

BIOMIMETIC TRANSFORMATIONS OF SESQUITERPENE LACTONES

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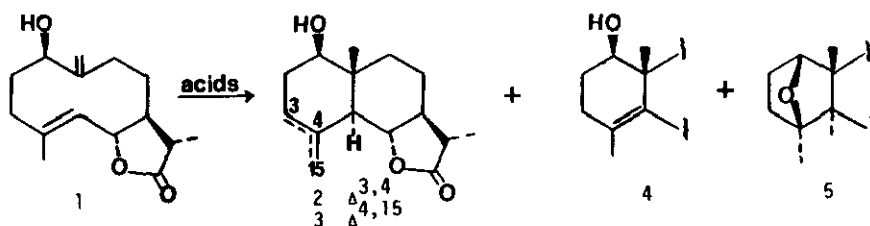
Abstract - Some of the biomimetic transformations of sesquiterpene lactones practised in our laboratory are presented here and the biogenetic implications of the work are discussed.

INTRODUCTION

While it is quite clear that the biosynthesis of the sesquiterpenes involves farnesyl pyrophosphate or its biological equivalents^{1,2}, the later stages of the process are not so well-documented, and the pathways proposed³ are frequently speculative and mostly mechanistic being based on the stereo-electronic factors which control organic reactions. Some of these hypotheses have received indirect experimental support from biomimetic transformations and others have stemmed from the results of biomimetic syntheses. Prerequisites for the transformations are chemo-, regio-, and stereoselectivity, a stereochemical course on the lines of that followed by the natural product and co-occurrence in associated taxonomical species of products which it is possible to correlate with the hypothesis proposed.

RESULTS AND DISCUSSION

Gallicin (1) is a germacrolide isolated from *Artemisia maritima gallica* Willd and its structure and absolute configuration were determined definitively by acid cyclization to the eudesmane derivatives 2, 3, 4 and 5⁴.



The complete stereoselectivity of the cyclization is due, most probably, to the fact that it takes place via a preferred conformation determined in this case⁶ by LIS studies. Interpretation of the coupling constant values $J_{1,2}$, $J_{5,6}$, $J_{6,7}$ and ^1H nmr taken at varying temperatures. Gallicin (1) was found in a CC conformation, 6, with the exocyclic methylene and the H-5 in the same disposition both at the beginning and at the end of the cyclization (Figure 1).

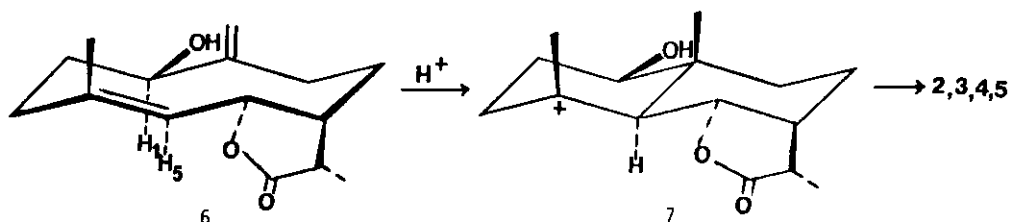


Figure 1

It has been suggested that the guaianolides are biosynthesized⁴ by an electrophilic anti-Markownikow attack on the system of double bonds of a germacradienolide (Figure 2). However, there is only one isolated instance⁷ of

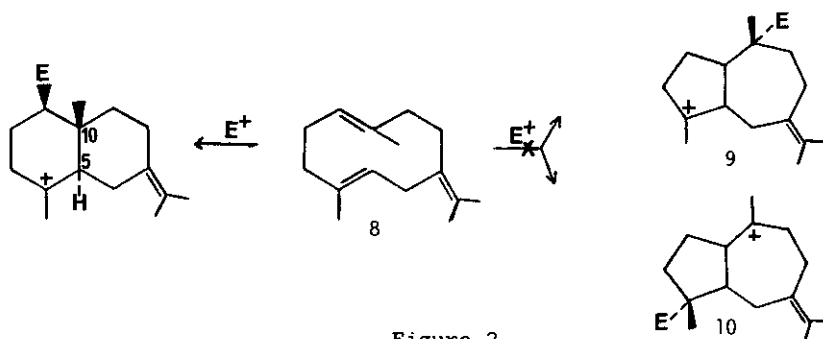
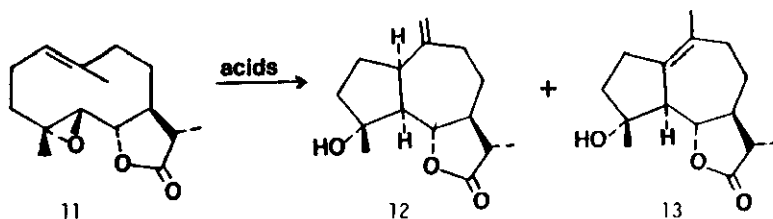


Figure 2

this attack taking place on the $\Delta^{4,5}$ and generally the electrophiles act chemoselectively on the double bond $\Delta^{1,10}$, and generate trans-(10 β ,5 α)-eudesmanolides⁸.

