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FURANOSESQUITERPENOIDS

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This article aims to review the occurrence, the structural variability, and the general chemistry of the known furanosesquiterpenoids and to cover developments in their synthesis as well as to discuss their biogenesis. A brief survey of the biological activities of some furanosesquiterpenoids is also made.

1. Introduction

Among the sesquiterpenoids, there are a number of analogs containing a furan nucleus in the molecule, and these represent a large and structurally varied group of natural products.

Furanosesquiterpenoids were first discovered as early as the first quarter of this century: collybolide from the fruit bodies of *Collybia maculata* by Goris[1] in 1911, atractylon from the rhizomes of *Atractylodes* (formerly *Atract-*

ylis) sp. by Takagi[2] in 1924, linderene and linderane from the tubers of *Lindera strychnifolia* by Kondo[3] in 1925, and ngaione from the leaves of *Myoporum laetum* by McDowall[4] in 1925. However, progress in the chemistry of furanosesquiterpenoids was very slow in the era of classical organic chemistry, and the structures of these substances remained unknown for many years. Ipomeamarone, isolated by Hiura[5] from the black-rotted tubers of *Ipomoea* sp., was the first furanosesquiterpenoid to have its constitution elucidated by Kubota[6] in 1953 (the relative and absolute stereochemistry solved later in 1958[7] and 1970,[8] respectively). Shortly afterwards, it was revealed by Birch and Kubota[9] that ngaione is the enantiomer of ipomeamarone. Meanwhile nupharidine, an alkaloid, was isolated by Arima[10] from *Nuphar japonicum* in 1931 and its furan-containing structure was determined by Kotake[11] in 1957 (the stereochemistry clarified in 1968[12]), though its sesquiterpenoid origin was probably unaware at that time. In 1962, the stereostructure of atractylon was established by Hikino,[13] and after a lapse of several years, the correct constitution of linderene (now lindenenol) was finally elucidated by Takeda.[14,15] For establishment of the structure of linderane by Takeda,[16,17] a further few years were required. Over a half century after the isolation, the structural problem of collybolide, the oldest companion, was at last settled by Bui[18] in 1974. It should be noted that Japanese workers played a particularly important rôle in the early elucidation of the furanosesquiterpenoid chemistry.

Up to 1960, the formulas of only 8 furanosesquiterpenoids possessing the farnesane skeletone alone had been established. With the development of separation methods and physico-chemical techniques for structural investigations, rapid advances in the chemistry of furanosesquiterpenoids have taken place. Thus, during the following 15 years, the number of known naturally-occurring furanosesquiterpenoids and their catabolites has risen to more than 250, possessing a variety of carbon skeletons.

Furanosesquiterpenoids are of very wide taxonomic distribution in the realm of plants and, to a small extent, even in the animal kingdom. Indeed, they are known from fungi, liverworts, gymnosperms, both monocotyledonous and dicotyledonous angiosperms but confined mainly to one of the most evolved families, Compositae.

In this review the occurrence and structures of the known furanosesquiterpenoids are surveyed. Apart from providing a broad view of the structural variability, the general chemistry, and synthesis within this group of natural products, this survey aims to provide a comprehensive structural basis for deducing the biogenetic relationship among the various classes of furanosesquiterpenoids. Attention is also focused on the biological activities of certain furanosesquiterpenoids.

Although no attempt has been made to cover the extensive literature of furanosesquiterpenoids comprehensively, some aspects of furanosesquiterpenoids of particular areas have been discussed in a number of reviews,[19-23] some of which are frequently quoted here. The available literature has been consulted up to the beginning of 1975.

2. Occurrence and biogenesis

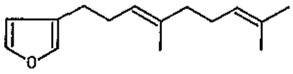
The known sesquiterpenoids may conveniently be classified into 12 types according to the basic carbon skeletons. In the following discussion of individual terpenoids, only those with special points of interest are mentioned.

2.1 Furanosesquiterpenoids possessing the farnesane skeleton

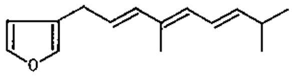
All of this type are characterized by having a furan ring at the terminal position of the farnesane chain.

Many of the simplest congeners have the common structure based on dendrolasin (1), initially discovered from a *Lasius* (*Dendrolasius*) ant[24] which constitutes the first example obtained from other than vegetable sources. The interesting fact is that dendrolasin (1) was later found to occur also in plant materials.[25,26] Biogenetical reduction-oxidation modification of the intermediate (1) could then lead to a series of congeners showing a diversity of ethylene bonds and oxygen functions (2-12). Besides these congeners, the presence of a substance tentatively ascribed to 10-dehydromyoporone in the foliage of *Myoporum deserti* was recorded.[19] The formation of 10-dehydromyoporone is quite probable because of the occurrence in the same plant of the myodesmones (59-60) considered to be its descendants (p. 826). As far as the plant kingdom concerns, sesquiterpenoids of this class are found in 4 families, Taxaceae, Convolvulaceae, Myoporaceae, and Compositae. It may be worthy to note that dehydrodendrolasin (2) was isolated from a marine sponge which also contains the cyclized companion (61) (p. 826).

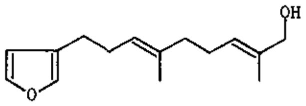
Some of the dendrolasins may be intermediates for the seco-derivatives,



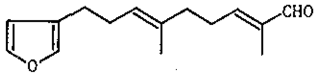
dendrolasin (1)[24]
Lasius fuliginosus,[24]
Torreya nucifera,[25]
Ipomoea sp. (fusel oil)[26]



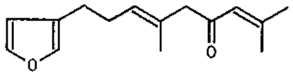
dehydrodendrolasin (2)
Pleraplysilla spinifera[27]



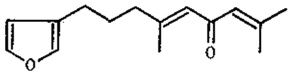
neotorreyol (3)[25,28]
Torreya nucifera[25]



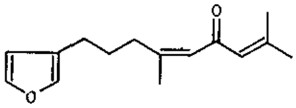
torreyal (4)[25,28]
Torreya nucifera[25]



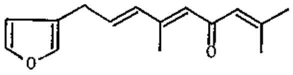
(5)[29]
Athanasia crithmifolia,
Lasiospermum radiatum,[29]
Stilpnophytum linifolium[30]



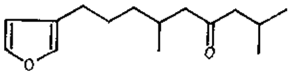
trans-dihydrophymaspermone (6)
Athanasia acerosa,
A. crithmifolia[29]



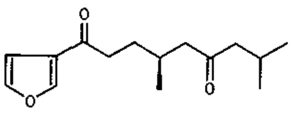
cis-dihydrophymaspermone (7)
Athanasia acerosa,
A. crithmifolia[29]



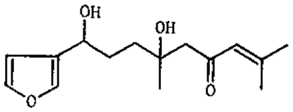
phymaspermone (8)
Phymaspermum parvifolium[30]



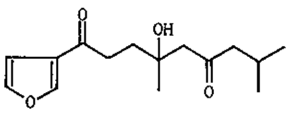
(9)
Ipomoea sp. (fusel oil)[31]



myoporone (10)[32,19]
Myoporum bontioides,[32]
M. deserti[19]

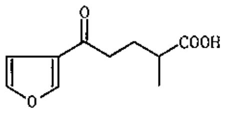


(11)
Athanasia crithmifolia[31]

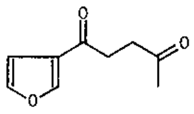


4-hydroxymyoporone (12)
Ipomoea sp. (infected with *F. solani*)[33]

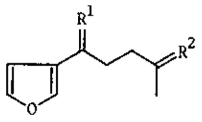
batatic acid (13) (alternatively this substance may possibly be a monoterpenoid), ipomeanine (14), and furan-β-carboxylic acid, as catabolites in sweet potato infected with the black-rot fungus, *Ceratocystis* (*Ceratostomella*) *fimbriata*.[34,35] 4-Hydroxymyoporone (12) was proved to be an intermediate for the norsesquiterpenoids (14-17) produced by *Fusarium solani*-infected sweet potato.[33]



batatic acid (13)
Ipomoea sp. (infected with *C. fimbriata*)[34]



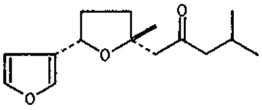
ipomeanine (14)[35]
Ipomoea batatas (infected with *C. fimbriata* and *F. solani*)[35,33]



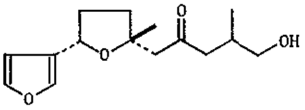
(15): $R^1=R^2=H,OH$
(16): $R^1=O$; $R^2=H,OH$
(17): $R^1=H,OH$; $R^2=O$
Ipomoea batatas (infected with *F. solani*)[33]

The close analogs are the ipomeamarones (18-27) whose biogenesis from intermediates of the dendrolasin pathway involves another heterocyclic ring (tetrahydrofuran) formation at C-4 and C-7. The representative is ipomeamarone (18) which is the bitter principle produced by the tubers of *Ipomoea* sp. infected by the sac fungus, *C. fimbriata*, and other pathogens.[5-8] Since ipomeamarone (18) is not found in the normal tubers, its biosynthesis is quite interesting in relation to its physiological activity (p. 856). This class of sesquiterpenoids is of limited taxonomic distribution, being restricted only to Myoporaceae and Compositae other than black-rotted sweet potato. Of interest biosynthetically is that during the tetrahydrofuran ring formation of dendrolasin type intermediates, introduction of an oxygen function at C-4 proceeds under stereochemical control, however, insertion of an oxygen function at C-7 may not be stereospecific to generate a pair of epimers at C-7 in a certain plant.

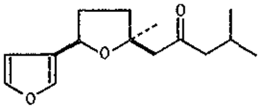
A significant feature in the ipomeamarones is the presence of the 9-oxo grouping which may cause facile formation of a catabolite, deisopropylngaione (28), in a myoporaceous plant.[39] Another relative, α-methyl-α'-(β-furyl)-



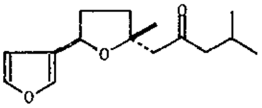
ipomeamarone (18)[6-8]
Ipomoea sp. (infected
with pathogens)[5]



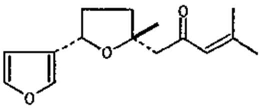
ipomeamaronol (19)
Ipomoea sp. (infected
with *C. fimbriata*)[36]



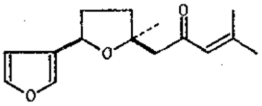
ngaione (20)[9,8]
Myoporum acuminatum,
M. deserti,[37] *M. laetum,*[4]
Eremophila latrobei[8]



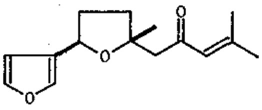
epingaione (21)
Myoporum deserti[38]



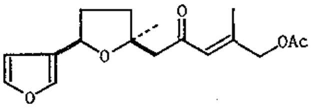
dehydroipomeamarone (22)
Ipomoea batatas (infected
with *C. fimbriata*)[39]



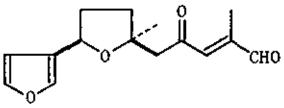
dehydrongaione (23)
Myoporum deserti[38]



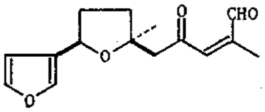
dehydroepingaione (24)
Myoporum deserti[38]



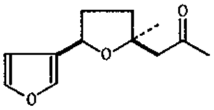
12-acetoxy-10,11-dehydro-
ngaione (25)
Stilpnophytum linifolium[30]



trans-dehydrongaional (26)
Athanasia crithmifolia[29]



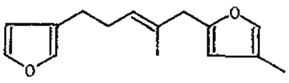
cis-dehydrongaional (27)
Athanasia crithmifolia[29]



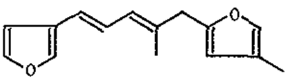
deisopropylngaione (28)
Myoporum deserti[38]

tetrahydrofuran, found in a sweet potato fusel oil,[31] may be a degradation product of some ipomeamarone type intermediates.

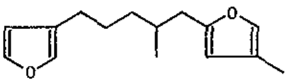
In a composite plant, dendrolasin type intermediates may be converted to the lasiospermans (29-34) with a further furan ring closure at another terminal of the carbon chain. When an intermediate of the lasiosperman type is subjected to further heterocyclic ring (tetrahydrofuran) formation, athanasin (35)[29] may be generated.



