# STEREOSPECIFIC COPE REARRANGEMENT OF THE GERMACRENE-TYPE SESQUITERPENES

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Abstract—Stable conformations of several germacrene-type sesquiterpenes in solution are deduced with the aid of intramolecular nuclear Overhauser effects (NOE) in the NMR spectra.

From these conformations, stereochemical aspects of the Cope rearrangement as well as the stereochemistry of the elementype rearrangement products can readily be understood.

## CHAPTER 1

*Conformations of germacrene-type cyclodeca-1,5-diene sesquiterpenes*

During the course of our past investigations on the components of various plants belonging to the Lauraceae family, we isolated many germacrene type cyclodeca-1,5-diene sesquiterpenes, for instance, neosericenyl acetate (1),[1] sericenine (2),[2] linderalactone (3),[3,4] neolinderalactone (4),[5] litsealactone (5),[6] linderane (6),[4,7] zeylanine (7),[8] laurenobiolide (8)[9] etc. It subsequently seemed to us that it would be of much interest to investigate the stable conformation in solution of these cyclodeca-1,5-diene type natural products.
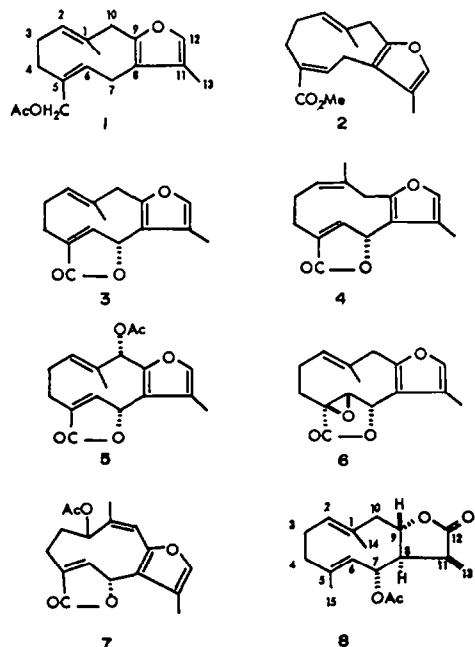
By X-ray crystallography on its 1 : 1 silver nitrate adduct, Allen and Rogers[10] have demonstrated that germacratriene (9) adopts conformation 10 with the 1-methyl group and the 6-proton *anti* as shown in Fig 2.

In 1968, Yoshioka *et al*[11] reported an NMR study of the conformation of isabelin (11), a germacrenolide dilactone, and they suggested that the compound exists in solution as two conformational isomers (Fig 3, A and B) in a ratio of 10:7. Bhacca and Fischer[12] determined the conformation in solution of a germacrenolide sesquiterpene lactone, dihydrotamaulipin A acetate (12), with the aid of the recently developed intramolecular nuclear Overhauser effect (NOE)[13] technique. Their results showed that dihydrotamaulipin A acetate has a crossed orientation of the two *trans*-double bonds, with the 1- and the 5-Me groups on the upper side of the plane of the 10-membered ring. In other words the 1- and 5-Me groups are in a *syn* relationship with the 7-β hydrogen, as shown in the Fig 4, the arrow indicating the presence of NOE.

If a compound contains suitable substituents in
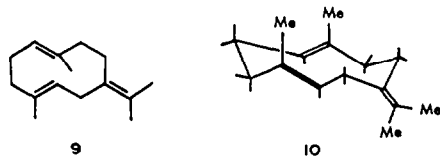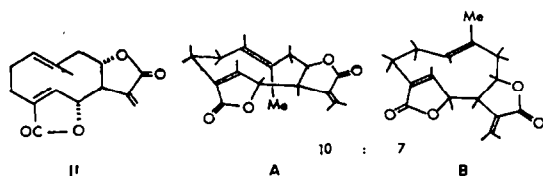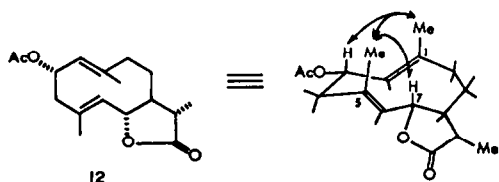


Fig 1.



Fig 2.



Fig 3.

Fig 4.

its molecule, the assignments of each NMR signal then becomes reliable, and measurement of the NOE provides a very effective tool for ascertaining the stable conformer in solution.

