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Ozonolytic transformations of labdane diterpenoids

P F Vlad, A N Aryku
Institute of Chemistry, Academy of Sciences of the Moldavian Republic, Kishinev

ABSTRACT. Information on the products of ozonolysis of labdane and *ent*-labdane diterpenoids is correlated. The effects of the ozonolysis conditions, the procedure for treating the products and the location of double bonds and other functional groups on the character of the resulting ozonolysis products are considered.

The bibliography contains 91 references.

Contents

I. Introduction 716
II. Ozonolysis of labd-8-enoids without functional groups at C(3) and labda-8(17),13-dienoids 716
III. Ozonolysis of labdenoids and norlabdanoids containing a functional group at C(8) and a double bond at C(9)–C(11), C(11) or C(12) 719
IV. Ozonolysis of labdanoids with oxygen-containing functional groups at C(8) and C(13) and a double bond at C(14) or with a hydroxyl group at C(8) and a double bond at C(13)–C(14) 721
V. Products of the ozonolysis of 8α,13-epoxy-14,15-di-norlabd-12-ene and its derivatives 723
VI. Products of the ozonolysis of labda-8(17),14-dien-13-ol (manool) and compounds related to it 723
VII. Ozonolysis of labda-13(16),14-diene compounds, furanolabdanoids and labd-13(14)-enoids with oxygen-containing functional groups at C(15) and C(16) 727

I. Introduction

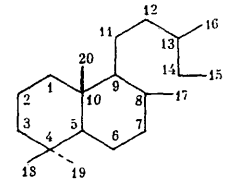
The labdane diterpenoids are bicyclic compounds based on the carbon skeleton (**1**).[1] A characteristic feature of many of them is their availability and practical value. Well known diterpenoids produced on an industrial scale (manool, sclareol, larixol, etc.) belong to this group. Raw materials for obtaining them are fairly accessible. For example, sclareol is isolated from the waste products of sage essential oil manufacture and the majority of the other compounds from the oleoresin of various coniferous plants.[2] Some of these diterpenoids display a high biological activity. For example forskolin proved to be an effective agent for the treatment of glaucoma, cardiac and other diseases[3] and sclareol displays antifungal activity.[4] However the chief practical value of the majority of the available labdanoids is that their transformation products are used in perfume manufacture as rich substitutes for the extremely precious, but unavailable at present, grey amber and in the tobacco industry for the aromatisation of tobacco products.[2]

Labdanoids are subjected to oxidative fission to obtain the indicated products. Compounds of hexavalent chromium or potassium permanganate serve as oxidising agents.[2] However these oxidising processes generally occur non-selectively and lead to a complex mixture of compounds from which the desired compounds are isolated with difficulty and in relatively low yield. Toxic aqueous effluents are formed which are difficult to purify. In addition potassium permanganate is not a readily available reagent. Consequently the development of alternative methods of obtaining the fission products of the available labdanoids using other inexpensive, more selective and ecologically clean oxidising agents is a pressing problem of both theoretical and practical interest.

Ozone is just such an oxidising agent. As is known, it is a powerful and at the same time selective oxidising agent, reacting with unsaturated compounds under mild conditions.[5–7] Thanks to this property ozone proved to be a convenient reagent to effect oxidative conversions of natural compounds in the clarification of their structures. It is perhaps used most frequently and successfully for these purposes in the terpenoid field,[8] the labdanoid diterpenoids amongst them.[1,2]

There are double bonds in the structure of the numerous known representatives of the labdanoid diterpenoid group, which most frequently occupy positions C(7), C(8)–C(9), C(8)–C(17), C(13)–C(14), C(13)–C(16) and C(14)–C(15) and only they react with ozone.[1,9] However the character of the resulting labdanoid ozonolysis products depends not only on the presence and position of the double bonds but also on such functional groups as hydroxyl and carbonyl groups.

In the present review, data on the ozonolysis of labdanoids are correlated according to the number, character and mutual disposition of functional groups in the molecule. Studies published up to 1991 are discussed. The numbering system used for the labdane carbon atoms (1) is taken from the IUPAC rules.[10]



(I)

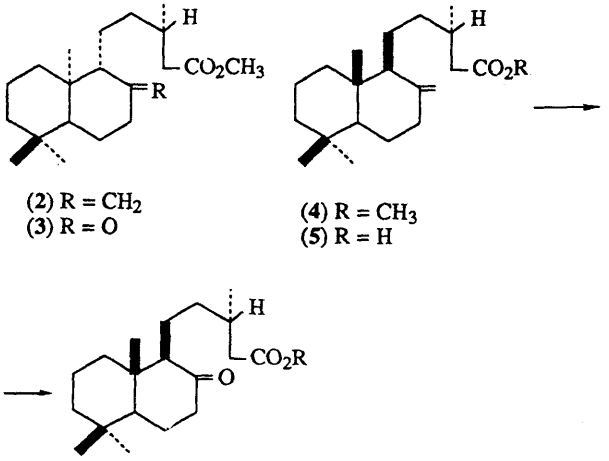
II. Ozonolysis of labd-8-enoids without functional groups at C(13) and labda-8(17),13-dienoids

Ozone proved to be the preferred reagent for the oxidation of labdane diterpenoids with an exocyclic double bond at C(8)–C(17) to the corresponding ketones. This bond is fairly stable, for

example, to such widely used oxidising agents as potassium permanganate or compounds of hexavalent chromium. Satisfactory yields of ketones were obtained only in the two-step oxidation of labd-8(17)-enoids in which osmic acid was used in the first step,[1,2] however this reagent is expensive and available with difficulty. Ozone also oxidises these compounds efficiently. It is convenient both preparatively and for the qualitative detection of this bond. In reality the formation of formaldehyde during the process in conjunction with IR spectroscopy serves as a strict confirmation of the presence of an exocyclic double bond in labdanoids at position C(8)–C(17).

King and Jones[11] effected the ozonolysis of eperuic acid (*2*) in dichloromethane by oxidative fission of the ozonide with hydrogen peroxide and obtained the ketoester (3) in 71% yield (Scheme 1). A good yield (91%) of a mixture of ketoester (**3**) with its epimer at C(13) was also achieved on ozonolysis of a mixture of the ester (**2**) and its epimer at C(13) in ethyl acetate and reduction of the ozonolysis product with zinc in acetic acid.[12] Ozonolysis of the methyl ester of labd-8(17)-en-15-oic acid (**4**) [13] and of labdenoic acid (5) itself,[14] which are structurally close but belong to the enantiomeric series, under analogous conditions led to the keto compounds (**6**) and (**7**) respectively but in poor yield. Replacement of ethyl acetate by dichloromethane affects significantly the result of ozonolysis of methyl labdenoate (**4**) [the yield of ketoacid (**7**) after saponification of the reaction product was 46%].[15] The one-step ozonolysis of methyl labdenoate (**4**) in the presence of pyridine proceeds more smoothly [yield of ketoester (6) was 60%].[16]

Scheme 1



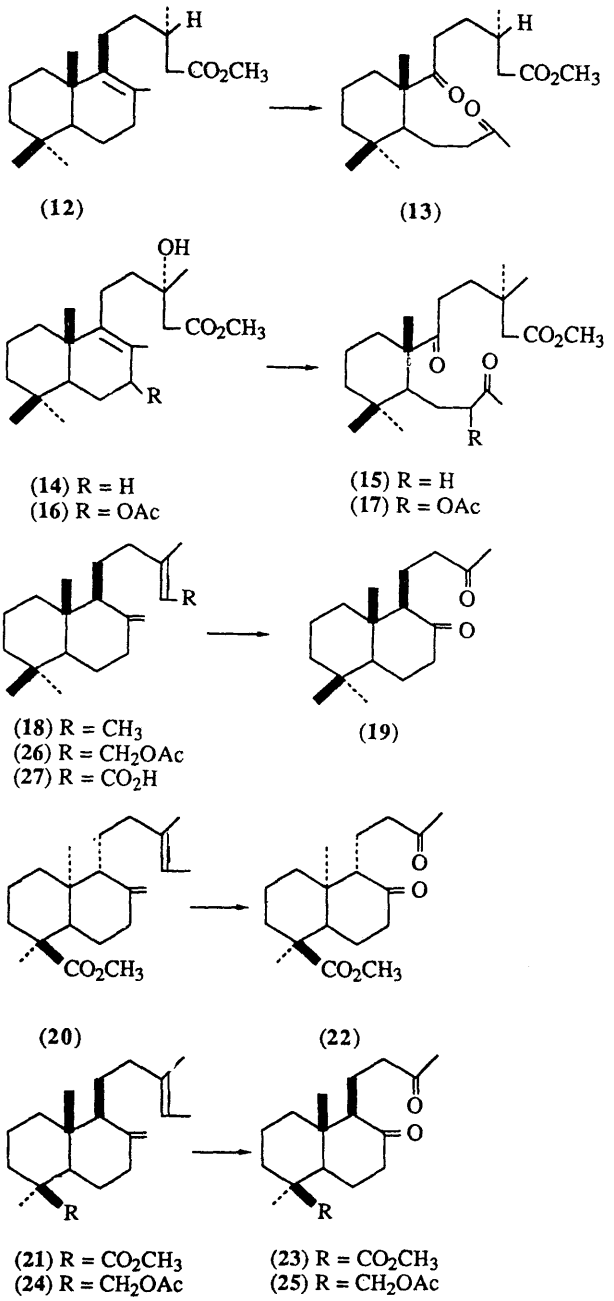
(**2**) R = CH_2
(**3**) R = O

(**4**) R = CH_3
(**5**) R = H

(**6**) R = CH_3
(**7**) R = H

(**8**) R = CH_2
(**9**) R = O

(**10**) R = CH_2
(**11**) R = O



Chandra and collaborators[17] ozonolysed labd-8(17)-ene-3,15-diol (**8**) in chloroform and reduced the ozonide with zinc in acetic acid. The reaction product proved to be the ketodiol (**9**). The ozonolysis of oliveric acid (**10**) in dichloromethane in the presence of pyridine gave formaldehyde and the ketoacid (**11**).[18] Thus the functional groups removed from C(8) [the hydroxyl group at C(3) and the axial carboxyl group at C(4)] have no effect on the course of ozonolysis.

