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Review

The Chemistry on Diterpenoids in 1974

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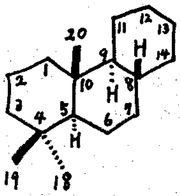
I. INTRODUCTION

This is one of a series of our annual reviews[1~10)] on diterpenoids chemistry. The classification of the compounds is the same as that adopted in our reviews since 1969.

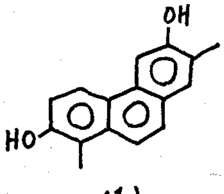
In each section, the related compounds of similar structures are collected to form groups. In each group, isolations, structure determinations, and spectroscopic investigations are first described, syntheses and reactions are secondly, and biosyntheses and the others are finally followed. In each compound or sometimes in each group, the full paper(s) is first described and the short communication(s) is followed.

II. PODOCARPANE DERIVATIVES

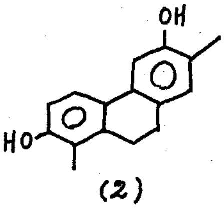


Podocarpane

Micrandrol–A(**1**), –B(**2**), and –C(**3**) tentatively classified as diterpenoids were isolated from *Micrandropsis scleroxylon*.[11)]



(1)



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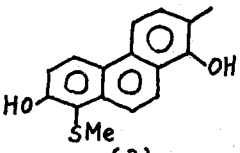

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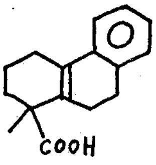
The rule of maximum compactness was put forward as a guide for establishing the stereochemistry of catalytic hydrogenation in many cases. The catalytic hydrogenation of **4** afforded **5** as the major product which was more compact compound than **6**.[12]



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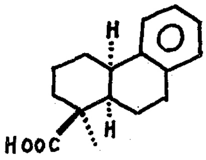

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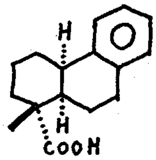

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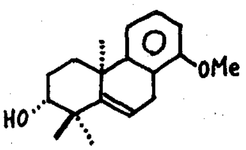
Birch reduction of the compound **7** was investigated, and the structure of the product was determined to be **8** from the X-ray crystallographic study.[13]



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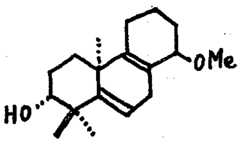

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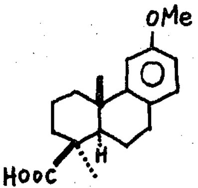

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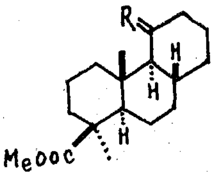
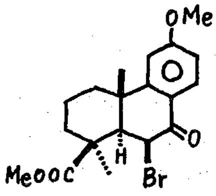
O-Methylpodocarpic acid (**9**) was transformed to methyl 11-oxopodocarpan-19-oate (**10**) and methyl 11β-hydroxypodocarpan-19-oate (**11**).[14]



(10) R = O

(11) R = α-H, β-OH



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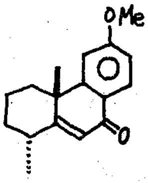
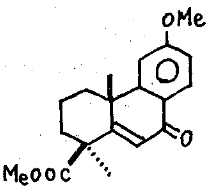


(13)

The conversion of bromo-ketone **12** to the α,β-unsaturated ketone **13** in 80% yield by 1,4-diazabicyclo[2,2,2]octane (Dabco) in *o*-xylene at reflux was reported. When the proposed intermediate **14** was treated with Dabco, a high (90%) yield of decarbomethoxylation product **13** was obtained.[15]



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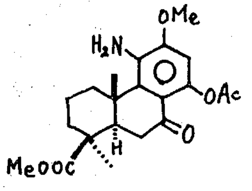

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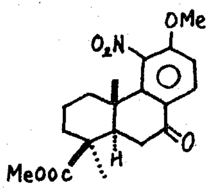

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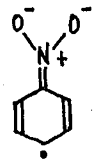
The formation of **15** in the reduction of podocarpanoic acid derivative **16** with zinc dust and AcOH presented an evidence for the intermediacy of an anion radical **17** during dissolving metal reduction in acidic medium.16)



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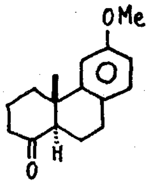

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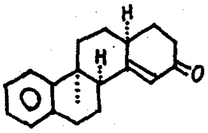

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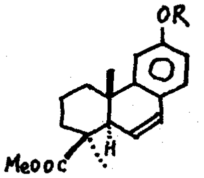
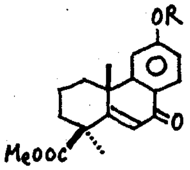
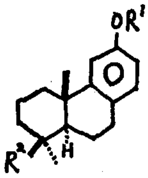


(20) R = Me
(21) R = Ac

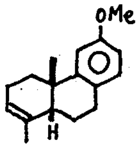
Attempts to utilize the kteone **18** for the preparation of steroidal analogs were reported. The ketone **18** was converted into the octahydrochrysene **19**.17) Photo-sensitized oxidation of the 6,7-dehydro ring-C aromatic diterpenoids **20** and **21** afforded high yields of the corresponding 5-ene-7-ones **22** and **23**.18)



(22) R = Me
(23) R = Ac



(24) R^1 = Me, R^2 = COOH
(27) R^1 = Me, R^2 = COCl
(28) R^1 = Ac, R^2 = COOH
(29) R^1 = H, R^2 = COOH



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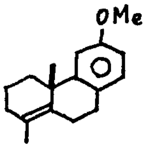

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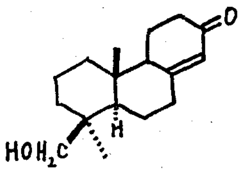
Methods for isomerization of the 12-methoxy-19-norpodocarpatetraene mixture obtained from oxidative decarboxylation of 12-methoxypodocarpa-8,11,13-trien-19-oic acid (**24**) with lead tetraacetate were reported. Acid-catalyzed isomerization gave a mixture of the endocyclic isomers **25** and **26**, while iodine-catalyzed isomerization gave a mixture enriched in the isomer **26** to the extent of 80%. Metal-catalyzed decarbonylation of the acid chloride **27** and oxidative decarboxylation of the acetoxy acid **28** were also examined.19) The conversion of podocarpic acid (**29**) into 19-hydroxypodocarp-8(14)-en-13-one (**30**), a useful intermediate for synthesis, was reported. Detosylations of derivatives of methyl 12-toluene-*p*-sulfonyloxypodocarpa-8,11,13-trien-19-oate were investigated using a modified W-7 Raney nickel catalyst.20)



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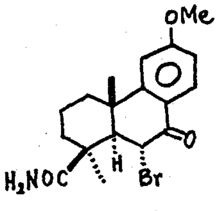

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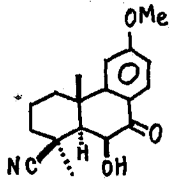
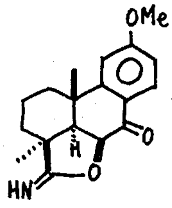


(32)