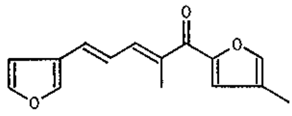
dehydrolasiosperman (29)[40]
Athanasia incisa,[29]
Lasiospermum radiatum[40]



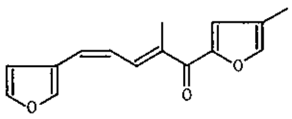
(30)
Lasiospermum radiatum[40]



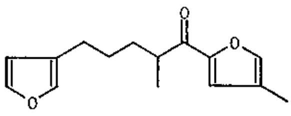
lasiosperman (31)
Lasiospermum radiatum[40]



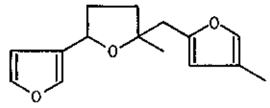
(32)
Athanasia acerosa,[29]
A. parvifolia,[29]
Lasiospermum sp.[29]



(33)
Athanasia acerosa,[29]
A. parvifolia,[29]
Lasiospermum sp.[29]

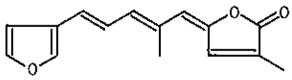


(34)
Eumorphia dregeana[30]

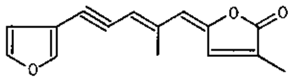


athanasin (35)
Athanasia crithmifolia[29]

Furanosesquiterpenoids considered to be the analogs of lasiosperman are the freelingynes (36-37) isolated from a composite plant whose terminal carbons (C-9, 10, 11, and 12) constitute an α,β;γ,δ-unsaturated γ-lactone instead of the furan ring.[41,42] Freelingyne (37) is the sole member in the furanosesquiterpenoids which has an acetylenic linkage. Since the furan and the unsaturated γ-lactone are close biogenetically, biosynthesis of the freelingynes is of particular interest (p. 843).

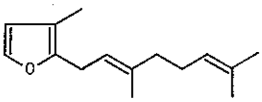


dihydrofreelingyne (36)
Eremophila freelingii[41]

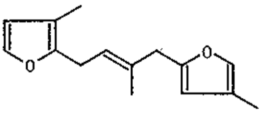


freelingyne (37)[42,41]
Eremophila freelingii[42]

Sesquirosefuran (38)[43] is related to dendrolasin (1); however, the furan ring in the former is constructed from C-1, 2, 3, and 4, while in the latter, the furan consists of C-1, 2, 3, and 13. Longifolin (39)[43] may be derived from sesquirosefuran (38) in the same fashion as dehydrolasiosperman (29) may



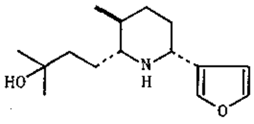
sesquirosefuran (38)
Actinodaphane longifolia[43]



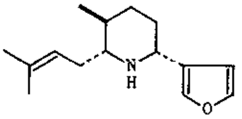
longifolin (39)[43]
Actinodaphane longifolia,[43]
Asaemia axillaris[32]

be formed from dendrolasin (1).

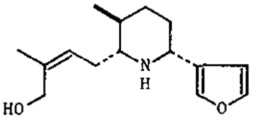
The nupharamines (40-44) from nymphaeaceous plants are certainly derived from intermediates of the dendrolasin type by forming a nitrogen bridge at C-4 and C-8. The piperidine ring formation appears to proceed under stereospecific control, but generation of the asymmetric carbon at C-7 is apparently taken place non-stereospecifically depending upon the original plants.



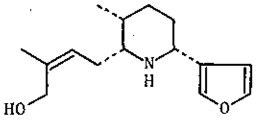
nupharamine (40)[45,46]
Nuphar japonicum[44]



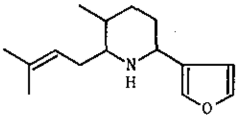
anhydronupharamine (41)
Nuphar japonicum[47]



nuphamine (42)[48,49]
Nuphar japonicum[48]

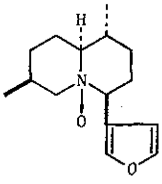


3-epinuphamine (43)
Nuphar luteum
subsp. *variegatum*[50]

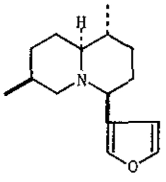


nuphenine (44)
Nuphar variegatum[51]

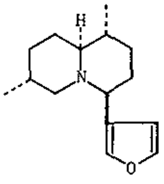
There are members (45-49) of the nupharidine type from nymphaeaceous plants, which are considered to be biogenetically originating from nupharamine type intermediates and characterized by their common possession of the extra heterocyclic ring to constitute a quinolizidine nucleus. A representative structure was first deduced for nupharidine (45) which is significant in having an N-oxide moiety.[11] Castoramine (49) is the only one of the furanoses-



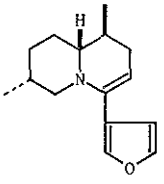
nupharidine
(45)[11,52,12]
Nuphar japonicum[10]



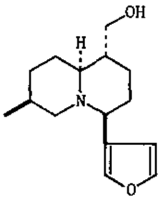
desoxynupharidine
(46)[11,52,12]
Nuphar japonicum[53]



7-epidesoxynupharidine (47)
Nuphar luteum
subsp. *variegatum*[54]



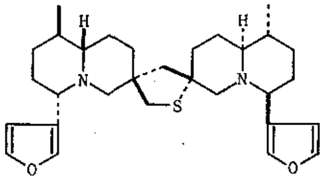
dehydrodeoxynupharidine (48)
Nuphar japonicum[55]

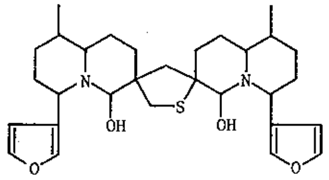


castoramine
(49)[57,58]
Castor canadensis[56]

quiterpenoids to be found in a higher animal, namely the beaver (the scent gland).[56-58] It is interesting to know whether the beaver constructs castoramine (49) from a precursor of smaller molecule or it starts the construction from an intermediate of the nupharamine type incorporated with a possible vegetable diet, a *Nuphar* plant.

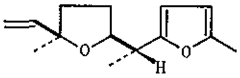
The other related substances belonging to this group are the dimeric nupharidines (50-52) found also in nymphaeaceous plants which are thought to arise by the oxidative coupling of two molecules of nupharidine-type intermediates to form a thioether bridge.

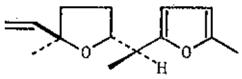

neothiobinupharidine (50)[60]
Nuphar luteum[59]

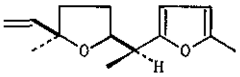

6,6'-dihydroxythionuphlutine A, B (51, 52)
Nuphar luteum subsp. *macrophyllum*[61]

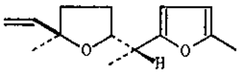
2.2 Furanosesquiterpenoids possessing the modified farnesane skeleton

This type of isoprenoids is first exemplified by the class of davanafurans (53-56) from a composite plant.[62] It consists of 4 stereoisomers having the unique norfarnesane skeleton where the furan and tetrahydrofuran rings involve C-8, 9, 10, and 11, and C-3, 4, 5, and 6, respectively.

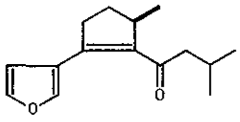

(53)
Artemisia pallens[62]


(54)
Artemisia pallens[62]

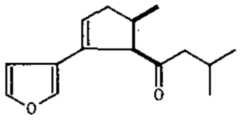

(55)
Artemisia pallens[62]


(56)
Artemisia pallens[62]

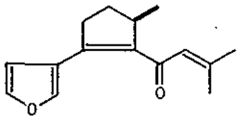
The first class of the cyclized farnesane types consists of the myodesmones (57-60) from a myoporaceous plant[63,64] in which a C-C bond has been generated between C-4 and C-8 of the farnesane chain to form a cyclopentane ring. The structures of the myodesmones indicate that they are derived from myoporone (10) and dehydromyoporone (p. 820) *via* β-hydroxyketone intermediates by a Michael-type condensation followed by dehydration.



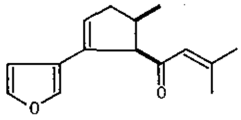
myodesmone (57)
Myoporum deserti[63]



isomyodesmone (58)
Myoporum deserti[63]

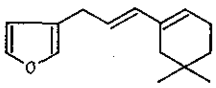


dehydromyodesmone (59)
Myoporum deserti[64]



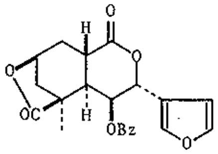
dehydroisomyodesmone (60)
Myoporum deserti[64]

Another modified furanofarnesane is pleraplysillin (61) from a marine sponge[27] in which a cyclohexane bond has been formed between C-11 and C-14.

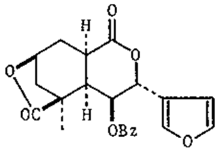


pleraplysillin (61)
Plaraplysilla spinifera[27]

Collybolide (62) and its epimer (63) from a tricholomataceous mushroom[1,66] are the other representatives. After the proposal of a tentative formula,[65] the longest history of the structural investigation of collybolide (62) finally came to a period quite recently.[18] The probable biogenesis of these terpenoids involves the construction of the furan ring at the terminal of the side chain and formation of the γ- and δ-lactone rings in the cyclized farnesane (farnesiferol B type) skeleton. From the structures of the collybolides, it may be considered that either of them is an artefact converted from another congener during the isolation procedure.



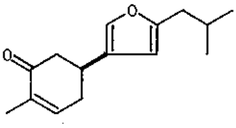
collybolide (62)[18]
Collybia maculata[1]



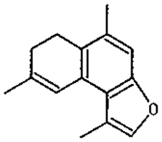
isocollybolide (63)
Collybia maculata[66]

2.3 Furanosesquiterpenoids possessing the bisabolane and cadinane skeletons

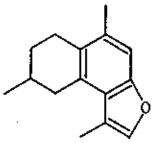
Although the sesquiterpenoids of the bisabolane and cadinane-type constitute relatively large groups of substances, bilobanone (64) from a ginkgoaceous plant,[67,68] pyrocurzerenone (65) from a zingiberaceous plant,[69] and dihydropyrocurzerenone (66) from a chloranthaceous plant[70] are the only examples yet known of furan-containing congeners.



bilobanone (64)[68]
Ginkgo biloba[67]



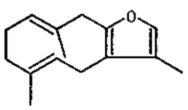
pyrocurzerenone (65)
Curcuma zedoaria[69]



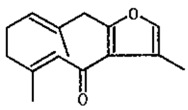
dihydropyrocurzerenone (66)
Chloranthus serratus[70]

2.4 Furanosesquiterpenoids possessing the germacrane skeleton

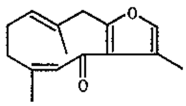
To data, the furanogermacranes (67-87) are known to occur only in Zingiberaceae and Lauraceae except for Myrtaceae, Umbelliferae, and Labiatae, the latter three containing furanodiene (67) and its diepoxide (77). A zingiberaceous plant, *Curcuma zedoaria*, provides a rich harvest of simpler furanosesquiterpenoids, the simplest being furanodiene (67).[71,72] Just as in furanodiene (67), all known congeners have the furan ring closure at C-8 and C-12. Many examples of the co-occurrence of the furanogermacranes with other types of furanosesquiterpenoids in the same or related plants have been noted. These facts are in excellent accord with the assumption that this group of substances (particularly furanodiene (67)) are the primary furanosesquiterpenoid products from the biosynthetic pathway, thus serving as progenitors of certain other groups of furanosesquiterpenoids. Furanodiene (67) was later isolated from other vegetable sources.[73,74] Curiously enough, however, furanodiene from a myrtaceous plant was distinguished from the authentic furanodiene and designated as isofuranodiene, though the formula of furanodiene was given to it.[74] The discrepancy of the melting points of both the furanodienes may be due to the difference in purity. In all congeners (71-76, 79-87) from lauraceous plants, C-14 is oxidized to a carboxyl which is further converted either to a carbomethoxy group or to a γ-lactone bridge with C-6 (the lactonic oxygen at C-6 being α-oriented). Modified analogs are zeylanine (86) and zeylanane (87)[81] considered to be arising from neolinderane (80) by epoxide ring opening followed by acetylation or less likely from litsealactone (76) by an allylic rearrangement. The geometry of the double bonds and the molecular conformation of several furanogermacranes were extensively studied by means of the NOE technique in ^1H NMR spectroscopy to yield the following conclusion. In this group, E-geometry of the C-1:C-10 and C-4:C-5 double bonds is general except for isofuranodienone (69) (4Z), sericenic acid (72) (4Z), sericenine (73) (4Z), and neolinderalactone (75) (1(10)Z). The 10-membered ring in the congeners of the general type having the 1(10)E,4E-diene system adopts a preferred conformation in which the two juxtaposing double bonds have a crossed orientation and C-14 and C-15 are *syn*, while in some modified analogs these carbons are *anti*.[20,22] Endocyclic double bonds of some congeners are subjected to biogenetic epoxidation and, in fact, 10 out of 21 companions possess at least 1 epoxide group, and some contain 2. The biogenetic epoxidation can be classed into 2 essentially different types; that of a prochiral substrate and that of a chiral substrate. The former may be exemplified by epoxidation of furanodiene (67) and furanodienone (68) which appears to proceed stereoselectively and also stereospecifically, yielding glechomafuran (77) (optically active though the



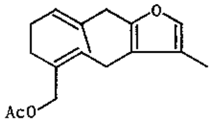
furanodiene (67)[71,72]
Curcuma zedoaria,[71]
Eugenia uniflora,[73]
Smyrnium olusatrum[74]



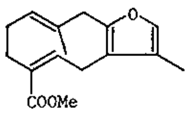
furanodienone (68)
Curcuma zedoaria[75]



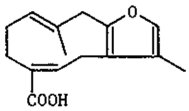
isofuranodienone (69)
Curcuma zedoaria[75]



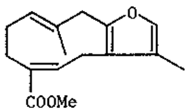
neosericenyl acetate (70)
Lindera strychnifolia[76]



