A SURVEY OF 6,9-EPOXYCYCLODECA[*b*]FURAN SESQUITERPENES

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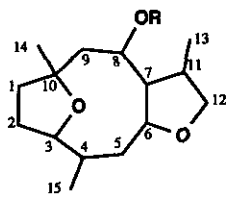
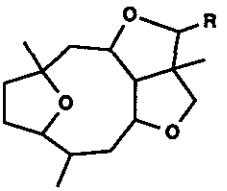
Abstract - The source, structure, and biological activities of the many known 6,9-epoxycyclodeca[*b*]furan natural products are compiled herein for ready reference.

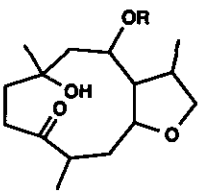
During the past twenty years, many compounds containing the heterotricyclic framework depicted in **A** have been isolated from natural product sources. Two characteristic structural features include oxygenation at C-8 and the presence of an alkyl substituent at C-10. Throughout this review, the natural product numbering shown in **A** is used rather than that associated with the systematic index name employed by Chemical Abstracts. To be inclusive, the eremantholides have been incorporated into the survey, as this class of compounds has the skeleton shown in **B**. Beyond the scope of our consideration, however, is the multitude of sesquiterpenes that are chemically equivalent to the products from either hydrolysis or elimination at C(3)-O and C(10)-O, respectively, leading to ring-opened compounds of the type illustrated in **C** and **D**.



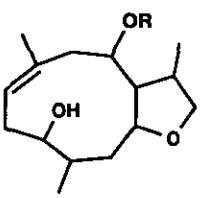
A



B



C



D

The aim of this survey is to collate the numerous references to natural products in this area and to depict, where possible, the correct structural features including stereochemistry. Relevantly, the structures shown in this review are not always the same as those found in the original papers because of subsequent corrections. Others have been modified because the original assignments were based on the stereochemistry of previously isolated products whose formulations have since been revised.

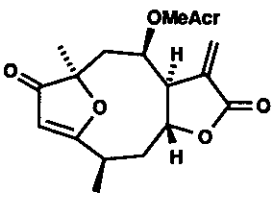
The source, biological activity, and relevant synthetic work are also included.

1. 3(2*H*)-Furanones: 8β-Series

In 1970, de Vivar and co-workers isolated the first natural 6,9-epoxycyclodeca[*b*]furan and called this compound zexbrevin (**1**).[2] Although this team derived the correct gross structure, they incorrectly assigned two of the stereochemical centers.[2,3] One of these, the ester side chain, was soon revised to the now accepted 8β-configuration,[4,5] but it was not until 1983 before some doubt was expressed about the 4-methyl stereochemistry.[6] Subsequent X-ray single crystal structure analysis on zexbrevin derivatives, including tetrahydro-[7] and phototetrahydrozexbrevin,[8,9] clearly showed a 4β-methyl group to be present. Dismayingly, however, the authors of these diffraction papers continued to depict zexbrevin and related compounds with a 4α-methyl substituent. This confusion surrounding zexbrevin and several allied structures was eventually clarified by Herz and co-workers.[10]

Additionally, there were some doubts concerning the source of zexbrevin. After careful morphological re-examination of the original plant material, it was found to be *Viguiera greggii*[11] and not *Zexmenia brevifolia* as previously reported.[2]

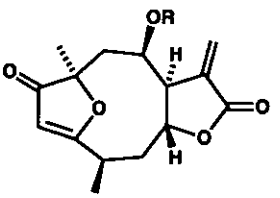
(1) Zexbrevin from:
Calea zacatechichi [12,13]
Viguiera greggii [2,11,14]



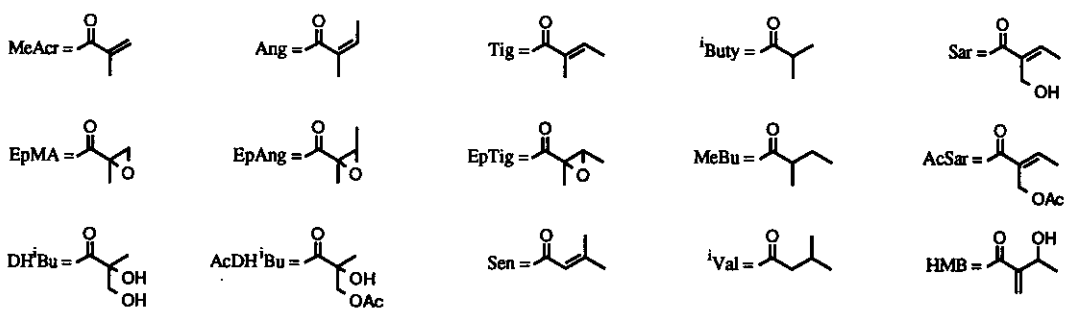
Two related compounds (**2,3**) were isolated more recently and these are simply different ester derivatives of the parent system.[12,15,16] In fact, such ester variations are a common feature in this series of natural products as reflected in the sequel.* Although there have been no biological studies on zexbrevin (**1**) or its ester analogues **2** and **3**, it has been reported that 11α,13,2',3'-tetrahydrozexbrevin is responsible for potentiation of the immune response in certain tests.[17]

(2) R = Ang, Ladibranolide from:
Trichogoniopsis morii [16,18]
Viguiera ladibractate [15]

(3) R = Tig from:
Calea zacatechichi [12]



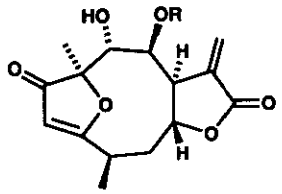
*) The structures of the ester side chains are as follows:



Several 9-hydroxylated (**4-11**), 5,9-bishydroxylated (**12,13**), and 15-hydroxylated (**14**) derivatives of zexbrevin have been isolated from various sources. Although some errors were initially made in the 4-methyl stereochemistry, subsequent X-ray analysis of two of these compounds (**5,6**) has helped to clarify the situation.[6,19] Some of these structures have still been incorrectly assigned a 4α-methyl group by comparison to zexbrevin. However, they all likely possess a 4β-methyl substituent as indicated by the nmr data.