Several methods for the introduction of a 6*β*,19 nitrogen bridge in podocarpane derivatives were reported. Attempted intramolecular N-alkylation in the 6α-bromo amide **31** gave ketol **32** *via* imino ether **33**. The diosphenol **34** gave lactam **35**, which was reduced to lactam **36**.[21)]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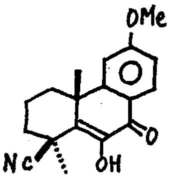
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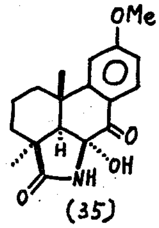
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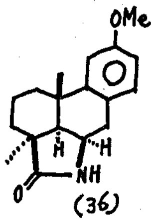
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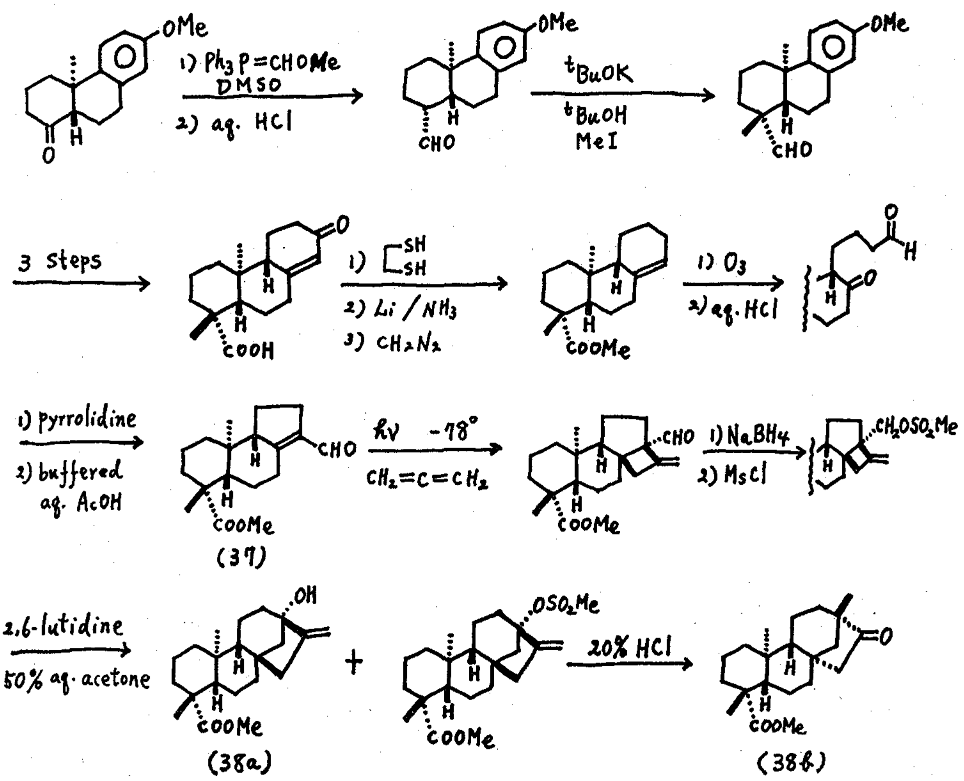
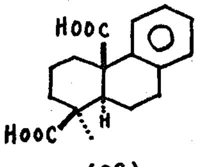


Chart 1

The syntheses of steviol methyl ester (38*a*) and isosteviol methyl ester (38*b*) were carried out. The route is shown in Chart 1. The key reaction was the photoaddition of allene to **37**.[22)] Attempts to synthesize **39**, an important intermediate in the synthesis of diterpenoids and diterpene alkaloids, led ultimately to the isolation of **40**.[23)]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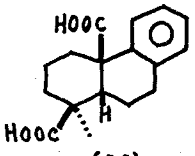
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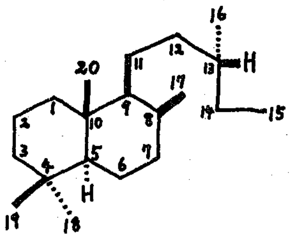
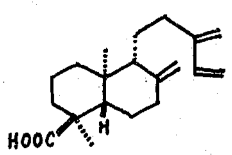
III. LABDANE DERIVATIVES



Labdane

Manool was isolated from *Salvia sclarea*.[24] 13-Epimanool was isolated from *Abies alba*.[25] *ent*-8(17),13(16),14-Labdatrien-18-oic acid (**41**) was isolated from *Hymenaea verrucosa*.[26] From the roots of *Hermas villosa*, four diterpenic acids were obtained: *cis*- and *trans*-Communic acid (**42** and **43**) and two further *cis, trans*-isomeric acids **44** and **45** with equatorial acid functions.[27]



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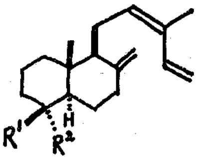
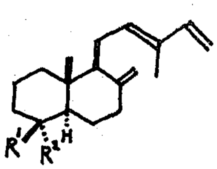


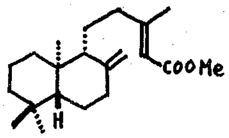
(42) R^1 = COOH, R^2 = Me

(44) R^1 = Me, R^2 = COOMe



(43) R^1 = COOH, R^2 = Me

(45) R^1 = Me, R^2 = COOH



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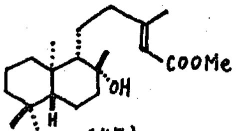

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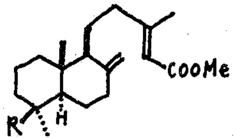


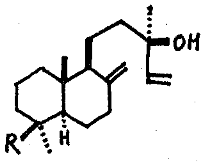
(48) R = CH$_2$OH

(49) R = CH$_2$OAc

(50) R = CHO

(51) R = COOMe

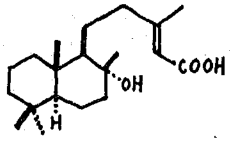
Six diterpene acids of the labdane type were obtained from the oleoresin of *Araucaria bidwilli* and characterized as their methyl esters: **46**, **47**, **48**, **49**, **50** and **51**.[18] From the neutral fraction of *Larix decidua* bark, 13-epimanool, torulosyl acetate (**52**), torulosol (**53**), torulosal (**54**), and 19-acetoxylabda-12,14-dien-8-ol were isolated.[29]



(52) R = CH$_2$OAc

(53) R = CH$_2$OH

(54) R = CHO



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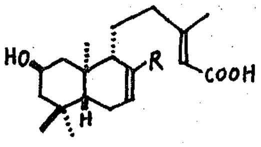
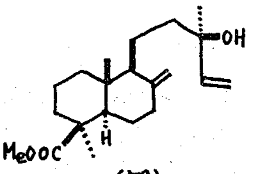


(56) R = Me

(57) R = CH$_2$OH

Labd-13-en-8-ol-15-oic acid (**55**) was isolated as the major component of the hardened trunk resin of *Hymenaea courbaril*.[30] Two new acids **56** and **57** were isolated from *D. microzyga*.[31]



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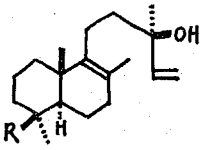
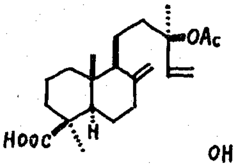


(59) R = COOMe
(60) R = CHO
(61) R = CH$_2$OH



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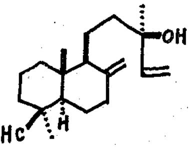

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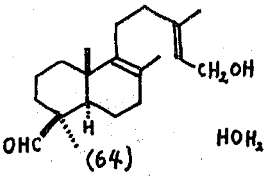

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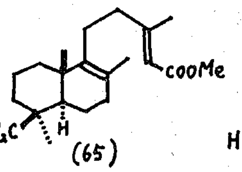

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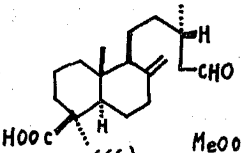

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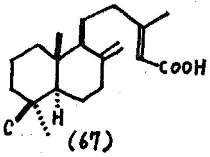
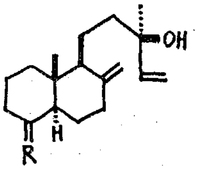
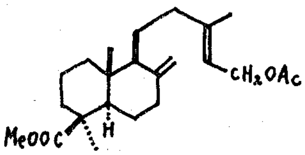


(67)

From *Araucaria cooki* were isolated methyl isocupressate, O-acetyl-isocupressic acid, 13-epitorulosol and agathadiol and eight new diterpenes. The structures **58**, **59**, **60**, **61**, **62**, **63**, **64**, and **65** were assigned to them.[32] Imbricataloic acid (**66**) and agathic acid 19-monomethyl ester (**67**) were isolated from *Pinus massoniana*.[33] Two new nor-diterpenes were isolated from *Araucaria excelsa* and their structures **68** and **69** determined on the basis of their IR, NMR, and MS, and by partial synthesis from O-acetylcupressic acid.[34]



(68) R = α-Me, β-OH
(69) R = α-OH, β-Me



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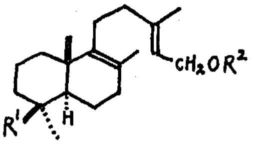
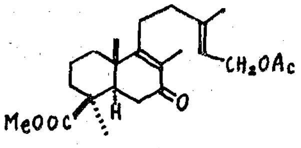


(71) R^1 = COOH, R^2 = H
(72) R^1 = COOMe, R^2 = Ac



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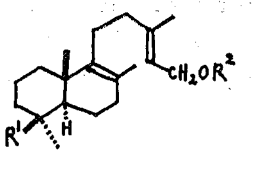
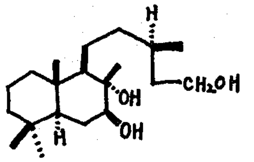


