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Natural aliphatic oxygenated unsaturated acids. Synthesis and biological activity

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Abstract. The review is devoted to natural unsaturated acyclic acids containing oxygen functions. Compounds of the aceto-genin and propiogenin types containing hydroxy, oxo, and epoxy groups as well as ether, hydrofuran, and hydropyran fragments are considered. Data are given on the biological activities of the acids themselves or of natural compounds whose structural elements are unsaturated acids. The methodology and strategy of the synthesis of both linear unsaturated hydroxy and alkoxy acids and those containing a heterocyclic fragment are discussed. The bibliography includes 172 references.

I. Introduction

The unique biological role of oxygen-containing unsaturated acids is generally acknowledged. By now, a unified theory for the arachidonic acid cascade has been elaborated, which provides, together with offering a deeper insight into the mechanism of oxidative metabolism, a means to important discoveries in bio-organic chemistry and medicine. More and more attention is being given to hydroxy unsaturated acids as promising tools in the self-defence of plants against fungal diseases. The development in the foreseeable future of radically new fungicides, which are active even when used at nanogram concentrations, is becoming ever more realistic. Of significant interest are unsaturated acids that possess the ability to control the biosynthesis of cholesterol. A striking diversity of biological activities has been found among the unsaturated acids and compounds containing their fragments, isolated from marine organisms.

Thus, the importance of biological screening, however modest are the means it employs, is in no doubt. At present, biotesting is becoming a more and more sophisticated procedure, which reflects the increasing interest in naturally occurring acids shown by numerous laboratories and firms engaged in the design of medicinal drugs and means for raising agricultural yields.

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Nevertheless, the chemistry and biochemistry of oxygen-containing unsaturated acids discussed herein needs further extensive research. It can be said with confidence that this class of natural compounds is of interest both to synthetic chemists and specialists dealing with the development of technological methods for the synthesis of natural compounds and their analogues with predetermined biological activity.

While preparing the present review, the authors were faced with the necessity to restrict its remit and exclude from the consideration:

lactones of hydroxy unsaturated acids meriting special attention;

macrolide antibiotics that are regularly covered in reviews and monographs;

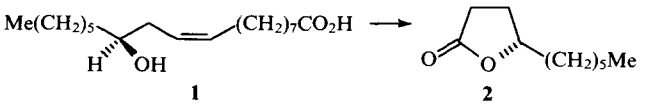
compounds of the arachidonic acid cascade with the exception of certain metabolites;

polyester toxins of the ocadaic acid type.

The review is concerned with the acids and their derivatives, in the structure of which a continuous carbon chain can be traced providing for the formation of oxygen-containing heterocycles of the hydrogenated furan and pyran type. In some cases, metabolites of unsaturated acids are considered that have an ether group, which interrupts the continuous carbon chain, as well as halogen-containing acids. Special attention is given to the biological activities and physiological functions of the compounds under discussion.

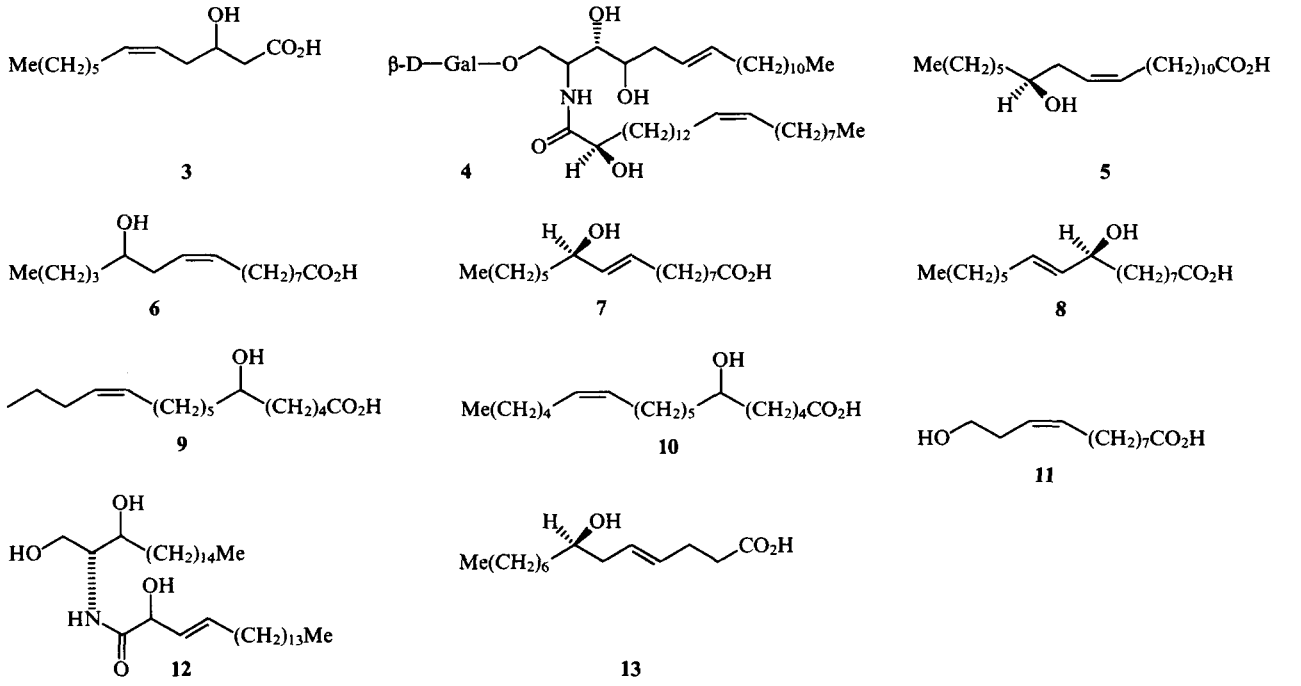
II. Linear unsaturated hydroxy and epoxy acids and their derivatives

Many unsaturated monohydroxy acids are related to the group of widely occurring natural compounds. Thus, in 1985 the worldwide production of castor oil containing ricinoleic acid **1** as the major acid component, amounted to 400 000 tons.[1] The technical significance of castor oil is great. This includes polymeric compounds and the production of sebacic and undecenoic acids, as well as enanthal. Of great practical utility is the microbial degradation of ricinoleic acid into the optically active decanolide **2**.



1 **2**

Scheme 1



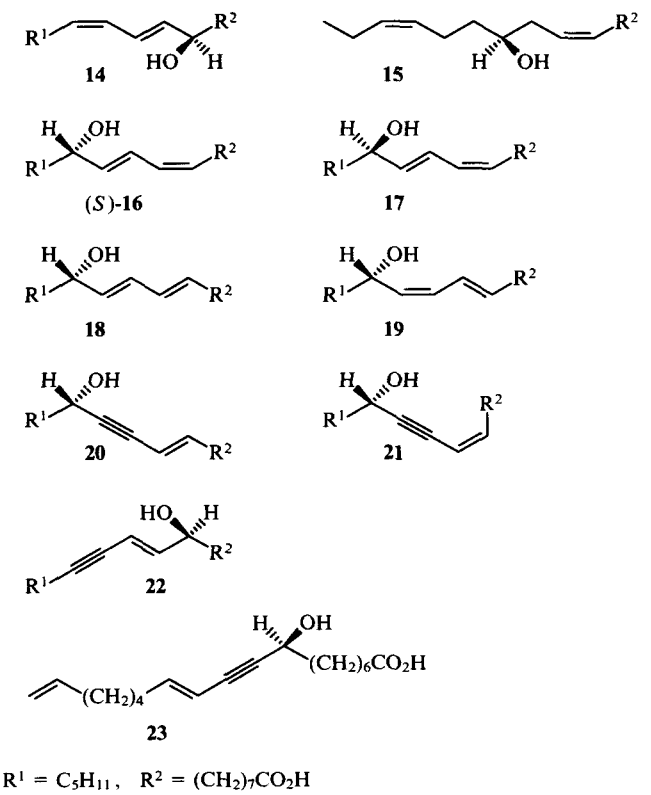
The isolation of several monohydroxy monoenoic acids has been described. Thus, 3-hydroxy-(5*Z*)-dodecenoic acid **3** has been obtained from the lipids of the plant *Serratia marcescens*.[2] (2*R*)-Hydroxy-(15*Z*)-tetracosenoic acid is a constituent of the galactosphingolipid **4** isolated from marine organisms.[3] Lesquerolic acid **5**[4] and the acid **6**[5] have been isolated from plants of the *Lesquerella* genus. Internodes of the timothy (*Phleum*) infested with the fungus *Epichloe typhii* have been found to contain the acids **7** and **8**; the enhanced resistance of the infested plants against some pathogenic fungi has been noted.[6] The plant *Acantopanax sessilifloria* contains the acids **9** and **10** with an unestablished configuration of the asymmetric centre.[7] The physiologically active 12-hydroxy-(9*Z*)-dodecenoic acid **11** has been isolated from homogenates of pea leaves;[8] the synthesis of this acid has been described.[9] The sphingolipid **12** containing (2*R*)-hydroxy-(3*E*)-octadecenoic acid possesses antileukemic activity.[10] The structure of the antibiotic malingamide A isolated from the marine alga *Lyngbya majuscula* involves (7*R*)-hydroxy-(4*E*)-tetradecenoic acid **13**[11] (Scheme 1).

An important role in the vital activity of plants is played by monohydroxy dienoic acids. Thus, dimorphecolic acid **14** isolated from rice stems,[12] from seed oils of *Dimorphotheca* and *Osteospermum*,[13] as well as from sea buckthorn oil,[14] belongs to the class of acids that provide defence against diseases in some rice varieties known for their high productivity and resistance against pathogenic fungi. Esters of the acid **14** also exhibit insecticidal activity.[15] The synthesis of four geometric isomers of dimorphecolic acid[16] has been performed. Densipolic acid **15** has been isolated from the lipids of *Lesquerella densipila*.[17]

Much attention in the current literature is being given to coriolic acid **16** detected as a component of sea buckthorn lipids[14] and isolated as the (13*S*) isomer from the roots of the rice plant.[18] This compound can influence Ca^{2+} transport in the cell system of some pathogens of rice diseases, which accounts for its role in self-defence of the plant. Its (13*R*)-isomer **17** and the geometric isomers **18** and **19** exhibit similar fungicidal activity. The synthetic dehydrocoriolic acids **20** and **21** display potent antifungal activity.[18]

The natural enynoic acids **22**[19] and **23**[20] possessing antibiotical and antifungal properties are also worth noting in this context (Scheme 2).

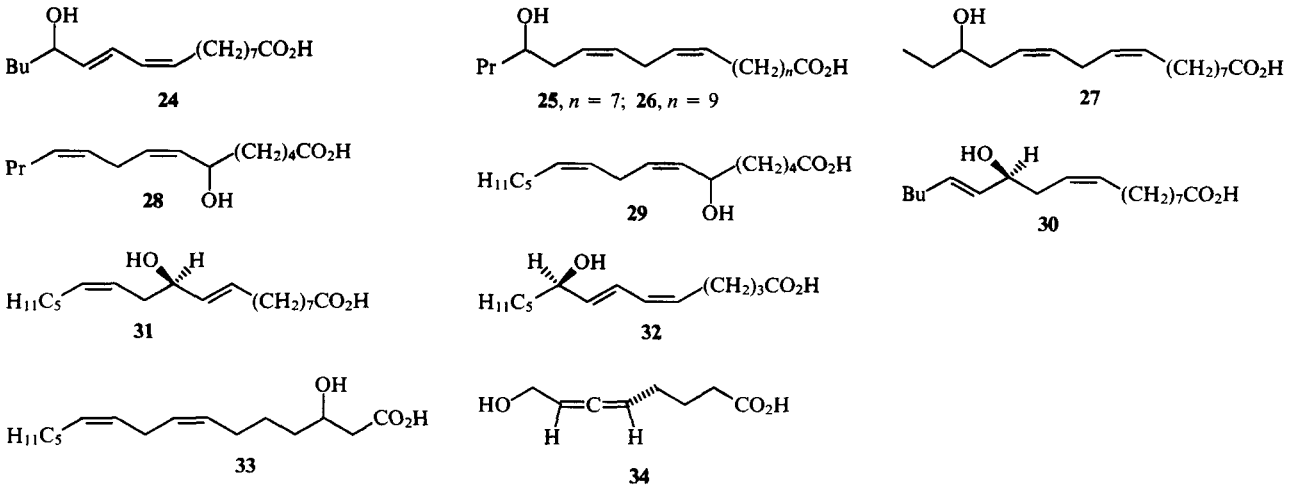
Scheme 2



$R^1 = C_5H_{11}$, $R^2 = (CH_2)_7CO_2H$

Of particular interest is the detection of coriolic acid in heart tissue mitochondria of patients with Mediterranean fever. Highlighted is the role of (*R*)-coriolic acid in the control of thrombosis, which is associated with its ability to block Ca^{2+} transport.[21] The synthesis of coriolic acid has been described in Refs 22 and 23.