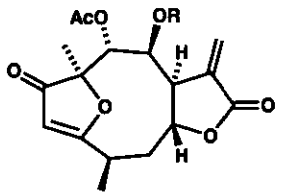
(4) R = MeAcr from:
Calea ternifolia [19]

(5) R = Ang from:
Calea leptocephala [20]
Calea ternifolia [19]



(6) R = MeAcr, 9α-Acetoxyzexbrevin from:
Calea ternifolia [21]

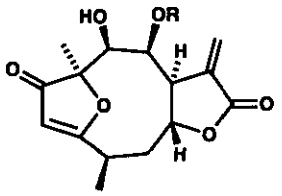
(7) R = Ang from:
Calea leptocephala [20]



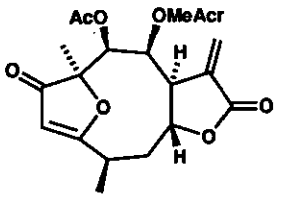
(8) R = MeAcr from:
Trichogonia prancii [22]

(9) R = Ang from:
Trichogonia villosa [23]

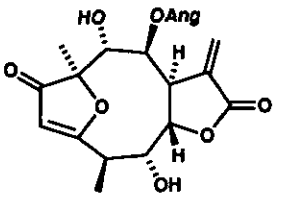
(10) R = Tig from:
Bejaranoa balansae [24]



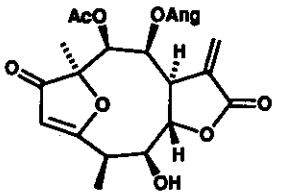
(11) from:
Trichogonia prancii [22]



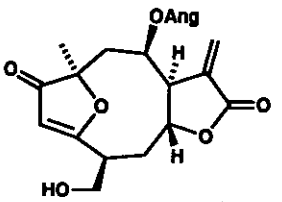
(12) from:
Calea hispida [25]



(13) from:
Trichogonia salviaefolia [22,26]

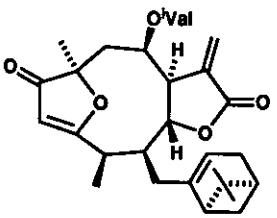


(14) from:
Viguiera linearis [27]

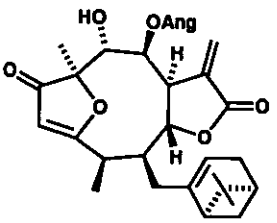


A 5β-myrtenyl derivative of zexbrevin (**15**) is also known, along with a 9α-hydroxy (**16**) and an 11α,13-epoxy analogue (**17**). Several similar α-epoxides have been isolated, although they contain a 4,5-double bond (see below).

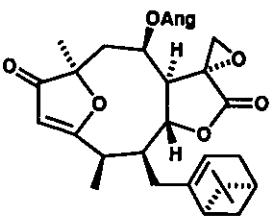
(15) from:
Calea rupicola [28]



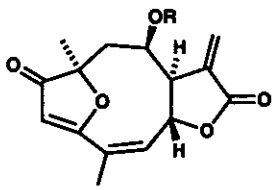
(16) from:
Calea hispida [25]



(17) from:
Calea mortii [29]
Calea pilosa [29]



Shortly after the isolation of zexbrevin (**1**), two unsaturated analogues were discovered and called calaxin (**18**) and ciliarin (**19**).[30] By correlation with zexbrevin, these new compounds were assigned 8α stereochemistry, but this error was also subsequently corrected.[4,5,31] Several ester analogues (**20-24**) and the free alcohol (**25**, known as atripliciolide[32]) have now been isolated.



(18) R = MeAcr, Calaxin from:
Calea pilosa [29]
Calea new species[33]
Helianthus ciliaris [30]
Isocarpha atriplicifolia [32]

(19) R = ^{i}Buty, Ciliarin from:
Calea rupicola [28]
Helianthopsis sagasteguii [34]
Helianthopsis utcubambensis [35]
Helianthus ciliaris [30]
Isocarpha atriplicifolia [32]
Viguiera acutifolia [34]
Viguiera pazensis [36]

(20) R = Ang from:
Calea angusta [37]
Calea divaricata [38]
Calea hymenolepis [39]
Calea lantanoides [40]
Calea pilosa [29]
Calea teucrifolia [33]
Calea villosa [41]
Calea new species [33]
Disynaphia halimifolia [42]
Helianthopsis bishopii [35]
Helianthopsis sagasteguii [34]
Helianthopsis stuebelii [34]
Helianthus nuttallii [43]
Trichogoniopsis morii [16]
Viguiera acutifolia [34]
Viguiera linearis [27]
Viguiera oblongifolia [44]
Viguiera sylvatica [45]

(21) R = Tig from:
Bejaranoa semistriata [46]
Calea angusta [37]
Calea mortii [29]
Calea pilosa [29]
Chresta sphaerocephala [47]
Helianthopsis stuebelii [34]
Isocarpha atriplicifolia [32]
Viguiera acutifolia [34]

(22) R = MeBu from:
Calea angusta [37]
Calea rupicola [28]
Helianthopsis bishopii [35]
Helianthopsis sagasteguii [34]
Helianthopsis stuebelii [34]
Helianthopsis utcubambensis [35]
Helianthus lehmannii [48]
Viguiera acutifolia [34]
Viguiera oblongifolia [44]

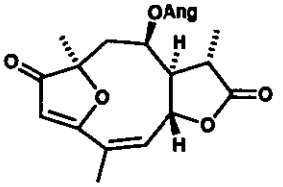
(23) R = ^{i}Val from:
Calea rupicola [28]
Isocarpha atriplicifolia [32]

(24) R = AcSar from:
Bejaranoa semistriata [46]