Cyclization of the 4 α ,5 β -epoxygermacrenes 11 stereoselectively generated⁹ the



cis-(1 α ,5 α)-guaianes **12** and **13** in a process which could be considered as the result of an electrophilic anti-Markownikow attack on the double bond $\Delta^{4,15}$.

Gallicin (**1**) could be stereoselectively cyclized to the cis-(1 α ,5 α)-guaianolides **16** by simple tosylation or mesylation at low temp. without the intermediate sulfonic ester¹⁰ ever being isolated.

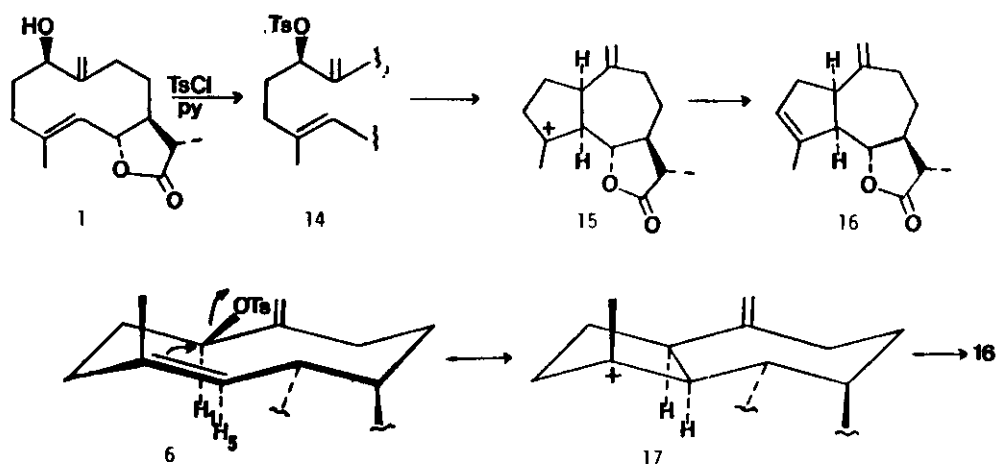


Figure 3

The stereoselectivity of the process is accounted for if one assumes that the cyclization takes place via the preferred conformation **6** in which the double bond $\Delta^{4,15}$ is ideally disposed to attack carbon C-1 on its dorsal face expelling the leaving group which is equatorially disposed, so that cis-(1 α ,5 α)-guaianolides are generated (Fig. 3). We have therefore proposed an alternative

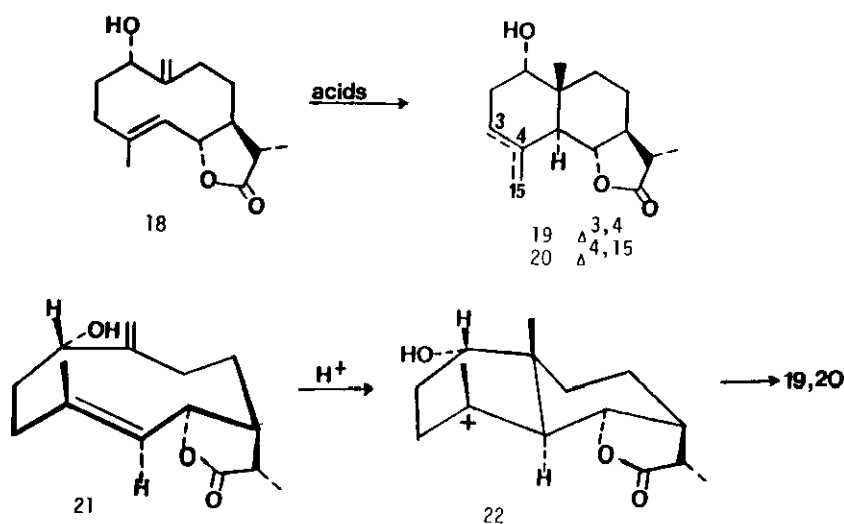


Figure 4

model to explain the biogenesis of the cis-(1 α ,5 α)-guaianolides. 1-Epigallicin (18) was prepared by oxidation and reduction of 1 and then cyclized by acid action to form trans-eudesmanolides 19 and 20 demonstrating that the process is stereospecific¹².

The conformational analysis of 1-epigallicin (18) showed that it is in a TC conformation 21 which perfectly explains the stereochemical course of the process. The cyclization favours Parker et al.'s theory¹³ whereby the biosynthesis of the α -hydroxy-trans-(10 β ,5 α)-guaianolides may take place via the anti-parallel Markownikow-type cyclization of a cis,trans-germacradiene (Fig.4).