(74) R^1 = CH$_2$OH, R^2 = H
(75) R^1 = CHO, R^2 = H
(76) R^1 = CH$_2$OH, R^2 = Ac
(77) R^1 = CHO, R^2 = Ac
(78) R^1 = CH$_2$OAc, R^2 = Ac

From the acid fraction of the oleoresin of *Araucaria cunninghami* were isolated methyl communate, methyl isocupressate, and four new diterpenes. The structures **70**, **71**, **72**, and **73** were assigned to them. From the neutral fraction of the same oleoresin were isolated five new diterpenes. The structures **74**, **75**, **76**, **77**, and **78** were assigned to them.[35] The structure of gymnospermin, a new diterpene triol isolated from *Gymnosperma glutinosa* was determined to be **79**.[36]



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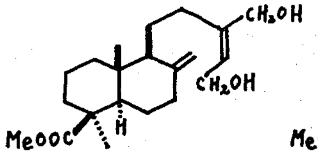

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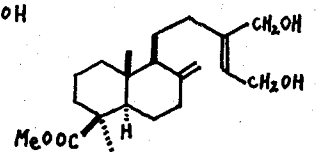
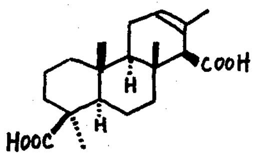
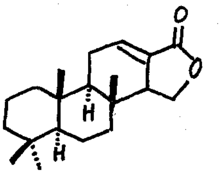


(81)

In the diterpene ester, methyl sciadopate, the substituted butenediol side chain was shown to be *trans* (as **80**)[37] and not *cis* (**81**) as had previously been supposed.[38,39] A new diterpene, isoagatholactone, isolated from *Spongia officinalis*, is the first natural compound with the carbon skeleton of isoagathic acid (**82**), the acid-catalyzed cyclization product of agathic acid. The structure **83** was assigned to isoagatholactone on spectral grounds and chemical correlation with grindelic acid (**84**).[40]



(82)



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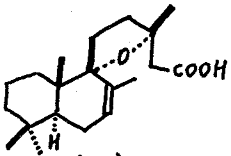
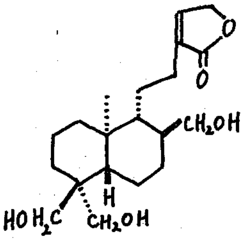


(84)

From *Calocedrus decurrens*, the following diterpenoids were characterized by GLC: lambertianic acid, isocupressic acid, *trans*-communic acid, isoagatholal, and pinusolide.[41] Wightionolide isolated from the leaves of *Andrographis wightiana* was shown to have structure **85**. The molecular structure of the derivative of wightionolide was determined by X-ray diffraction studies.[42]



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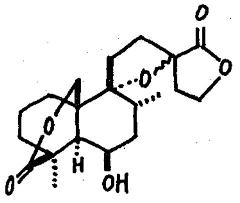

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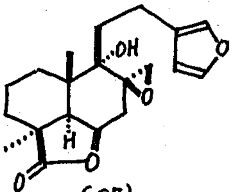
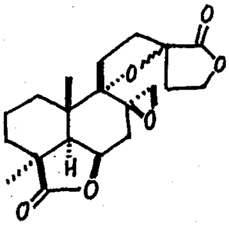


(87)

Nepetaefolinol, a new diterpenoid from *Leonotis nepetaefolia,* was identified as 9,13-epoxy-6β-hydroxy-8α-labdane-16,15; 19,20-dilactone (**86**) on the basis of chemical and spectroscopic eivdence. From the same plant, two new minor compounds, leonotinin (**87**) and **88** were isolated.[43]



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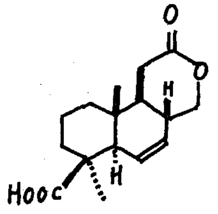

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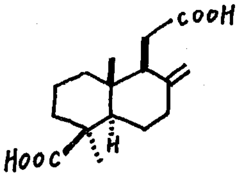
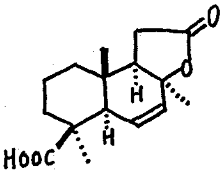
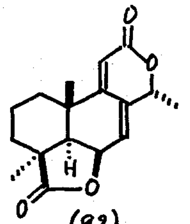
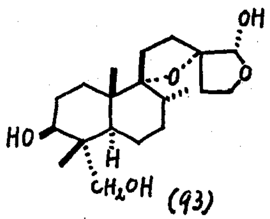


(90)

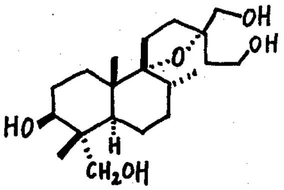
From the culture of *Acrostalagmus* NRRL-3481 were isolated three new C_{16}-terpenoids, acrostalidic acid (**89**), acrostalic acid (**90**), and isoacrostalidic acid (**91**), some of which were assumed to be biosynthetic intermediates for the lactone **92**.[44]

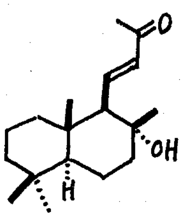

(91)


(92)


(93)

From *Lasiocorys capensis* was isolated a new diterpenoid, lasiocoryin. Its structure was determined to be **93** by X-ray analysis,[47] and the structure of lagochilin, originally isolated from *Lagochilus nebrians*,[45,46] was revised to **94** which was identical with the reduction product of **93**.[47]


(94)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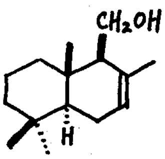
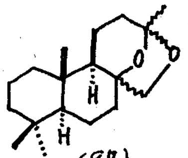

(96)

A new diterpenoid degradation product **95** was isolated from an extract of *Nicotiana tabacum*. The structure was confirmed by total synthesis using drimenol (**96**).[48]

Mass spectra of the diterpenes; Δ^{12}-*cis*- and Δ^{12}-*trans*-abienol, isoabienol, Δ^{13}-*cis*- and Δ^{13}-*trans*-neoabienol were investigated.[49] The mass spectra of bisnorlabdanes **97**, **98**, **99**, **100**, and **101** were studied at both low and high resolution. All compounds gave characteristic $C_{13}H_{21}$ and $C_{10}H_{17}$ ions. Comparison of fragmentation patterns allowed ready distinction between isomeric acetals **97** and **98**. The structure of **100** was assigned on the basis of its fragmentation pattern.[50]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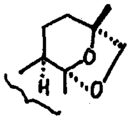
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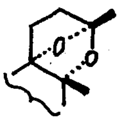
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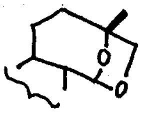
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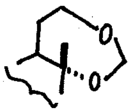
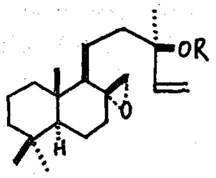
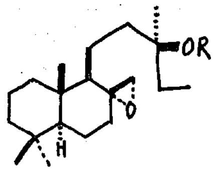
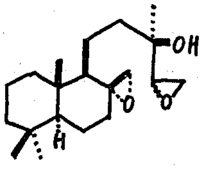

(101)

In an attempt to establish the origin of the long range coupling in exocyclic epoxides, a series of 8,17-epoxylabdanes (**102**~**115**) were synthesized. All the α-epoxides (*quasi*-axial methylenes) unsubstituted in ring B exhibited long range coupling but the two β-epoxides **114** and **115** were not long range coupled.[51]


(102) R=H
(103) R=Ac


(104) R=H
(105) R=Ac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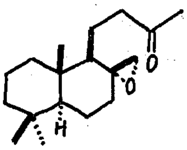
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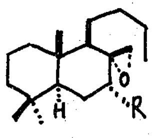
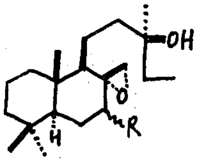
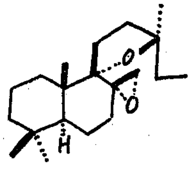
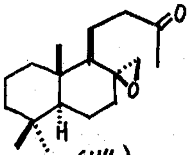