(25) R = H, Atripliciolide from:
Eremanthus glomerulatus [47]

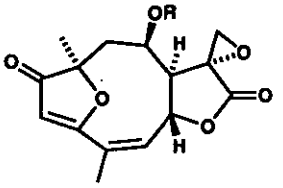
There are many known structural variations of the calaxin / ciliarin system. These include an 11β,13-dihydro (**26**) and some 11α,13-epoxy derivatives (**27-30**), as well as two chlorohydrins (**31,32**) and several 4,15-dehydro congeners (**33-36**). Another unusual compound (**37**) is formally the product of a Diels-Alder reaction with a monoterpene residue. Note that epoxides (**27-30**) were initially assigned with β-stereochemistry.[29,33,37,41] A subsequent X-ray analysis of a 9-hydroxy derivative[21] suggests that they are indeed all 11α,13-epoxides.[19,38] This in turn raises questions concerning the stereochemical assignment to the chlorohydrins (**31**) and (**32**).

(26) from:
Viguiera sylvatica [45]



(27) R = MeAcr from:
Calea pilosa [29]
Calea ternifolia [19]
Calea new species [33]

(28) R = Ang from:
Calea divaricata [38]
Calea mortii [29]
Calea pilosa [29]
Calea ternifolia [19]
Calea villosa [41]
Calea new species [33]

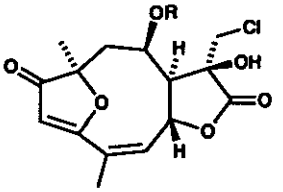


(29) R = Tig from:
Calea mortii [29]
Calea pilosa [29]

(30) R = MeBu from:
Calea angusta [37]

(31) R = Ang from:
Calea mortii [29]
Calea pilosa [29]

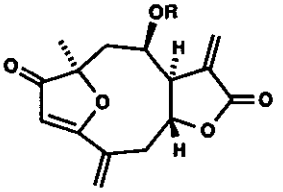
(32) R = Tig from:
Calea mortii [29]



(33) R = MeAcr from:
Helianthus tuberosus [49]

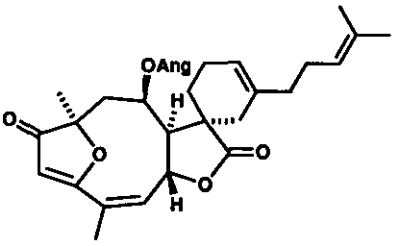
(34) R = ^{i}Buty from:
Helianthus tuberosus [49]

(35) R = Ang from:
Helianthus tuberosus [49]



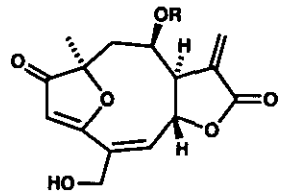
(36) R = Tig from:
Helianthus schweinitzii [50]
Helianthus tuberosus [49]

(37) from:
Calea hymenolepis [39]



Other derivatives include the numerous 9-hydroxy, 15-hydroxy, and 9,15-dihydroxy analogues (**38-59**) along with their 11α,13-epoxides and chlorohydrins (**60-69**). Many of these compounds, such as the cytotoxic substance budlein A (**40**),[51] have been found in a large variety of species. Note that, as for the previous epoxides (**27-30**), the epoxides here (**60-67**) were initially assigned with β-stereochemistry.[29,33,37,41] Once again, however, a later X-ray

(38) R = MeAcr from:
Calea zacatechichi [12]
Helianthus tuberosus [49]
Viguiera eriophora [53]
Viguiera linearis [27]
Viguiera pinnatilobata [54]



(39) R = ^{i}Buty, Viguiepinin from:
Helianthopsis microphylla [35]
Helianthopsis sagasteguii [34]
Helianthopsis stuebelii [34]
Helianthopsis utcubambensis [35]
Helianthus tuberosus [49]
Viguiera acutifolia [34]
Viguiera pazensis [36]
Viguiera pinnatilobata [54,55]

(40) R = Ang, Budlein A from:
Ayapana elata [56]
Calea divaricata [38]
Calea hispida [25]
Calea hymenolepis [39]
Calea villosa [41]
Helianthopsis sagasteguii [34]
Helianthopsis stuebelii [34]
Helianthus angustifolius [57]
Helianthus hirsutus [58]
Helianthus petiolaris [58]
Helianthus schweinitzii [50]
Helianthus tuberosus [49]
Viguiera acutifolia [34]
Viguiera augustifloria [59]
Viguiera buddleiaeformis [60]
Viguiera cordata [36]
Viguiera excelsa [61]
Viguiera hypochlora [53]
Viguiera linearis [27]
Viguiera quinqueradiata [62]
Viguiera schultzii [53]
Viguiera sylvatica [45]

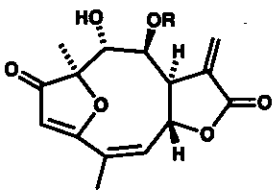
(41) R = Tig from:
Calea zacatechichi [12]
Helianthopsis sagasteguii [34]
Helianthus tuberosus [49]
Viguiera linearis [27]

(42) R = MeBu from:
Calea rupicola [28]
Helianthopsis microphylla [35]
Helianthopsis sagasteguii [34]
Helianthopsis utcubambensis [35]
Helianthus debilis [63]
Helianthus strumosus [58]
Helianthus tuberosus [49]
Viguiera acutifolia [34]
Viguiera hemsleyana [53]
Viguiera procumbens [27]

(43) R = ^{i}Val from:
Helianthus grosseserratus [52]

analysis of the 9-hydroxy derivative (**62**)[21] suggests that they are all 11α,13-epoxides.[19,21,38] As before, this raises doubts about the stereochemical assignment to the chlorohydrins (**31, 32, 68** and **69**).