Treatment of 1-epigallicin (18) with tosyl chloride in pyridine afforded¹⁴ trans-guaianolide (25) by a 5-exo-tet stereospecific process¹⁵ which, in conjunction with the non-isolation of the intermediate sulfonic ester (23) strongly suggests that the cyclization must take place via a concerted process with assistance of the double bond $\Delta^{4,5}$ to produce the cation 24 via the reacting conformation 26 (Fig 5). It should be noted that if gallicin (1) and 1-epigallicin (18) were cyclized via the carbenium ion, 5-endo-trig ring closures would be involved and these, according to Baldwin¹⁶, are not favoured.

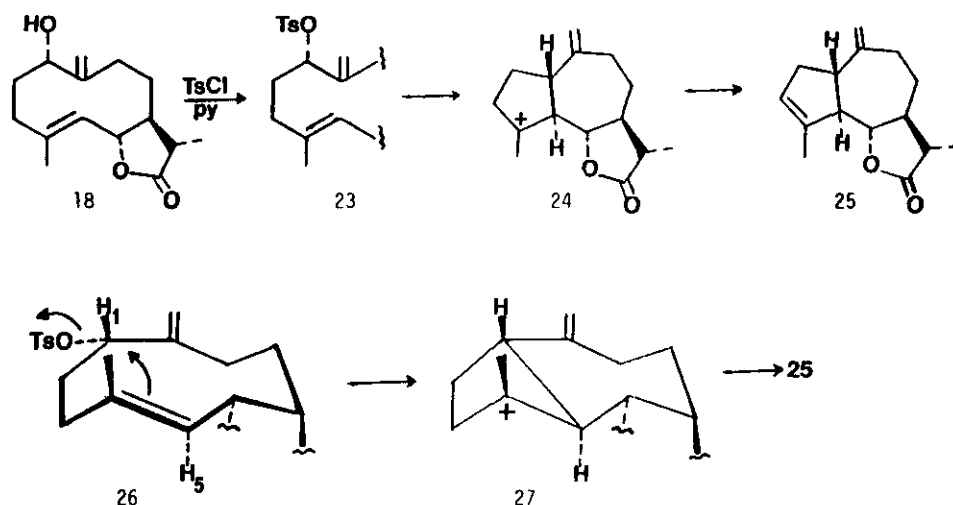


Figure 5

The stereochemistry of the cyclization product is the same as that found in the few natural trans-guaianolides, pleniradin¹⁴, gaillardin¹⁷, neogaillardin¹⁸, florilenalin¹⁹ etc. These results point to the biosynthesis of the trans-guaianolides proceeding via the melampolide pathway formulated by Parker et

al.¹³ rather than that proposed by Fischer et al.²⁰ where a 4 α ,5 β -epoxy-trans-germacrene in the quasi-parallel conformation **31** would be a precursor of the trans-guaianes, since the centre-to-centre distance between the two double bonds of **28** would be considerably greater than in the four possible conformations of a trans, trans-germacradiene (Fig 6).

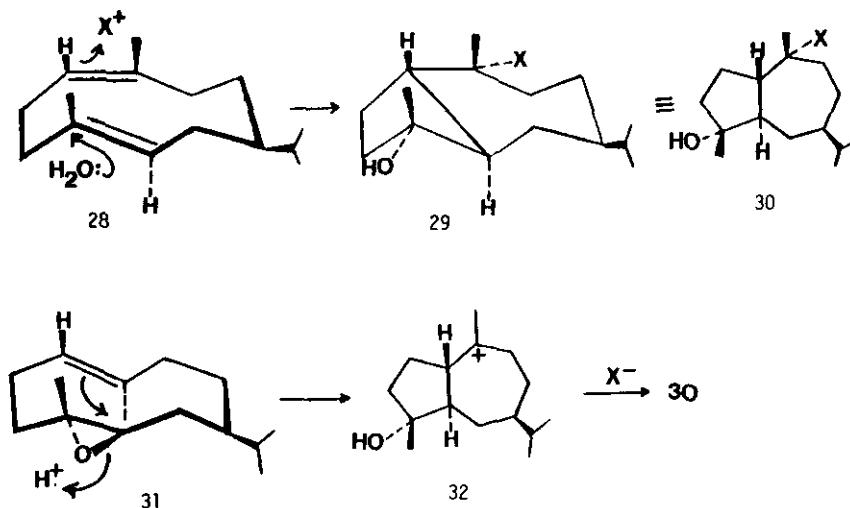
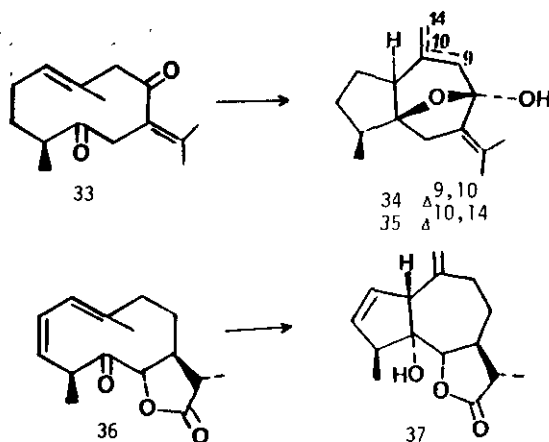


Figure 6

The 5-oxo-trans-germacrenes have been considered as biogenetic precursors of 5-hydroxyguaianes and dehydrocurdione (**33**) has been transformed²¹ to curcumenol (**34**) and isocurcumenol (**35**). Similarly, when dienone **36** was treated with refluxing benzene or silica gel, an abundant yield²² of guaianolide **37** was obtained.