(108) R=H
(109) R=OH


(110) R=α-OH
(111) R=α-OAc
(112) R=β-OH


(113)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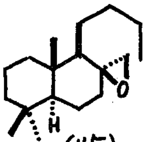
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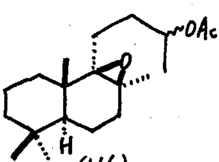
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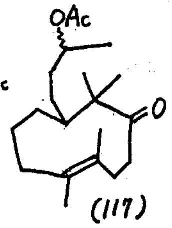
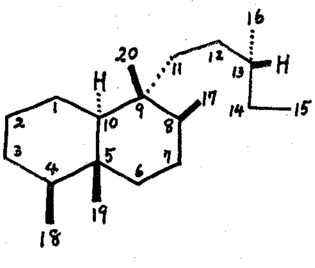

(117)

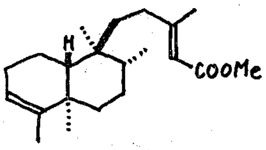
The preparation and rearrangement with BF_3-Et_2O complex of a number of 8α,9α- and 8β,9β-epoxy-14,15-bisnor- and 14,15,16-trisnor-labdane derivatives were carried out to determine whether the clderodane diterpene skeleton could be obtained. A variety of rearranged carbon skeleton was obtained but not that of clerodane, proabbly because formation of this would involve the generation of a 1,3-diaxial interaction between the methyl groups of C-5 and C-9. A novel product from the bisnorlabdane epoxide **116** was the cyclodecenone **117**.[52)]

IV. CLERODANE DERIVATIVES

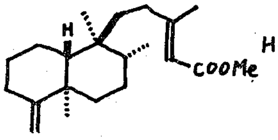


Clerodane

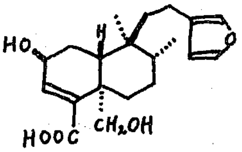
Two diterpenes were obtained from the oleoresin of *Araucaria bidwilli* and characterized as their methyl esters; **118** and **119**.[28)] A new diterpene was isolated from *Olearia muelleri* and structure **120** was assigned to it.[53)]



(118)

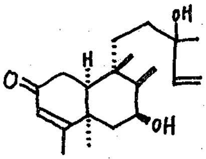


(119)



(120)

Annanone, a diterpenoid lactone isolated from *Stachys annua,* was shown to have structure **121**.[54] One known (**122**) and eight new (**123**, **124**, **125**, **126**, **127**, **128**, **129**, and **130**) diterpenoids were isolated from *Solidago serotina.* The constitution and stereochemistry of the new compounds were deduced from their spectroscopic properties and chemical reactions.[55]



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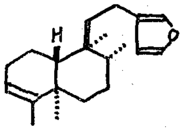

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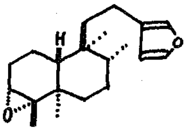

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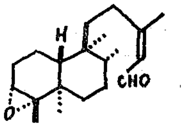

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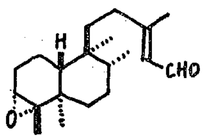

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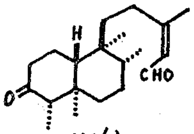

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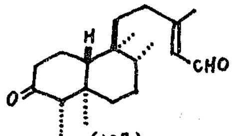

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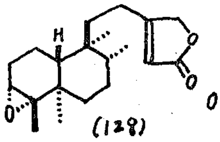

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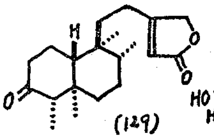

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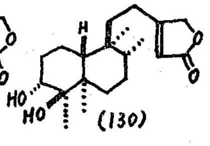

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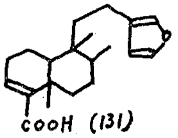
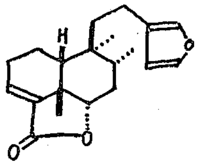
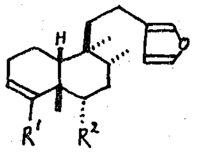


(131)

Hardwickiic acid (**131**) was isolated from *Ribes nigrum*.[56] Six new diterpenoids from *Solidago arguta* were isolated. The structures **132**, **133**, **134**, **135**, **136**, and **137** were assigned to them on the basis of chemical and spectroseopic evidence and comment was made on the stereochemistry of several related, known *cis*-clerodanes.[57]

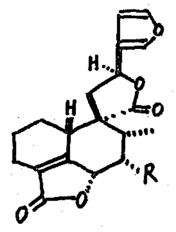


(132)

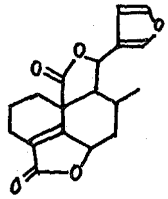


(133) R^1=Me, R^2=H
(134) R^1=CH_2OAc, R^2=H
(135) R^1=CH_2OH, R^2=H
(136) R^1=CH_2OAc, R^2=OH
(137) R^1=CH_2OH, R^2=OH

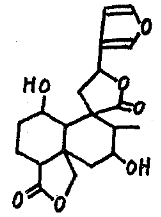
On the basis of the results of an X-ray analysis and some chemical reactions, the structure of teucvin isolated from *Teucrium viscidum var. Miquelianum* was shown to be **138**.[58] Eugarzasadone was obtained from *Teucrium cubense,* and structure **139** was assigned to it.[59] But later this compound was proved to be identical with teucvin,[60] and the structure was revised to **138**.[61]



(138) R=H
(140) R=OH

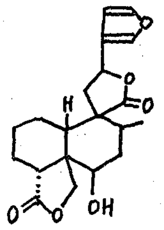


(139)

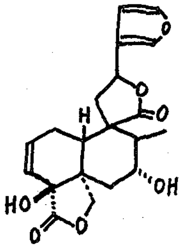


(141)

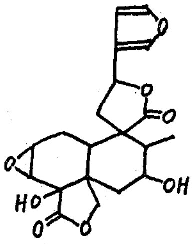
Teucrin A, a diterpene lactone isolated from *Teucrium chamaedrys,* was shown to have absolute structure **140** according to its UV and IR spectra and its chemical reactions.[62] Teucrins B, E, F, and G, new diterpenoids isolated from *T. chamaedrys,* were proved to have structure **141**, **142**, **143**, and **144**, respectively, according to their IR, CD, and NMR spectra and their acetylation products.[63]



(142)

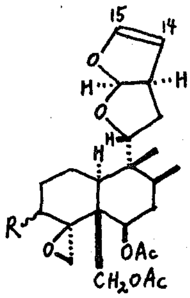


(143)

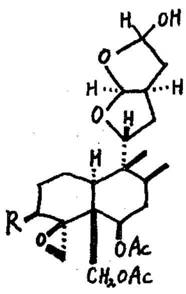


(144)

Caryoptinol (**145**) and dihydrocaryoptinol (**146**) were isolated as the minor components in *Caryopteris divaricata.*[64] A new diterpenoid 3-epicaryoptin (**147b**) was isolated from *Clerodendron calamitosum.* This compound possessed antifeeding activity against the larvae of *Spodoptera litura.*[65] The confirmation of the absolute configuration of caryoptin (**147a**) and 3-epicaryoptin (**147b**), and the noteworthy experimental results about the CD spectroscopy for these dibenzoate derivatives were reported.[66] Six antifeeding active diterpenes clerodin (**148**), caryoptin (**147a**), dihydroclerodin, dihydrocaryoptin, clerodin hemiacetal (**149**), and caryoptin hemiacetal (**147c**) were isolated from *Caryopteris divaricata.*[67] The survey of the presence of chemical resistant factors in



(145) R = β-OH
(146) 14,15-saturated R = β-OH
(147a) R = β-OAc
(147b) R = α-OAc
(148) R = H



(147c) R=OAc
(149) R=H

plants against the larvae of *Spodoptera litura* was examined. In addition, the antifeeding diterpenes were surveyed from thirteen species of plants that belong to Verbenaceae family.68) Among thirteen antifeedants, caryoptinol (**145**) and dihydrocaryoptinol (**146**) from *Caryopteris divaricata* and 3-epicaryoptin (**147b**) from *C. calamitosum* are contained.

