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The Chemical Constituents of the Soft Coral Species of the Genus *Lobophytum* (Alcyoniidae): A Review

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Abstract—The chemical constituents of the soft corals of *Lobophytum* are reviewed.
Keywords—medicinal plants · tumo

Marine natural products chemistry and the literature was reviewed initially (Scheuer, 1973) and later, the chemical and biological perspectives by experts during 1978-83 in a five volume series entitled "*Marine Natural Products : Chemical and Biological Perspectives*" (Scheuer, 1978-82) and more recently in seven volume series entitled "*Bio-organic Marine Chemistry*" (Scheuer, 1987-92). A monograph, "*Marine Natural Products Chemistry*" was published (Faulkner and Fenical, 1977). Regular reviews covering the literature except lipids and steroids have been provided in "*Natural Products Reports*" (Faulkner, 1995). A review on the chemistry and chemical ecology of Octocorals appeared (Coll, 1992). A few of well known scientists reviewed on different aspects of marine natural products in a recent issue of *Chemical Reviews* in 1993. The chemistry and biological activities of the secondary metabolites of the marine invertebrates were reviewed in two parts (Bhakuni, 1990, 1994a). Very recently a review on bioactive marine alkaloids has appeared (Bhakuni, 1994b).

Against this background of extensive literature coverage, reviews on the chemical constituents of marine organisms belonging to a particular family or even a genus become appropriate. The soft corals (Phylum: Coelenterata, Order: Alcyonacea) comprise of three families, Alcyoniidae, Nephtheidae and Xeniidae. The family Alcyoniidae comprises a large number of genera, of which *Lobophytum* is an important genus, common to most of the coral reefs. Till now, nearly eighteen species of this genus have been chemically examined by various research groups. This genus yielded a variety of novel structures, like sesquiterpenes, norsesquiterpenes, diterpenes, norditerpenes of lobane skeleton, diterpenes of cembrane, germacrane nucleus, prostaglandins, polyhydroxysteroids etc. Some of these secondary metabolites have shown significant biological activity. An attempt is, therefore, made to review the chemical constituents of the soft corals of *Lobophytum* genus in continuation of our similar and recent reviews on the chemical constituents of the soft corals of *Sinularia* (Anjaneyulu and Rao, 1995) and *Sarcophyton* (Anjaneyulu and Rao, 1996a).

Soft corals are often reported to contain significant quantities of secondary metabolites (1-5%) of their dry weight. *Lobophytum* species were reported to possess, occasionally upto 10% of a single compound (Coll, 1992). Such large amounts of secondary metabolites produced by these species presumably, play functional roles in the survival of Octocorals, *i.e.*, defence, competitive, reproduction and pheromonal roles. Seventy % of the diterpenoid metabolites are based on the cembrane nucleus and the rest are of germacrane nucleus (Coll, 1992).

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Chemical constituents from Lobophytum genus - Chinese research group (Su *et al.*, 1992) isolated a metabolite [1] from *L. caledonense* of the South China sea. Its structure and relative stereochemistry were confirmed by 2D NMR (1H-1H COSY and NOESY) spectral data. Later, the same group isolated its antipode, lobo calone [2] (Su *et al.*, 1993). Lobocalone was, however, erroneously reported as a new compound as it was identical with elemene isolated long ago from the gorgonian *Eunicea fusca* (Gopichand and Schmitz, 1978) and subsequently reported from an Indian soft coral of the genus *Lobophytum pauciflorum* (Kumar, 1992) and an unidentified species of the *Lobophytum* (Raju *et al.*, 1993). The Russian workers (Latyshew *et al.*, 1986) isolated eighteen fatty acids along with two prostaglandins PGA_1 & PGA_2 [4, 3] from *L. carnatum*. Gorgosterol [5], 24-methylcholestane-3β,5α,6β,25-tetrol-25-monoacetate [6] along with thirteen other steroids were isolated from *L. chevaleiri* (Li *et al.*, 1988). Lobophytamide-L_5 [7], lobophytamide-L_8 [8] (Li *et al.*, 1989a), chevaleiramide [9] (Li *et al.*, 1989b) and mesoerythritol [10] were reported later from the same species collected from South China. A new cembranolide [11], thymidine [12] and thymine [13] along with twelve other compounds have been subsequently reported from it (Li *et al.*, 1989c). An Australian specimen *L. crassospiculatum* yielded four cembranolides [14-17] (Ahond *et al.*, 1979) and their structures were determined on the basis of spectroscopic data and chemical conversions.

An epoxycembranolide, isolobophytolide [18] was isolated from *L. crassum* (Bowden *et al.*, 1977). A new cembranolide, crassolide [19] was reported later from it and its structure and stereochemistry was determined by spectral data and X-ray diffraction (Tursch *et al.*, 1978). Three new compounds [20-22] and epimers of 13-hydroxylobolides [23 & 24] were reported along with lobolide [25] from this species collected at Dahab, Gulf of Eilat (Kinamoni *et al.*, 1983). Three polyhydroxysteroids, (24R)-ergosta-7,22-dien-3β-5α,6β-triol [26], (24S)-ergostane-3β,5α,6β,7β-tetrol [27], (24S)-ergostane-3β,5α,6β,7β,15β-pentol [28] were reported from the same species collected at Rangat Island of A & N Islands (Kobayashi *et al.*, 1993). Two new 13-hydroxylobolides [23,24] and lobolide [25] were reported later from it, collected at Dahab, Gulf of Eilat (Kashman *et al.*, 1981).

A cembranolide diterpene, lobophytolide [29] was reported from the soft coral *L. cristagalli*, collected from Leti Island, Indonesia (Tursch *et al.*, 1974). Its structure was determined based on spectral data, chemical conversions and X-ray diffraction analysis. A Sri Lankan species of the same genus yielded two new cembranolides, (7E,11E,1R, 2S,3R,4R,14S)-14-acetoxy-3,4-epoxycembra-7,11,15-trien-17,2-olide [31] and the corresponding alcohol [30] (Bowden *et al.*, 1984). Their structures were established by spectroscopic analysis and the stereochemistry by X-ray studies.