Finally, three isoatripiciolides (**70-72**) have been isolated. The initially assigned 5α-hydroxy stereochemistry[39,52] was later corrected[50] to the now accepted β-isomer.[27]

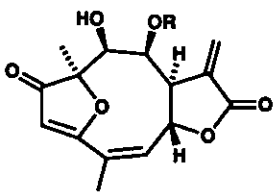


(44) R = MeAcr from:
Calea pilosa [29]
Calea ternifolia [21]
Calea urticifolia [64]

(45) R = ^{i}Buty, Lobatin-B from:
Calea rupicola [28]
Neurolaena lobata [65]

(46) R = Ang from:
Calea angusta [37]
Calea hispida [25]
Calea pilosa [29]

(47) R = Tig from:
Calea angusta [37]
Calea pilosa [29]



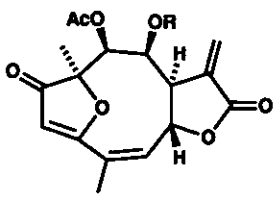
(48) R = MeAcr from:
Trichogonia prancii [22,23]

(49) R = Ang from:
Trichogonia villosa [22,23]

(50) R = Tig from:
Conocliniopsis prasiifolia [66]

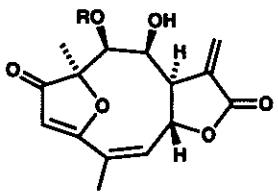
(51) R = Sar, Conoprasiolide from:
Conocliniopsis prasiifolia [66,67]

(52) R = AcSar from:
Conocliniopsis prasiifolia [66,67]
Lourteigia ballotaefolia [68]
Trichogonia scottmorii [23]



(53) R = MeAcr from:
Trichogonia prancii [23]

(54) R = AcSar from:
Conocliniopsis prasiifolia [66]



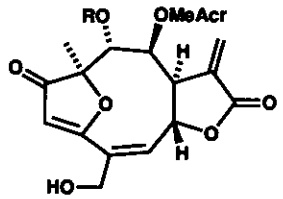
(55) R = MeAcr from:
Trichogonia prancii [23]

(56) R = AcSar from:
Lourteigia ballotaefolia [68]

(57) R = Ang from:
Calea urticifolia [64]

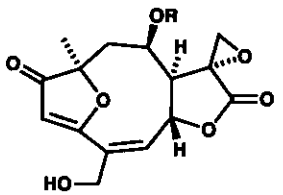
(58) R = ^{l}Val from:
Calea urticifolia [64]

(59) R = Sen from:
Calea urticifolia [64]



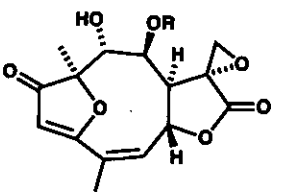
(60) R = MeAcr from:
Calea ternifolia [19]

(61) R = Ang from:
Calea divaricata [38]
Calea ternifolia [19]
Calea villosa [41]



(62) R = MeAcr from:
Calea crocinervosa [69]
Calea nelsonii [70]
Calea pilosa [29]
Calea ternifolia [21]
Calea zacatechichi [71]

(63) R = Ang from:
Calea pilosa [29]
Calea ternifolia [19]

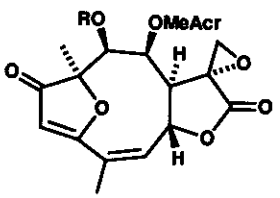


(64) R = Tig from:
Calea pilosa [29]

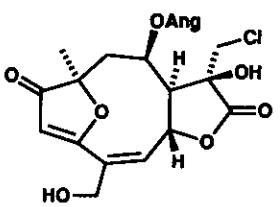
(65) R = MeBu from:
Calea angusta [37]

(66) R = H from:
Trichogonia prancii [22,23]

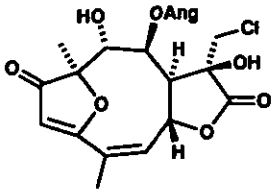
(67) R = Ac from:
Trichogonia prancii [23]



(68) from:
Calea villosa [41]

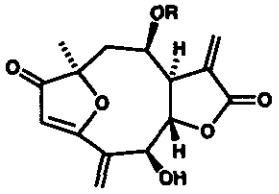


(69) from:
Calea pilosa [29]



(70) **R = ^{i}Buty**
Helianthopsis sagasteguii [34]
Helianthus tuberosus [49]
Viguiera acutifolia [34]

(71) **R = Ang** from:
Calea hymenolepis [39]
Calea linearis [27]
Viguiera cordata [36]



(72) **R = ^{i}Val** from:
Helianthus grosseserratus [52]

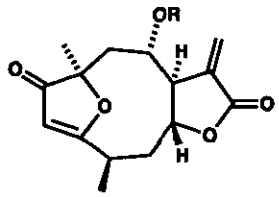
2. 3(2*H*)-Furanones: 8α-Series

Soon after the stereochemistry of the ester side chain in zexbrevin and related compounds was corrected,[4,5] it was realized that there was a companion 8α-series of sesquiterpenes (**73-99**).[72] However, at the time of their discovery, this second group of compounds was assigned with a 6α-ester sidechain and lactone ring closure to the 8α-position.[73] This error was corrected after an X-ray crystal structure determination was carried out on goyazensolide (**92**).[72] Note that this meant that the structure of centratherin, supposedly an 8α-lactone,[74] was in fact the same as that determined X-ray crystallographically[75] for lychnophorolide A (**93**).[72]

(73) **R = MeAcr** from:
Eremanthus bicolor [76]

(74) **R = Ang** from:
Alcantara ekmaniana [77]
Lychnophora crispa [78]
Piptolepis ericoides [79]

(75) **R = Tig** from:
Eremanthus bicolor [76]
Lychnophora crispa [78]

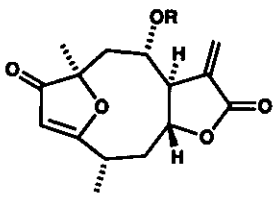


Other structural assignment errors include the configuration of the methyl group at C-4 in molecules with a saturated C4-C5 bond. The initially isolated compounds of this type (**73** and **75**)[76] were wrongly depicted with a 4α-methyl substituent although this was subsequently corrected.[10,80] However, the 4β-methyl isomeric compounds are also known (**76-79**).[10]