The diene-ester **150** on heating underwent an intramolecular Diels-Alder reaction *via* the intermediate **151**. The β-alkyl furan moiety in **151** reacts as the dienophile adding to the cyclohexadiene unit to give **152** as shown in Chart 2.69)

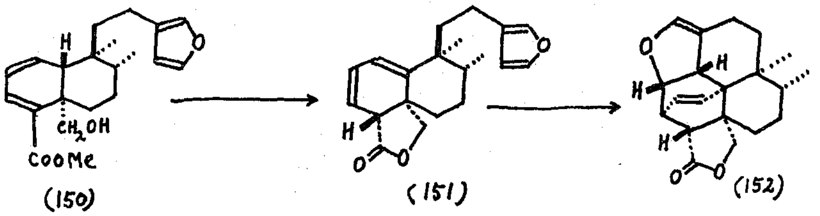
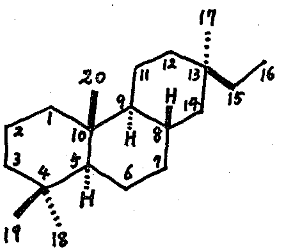
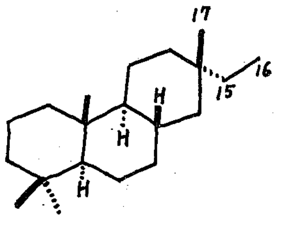


Chart 2

V. PIMARANE AND ISOPIMARANE DERIVATIVES



Pimarane



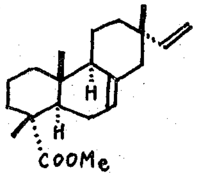
Isopimarane

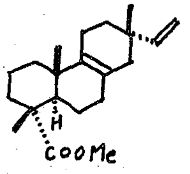
Sandaracopimaradienol was isolated from *Araucaria cooki*.32) GLC of the methylated resin of *Calocedrus decurrens* showed the peak of methyl sandaracopimarate.41) Isopimarol, isopimaric acid, and sandaracopimaric acid were isolated from *Podocarpus ferrugineus*.70) Chromatography of a cyclohexane extract of commercial "dragon's blood" resin (obtained from the exudate of the fruits of *Daemonorops draco*) yielded a fraction containing pimaric, isopimaric, and sandaracopimaric acids.71)

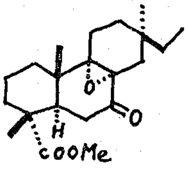
The investigation of the mass spectra of twelve naturally occurring isopimarane derivatives with three oxygen functions showed that constitution as well as configuration were important for the special fragmentation pattern.72) Raman spectral absorption bands were correlated with tri- and tetra-substituted double bonds in methyl $\Delta^{7(8),15}$-isopimarate (**153**) and methyl $\Delta^{8(9),15}$-isopimarate (**154**).73)

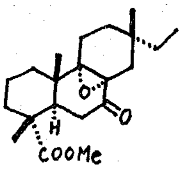
The substances formed by chromic acid oxidation of methyl pimar-8(9)-en-18-oate and isopimar-8(9)-en-18-oate were identified as 8,9-epoxy 7-ketones, for instance, **155** and **156**. Long-range shielding effects in 8,9-epoxides of pimaranes and isopimaranes were reported.74)

A modification of the solvomercuration-demercuration reaction was reported which

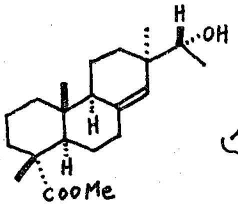

(153)

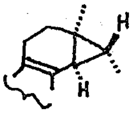

(154)

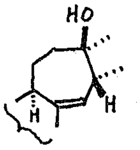

(155)

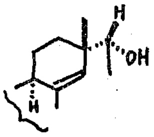

(156)

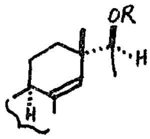
prevented the formation of cyclic ethers from dienes. Application of the procedure to methyl pimarate permitted the stereospecific synthesis of compound **157**. Treatment of **157** with toluenesulfonyl chloride-pyridine resulted in rearrangement to **158** and **159**. Similar treatment of **160** and **161a** did not result in rearrangement. The results were ascribed to differences in the geometries of the homoallylic cations produced from **157**, **160**, and **161b**.[75]


(157)

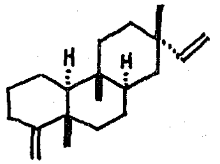

(158)

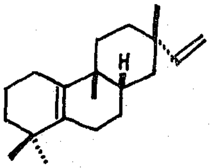

(159)

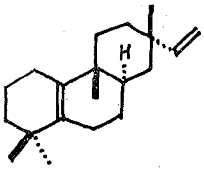

(160)

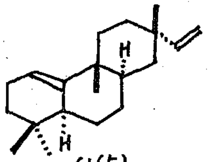

(161a) R=Ac
(161b) R=H

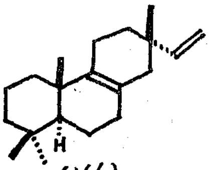
Upon heating in formic acid dolabradiene (**162**) gave a mixture of hydrocarbons. Five backbone rearrangement products isolated from the mixture were assigned to **163**, **164**, **165**, **166**, and **167**.[76]

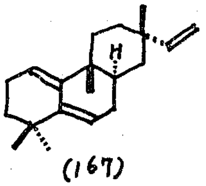

(162)


(163)


(164)

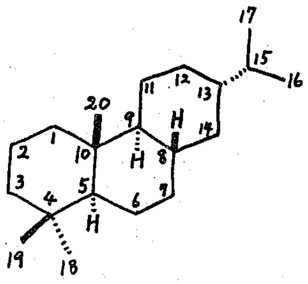

(165)


(166)


(167)

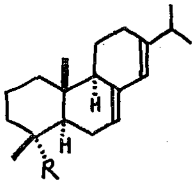
Esterification of maleopimaric acid by $EtC(CH_2OH)_3$ was investigated. It proceeded in two steps, and their rate constant, apparent activation energy and entropy were calculated.[77]

VI. ABIETANE DERIVATIVES

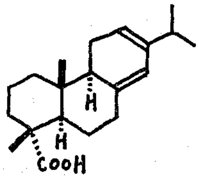


Abietane

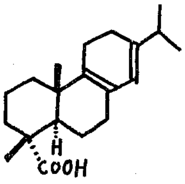
Abieta-8,11,13-triene and abieta-8,11,13-trien-7-one were obtained from *Abies alba*.[25] Abietinal (**168**) and abietic acid (**169**) were found in the oleoresin of *Araucaria cooki*.[32]



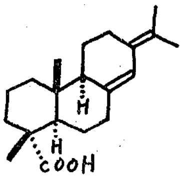
(168) R = CHO
(169) R = COOH



(170)



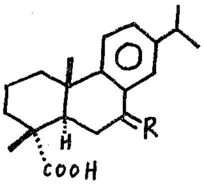
(171)



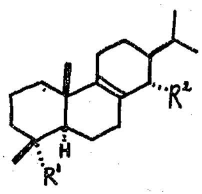
(172)

Levopimaric acid (**170**), palustric acid (**171**), and neoabietic acid (**172**) were isolated from the cortex of *Pinus massoniana*.[33] A paper related to the conformational analysis of levopimaric acid (**170**) was published.[78]

From a cyclohexane extract of commercial "dragon's blood" resin (obtained from the exudate of the fruits of *Daemonorops draco*) was isolated dehydroabietic acid (**173**) and abietic acid (**169**) with some pimarane type diterpenes.[71]



(173) R = H_2
(174) R = O



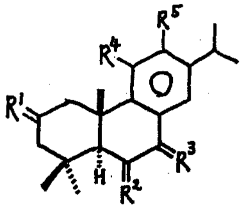
(175) R^1 = COOH, R^2 = OH
(176) R^1 = CH_2OH, R^2 = OH

Calocedrus decurrens was shown to contain dehydroabietic acid (**173**) and 7-oxo-dehydroabietic acid (**174**).[41]

The structures of suaveolic acid (**175**) and suaveolol (**176**), diterpenes in *Hyptis suaveolens* (Labiatae), were reported.[79]

Several abietane type diterpenes were isolated from the bark of *Podocarpus ferrugi-*

neus. They were ferruginol (**177**), sugiol (**178**), sugiyl methyl ether (**179**), xanthoperol (**180**), royleanone (**181**), 6-dehydroroyleanone (**182**), cryptojaponol (**183**), 5β-hydroxy-6-oxasugiyl methyl ether (**184**), 2-ketoferruginol (**185**), and 2β-acetoxysugiyl methyl ether (**186**), respectively.[70]



(177) $R^1=R^2=R^3=H_2$, $R^4=H$, $R^5=OH$

(178) $R^1=R^2=H_2$, $R^3=O$, $R^4=H$, $R^5=OH$

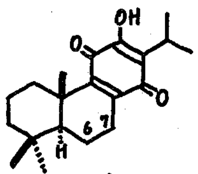
(179) $R^1=R^2=H_2$, $R^3=O$, $R^4=H$, $R^5=OMe$