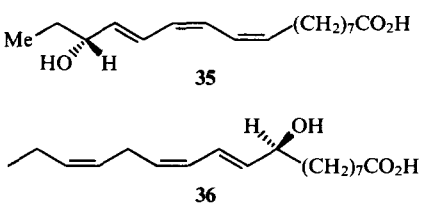
Hydroxydienoic acids **24**–**27** of unknown configuration have been isolated from the seeds of the plant *Galeopsis bifida*.[24] The configuration of the asymmetric centres of the acids **28** and **29** detected in some plants of the *Acantopanax* genus is



also unknown.[7] The fungistatic activity of the fungus *Epichloe*, which infests the timothy, is ascribed to the presence of the acids **30** and **31**; the latter has been obtained synthetically.[25]

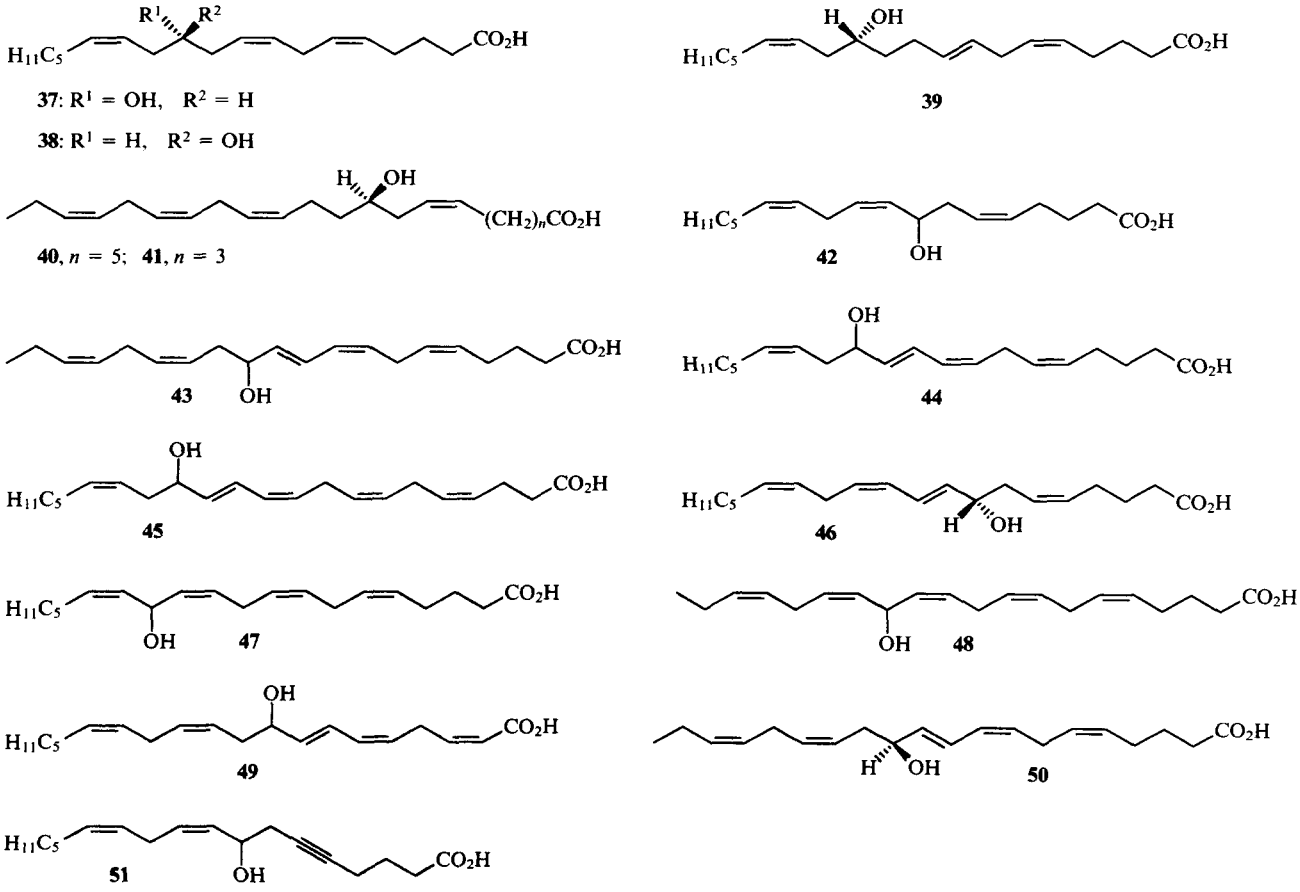
The seed oil of *Securidaca longipedunculata* contains (9*R*)-hydroxy-(5*Z*,7*E*)-tetradecadienoic acid **32**.[26] The acid **33** is the structural component of the nucleoside antibiotic produced by *Streptomyces griseosporeus*.[27] The optically active allenic acid **34** isolated from the plant *Sapium japonicum* has a potent antifungal action.[28]

High biological activity has been detected in some monohydroxy tri- and monohydroxy polyenoic acids. The disease-resistant rice variety Fukuyuki contains the C_{18}-trienoic acids **35** and **36** endowed with strong fungicidal activity.[29] Their structures have been confirmed by total synthesis.[30]



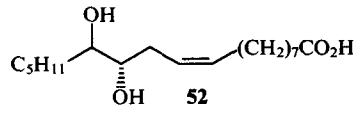
The acid **37** isolated from wheat epithelium turned out to be a strong vasodilator that stimulates the protein inflow into the ocular fluid. Noteworthy, its enantiomer **38** is fully devoid of activity, while the (8*E*)-isomer **39** displays only 10% of the activity of the natural acid (Scheme 3).[31] The lipids of the Indian Ocean

Scheme 3



black coral *Leiopathes* contain leiopathic acid **40** as well as the acids **41** and **42**.[32] The sponge *Echinochalina mollis* inhabiting the Coral Sea produces three hydroxypolyenoic acids, **43–45**.[33] The eicosanoid **46** has been isolated from the starfish *Patiria miniata*.[34] Biologically active acids have been detected in red algae. Thus, *Litotamnion coralliodes* and *Litotamnion calcareum* produce the acids **47** and **48**;[35] pentaenoic acid **49** exhibiting antimicrobial activity has been isolated from the alga *Laurensia hybrida*.[36] The high content of the acid **50** which inhibits platelet aggregation has been found in the alga *Murrayella periclados*.[36,37] The acid **51** isolated from the lipids of the alga *Liagora farinosa* is ichthiotoxic[38].

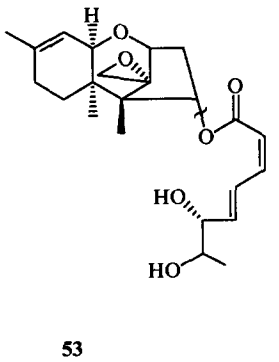
Only a few unsaturated dihydroxy acids have been described, and among them there are *threo*-12,13-dihydroxyoleic **52**,[39] 6,7-dihydroxy-(2*Z*,4*E*)-octadienoic, and 8,9-dihydroxy-(2*E*,4*E*,6*E*)-decatrienoic acids.



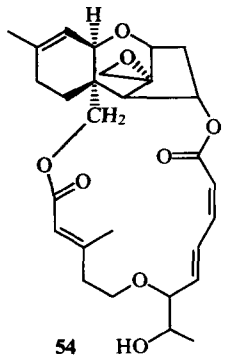
52

Dihydroxyoctadienoic acids are structural components of the trichotecenoid toxins produced by the fungi *Fusarium*, *Myrothecium*, *Trichoderma*, and *Cylindrocarpon*. Trichotecenes are strong poisons inhibiting such vital processes as protein and DNA biosynthesis. Also known are mycotoxicoses, e.g., the vomiting factor of *Fusarium* and toxic aleukia of pigs and cattle fed on a pathogenic fungi-infested forage. Two types of toxins, **53** and **54**, exist that contain dihydroxyoctadienoic acids. The antibiotic dioxamycin **55** comprises a fragment of decatrienoic acid.[40]

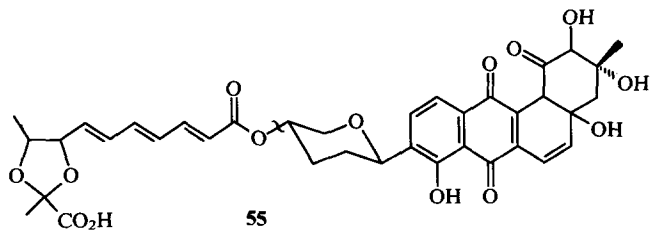
The extensive literature on trichotecenoid toxins has been generalised in various monographs.[41–43]



53

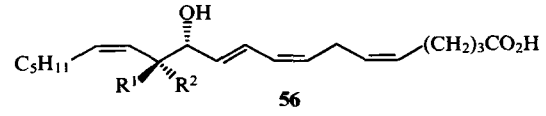


54



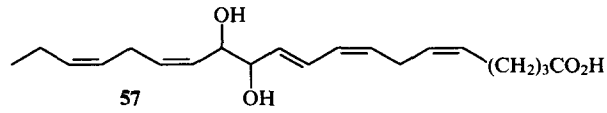
55

The dihydroxytetra- and pentaenoic acids **56** and **57** have been isolated from the lipids of the red alga *Farlowia mollis*.[44]



56

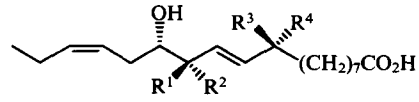
$R^1 = H, R^2 = OH$; $R^1 = OH, R^2 = H$



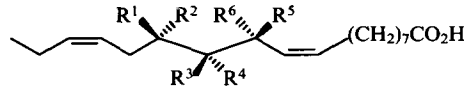
57

A group of trihydroxy acids **58–62** has been isolated from the stems of some rice varieties resistant to fungal diseases.[45,46] It has been demonstrated that wetting of rice seedlings in aqueous solutions of these acids increases the resistance of the plant against fungal diseases throughout the whole vegetation period.[47] The pharmacologically promising trihydroxy acids **63–66** are contained in the lipids of the medicinal plant *Brionia alba*.[48–50] Like prostaglandins, the complex of these lipids increases smooth muscle tonicity, lowers the glucose level in the blood, normalises the lipid composition in liver and brain of experimental animals, and produces stimulating and tonic effects. These acids are formed by lipoxygenase oxidation of α-linolenic acid.

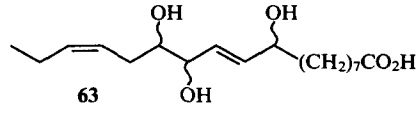
The sea alga *Lyngbya majusculus* contains malyngic acid **67**,[51] whereas the cyanobacteria (blue-green algae) produce its stereoisomer **68**.[52]



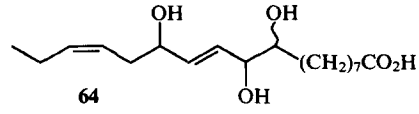
	R^1	R^2	R^3	R^4
58	OH	H	H	OH
59	OH	H	OH	H
67	H	OH	H	OH
68	H	OH	OH	H



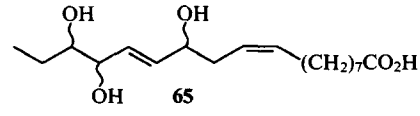
	R^1	R^2	R^3	R^4	R^5	R^6
60	H	OH	OH	H	H	OH
61	OH	H	H	OH	OH	H
62	OH	H	H	OH	OH	H



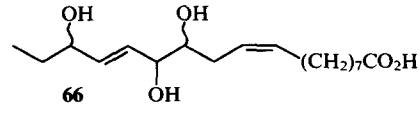
63



64



65

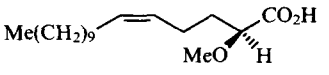


66

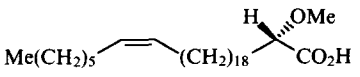
Syntheses of some of these acids have been described in Refs 47, 51–55.

Natural unsaturated acids are known that contain alkoxy, oxo, and epoxy groups. The structural element of the malyngamides isolated from the alga *Lyngbya majusculaus* is (7*R*)-methoxy-(4*E*)-tetradecenoic acid.[56] Nontoxic stylocheiamides have been isolated from the tissues of the ugrug *Stylocheilus longicanela*, which feeds on this alga.[57]

Malyngamide G contains (7*R*)-methoxy-(4*E*)-tridecenoic acid.[58] (2*S*)-Methoxy-(5*Z*)-hexadecenoic acid **69**, a tentative structural component of sphingolipids, has been isolated from the sea sponge *Amphimedon compressa*.[59] The lipids of the green sea alga *Higginsia tethyoides* contain the unique C_{28}-acid **70**.[60]

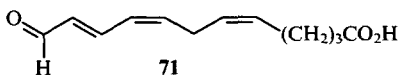


69

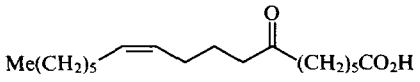


70

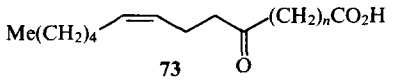
The aldehydo acid **71** with antimicrobial action is present in the lipids of the red alga *Laurensia hybrida*.[36] The C_{18}-oxo acid **72** has been found in the seed oil of *Gardenia lucida*.[61] The acids **73** isolated from the lipid fraction of *Cuspidaria pterocarpa* seeds have a longer chain.[62,63] The hydroxyoxo acid **74** is formed in the potato plant as a result of lipoxygenase oxidation of linolenic acid.[63]



71

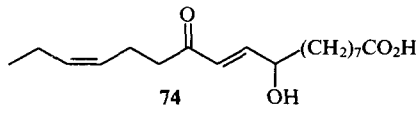


72



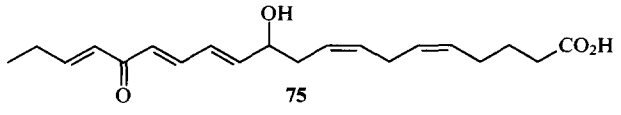
73

n = 13, 15, 17

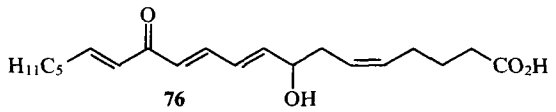


74

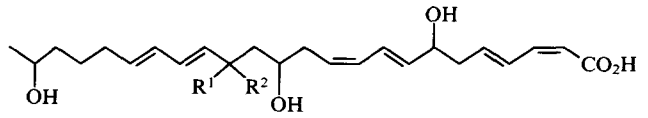
The red alga *Ptilota filicina* produces the oxo acid **75** manifesting antimicrobial activity and the ability to inhibit 5-lipoxygenase and Na^+/K^+-ATPase.[64] The oxo acid **76** has been isolated from the alga *Lithotomnion coralliodes*.[65] Gram-positive bacteria of the deep-sea sediment core produce macrolides and open-chain acids exhibiting antiviral activity. Among them, macrolactinic **77** and isomacrolactinic **78** acids have been identified; however, their absolute configurations have not been established.[66]



75



76



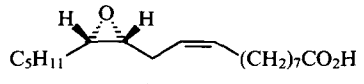
77: R^1 = OH, R^2 = H; **78**: $R^1 + R^2$ = O

The *Cantharellus cibarius* (chanterelle) is one of the most widespread edible mushrooms. Its resistance against parasites, insects, and snails is due to the high content of cibaric acid **79**.[67] The dioxoacid **80**, which has been named ostopanic acid, has been isolated from the stems and fruits of the plant *Ostodes paniculata*. Its ability to inhibit the growth of lymphocytic leukemia cells has been reported.[68]

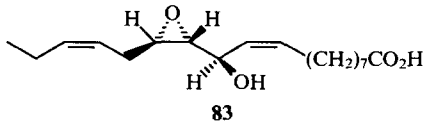
The antibiotic MG 398HF9A **81** with a unique structure isolated from the culture of *Pseudomonas azurea*, has been recommended for the treatment of fungal diseases[69] (Scheme 4).