(76) R = MeAcr from:
Eremanthus goyazensis [10]
Eremanthus seidelii [10]

(77) R = EpMA from:
Eremanthus goyazensis [10]
Eremanthus seidelii [10]

(78) R = DH^{i}Bu from:
Eremanthus goyazensis [10]
Eremanthus seidelii [10]

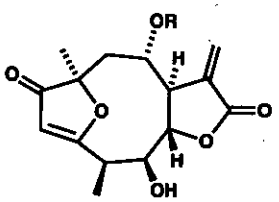


(79) R = AcDH^{i}Bu from:
Eremanthus seidelii [10]

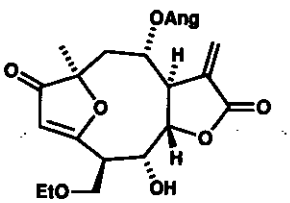
(80) R = MeAcr from:
Eremanthus crotonoides [47]

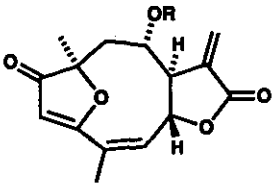
(81) R = ^{i}Buty from:
Eremanthus crotonoides [47]

(82) R = EpAng from:
Eremanthus glomerulatus [47]



(83) from:
Centratherum punctatum [80]





(84) R = MeAcr, 15-Deoxygoyazensolide from:
Alcantara ekmaniana [77]
Eremanthus bicolor [76]
Eremanthus crotonoides [47]
Lychnophora bahiensis [78]
Lychnophora blanchetti [81]
Vanillosmopsis erythropappa [10,82]

(85) R = ^{i}Buty from:
Eremanthus crotonoides [47]

(86) R = Ang, Lychnopholide from:
Alcantara ekmaniana [77]
Eremanthus crotonoides [47]
Lychnophora bahiensis [78]
Lychnophora blanchetti [81]
Lychnophora columnaris [83]
Lychnophora crispa [78]
Lychnophora hakeaefolia [84]
Lychnophora sellowii [78]
Lychnophora uniflora [85]
Piptolepis leptospermoides [86]
Proteopsis argentea [87]
Vanillosmopsis erythropappa [10]

(87) R = Tig from:
Eremanthus bicolor [76]
Eremanthus crotonoides [47]
Lychnophora crispa [78]

(88) R = MeBu from:
Piptolepis leptospermoides [86]

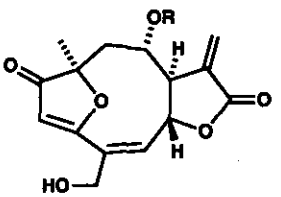
(89) R = EpAng from:
Alcantara ekmaniana [77]
Eremanthus glomerulatus [47]
Proteopsis argentea [87]

(90) R = Sar from:
Eremanthus glomerulatus [47]

(91) R = HMB from:
Eremanthus glomerulatus [47]

(92) R = MeAcr, Goyazensolide from:
Centratherum punctatum [88]
Eremanthus goyazensis [10,73]
Eremanthus mollis [89]
Lychnophora passerina [85]
Oliganthes discolor [90]
Vanillosmopsis brasiliensis [79]
Vanillosmopsis erythropappa [10]
Vanillosmopsis pohlii [79]

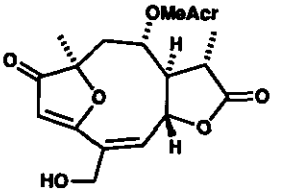
(93) R = Ang, Centratherin (Lychnophorolide A) from:
Centratherum punctatum [74,80,88]
Eremanthus mollis [89]
Lychnophora affinis [75]
Lychnophora bahiensis [78]
Lychnophora sellowii [78]
Oliganthes discolor [90]



(94) R = Tig, Lychnophorolide B from:
Eremanthus glomerulatus [47]
Lychnophora affinis [75]
Oliganthes discolor [90]

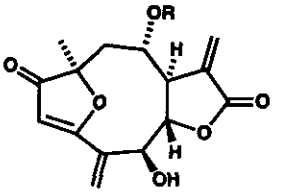
(95) R = EpMa from:
Centratherum punctatum [88]

(96) from:
Eremanthus goyazensis [10]

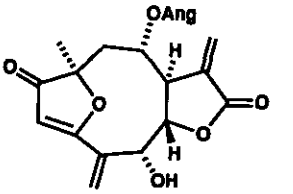


(97) R = MeAcr from:
Vanillosmopsis brasiliensis [79]
Vanillosmopsis pohlii [79]

(98) R = Ang from:
Lychnophora sellowii [78]



(99) Isocentratherin from:
Centratherum punctatum [80,88,91,92]
Lychnophora sellowii [78]



3. 3(2*H*)-Furanones: the Eremantholides

Related to the 8α-series are the eremantholides (**100-118**). These compounds are formally the result of an intramolecular cyclization from the 11-position to the ester carbonyl in an 11,13-dihydro derivative (eg., **96**), resulting in formation of the hemiketal unit. The stereochemistry in three of these molecules (**101,104,114**) has been determined unambiguously by X-ray crystallography.[10,93,94] However, a commonplace error occurred in the assignment of the 4-methyl group in molecules with a saturated C4-C5 bond. Again, the initially isolated compounds of this type (**115-118**)[76,78] were wrongly depicted with a 4α-methyl substituent. This situation was subsequently rectified.[10,80] The 4β-methyl isomeric compounds (**112-114**) were isolated at a later date.[10]

Note that several ketal derivatives, *viz.* the 16-*O*-methyl ethers and the 16-*O*-ethyl ethers of **102** and **108**, have also been found, but these are probably artifacts of the isolation procedure.[75,95]

Some synthetic methodology for the preparation of 2,5-disubstituted 3(2*H*)-furanones has been published.[96-98] This work was aimed mainly at the synthesis of eremantholides and includes the synthesis of eremantholide A (**101**),[97] although it is perhaps applicable to all of the 6,9-epoxycyclodeca[*b*]furans.