(180) $R^1=H_2$, $R^2=R^3=O$, $R^4=H$, $R^5=OH$

(183) $R^1=R^2=H_2$, $R^3=O$, $R^4=OH$, $R^5=OMe$

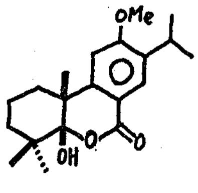
(185) $R^1=O$, $R^2=R^3=H_2$, $R^4=H$, $R^5=OH$

(186) $R^1=\alpha\text{-H},\beta\text{-OAc}$, $R^2=H_2$, $R^3=O$, $R^4=H$, $R^5=OMe$

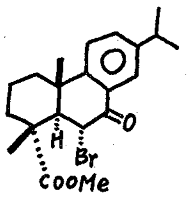


(181)

(182) $\Delta^{6(7)}$



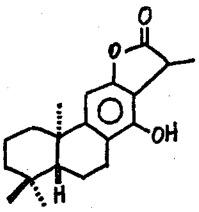
(184)



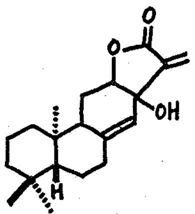
(187)

The absolute configuration of compound **187** was established by means of the X-ray analysis.[80]

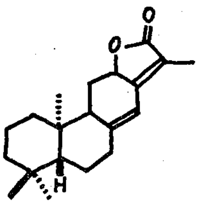
The structures of jolkinolides C (**188**), D (**189**), and E (**190**), new ditepenes in *Euphorbia jolkini,* were published.[81]



(188)

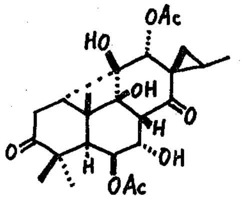


(189)

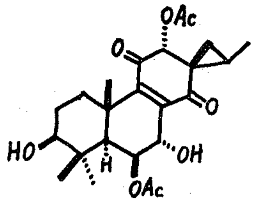


(190)

Cyclobutatusin (**191**) and 3β-hydroxy-3-deoxobarbatusin (**192**) were isolated as two minor constituents from *Coleus barbathus* and their structures were determined. The former was found to contain a four-membered ring in the molecule.[82]

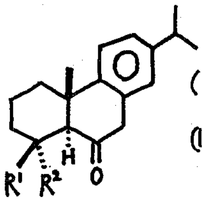


(191)



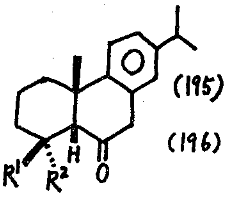
(192)

In an effort to explore the stereochemistry of 6-ketoabieta-8,11,13-trienes, the related compounds, **193**, **194**, **195**, and **196** were prepared.[83)]



(193) $R^1=R^2=Me$

(194) $R^1=H, R^2=Me$

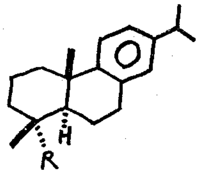


(195) $R^1=Me, R^2=H$

(196) $R^1=H, R^2=Me$

Some reactions (hydrolysis, substitution, reduction, and so on) using a dehydroabietic acid derivatives were reported.[84)]

The influence of steric factors on autoxidation of terpenic aldehydes having tertiary formyl groups was investigated. For instance, the autoxidation of dehydroabietic aldehyde (**197**) gave the starting aldehyde (45%), the related acid (20.4%), and other several neutral compounds, **198** (1.8%), **199** (9.6%), **200** (4.5%), **201** (1.2%), **202** (0.6%) and 203 (4.8%).[85)]

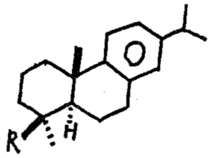


(197) R=CHO

(198) R=OCHO

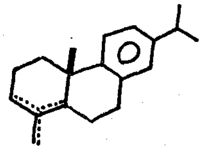
(199) R=OOH

(201) R=OH



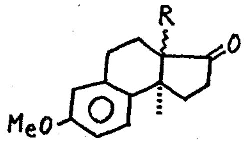
(200) R=OOH

(202) R=OH



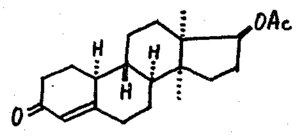
(203)

Dehydroabietic acid (**173**) was chemically transformed, *via* 18 steps of reactions, into ketone **204** and **205** which are convenient starting materials for the preparation of 14α-methylsteroids.[86)] 3-Oxo-17β-acetoxy-14α-methyl-Δ⁴-8α,9β,10α,13α-estrene (**206**) was succesively synthesized from **205**.[87)]



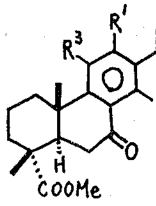
(204) R=β-Me

(205) R=α-Me

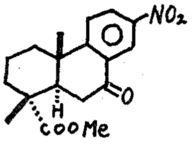


(206)

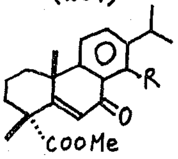
The nitration of **207** gave 14-nitro (**208**) and 13-nitro ester (**209**), in ca. 1 : 1 ratio. The similar nitration of some methyl 7-oxo-derivatives having a substituent in 12 position (**210**, **211**, **212**, and **213**) smoothly took place to yield selectively the corresponding 13-nitro-deisopropyl ester. In the case of 14-substituted ester (**214**), a mixture consisting of three compounds was obtained. A nitration of **215**, however, gave only 14-nitro product **216**. Compound **217** on nitration gave an addition product **218** to the double bond.[88)]



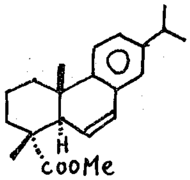
(207) $R^1 = R^2 = R^3 = H$
(208) $R^1 = R^3 = H,\ R^2 = NO_2$
(210) $R^1 = OH,\ R^2 = R^3 = H$
(211) $R^1 = OAc,\ R^2 = R^3 = H$
(212) $R^1 = OMe,\ R^2 = R^3 = H$
(213) $R^1 = Br,\ R^2 = R^3 = H$
(214) $R^1 = R^3 = H,\ R^2 = OH$



(209)



(215) $R = H$
(216) $R = NO_2$



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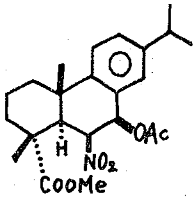

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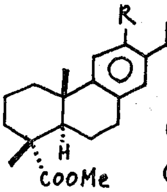


(219) $R = OH$
(220) $R = OMe$
(221) $R = Br$

The nitration of methyl dehydroabietate derivatives, **219** and **220**, gave only the corresponding 11-nitrated compound. However, 12-bromo compound **221** was nitrated in different behavior and afforded more complex result.[89)]

A transformation of *l*-abietic acid (**169**) to a compound **222** having a benzohydroazulene skeleton was reported. The outline is shown in Chart 3.[90)]

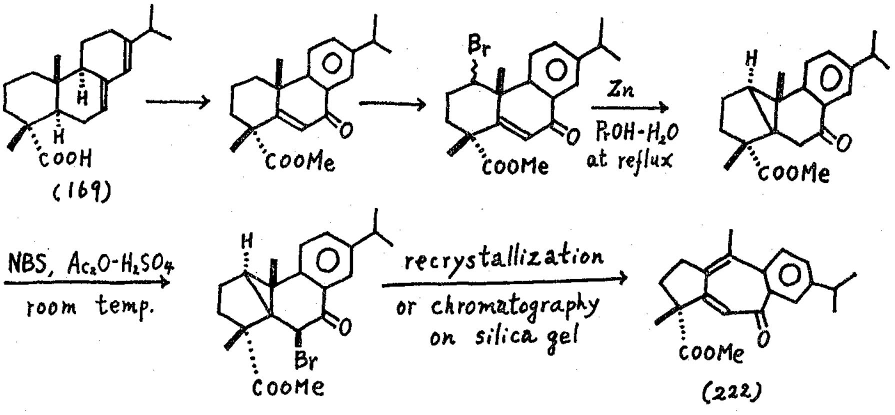


Chart 3

Intramolecular functionalizations of 11-oxygenated abietanes were published. Hypoiodite reaction and oxidative cyclization of C-11 epimeric alcohols **223** and **224** resulted in functionalization at C-1 or C-20, as shown in Chart 4.[14)]