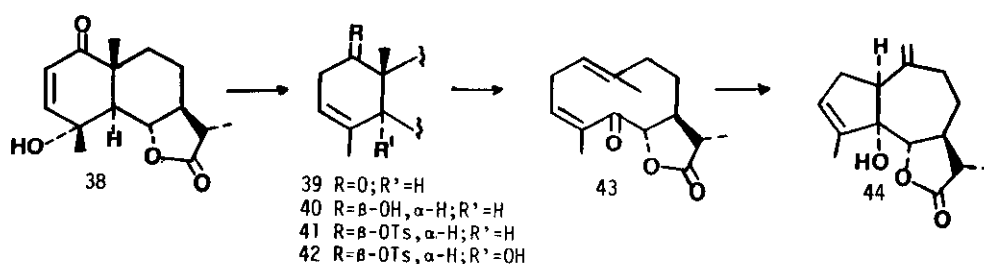


A notable feature of these cyclizations is the different stereochemical course they follow since, although both lead to trans derivatives, the two types of

junction may be considered enantiomeric. Moreover, the majority of natural 5-hydroxyguaianolides have a cis-(1 α ,5 α)-junction²³ which is in marked contrast with the stereochemical course of the earlier cyclizations.

Dienone **43** was prepared in five stages using vulgarin (**38**) as starting material²⁴.

Treatment of vulgarin (**38**) with Zn-HOAc, NaBH₄ and TSCl-py gave **41** which, after allylic oxidation, gave the hydroxytosylate **42** (57% yield on **38**). When **41** was treated with KOBu^t-HOBu^t, guaiane derivative **44** was produced stereoselectively



(79%). A H-nmr study detected the presence of the highly unstable ketone **43** which decomposed to the guaiane **44** in CHCl₃ solution or as a consequence of silica gel action²⁵.

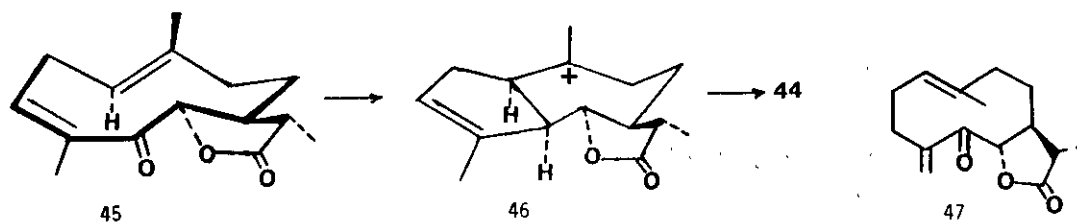


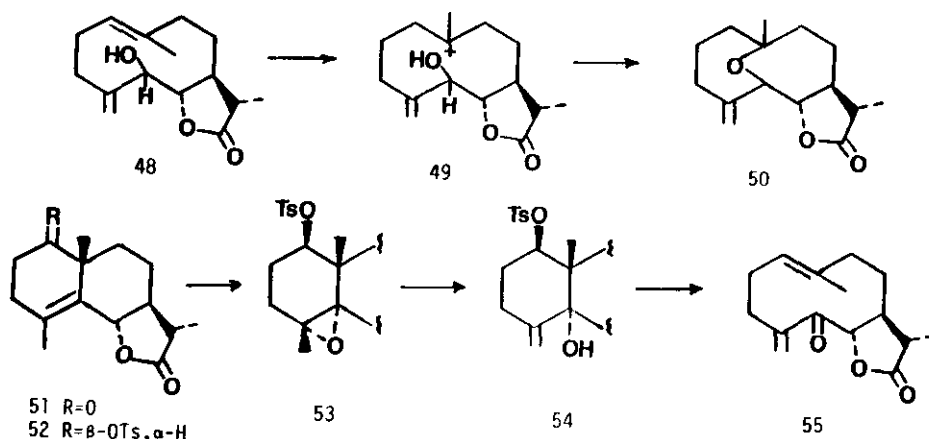
Figure 7

The stereoselectivity of the cyclization and the cis (1 α ,5 α) stereochemistry of the junction have been credited to the pyridine-induced chemical shifts²⁶ and to the cyclization taking place via the preferred conformation **45**. The conformational analysis of **43** in solution (LIS studies) afforded experimental evidence corroborating this theory²⁵.

It should be noted that the stereochemical course of the cyclization is identical to that of the majority of the natural 5-hydroxyguaianolides (A/B cis,

1 α -H; 5 α -OH)²³ and that it differs from the previously published cyclizations of **33** and **36**²². To our knowledge, no natural (Z)-3(4)-germacren-5-one is known while very stable 4(15)-germacren-5-one derivatives such as **47**²⁷ have been isolated.