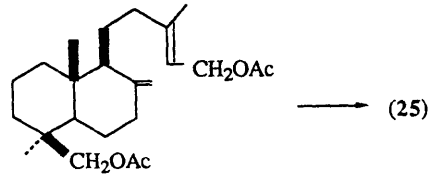
The ozonolysis of the methyl ester of labd-8(9)-en-15-oic acid (**12**) proceeds smoothly when carrying out the reaction in ethyl acetate with hydrogenation of the ozonide over palladium on calcium carbonate.[16] The yield of the diketoester (**13**) was 94%. The position of the double bond, the presence of a hydroxl group at C(13) or a hydroxyl group at C(13) and an acetoxy group at C(7) does not

affect the ozonation reaction. In fact on carrying it out in a mixture of dichloromethane and methanol (1:1) and treating the reaction product with triethyl or trimethyl phosphite, the hydroxyester (**14**) gave the hydroxydiketoester (**15**) in 76% yield[19] and the related diterpenoid (**16**) gave the polyfunctional compound (**17**) in 77% yield (see Scheme 1).[20] It should be noted that oxidation of $\Delta^{8(9)}$-labdanoids with other reagents frequently does not occur at the double bond but at position C(7),[1,2] i.e. ozonolysis is a selective process.

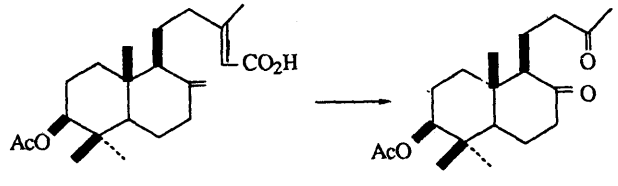
Ozonolysis also proved to be an efficient process for the oxidation of labdenoids with double bonds at C(8)–C(17) and C(13)–C(14). For example, the diketone (**19**) proved to be the sole product (74% yield) of the ozonolysis of labda-8(17),13-diene (18) in dichloromethane in the presence of pyridine.[21] Although the esters (**20**)[22] and (**21**)[23] were also ozonolysed in an aprotic solvent (ethyl acetate) the reduction of the ozonides with zinc in acetic acid led to the diketoesters (**22**) and (**23**) respectively in relatively low yield (~40%). However, the diketoacetate (**25**) was isolated in 78% yield on reduction of the ozonide obtained from 19-acetoxylabda-8(17),13-diene (**24**) in dichloromethane by the same method.[24]

The functionalisation of the carbon atom C(15) in labda-8(17),13-dienes apparently does not ease the fission of the double bond at C(13)–C(14). 15-Acetoxylabda-8(17),13-diene (**26**) is oxidised by ozone (dichloromethane solvent, reducing agent zinc in acetic acid) to the diketone (**19**) in 84% yield.[25] The latter is also formed, though in far poorer yeild (42%), on ozonolysis of labda-8(17),13-diene-15-oic acid (**27**) in ethyl acetate and reduction of the ozonide with the same reagent.[26] Additional functional groups in ring A have no effect on the ozonolysis which is evident in the example of the oxidation of the acetoxydienes (**28**)[24] and (**29**)[27] giving the corresponding acetoxydiketones (**25**) and (**30**) in identical yield (89%) (Scheme 2). In the first case the reaction was carried out in dichloromethane and the ozonide was reduced with zinc and acetic acid and in the second in ethyl acetate and the ozonide was hydrogenated over palladium on carbon.

Scheme 2



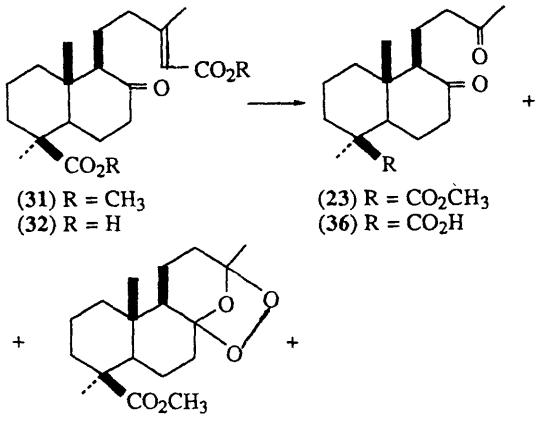
(28)



(29) (30)

These data show that the result of the ozonolysis of the labdanones depends significantly on the conditions, especially on the solvent. In particular ozonolysis in ethyl acetate with subsequent reduction of the ozonides with zinc in acetic acid leads to a low yield of ozonation product (Scheme 3).

Scheme 3

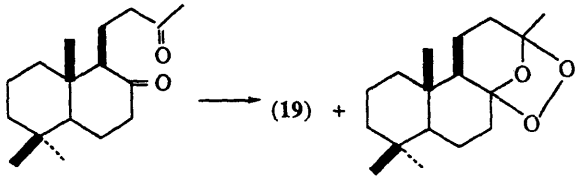


(31) R = CH_3
(32) R = H
(23) R = CO_2CH_3
(36) R = CO_2H

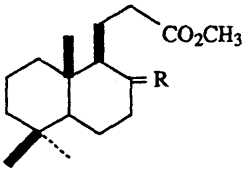
(34)



(35) (33)



(37) (38)



(39) R = CH_2
(40) R = O

Ruzicka and collaborators[28] carried out the ozonolysis of the dimethyl ester (**31**) of agathic acid (**32**) under forcing conditions in acetic acid and, after reduction of the product by boiling in water with zinc dust, obtained a complex mixture of compounds of which the main was the labile diketoester (**23**) (20% yield). In addition an intramolecular peroxide (10%) was isolated to which the authors assigned the structure (**33**). In reality it has the structure (**34**),[5] and a ketoesteracid (**35**) was isolated from the acid fraction. Compound (**34**) is fairly stable and is not reduced by zinc dust in water. The ozonolysis of the same agathic acid (**32**) occurs less ambiguously under milder conditions. In an aprotic solvent (dichloromethane) in

the presence of pyridine it leads mainly to the diketoacid (**36**) 61% yield.[29]

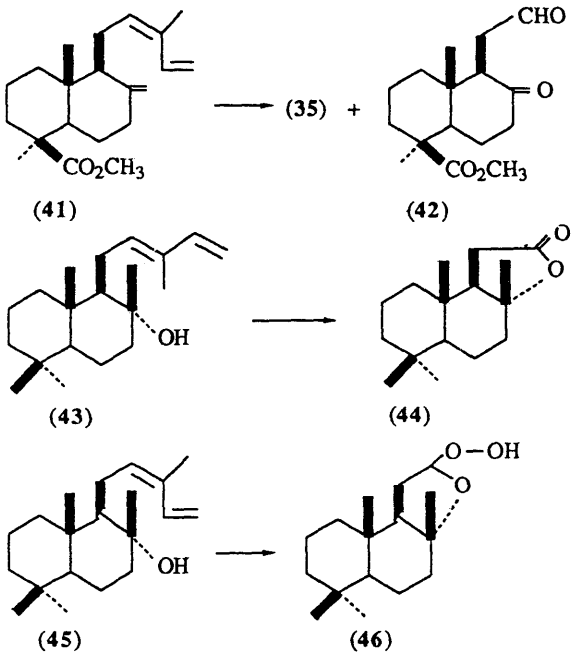
The double bond at C(8)–C(17) is norlabdanoids also reacts smoothly with ozone. Thus 14,15-bisnorlabd-8(17)-en-13-one (**37**) gives the diketone (**19**) (84%) on ozonolysis in dichloromethane in the presence of pyridine.[30] The indicated yield of diketone (**19**) was however achieved after additional treatment of the ozonolysis product with sodium iodide solution. Evidently this treatment was carried out to decompose stable peroxide compounds which were still present since it was later[31] shown from example that one of the ozonolysis products of the unsaturated ketone (**37**) was the oxonide (**38**), an analogue of compound (**34**). Its yield reached 33% if the ozonolysis product was subjected to oxidative fission with hydrogen peroxide.

The tetranorlabdene ester (**39**) is also ozonised smoothly (solvent is chloroform, reducing agent zinc in acetic acid). The sole ozonolysis product was the expected ketoester (**40**).[32]

III. Ozonolysis of labdanoids and norlabdanoids containing a functional group at C(8) and a double bond at C(9)–C(11), C(11) or C(12)

Few labdanoids with the functionalisation indicated are known. Of the compounds with a double bond at C(12) the first investigations were of the ozonolysis of the methyl ester of *cis*-communic acid (**41**) (Scheme 4).[24] The reaction was carried out in dichloromethane and the ozonide was decomposed by boiling with water or with aqueous methanol. A mixture of compounds (**35**) and (**42**) was formed in both cases. In the first case the aldehyde (**42**) predominated in the product [yields of (**35**) and (**42**) were 9 and 59% respectively] and in the second the ketoacid (69.5%) predominated [yield of ketoaldehyde (**42**) was 22.6%]. The conditions therefore affected significantly both the product ratio (6.5 : 1 and 1 : 3) and their overall yield.

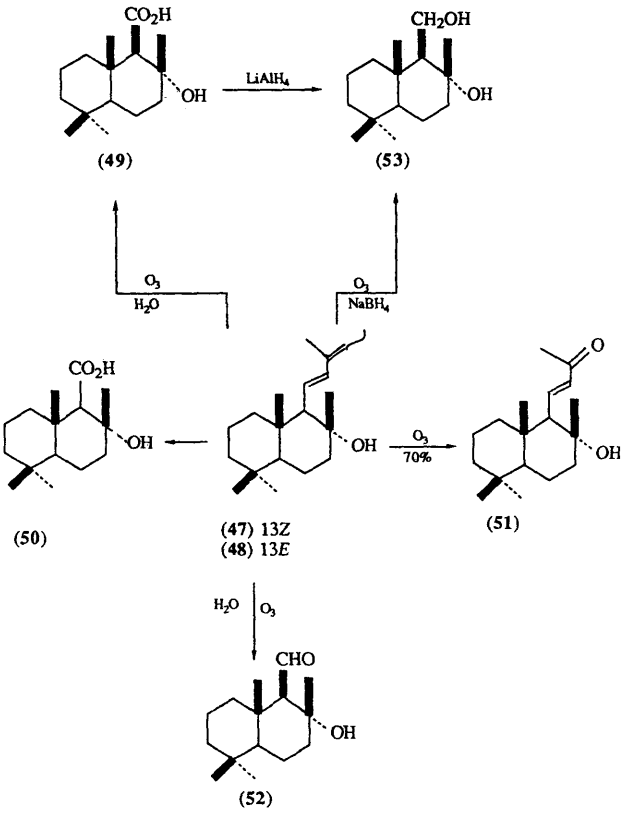
Scheme 4



Chirkova and collaborators[33] have carried out the ozonolysis of *trans*-abienol (**43**) which was isolated by them from Siberian fir and was erroneously mistaken for isoabienol.[34] Ozonolysis was effected in dichloromethane, the ozonide was decomposed by boiling with water, the product was oxidised again with potassium permanganate in acetic acid and norambreinolide (**44**) (70%) was obtained.