We first chose to study the conformation of linderalactone (3), since this compound has a γ-lactone at positions 5 and 7 which should fix the cyclodecadiene ring. We therefore expected not only good separation of signals in the NMR spectrum, but also reliable assignment of them. Molecular models show that four major conformations are possible for linderalactone, (A to D) in Fig 5. Conformations (A and B) have crossed orientation of the two double bonds, whereas conformations (C and D) have their double bonds parallel. For our purpose, the interactions between the pairs of groups joined by an arrow in Fig 5 are important; if there is recognized an NOE between these pairs of protons, then the major conformer should be ascertainable. Fortunately, an NOE was in fact observed between each pair of protons, positions 2 and 6 and positions 2 and 10, and the main conformer of linderalactone could be determined as A in Fig 5.[14]

As mentioned-above, Yoshioka et al.,[11] concluded that isabelin (11) exists in solution as two isomeric conformers. On recent reinvestigation[15] of this compound it has been found that the ^{1}H NMR spectrum at 100 MHz in CDCl3 clearly shows two sets of signals, one set corresponding to each conformer (cf Fig 6). In the major conformer NOE's were observed between the protons 2-H and 6-H and between 6-H and 9-H, fixing its conformation as A; NOE's were observed in the minor isomer between 6-H and 9-H, 6-H and 14-H, and 9-H and 14-H, showing it to have structure B in Fig 3. These NOE findings clearly confirmed the proposal previously made by Yoshioka et al.

Analogous phenomena were seen with laurenobiolide (8),[16] whose NMR spectra is shown in Fig 7. At temperatures over 100° the spectrum shows only one set of signals, but at temperatures lower than − 20° there are two sets of sharp signals. NOE measurements indicate that the major and minor conformers should be represented as A and B in Fig 7. It was deduced from the intensities of the corresponding signals in the NMR spectra that these two conformers exist in the ratio of ca 8:2 at low temperature.

With costunolide (13), a 10-membered ring sesquiterpene lactone isolated from Artemisia balchanorum, Compositae, the important NMR signals for determination of its conformation, H-2, H-6, H-7 and H-8 were found to be inseparable in several solutions. We therefore tried separation by application of a shift-reagent. In the presence of a 0·4 molar ratio of [²H₂₇]Eu(fod)₃ the important signals were all completely separable and NOE measurements were successfully made.[17] Though the NOE was decreased to some extent in the presence of paramagnetic shift-reagent, the decrease was fortunately fairly low even when the concentration
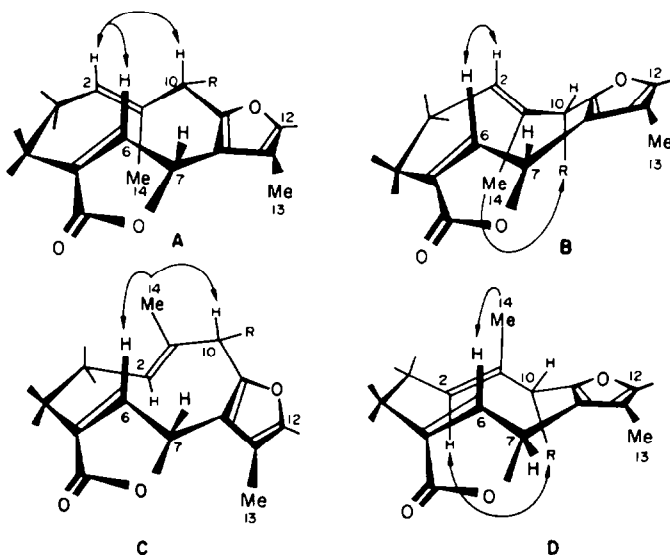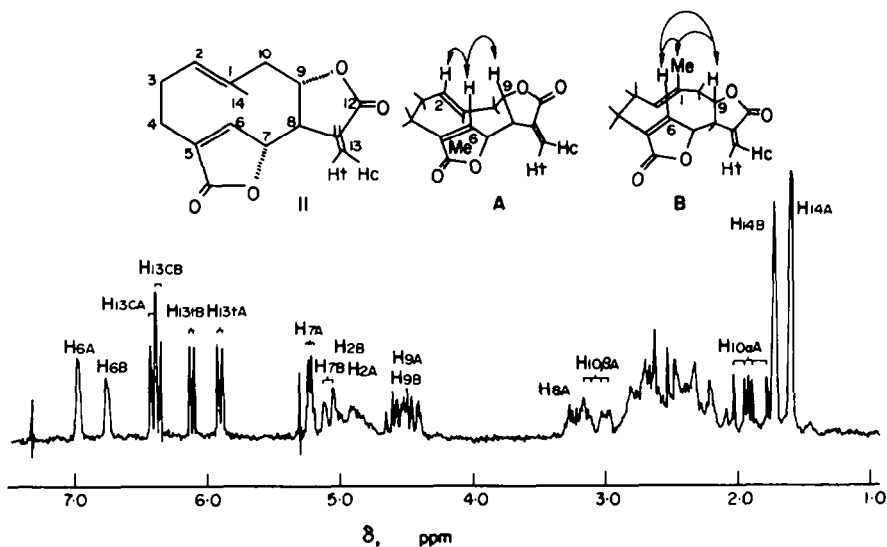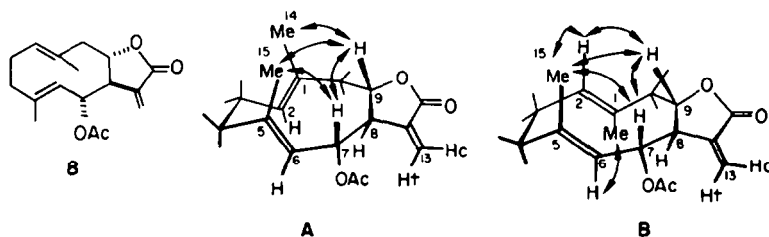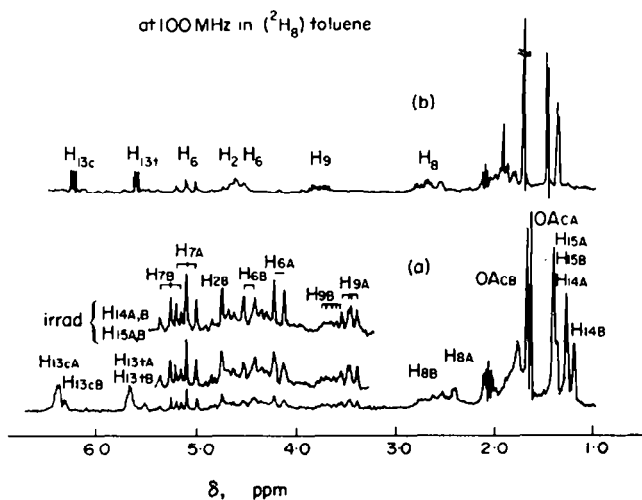