In order to evaluate the possible role played by **48**-type compounds in the biosynthesis of substances such as chapliatrin and its congeners^{28,29} this allylic alcohol was prepared. It was thought that acid treatment of **48** might generate cation **49** which by carbocyclization would afford **50**, a chapliatrin-skeleton compound³⁰.



Compound **55** was prepared from **51**³¹ by reduction, tosylation, epoxidation and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -opening to obtain **54** (33% overall). When **54** was treated with KOBu^t - HOBu^t , followed by reduction of **55**, it afforded the allylic alcohol **48** stereoselectively and hydrogen chloride-saturated chloroform acted upon **48**³² to give the desired oxide **50**, the structure and absolute configuration of which were established by X ray diffraction analysis as **56** (Fig.8).

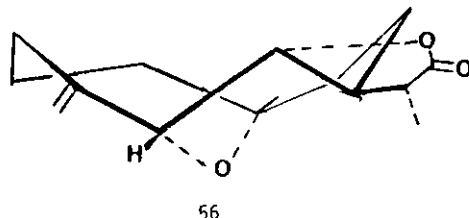


Figure 8

The results of this cyclization do suggest that **48**-type compounds may be biogenetic precursors in the biosynthesis of chapliatrin and its congeners.

The biosynthesis of the trans-(1 α ,5 β)-pseudoguaianolides, e.g. neopulchellin, has been explained¹² by assuming that they proceed from the trans-(1 β ,5 α)-guaianolides **57** via the stereo-electro chemical shifts¹³ shown in Figure 9.

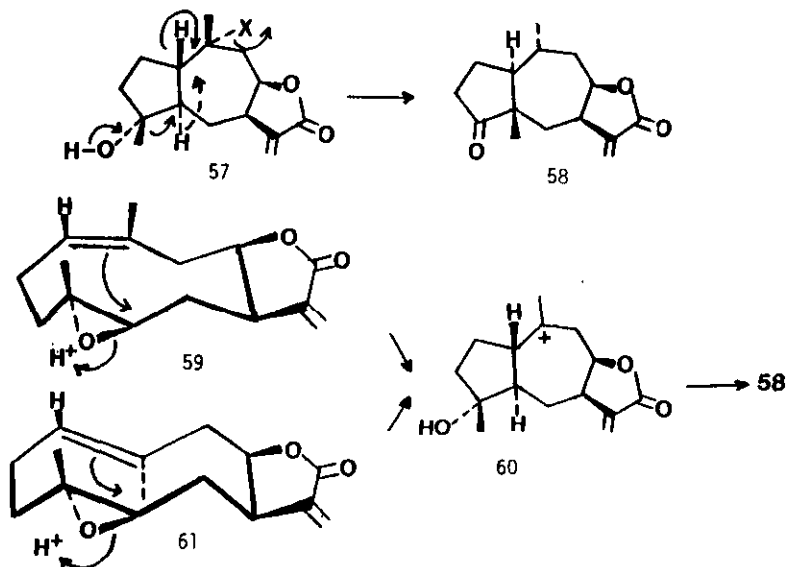


Figure 9

The 4 α ,5 β -epoxymelampolides **59** have been proposed as precursors of the helenanolides³ and accordingly, the acid cyclization of **59** could give cation **60** which already possesses the antiperiplanar stereochemistry suitable for originating natural helenanolides. The epoxymelampolide must be in the TC conformation shown in **59** since only thus, can it generate the trans-guaiane cation **60**. Fischer²⁰ has also suggested an epoxygermacranolide with a TT conformation such as **61** as a possible precursor (Fig. 9).

To check out the feasibility of a rearrangement similar to that shown in Fig 9 (**57** to **58**) the norguaiane alcohols **62** and **63** were prepared. Tosylation of **62**

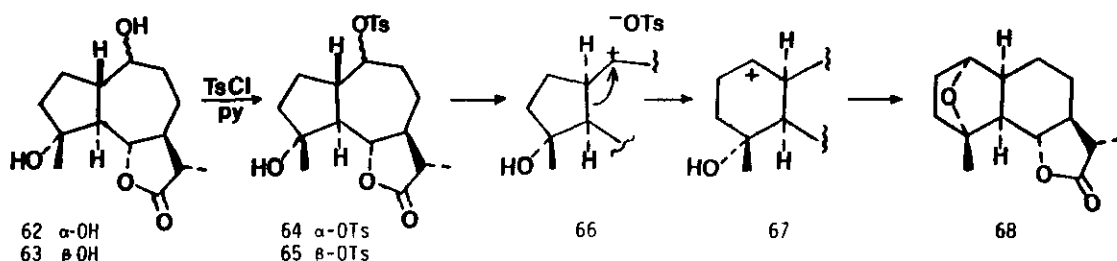
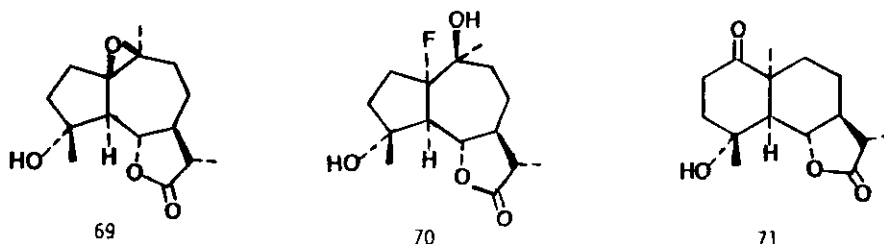