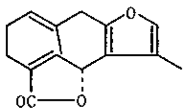
neosericenine (71)
Neolitsea sericea[77]



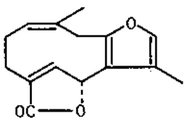
sericenic acid (72)[78,77]
Neolitsea sericea[78]



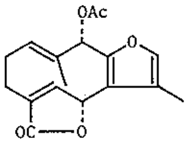
sericenine (73)[78,77]
Neolitsea sericea[78]



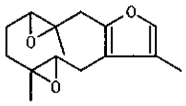
linderalactone (74)[79,80]
Lindera strychnifolia,[79]
Neolitsea aciculata,[81]
N. sericea,[22]
N. zeylanica[82]



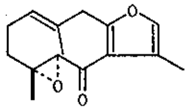
neolinderalactone (75)[80,83]
Lindera strychnifolia[80]



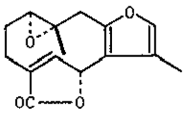
litsealactone (76)[81,84]
Neolitsea aciculata[81]



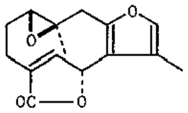
glechomafuran (77)[85]
Smyrnium olusatrum,[74]
Glechoma hederacea[85]



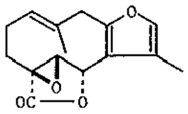
zederone (78)[86,87]
Curcuma zedoaria[86]



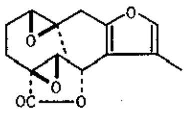
pseudoneolinderane (79)[81,88]
Lindera strychnifolia,[22]
Neolitsea aciculata[81]



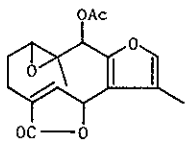
neolinderane (80)[89,88]
Neolitsea aciculata,[81]
N. zeylanica[82]



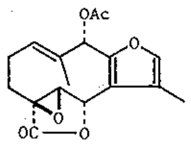
linderane (81)[16,17]
Lindera strychnifolia,[3]
Neolitsea aciculata,[81]
N. zeylanica[82]



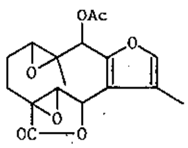
linderadine (82)[81,88]
Neolitsea aciculata[81]



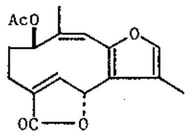
zeylanicine (83)[89]
Neolitsea zeylanica[82]



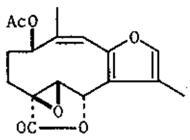
litseaculane (84)[81,84]
Neolitsea aciculata[81]



zeylanidine (85)[89]
Neolitsea zeylanica[82]



zeylanine (86)[81]
Neolitsea aciculata,[81]
N. zeylanica[82]

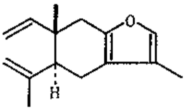


zeylanane (87)
Neolitsea aciculata[81]

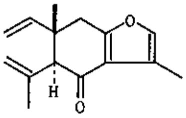
stereochemistry unknown) and zederone (78) in certain plants. Examples of the latter may be epoxidation of linderalactone (74), litsealactone (76), and zeylanine (86) taking place in lauraceous plants. In these possible substrates, there exists a lactone system at C-14 and C-6 which makes the neighboring conformation fixed. Since an oxidation enzyme can add an oxygen atom to a double bond only from the outside of the 10-membered ring, all the 4,5-epoxides (81, 82, 84, 87) have the epoxy ring in the β-configuration. On the other hand, the conformation around the C-1:C-10 double bond is flexible, and in the case of linderalactone (74), an oxidation enzyme would have affinity not only to a preferred conformation but also to an alternative one to afford a pair of 1,10-epoxides (79, 80). A notable feature of the last reaction is that the enzymatic oxidation occurs at an alternative conformation (undoubtedly C-14,C-15 *anti*) rather than a preferred conformation (C-14,C-15 *syn*).[90]

2.5 Furanosesquiterpenoids possessing the elemane skeleton

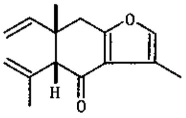
The furanoelemanes (88-93) are considered to be originating from furanogermacrane-type intermediates by biogenetic Cope rearrangement. In fact, the simplest representative, isofuranogermacrene (88) and its 6-oxygenated deriva-



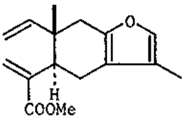
isofuranogermacrene
(curzerene) (88)[71,91]
Curcuma zedoaria,[71]
Lindera strychnifolia,[91]
Smyrnium olusatrum[74]



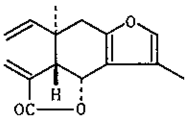
curzerenone (89)[92,93,75]
Curcuma zedoaria[92]



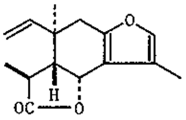
epicurzerenone (90)[92,75]
Curcuma zedoaria[92]



isosericenine (91)
Neolitsea sericea[93]



isolinderalactone
(92)[79,94]
Lindera strychnifolia,[79]
Neolitsea aciculata,[81]
N. sericea[22]

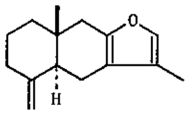


epidihydroisolinderalactone (93)[95,96]
Lindera strychnifolia[95]

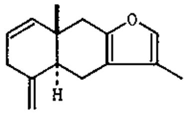
tives (89, 90) are corresponding to the germacrane analogs (67-69) occurring in the same plants, and the latter companions can be converted into the former companions by Cope rearrangement *in vitro*.[72,92,75] Similarly, the elemanes (91, 92) could be formed from the germacranes (71, 74) having the same substitution patterns by direct rearrangement in lauraceous plants. So far the furanoelemanes are known to distribute in Zingiberaceae, Lauraceae, and Umbelliferae. The occurrence of the dihydro-derivative (93) of a Cope rearrangement product in a lauraceous plant is noteworthy.

2.6 Furanosesquiterpenoids possessing the eudesmane skeleton

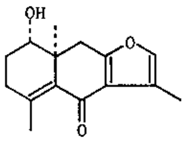
In contrast to a large number of eudesmane derivatives (particularly eudesmanolides) encountered as natural products, only 3 members (94-96) containing the furan nucleus are known at present. They are scattered separately in 3 plant families (Zingiberaceae, Lauraceae, and Compositae) lacking close taxonomical relationship. The rôle of transannular cyclization of intermediates of the germacra-1(10),4-diene or germacr-4-ene 1,10-epoxide-type in the formation of the eudesmanes has now been placed beyond doubt. Atractylon (94) was related through the common derivatives to an eudesmanolide alantolactone of known absolute stereostructure.[13] What is significant from a biogenetic point-of-view is that in the known furanoeudesmanes, one terminus of the oxide ring is found only at C-8 as in the furanogermacranes and the furanoelemanes, while in the eudesmanolides, which have a close relationship to the furanoeudesmanes biogenetically (p. 843), the γ-lactone ring closure is observed both at C-6 and C-8.



atractylon (94)[13]
Atractylodes sp.,[2]
A. japonica[13]



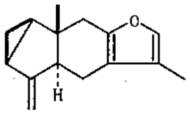
lindesterene (95)[97]
Lindera strychnifolia,[97]
Neolitsea sericea[22]



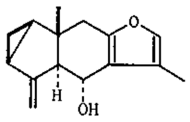
curcolone (96)
Curcuma zedoaria[98]

2.7 Furanosesquiterpenoids possessing the lindenane skeleton

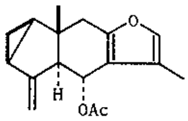
There are several furanosesquiterpenoids with the modified (cyclopropane-containing) eudesmane skeleton (97-102) which all have come from plants of Lauraceae. The first congener to be unraveled was lindenenol (linderene) (98)[3,14,15] whose structural elucidation presented considerable difficulties, and the chemistry of it and its derivatives was extensively investigated. Allylic hydroxylation at C-5 or C-14 of eudesm-3-ene intermediates followed by dehydration is a probable step in the biosynthesis. This group of substances is characterized by oxygenation at C-6 and the presence of a methoxyl function at C-13 in certain congeners.



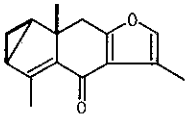
lindenene (97)[99]
Lindera strychnifolia,[99]
Neolitsea sericea[22]



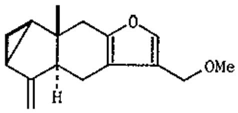
lindenenol (linderene)
(98)[14,15]
Lindera strychnifolia[3]



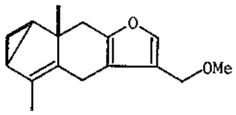
lindenenyl acetate (99)
(99)[97,15]
Lindera strychnifolia[97]



linderenone (100)
Lindera strychnifolia[83]



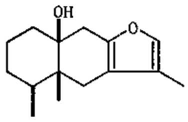
linderoxide (101)
Lindera strychnifolia[91]



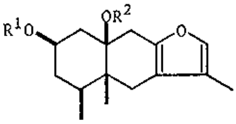
isolinderoxide (102)
Lindera strychnifolia[100]

2.8 Furanosesquiterpenoids possessing the eremophilane skeleton

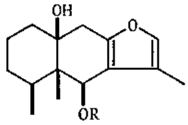
The most significant fact regarding the furanosesquiterpenoids is that those possessing the eremophilane skeleton (103-224) are much more abundant than the other types. Possession by plants of the capability to rearrange a furanoeudesmane to a furanoeremophilane structure is considered to be an isolated character, since it is limited essentially to one group of phylogenetically related plants, Compositae. The only exceptions are furanoeremophilone-(1) (191) from Umbelliferae[74] and wargburgin (137) from Canellaceae[113] which is also significant as this group in the respect that C-13 constitutes a carbomethoxy group. The furanoeremophilanes, though numerous, appear to conform fairly closely to the biogenetic pattern and as a result, they show a little diversity of structural features. Among the furanoeremophilanes, the ones possessing the most basic structure are tetradymol (103)[101] and furanoeremophilane (163)[120] which are probably subjected to dehydration and oxidation at various positions including epoxidation at C-1:C-10 to yield a number of descendants. Positions 3, 6, and 9 are most frequently oxygenated. This substitution seems specific for certain types of plants. Thus, substituents at C-6 prevail in components from a certain plant, while substituents at C-9 are more common in constituents from another plant. Derivatives having a hydroxyl at C-1 are likely formed by ring fission of 1,10-epoxides and have either the *trans*-1,10-glycol system or the 10α(H)-1-ol-9-one moiety. The major characteristic structural features in the furanoeremophilanes are the predominance of A/B *cis* ring junction, the prevalence of esterification of hydroxyls with a variety of acids among which methacrylic, 2-methylbutyric, isobutyric, angelic, tiglic, and senecionic acids are more common than acetic acid (in rare instances, the 6-hydroxyl forms a 2-hydroxymethylprop-2-enoic acid ester, a 2-hydroxymethylbut-2-enoic acid ester, a 2,3-epoxy-2-methylbutanoic acid ester, a *cis*-β-methylthioacrylic acid ester, or a methyl ether), and the preferential presence of 6-hydroxyls in the β-configuration (the only exception being one member (224)). The last finding, when compared with the fact that none of the furanogermacranes possess a 6-hydroxyl in the β-configuration (p. 828), demonstrates that 6-hydroxylation takes place after transannular cyclization. Although all the furanoeremophilanes have been assigned to have the 4β,5β-dimethyl arrangement, the assignment in some congeners has been made only based on the environmental evidence. The occasionally-found 10α(H)-furanoeremophil-9-one analogs may be artefacts and originally present as their 10β(H)-counterparts in plants, since the *cis* ketones are very unstable and epimerized easily



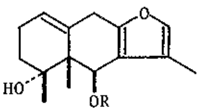
tetradymol (103)
Tetradymia glabrata[101]



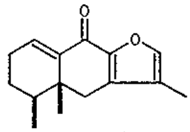
(104): R^1=H, R^2=Ang
Euryops abrotanifolius,
E. linifolius,
E. spathaceus,
E. tenuisissimus,
E. virgineus[102]
(105): R^1=Mac, R^2=H
E. abrotanifolius,
E. linifolius[102]



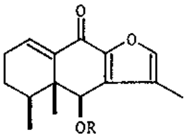
(106): R=H[103]
Ligularia japonica,[103]
Othonna amplexicaulis[104]
(107): R=Me
Ligularia japonica[103]
(108): R=Ang
Othonna amplexicaulis[104]
(109): R=Tig
O. amplexicaulis[104]
(110): R=Sen[105]
Farfugium japonicum,[105]
Othonna amplexicaulis[104]
(111): R=Meb[103]
Ligularia japonica,[103]
Othonna amplexicaulis[104]
(112): R=Iva
O. amplexicaulis[104]



(113): R=Ibu
Euryops hebecarpus[102]
(114): R=Ang
E. chrysanthemoides,
E. hebecarpus,
E. tenuisissimus[102]
(115): R=Tig[102]
E. virgineus,[102]
Senecio elegans[106]
(116): R=Sen
S. elegans[106]
(117): R=Meb
S. elegans[106]
(118): R=Iva
Euryops hebecarpus[102]