Vernolic acid **82**, which has an epoxy group in its structure, has been detected in the seeds of *Euphorbia lagascea*.[1,21] The epoxy acid **83**, whose structure was confirmed by total synthesis, had been isolated from rice.[70] Like coriolic and vernolic acids, this compound has been attributed to the factors that ensure self-defence of the rice plant against pathogenic fungi. The fungus *Cephalosporium caerulens* produces cerulenin **84**, which inhibits the biosynthesis of steroids and lipids. Its inhibition index for fatty acid synthetase is very high (JC = 1 μg ml^{-1}).[71] As stated in Ref. 13, sea buckthorn oil contains more than twenty epoxy acids which have been identified by chromatomass spectrometry; their major component is the 15,16-epoxy-octadeca-9,12-dienoic acid of an unestablished stereochemistry.

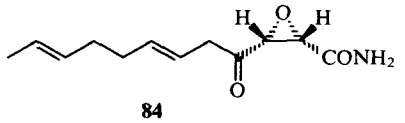
Incubation of (8*R*)-hydroperoxyeicosatetraenoic acid with homogenates of the coral *Plexaura nomomalea* affords the allenic epoxide **85**, an intermediate in the biosynthesis of the cyclopropane eicosanoid **86** isolated from the coral.[72]



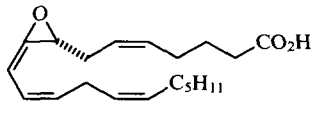
82



83

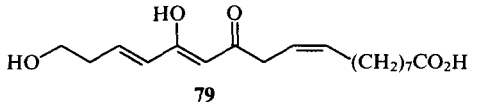


84

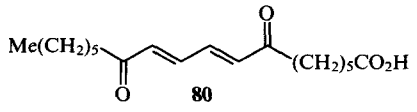


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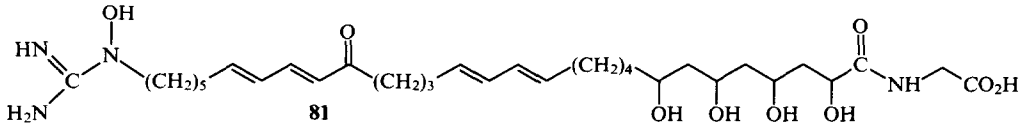
Scheme 4



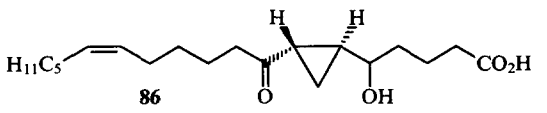
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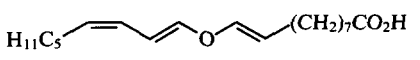
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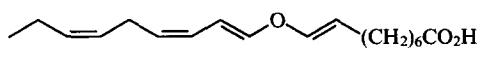
81



86



87

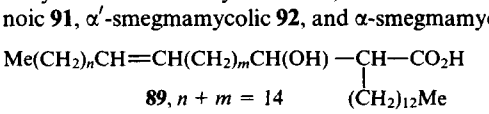


88

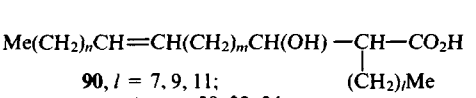
Colnelic **87** and colnelenic **88** acids from potato have a unique structure.[73-75] It is assumed that these acids are formed due to enzymatic rearrangements of the hydroperoxides produced by lipoxygenase oxidation of linoleic and linolenic acids. It is remarkable that the above compounds have a strong inhibiting action on potato lipoxygenase.

III. Branched-chain unsaturated acids

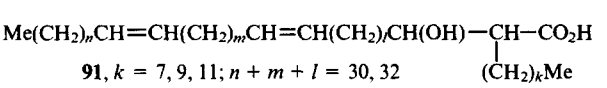
Several α-branched mono- and dienoic acids have been isolated from the lipids produced by mycobacteria and actinomycetes. They involve corinomycolenic **89**,[76] nocardenoic **90**,[77] nocardienoic **91**, α′-smegmamycolic **92**, and α-smegmamycolic **93** acids.[78]



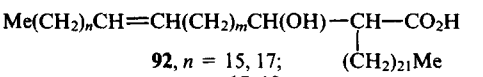
89, $n + m = 14$



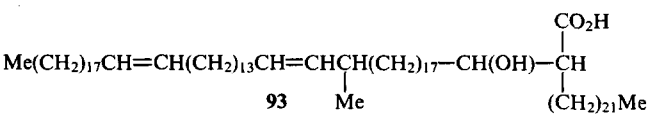
90, $l = 7, 9, 11$; $n + m = 30, 32, 34$



91, $k = 7, 9, 11$; $n + m + l = 30, 32$



92, $n = 15, 17$; $m = 17, 19$



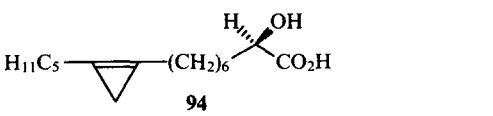
93

Hydroxysterculic acid **94** is contained in the roots of the plant *Hibiscus rosa*.[79,80] The fungus *Nocardia* produces the acid **95** possessing antiulcerous activity.[81] The green alga *Bifurcaria bifurcata* contains isoprenoid acid **96**.[82] The acid **97** has been isolated from the fruits of *Cydonia oblonga*.[83] Some hydroxy acids containing methyl substituents are structural fragments of the molecules of natural compounds. Thus, dendriphiellin **98** isolated from the sea sponge *Dendriphiella salina* contains a fragment of 8-hydroxy-(6*R*)-methylocta-(2*E*,4*E*)-dienoic acid[84] and variotin **99**, a potent inhibitor of fatty acid synthetase, is an amide of 6-methyltrienoic acid.[71] The fungus *Papularia spherosperma* produces the glycolipids, xanthicandin **100a** and papulacandins, e.g., papulacandin B **100b** possessing strong fungicidal activity.[85-87] Structurally related fungicides have been isolated from cell cultures of the fungi *Pialophora cyclaminis*[88] and *Dictyochaeta simplex*[89] (Scheme 5).

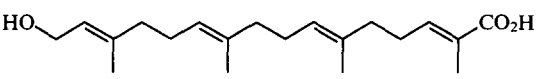
The pathogenic fungus *Alternaria kikuchiana*, the agent of the black spot disease in strawberry, produces the toxins AF-II a, b, c **101-103**, AK-I, and AK-II **104**,[90,91] whose structures have been confirmed by total synthesis.[92,93] The ester of the oxotetraenoic acid **105** isolated from the culture of *Aspergillus versicolor* has been patented as a means for reducing the cholesterol level in the blood.[94] The sea sponges of *Choristid* sp.[95] and *Jaspidae*[96] contain the antibiotics bengamides A-F **106** and isobengamide **107**, which are highly active against the parasites *Nippostrongies brasiliensis*, streptococci, and fungi[97,98] (Scheme 6).

The isolation of amides of the polyenoic acid with a more complex structure has been described. Thus, *Myxococcus xanthes* produces the antibiotics myxalamides **108**, which demonstrate high activity against gram-positive bacteria and yeasts.[99] The fungus *Myxococcus stipitatus* is a source of phenalamides **109** and

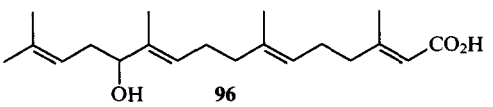
Scheme 5



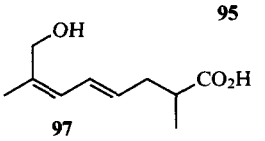
94



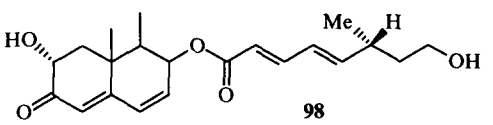
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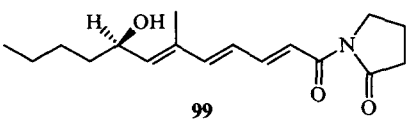
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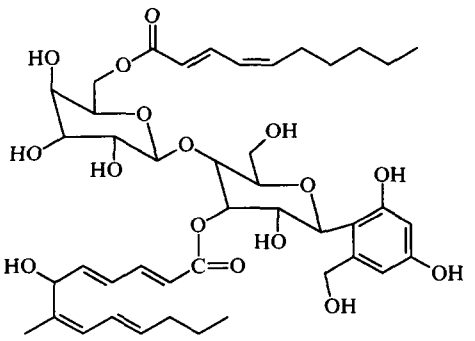
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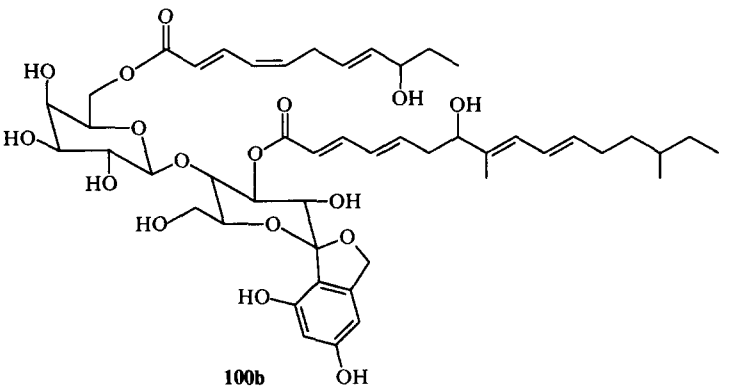
98



99

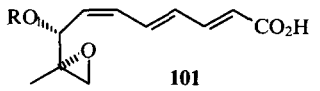


100a

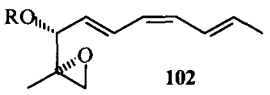


100b

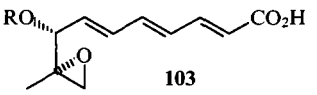
Scheme 6



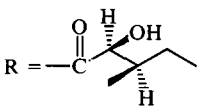
101

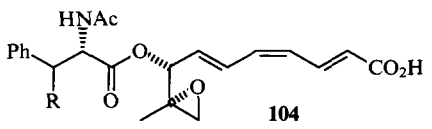


102



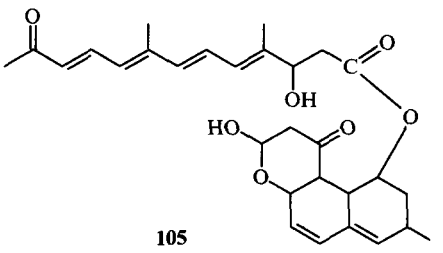
103



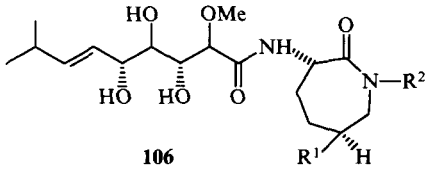


104

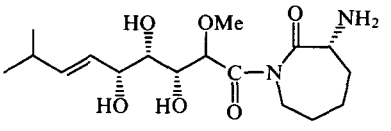
R = Me, H



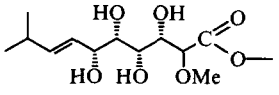
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106



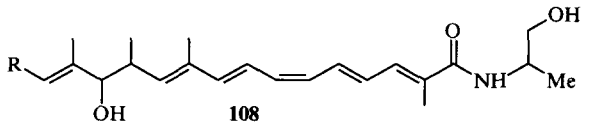
107

R^1 = H, $C_{12}H_{25}CO_2$;  ; R^2 = H, Me

110, which have been patented as a basis for medicinal drugs designed for the treatment of fungal and parasitic diseases.[100-103] Phenalamide C **111** has been noticed to inhibit strongly the reproduction of the human immunodeficiency virus. Malingamide E isolated from algae is the amide of 7-methoxy-9-methyl-hexa-(4*E*)-decenoic acid **112**.[104] The sea sponge *Clathria* contains clathrinamides **113** capable of inhibiting cell division, as has been established in experiments with starfish eggs.[105] The molecule of the antitumour antibiotic AJL produced by *Streptomyces* contains the acid **114** linked via an amide bond with the fragment of a complex structure.[106] The structurally simple hydroxy acid **115** is a constituent of the molecule of oxazole macrolides (virginiamycins), which have found wide use as antibiotic drugs.[107] The antibiotic enacyloxin **116**, which is active against gram-positive bacteria and influences protein synthesis, has a unique structure.[108]

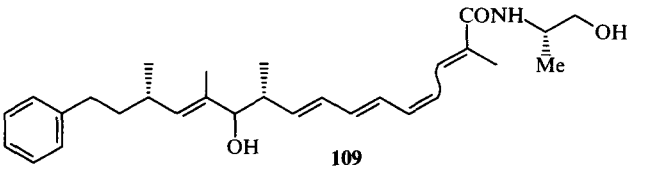
The antibiotic conocandin **117**[109] and the compound **118**[110] are free acids. The fungus *Xylaria cubensis* produces the antibiotic, cubensic acid **119**[111] (Scheme 7).