Fig 5.

Fig 6. $^1$H NMR spectrum of isabelin in CDCl$_3$ at 100 MHz.



Fig 7.

of shift reagent was fairly high, probably because of the low proton–electron relaxation efficiency of the reagent. This result would indicate that the NOE technique is widely applicable in the presence of shift reagents.

Sericenine (2), isolated from *Neolitsea sericeae*, and neolinderalactone (4), from *Lindera strychnifolia*, are both 10-membered ring furanosesquiterpenes. The former compound has *trans* C-1 : C-2 and *cis* C-5 : C-6 double bonds, while the latter has

Fig 8.
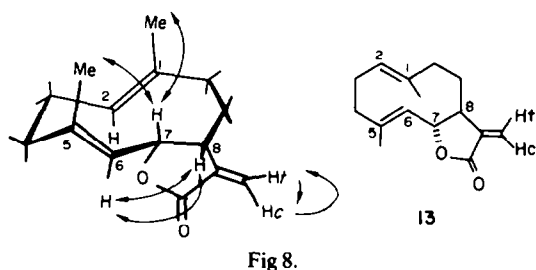
cis C-1:C-2 and trans C-5:C-6 double bonds.

The 100-MHz NMR spectra of sericenine (2)[18] at room temperature showed rather broad signals as shown in Fig 9, while at higher and lower temperatures the spectra exhibited single but different sets of sharp signals (Fig 9, a and c respectively). It may be concluded that the sharp signals seen at high temperatures are due to a rapidly inverting 10-membered ring, and that those observed at low temperatures arise from the major conformer of the ring which is frozen on the NMR time scale. From the results of NOE measurement at − 10° the major conformation of sericenine was assigned as illustrated in Fig 9, (A). An attempt to detect the minor conformer was unsuccessful, even in the 220-MHz spectra, owing to a decrease in its population with lowering of temperature.
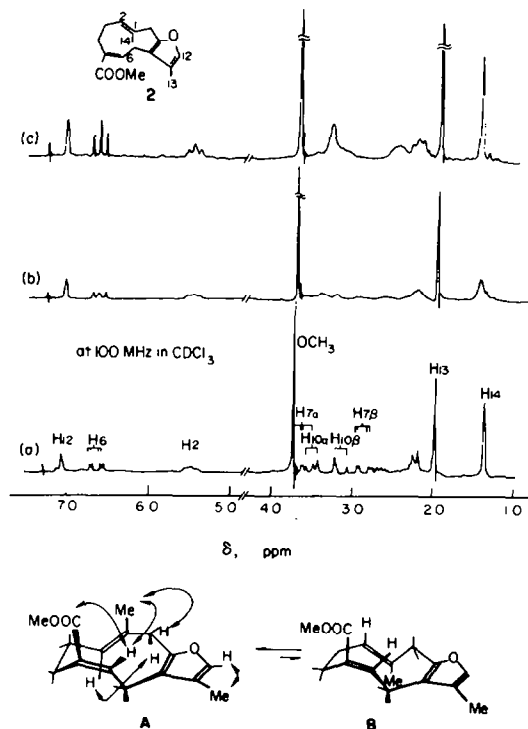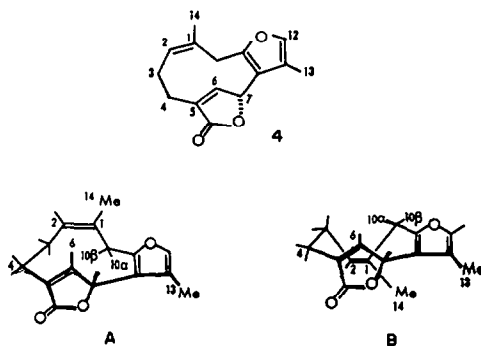


