxial also holds in medium-ring compounds.

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