Denticulatolide [32] (Uchio *et al.*, 1985), an ichthyotoxic cembranoid and its 7-epimer [33] (Uchio *et al.*, 1992) were isolated from the Okinawan soft coral *L. denticulatum*. Their structures were determined by spectral data, chemical evidence and X-ray crystallographic data. Four prostaglandins, (15S)-PGF_2-11-acetate methylester [34], 18-acetoxy derivative of PGF_2-11-acetate methylester [36] and their corresponding free carboxylic acid [35 & 37] were isolated from *L. depressum* of the Gulf of Eilat (Carmely *et al.*, 1980). Five new polyoxygeneted sterols; 5β,6β-epoxy-24ξ-methylcholestane-3β,22(R),25-triol [38], 22(R), 28-oxido-24ξ-methylcholest-5-en-3β,25,28-triol (lobophytosterol) [42], depressosterol [41] and epoxy derivatives of lobophytosterol and depressosterol [39 & 40] were subsequently reported from the Red sea variety of *L. depressum* (Carmely and Kashman, 1981). The structures were determined mainly on the basis of spectral data and chemical transforma-

tions.

The first non cembranoid diterpene, (3E,5E)-2-methyl-6-[(2'R,4a'S,8a'R)-4a'-methyl-8'-methylene-transperhydronaphthalene-2'-yl] hepta-3,5-dien-2-ol [43] and its 7-hydroxy derivative [43a] were isolated from an Australian soft coral *L. hedleyi* (Bowden *et al.*, 1978). Their structure determination was done by spectral data, degradation and chemical conversions into known compounds. A cembranolide acid, lobohedleolide [44] and its isomer (7Z)-lobohedleolide [45] were reported from *L. hedleyi* (Uchio *et al.*, 1981a) collected at Yayegama Island of Okinawan coast, Japan. Their structures were elucidated from spectral data, chemical evidence, and the absolute configuration by X-ray analysis. Lobohedleolide showed growth inhibition of the Hella cells, in vitro.

A cembranolide diterpene [46] was reported from an Australian soft coral species of *L. michaelae* (Coll *et al.*, 1977). One new cytotoxic cembranolide, lobomichaolide [47] and a known cytotoxic cembranolide, crassolide [19] were isolated from Taiwan species of *L. michaelae* (Wang *et al.*, 1992). The structure of the new compound was confirmed by spectroscopic data and the stereochemistry fixed by X-ray studies. An Australian soft coral species *L. microlobulatum* was reported to yield nine diterpenoids (Coll *et al.*, 1986). Of these, three are cembranoids [50-52], two lobanes [53,54], two germacrane derivatives [57,58] and two eudesmane derivatives [55,56]. Four lobanes [2,53a,58a,58b,] along with three glycosides [58c,d,e] were reported from the Andaman specimen of the same species (Anjaneyulu and Raju, 1995). A species from the South China sea was reported to yield a polyhydroxysteroid, 24-methylcholestane-3β,5α,6β, 25-tetrol-25-monoacetate [6] which showed moderate cytotoxicity towards P388 Cells. (Sheu and Yeh, 1991).

Lobophytum pauciflorum occurring in different sea waters has been examined by several workers. Lobosterol [59], the first sterol with 3β,4β,5β-trihydroxy system was reported from it (Tursch *et al.*, 1976a). Diterpenes [60,61] with a 13-membered carbocyclic ring were isolated for the first time from it (Yamada *et al.*, 1979). Two epoxycembranolides [11,62] (Yamada *et al.* 1980a) and four polyhydroxysteroids [6,63-65] (Yamada *et al.*, 1980b) were reported from the Okinawan variety of the same species. The workers of Fujisawa pharmaceutical company (1993), isolated four cembranolides [60,61,66,67] along with six steroids from this species. Nephthenol [68], pauciflora-A [69] and pauciflora-B [70] were reported from the Red sea variety (Kinamoni *et al.*, 1983). 14-Hydroxycembra-1,3,7,11-tetraene [71] and 15-hydroxycembra 1,3,7,11-tetraene [72] were reported from an Australian variety (Bowden *et al.*, 1987). Two lobanes [2,74] (Rao *et al.*, 1990) along with six steroids; 25-deacetylobosterol [75], (24S)-24-methylcholest-7-en-3β,5α,6β,25-tetrol-25-monoacetate (76), (24S)-24-methylcholest-22E-ene-3β,5α,6β,25-tetrol [77], (24S)-24-methylcholestane-3β,5α,25-triol-6-one-25-monoacetate [78] and its C-25-deacetoxy analogue [79] and lobosterol [59] were reported from the same species (Kumar, 1992) which was collected from the Andaman & Nicobar Islands and initially described as *Sclerophytum* species (Kobayashi *et al.*, 1991). Two new norlobanes [80,81] have been recently reported along with 15-nor-13-keto-β-elemene [2] from the same species collected from A & N Islands (Anjaneyulu and Hari Babu, 1993a).

Six monohydroxysterols [5,82-86], two polyhydroxysterols [6,59] (Parameswaran *et al.*, 1989), two salts [129,130] (Parameswaran *et al.*, 1991) and batylalcohol [87] were reported from *L. strictum* off Lakshadweep Islands of Indian Ocean. One new cembranolide [88], two known cembranolides [44,46], one sesquiterpene, Δ^9(15)-africanene [89] along with three steroids [6,86,86a] were reported from *L. strictum* collected at Diglipur Island of the A & N Islands (Anjaneyulu *et al.*, 1994). The sesquiterpene, Δ^9(15)-africanene was

reported by them for the first time from a *Lobophytum* species. Three polyoxyagenated steroids, gorgost-5-en-1β,3β,11α,21-tetrol [91], gorgost-5-en-3β,9α,11β,21-tetrol [andamansterol, 92], gorgost-5-en-1β,3β,9α,11α,21α-pentol [90] were reported from the same species collected from A & N Islands (Anjaneyulu *et al.*, 1993b). Another Andaman soft coral of the same species yielded, methylarachidonate, (2S,11R,12R)-isosarcophytoxide (95a) and batylalcohol [107] were reported (Rani *et al.*, 1994b).