Fig 9. The variable-temperature PMR spectra of sericenine (2) in CDCl₃ at 100 MHz; (a) − 30°, (b) 40°, (c) 70°C.



Fig 10.

The spectrum of neolinderalactone (4)[19] at various temperatures showed similar phenomena, the only difference being that at lower temperatures, from 30° ∼ − 40°, two sets of the sharp signals corresponding to the conformations A and B in Fig 10 respectively, in the ratio of about 8:2, were clearly observed. Each of these conformers was determined by NOE technique as described above.

The stable conformations in solution of the germacrene type sesquiterpenes linderane (6), zeylanine (7), zeylanane (14),[20] furanodienone (15), and isofuranodienone (16)[21] were also determined by the same techniques. These conformations are shown in the following figure.
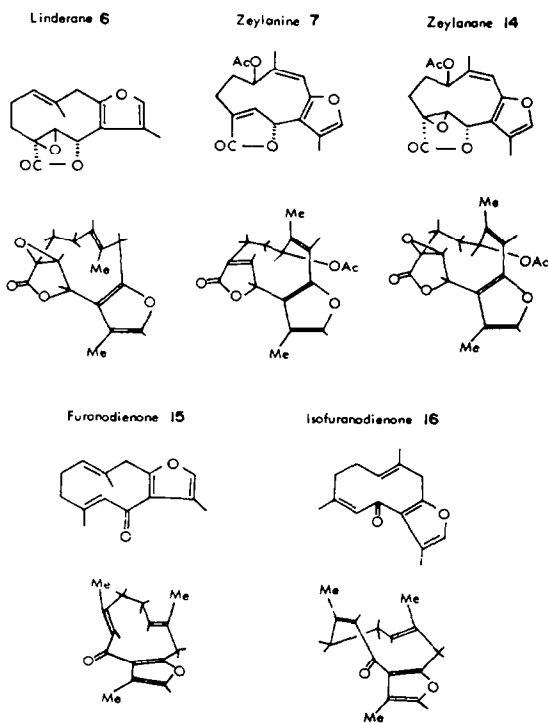


Fig 11.

## CHAPTER 2

*Relationship between conformation of cyclodeca-1,5-diene-type sesquiterpenes and the stereochemistry of their Cope rearrangement products*

It is well known that germacrene type cyclodeca-1,5-diene sesquiterpenes undergo Cope rearrangement to give elemene type derivatives. The mechanism of the Cope rearrangement was well predicted by W. v. E. Doering,[22] E. Vogel,[23] and G. B. Gill,[24] as well as by Woodward–Hoffmann,[25] and the reaction is now defined as a sigmatropic change of order[(3,3)] and proceeds through a 4-center cyclohexane chair-like transition state.
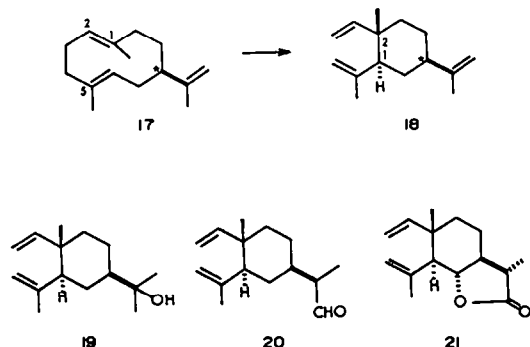
The angular Me group of the element type derivatives, at position 2 in **18** for example in Fig 12, corresponding to the Me on the double bond at position 1 in the cyclodeca-1,5-diene ring (**17**), generally has a $\beta$-configuration if the elemene is a naturally occurring optically active one, e.g. $\beta$-elemene (**18**), elemol (**19**), elemenal (**20**), saussurea lactone (**21**) etc.