Scheme 7

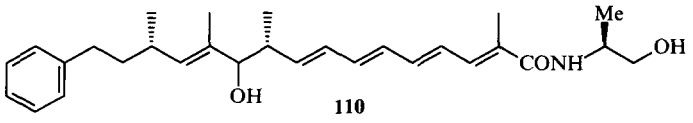


108

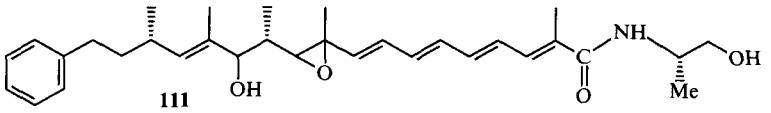
R = Me, Et, Pr^i, CH_2CHEt (Me)



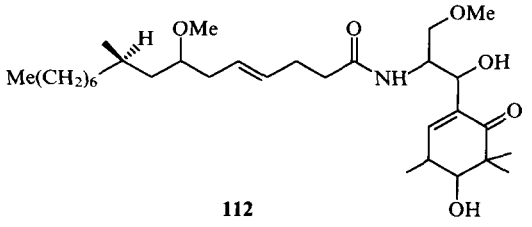
109



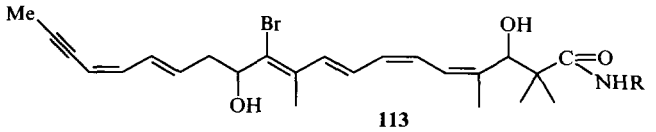
110



111



112

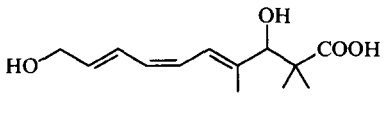


113

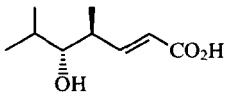
R = H, —CH(Me)$(CH_2)_2$CH(OH)Me

continued over

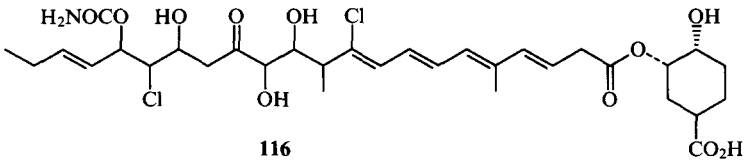
Scheme 7 (continued)



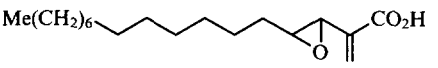
114



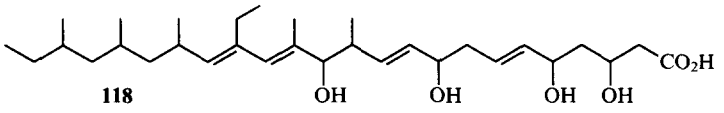
115



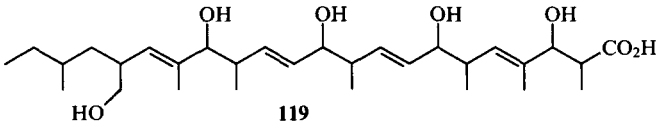
116



117



118



119

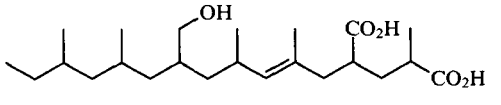
IV. Unsaturated di- and tricarboxylic acids and their derivatives

The group of unsaturated dicarboxylic acids is not too numerous but diverse as regards their structural elements. The ability to control plant growth is characteristic of radiclonic acid **120** isolated from *Penicillium* sp.[112] The antibiotic 123313 **121** has been obtained from *Cephalosporium*.[113] Bongkrekic acid **122** produced by the fungus *Pseudomonas cocorenenaus* causes severe (sometimes, lethal) food poisoning. 'Bongkrek' coconuts, commonly used as a dietary product in Indonesia, are infested with a culture of *Pseudomonas*. The high toxicity of the acid **122** produced by this culture is due to its effect on ATP/ADP translocation in mitochondrial membranes and blocking of oxidative phosphorylation.[114] Isobongkrekic acid **123** isolated from an unidentified strain of *Eubacterium* strongly inhibits the activity of phytopathogenic fungi when used at concentrations of 7–125 μg ml^{-1}. The antibiotic activity of compound **123** is lower than that of bongkrekic acid. Both compounds are characterised by high toxicity: LD_{50} is 4.5 mg kg^{-1}. Tetraenedioic acid is a structural element of the molecule of the calbistrin antibiotic **124** produced by *Penicillium restrictum*.[115]

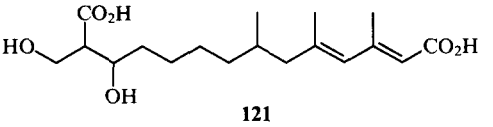
Baccharinoids related to toxins of the trichotecenoid series and produced by the fungus *Baccharis megapotamica* are cyclic esters of the dicarboxylic acids **125**–**127**.[116,117] The alkaloids of the groundsel *Senecio* possessing valuable biological properties contain dicarboxylic acids, of which intergerrineceic acid **128** as well as the acids **129** and **130**, are especially widespread.[118,119] Platyphilline **131** has found use in medicine as a cholinolytic agent.

The oxotricarboxylic acid peptide derivatives, viridiofungins A and C **132**, produced by *Trichoderma viride*, exert a strong antifungal action against *Candida*, *Aspergillus*, and *Cryptococcus*. Their ability to inhibit squalene synthetase has also been reported[120] (Scheme 8).

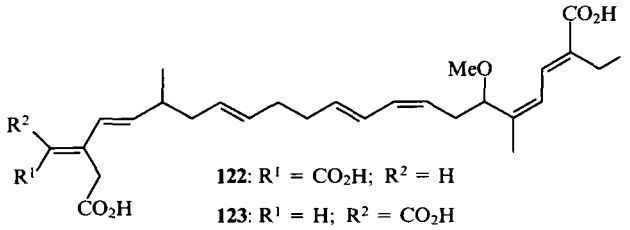
Scheme 8



120

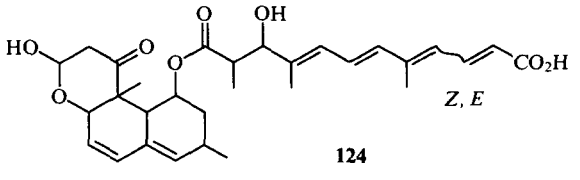


121

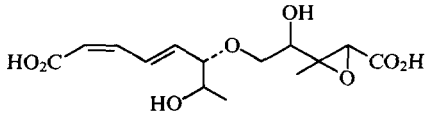


122: R^1 = CO_2H; R^2 = H

123: R^1 = H; R^2 = CO_2H

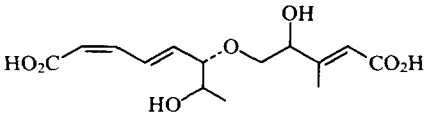


124

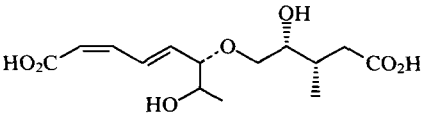


125

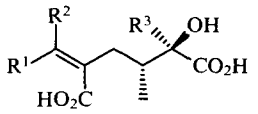
Scheme 8 (continued)



126



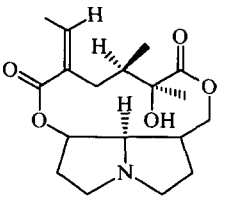
127



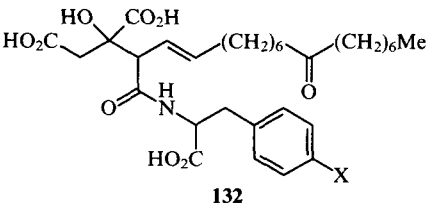
128: R^1 = H; R^2 = Me; R^3 = Me

129: R^1 = H; R^2 = Me; R^3 = CH_2OH

130: R^1 = Me; R^2 = H; R^3 = CH_2OH



131



132

X = H, OH

V. Acids with oxygen-containing heterocyclic fragments

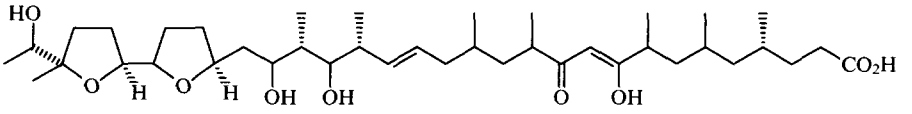
The formation of tetrahydrofuran or tetrahydropyran cycles is rather typical of linear polyhydroxy compounds. Polyhydroxy-unsaturated acids are not exceptional in this respect. If their molecules contain oxo groups, appropriate arrangement of the hydroxyl groups gives rise to heterocyclic systems containing two oxygen atoms which represent internal ketals.

Among the variety of acids containing the tetrahydrofuran fragment, we shall note the antibiotic ionomycin **133** possessing the properties of an ionophore selective towards calcium ions.[121] The cycloeicosanoids **134** and **135** isolated from ram seminal fluid are the metabolites of arachidonic acid.[122,123]

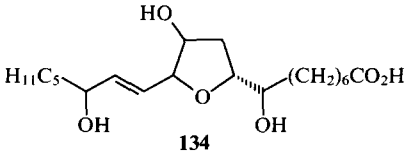
Of practical significance is pseudomonic acid **136** and its structural analogues containing the tetrahydropyran fragment **137**.[124-126]

The antibiotic zincoforin **138** produced by *Streptomyces griseus* selectively binds Mg^{2+} and Zn^{2+} ions which accounts for its ability to stimulate the growth and development of ruminant animals.[127,128] Some strains of *Streptomyces* produce the antibiotic gerboxydiene **139**, which has a strong antimicrobial action.[129] The 8,12-epoxy-9,11,15-trihydroxy-(5*Z*,13*E*)-eicosadienoic acid with an unestablished configuration of the asymmetric centres is the product of enzymatic conversion of arachidonic acid in humans.[130] The synthesis of its (8*R*,9*R*,11*S*,12*R*)-diastereoisomer **140** has been carried out[131] (Scheme 9).

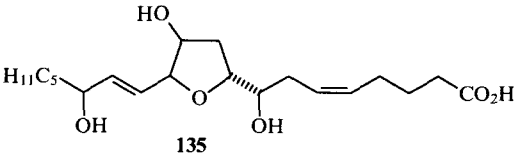
Scheme 9



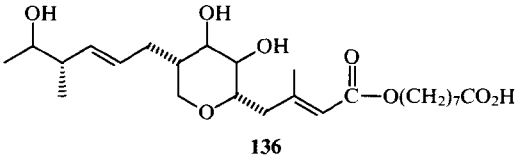
133



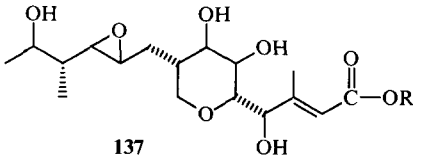
134



135

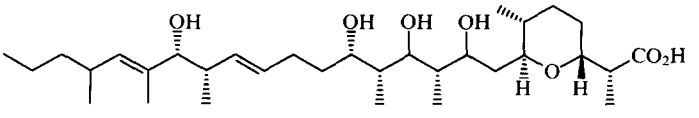


136

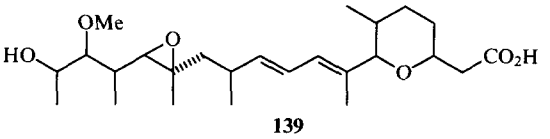


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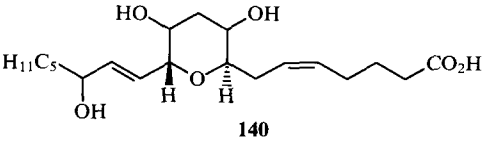
R = $(CH_2)_7CO_2H$, $(CH_2)_7CONH$



138



139



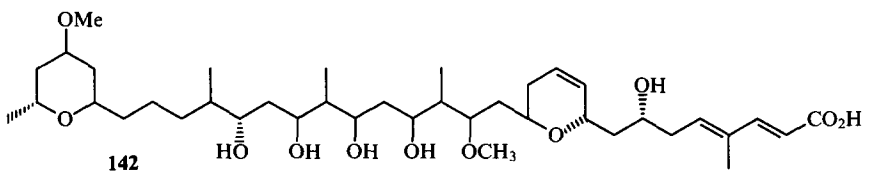
140

Scheme 10

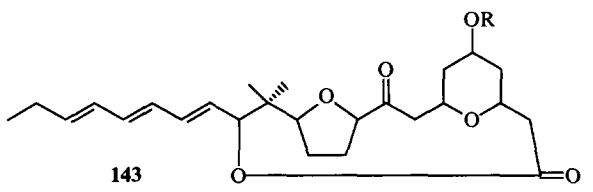


141

R = OH, NH_2, NHMe, NMe_2, $ONMe_2$, $\overset{+}{N}Me_3$

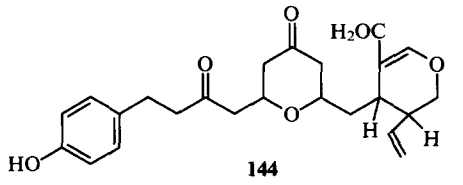


142

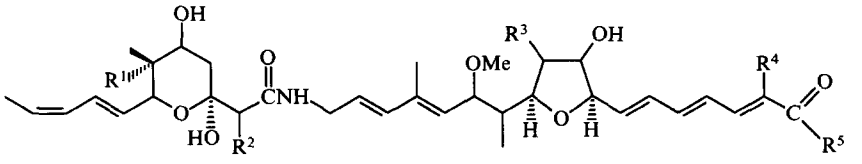


143

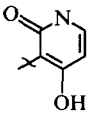
R = trisaccharide



144



145, 146

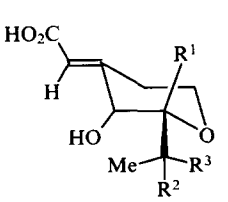
	R^1	R^2	R^3	R^4	R^5
145	OH	Et	H	H	H
146	H	Me	OH	Me	

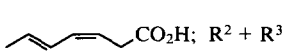
The acids of this series, which contain two heterocyclic fragments, possess valuable biological activity. For example, ambruticin[132] **141** (R = OH) and its amino derivatives[133] are active against many pathogenic fungi. A potent cytostatic action is exerted by swincholide D **142** isolated from the sea sponge *Theonella*.[134] The alga *Polycavernosa tsudai* contains the antibiotic polycavernoside A **143**.[135] Hydrangenoside A **144** detected in the plant *Hydrangea macrophylla* is a glycoside.[136] Some strains of *Streptomyces* produce antibiotics L 681.217 **145**[137] and SB 22.484 **146**[138] (Scheme 10).