Figure 10

led to the epoxy derivative **68** although the intermediate tosylate **64** could not be isolated. When the epimer **63** was treated the same way³⁴ as **62**, the same result was arrived at and has been interpreted as shown in Fig. 10.

Our results are in complete agreement with those obtained by Fischer *et al.*³³ when they treated epoxyguaiane **69** with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and isolated the fluoride derivative **70** and the *cis*-eudesmanolide **71**.



These data would seem to imply that, contrary to biogenetic theory, the σ (1,10) bond migrates with greater ease than the H-1.

In this context, we studied the cyclizations of melampomagnolide **72** and its 11,13-dehydro derivative **73** prepared in accordance with El-Feraly³⁵.

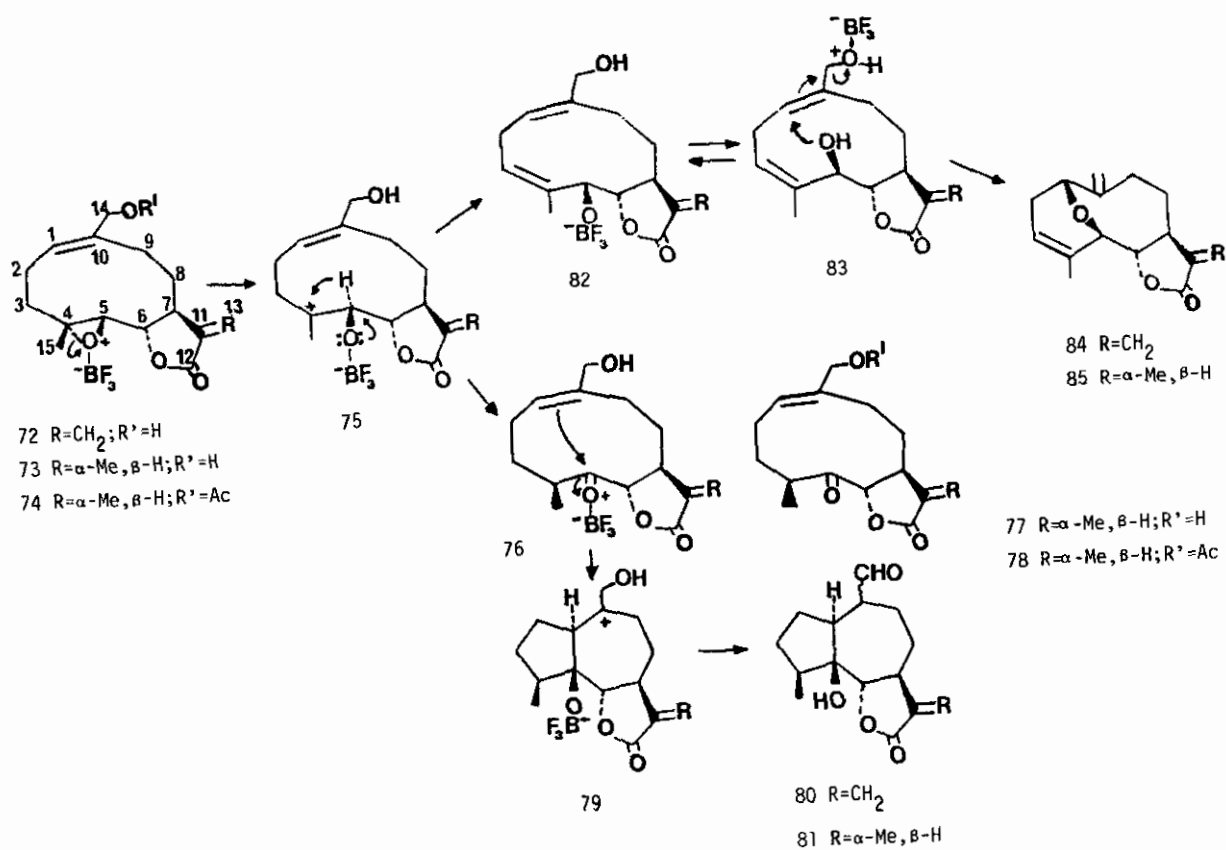
Acid treatment of **72** with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ gave the two epimeric guaianolides **80** and traces of the epoxygermacranolide **84**. The skeleton of **84** is similar to that of badgerin, a germacranolide isolated by Shafizadeh and Bhadane³⁶ from *Artemisia arbuscula* ssp *arbuscula*.