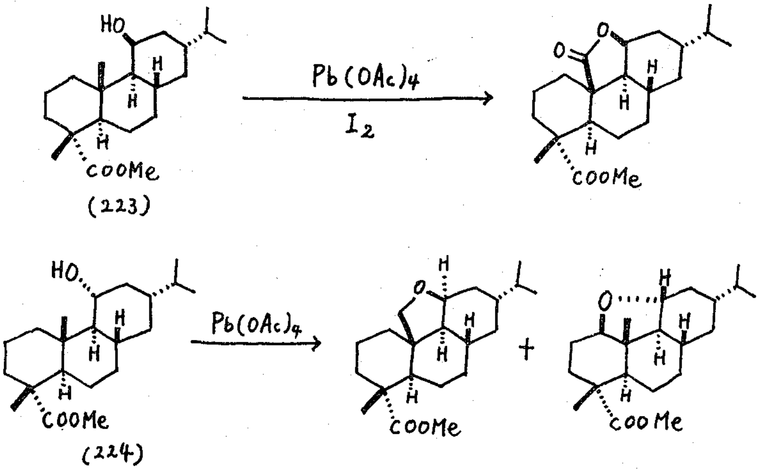
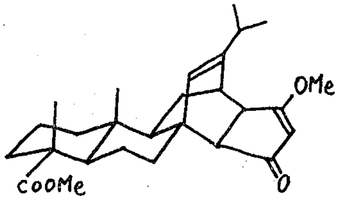


Chart 4

The structures **226** and **227** of the products resulting from photochemically induced hydrogen transfers in the levopimaric acid methyl ester-cyclopentadione adduct **225** were established by X-ray analysis of a heavy-atom derivative **228**.[91,92]



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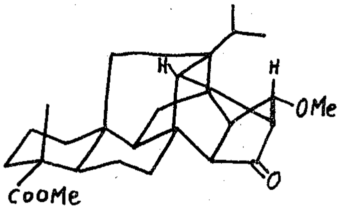

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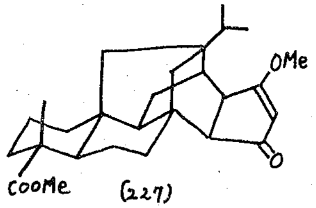

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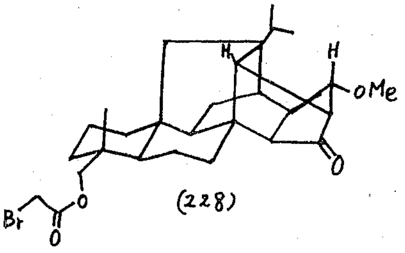
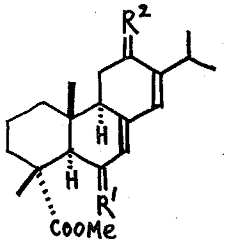


(228)

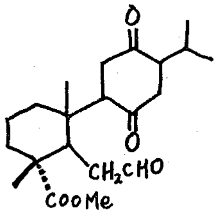
Compound **217** on photo-sensitized oxidation yielded unsaturated ketone **215**.[18]

Oxidation of methyl abietate (**229**) by CrO$_3$ in AcOH at 80° gave methyl 7-oxo-dehydroabietate (**207**) (17%), methyl 6,12-dioxoabietate (**230**) (12.5%), and oxoaldehyde **231** (∼3%). Treatment of **229** with kMnO$_4$ in pyridine afforded 45% of **207** and ∼23% of **230**.[93]

Methyl levopimarate (**232**) was autoxidized in daylight to give compounds **233∼239**. Peroxide **240**, which was formed in the initial stage of the photooxidation, gave **233∼235** when exposed to light.[94]



(229) $R^1 = R^2 = H_2$
(230) $R^1 = R^2 = O$



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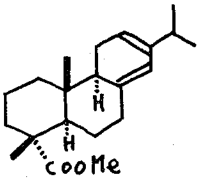

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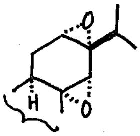

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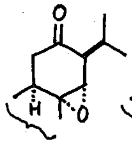

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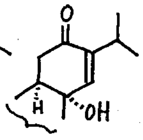

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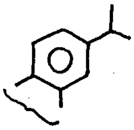

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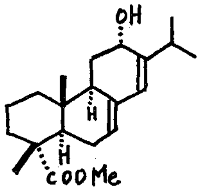

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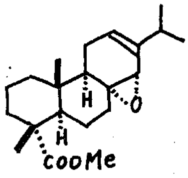

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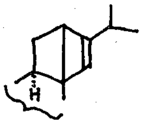

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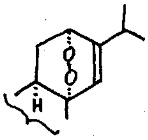


(240)

In concentrated sulfuric acid at 0° all-*trans*-tetrahydroabietic acid (**241**) was shown to rearrange to optically inactive 7-(1,1-dimethyl-tetradecahydrophenanthryl) dimethylacetic acid (**242**). A mechanism of the novel rearrangement was presumed as shown in Chart 5.[95]

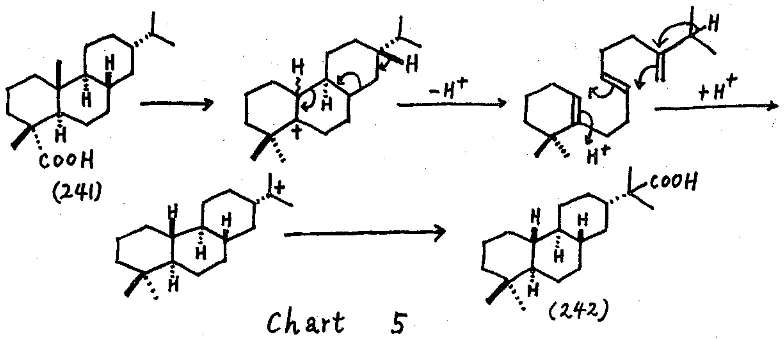
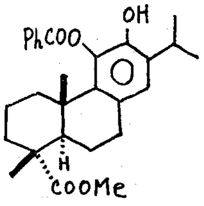


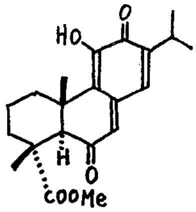
Chart 5

Phenol **219**, derived from *l*-abietic acid, was oxidized with benzoyl peroxide to obtain **243**, which was transformed into natural taxodione (**244**) and compound **245**.[96]

6α-Hydroxy-7-oxoabieta-8,11,13-triene (**246**), converted from 7-oxoabieta-8,11,13-triene, was treated with *p*-toluenesulfonyl chloride and then heated at 200°C to afford a



(243)



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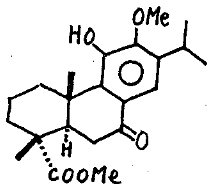
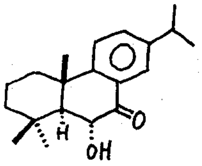


(245)

β-naphthol derivative **247**.[97)]



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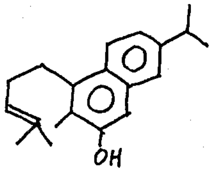

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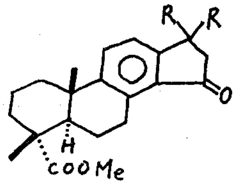
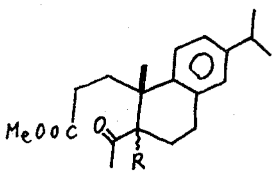


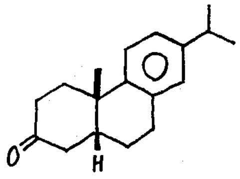
(248) R = H
(249) R = Me

The chemical conversion of dehydroabietic acid (**173**) into **248** and **249** having the steroidal skeleton was reported.[98)]

The synthesis of 3-oxo compound **252** from dehydroabietic acid (**173**) was attempted in relation to the formation of the ring A in steroidal skeleton, and was successfully completed *via* the intermediates **250** and **251** by two methods.[99)]



(250) R = β-H
(251) R = α-H



(252)

It was observed that the benzonilidene type compounds **215** and **253** behaved in a completely different manner according to the variation of the reagent. The outline is illustrated in Chart 6.[100)]

The benzonilidene ester **215** was readily brominated (NBS, Ac_2O-H_2SO_4, r.t., 6 hr.) to yield β-bromide **254** (85% yield), which was successively converted to terideadiol (**255**). The synthetic sequence is shown in Chart 7.[101)]