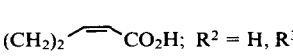
The di- and tricarboxylic acids of this type are structurally very diverse. Some trichotecenes comprise dicarboxylic acids carrying the tetrahydropyran fragment,[139] e.g., the acids **147–150** are present in satratoxin H, roritoxin A, mitoxin B, and vertisporin, respectively. The epoxy acids **151–155** are the structural components of myratoxin, satratoxin F, roritoxins D and C, and of mitoxin C (Scheme 11).

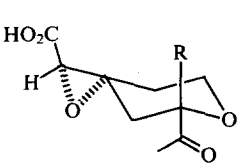
Some acids are of the ketal type. For example, the potent antibiotics, reversomycins F, C, D **156**, and B **157**, have been

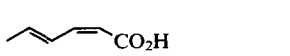
Scheme 11

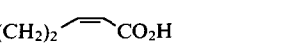


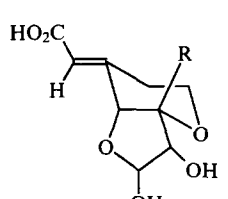
147: R^1 = ; $R^2 + R^3 = O$

149: $R^1 = (CH_2)_2$; $R^2 = H$, $R^3 = H$

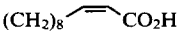


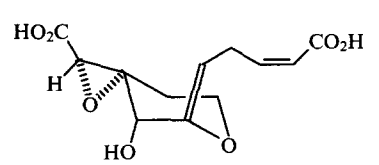
152: R = 

155: $R = (CH_2)_2$

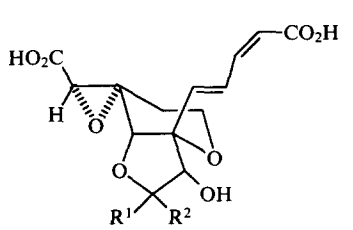


148: R = 

150: $R = (CH_2)_8$

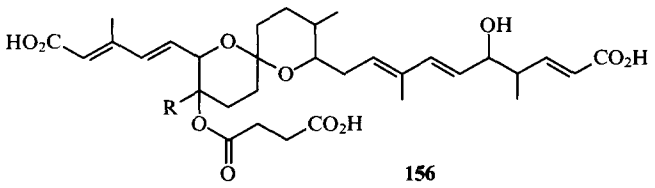


151



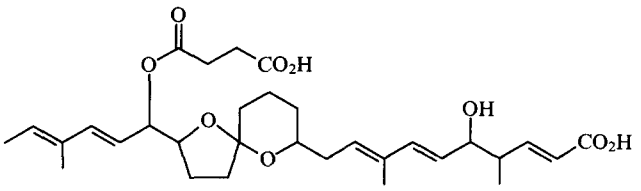
153: R^1 = H, R^2 = OH; **154**: $R^1 + R^2 = O$

isolated from some strains of *Streptomyces*.[140] The ionophore antibiotics, didemnoketals A and B **158**, possess high antimicrobial activity.[141]

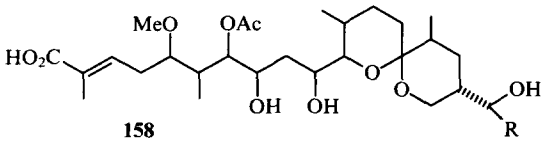


156

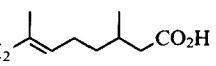
R = Bu, C_5H_{11}, $(CH_2)_2CHMe_2$



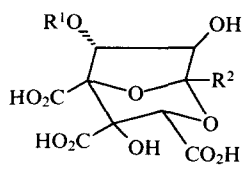
157

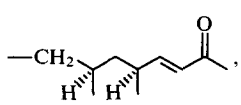
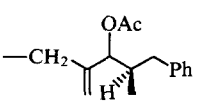


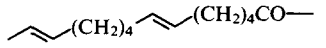
158

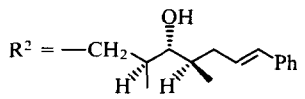
R = COMe, 

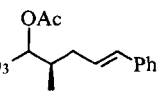
Considerable attention has recently been focussed on the tricarboxylic acids of the ketal type, which can effectively reduce the cholesterol level. These extremely active farnesyl transferase inhibitors produced by the cultures of *Sporomiella intermedia*, and *Leptodontium elatius*[142] as well as by the fungi of *Phoma* species,[143,144] have been named zaragozic acids A, B, C, D_1, and D_2, and squalestatins S_1, S_2, and H_1. The identity of the zaragozic acid A with squalestatin S_1 has been established. These metabolites are of particular importance for cardiology, since it has been

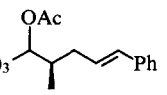


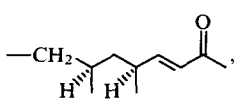
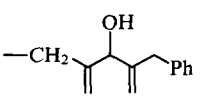
159: R^1 = , R^2 = 

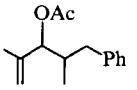
160: R^1 = ,

R^2 = 

161: R^1 = $C_7H_{15}CO-$, R^2 = 

162: R^1 = $C_9H_{19}CO-$, R^2 = 

163: R^1 = , R^2 = 

164: R^1 = H, R^2 = 

reported that they have a number of advantages over clinically widespread hypocholesterolinemic drugs, such as lovastatin mevinoids.[145,146] The structures **159–162** are considered to be correct for the zaragozic acids A, B, D_1, and D_2, and structures **163** and **164**, for squalestatins S_2 and H_2.[147–150]

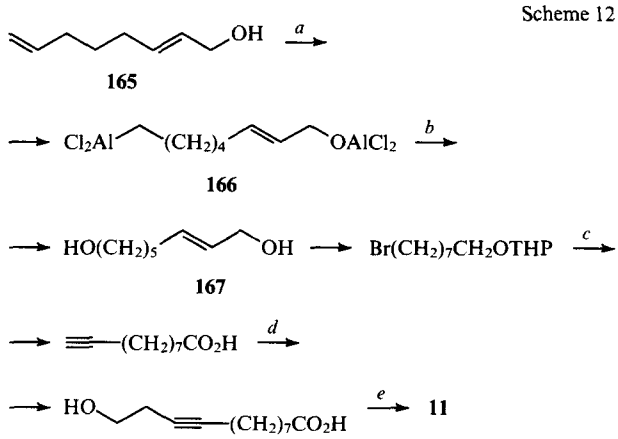
VI. Total synthesis of natural unsaturated acids with oxygen-containing functions

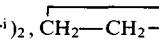
Total synthesis of natural acids of the above type has received much attention. Its significance is growing with increasing frequency far beyond the scope of the laboratory studies aimed at confirming a structure or elaborating a methodology. Many synthetic schemes are of technological value and suitable for obtaining the target products in amounts having practical significance.

An exhaustive discussion of papers dealing with the complete synthesis of unsaturated acids with oxygen-containing functions is not the specific goal of the present review. It seemed more reasonable to trace the strategy and methodology of the synthesis; therefore, our attention was focussed not only on enantiospecific approaches but on the syntheses of achiral compounds as well.

The first stage in the synthesis of a 12-hydroxy-dodec-(9*Z*)-enoic acid metabolite **11**[9] is particularly remarkable, for it makes use of a novel procedure of hydroalumination with $AlHCl_2$.[151] Hydroalumination of octa-2,7-dien-1-ol **165** followed by oxidation of the organoaluminium compound **166** affords oct-2-en-1,8-

Scheme 12

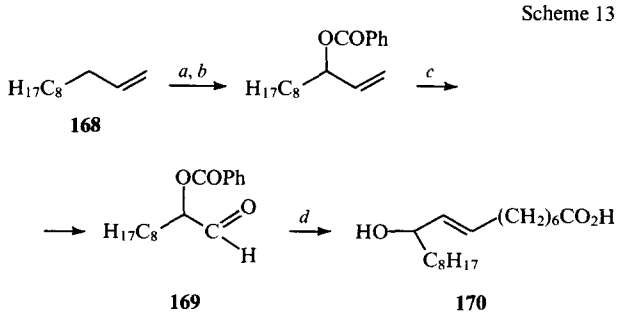


THP – tetrahydropyran-2-yl; (*a*) $AlHCl_2$; (*b*) O_2, H_3^+O; (*c*) $HC{\equiv}CNa$, H_3^+O, H_2CrO_4; (*d*) $LiN(Pr^i)_2$, ; (*e*) H_2, Pd – $BaSO_4$

diol **167**; its further conversions are depicted in Scheme 12.

The racemic 10-hydroxy-octadec-(8*E*)-enoic acid **170** isolated from rice stems, which provides self-defence in the plant against fungal diseases, has been synthesised from undecene **168**

Scheme 13

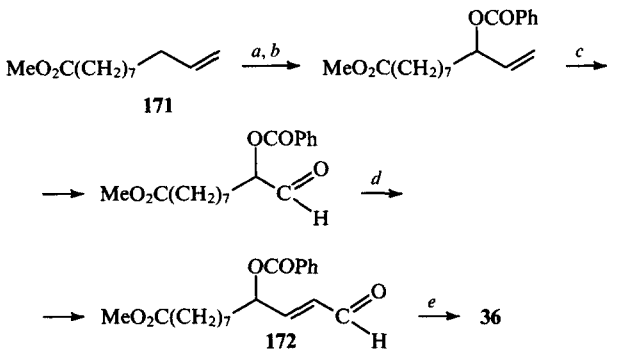


(*a*) $Bu^tO_2H-SeO_2$; (*b*) PhCOCl–Py; (*c*) OsO_4, $NaIO_4$; (*d*) $HO_2C(CH_2)_6CH{=}PPh_3$

(Scheme 13).[152] Allylic oxidation, benzoylation, and periodate cleavage of the double bond results in 2-benzoyl oxydecanal **169** which, after Wittig olefination and hydrolysis, gives the target product.

The preparation of the C_{12}-synthon **172** used in the synthesis of the optically inactive 9-hydroxy-(10*E*,12*Z*,15*Z*)-octadecatrienoic acid **36** is based on the allylic oxidation of methyl undec-10-enoate **171** (Scheme 14).[152]

Scheme 14

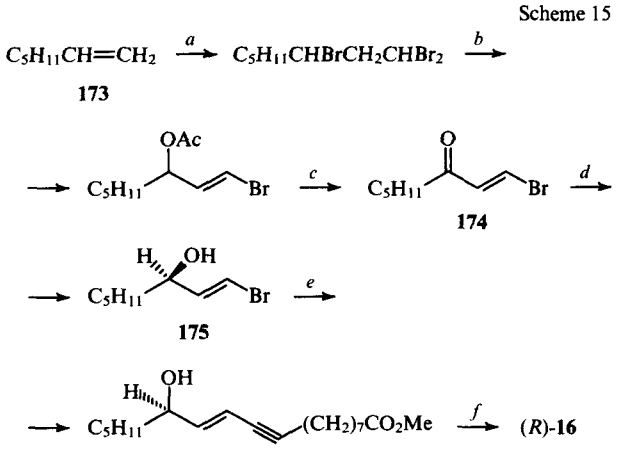


(*a*) $Bu^tO_2H-SeO_2$; (*b*) PhCOCl–Py; (*c*) O_3; (*d*) $Ph_3P{=}CHC(=O)H$;
(*e*) PPh_3Br, Bu^tOK

The syntheses of biologically active C_{18}-acids employ a wide variety of approaches, from metal complex catalysis to enantiospecific methods based on the use of the initial chiral compounds.

The palladium phosphine complex-catalysed coupling of vinyl halides with alkynes has been used in the synthesis of (13*R*)-coriolic acid **16**. One of the key synthons, 1-bromo-oct-1-en-(3*R*)-ol **175**, has been obtained from hept-1-ene **173** as shown in Scheme 15, which involves the asymmetric reduction of 1-bromoct-1-en-3-one **174** in the presence of baker's yeast (Scheme 15).[153]

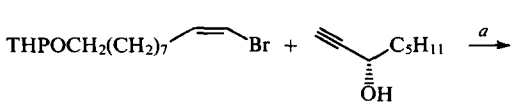
Scheme 15

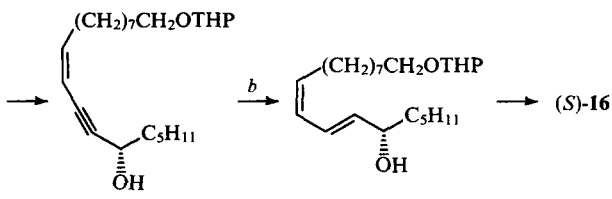


(*a*) $CHBr_3$; (*b*) AcOK, 18-crown-6;
(*c*) NaOH, PCC (pyridinium chlorochromate); (*d*) baker's yeast;
(*e*) $HC{\equiv}C(CH_2)_7CO_2Me$, $Pd(PPh_3)_4$, CuI; (*f*) H_2, $Pd-CaCO_3$

This approach, in a slightly modified form, has been used in the synthesis of the *S*-enantiomer of coriolic acid **16** (Scheme 16).[154]

Scheme 16

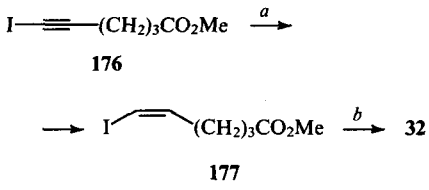




(*a*) $Pd(PPh_3)_4$, CuI; (*b*) $LiAlH_4$

Interesting procedures have been employed in the synthesis of (9*R*)-hydroxytetradeca-(5*Z*,7*E*)-dienoic acid **32**.[155] The stages of stereospecific reduction of methyl 6-iodo-hept-5-ynoate **176** in the presence of dipotassium azodicarboxylate and the $Pd(OAc)_2$-catalysed oxidative coupling of methyl-6-iodohex-5-enoate **177** with oct-1-en-(3*R*)-ol **178** (Scheme 17) have attracted our attention.