Lobolide [25] was reported (Kashman and Groweiss, 1977) from an unidentified species of *Lobophytum* from the Red sea and it was found to be toxic to fish. Cembranolides having seven membered lactones, 11-episinulariolide acetate [93], dehydrosinulariolide [94] along with two known compounds, nephthenol [68], 16-deoxysarcophine [95] were reported from another unidentified *Lobophytum* species (Kashman *et al.*, 1977). An Australian soft coral of *Lobophytum* yielded two cembranolides, one of which is a novel -ketoepoxycompound [96] along with the 13-membered carbocyclic ring cembranoid [61] (Bowden *et al.*, 1978). These structures were confirmed by spectral data and chemical conversions. Eight lobanes [2,97-103] along with germacrene-A [104] and sarcophine [105] were reported for the first time from a *Lobophytum* species of Great Barrier Reef (Dunlop and Wells, 1979). These structures were confirmed by spectral data and chemical conversions.

An epoxycembranolide [11] (Su *et al.*, 1982), a 13-membered carbocyclic ring compound [61] and batyl alcohol [87] were reported from another unidentified *Lobophytum* species (Long *et al.*, 1981). A cytotoxic cembranolide [106] was isolated from a *Lobophytum species* (Long *et al.*, 1980). Three cembranoides [107-109] were reported from an Australian soft coral of *Lobophytum* species (Bowden *et al.*, 1983). Two biologically active compounds [110,111] were isolated from another *Lobophytum* species (Suleimenova *et al.*, 1990). A new trihydroxysterol [112] was reported along with two known sterols [113,114] from another unidentified Lobophytum species (Anjaneyulu and Hari Babu, 1992) collected at Neil Island of the A & N group of Islands. Two monohydroxy sterols; dihydrobrassicasterol [86] and gorgosterol [5] were reported from a *Lobophytum* species of A & N Islands (Subrahmanyam and Rao, 1993). Two new lobanes [115,116] along with 15-nor-13-keto-β-elemene [2] (Raju *et al.*, 1993) have been recently reported from an unidentified *Lobophytum* species of A & N Islands. Their structures were elucidated by 2D NMR spectral data and chemical conversions. A detailed chemical examination of the same species yielded one more new norlobane [129a], a diastereomeric mixture of a new lobane [130a] and six polyhydroxysteroids [6,63,64,131-133] (Raju *et al.*, 1994a). Two new cembranoid diterpenes [118,120], one novel neodolabellane diterpene [119], seven known diterpenes [73,109,117,121-124], two known monohydroxysteroids [5,86] along with five lipids [87,125-128] were reported from another *Lobophytum* species collected from A & N Islands (Subrahmanyam *et al.*, 1992). The novel dolabellane structure was confirmed by X-ray analysis. The remaining structures were determined from spectral data and chemical conversions.

An Andaman specimen of *Lobophytum hirsutum* yielded three new lobanes; 13-hydroxyloba-8,10,15,17-tetraen-19-al [134] and two diastereomers [135 & 136] of 13,15-epoxyloba-8,10,16-trien-18-ol, in addition to three known lobane derivatives [2,97,98] and five polyhydroxysteroids [6,64,132,132a,133] (Raju *et al.*, 1995). Two new cembranolides, 2-epi-11(Z)-lobohedleolide [48] and (1R,2S,3E,7R,8R, 11E)-7,8-epoxycembra-3,11,15-trien-16,2-olide [49] along with two known derivatives, lobohedleolide [44] and denticulatolide [47] were isolated from a new species of the genus *Lobophytum* from the Indian Ocean (Rao *et al.*, 1994). Another unidentified *Lobophytum*

species gave a new sterol, 24(S)-24-methylcholesta-5,22E-dien-3β,25-diol [137], along with two known monohydroxy sterols, 4α-methylgorgostanol [138], 4α-methyl-24-methylenecholestanol [139], three known polyhydroxysteroids [6,63,64] and two known cembranolide diterpenes [44 & 46] (Anjaneyulu *et al.*, 1994).