A compound of an altogether different nature was obtained in fairly good yield (50–70%) on ozonolysis of *cis*-abienol (**45**), which is distributed in the oleoresin of conifers, in ethyl acetate with oxidative fission of the ozonolysis product with hydrogen peroxide in acetic acid.[35] It turned out to be the epoxyhydroperoxide (**46**) which is formed by intramolecular attack of the Criegee zwitterion by the hydroxy group at C(8).[5,6] This was the first recorded case of the formation of an intramolecular alkoxyhydroperoxide in an aprotic solvent, analogous to the preparation of acyclic alkoxyhydroperoxides on ozonolysis of unsaturated compounds in alcoholic solvents.[6]

Scheme 5

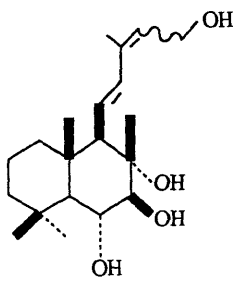


A detailed investigation has been made of the ozonolysis of *cis*- and *trans*-neoabienols (**47**) and (**48**), the stereoisomeric labdanoids with a double bond at C(11) and a hydroxyl group at C(8) which are artefacts formed from *cis*-abienol (**45**) on distillation of oleoresins containing it.[36–39] The authors[36] isolated a hydroxyacid which was assigned the structure (**49**) on ozonolysis of *cis*-neoabienol (**47**) under the conditions indicated above for *trans*-abienol (**43**) (Scheme 5). However its constants differed from those described.[41] Seemingly it is an epimer of compound (**50**). The ozonolysis of a mixture of *cis*- and *trans*-neoabienols (**47**) and (**48**) has been investigated in detail.[42]

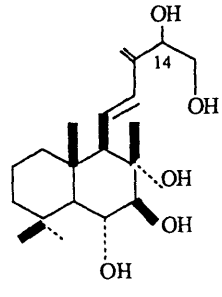
It was shown that the character of the ozonolysis products depends significantly on the quantity of oxidising agent and the method of decomposing the ozonide or peroxide. Thus on using one mole equivalent of ozone and carrying out the reaction at −60 to −70 °C in ethyl acetate in the presence of pyridine or in methanol with subsequent decomposition of the peroxide reaction products with dimethyl sulphide, the selective formation occurs of the conjugated hydroxyketone (**51**) (yield 70%), which is a component of the oleoresin of Siberian fir together with neoabienols (**47**) and (**48**).[40] On increasing the temperature the yield of the hydroxyketone (**51**) is reduced and is 55% at 0 °C. Exhaustive ozonolysis of a mixture of neoabienol in hexane with subsequent heating of the ozonide with water leads to a mixture of driman-8α-ol-11-al (**52**) (60%) and the hydroxyacid (**49**) (25%),[42] the structure of which was demonstrated unequivocally by reduction with lithium aluminium hydride to the known drimane-8α-11-diol (**53**). A mixture of the same compounds is formed on ozonolysis of a mixture neoabienols in ethyl acetate or dichloromethane in the presence of pyridine or in methanol and reduction of the peroxides with dimethyl sulphide. The acid (**49**) is the chief reaction product (yield 71%) on ozonolysis in hexane with oxidative fission of the ozonide with hydrogen peroxide. If the reaction is carried out in methanol at −75 to −78 °C and peroxides are reduced with sodium borohydride, the main reaction product is the diol (**53**) (74%) which is an important starting material for the synthesis of the natural drimane sesquiterpenoids.[43] The yield of the diol (**53**) falls with increasing temperature. The ozonolysis of the hydroxyketone (**51**) has also been investigated in detail and it was shown that there is a definite parallel between the yields of the individual products on ozonolysis under the same conditions of a mixture of neoabienols (**47**) and (**48**) and the hydroxyketone (**51**).

Japanese chemists[44] have ozonolysed sterebins E (**54**), F (**55**), G (**56**) and H (**57**) and 14,15-dinorsterebin (**58**), isolated from the leaves of *Stevia rebaudiana*, in methanol and the ozonolysis products were reduced with sodium borohydride. The tetrol (**59**) was isolated in 60−65% yield in all cases (Scheme 6).

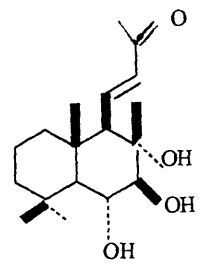
Scheme 6



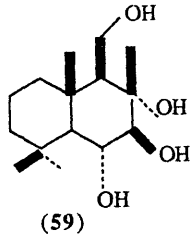
(**54**) 13*E*
(**55**) 13*Z*



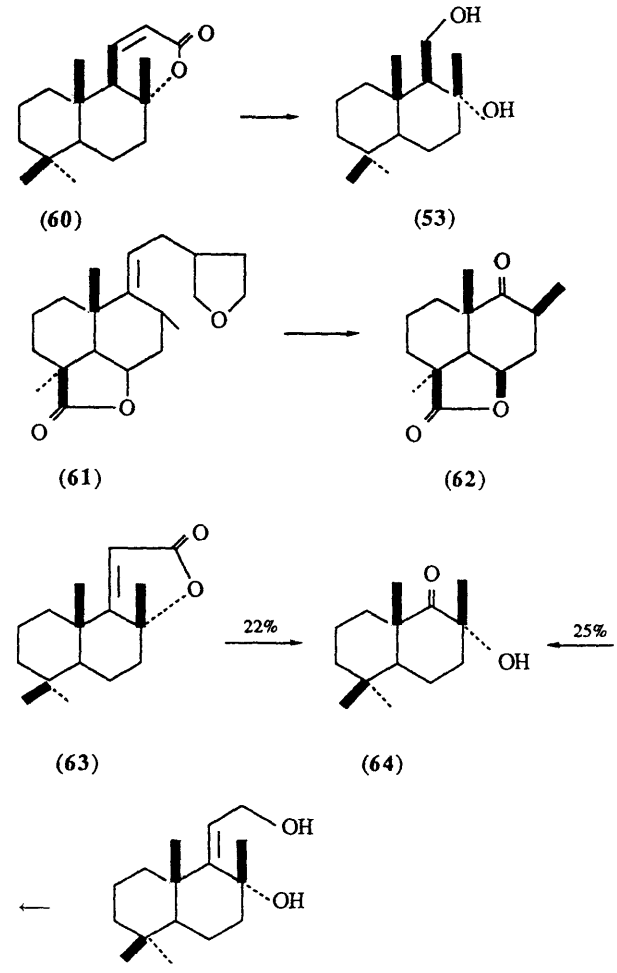
(**56**) 14*R*
(**57**) 14*S*



(**58**)



(**59**)



(**60**) (**53**) (**61**) (**62**) (**63**) (**64**) (**65**)

The tetranorlabdanoid Δ^{11}-dehydroabreinolide (**60**) is also smoothly ozonolysed giving driman-8α,11-diol (**53**) in 70% yield on carrying out the reaction in dichloromethane with reduction of the ozonide with sodium bis(2-methoxyethyl)aluminium hydride in benzene.[45] If the ozonide is reduced with lithium aluminium hydride in ether the yield of diol (**53**) was greater (92%).[21]

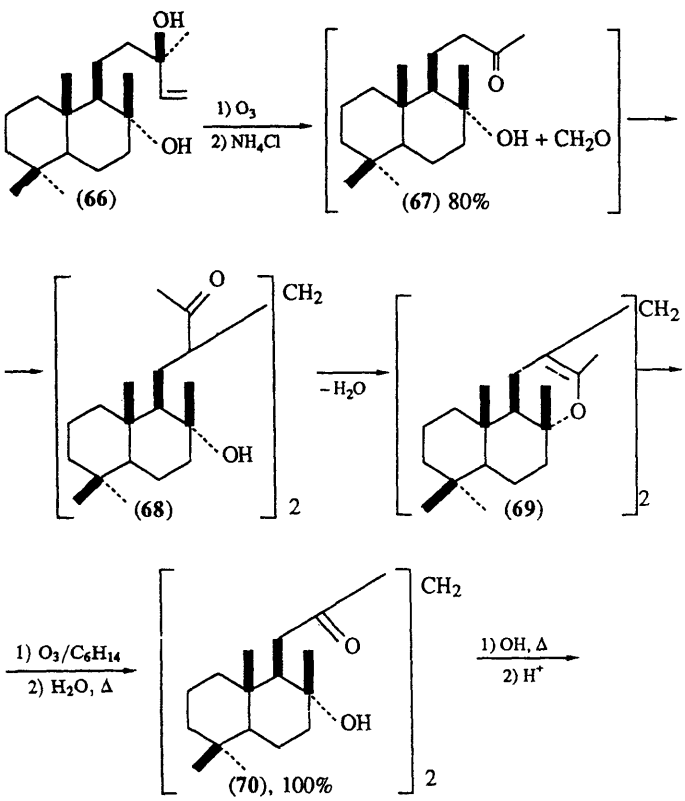
The 9,11-double bond in labdanoids and norlabdanoids is sterically hindered and reacts with ozone with difficulty. It has not as yet been detected in such compounds from natural sources.