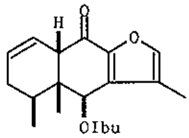


9-oxoeuryopsin (119)
Euryops hebecarpus,
E. virgineus[102]

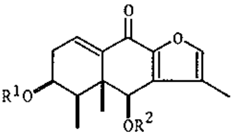


decompositin (120):
R=Ac[108]
Cacalia decomposita,[107]
Euryops othonnoides[109]
(121): R=Mac
E. spathaceus[102]
adenostylone (122):
R=Ibu[110,108]
Adenostyles alliariae[110]
neoadenostylone (123):
R=Ang[110,108]
A. alliariae[110]
(124): R=Iva
Senecio pterophorus[106]
(125): R=CO

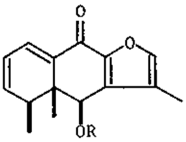
Euryops abrotanifolius[102]



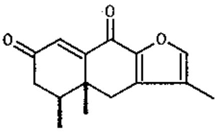
isoadenostylone
(126)[110,108]
Adenostyles alliariae[110]



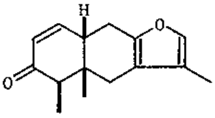
(127): R^1=H, R^2=Mac
Euryops spathaceus[102]
(128): R^1=H, R^2=Ang
E. spathaceus[102]
(129): R^1=R^2=Mac
E. spathaceus[102]
(130): R^1=Mac, R^2=Ang
E. spathaceus[102]
(131): R^1=R^2=Ang
E. spathaceus[102]



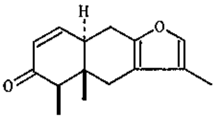
(132): R=Mac
Euryops spathaceus[102]
(133): R=Ang
E. spathaceus[102]



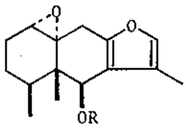
(134)
Euryops tenuisissimus[102]



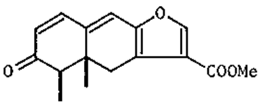
10βH-furanoligularenone
(135)
Ligularia fischeri[111]



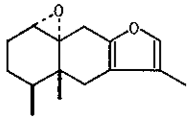
furanoligularenone (136)
Aster tataricus[112]



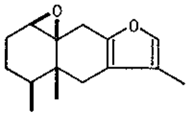
(140): R=Ac
Euryops othonnoides[109]
(141): R=Ang
E. othonnoides[109]



wargburgin (137)
Wargburgia ugandensis[113]

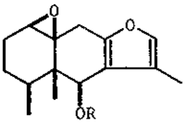


8,8a-epoxyfuranoligular-
ane (138)
Senecio stylvaticus[114]

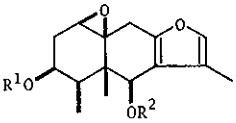


(139)
Senecio glastifolius[106]

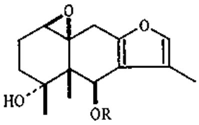
Abbreviations: Mac=methacryloyl (2-methylpropenoyl), Ibu=isobutyryl, Ang=angeloyl, Tig=tigloyl, Sen=senecioyl, Meb=2-methylbutanoyl, Iva=isovaleryl.



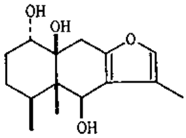
(142): R=H
Ligularia fischeri^{115}
(143): R=Ac
Senecio rigidus^{106}
(144): R=Mac
S. rigidus^{106}
senemorin (145): R=Ang
S. nemorensis^{116}
(146): R=Sen
S. rigidus^{106}
(147): R=COC(CH$_2$OH)=CH$_2$
Ligularia fischeri^{117}



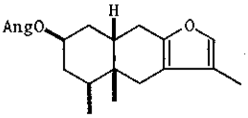
nemosenin C (148):
R^1=H, R^2=Ibu
Senecio nemorensis^{116}
nemosenin A (149):
R^1=H, R^2=Ang
S. nemorensis^{116}
nemosenin B (150):
R^1=H, R^2=Meb
S. nemorensis^{116}
nemosenin D (151):
R^1=Ac, R^2=Ibu
S. nemorensis^{116}



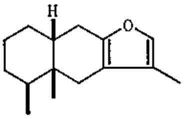
(152): R=Ibu
Euryops hebecarpus^{102}
(153): R=Ang
E. abrotanifolius^{102}
(154): R=Iva
E. abrotanifolius^{102}



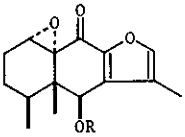
euryopsol (155)
Euryops floribundus,
E. tenuisissimus^{118}



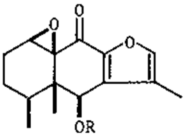
furanojaponin (164)
Petasites japonica^{121}



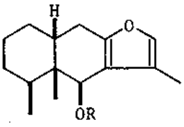
furanoeremophilane
(163)^{120}
Petasites hybridus,^{119}
P. officinalis^{120}



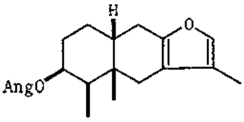
(156): R=Ac^{109}
Euryops linifolius,^{102}
E. othonnoides^{109}
(157): R=Mac
E. linifolius,
E. spathaceus^{102}
(158): R=Ibu
E. othonnoides,
E. speciosissimus^{109}
(159): R=Ang^{109}
E. linifolius,^{102}
E. othonnoides,
E. speciosissimus^{109}
(160): R=Iva
E. othonnoides,
E. speciosissimus^{109}



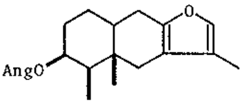
(161): R=Ang
Senecio glastifolius^{106}
(162): R=Sen
S. glastifolius,
S. rigidus^{106}



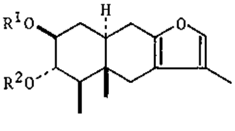
petasalbin (ligularol):
(167): R=H^{122,123}
Ligularia sibirica,^{122}
Petasites albus^{123}
petasalbin methyl ether
(168): R=Me
P. japonicus^{121}
(169): R=Sen
Farfugium japonicum^{105}



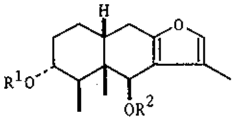
(165)
Farfugium japonicum^{105}



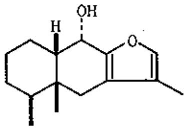
(166)
Othonna filicalis^{104}



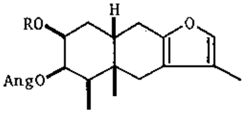
(173): R^1=Ang, R^2=Ac
Othonna bulbosa^{104}
(174): R^1=R^2=Ang
O. bulbosa^{104}
(175): R^1=Ang, R^2=Sen
O. bulbosa^{104}
(176): R^1=Sen, R^2=Ac
O. bulbosa^{104}



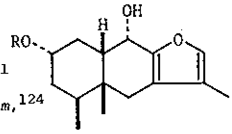
furanofukinol (179):
R^1=R^2=H^{121}
Farfugium hiberniflorum,^{124}
Petasites japonicus^{121}
6-acetyl furanofukinol
(180): R^1=H, R^2=Ac
P. japonicus^{121}
6-angelyl furanofukinol
(181): R^1=H, R^2=Ang^{121}
Farfugium hiberniflorum,^{124}
Petasites japonicus^{121}
(182): R^1=Ang, R^2=H
Farfugium hiberniflorum^{124}
(183): R^1=Ang, R^2=Ac
F. hiberniflorum^{124}
S-furanopetasitin (184):
R^1=CO$\smile$SMe, R^2=Ang
Petasites japonicus^{121}



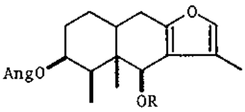
9-hydroxyfuranoeremophilane (170)
Petasites hybridus^{124}



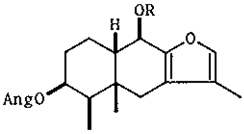
(171): R=Ac
Othonna barkerae^{104}
(172): R=Ang
O. barkerae^{104}



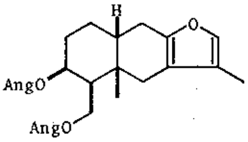
furanopetasol (177):
R=H
Petasites officinalis^{125}
furanopetasin (178):
R=Ang^{125}
P. officinalis^{119}



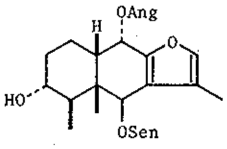
(185): R=H
Othonna filiculis^{104}
(186): R=Ac
O. filiculis^{104}



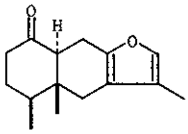
(187): R=H
Farfugium japonicum^{105}
(188): R=Sen
F. japonicum^{105}



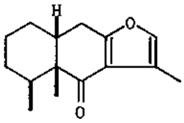
(189)
Othonna amplexicaulis[104]



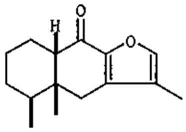
kablicin (190)
Petasites kablikianus[125]



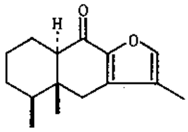
furanoeremophilone-(1)
(191)
Smyrnium olusatrum[74]



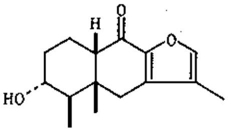
ligularone (192)
Ligularia sibirica[122]



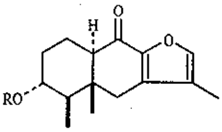
10βH-furanoeremophilone
(193)
Petasites albus[123]



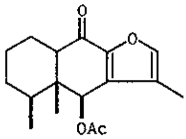
furanoeremophilone
(194)[126]
Euryops othonnoides,[109]
Petasites hybridus[126]



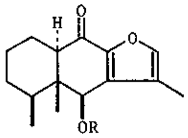
euryopsonol (195)
Euryops floribundus[127]



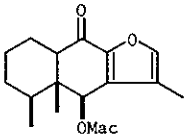
(196): R=Mac
Euryops linifolius[102]
(197): R=Ibu
E. speciosissimus[109]
(198): R=Ang
E. abrotanifolius,
E. chrysanthemoides,
E. hebecarpus,
E. linifolius,
E. tenuisissimus[102]
(199): R=Iva
E. speciosissimus[109]
(200): R=COC(CH_2OH)=CH-CH_3
E. speciosissimus[109]



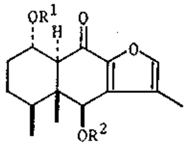
dihydrodecompositin
(201)
Euryops othonnoides[109]



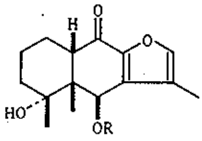
(203): R=Ibu
Senecio umbellatus[106]
(204): R=Ang
S. umbellatus[106]
(205): R=Iva
S. umbellatus[106]



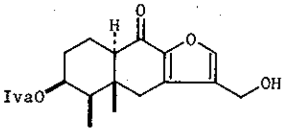
(202)
Euryops spathaceus[102]



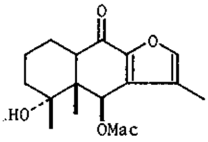
(206): R^1=H, R^2=Ibu
Senecio umbellatus[106]
(207): R^1=H, R^2=Ang
S. rigidus[106]
(208): R^1=Ac, R^2=Ibu
S. umbellatus[106]
(209): R^1=Ac, R^2=Ang
S. rigidus[106]
(210): R^1=Ac, R^2=Tig
S. umbellatus[106]
(211): R^1=Ang, R^2=Ac
S. rigidus[106]



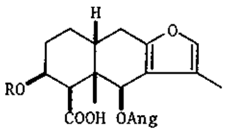
(212): R=Ibu
Euryops hebecarpus,
E. spathaceus[102]
(213): R=Ang
E. hebecarpus[102]
(214): R=Tig
E. virgineus[102]
(215): R=Sen
E. abrotanifolius[102]



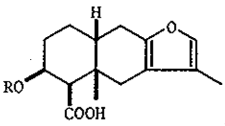
(217)
Euryops speciosissimus[109]



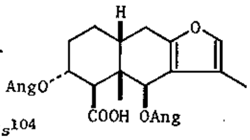
(216)
Euryops spathaceus[102]



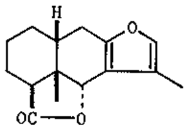
(221): R=Ibu
Othonna barkerae,[104]
O. coronopifolia
(222): R=Ang
O. amplexicaulis,
O. barkerae,
O. coronopifolia,
O. dentata,
O. quercifolia[104]
(223): R=Sen
O. quercifolia[104]



(218): R=Mac
Othonna amplexicaulis[104]
(219): R=Ang
O. amplexicaulis,
O. dentata[104]



(220)
Othonna arborescens,
O. barkerae[104]



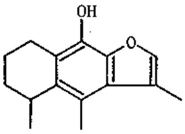
furanoeremophilan-
14β,6α-olide (224)
Ligularia hodgsoni[128]

to the stable *trans* ketones. Another companion having the special feature in structure is furanoeremophilan-14β,6α-olide (224)[128] which possesses a γ-lactone moiety unique both in functionality and configuration at C-6 (α-oxygen) as this group.