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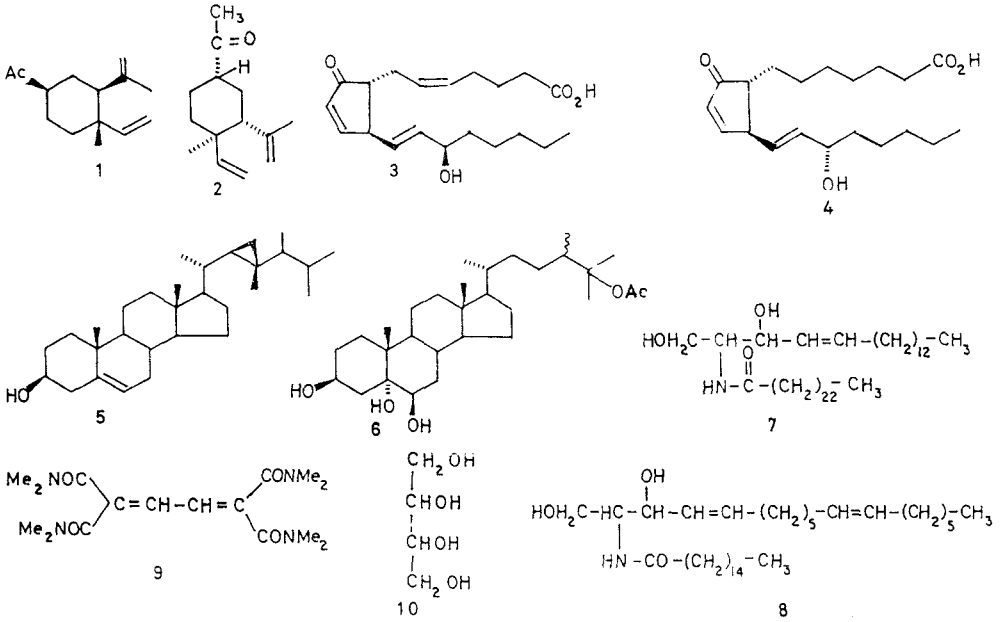
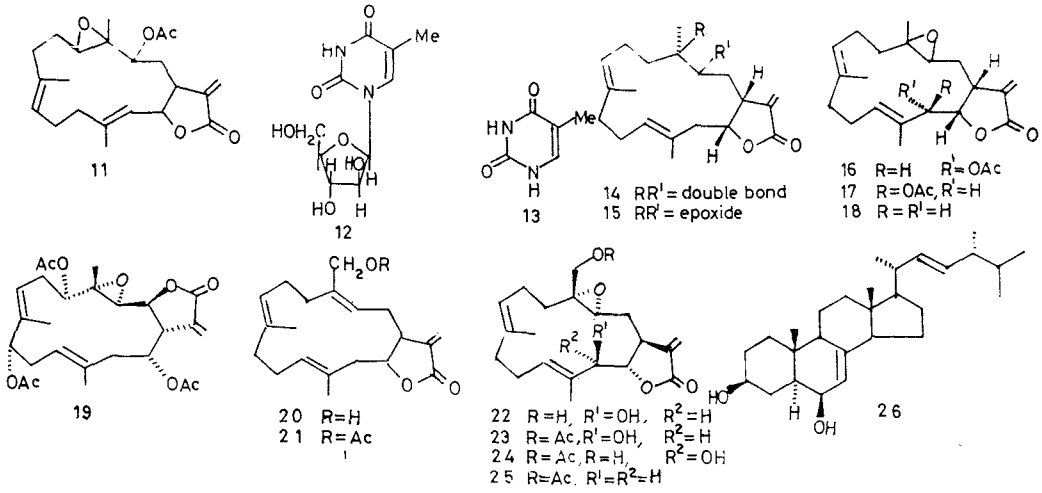
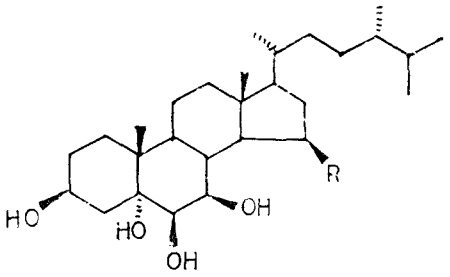
Appendix: Chemicals cited in the text.







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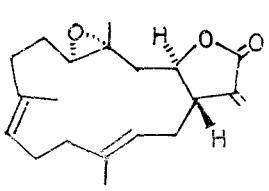

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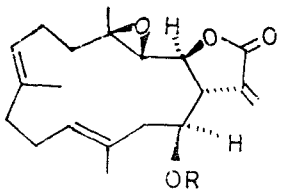

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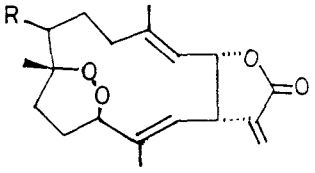

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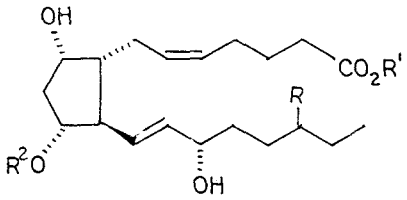
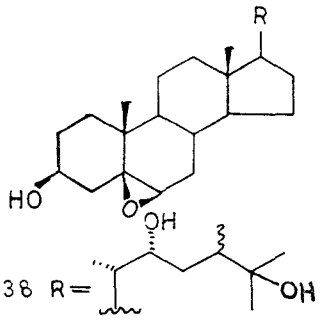


34 R'=Me, R^2=Ac, R=H
35 R'=H, R^2=Ac, R=H
36 R'=Me, R^2=Ac, R=OAc
37 R'=H, R^2=Ac, R=OAc



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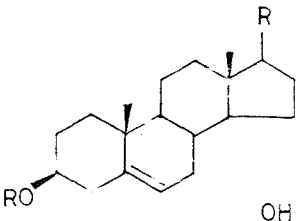

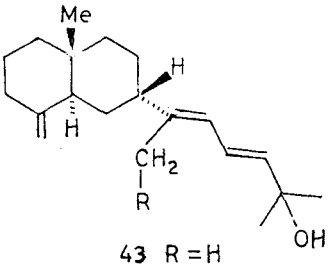

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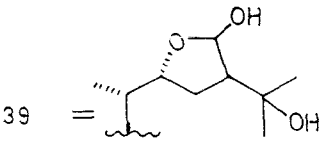

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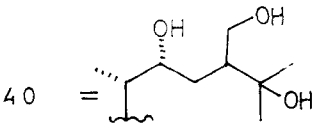

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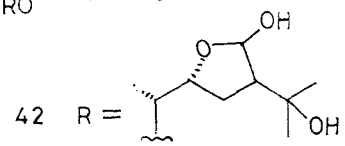

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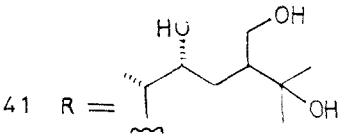

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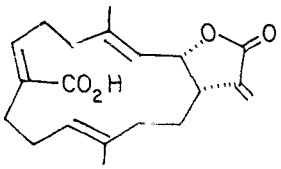

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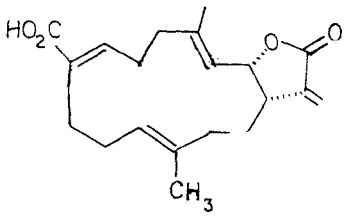

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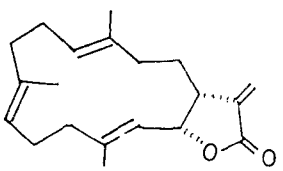