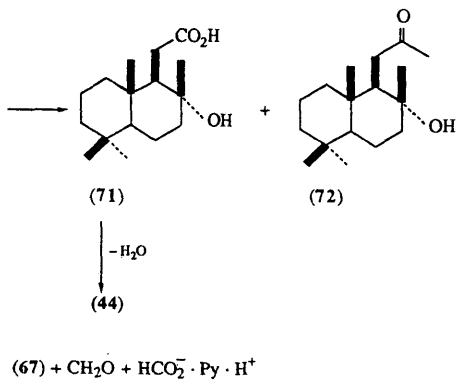
The ozonolysis of anhydrotetrahydromarrubiin (**61**) in ethyl acetate at a relatively high temperature (−5 °C) and hydrogenation of the ozonide over palladium on carbon gave the ketolactone (**62**) in only 18.5% yield.[46] $\Delta^{9(11)}$-Dehydronorambreinolide (**63**) proved to be very inert towards the action of ozone. On ozonolysis in a mixture of ethyl acetate and methanol, hydrogenation of the ozonolysis products over Lindlar catalyst and subsequent saponification with alkali, only a small quantity (22%) of the hydroxyketone (**64**) is formed, a large portion of the initial compound is recovered unchanged in spite of the use of an excess of ozone and forcing conditions.[47] An analogous result was also obtained on ozonation (methanol, hydrogenation of the peroxide over Pd/C) of the product of reduction of this lactone, viz. the diol (**65**) (see Scheme 6).[48]

IV. Ozonolysis of labdanoids with oxygen-containing functional groups at C(8) and C(13) and a double bond at C(14) or with a hydroxy group at C(8) and a double bond at C(13)–C(14)

Sclareol (**66**) was one of the first labdanoids of this type to be subjected to ozonolysis (CCl_4, fission of the ozonide by boiling with water).[49] However the product was not identified exactly. It was only recorded that is has the composition $C_{18}H_{30}O$ and was an oxide in character. On carrying out the reaction under the conditions indicated we obtained a complex mixture of products.[50] Subsequently sclareol was treated with ozone in a polar solvent (methanol) and the ozonolysis product was decomposed with ammonium chloride.[51] The epoxide (**69**) was readily isolated by crystallisation in high yield (80%) in this way. It is formed by the condensation of the primary ozonolysis products, formaldehyde and the hydroxyketone (**67**), and subsequent dehydration of the dihydroxydiketone (**68**) (Scheme 7). Compound (**69**) is either not formed or its yield is reduced significantly on using other compounds (common acids, Lewis acids, acid salts, etc.) for the decomposition of the peroxide oxidation products. Ozonation of compound (**69**) in hexane with subsequent heating of the ozonide with water leads quantitatively to the 1,3-diketone (**70**). This was decomposed with alkali to the hydroxyacid (**71**), which lactonises to norambreinolide (**44**) and to 14,15,16-trinorlabd-8α-ol-12-one (**72**),[52,53] important compounds in practice for the synthesis of perfumes. In particular, a mixture of them may be converted readily into an analogue of the known perfume ambroxide.[52]

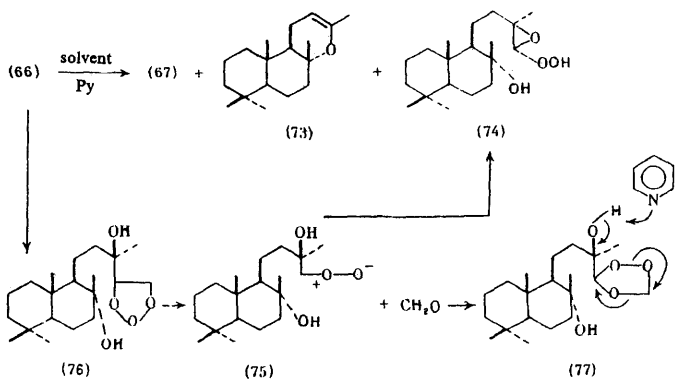
Scheme 7





(67) + CH_2O + HCO_2^- · Py · H^+

Scheme 8

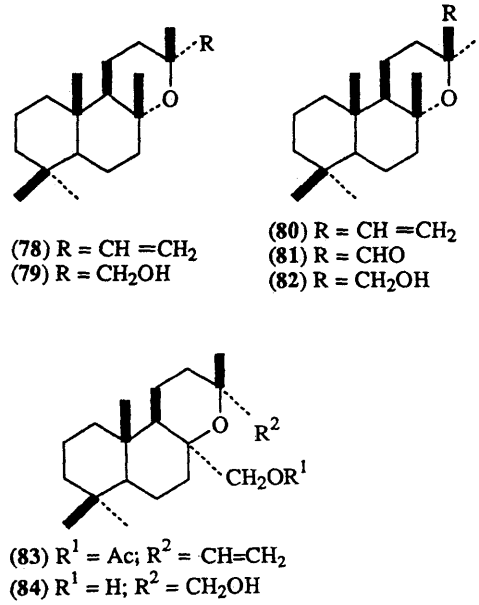


The ozonolysis of sclareol (**66**) has been investigated by other authors.[50] It was shown that on carrying it out in methanol and treating the product with dimethyl sulphide a mixture of at least six compounds is formed. Ozonolysis in dichloromethane, carbon tetrachloride, methanol or ethyl acetate in the presence of pyridine or in ethyl acetate with subsequent heating of the ozonide with water gives a mixture of the hydroxyketone (**67**), the epoxide (**73**) and the α-epoxyhydroperoxide (**74**) (Scheme 8). The latter is unstable and was characterised by spectral data and chemical conversions. Its formation is in agreement with and confirms the ozonation mechanism of allyl alcohols proposed by Everest and collaborators,[54] according to which the zwitterion (**75**), generated from the initial ozonide (**76**) of sclareol, is stabilised as the epoxyhydroperoxide (**74**). The nature of the solvent therefore has little effect on the composition of the reaction products in the ozonolysis of sclareol in the presence of pyridine. It was shown that pyridine does not react with hydroperoxide (**74**). Consequently if the ozonolysis of sclareol (**66**) occurs only by the mechanism proposed by Everest and collaborators,[54] then the presence of pyridine in the reaction mixture must have no effect on the yield and ratio of the compounds (**67**), (**73**), and (**74**). However, experimentally this is not so. This may be explained by the ozonolysis of sclareol proceeding partially according to the mechanism of Criegee[5,6] with the formation of the normal ozonide of sclareol (**77**) and its decomposition involving pyridine evidently as indicated in Scheme 8. The course of the reaction according to the latter mechanism depends to a definite extent on the solvent used.

The oxidation with ozone of those labdanoids in which the carbon atoms C(8) and C(13) are linked by an oxygen bridge, i.e. the manoyl oxides, proceeds in a different way.

The ozonolysis of manoyl oxide (**78**) (CCl_4, the ozonide was decomposed by boiling with water) was carried out for the first time by Hosking and Brandt.[55] However the nonvolatile products were not investigated by them. Later Cambie and collaborators[56] ozonised manoyl oxide (**78**) in dichloromethane in the presence of pyridine and the product was reduced with sodium borohydride giving 15-nor-8-α,13-epoxy-14-hydroxylabdane (**79**) (80%) (Scheme 9).

Scheme 9

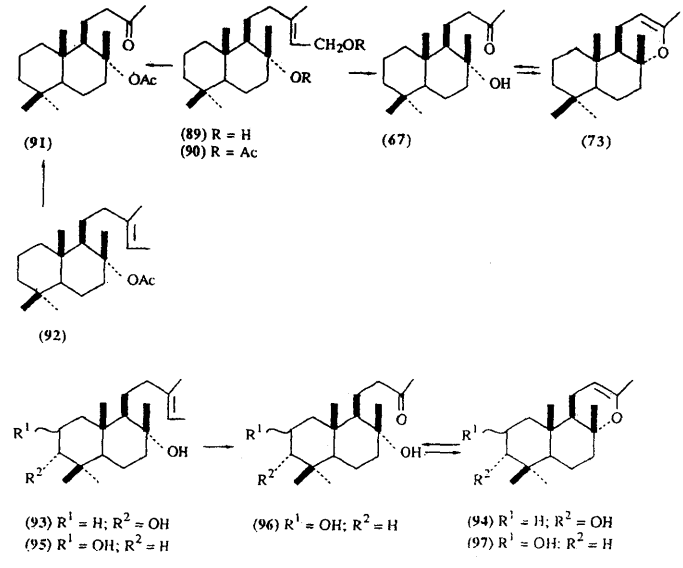


13-Epimanoyl oxide (**80**) was ozonised in carbon tetrachloride with subsequent heating of the ozonide with water. The reaction product proved to be the aldehyde (**81**) (70%).[57] On ozonising the epoxide (**80**) in dichloromethane in the presence of pyridine and reducing the product with sodium borohydride, the alcoholic epoxide (**82**), an epimer of compound (**79**), was isolated in 78% yield.[58] The ozonolysis of 8-epi-20-acetoxymanoyl oxide (**83**) to the dihydroxyepoxide (**84**) (75%) was effected fairly smoothly under the conditions indicated above.[56]

The appearance of a functional group at C(12) in manoyl oxides leads to the fission of the C(12)–C(13) bond on ozonolysis. Norambreinolide (**44**) (40%) and the acetoxyacid (**86**) (15%) were formed on ozonation of 12α-hydroxy-13-epimanoyl oxide (**85**) in chloroform followed by oxidative fission of the ozonide with hydrogen peroxide.[59]

The first of the labdanoids with a hydroxyl group at C(8) and a double bond at C(13) to be subjected to ozonation was (13*E*)-*ent*-8β,15-dihydroxylabd-13-ene (afanamixol) (**87**). The reaction was carried out in acetic acid and the ozonolysis product was reduced with metallic magnesium in hydrochloric acid. The hydroxyketone (**88**) was obtained in 88% yield.[60] The unsaturated epoxide (**73**) (75%) was isolated on ozonolysis of the antipode (**89**) of afanamixol (**87**) in a mixture of methanol and dichloromethane and reduction of the peroxide compounds with dimethyl sulphide.[61] In this case also the first reaction product is the hydroxyketone (**67**), which, as is known,[62] on heating or by the action of acid is transformed into the epoxide (**73**) with which it is in equilibrium. The equilibrium transition (**67**) ⇆ (**73**) is impossible if the hydroxy group of the starting material (**89**) is esterified. In fact the ozonation of the diacetate (**90**) [$CH_3OH-CH_2Cl_2$; $(CH_3)_2S$] leads to ketoacetate (**91**) (90%).[61] This same compound is also formed in almost quantitative yield (98%) on ozonation of the unsaturated acetate (**92**) in dichloromethane in the presence of pyridine.[21] Under the same conditions (13*E*)-3α,8α-dihydroxylabd-13-ene (**93**) gave 3α-hydroxy-8α,13-epoxy-14,15-dinorlabd-12-ene (**94**) (90%),[63] and a mixture of (13*E*)-2α- and 2β,8α-dihydroxylabd-13-enes (**95**) gave an equilibrium mixture of the 2α- and 2β,8α-dihydroxyketones (**96**) and the epoxides (**97**) (91%) (Scheme 10).[64]