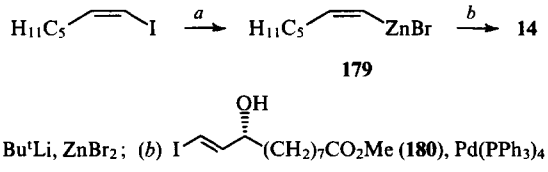
Scheme 17



(*a*) $KO_2CN{=}NCO_2K$, $BuNH_2$;
(*b*) C_5H_{11} (**178**); 5 $Pd(OAc)_2$–AgOAc

The formation of the carbon–carbon bond at the key stage of the synthesis of dimorphecolic acid **14** is effected by cross-coupling of the *Z*-vinylzinc intermediate **179** with the vinylic iodide **180** catalysed by $Pd(PPh_3)_4$ (Scheme 18).[156]

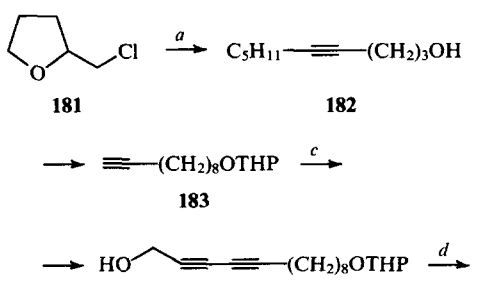
Scheme 18

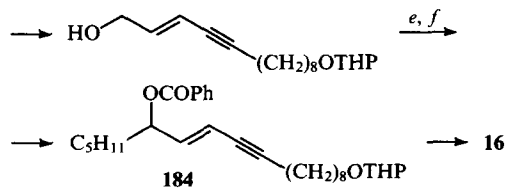


(*a*) Bu^tLi, $ZnBr_2$; (*b*) I–CH=CH–$(CH_2)_7CO_2Me$ (**180**), $Pd(PPh_3)_4$

An interesting procedure involved in the synthesis of coriolic acid **16** which has been developed by Indian investigators[157] is the preparation of the acetylenic precursor **184**. Tetrahydroxyfurfuryl chloride **181** gives dec-4-yn-1-ol **182** under the action of lithium bromide and bromopentane; this is further isomerised into dec-9-yn-1-ol **183** in the presence of sodium amide and propane-1,3-diamine. Further synthesis is depicted in Scheme 19.

Scheme 19





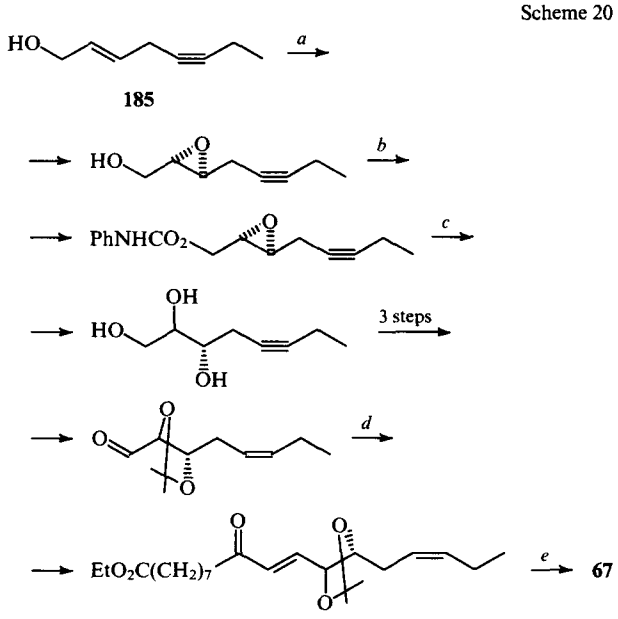
(*a*) $LiNH_2$, $C_5H_{11}Br$; (*b*) $NaNH_2$, $(CH_2)_3(NH_2)_2$; DHP (dihydropyran);

(*c*) $BrC{\equiv}CCH_2OH$, CuCl, NH_2OH, Pr^iNH_2; (*d*) $LiAlH_4$;

(*e*) MnO_2; (*f*) $C_5H_{11}MgBr$, PhCOCl–Py

The Sharpless asymmetric epoxidation has been widely used to obtain optically active hydroxy- and epoxyunsaturated acids. For example, the first stage in the enantioselective synthesis of malingic acid **67** is the epoxidation of the initial oct-(2*E*)-en-5-yn-1-ol **185** (Scheme 20).[158]

Scheme 20



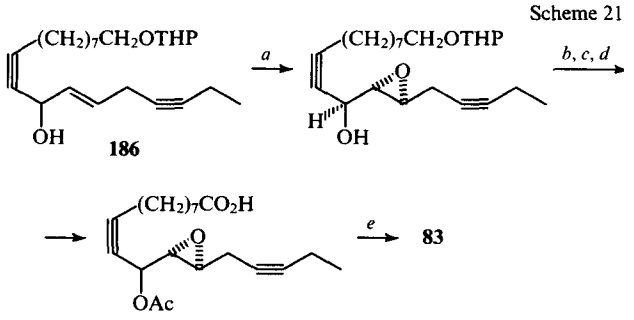
(*a*) Bu^tO_2H, $Ti(OPr^i)_4$, (+)DIPT (diisopropyl tartrate); (*b*) PhNCO;

(*c*) $BF_3{\cdot}OEt_2$, NaOH; (*d*) $EtO_2C(CH_2)_7COCH{=}PPh_3$;

(*e*) $NaBH_4$, NaOH

The asymmetric epoxidation of the compound **186** containing the fragment of allylic alcohol, has been used in the synthesis of (12*S*,13*S*)-epoxy-(11*R*)-hydroxyoctadeca-(9*Z*,15*Z*)-dienoic acid **83** possessing antifungal activity.[159] The two-step oxidation of the primary hydroxyl group into the carboxyl group (Scheme 21) is noteworthy. It is based on the use of pyridinium chlorochromate and then of $NaClO_2$ in the presence of 2-methylbut-2-ene.

Scheme 21



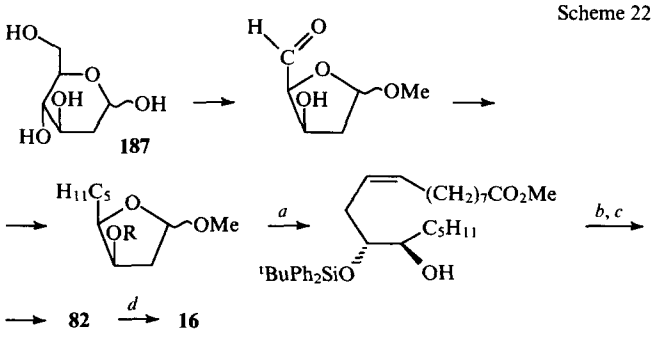
(*a*) Bu^tO_2H, $Ti(OPr^i)_4$, (+)DIPT; (*b*) Ac_2O, Py, H_3^+O;

(*c*) PCC; (*d*) $NaClO_2$, $NaHPO_4$, $Me_2C{=}CHMe$;

(*e*) H_2, Pd–$CaCO_3$

Monosaccharides have been widely employed in the past decade for enantiospecific syntheses of low molecular weight bioregulators, including hydroxyunsaturated acids as the starting chiral compounds. Thus, the scheme of synthesis of vernolic **82** and coriolic **16** acids is based on the transformations of 2-deoxy-D-glucose **187**. A noteworthy step in this chain of conversions is the allyl isomerisation of the epoxy group in the acid **82** under the action of cyclohexy(isopropyl)methylmagnesium amide **188** (Scheme 22).[160]

Scheme 22

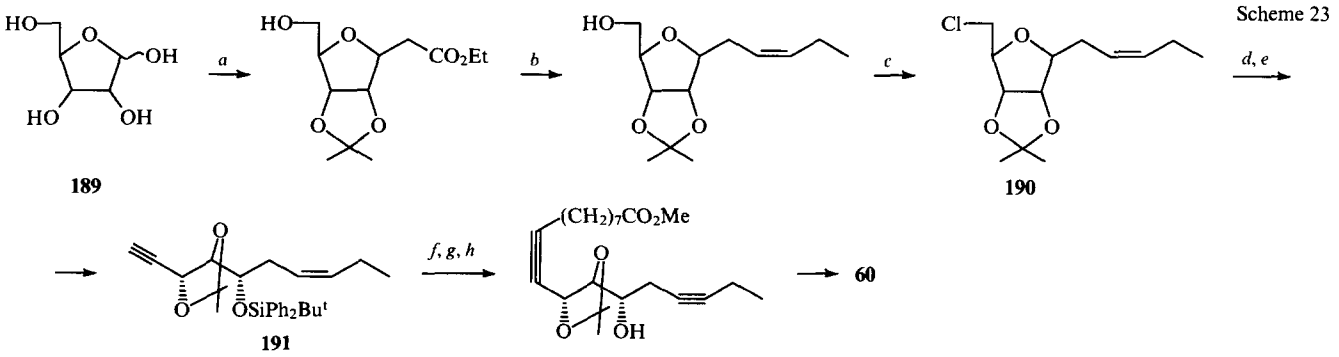


(*a*) $HO_2C(CH_2)_8PPh_3Br$, $LiN(SiMe_3)_2$, CH_2N_2; (*b*) TsCl–Py;

(*c*) Bu_4NF; (*d*) $C_6H_{11}(Pr^i)NMgMe$ (**188**)

The synthesis of (11*S*,12*S*,13*R*)-trihydroxy-(9*Z*,15*Z*)-octadienoic acid **60** has been performed on the basis of D-ribose **189** (Scheme 23).[161] In this series of transformations, the conversion

Scheme 23

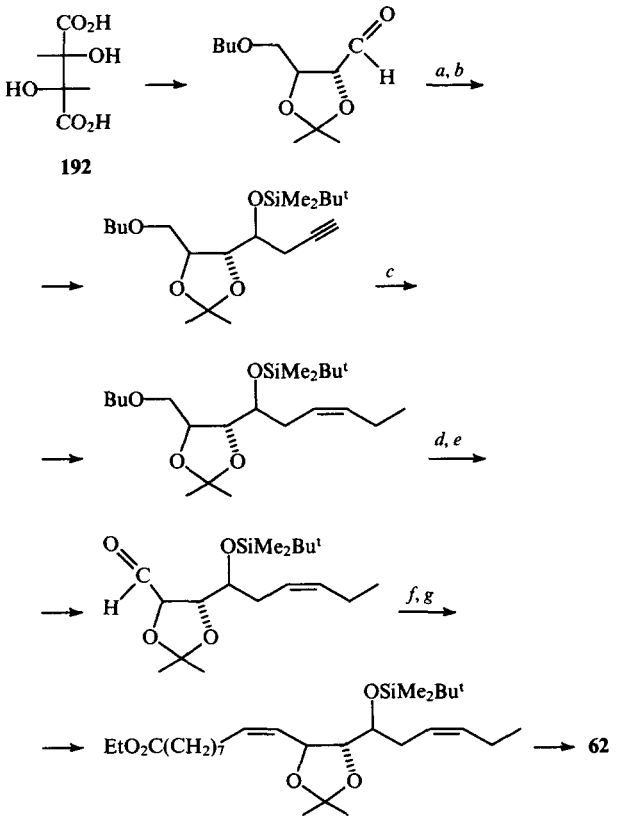


(*a*) $Ph_3P{=}CHCO_2Et$; (*b*) Bu^i_2AlH, $C_2H_2CH{=}PPh_3$; (*c*) CCl_4–PPh_3; (*d*) $LiNH_2$; (*e*) Bu^tPh_2SiCl; (*f*) $Br(CH_2)_7CO_2Li$, BuLi; (*g*) CH_2N_2; (*h*) $C_5H_5N{\cdot}HF$

of the chloro derivative **190** into the acetylenic compound **191** deserves special notice.