In view of the low solubility of **72** in benzene, we decided to use CH_2Cl_2 as solvent and in these conditions **73** and **74** led to **81** and **78**, respectively. The transformation of **74** to **78** suggests that the process takes place as shown in Scheme 1. The Markownikow opening of the oxirane ring followed by β -elimination may give **83** which would lead to **85** by a $\text{S}_{\text{N}}2'$ process and a hydride shift in **75** followed by intramolecular cyclization may afford the guaiane derivatives **81**.

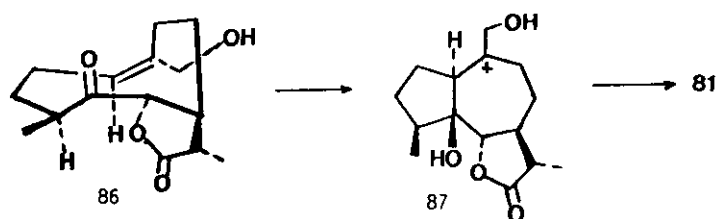
The fact that **55**³², hydrogenated according to Haruna and Ito³⁷, is allylically oxidated and afterwards acetylated to give **78**, a compound identical to that prepared from **74** provides support for the above theory. The treatment of alcohol **76** with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ gives the same epimer mixture, **81** (Scheme 1).

The *trans*-(1 α -H;5 β -OH)-stereochemistry of **81** was established by assuming that

SCHEME I



the cyclization takes place via **86** as Molecular Mechanics calculations³⁰ indicate that this is the more stable conformation.



The data obtained about the chemical behaviour of **73**³⁰ agree with those given by Doskotch and Wilton³⁰ for lipiferolide, a 4 α ,5 β -epoxy-trans-1(10)-germacrenolide and no traces of pseudoguaianolides were discernible. These results do not support Herz' biogenetic hypothesis³ but this may be due to the fact that the melampomagnolide is not in the required TC conformation. An X ray diffraction analysis would seem to confirm this idea, since Figure 11 is a perspective view

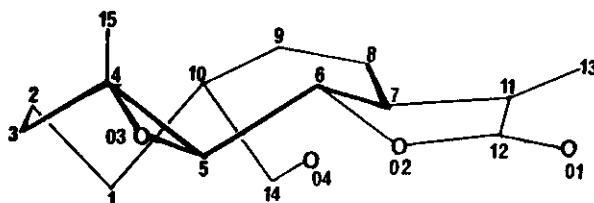
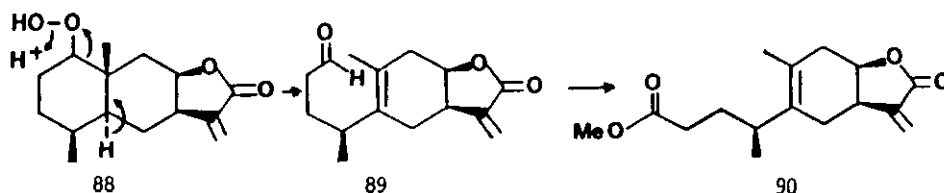


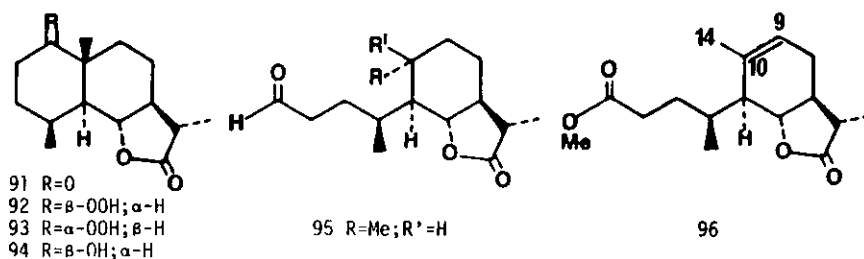
Figure 11

of the molecular structure of **72**, and the C-15 methyl group and the C-14 hydroxymethyl group are seen to be anti in relation to the median plane of the ring with the C-14 on the opposite side to the H-6.

The 1,10-sec-eudesmanolides are a small group of sesquiterpene lactones, the biogenesis of which Herz³ postulated as occurring by the fragmentation of a 1-hydroperoxyeudesmanolide **88**.



To check out this theory, the 1-hydroperoxyeudesmanolides **92** and **93** were prepared using ketone **91** as starting material. When **91** was treated with tosyl hydrazine, then diborane and sodium peroxide-hydrogen peroxide³¹, the epimers **92** and **93** (8:10, 46%) were obtained.