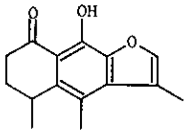
2.9 Furanosesquiterpenoids possessing the modified eremophilane skeleton

There are 2 groups of furanosesquiterpenoids considered to represent the metabolic products of eremophilane intermediates.

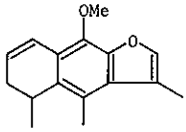
The first group may conveniently be divided into 2 subgroups. The one involves 7 members (225-231) where C-15 has suffered further 1,2-migration from C-5 to C-6. Another subgroup consists of 2 further metabolites, maturinone (232) and maturone (233)[130,131] in which C-15 has been replaced by the carbonyl oxygen of a quinone moiety, thus giving rise to norsesquiterpenoids.



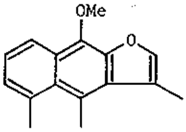
cacalol (225)[130]
Cacalia decomposita[129]



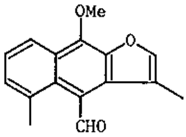
cacalone (226)[130]
Cacalia decomposita[129]



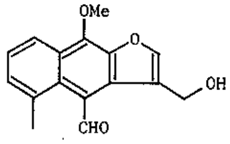
O-methyldehydrocacalol (227)[132,133]
Cacalia auriculata var. *kamtschatica*,[132]
C. hastata,[133]
Euryops linifolius[102]



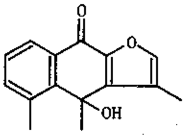
O-methylcacaldienol (228)[132,133]
Cacalia auriculata var. *kamtschatica*,[132]
C. hastata[133]



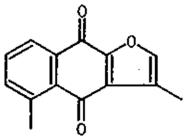
maturinin (229)[130]
Cacalia decomposita[131]



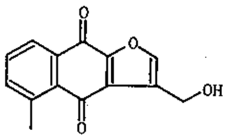
maturin (230)[130]
Cacalia decomposita[131]



cacalonol (231)
Cacalia auriculata var. *kamtschatica*[132]



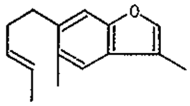
maturinone (232)[130]
Cacalia decomposita[131]



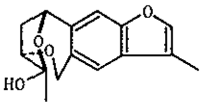
maturone (233)[130]
Cacalia decomposita[131]

The above substances can be characterized by the facts that they occur conclusively in composite plants and their furan ring is condensed with a tetralin, a 1,2-dihydronaphthalene, a naphthalene, or a naphthoquinone. The only exception (231) is probably an intermediate between the 2 subgroups.

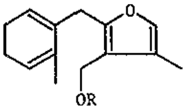
The remainders constituting the second group can be classed as the seco-eremophilanes. In one subgroup, there are 4,5-seco-derivatives (234-237) which exhibit a diversity of structures (including ether, hemiacetal, methyl ketone, and lactone). Among them, farfugin A (237)[134] is unique because the C_5 unit once generated by the A-ring fission has been migrated to C-9. The remaining congeners are 5,6-seco-derivatives (238-240) which are characterized by having a dihydrobenzene moiety and an acyloxy group at C-6.



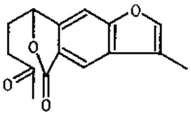
farfugin B (234)
Farfugium japonicum[134]



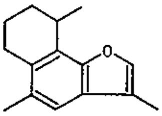
(235)
Euryops hebecarpus[102]



(238): R=Mac
Euryops hebecarpus,
E. tenuisissimus[102]
(239): R=Ang
Senecio elegans[106]
(240): R=Sen
Euryops abrotanifolius,
E. hebecarpus[102]



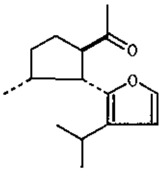
(236)
Euryops hebecarpus[102]



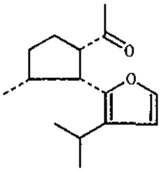
farfugin A (237)
Farfugium japonicum[134]

2.10 Furanosesquiterpenoids possessing the modified guaiane skeleton

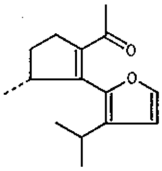
A peculiality of the furanosesquiterpenoid chemistry is the lack of com-



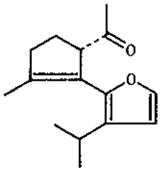
furopelargone A
(241)[136,137]
Pelargonium roseum,[135]
Geranium bourbon[136]



furopelargone B
(242)[136,137]
Pelargonium roseum,[135]
Geranium bourbon[136]



furopelargone C (243)
Geranium bourbon[138]

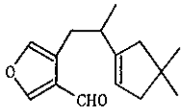


furopelargone D (244)
Geranium bourbon[138]

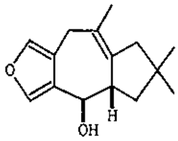
panions with a complete guaiane skeleton. Probable metabolites which could be derived from guaiane intermediates by an oxidative cleavage between C-9 and C-10, are the furopelargones (241-244) from Geraniaceae.

2.11 Furanosesquiterpenoids possessing the modified humulane skeleton

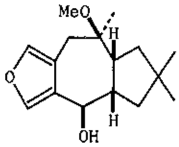
The curious family of structures elaborated by russulaceous fungi are unlike any of the sesquiterpenoids produced by higher plants. Thus, lactaral (245) and its relatives (246-249) have the complexed skeletons consisting of a furan nucleus and a cyclopentane ring. Although the carbon skeletons of the lactarals are not apparently divisible into isoprene units in the regular head-to-tail order, they could arise from the cyclobutyl cation (252) which is the common intermediate from humulene to a number of fungal metabolites.[142] The common occurrence of isovelleral (253) and velleral (254) in the same fungi[143,144] can be used as supporting evidence for this belief.



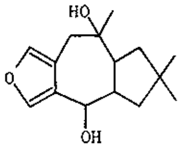
lactaral (245)
Lactarius pergamenus,
L. vellereus[139]



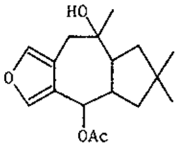
(246)[141]
Fomitopsis insularis,[140]
Lactarius helvus,
L. pergamenus,
L. vellereus[141]



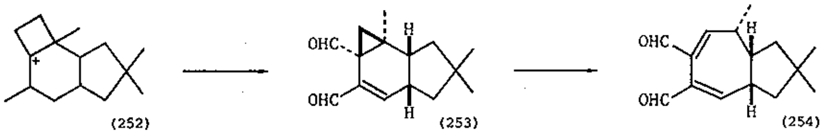
(249)
Lactarius helvus,
L. pergamenus,
L. vellereus[141]



(247)
Fomitopsis insularis[140]

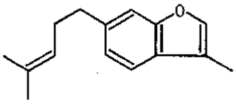


(248)
Fomitopsis insularis[140]

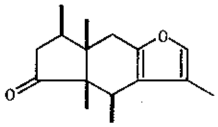


2.12 Furanosesquiterpenoids possessing the other carbon skeleton

Furoventalene (250) from a coelenterate[145] is an example of monocarbocyclic sesquiterpenoids with an abnormal ring substitution pattern. Since this substance was successfully isolated only by steam distillation, it was suggested to be unknown whether or not this was formed by degradation from a larger molecule. If this were biosynthesized as it is in the animal, its biogenesis seems most probable by the addition of a C_5 unit, such as dimethylallyl pyrophosphate, to C-7 of a monoterpenoid intermediate, bisdehydromenthofuran, so that this may be the only example which is not biosynthesized *via* farnesyl pyrophosphate.



furoventalene (250)
Gorgonia ventalina[145]



pinguisone (251)[146,147]
Aneura pinguis[146]

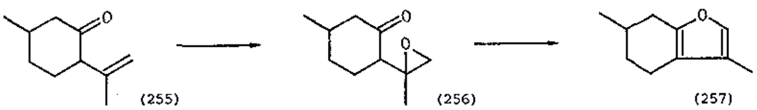
Another abnormal example is pinguisone (251) from an aneuraceous liverwort[146,147] whose constitution was firmly established by X-ray analysis. Since this substance is claimed to be sesquiterpenoid in origin, its biosynthesis is of great interest because its carbon skeleton does not show obedience to the isoprene rule.

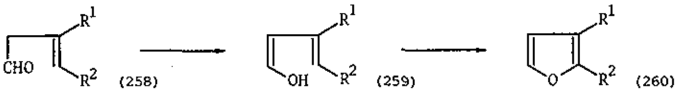
2.13 Biogenesis of furan

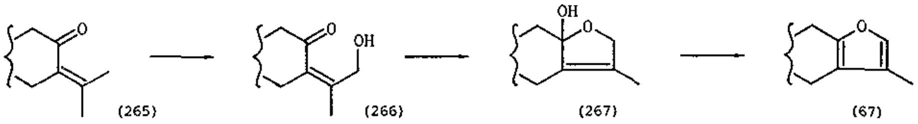
The intermediacy of farnesyl pyrophosphate in the biogenesis of almost all of the furanosesquiterpenoids can be accepted. Experimental support for this view came initially from tracer studies which showed that [2-^{14}C]mevalonate was incorporated into ipomeamarone (18) by *C. fimbriata*-infected sweet potato, though the rate of utilization was much less than that of [2-^{14}C]acetate.[148] Later, incorporation of [2-^{14}C]farnesol into ipomeamarone (18) under similar conditions was proved.[149] There are other examples in which incorporation has been experimentally verified: [2-^{14}C]acetate into 4-hydroxymyoporone (12) by *C. fimbriata*-infected sweet potato,[33] [4,5-$^{14}C_2$]mevalonic acid into neothiobinupharidine (50) in *Nuphar luteum*,[150] and [1,5-$^{14}C_2$]cadaverine into neothiobinupharidine (50) (*via* acetate ?) in *Nuphar luteum*.[150]

Given the proposition that almost all the furanosesquiterpenoids are derived from farnesol, the question first arises as to whether or not several furan-forming reactions can take place in the normal sesquiterpenoid pathway, leading independently to different groups of furanosesquiterpenoids, or whether or not a unique step from some point on the pathway leads to a primary furanoid intermediate which is the common progenitor of all the other furanosesquiterpenoids. Comparison of the structures of the furanosesquiterpenoids eliminates the possibility of a common origin, and suggests the presence of at least several intermediates from which the respective groups of furanosesquiterpenoids may be generated.

The first postulate concerning the biogenesis of the furan ring was made by Fritel[151] and it involved a β,γ-epoxy ketone (256) as an immediate intermediate for a furan (257). In fact, this was shown to be true for the *in vitro* synthesis of furan.[151] This pathway, however, seems unlikely, since it requires isomerization of α,β-unsaturated ketones to give rare or unknown isomers (β,γ-unsaturated ketones (255)) prior to epoxide formation and cyclization. Secondly, Naves[152] suggested an alternative scheme from β,γ-unsaturated aldehydes (258) *via* enols (259) for the biogenesis of furans (260) which, however, is not mechanistically related to well-known reactions either *in vitro* or *in vivo*. A much better proposal was presented by Sutherland[19] who alleged a biogenetic pathway from allyl alcohols (*e.g.*, farnesol (261)) for furans (264). An alternative possibility that farnesol, for example, may undergo allylic hydroxylation to yield dendrolasin (1) was considered unlikely due to the apparent rarity of the postulated intermediates. The validity of







1,4-dicarbonyl compounds as starting meterials for *in vitro* synthesis of furan has been well known (p. 855). In summary, it appears that substances which have a moiety equivalent to the 1,4-dicarbonyl system play the part of intermediates for furan formation. The Sutherland's hydroxy-enal (262), whose oxygenated part-structure is equivalent to a 1,4-dicarbonyl moiety, may be a most probable intermediate for furan. Biosynthesis of furanodiene (67), which is the simplest representative of β-methyl-α',β'-disubstituted furans and may be the common intermediate for a number of analogs, should be initiated by an allylic oxidation at C-12 of germacrone (265) to give 12-oxygermacrone (266). Although the Fritel's β,γ-epoxy-ketone (256), also equivalent to a 1,4-dicarbonyl, seems to be unlikely as an intermediate as it is, their postulate appears now not to be irrelevant.

Once this unique enzymatic furan-forming step is acquired, the eleboration of a profusion of furanosesquiterpenoid classes represents only a secondary (common) phenomenon, which need not necessarily be specific to furanosesquiterpenoid biosynthesis.

The important question now becomes—at what stage of the furanosesquiterpenoid pathway does the formation of the furan ring take place? A difinite answer to this question, however, cannot be obtained. Thus, although Naya[153] thought that certain furanoeremophilanes are converted from fukinone (268), an alternative scheme from germacrone (265) to eremophilanes *via* furanodiene (67) but not *via* fukinone (268) cannot be excluded. In this review, formation of the furan ring is tentatively assumed to occur in the earlier phases of the terpenoid biosynthesis.