As linderalactone (**3**) has an asymmetric center at C-7, the Cope rearrangement of this lactone was examined. Linderalactone or litsealactone (**5**) was easily equilibrated at moderate temperature (*ca* 150–170°) to give a 2:3 mixture with isolinderalactone (**22**) or isolitsealactone (**23**),[26] and even at room temperature linderalactone was partially isomerized to the elemene type derivative.

It is very interesting that the angular Me group in isolinderalactone has an $\alpha$-configuration, as con-
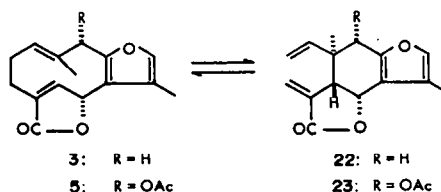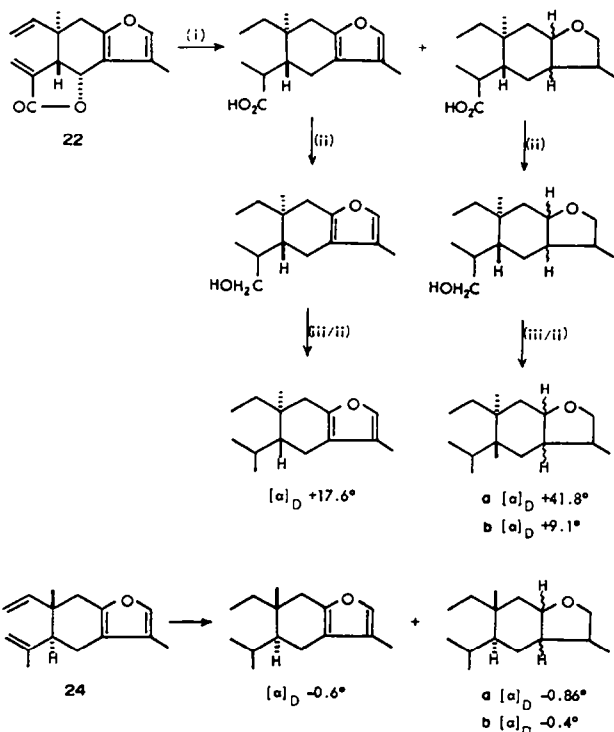


Fig 12.



Fig 13.



(i.) $H_2$/Pt, (ii), LiAlH$_4$, (iii), TsCl/Py

Fig 14.

23

22

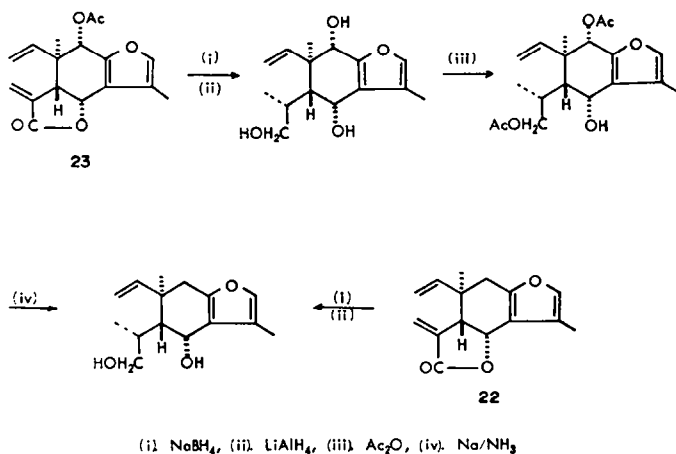(i) NaBH₄, (ii) LiAlH₄, (iii) Ac₂O, (iv) Na/NH₃

Fig 15.

firmed by the following chemical reaction sequence.[4] The hydrogenated products of isolinderalactone are enantiomeric with the corresponding products derived from isofuranogermacrene (24),[27] the absolute configuration of which has already been determined. (cf Fig 14.)

The structure of isolitsealactone was also correlated with isolinderalactone.[6]

Unlike linderalactone, dihydrotamaulipin-A acetate (12), whose stable conformation in solution was determined as mentioned in Chapter 1, gave an elemene type compound (25) having a β-angular Me group.[28] These results turned our attention towards the relationship between the conformation of the cyclodeca-1,5-diene derivative and the configuration of the angular Me group in the Cope rearrangement product.