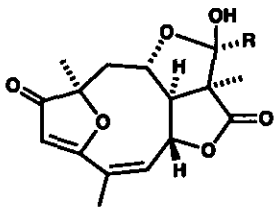
It has been proposed that some of these eremantholides may have possible uses in anti-cancer therapy.[93] In addition, epoxide (**105**) has been shown to be an allergic sensitizing agent.[99]

(100) Eremantholide C (MeAcr) from:
Eremanthus bicolor [76]
Eremanthus crotonoides [47]
Eremanthus elaeagnus [93,94]
Eremanthus glomerulatus [95]
Eremanthus goyazensis [10]
Lychnophora affinis [75]
Lychnophora uniflora [85]
Piptolepis leptospermoides [86]

(101) Eremantholide A (ⁱButy) from:
Centratherum punctatum [81]
Eremanthus bicolor [76]
Eremanthus crotonoides [47]
Eremanthus elaeagnus [93,94]
Eremanthus incanus [76,100]

(102) (Ang) from:
Eremanthus glomerulatus [47,95]
Lychnophora affinis [75]
Lychnophora bahiensis [78]
Lychnophora crispa [78]
Lychnophora uniflora [85]
Proteopsis argentea [87]
Piptolepis leptospermoides [86]

(103) (Tig) from:
Eremanthus bicolor [76]
Eremanthus crotonoides [47]



(100) R = 
(101) R = 
(102) R = 
(103) R = 
(104) R = 
(105) R = 
(106) R = 

(104) Eremantholide B (MeBu) from:
Eremanthus elaeagnus [93]
Eremanthus incanus [100]

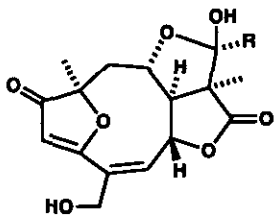
(105) (EpAng) from:
Eremanthus glomerulatus [47]
Proteopsis argentea [87]

(106) (EpTig) from:
Eremanthus glomerulatus [47]

(107) (MeAcr) from:
Eremanthus glomerulatus [95]
Eremanthus goyazensis [10]
Piptolepis leptospermoides [86]

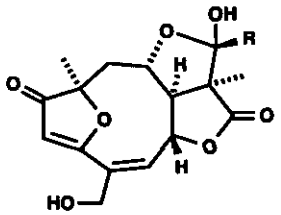
(108) (Ang) from:
Eremanthus glomerulatus [95]
Lychnophora affinis [75]
Lychnophora bahiensis [78]
Lychnophora crispa [78]

(109) (Tig) from:
Eremanthus glomerulatus [47]



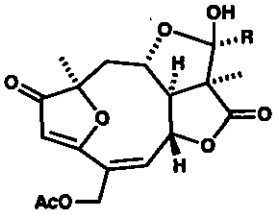
(107) R = 
(108) R = 
(109) R = 

(110) (Tig) from:
Vernonia poskeana [101]



(110) R = 

(111) (Ang) from:
Lychnophora bahiensis [78]

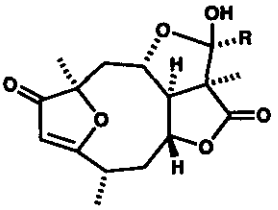


(111) R = 

(112) (MeAcr) from:
Eremanthus goyazensis [10]
Eremanthus seidelii [10]

(113) (^{i}Buty) from:
Eremanthus seidelii [10]

(114) (EpMA) from:
Eremanthus goyazensis [10]



(112) R = 

(114) R = 

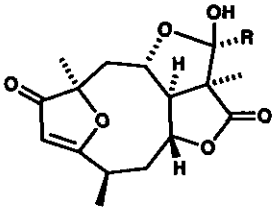
(113) R = 

(115) (MeAcr) from:
Eremanthus bicolor [76]

(116) (^{i}Buty) from:
Eremanthus bicolor [76]

(117) (Ang) from:
Lychnophora crispa [78]

(118) (Tig) from:
Eremanthus bicolor [76]



(115) R = 

(117) R = 

(116) R = 

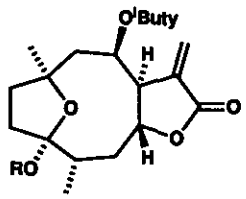
(118) R = 

4. Non 3(2*H*)-Furanone Systems.

Of the 6,9-epoxycyclodeca[*b*]furans that have now been isolated, there are many that do not possess the unsaturated 3(2*H*)-furanone nucleus (**119-172**). However, nearly all of these substances contain some alternative furan oxygenation such as the 3-hydroxy compound called tirotundin (**119**) and the corresponding 3-ethoxy derivative (**120**).[102] Errors originally committed in the stereochemical assignment to the ester sidechains were subsequently corrected after X-ray analysis of the ethyl ether (**120**).[103] Note that **120** and all other similar ketals (**122,128,132,138,157**) could be artifacts of either the isolation or the purification procedures.[102,104,105]

Several of these compounds have been shown to have interesting biological activities. In one study, niveusin B (**130**), its 3-*O*-ethyl derivative (**132**), and niveusin C (**146**) exhibited cytotoxic, antibacterial, antifungal, and DNA/RNA replication inhibitory properties.[105] Another compound, liatrin (**137**), shows significant tumor inhibitory activity against P-388 lymphocytic leukemia in mice.[106-108] The related ester analogue tagitinin F (**134**)[109] has also shown antileukemic activity, but tagitinin A (**140**), tagitinin B (**165**), and tirotundin (**119**, also called tagitinin D[110]) were inactive in the same screen.[111]

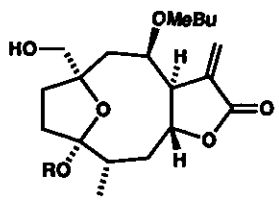
(119) R = H, Tirotundin from:
Helianthus niveus [112]
Tithonia diversifolia [5,111,113-116]
Tithonia rotundifolia [102]