Besides the furanosesquiterpenoids, there is a huge group of sesquiterpenoids containing a γ-lactone moiety in Nature. Some substances from both groups are closely related biogenetically and, in fact, even those having the same carbon skeleton and the same substitution pattern are found in certain organisms. Another question arises as to whether the furan analogs and the lactone analogs originate from their respective intermediates by parallel routes or whether they are formed sequentially, one from another. Šorm[21] postulated that furanoeremophilanes are direct progenitors of the corresponding eremophilanolides on the basis of the observations that *in vitro* autoxidation of the furan gives rise to two types of α,β-unsaturated γ-lactones (*cf.* 269 and 270) (p. 849). Although the final evidence is not yet available, circumstantial evidence suggests that in most cases, the furans and the lactones are developed in parallel rather than generated sequentially. In any case, the biosynthesis of the freelingynes (36-37) is of particular interest because the enzyme build-up of the furan ring and the lactone ring is highly selective.

3. Properties and reactions

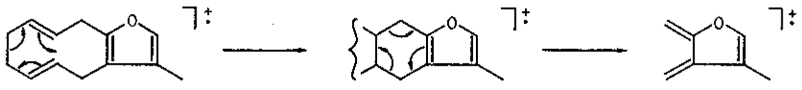
3.1 Color reactions

The presence of the furan moiety is readily detected by several simple and reasonably specific color reactions: pine stick reaction, vanillin-hydrochloric acid reaction, Ehrlich reaction, Liebermann-Burchard reaction, Shear reaction, and Carr-Price reaction.

3.2 Spectral properties

3.2.1 Mass spectroscopy

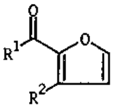
Mass spectroscopy has been very valuable as a source of structure information because of the characteristic way in which furan moieties break down on ionization. In particular, mass spectra of the analogs of the A and A' types serve usefully for determining the terminal end of the molecule whose retro-Diels-Alder type cleavage always gives the strongest peak corresponding to B.



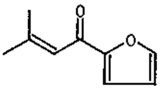
A A' B

3.2.2 UV spectroscopy

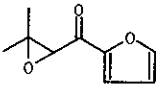
The UV spectra of furan derivatives provide evidence on conjugation. Unconjugated furans have a K-band of high intensity in the region 200-225 nm, the absorption properties being affected by the nature of alkyl substituents. The UV maxima of the furoyl derivatives having a variety of structural features are shown below. It may be noticeable that in a certain report[102] some



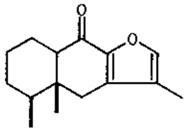
275 nm



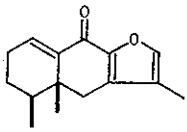
295 nm



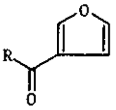
282 nm



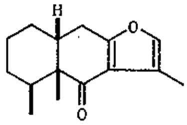
280-282 nm



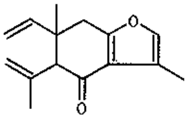
302-303 nm



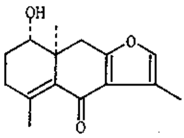
250-255 nm



269 nm



270-272 nm



261,292 nm

eremophilan-9-ones are recorded to exhibit the UV maxima at considerable shorter wave-length regions (10α(H)-3α-acyloxy-9-one 269 nm, 10β(H)-6β-acyloxy-9-one 269 nm, 10β(H)-4α-hydroxy-6β-acyloxy-9-one 269 nm, and 1(10)-en-9-one 291 nm).

Of particular interest is the UV absorption of the furanogermacranes having a 6-carbonyl which is greatly dependent upon the conformation of the molecule. Thus, the UV maxima (223, 248 nm) for isofuranodienone (69), in which the furoyl system is much distorted, show hypsochromic shift relative to those (241, 269 nm) for furanodienone (68), in which the furoyl system is almost planer.[75] Zederone (78), in which the distortion of the 6-carbonyl and the furan ring is small, shows a UV maximum at 284 nm[87] as expected from the values of ligularone (192)[122] and curcolone (96).[98]

3.2.3 IR spectroscopy

In the IR spectra of furan derivatives, there is a characteristic band at 1510-1590 cm^{-1} regardless of the nature of alkyl substituents and of the presence of conjugation. A band at 1010-1040 cm^{-1} originating from an ether linkage is also observable. Although at an earlier period, IR spectroscopy was useful in structure elucidation,[154] its rôle is much diminished at present.

3.2.4 ^1H NMR spectroscopy

Major advances in the furanosesquiterpenoid chemistry have been made in the increase use of physical methods in particular ^1H NMR spectroscopy. The spectra permit readily recognition of the furan nucleus by the signals for α- and β-hydrogens. Thus, the α-hydrogens of the furan ring appear as characteristic downfield signals at 6.9-8.1 ppm, while the β-hydrogens occur at 6.1-6.8 ppm from TMS in CCl_4 or $CDCl_3$. A change of solvent from CCl_4 to $CDCl_3$ causes an upfield shift of 0.04 and 0.17 ppm for α- and β-hydrogens, respectively.[155] In open chain derivatives, chemical shifts of the furan hydrogens can be calculated using parameters for substituted furans, from which the substitution pattern in the furan ring can be deduced.[156,157] The shift of the β-methyl hydrogens lies at 1.8-2.5 ppm. In the spectra of the sesquiterpenoids in which the furan is fused with an alipahtic ring (such as the furano-

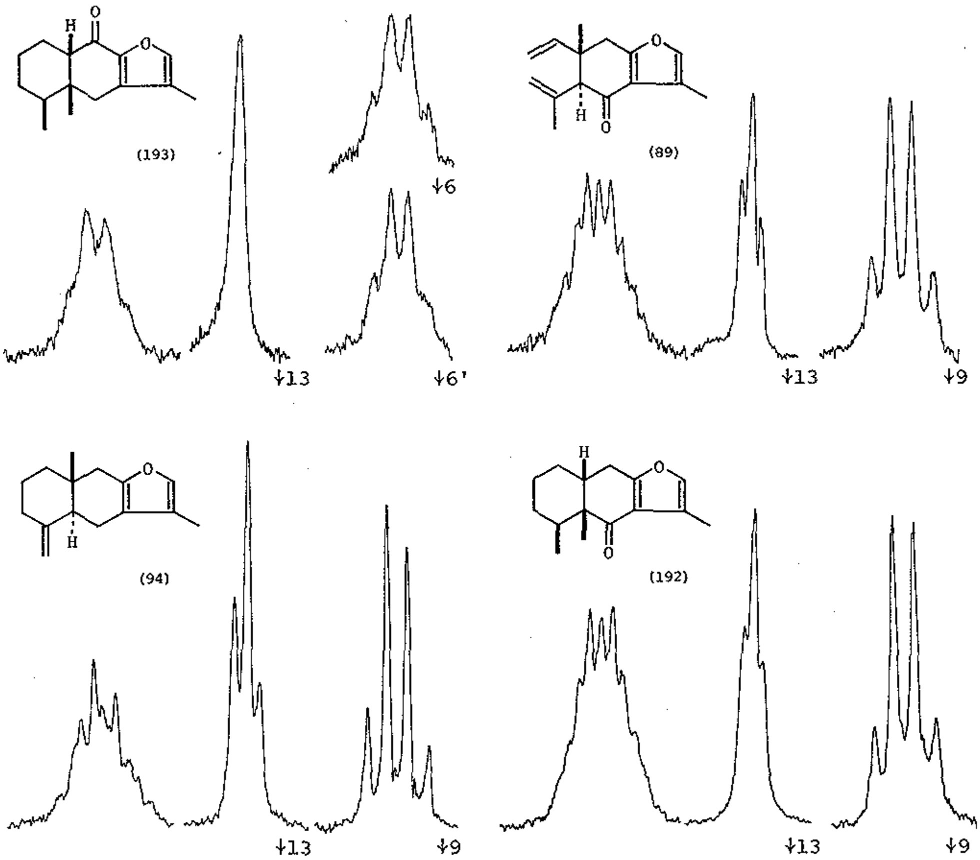
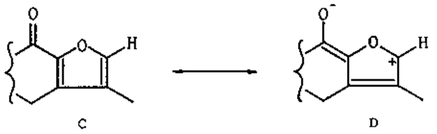


Fig. 1. ^{1}*H NMR signals of C-12 hydrogens of furanosesquiterpenoids*
(Abbreviation: ↓6=irradiated at C-6 hydrogen)

germacranes and their descendants), the shift of the C-12 (α) hydrogen is displaced towards lower field in the case where a carbonyl is located at C-9 (α') (7.2-7.4 ppm) as compared with the cases where no carbonyl is situated at C-9 (6.8-7.1 ppm) or a carbonyl is present at C-6 (β') (~7.1 ppm). This observation has been rationalized by the contribution of the tautomeric modi*fication in a 9-oxo derivative as in D.*[118]

In the above mentioned trisubstituted furans, since the α(C-12)-hydrogen is long-range coupled not only with the β(C-13)-methyl hydrogens but also with



the α'(C-9)-hydrogens and even β'(C-6)-hydrogens, the α-hydrogen signal is more or less complexed when the α'- and/or β'-carbons are not quaternary (Fig. 1).

NOE has proved to be an effective tool for signal assignments (a typical example being shown in Fig. 2) and stereochemical and conformational studies, particularly in the germacrane analogs of flexible features. A strong NOE is always observed between the α-hydrogen and the β-methyl hydrogens, the increase in intensity being over 20%.

Benzene-induced solvent effects provided evidence for relative locations

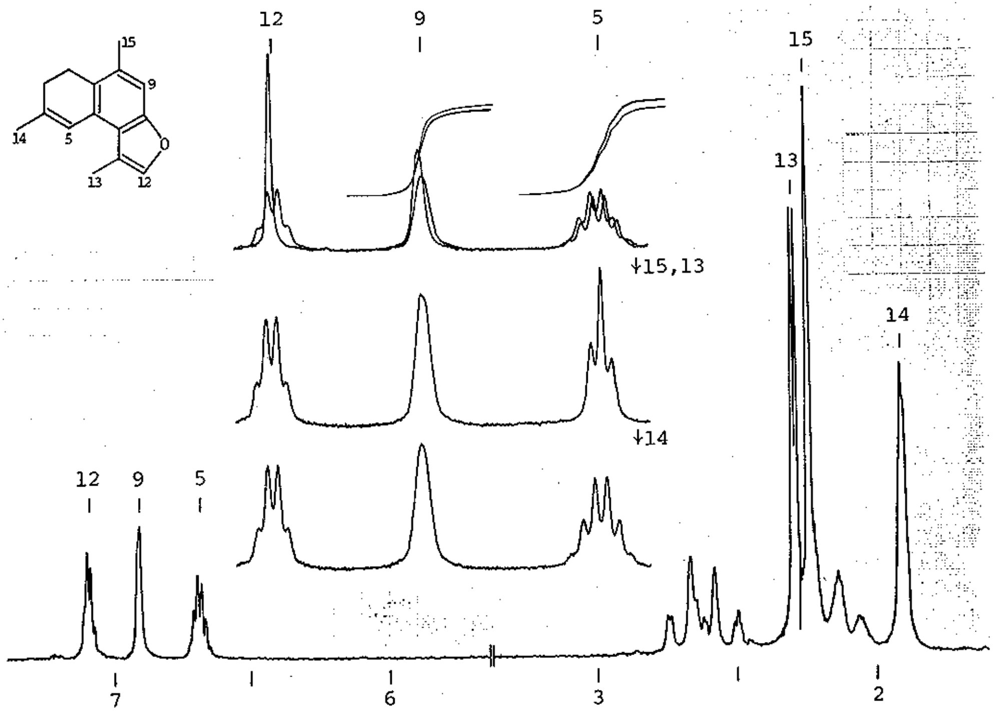


Fig. 2. ^{1}H NMR spectrum of pyrocurzerenone (65) (100 MHz, CCl_4)

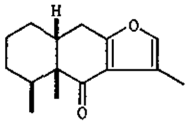
of hydrogens in some furyl ketones (*e.g.*, 68, 69[75]). However, the solvent shift study appeared unfruitful for deducing the relative orientation of the hydrogens in certain furoyl systems.[92,75]

3.2.5 ^{13}C NMR spectroscopy

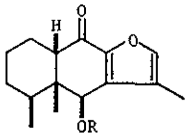
Collections of ^{13}C NMR data on furanosesquiterpenoids are still limited. In some members (245, 251),[139,147] the α-carbons of the furan ring appear at 141-153 ppm and the β-carbons occur at 109-128 ppm from TMS. In the future, ^{13}C NMR spectroscopy will certainly be a useful technique for structure examination of furanosesquiterpenoids.