As the two double bonds in the 10-membered ring have a crossed orientation in both conformers of dihydrotamaulipin-A acetate and linderalactone, these conformers should be converted to the preferable chair-like transition state very easily, so it is

readily understandable that each conformer gave an enantiomeric elemene type derivative by the Woodward–Hoffmann rule. (cf Fig 17.)

The difference between these two conformers is likely to be due to the presence of a γ-lactone ring at C-5 and C-7 in linderalactone. This lactone ring fixes the bonds between C-5–C-7 in its 1,3-position and thus prohibits rotation of the fragment containing the C-5 double bond. If this lactone ring were opened, the C-5–C-7 bonds would become free to rotate and the compound could take another conformation by interaction between the C-7 and C-15 oxygens.
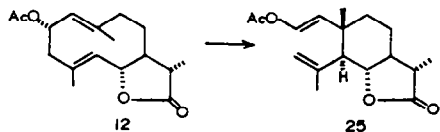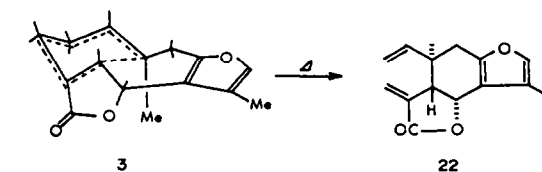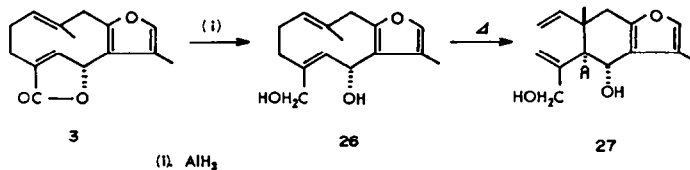


12                              25



12              25

Fig 16.



3              22

Fig 17.



3                    26                  27

(i) AlH₃

Fig 18.

**Fig 19.**

(i) OH⁻, (ii) MnO₂, (iii) H⁺

(i) $OH^-$, (ii) $MnO_2$, (iii) $H^+$
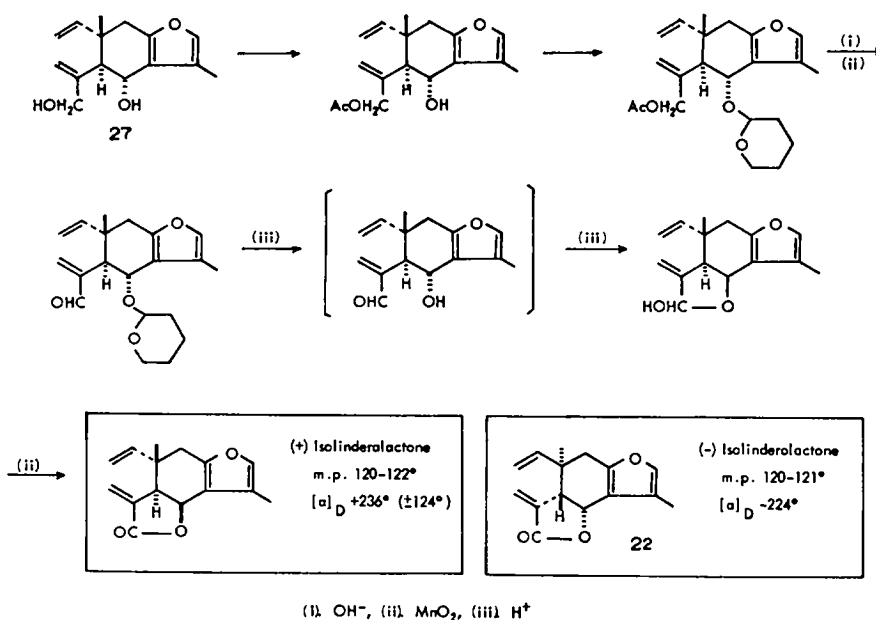
Reductive cleavage of the lactone ring was achieved by the use of aluminum hydride without reduction of the conjugated double bond at C-5–C-6. The diol obtained (26) underwent the Cope rearrangement to give an elemene-type iso-diol (27). The configuration at the angular Me group of this iso-diol was determined by the following chemical reactions (cf Fig 19) and was deduced as β. Since the C-7 α-OH group in this compound is located at an allylic position, it is epimerized in this reaction to the β-configuration by the action of proton, to stabilize the molecule by the formation of the cis-fused 5-membered ether-ring.[26]

Next the conformation of the 10-membered ring diol (27) was examined by means of NOE measurement. Unfortunately the diol is insufficiently soluble in the solvent used, so its methyl ether (28) was used to determine the NOE.[14] This compound can be represented in eight major conformations (A ~ H) as shown (Fig 20), with the proton interactions relevant to an NOE study indicated by arrows. The most important NOE, between 2-H and 6-H, was not determinable. However, the effects between 2-H and 10-αH, 7-H and 15-AH, and 14-H and 15-BH were clearly observed and sufficed to indicate that conformer A is predominant.