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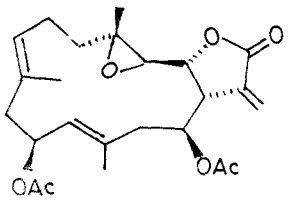

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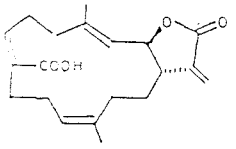

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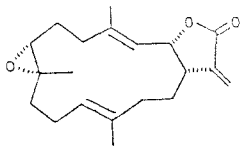

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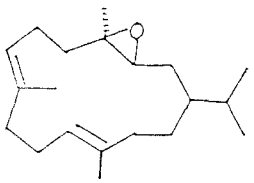

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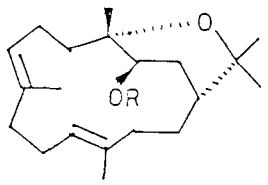

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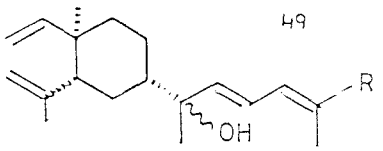
52 R = Ac



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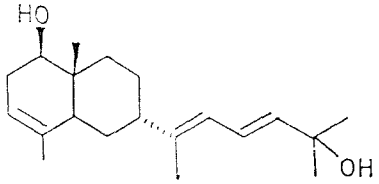
53a R = CO_2H



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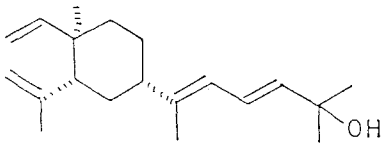

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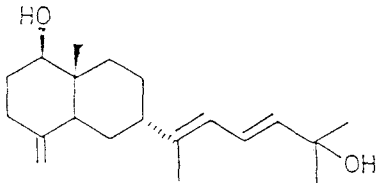

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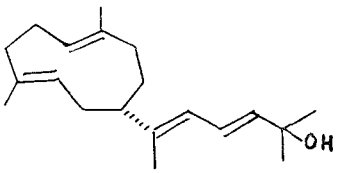

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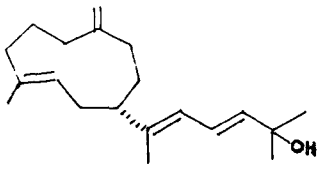

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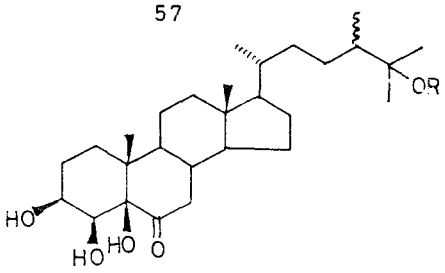
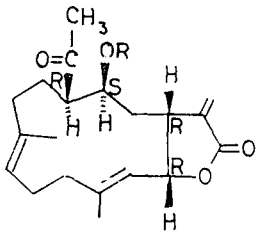


59 R = Ac
75 R = H



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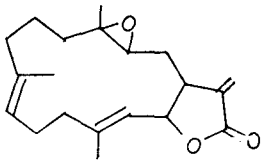
61 R = Ac



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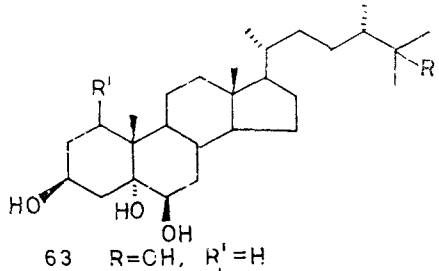
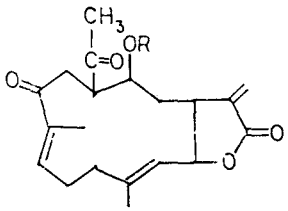


63 R=CH, R' = H
64 R= H R' = βOH



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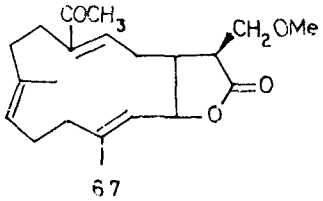

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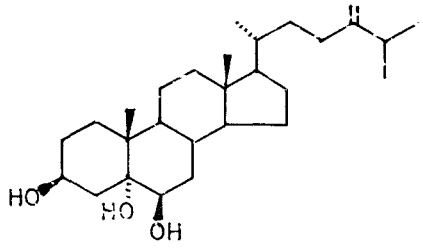

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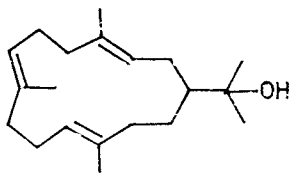

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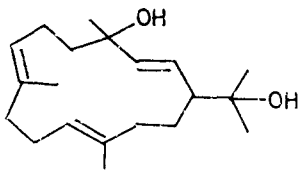

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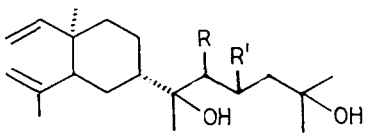
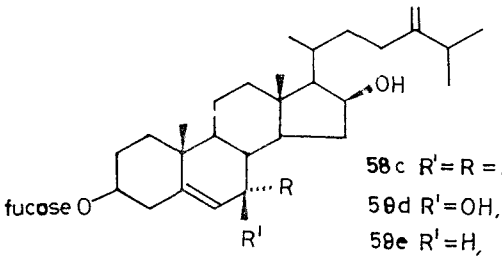
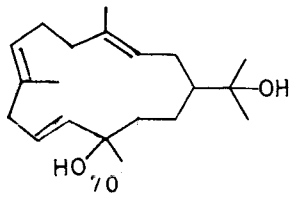