3.2.6 ORD and CD spectroscopy

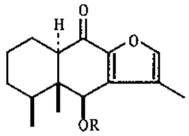
The ORD and CD data of furyl ketones have been accumulated mainly on the eremophilane derivatives, which are shown below. The difference in sign between the 10β(H)-6-one and the 10β-hydroxy-6-one is interpreted as meaning that they have a non-steroidal-like and a steroidal-like preferred conformation, respectively.[158] The Cotton effect at 240-250 nm shown by 9-ones is apparently sensitive to the character of the 6-substitution.[108]



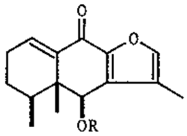
+ (327 nm)



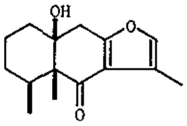
+ (280-285 nm)
- (240-250 nm)



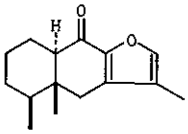
- (280-290 nm)
- (239-250 nm)



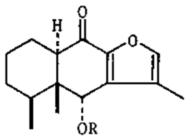
- (240-250 nm)



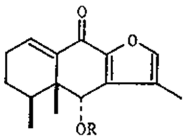
- (327.5 nm)



- (280 nm)



- (280-295 nm)
+ (240-250 nm)



+ (240-250 nm)

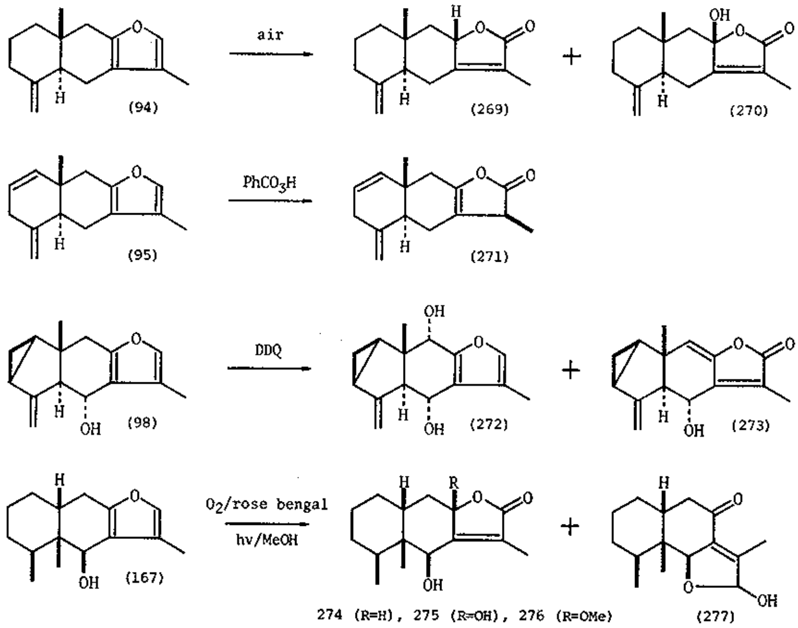
The stereochemistry and the conformation of zederone (78) were deduced from its CD curve showing the strong negative and strong positive Cotton effects for the R and CT transitions, respectively, in an α-epoxy-α',β'-enone system, a fact which indicates that the epoxide and the furan are situated in the octant diagram in the far lower-right and the far upper-left octants, respectively.[87]

The variable temperature CD spectroscopy is quite informative about the flexibility of molecules. For example, the CD curve of zederone (78) exhibited no significant change over the range +60—-192°, demonstrating that it is highly rigid.[87]

3.3 Reactions in which furan is involved

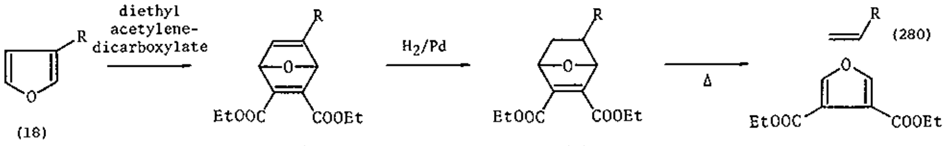
Catalytic hydrogenation of furan yields the corresponding tetrahydrofuran (*via* dihydrofuran in some case[101]) but ring opening to give ketones and subsequently alcohols can also occur. The actual product distribution depends upon the conditions of the reaction and the catalyst employed.

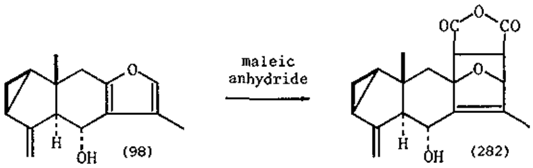
The furan ring readily undergoes autoxidation under normal atmospheric conditions (*e.g.*, 94→269, 270[13]), Pt-catalyzed autoxidation, peracid oxidation (*e.g.*, 95→271[97]), DDQ oxidation (*e.g.*, 98→272, 273[14]), yielding a variety of



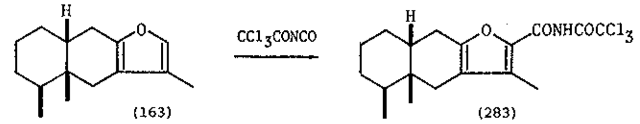
unsaturated γ-lactones. Photosensitized oxidation of petasalbin (167) afforded similar unsaturated γ-lactones (274-276) along with a rearranged hemiketal (277).[159]

The furan ring is the ideal diene for the Diels-Alder reaction and readily reacts with dienophiles to form adducts (*e.g.*, 278,[160] 282[161]), which has been used not only for identifying the furan ring but also for determining the substitution pattern of the furan nucleus in combination with Alder-Rickert degradation (18→278→279→280, 281[160]).

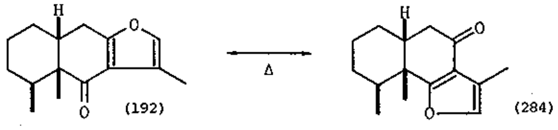




An electrophilic substitution reaction of furan at the α-position has been reported on furanoeremophilane (163→283).[162]

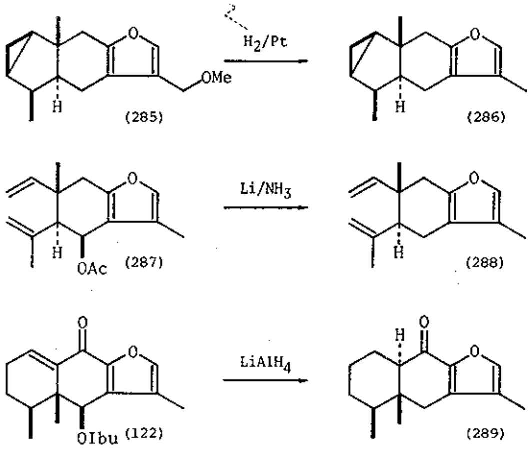


The last example of reactions in which the furan ring is involved is the reconstraction of the furan ring fusion (192→284) which is conducted simply by heat and is an equilibrium reaction.[163]

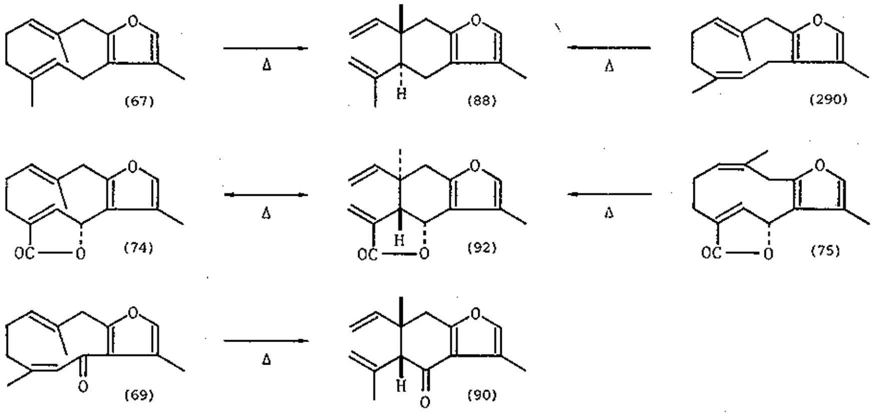


3.4 Reactions in which furan is participates

The first example is removal of an oxygen function located at the allylic position with respect to the furan ring by reduction (*e.g.*, 285→286,[91] 287→288,[75] 122→289[21]).

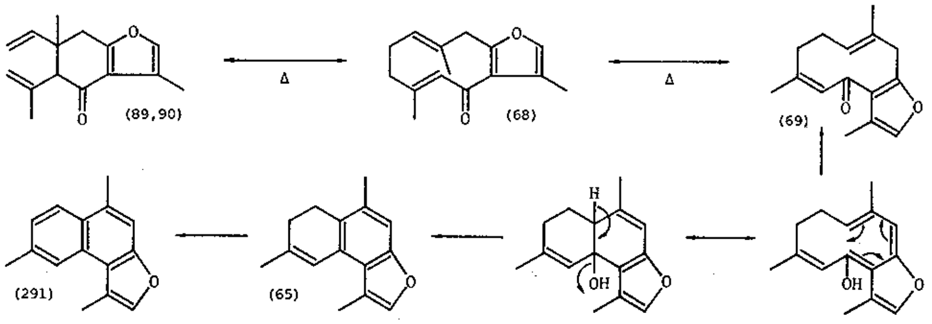


The reaction in which furan plays some rôle is claimed to be Cope rearrangement of furanogermacra-1(10),4-dienes. Germacra-1(10)E,4E-diene congeners in general adopt preferred conformation involving a cross orientation of the two confronting double bonds and consequently with C-14 and C-15 *syn* (p. 828). Therefore, Cope rearrangement of the furanogermacra-1(10)E,4E-dienes



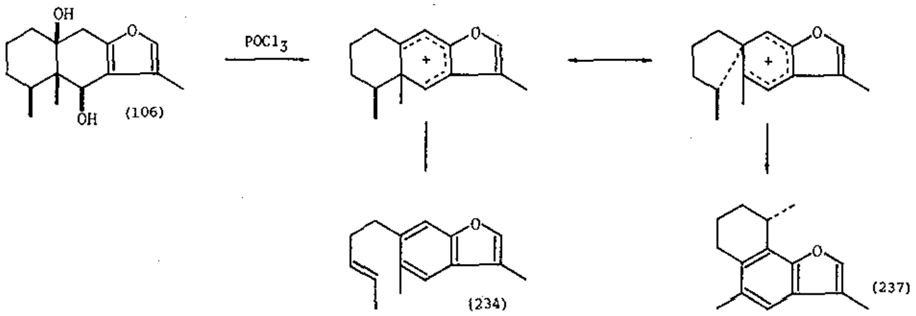
(*e.g.*, 67, 74) affords *trans*-1,2-divinyl derivatives (88, 92),[71,164] as is predicted by the Woodward-Hoffmann rule.[165] The absolute configuration of the rearrangement products is defined by the conformation of the starting dienes.[166] Although a furanoelemane derivative is usually the exclusive product at equilibrium, in the case of isolinderalactone (92) (or litsealactone (76)) having the γ-lactone system between C-14 and C-6, the reverse Cope reaction also easily occurred to generate a 2:3 mixture of linderalactone (74) and isolinderalactone (92) (or that of litsealactone (76) and isolitsealactone). This has been rationalized by the difference of the preferred conformation of the furanoelemanes.[167] The 1(10)E,4Z-diene (*e.g.*, 290) and the 1(10)Z,4E-diene (*e.g.*, 75) undergo abnormal Cope rearrangement to yield *trans*-1,2-divinyl products (88 and 92, respectively) rather than the expected *cis*-1,2-divinyl derivatives.[168] On the basis of results from model compounds, it was first assumed that the presence of the methyls on the double bonds has an important effect on the stereospecificity of this rearrangement[168] but later postulated that the abnormality is due to the effect of the furan ring.[169] However, since Cope rearrangement of isofuranodienone (69), a 1(10)E,4Z-diene, gives the normal *cis*-1,2-divinyl product (90),[75] more detailed examination on the stereospecificity of the reaction is required.

Thermal rearrangement of the curzerenones (89, 90) is also noteworthy. Heating the curzerenones (89, 90) at 240° caused their slow interconversion by

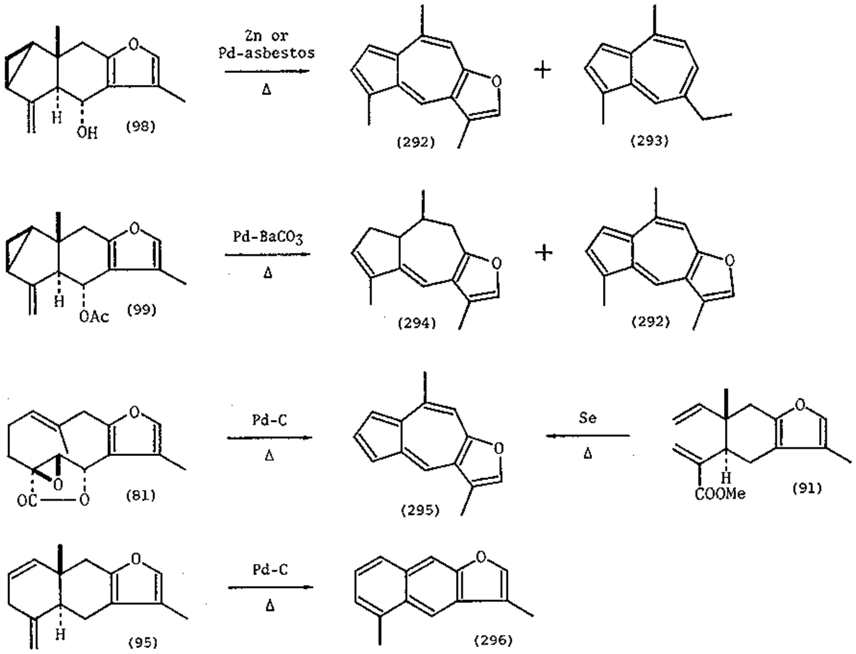


double Cope rearrangement and partial keto-enol tautomerization. Heating at 270° led to pyrocurzerenone (65) which is considered to proceed through the mechanism shown in the scheme (89,90→65). Heating at 350° generated pyrocurzerenone (65) and furanocadalene (291) in 1:4 together with dihydropyrocurzerenone (66, racemic) and hydrogen.[75]

Transformation of furanoeremophilane-6β,10β-diol (106) to farfugin A and B (237 and 234), with the probable mechanism indicated below,[170] is of interest since it could be a chemical analogy for the biosynthesis of the latter natural products (234, 237).