L-(+)-Tartaric acid **192** has been used as the starting compound in the synthesis of (11*S*,12*R*,13*R*)-trihydroxyoctadeca-(9*Z*,15*Z*)-dienoic acid **62** (Scheme 24).[162]

Scheme 24

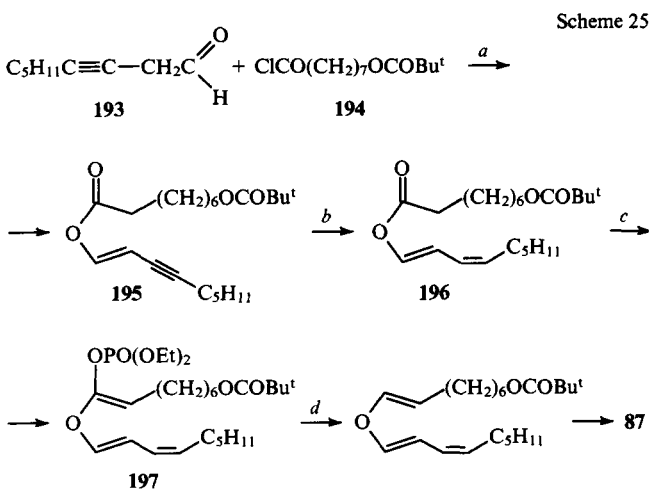


(*a*) $CH{\equiv}CCH_2Br$, Zn; (*b*) Bu^tMe_2SiCl;

(*c*) BuLi, C_2H_5Br, Pd – $CaCO_3$; (*d*) Li – NH_3; (*e*) $(COCl)_2$, DMSO; (*f*) $EtO_2C(CH_2)_7CH{=}PPh_3$; (*g*) Bu_4NF

The synthesis of colnelic acid **87** having in its structure a rather rare fragment of divinyl ether also presents certain interest.[163] The key step in the synthesis of this compound is the acylation of non-3-ynal **193** with 8-pivaloyloxyoctanoyl chloride **194** in the presence of bis(trimethylsilyl)sodium amide to form the enynyl ester **195**. The creation of the divinyl ether fragment has required the phosphorylation of the dienyl ester **196** in the presence of lithium diisopropylamide (LDA) and triethylaluminium-mediated hydrogenolysis of phosphate **197** in the presence of $Pd(PPh_3)_4$ (Scheme 25).

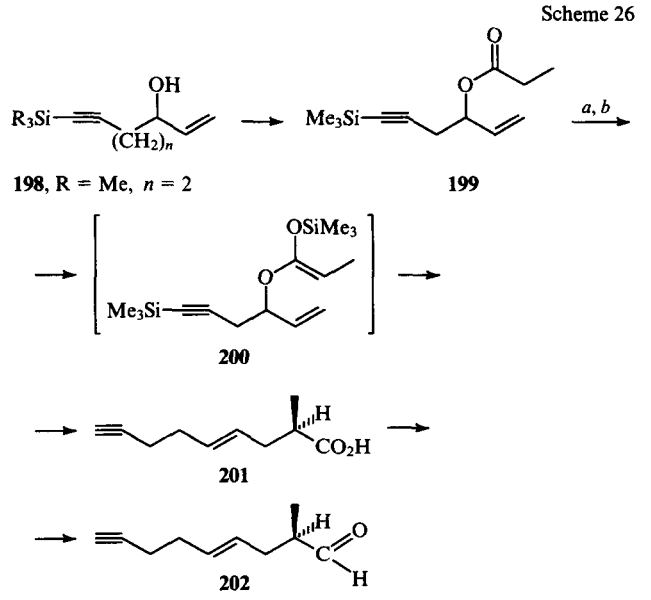
Scheme 25



(*a*) $(Me_3Si)_2NNa$; (*b*) H_2, Pd–$CaCO_3$; (*c*) LDA, $(EtO)_2POBr$; (*d*) Et_3Al, $Pd(PPh_3)_4$

The synthesis of bongkrekic acid **122** is related to syntheses of higher complexity.[164] Hydroxysylans **198** were the starting compounds for the preparation of bongkrekic acid. Thus, in the synthesis of the synthone **201**, hydroxysylane **198** (n = 2) was converted into propionate **199**, which after silylation was subjected to Klaisen–Ireland rearrangement. The necessary (*S*)-enantiomer was isolated from the racemic mixture of 2-methylnon-4-nonen-8-ynoic acid **201**, using HPLC on a column with a chiral adsorbent. The latter was transformed into the key synthone **202** in several steps (Scheme 26).

Scheme 26

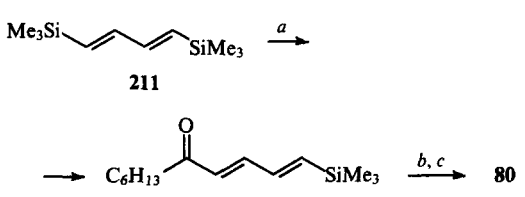


(*a*) Me_3SiCl, LDA; (*b*) HF

A parallel scheme for the conversion of C_6-hydroxysylane **198** (n = 1) involves its asymmetric epoxidation to form the optically active epoxide **203**. An important step in these transformations is the preparation of cyanodiyne **205** from α-cyanoketone **204** with elimination of trifluoromethanesulfonic acid by NaH. Further conversions resulting in the block **206** are shown in Scheme 27.

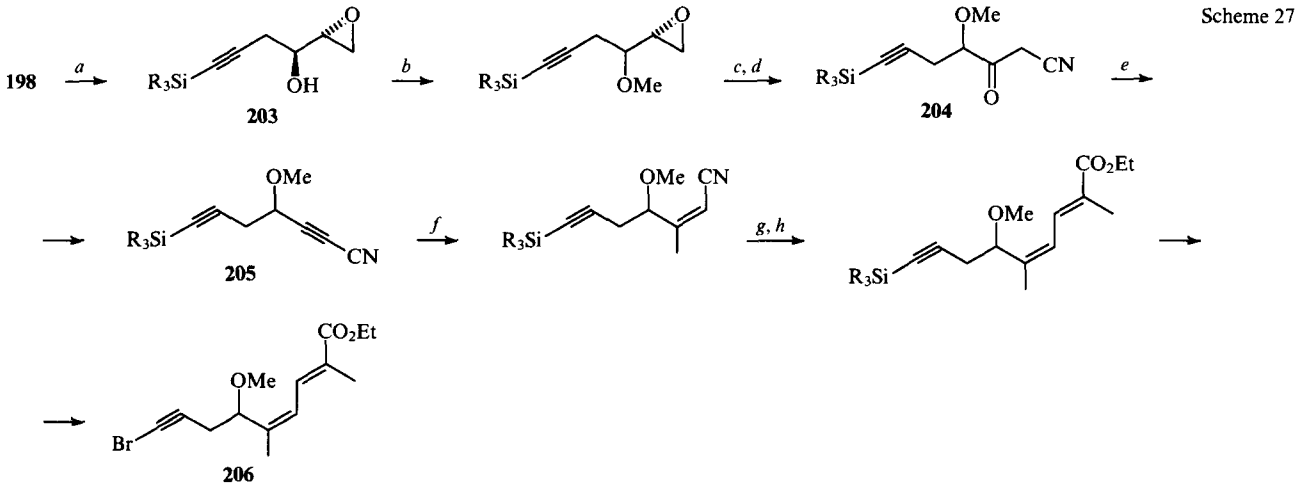
The final step in the synthesis of the acid **122** involved interaction of the dilithium derivative of methyl 3-methylglutaconate **207** with the aldehyde **202**. This was followed by hydroboration of acetylene **208** with diisoamylborane, preparation of the cuprate reagent **209**, and its stereoselective coupling with the bromide **206**. Hydrogenation of the triple bond in the precursor **210** and alkaline hydrolysis gave bongkrekic acid **122**, whose characteristics were identical with those of the natural toxin (Scheme 28).

The high reactivity of vinylsilanes has been employed in the synthesis of ostopanoic acid **80**.[165] The interaction of 1,4-bis(trimethylsilyl)buta-1,3-diene **211** first with heptanoyl chloride and then with pimeloyl chloride made it possible to obtain the target dioxocarboxylic acid.



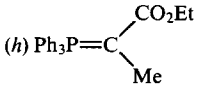
(*a*) $C_6H_{13}COCl$, $AlCl_3$; (*b*) $ClOC(CH_2)_5COCl$; (*c*) NaOH

Scheme 27

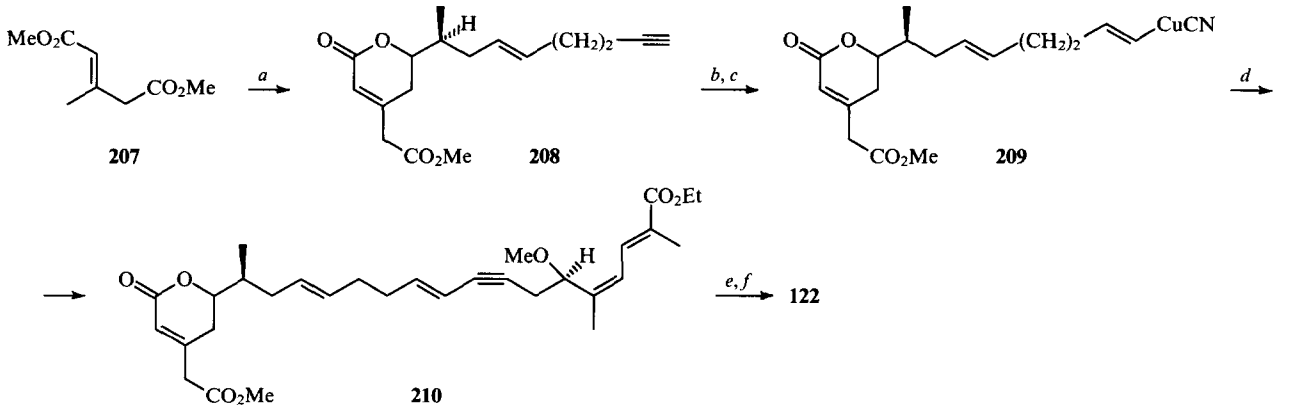


R = Pr^i, n = 1

(*a*) Bu^{t}O$_2$H, Ti(OPr^i)$_4$, (+)DIPT; (*b*) NaH, MeI; (*c*) NaCN; (*d*) PCC; (*e*) $(CF_3SO_2)_2O$, NaH; (*f*) Me_2CuLi; (*g*) $(Bu^i)_2AlH$;



Scheme 28



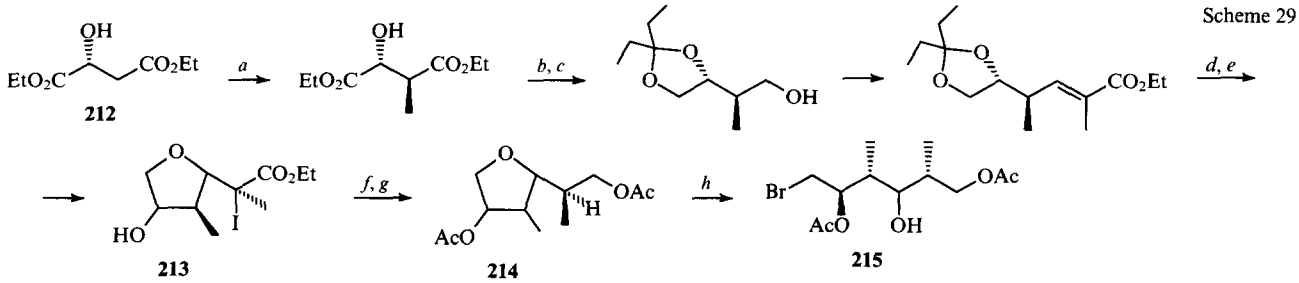
(*a*) LDA, **202**; (*b*) $(Me_2CHCHMe)_2BH$; (*c*) CuCN; (*d*) **206**; (*e*) Pd, Pb–$CaCO_3$; (*f*) KOH, MeOH

The synthesis of unsaturated acids carrying a heterocyclic fragment is acknowledged to be rather difficult to realise. This is the reason for the appearance of a large number of publications dealing with the problems of stepwise synthesis of these structures. For example, the synthesis of the C_{22}-fragment of ionomycin **133** has been carried out on the basis of (*S*)-malic acid **212** via compound **215** (Scheme 29).[166]

In this sequence of conversions, the formation of the tetrahydrofuran derivative **213** and the heterocycle ring-opening in the product **214** by dimethylbromoborane are of interest.

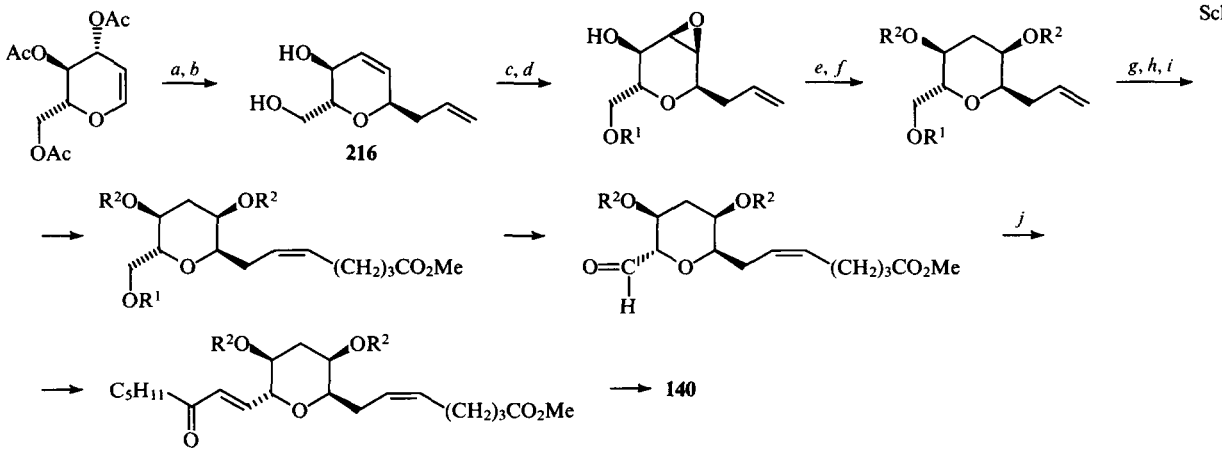
Triacetyl-D-glucal has been used as the starting compound in the enantioselective synthesis of the arachidonic acid metabolite **140**.[131] Its interaction with trimethylallylsilane accompanied by Ferrier rearrangement gives the diol **216**, the subsequent conversions of which are shown in Scheme 30.