58a R-R' = double bond
58b R = R' = H



58c R' = R = H
58d R' = OH, R = H
58e R' = H, R = OH



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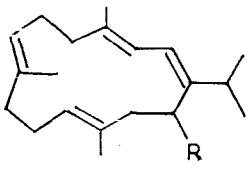
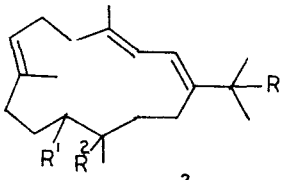
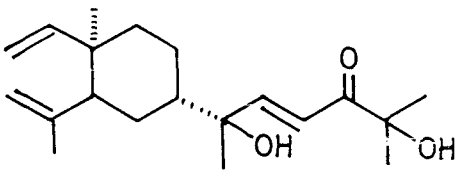


71 R = OH



72 R = OH, R'R^2 = double bond
73 R = H, R'R^2 = epoxide



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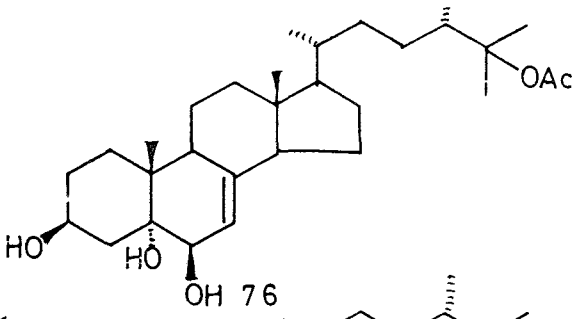

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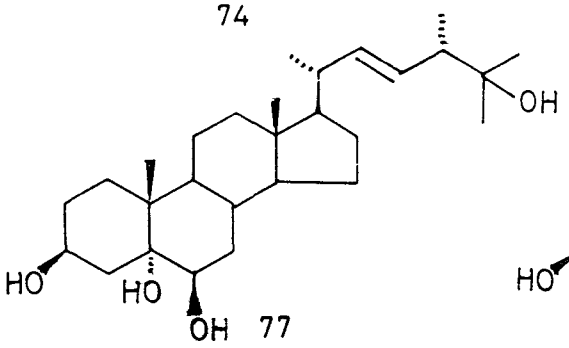

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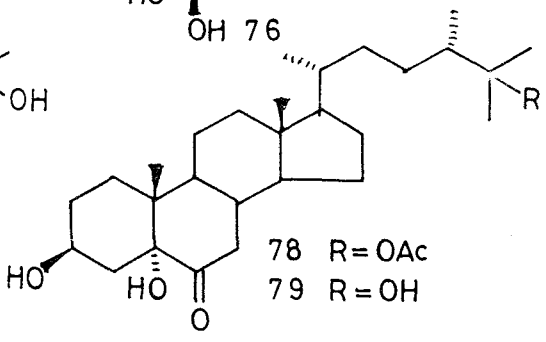
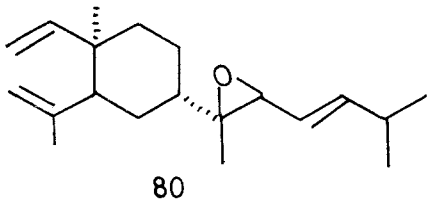
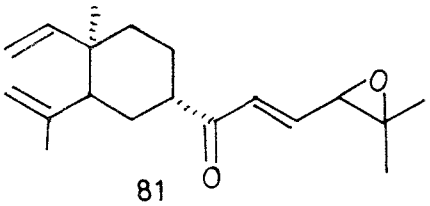


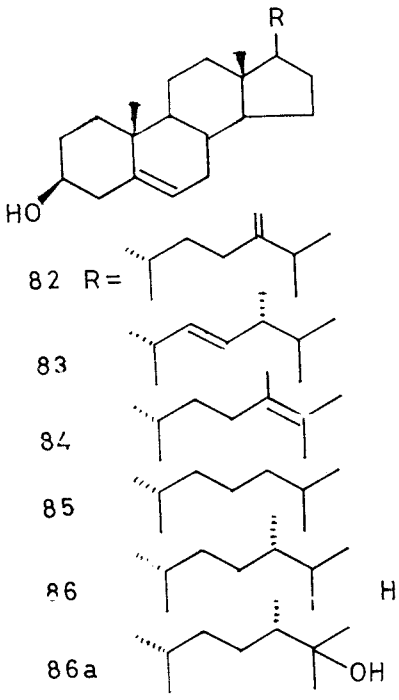
78 R = OAc
79 R = OH

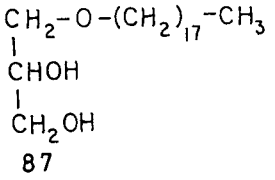


80

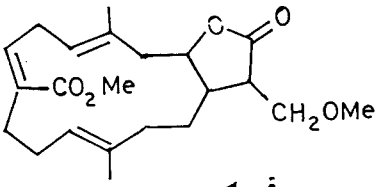


81

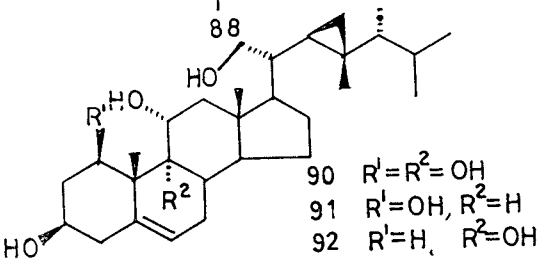




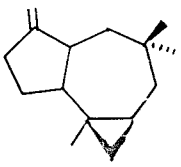
87



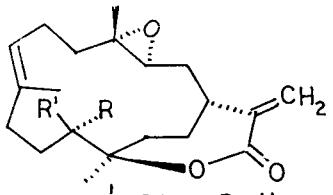
88



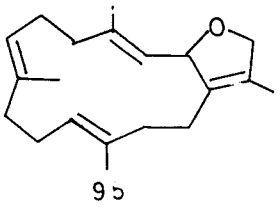
90 $R^1=R^2=OH$
91 $R^1=OH$, $R^2=H$
92 $R^1=H$, $R^2=OH$