The last example to be specified is the dehydrogenation of the furanosesquiterpenoids. This was first performed on lindenenol (98) furnishing linderazulene (292) and chamazulene (293),[171] which gave rise to considerable confusion in the structure investigation of lindenenol for a long time. Dehydrogenation of lindenenyl acetate (99) and its relatives was subjected to detailed examination. Thus, on heating with Pd-BaCO$_3$ lindenenyl acetate (99) gave a reaction mixture from which linderazulene (292) and an optically active proazulene (294) were isolated along with lindenene and anhydrolindenenol.[20] Possible routes for this reaction have been postulated.[20] Other types of dehydrogenation may be exemplified (81→295,[172] 91→295,[93] 95→296[97]). A special case is that simple heating of pyrocurzerenone (65) resulted in dehydrogenation to give furanocadalene (291) during which the liberated hydrogen was



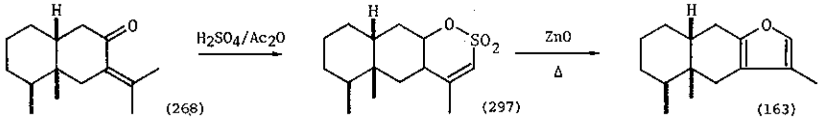
either transformed to another molecule of the starting material (65) yielding dihydropyrocurzerenone (66, racemic) or released as free hydrogen gas.[75]

4. Synthesis

Due to the great structural variety of the furanosesquiterpenoids, their synthesis has attracted the attention of many workers. These will be classified according to the methods employed for the synthesis of the furan ring.

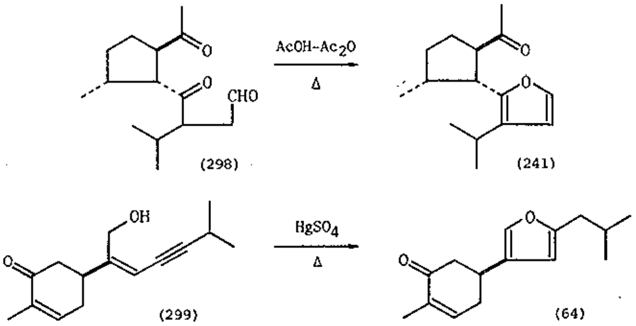
Methods using furan derivatives as intermediates have been reported for the synthesis of the furanofarnesanes, including dendrolasin (1),[173,174] neotorreyol (3),[173,174] torreyal (4),[173] ipomeamarone (18),[175,176] epingaione (21),[175,176] dihydrofreelingyne (36),[41] freelingyne (37),[177] sesquirosefuran (38),[178,179] nupharamine (40),[180] and castoramine (49).[56] The synthetic routes involve condensation of a suitable furan derivative with an appropriate acyclic fragment and, if needed, subsequent lengthening of the chain and modification of functional groups.

The procedure, which utilizes the reaction of pulegone with sulfuric acid in acetic anhydride to give pulegenol sulfuric acid cyclo-ester, pyrolyzed to menthofuran, was applied for the preparation of furanoeremophilane (163).[181]

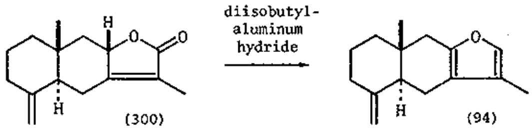


Application of this method for the synthesis of furanodiene (67) from germacrone (265) was unsuccessful, however, since the opposing dienes are attacked by acid to give a complex mixture.

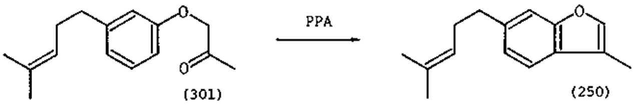
The method using 1,4-dicarbonyl intermediates has become well established for the synthesis of furan nuclei. Furanosesquiterpenoids synthesized by this route include furopelargone A and B (241 and 242).[182] A modified method was developed for the synthesis of bilobanone (64).[183]



Reduction of an α,β-unsaturated-γ-lactone with the selective reducing agent diisobutylaluminum hydride to a furan has been exploited to synthesize atractylon (94)[184] and lindesterene (95).[185]



The route to benzofurans *via* polyphosphoric acid-catalyzed cyclization of phenoxyacetones has been applied for the synthesis of pyrocurzerenone (65),[186] farfugin A (237),[187] and furoventalene (250).[188]



5. Biological activities

Although the chemistry of the furanosesquiterpenoids has been the subject of numerous investigations, only a small number of reports have been made of the biological activities of some furanosesquiterpenoids which, furthermore, are mostly confined to the farnesane derivatives.

Dendrolasin (1) is a kind of aggressive substances and/or alarm pheromones excreted, together with formic acid, by the madibular gland of a *Lasius* ant which exhibits remarkable toxicity against ants but not against other insects.

The norsesquiterpenoids (14-17) derived from 4-hydroxymyoporone are potent pulmonary toxins in laboratory animals and appear to be the causative substances in the atypical interstitial pneumonia occurring in cattle which have ingested mold-damaged sweet potatoes.[189]

Ipomeamarone (18) and ipomeamaronol (19) along with their relatives, batatic acid (13), ipomeanine (14), and furan-β-carboxylic acid, are phytoalexins which arises from pathological infections of sweet potatoes by several pathogens (the parasitic fungi, *C. fimbriata*, *H. mompa*, *F. oxysporum*, and *T. basicola*, as well as insects and $HgCl_2$) and show the antimicrobial activity at the infected region where they are biosynthesized.[190-192,39] Ipomeamarone (18) is also toxic to higher animals[193] and exhibits the anthelmintic activity.[194] Ngaione (20), epingaione (21), dehydrongaione (23), and dehydroepingaione (24) when dosed intraperitoneally to mice resulted in the so-called ngaione liver pathology (the ip LD_{50}: 0.198 g/kg for ngaione, 0.215 g/kg for epingaione).[39] A mixture of dehydrongaione (23) and dehydroepingaione (24) is toxic to sheep and mice, causing the symptoms characteristic of *Myoporum* poisoning.[39] Intraperitoneal administration to mice of deisopropylngaione (28), a probable catabolite of ngaione, brings about liver and kidney degeneration.[39]

Despite the fact that myoporone (10) is biologically inactive, its probable descendants, dehydromyodesmone (59) and dehydroisomyodesmone (60), are toxic to mice and cause the pathology typical of ngaione poisoning, the ip LD_{50} values being 0.234 g/kg and 0.19 g/kg, respectively.[64]

Concerning desoxynupharidine (46), the following pharmacological actions have been described. Thus, it produced a slight increase in respiratory rate, carotid pressure, and tonus of the small intestine. The amplitude of the heart contractions was considerably increased. It augmented the effects of adrenaline.[195] From its pharmacological actions and behaviors on the electroencephalograms, it is expected to show cholinergic effects.[196]

Investigations reported in the literature on the biological activities of furanosesquiterpenoids other than the furanofarnesanes are very limited. Thus, tetradymol (103) is a moderate hepatotoxin in mice, rats, gerbils, rabbits, guinea pigs, and sheep, the po LD_{50} value being 0.25 g/kg in mice.[101] Pinguisone (251) is an antifeeding repellent for the larvae of *Prodenia litura*.[197]

The constituents of *Lindera strychnifolia* have been examined for the pharmacological actions and as the result it was found that none of them showed significant activity except for linderane (81) which caused the increase of the adrenal gland weight and exhibited the anti-inflammatory effect in formalin-induced edema.[198]

Whether not nor castoramine (49) from a beaver, dehydrodendrolasin (2) and pleraplysillin (61) from a marine sponge, and furoventalene (250) from a sea fan play some physiological rôles in the respective animals or to organisms interacting with them is open to question.

Further biological activities of the furanosesquiterpenoids await discovery by future investigations.

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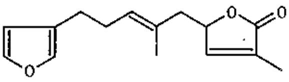
7. Addendum

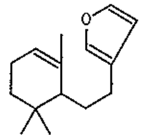
Quite recently, a number of novel furanosesquiterpenoids were isolated, among which some are unique. Those are a companion of the farnesane skeleton (297) from a composite plant, *Eremophila freelingii*,[199] farnesiferol B type derivatives (298, 299) and their variously cyclized catabolites possessing new skeletons (300-306) from a sponge, *Disidea pallescens*,[200-202] 3 germacranes (307-309) and 1 elemane derivative (310) from a aristolochiaceous plant, *Asarum caulescens*,[203] the 4th example of the eudesmane group (311) from a composite plant, thought to be a hybrid belonging to *Atractylodes*,[203] several modified eremophilane congeners (312-316) from composite plants, *Cacalia* spp.,[205] and a series of pinguisane and norpinguisane analogs (317-320) from a liverwort, *Pollera vernicosa*.[206]

It was also revealed that *Cacalia delphiniifolia* contains cacalol (225) and maturinone (232), and *C. hastata* var. *tanakae* contains O-methyldehydrocacalol (227), O-methylcacaldienol (228), and cacalonol (231).[205]

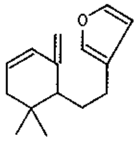
An alternative synthesis of dendrolasin (1) was achieved.[207]



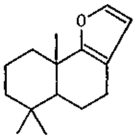
freelingnite (297)
Eremophila freelingii[199]



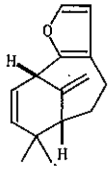
pallescensin-1 (298)
Disidea pallescens[200]



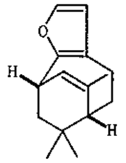
pallescensin-2 (299)
Disidea pallescens[200]



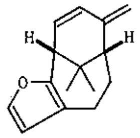
pallescensin A (300)[201]
Disidea pallescens[200]



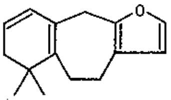
pallescensin D (301)[201]
Disidea pallescens[200]



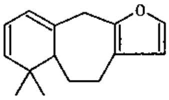
pallescensin B (302)[201]
Disidea pallescens[200]



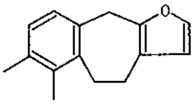
pallescensin C (303)[201]
Disidea pallescens[200]



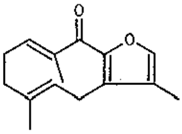
pallescensin F (304)[202]
Disidea pallescens[200]



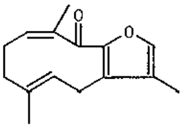
pallescensin G (305)[202]
Disidea pallescens[200]



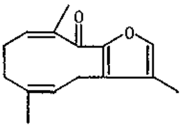
pallescensin E (306)[202]
Disidea pallescens[200]



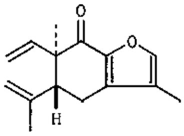
furanocaulesone-A (307)
Asarum caulescens[203]



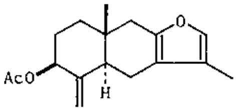
furanocaulesone-B (308)
Asarum caulescens[203]



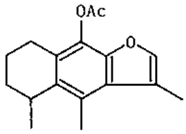
furanocaulesone-C (309)
Asarum caulescens[203]



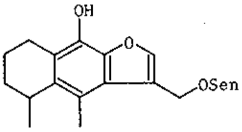
(+)-aoifuranone (310)
Asarum caulescens[203]



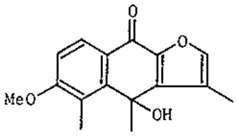
acetoxyatractylon (311)
Atractylodes lancea var.
chinensis × *A. japonica*[204]



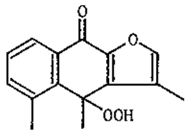
cacalol acetate (312)
Cacalia delphiniifolia[205]



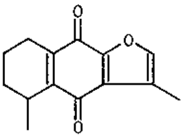
senecioyloxycacalol (313)
Cacalia delphiniifolia[205]



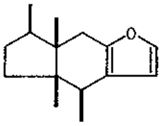
6-methoxycacalonol (314)
Cacalia hastata var.
tanakae[205]



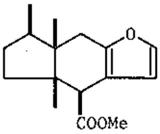
peroxycacalonol (315)
Cacalia hastata var.
tanakae[205]



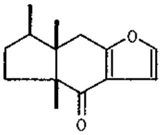
tatrahydromaturinone
(316)
Cacalia delphiniifolia[205]



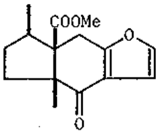
deoxopinguisone (317)
Ptilidium ciliare,
Pollera vernicosa[206]



(318)
Pollera vernicosa[206]



(319)
Pollera vernicosa[206]



(320)
Pollera vernicosa[206]

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