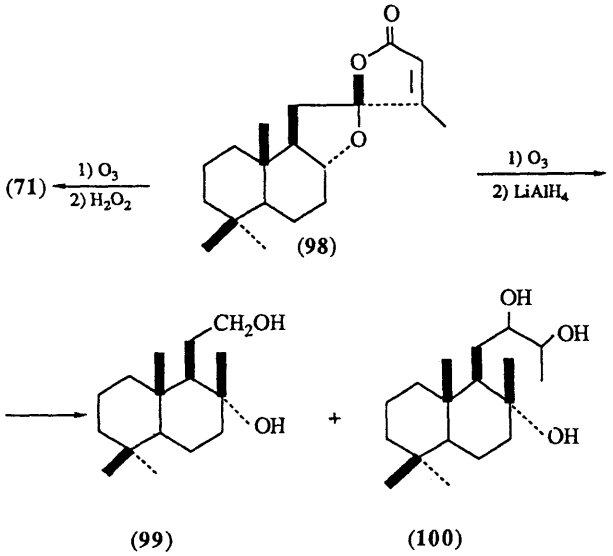
Scheme 10



If an oxygen-containing group is present at C(12) in addition to the hydroxyl group at C(8) and a double bond at C(13) in a labdanoid then depending on the conditions fission of the single

bond at C(12)–C(13) may result. The diol (**99**) (55% yield) and the triol (**100**) (~45%) were isolated on ozonolysis of α-levantenolide (**98**) in ethyl acetate and reduction of the ozonide with lithium aluminium hydride (Scheme 11). On oxidative fission of the ozonide with hydrogen peroxide the sole reaction product is norambreinolide (**44**) (78.5%).[65]

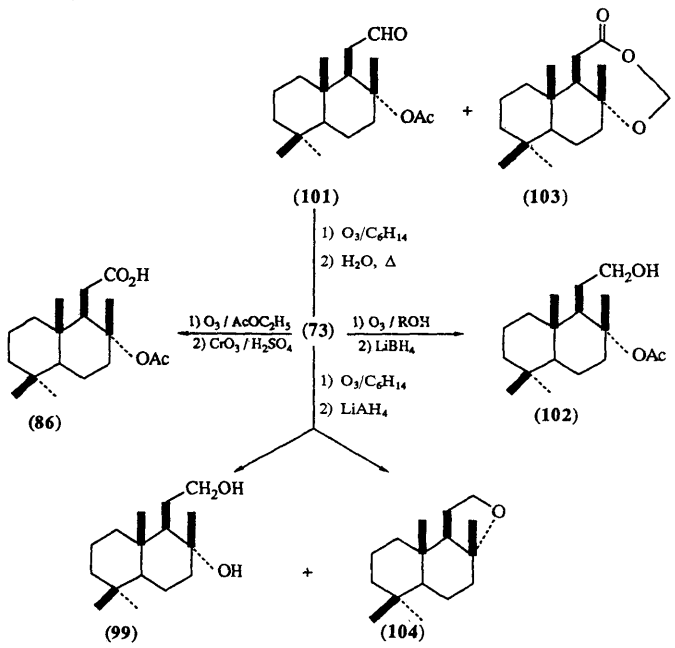
Scheme 11

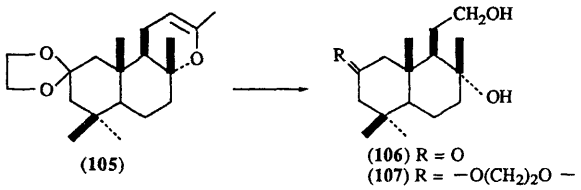


V. Products of the ozonolysis of 8α,13-epoxy-14,15-dinorlabd-12-ene and its derivatives

8α,13-Epoxy-14,15-dinorlabd-12-ene (**73**) and its derivatives are important intermediates on the route from the labdanoids to valuable perfumes,[2] consequently its ozonolysis is not solely of theoretical interest and has been investigated in detail (Scheme 12).

Scheme 12





The ozonolysis of the epoxide (**73**) was effected for the first time in hexane with subsequent treatment of the ozonide with water.[62] The acetoxyacid (**86**) was isolated in 24% yield. Later Stoll and Hinder[66] showed that if the reaction is carried out in ethyl acetate and the ozonide is decomposed with an excess of Raney nickel, then the main reaction product is the acetoxyaldehyde (**101**) (~48%), minor products being the acetoxyacid (**86**) (~3%) and the hydroxyacetate (**102**) (traces). On decomposing the ozonide by boiling with water yield of the acetoxyaldehyde was increased to 61–67% and that of the acetoxyacid (**86**) remained unchanged. A small quantity of the lactone acetal (**103**) was also isolated.[66,67] The same authors[68] ozonolysed the epoxide (**73**) in hexane and reduced the ozonide with lithium aluminium hydride. As a result the glycol (**99**) (57 to 73%) and the epoxide (**104**) (14 to 1.2%) were obtained the ratio of which depended on the conditions. Ozonolysis of the epoxide (**73**) has been repeated[58,61,69] in hexane with reduction of the ozonide with lithium aluminium hydride. The diol (**99**) was obtained in 67, 68, and 76% yield respectively but no formation of the epoxide (**104**) was observed.

A study[69] has been devoted to the search for conditions for a purpose-directed synthesis of bicyclohomofarnesane compounds from sclareol oxide. It was shown that the most convenient route to the acetoxyaldehyde (**101**) was the ozonolysis of the epoxide (**73**) in dichloromethane or ethyl acetate in the presence of pyridine or in hexane with decomposition of the ozonide by heating with water. A small quantity (13–19%) of the acetoxyacid (**86**) was formed in addition to the acetoxyaldehyde (80% yield). If the ozonide obtained in hexane was decomposed by heating with hydrogen peroxide then the reaction product was a 3:2 mixture of the compounds (**86**) and (**101**). The acetoxyacid (**86**) is the predominant product on oxidative fission of the ozonide with Jones reagent (65% yield) or on ozonolysis in cyclohexane in the presence of acetic acid and silica gel (74% yield under optimal conditions). The hydroxyacetate (**102**) (62–64% yield) was obtained on ozonolysis of sclareol oxide (**73**) in isopropanol or methanol and reduction of the peroxide products with lithium borohydride.

The ozonolysis products of the ethyleneketal of 2-ketomanoyl oxide (**105**) have also been investigated. A mixture of the dihydroxyketone (**106**) (39%) and the dihyroxyketal (**107**) (40%) was formed on carrying out the ozonolysis then reducing the ozonide with lithium aluminium hydride.[70]

VI. Products of the ozonolysis of labda-8(17),14-dien-13-ol (manool) and compounds related to it

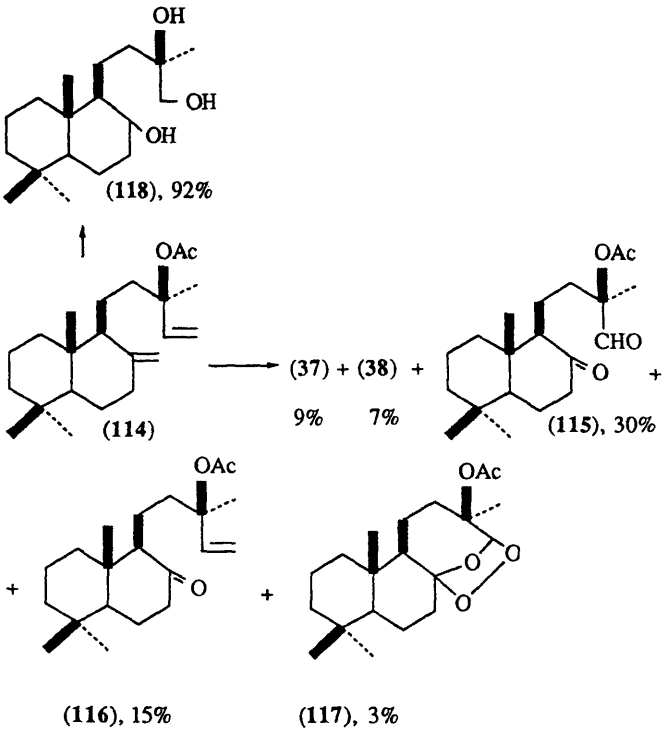
The ozonolysis of manool (**108**), one of the most important labdanoids in practice, has been investigated fairly thoroughly. It was first carried out by Hocking (CCl_4, 0 °C, decomposition of the ozonide by heating with water)[71] who identified the diketone (**19**) (34% yield). 14,15-Dinorlabd-8(17)-en-13-one (**37**) (13%) and the unsaturated epoxide (**109**) (9%) were obtained by the same

procedure for decomposing the reaction products but carrying it out under more forcing conditions in acetic acid.[72] Barltrop and collaborators[73] ozonolysed manool (**108**) in ethyl acetate, decomposed the ozonide with zinc dust in boiling water and isolated the diketone (**19**) (36%) and a product of its further transformation (**110**) (6%). A far more complex mixture of neutral products (**37**), (**38**), (**111**)–(**113**) is formed on ozonation of manool (**108**) in dichloromethane with oxidative fission of the ozonolysis products with hydrogen peroxide.[31] Compounds (**37**) and (**113**) are formed in trace amounts. The yields of the remaining product are shown in Scheme 13 under the formulae. Products of an acid character were not investigated by these authors.