Scheme 29



(*a*) MeI, LDA; (*b*) $BH_3 \cdot Me_2S$; (*c*) $Et_2C(OMe)_2$; (*d*) H_3^+O; (*e*) I_2, $NaHCO_3$; (*f*) Ac_2O–Py; (*g*) Bu_3SnH; (*h*) Me_2BBr, Et_3N.

Scheme 30



R^1 = Bu^tMe_2Si; R^2 = $MeO(CH_2)_2OCH_2$

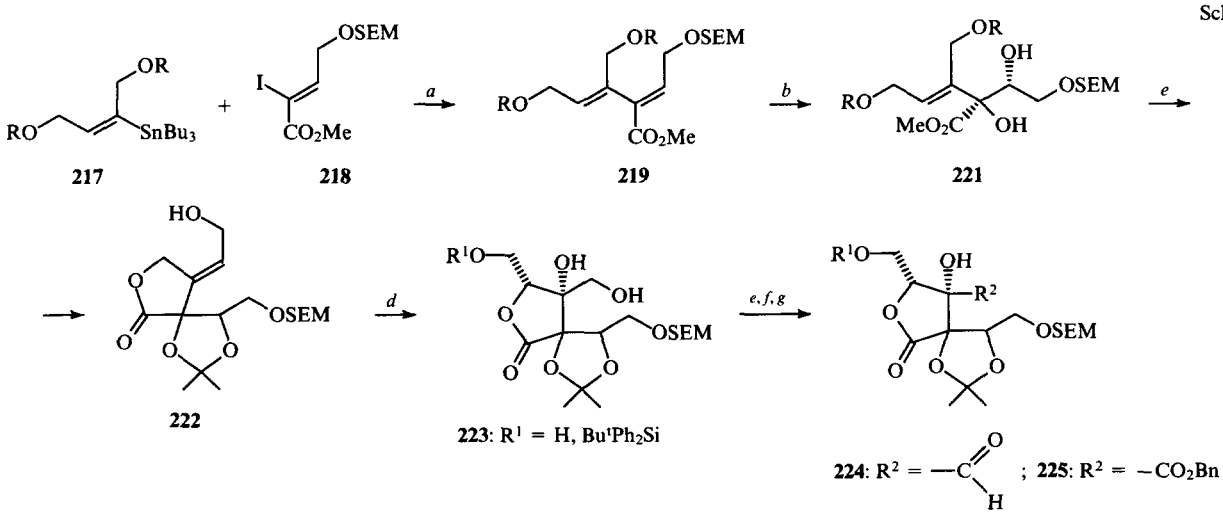
(*a*) $Me_3SiCH_2CH=CH_2$, $BF_3 \cdot Et_2O$; (*b*) KOH, MeOH; (*c*) *m*-$ClC_6H_4CO_3H$; (*d*) Bu^tMe_2SiCl; (*e*) $LiAlH_4$; (*f*) $MeOCH_2CH_2OCH_2Cl$; (*g*) O_3; (*h*) $Ph_3P=CH(CH_2)_3CO_2Na$; (*i*) CH_2N_2; (*j*) $(MeO)_2POCH_2COC_5H_{11}$, K_2CO_3

In the scheme of synthesis of the zaragozic acid A **159** (squalestatin S_1) published recently, the synthesis of the key synthon **228** merits attention.[167,168] This synthesis begins with coupling of the vinylstannane **217** with the iodide **218** catalysed by a palladium complex. This is followed by chiral Sharpless hydroxylation of the diene ester **219** with the $K_3Fe(CN)_6$–$K_2OsO_2(OH)_4$ complex in the presence of the bidentate ligand, $(DHQD)_2PHAL$ **220** responsible for the stereodifferentiating effect (Scheme 31).[169]

The thus formed optically active ester **221** is lactonised by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to give the lactone **222**, which is further converted into the diol **223**. The latter undergoes a series of conversions aimed at differentiated protection of the hydroxyl groups and is further oxidised with the Dess–Martin reagent.[170] The resulting aldehyde **224** is oxidised with $NaClO_2$ to the corresponding acid, which was benzylated with *N*,*N*′-dicyclohexyl-*O*-benzylisourea (DCBI) into the ester **225** (Scheme 31).

After removal of the protecting silyl group, the benzyl ester **225** is converted into the ester **226** in three steps. Its hydrolysis with trifluoroacetic acid and treatment of the reaction product with $CF_3CON(CH_3)SiMe_3$ in the presence of toluene-*n*-sulfonic acid in pyridine results in the bissilyl ether **227**. The oxidation of compound **227** with the Dess–Martin reagent is regiospecific and does not involve the tertiary Me_3SiO group, giving the key aldehyde **228**.

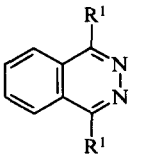
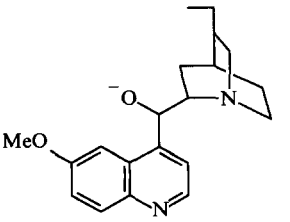
Scheme 31

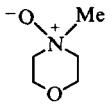


224: R^2 = ; **225**: R^2 = $-CO_2Bn$

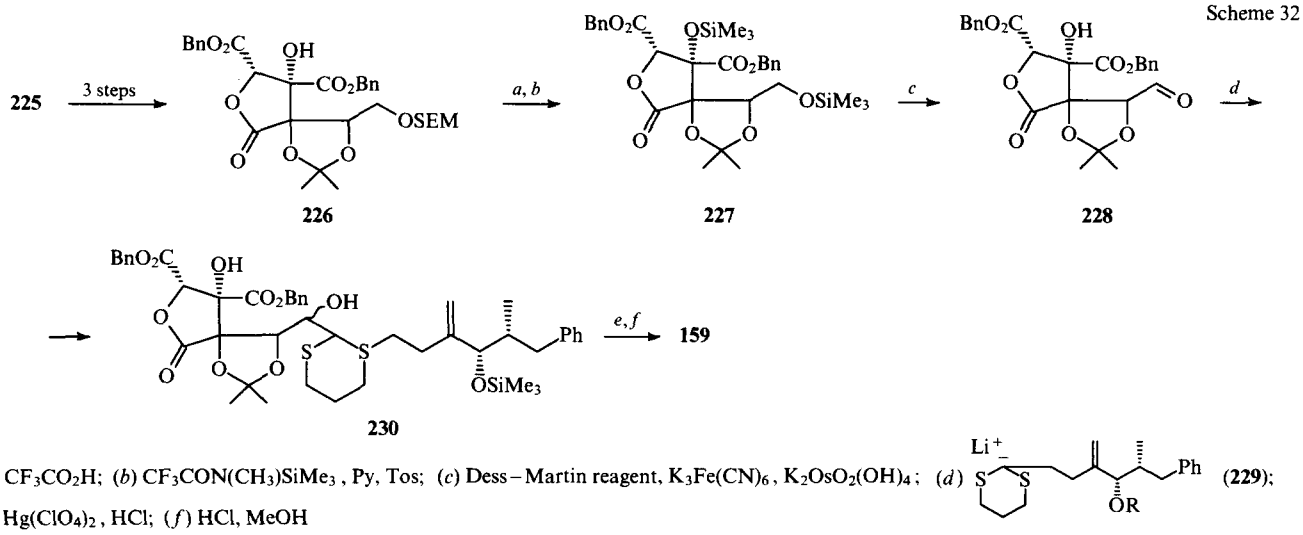
R = COC_6H_4OMe; SEM = $Me_3Si(CH_2)OCH_2$

(*a*) $PdCl_2(MeCN)_2$; (*b*) $(DHQD)_2PHAL$ (**220**), $K_3Fe(CN)_6$, $K_2OsO_2(OH)_4$;

$(DHQD)_2PHAL$—  , where R^1 = 

(*c*) DDQ; (*d*) OsO_4,  ; (*e*) Dess-Martin reagent; (*f*) $NaClO_2$, $NaHPO_4$, $Me_2C=CHCH_3$; (*g*) DCBI

Scheme 32

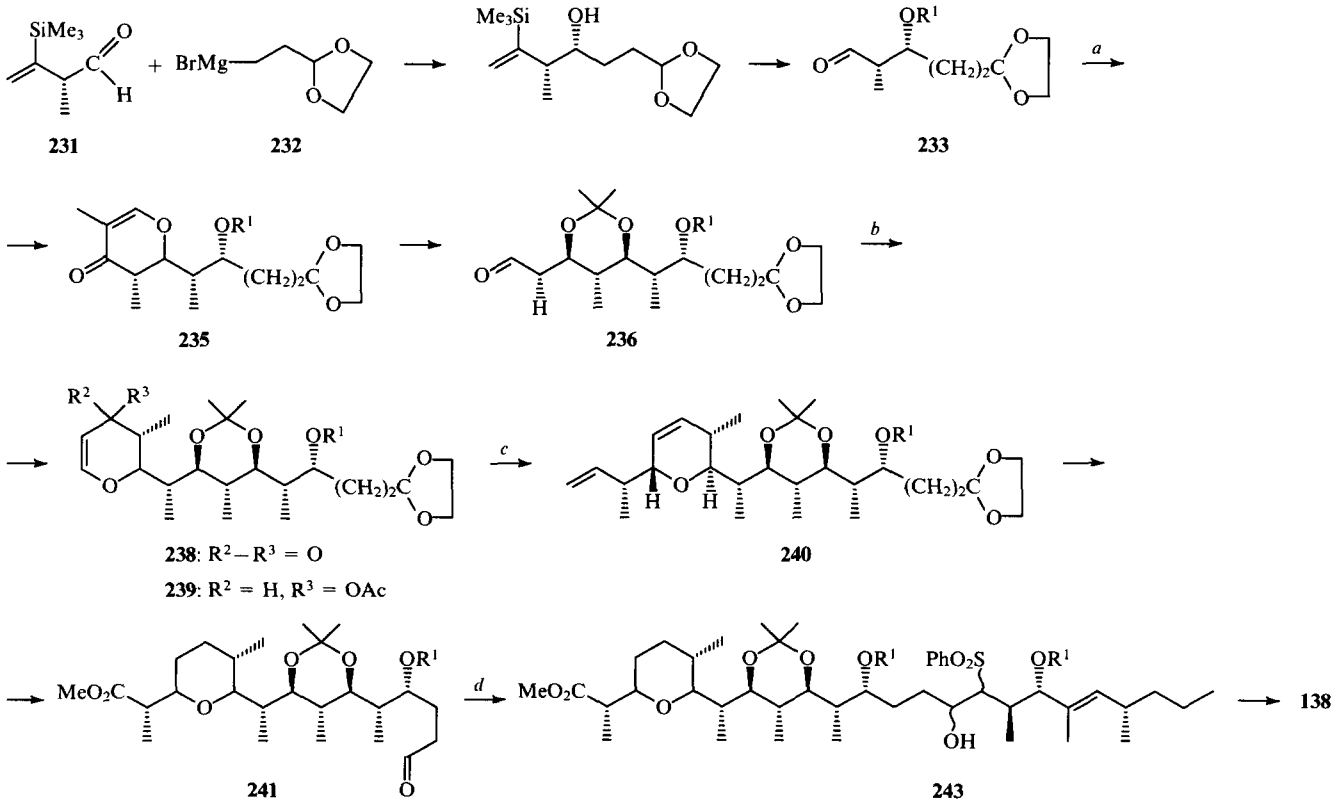


(*a*) CF_3CO_2H; (*b*) $CF_3CON(CH_3)SiMe_3$, Py, Tos; (*c*) Dess–Martin reagent, $K_3Fe(CN)_6$, $K_2OsO_2(OH)_4$; (*d*) (**229**); (*e*) $Hg(ClO_4)_2$, HCl; (*f*) HCl, MeOH

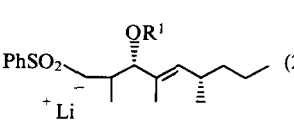
Similar conversions of bissilyl ethers under the action of a $(COCl)_2$–DMSO system has been used to obtain synthons for prostaglandins.[171] The aldehyde **228** reacts with the lithium derivative of the dithiane **229**, giving the compound **230**, and is then converted into zaragozic acid A in two steps **159** (Scheme 32).

The total synthesis of zincoforin **138** is marked by multiple application of organosilicon reagents.[172] For example, the role of the Me_3Si group in the reaction of the aldehyde **231** consists in stereodifferentiation of the attachment of the Grignard reagent **232**; the aldehyde-acetal **233** obtained upon desilylation and ozonolysis reacts with siloxy-1,3-diene **234** to form dihydropyran **235**. The latter undergoes a series of conversions to give the aldehyde **236** which, after an analogous reaction with siloxy-1,3-diene **237**, affords the ketone **238**; the latter is further converted into the acetate **239**. This is followed by $BF_3 \cdot Et_2O$-catalysed cross-coupling with trimethylcrotylsilane, eventually resulting in the compound **240**. The conventional procedures gave the methylformylcarboxylate **241**, which was then introduced in the reaction with the sulfone anion **242**. The obvious conversions of the hydroxysulfone **243** afforded zincoforin **138** (Scheme 33).

Scheme 33



$R^1 = CH_2OCH_2Bn$

(*a*) $MeCH{=}C(SiMe_3O)–C(Me)(OMe){=}CH$ (**234**); (*b*) $MeCH{=}C(SiMe_3O)–CH{=}CH(OMe)$ (**237**); (*c*) $Me_3SiCH_2CH{=}CHMe$; (*d*)  (**242**)

The authors of the present review would like to call the reader's attention to the prospects that emerge from synthetic studies in the area of unsaturated acids. For example, polyhydroxy acids present interest as potential immunizing agents capable of protecting plants from pathogenic fungi even when used in nanogram quantities. Metabolites of the zaragozic acid type are of prime interest for large pharmaceutical firms involved in the solution of vital problems of cardiology, such as regulation of cholesterol biosynthesis. Bengamides, the technological synthesis of which is quite feasible, are also of substantial interest.

The authors express the hope that synthetic chemists will not only further advance the problems discussed in this review but will also proceed along interesting and promising paths.

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