The present results strongly support the theoretical predictions for the Cope rearrangement. In addition we can expect that knowledge of the absolute configuration of a Cope rearrangement product will provide evidence as to the conformation of the 10-membered ring in the starting material.

Recently, bicyclogermacrene (29), isolated from Citrus junos, Rutaceae, by Nishimura et al.,[29] was shown to give a mixture of bicyclo-elemene (30), isobicyclogermacrene (31) and the starting material when heated (29) at 200° for 30 min. The absolute configuration of bicycloelemene was determined as 30[30] by the following chemical transformation to maaliol (32), the absolute structure of which was already established (cf Fig 21). As the configuration of the angular Me group in maaliol is α, i.e. bicycloelemene is an antipodal elemene, the conformation of bicyclogermacrene should be represented as 33 from the above-mentioned assumptions. The stable conformation of bicyclogermacrene in solution was clarified by NOE technique. As NOE were observed between 2-H and 9-βH, 6-H and 9-βH, and 6-H and 12-H, the conformation of bicyclogermacrene was assigned as the structure 33 as expected.[31]

Endo et al[32] reported a very interesting result in the Cope rearrangement of caulesol or its acetate. Caulesol is germacra-1,5,8(11)-triene-10α-ol (34), a germacrene type sesquiterpene isolated from Japonasarum caulescense of the family Aristolochiaceae. When heated at about 200° for 30 min acetyl caulesol gave a mixture of antipodal and normal elemene type compounds (35 and 36) in a ratio of 5:3. From this it is postulated that the stereostructure of caulesol should also be a mixture of conformers (A and B) in Fig 23. NMR spectra of this compound at various temperatures are shown in the Fig 24.[33] Since NOE experiments at 30° indicated that inversion of the 10-membered ring
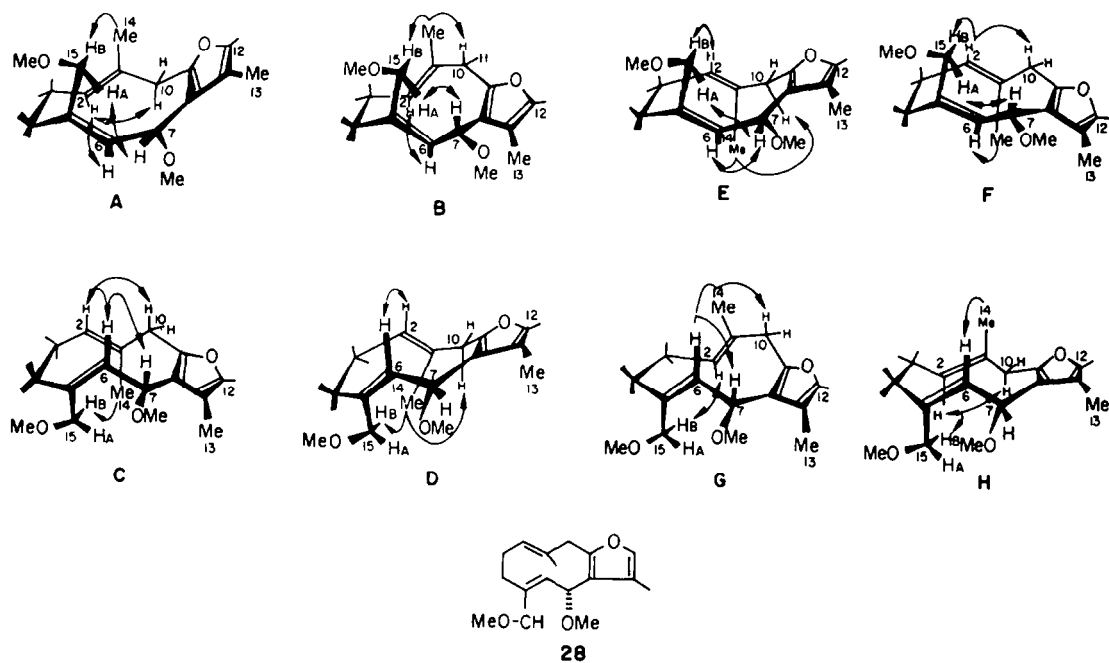
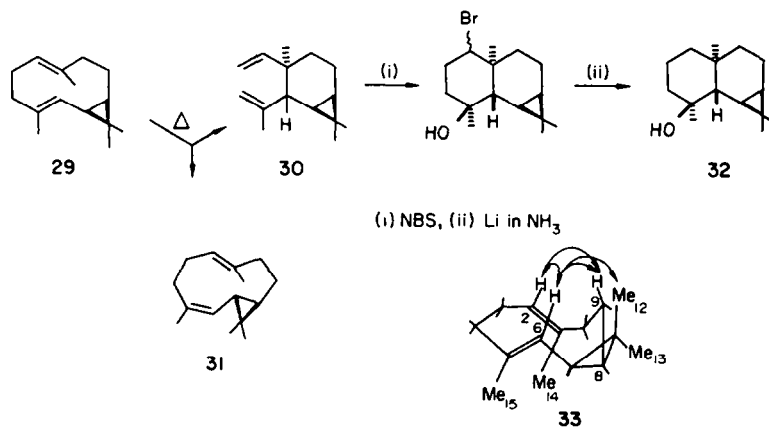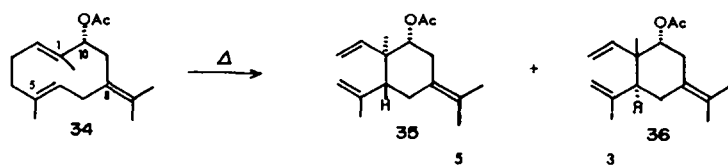Fig 20.   Possible conformations for the dimethoxy compound (28).