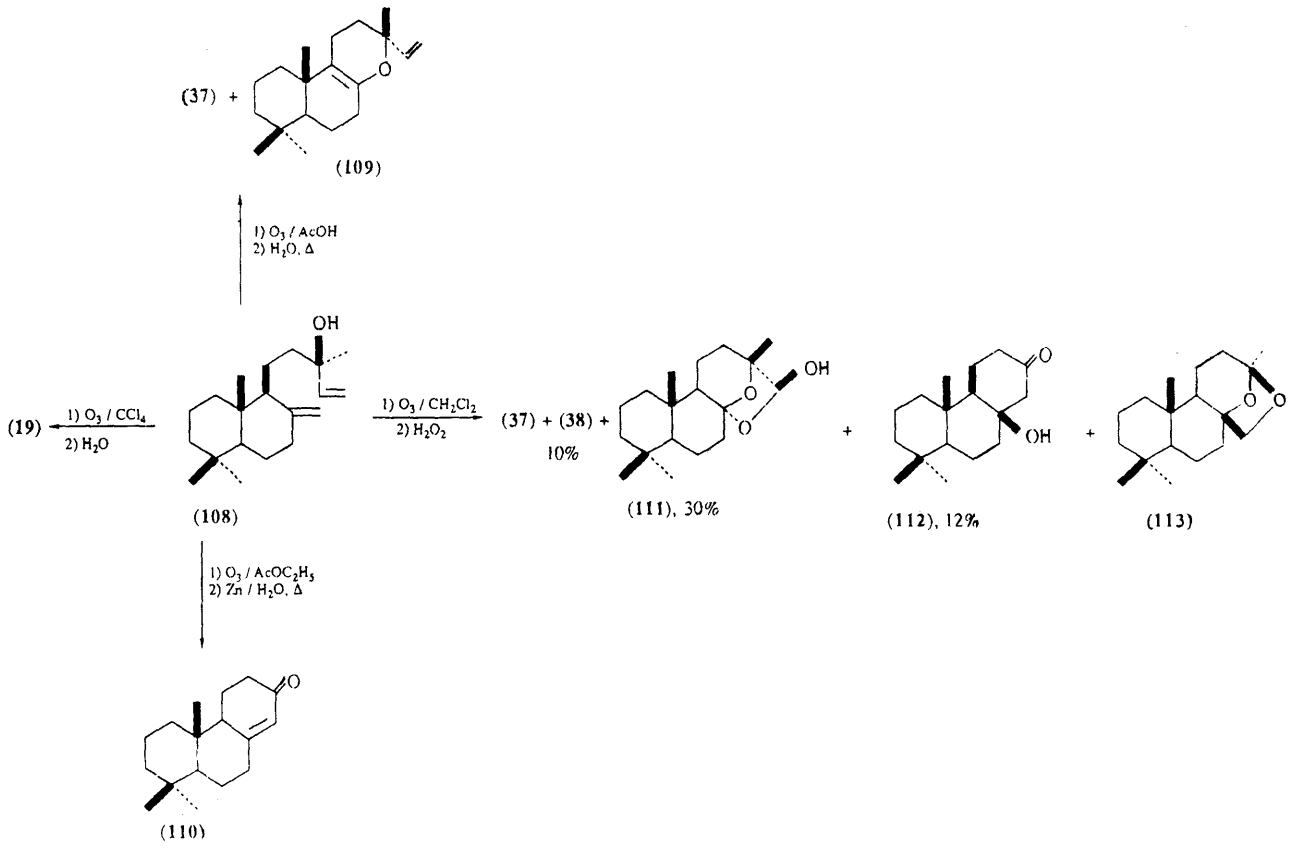
These authors[31] also investigated the ozonolysis products of manool acetate (**114**) under the same conditions. In this case also a complex mixture of products was obtained which are shown in Scheme 14 (with an indication of the yield). The cyclic products (**38**) and (**117**), called oxonides by the authors, were the unusual products of the ozonation and are unstable compounds. The ozonolysis of manool acetate (**114**) in dichloromethane in the presence of pyridine occurs in an altogether different way.[58] The triol (**118**) is isolated in 92% yield after reduction of the ozonolysis products with lithium aluminium hydride, i.e. only the double bond is broken under these conditions.

In view of the data given above it may be concluded that the ozonolysis of manool (**108**) does not as yet have any practical value.

Scheme 14

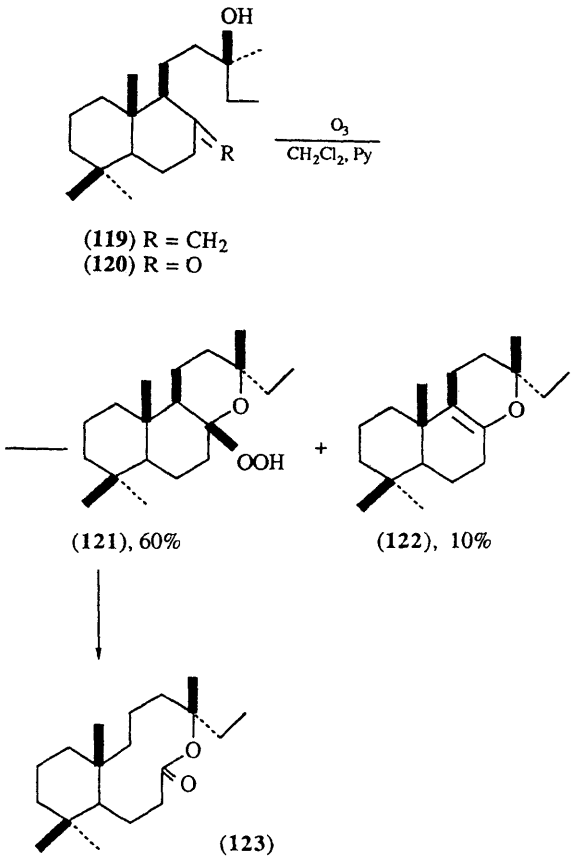


Scheme 13



The ozonolysis of dihydromanool (**119**) has also been investigated. Conducting the reaction in methanol and reducing the peroxide compounds with dimethyl sulphide leads smoothly to the hydroxyketone (**120**) (81%).[74] A mixture (6:1) of compounds (**121**) and (**122**) is formed in dichloromethane in the presence of pyridine (Scheme 15).[75] This result indicates that pyridine is ineffective as a reducing agent when hydroperoxides and not ozonides are formed as a result of the ozonolysis. The hydroperoxide (**121**) is unstable and on storage is converted into the epoxide (**122**). This hydroperoxide undergoes an interesting conversion under the action of mesyl chloride into the lactone (**123**) containing a ten-membered lactone ring. This reaction is of a general nature.

Scheme 15



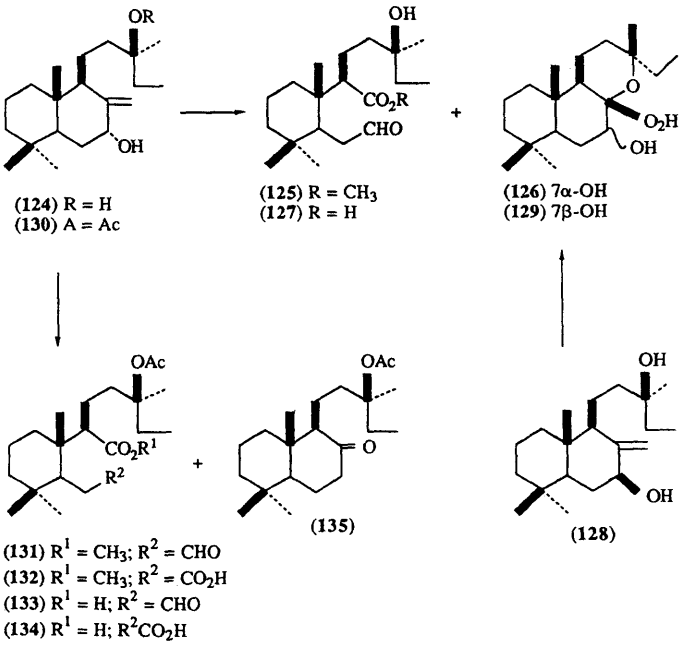
(**119**) R = CH_2
(**120**) R = O

(**121**), 60% (**122**), 10%

(**123**)

Interesting results were obtained by Everest and collaborators on ozonolysis of a series of allyl derivatives of dihydromanool.[54] They found that the character of the products formed depends on the solvent used and the conditions. Anomalous ozonolysis products were formed on simple evaporation of the solvent at low temperature, and differed depending on whether an aprotic solvent or an alcohol was used. On reduction of the ozonation product either a normal or a mixture of normal and anomalous reaction products was formed. The stronger the reducing agent the greater was the quantity of the normal product. For example, ozonolysis of 7α-hydroxydihydromanool (**124**) in methanol and evaporation of the solvent gave compounds (**125**) (40%) and (**126**) (34%) but with the same treatment and in dichloromethane compounds (**126**) (26%) and (**127**) (14%) were formed. The configuration of the hydroxyl group at position C(7) is important. 7β-Hydroxydihydromanool (**128**) gave a mixture of compounds (**125**) (8%) and (**129**) (30%) on ozonolysis in methanol (Scheme 16).