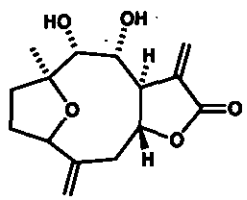
(120) R = Et from:
Blumea densiflora [117]
Tithonia rotundifolia [102]

(121) R = H, Tithonin from:
Tithonia rotundifolia [118]

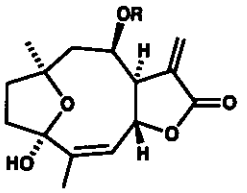
(122) R = Me from:
Tithonia rotundifolia [118]



(123) Tanargyrolide from:
Tanacetum argyrophyllum [119]



(124) R = ^{i}Buty, Diversifoline from:
Greenmaniella resinosa [104]
Syncretocarpus sericeus [120]
Tithonia diversifolia [121]
Viguiera dentata [122]

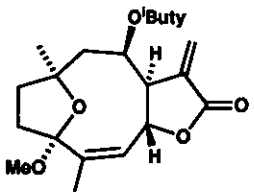


(125) R = Ang from:
Viguiera sylvatica [45]

(126) R = Tig from:
Viguiera gilliesii [123]

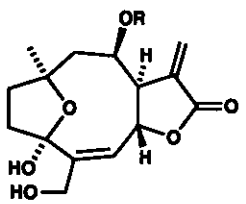
(127) R = MeBu from:
Viguiera gilliesii [123]

(128) from:
Greenmaniella resinosa [104]



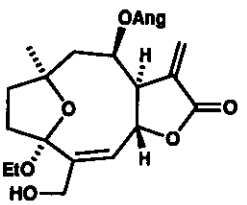
(129) R = ^{i}Buty, from:
Helianthopsis sagasteguii [34]

(130) R = Ang, Niveusin B from:
Helianthus annuus [124,125,126]
Helianthus niveus [127]



(131) R = MeBu from:
Viguiera deltoidea [128]
Viguiera gilliesii [123]
Viguiera procumbens [27]

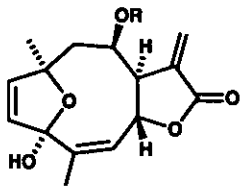
(132) from:
Helianthus annuus [124]



(133) R = MeAcr, 1,2-Dehydrozexbrevin B from:
Viguiera greggii [2,11,14]

(134) R = ^{i}Buty, Tagitinin F from:
Greenmaniella resinosa [104]
Tithonia diversifolia [5,111,113,115,116,129,130]

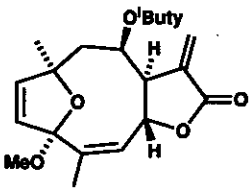
(135) R = Mebu from:
Greenmaniella resinosa [104]



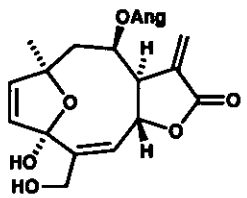
(136) R = EpAng from:
Viguiera microphylla [131]

(137) R = AcSar, Liatrin from:
Liatris chapmanii [106,108]

(138) from:
Greenmaniella resinosa [104]



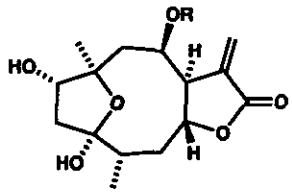
(139) from:
Helianthus annuus [132]



Several 2,4-bishydroxylated furan derivatives have been found and again errors were made in the initial structural assignment. Thus, tagitinin A (**140**),[133] zexbrevin B (**144**)[134] and orizabin (**145**)[134] were assigned 8α stereochemistry by correlation with zexbrevin (**1**), but suitable changes were made[4,5] and later confirmed for tagitinin A by X-ray analysis.[135] The fact that zexbrevin B and orizabin can be converted into calaxin (**18**) and ciliarin (**19**) by chromium trioxide oxidation is further evidence that these molecules are all stereochemically related.[134] Note that tagitinin A (**140**)[136] has been converted[4] into zexbrevin (**1**) (which has a 4β-methyl group), but it is postulated that the initial oxidation step results in epimerization at the 4-position.[10]

Interestingly, tagitinin A (**140**) has caterpillar feeding deterrent properties,[113] whereas niveusin C (**146**) is thought to be a growth regulator in plants.[137] This property of niveusin C may partially explain why intense light induces an increase in the synthesis of this compound.[138,139] A further biological effect observed for niveusin C (**146**) and for both the 1,2-anhydro- and the 1-*O*-methyl-4,5-dihydro derivatives of niveusin A (**139** and **143**, respectively) is their ability to induce allergic contact dermatitis.[140] Some of the other relatives such as zexbrevin B (**144**), orizabin (**145**), calaxin (**18**), and tagitinin F (**134**) exhibit cytotoxic properties[129,141] and the immune response to one of these, zexbrevin B, was tested *in vitro* and also *in vivo* using mice.[17]

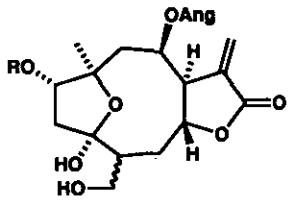
(140) R = ^{i}Buty, Tagitinin A from:
Blumea densiflora [117]
Helianthus niveus [112]
Tithonia diversifolia [5,111,113,116,129,133]



(141) R = MeBu, Viguilenin from:
Viguiera linearis [142]

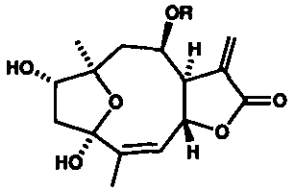
(142) R =H from:
Helianthus annuus [125,126]

(143) R = Me from:
Helianthus annuus [132]



(144) R = MeAcr, Zexbrevin B from:
Viguiera greggii [11,14,134,143]