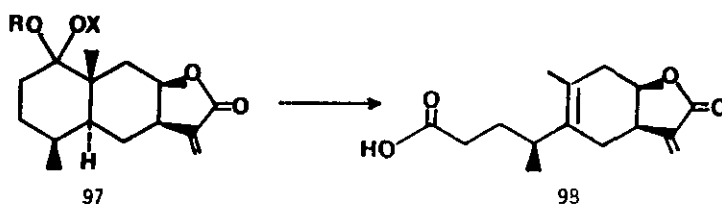


If **92** was treated with Ac_2O -py or HClO_4 -HOAc, ketone **91** was obtained either in 87% or 62% yields, the result of a hydride migration instead of the $\sigma^{1,10}$ migration suggested by Herz³. Its epimer, **93**, reacted identically, with no signs of fragmentation products, again in apparent contradiction of Herz' hypothesis.

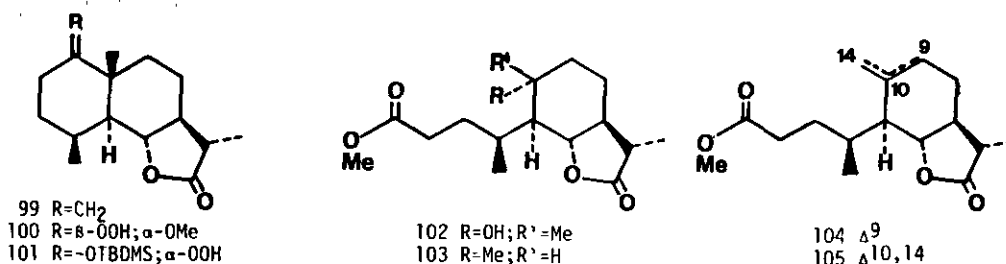
However, when FeSO_4 - $\text{Cu}(\text{OAc})_2$ ¹⁰ was applied to **92** or **93**, aldehyde **95** was obtained. This reaction probably takes place through the intermediate alkoxy radical which undergoes β-fragmentation to generate **95**. This possibility is favoured by the fact that alcohol **94**, when treated with $\text{Pb}(\text{OAc})_4$ - I_2 ⁴² or with iodosobenzene diacetate- I_2 ⁴³, yields the unsaturated aldehyde **96**, (72 and 56%, respectively).

Enzymatic transformations of hydroperoxides to aldehydes in various plants⁴⁴ have been observed and may be the pathway to the formation of 1,10-sec-eudesmanes. However, the homolytic fragmentation of 1-hydroperoxyeudesmanolides described here cannot be reconciled with such enzymatic processes since fragmentation of linoleic acid 9- and 13-hydroperoxides gives only the volatile aldehydes, cis-3-nonenal and hexanal, respectively, together with 9-oxo-nonanoic and 12-oxo-cis-dodecenoic acid⁴⁵ and if the fragmentation of these hydroperoxides were homolytic, one would expect a greater number of fragmentation products.

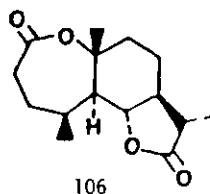
A second hypothesis put forward by Herz⁴⁶ is that the 1,10-sec-eudesmanolides may be formed from a eudesmane precursor such as **97** by a process identical to that proposed by Barton and co-workers for the biogenesis of nychthantic and dammarenolic acids⁴⁷.



We prepared **100** from olefin **99** by ozonolysis in the presence of methanol⁴⁸ to test the feasibility of this proposal. The crude product from the reaction was treated with Ac_2O -py and after concentration at low temperature, the sec-eudesmanolide **102** was obtained. When the fragmentation of **100** was carried out by treatment with FeSO_4 - $\text{Cu}(\text{OAc})_2$, methyl ester **103** and the olefins **104** and **105** were obtained. All these compounds had 1,10-sec-eudesmanolide skeletons.



Given the low stability of **100**, the 1-silyloxy-1-hydroperoxy derivative **101** was prepared from the *t*-butyldimethylsilyl enol ether of the ketone corresponding to **99** by treatment with H_2O_2 -TFA⁴⁹. When **99** was cleaved with Ac_2O -py, dilactone **106** was obtained and when FeSO_4 - $\text{Cu}(\text{OAc})_2$ was used, the product obtained was methyl ester **103**.



These results⁵⁰ seem to support the hypothesis that the 1,10-sec-eudesmanolides may be derived from 1-hydroperoxy-1-hydroxyeudesmanes via a hydroperoxide transposition essentially equivalent to a Baeyer-Villiger oxidation. It is less likely that the 1-hydroperoxyeudesmanes are involved as precursors, in view of the preferred migration of the hydrogen on the $\sigma^{1,10}$ bond. However, mono-

oxgenases capable of converting ketones to lactones are known²¹, with some discrepancies between the chemical and enzymatic data, as Chapman *et al.*²² have shown in the microbial conversion of fenchone by the action of species of Corynea bacterium.

These are just a few of our results to date. The field is fluid and full of interest. These biomimetic transformations between various types of sesquiterpene lactones may afford a valuable insight about their possible biosynthetic relationships and in some cases the transformation may provide a new pathway to their real biosynthesis. Any day may prove to be the breakthrough.

ACKNOWLEDGEMENTS

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