Scheme 16



(**124**) R = H
(**130**) A = Ac

(**125**) R = CH_3
(**127**) R = H

(**126**) 7α-OH
(**129**) 7β-OH

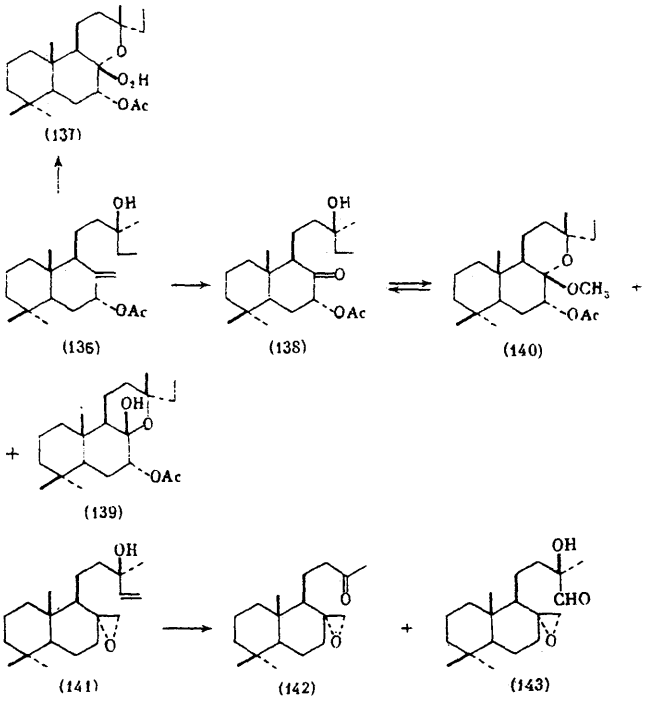
(**135**)

(**128**)

(**131**) R^1 = CH_3; R^2 = CHO
(**132**) R^1 = CH_3; R^2 = CO_2H
(**133**) R^1 = H; R^2 = CHO
(**134**) R^1 = H; R^2CO_2H

7α-Hydroxydihydromanool 13-monoacetate (**130**) is converted on ozonolysis in methanol into a mixture of the products (**131**) (37%) and (**132**) (46%), in dichloromethane into a mixture of compounds (**133**) (40%) and (**134**) (41%) and in methanol and reduction with dimethyl sulphide into the acetoxyketone (**135**) (88%). As might have been expected only the normal product, the unstable acetoxyhydroperoxide (**137**) (67%), is formed on ozonolysis of 7α-hydroxydihydromanool 7-monoacetate (**136**) (with a protected allylic hydroxyl group) in methanol with subsequent distillation of the methanol. An equilibrium mixture of substances (**138**) and (**139**) was isolated in 60% yield on reducing the ozonolysis product of the same compound with triethyl phosphite. If dimethyl sulphide is used as the reducing agent then a small quantity (17%) of the methoxyacetate (**140**) is formed in addition to compounds (**138**) and (**139**) (58%) (Scheme 17).[74]

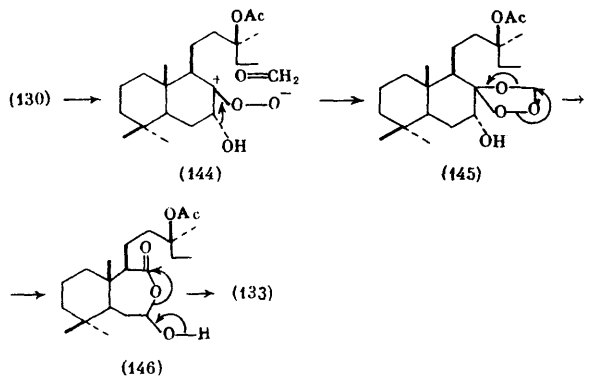
Scheme 17



The ozonolysis of 8(17)α-epoxymanool (**141**) has also been investigated.[54] The epoxyketone (**142**) (32%) was isolated on ozonolysis in methanol and evaporation of the solvent, but on reduction of the ozonolysis product with dimethyl sulphide a mixture of the epoxyketone (**142**) (15%) and aldehyde (**143**) (30%) was formed. If the same reduction is carried out with triethyl phosphite then the yields of compounds (**142**) and (**143**) are 6 and 36% respectively. Demole[76] effected the ozonolysis of the epoxymanool (**141**) in carbon tetrachloride and decomposed the ozonide with an aqueous solution of sodium bicarbonate. The ozonolysis product was subjected to further conversions without isolation, but judging by the results the yield of the epoxyketone (**142**) did not exceed 25–30%.

When analysing the above data it was concluded[54] that the mechanism proposed by Criegee for the ozonolysis of allylic alcohols[5,6] does not provide an adequate explanation. According to Criegee's mechanism the ozonolysis of compound (**130**) must proceed as in Scheme 18.

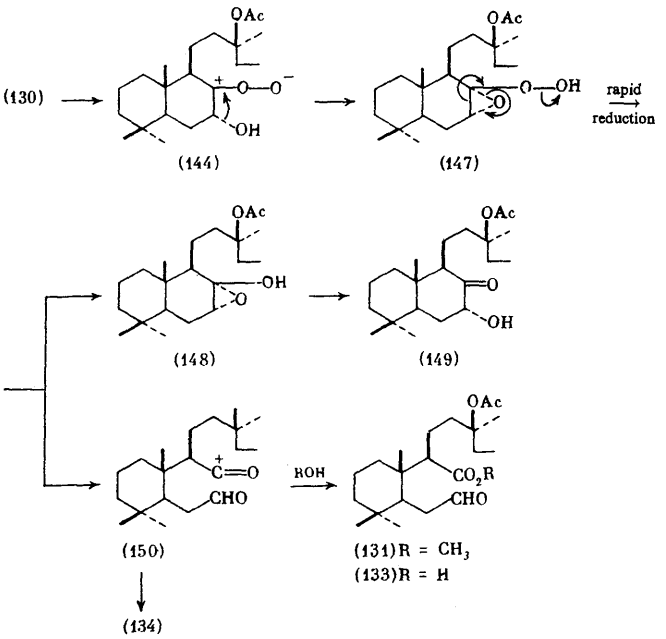
Scheme 18



If the reaction goes by this mechanism then: 1) the zwitterion (**144**) must react with methanol and give the corresponding methoxyhydroperoxide, 2) the C(9) atom, which is more electrophilic than C(7), should migrate preferentially to oxygen in the ozonide (**145**) and 3) the aldehydoacid (**133**) should be the reaction product and not its methyl ester which was in fact obtained.

Another mechanism has been proposed[54] for the ozonolysis of allylic alcohols [this is illustrated in Scheme 19 for compound (**130**) as an example] which explains all the facts mentioned above. In particular: 1) the rapid reduction of the ozonolysis product suppresses the formation of anomalous compounds, 2) carbon monoxide is evolved on ozonolysis of compounds in which there is a proton on the carbon atom bound to the carbonyl carbon atom and 3) specifically, the acids (**133**) and (**134**) are formed on ozonolysis of the unsaturated compound (**130**) in an aprotic slvent

Scheme 19

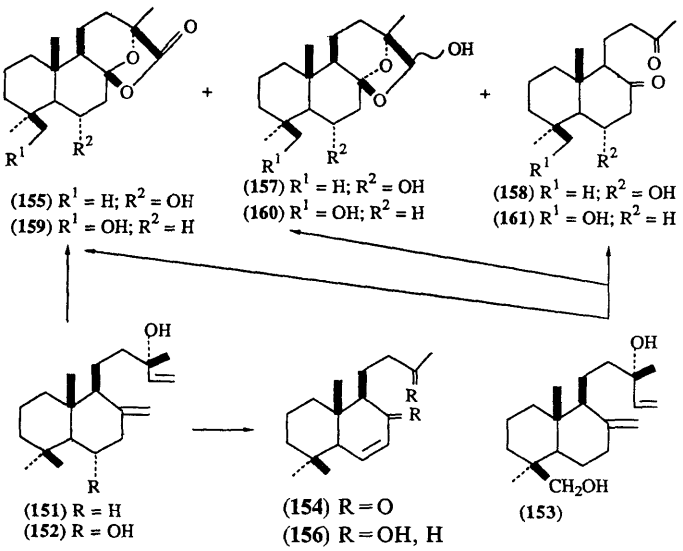


The very strained α-epoxyhydroperoxide (**147**) is spontaneously converted into the carbocation (**150**) which is neutralised by the solvent. When the grouping $-CH_2=CH-C-OH$ is present in the molecule, expulsion of proton occurs and carbon monoxide is evolved.

The ozonolysis of two derivatives of 13-epimanool (**151**) has also been investigated. These were larixol, labda-8(17),14-diene-6α,13(*S*)-diol, (**152**) and 13-epitorulosol, labda-8(17),14-diene-19,13(*S*)-diol (**153**).

The formation of a peroxide of composition $C_{19}H_{32}O_7$ of unestablished structure was recorded on ozonolysis of larixol (**152**), however, its decomposition was not carried out.[77] On carrying out the reaction in absolute methanol and treating the product with ammonium chloride a mixture was formed of no less than seven compounds among which the unsaturated diketone (**154**) and the hydroxylactone acetal (**155**) predominated (Scheme 20).[78] Other authors[79] have also ozonolysed larixol in methanol but the product was reduced with di-isobutylaluminium hydride. The diol (**156**) was isolated in low yield from the reaction products. Its structure was confirmed by X-ray structural analysis.

Scheme 20



The ozonolysis of larixol in methanol and reduction of the peroxide products with dimethyl sulphide or in dichloromethane in the presence of pyridine leads to a mixture of five compounds, identical in qualitative composition, the predominating components of which, compounds (**157**) and (**158**), were isolated and identified.[78]

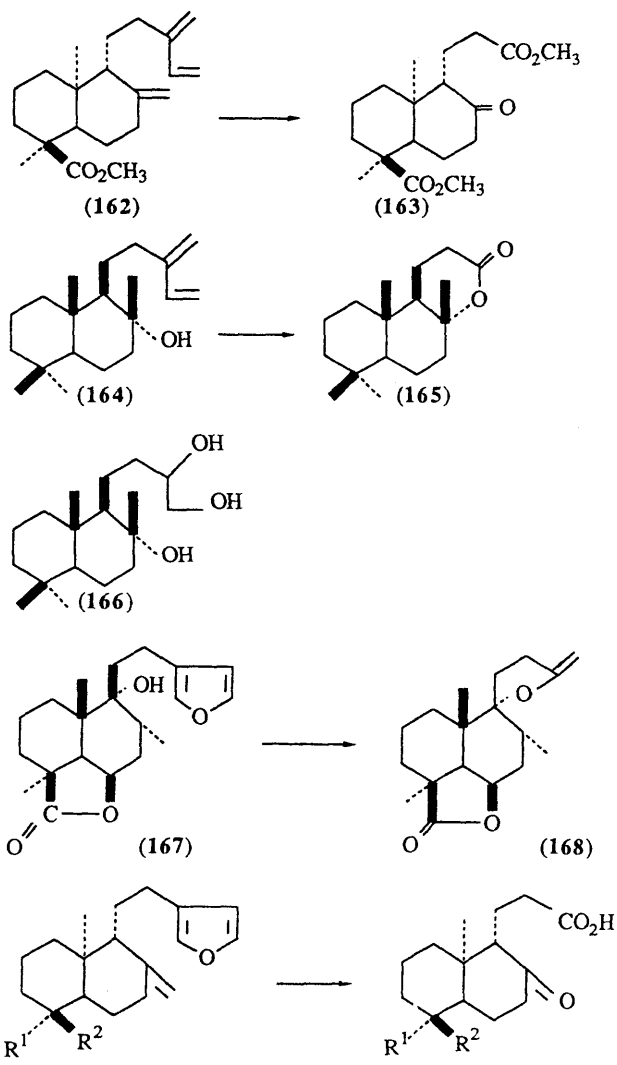
The ozonolysis of 13-epitorulosol (**153**) has been carried out under a variety of conditions: in methanol with subsequent treatment of the ozonation product with dimethyl sulphide, in a mixture of dichloromethane and pyridine and in hexane with decomposition of the ozonide by heating with water.[80] In all cases the reaction product was a mixture of three compounds (**159**)–(**161**). In the first case the hydroxylactone (**159**) predominates and in the latter the two compounds (**160**) and (**161**) predominate (Scheme 20).