(145) R = ^{i}Buty, Orizabin from:
Helianthus niveus [112]
Tithonia tubae-formis [134]

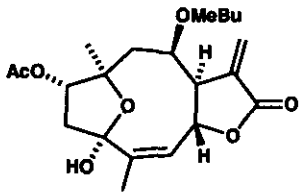


(146) R = Ang, Niveusin C from:
Helianthus annuus [124,126,132,137,144,145]
Helianthus niveus [127]
Helianthus maximiliani [146,147]
Melampodium camphoratum [148]
Viguiera sylvatica [45]

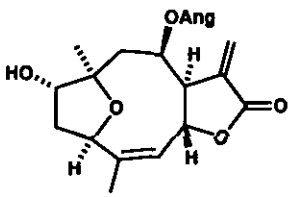
(147) R = MeBu from:
Helianthus heterophyllus [149]

(148) R = EpAng from:
Viguiera microphylla [131]

(149) from:
Calea oxylepsis [150]

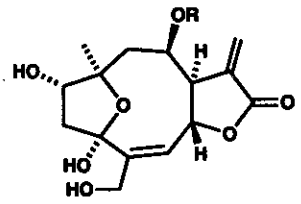


(150) from:
Helianthus maximiliani [146]



(151) R = ^{i}Buty, from:
Helianthopsis sagasteguii [34]

(152) R = Ang, Niveusin A from:
Helianthus gracilentus [151]
Helianthus niveus [127]
Viguiera sylvatica [45]

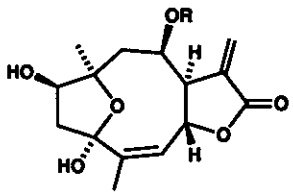


(153) R = MeBu,
17,18-dihydroNiveusin A from:
Helianthopsis sagasteguii [34]
Viguiera deltoidea [128]
Viguiera procumbens [27]

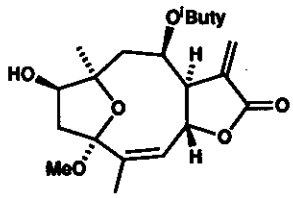
(154) R = ^{i}Buty from:
Greenmaniella resinosa [104]

(155) R = Ang from:
Viguiera cordata [36]

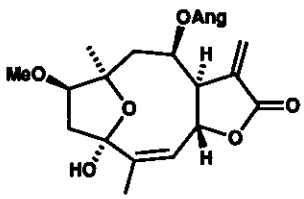
(156) R = MeBu from:
Calea oxylepsis [150]



(157) from:
Greenmaniella resinosa [104]

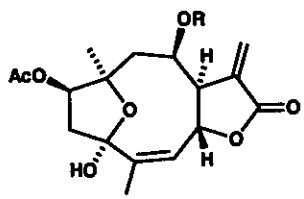


(158) from:
Viguiera sylvatica [45]



(159) R = MeAcr,
1α-Acetoxyzacatechinolide from:
Calea zacatechichi [152]

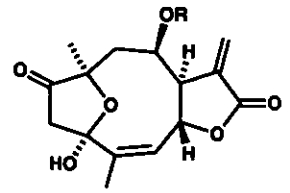
(160) R = Ang from:
Calea new species[33]



(161) R = MeAcr, 1-Oxozacatechinolide from:
Calea zacatechichi [152]

(162) R = Ang from:
Viguiera cordata [36]
Viguiera sylvatica [45]

(163) R = Tig from:
Helianthus tuberosus [49]

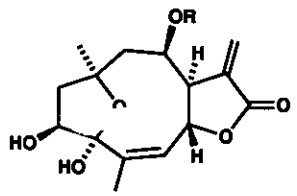


(164) R = MeBu from:
Calea oxylepsis [150]

Some 2,3-bishydroxylated furan derivatives are also known. The initial stereochemical assignment of the ester sidechain in tagitinin B (**165**)[153] and woodhousin (**168**)[154] was corrected after X-ray crystal analysis of the latter compound.[5,31]

(165) R = ^{i}Buty, Tagitinin B from:
Tithonia diversifolia [5,119,116,129]

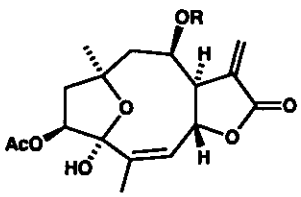
(167) R = Ang from:
Viguiera sylvatica [45]



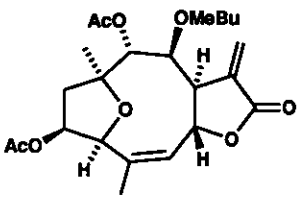
(168) R = ^{i}Buty, Woodhousin from:
Bahia woodhousei [154]
Picradeniopsis woodhousei [155]

(169) R = Tig from:
Picradeniopsis woodhousei [155]

(170) R = MeBu from:
Picradeniopsis woodhousei [155]
Brasilia sickii [156]

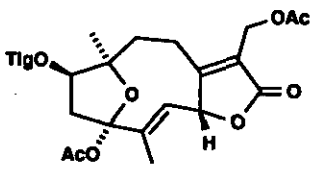


(171) from:
Brasilia sickii [156]



Finally, a compound lacking oxygenation at the C-8 position and containing a trans double bond has been isolated.[157] This sesquiterpene (**172**) possesses structural features related to the hirsutinolides.[157]

(172) from:
Chresta sphaerocephala [157]



5. Summary

In conclusion, there exists a wide variety of natural products that feature the 6,9-epoxycyclodeca[*b*]furan skeleton. Although these compounds exhibit a diverse degree of functionality, they nevertheless share a common pattern of substitution and stereochemistry.

The chemotaxonomy of these compounds and other sesquiterpene lactones is presently being surveyed in order to help in the classification of the genus *Calea*[158] and the genus *Helianthus*.[63,145,159]

Finally, stereocontrolled construction of the oxygen-bridged tricyclic framework of these systems has recently been accomplished.[160]

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