(i) NBS, (ii) Li in NH₃
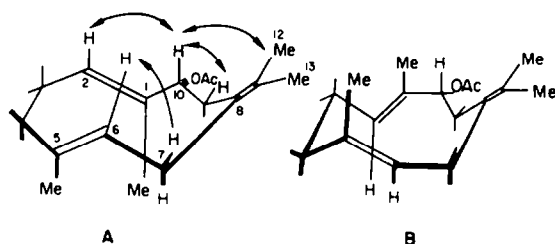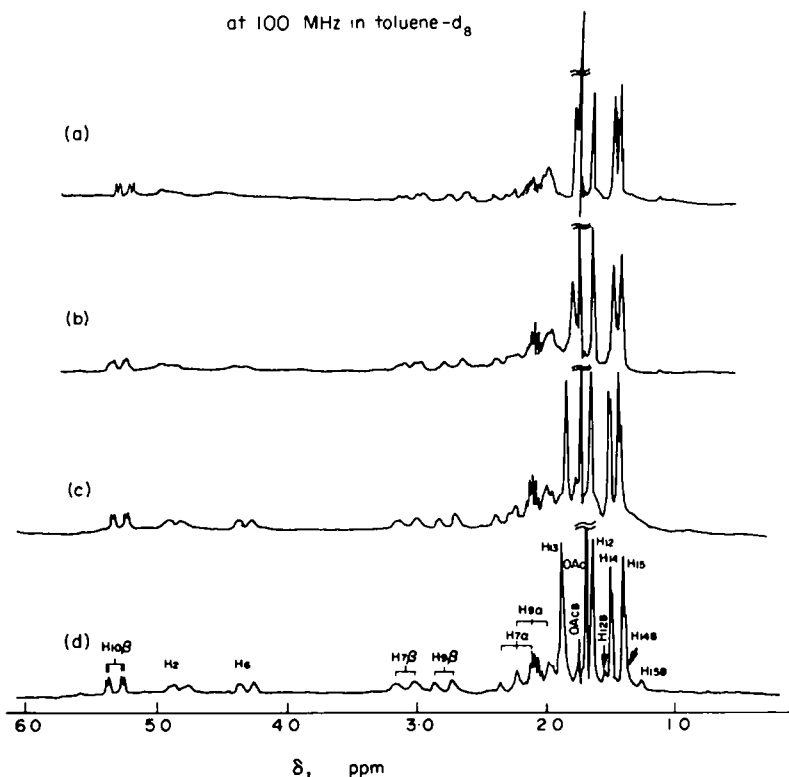
Fig 21.



Fig 22.

Fig 23.



at 100 MHz in toluene-$d_8$

Fig 24. Variable-temperature 100 MHz NMR spectra of (34) in toluene-$d_8$. (a) 105°, (b) 60°, (c) 30°, and (d) − 8°C.

occurred at this temperature, measurements of NOE were carried out at − 8°. The NOE's observed between 2-H and 10-H, 6-H and 7-$\beta$H, and 10-$\beta$H and 12-H indicate that the major conformation takes a stereostructure as shown in Fig 23 (A). Although unfortunately the minor conformer seemed undeterminable because of its insufficient population, from the structure of the Cope rearrangement products it seems likely that it has the conformation shown in Fig 23 (B).

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