The data given above indicate that the main products of the ozonolysis of larixol (**152**) and 13-epitorulosol (**153**) are formed by fission of their double bonds and the single bond at C(13)–C(14) and by the reaction of the keto group at C(8) with the hydroxyl group at C(13) and the functional group generated at C(14).

VII. Ozonolysis of labda-13(16),14-diene compounds, furanolabdanoids and labd-13(14)-enoids with oxygen-containing functional groups at C(15) and C(16)

On treating representatives of this structural group of labdanoid diterpenes with ozone the side chain is, as a rule, shortened by three carbon atoms. On ozonolysis of the methyl ester of *ent*-labda-8(17),13(16),14-trien-18-oic acid (**162**) in a mixture of acetic acid and ethyl acetate at 0 °C followed by oxidative fission of the ozonation products with alkaline hydrogen peroxide, Ourisson and collaborators[81] isolated, after methylation and diazomethane, the ketodiester (**163**) (25%) (Scheme 21). In contrast to compound (**162**) the ozonolysis of isoabienol (**164**) in absolute methanol with subsequent hydrogenation of the product over Lindlar catalyst leads to ambreinolide (**165**) (93%). The yield of ambreinolide was less (85%) on using dimethyl sulphide as reducing agent.[82] It is more convenient to carry out the ozonolysis of isoabienol (**164**) in ethyl acetate in the presence of pyridine (72% ambreinolide yield).[83] If the ozonolysis of isoabienol is carried out in methanol and the peroxide products are reduced with lithium borohydride then the triol (**166**) is the main reaction product (72%). These data show that on using dimethyl sulphide for the reduction of the peroxide ozonolysis products of isoabienol, there is an initial rearrangement with fission of the single carbon–carbon bond at C(13)–C(14) and then reduction occurs. Potassium borohydride only reduces the peroxide compounds. In view of the value of the ambreinolide for perfume manufacture[2] and the cheapness of isoabienol (it is contained in large amounts in the needles of the Scots pine[84]), the ozonolysis of the latter may be of practical interest.

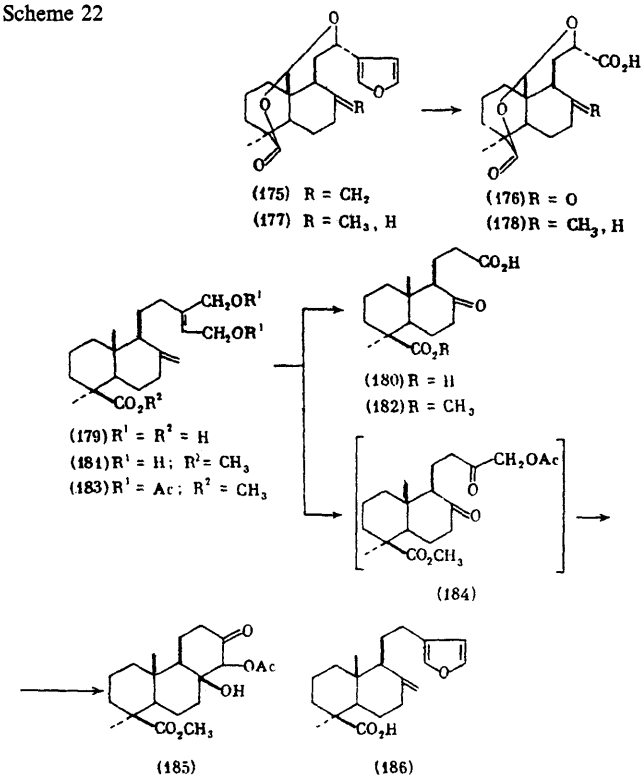
Scheme 21



Marrubiin (**167**) was one of the first of the furanolabdanoids to be subjected to ozonolysis (see Scheme 21).[85] The reaction was carried out in acetic acid and the reaction product proved to be the dilactone (**168**) (20%). Polyalthic acid (**169**) was ozonolysed in the same solvent. The ketodiacid (**170**) (17%) was isolated after treatment of the reaction product with hydrogen peroxide in alkali.[86] On ozonolysis of polyalthic acid methyl ester (**171**) in chloroform and fission of the ozonide with hydrogen peroxide, the reaction product was the monoester (**172**) (25%) of the ketodiacid (**170**). An epimer of polyalthic acid, daniellic acid (**173**), was oxidised with ozone in dichloromethane in the presence of pyridine and the product oxidised further with hydrogen peroxide in alkali. These conditions are appropriate since the yield of the ketodiacid (**174**) proved to be fairly high (66.5%).[29] Sciadin (**175**), which is more complex in structure, gave a product (**176**) on ozonolysis in chloroform in only 8.7% yield.[87] The ozonation of dihydrosciadin (**177**) to compound (**178**) proceeded with a better yield (17.4%) but in this case the products of ozonolysis were boiled with water.

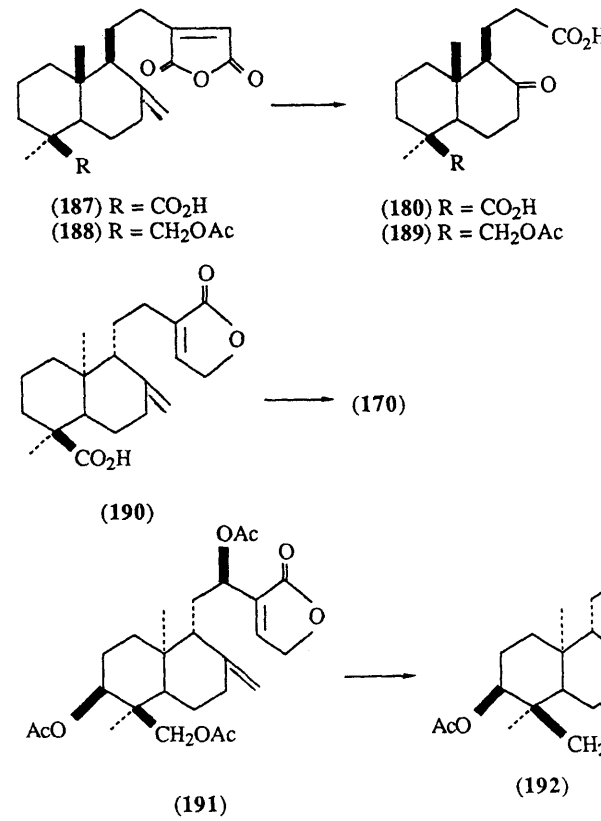
Sciadopic acid (**179**) is an example of a compound with a double bond at C(13)–C(14) and functional groups at C(15) and C(16) (Scheme 22).[84] The ketodiacid (**180**) (27%) was isolated on treating it with ozone in dichloromethane with oxidative fission of the product with hydrogen peroxide in alkali. Fission of the ozonolysis product by heating with water proved to be less effective. In such cases methyl sciadopate (**181**) was converted into compound (**182**) in only 10% yield (after alkaline saponification). The ozonolysis of the diacetoxyester (**183**) occurs in an altogether different way. The ozonolysis was carried out in dichloromethane and the product was reduced with zinc in acetic acid. The tricyclic compound (**185**) was obtained in this case in 77% yield, evidently formed by aldol cyclisation of the ozonation product, via. the diketoester (**184**) (Scheme 22).

Scheme 22



The transformation products of lambertianic acid (**186**) and the anhydrides (**187**) and (**188**) belong to the same group of labdanoids. On ozonolysis in a mixture of ethyl acetate and acetic acid with oxidative fission of the products with hydrogen peroxide the ketodiacid (**180**) (56%) and the ketoacid ester (**180**) (56%) and the ketoacid ester (**189**) (44%) respectively were obtained (Scheme 23).[89]

Scheme 23



The ozonolysis labdanoids containing an unsaturated γ-lactone grouping in the side chain, such as nivenolide (**190**), occurs in a similar manner.[90] On ozonolysis in methanol and treatment of the product with hydrogen peroxide in alkali the ketodiacid (**170**) (49%) was isolated (Scheme 23).

If there is an oxygen-containing functional group at position C(12) in a labdanoid with an unsaturated γ-lactone grouping then fission of the single bond at C(12)–C(13) occurs on ozonolysis. For example, the derivative andrographolide (**191**) gave the ketoacid (**192**) on ozonolysis in ethyl acetate and treatment of the product with hydrogen peroxide.[91]

* * *

The data accumulated show that ozonolytic transformations of labdanoids affect the carbon side chain and ring A. If there are isolated double bonds and no functional groups in the positions 4 and 5 relative to them in this structural fragment then the ozonolysis proceeds fairly unequivocally. If there are functional groups in the labdanoids at positions C(8) and C(12)–C(16) then ozonolysis leads to a complex mixture of compounds. This is a particular feature of labdanoids with an allyl structural fragment, a furan ring and an

unsaturated γ-lactone grouping. The latter two types of compound give α-dicarbonyl compounds as primary ozonolysis products.

The investigation of the ozonolysis products of the available labdanoids (sclareol, manool, abienols, etc.) and the effect of the reaction conditions on the route of the process, the clarification of the mechanism and principles of the ozonolysis reaction and the development of industrial ozonolytic processes are all problems of both theoretical and practical interest.

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