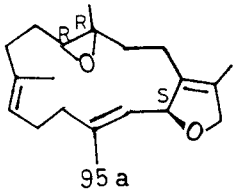
89



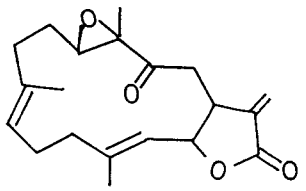
93 $R^1=OAc$, R=H
94 $RR^1=O$



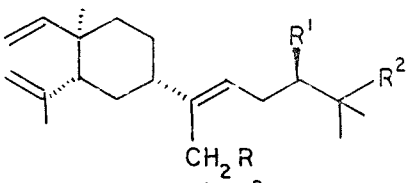
95



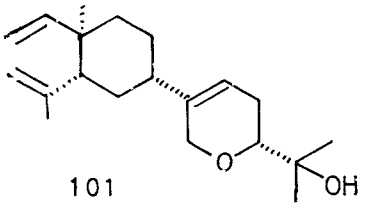
95a



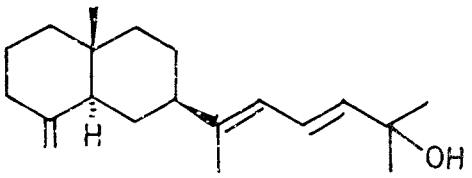
96



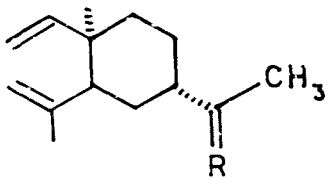
97 R=H, $R^1=R^2=OH$
98 R=H, $R^1R^2=O$
99 $R=R^1=OAc$, $R^2=OH$
100 R=OAc, $R^1=R^2=OH$



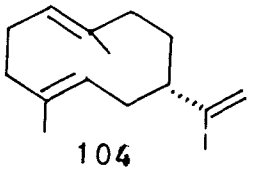
101



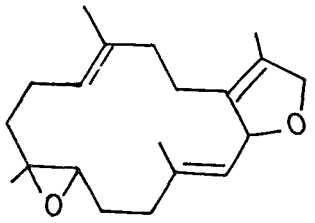
102



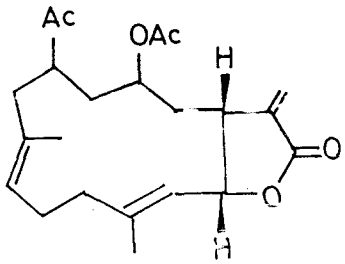
103 R = CH_2



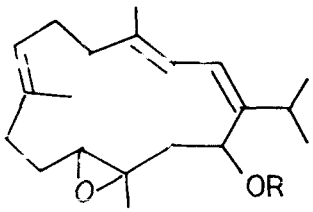
104



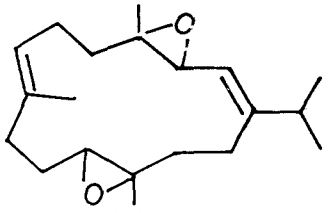
105



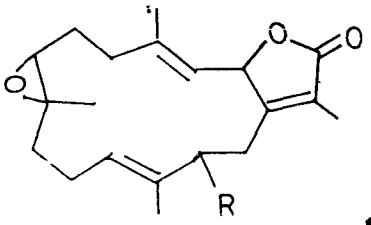
106



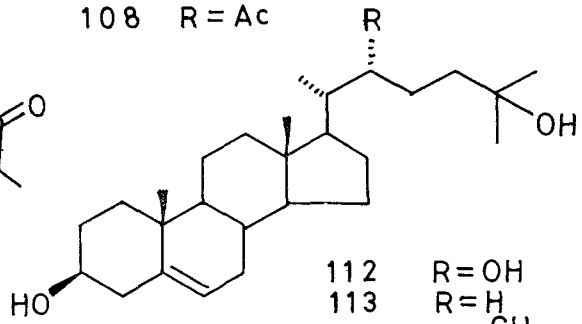
107 R = H
108 R = Ac



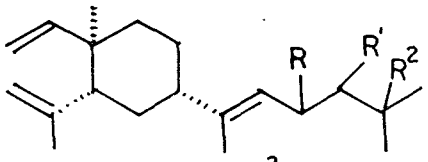
109



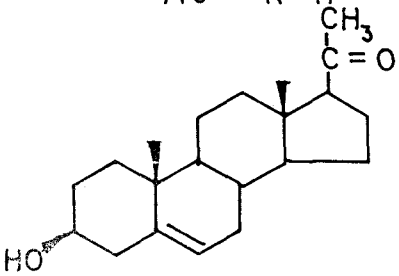
110 R = H
111 R = OAc



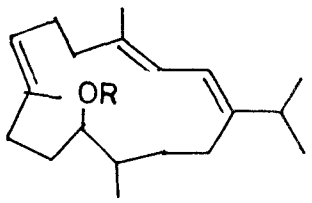
112 R = OH
113 R = H



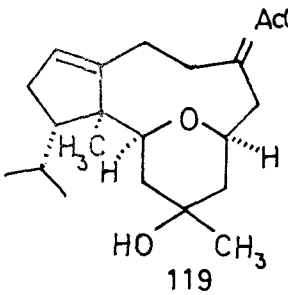
115 R = OH, R^2R' = O
116 R = R' = R^2 = OH



114



117 R=H
118 R=Ac



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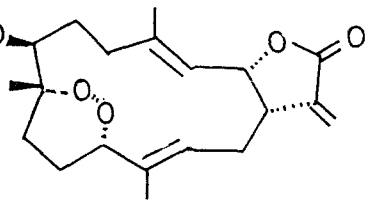
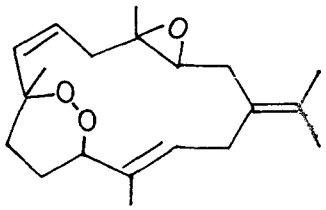


121



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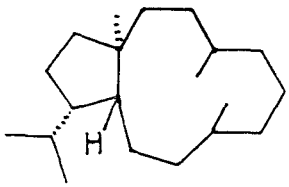

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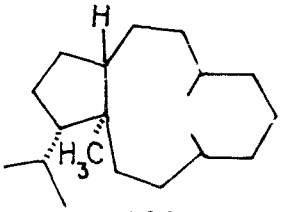
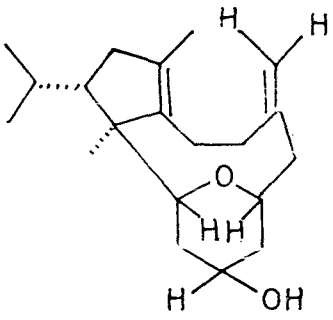


123



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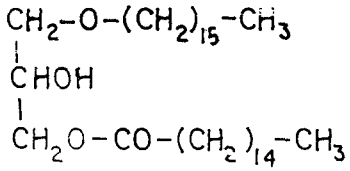

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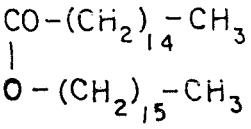

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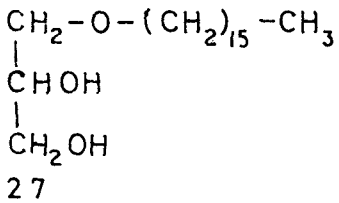

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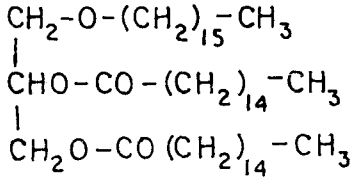

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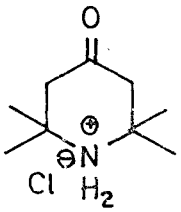

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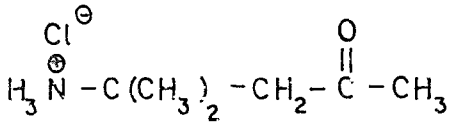

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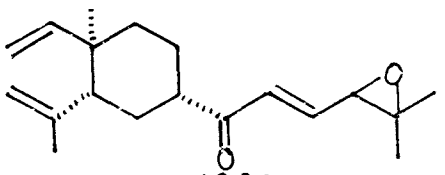
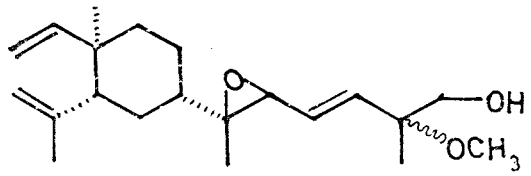
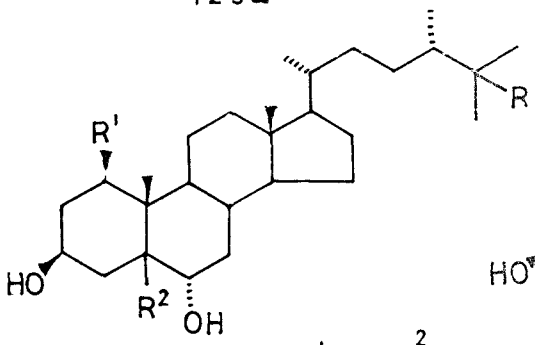


129a



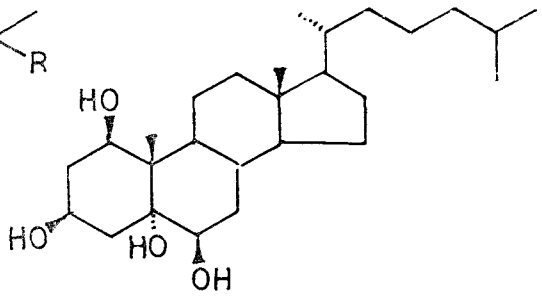
130a



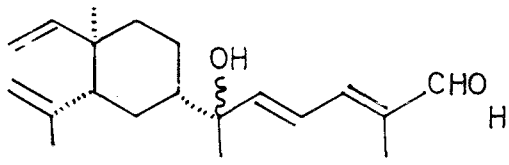
131 R=OH, R'=H, R^2=β-OH

132 R=OAc, R'=OH, R^2=α-OH

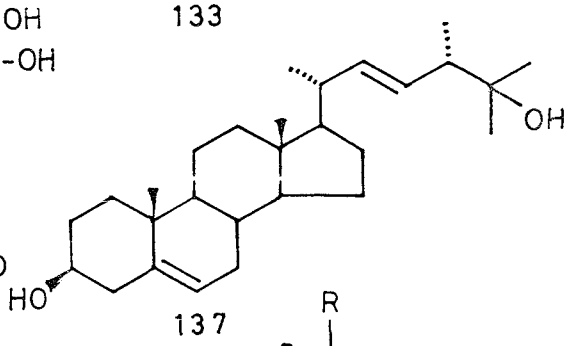
132a R=R'=OH, R^2=α-OH



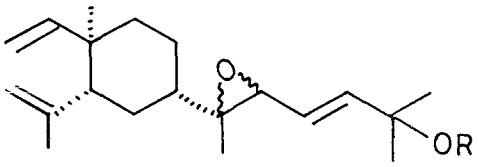
133



134

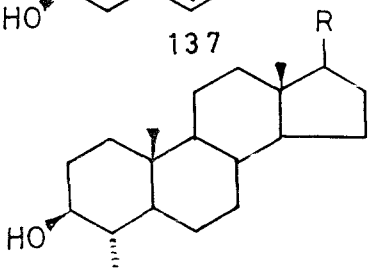


137

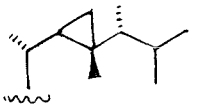


135 R=H, RR or SS at the epoxide

136 R=H, SS or RR at the epoxide



138 R =



139 R =