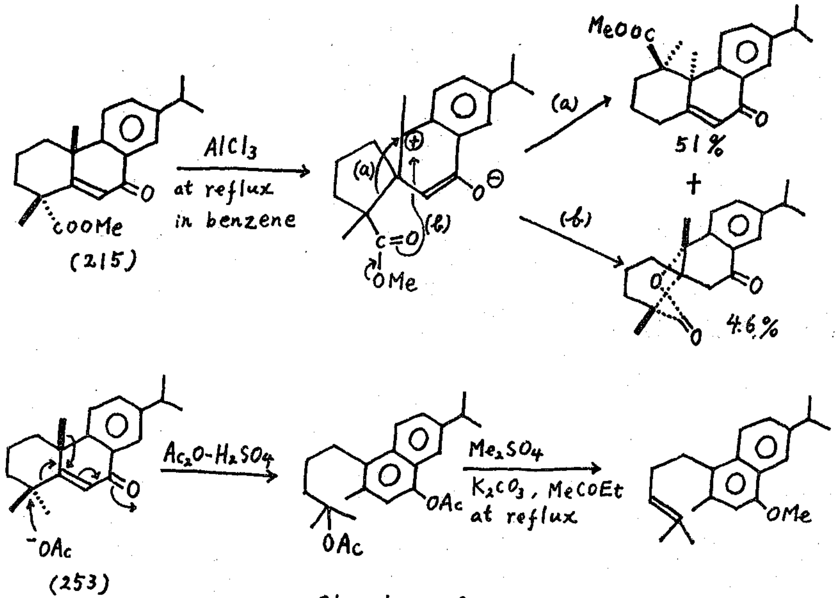


Chart 6

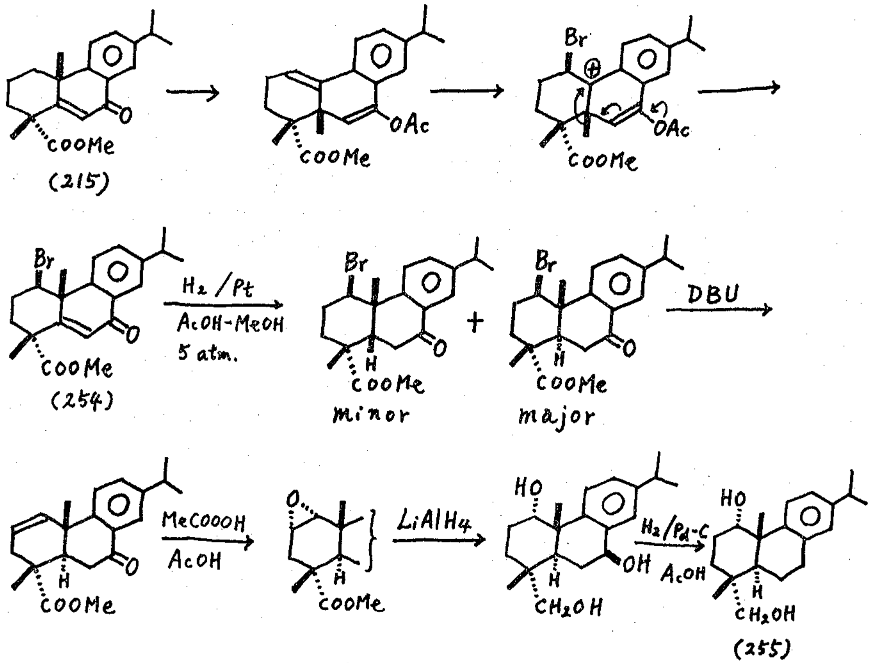
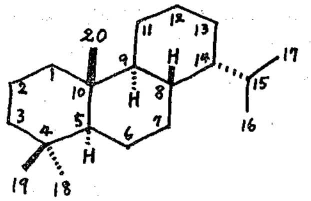


Chart 7

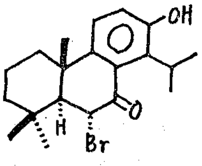
VII. TOTARANE DERIVATIVES

The X-ray analysis of compound **256** was carried out.[80] Photo-sensitized oxidation of 13-methoxy-totara-6,8,11,13-tetraene (**257**) gave a hydroperoxide **258**, which underwent



Totarane

a facile rearrangement to a naphthyl derivative **259** in the presence of acid.[18]



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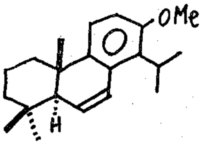

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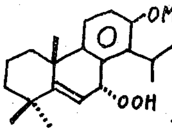

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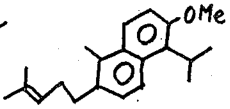
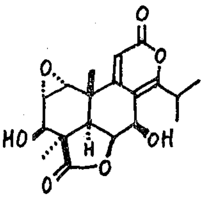


(259)

Nagilactone C (**260**) was isolated from *Podocarpus purdieanus*.[102]

The lactone **261** obtained from the culture of *Acrostalagmus* NRRL-3481 showed a strong inhibitory activity on the growth of an Avena coleoptile section.[44]



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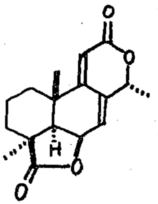

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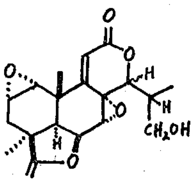

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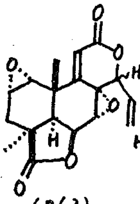

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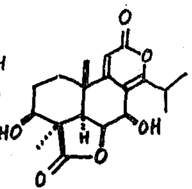
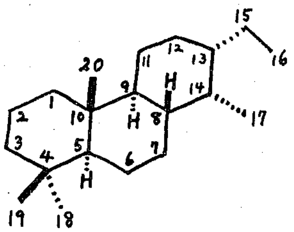


(264)

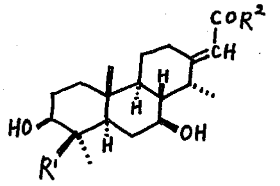
Some chemical transformations of sellowin-A (**262**), B (**263**), and C (**264**), norditerpene dilactones from *Podocarpus sellowii*, were carried out.[103]

VIII. CASSANE DERIVATIVES



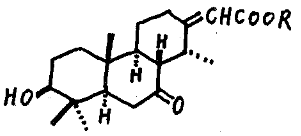
Cassane

The structures of norerythrostachamine (**265**) and norcassaidide (**266**), new alkaloids from the bark of *Erythrophleum chlorostachys*, were chemically determined. The known alkaloids, cassaidine, cassamidine, and norerythrophlamide were also isolated.[104)]



(265) $R^1 = COOMe$, $R^2 = OCH_2CH_2NHMe$

(266) $R^1 = Me$, $R^2 = NMeCH_2CH_2OH$



(267) $R = CH_2CH_2NMeCH_2CH_2Cl$

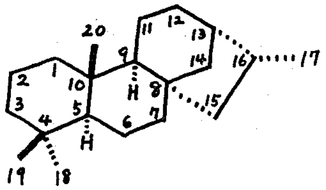
(268) $R = CH_2CH_2NMe_2$

(269) $R = H$

Cassaine mustard (**267**) was prepared. Hydrolysis of cassaine (**268**) with HCl yielded the acid **269** which was converted *via* the NH_4 salt into the Ag salt. This reacted with $MeN(CH_2CH_2Cl)_2$ to give 29% of **267**. The pharmacological properties of **267** were discussed.[105)]

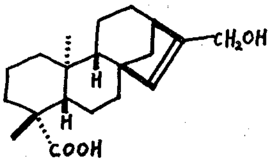
The structure-cardiatonic activity relationships of cassaine (**268**) and the related semisynthetic analogs were studied.[106)]

IX. KAURANE DERIVATIVES*

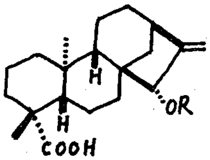


Kaurane

A new diterpene, *ent*-17-hydroxy-15-kauren-19-oic acid (**270**) and the known *ent*-15β-hydroxy-16-kauren-19-oic acid (**271**) (=grandifloric acid) were isolated as the minor consittuents from the roots of *Aralia cordata*.[107)]



(270)



(271) $R = H$

(272) $R = COCH_2CHMe_2$

(273) $R = COCMe=CHMe$ cis

The petroleum ether extract of *Enhydra fluctuans* yielded three new diterpenes, *ent*-17-hydroxy-15-kauren-19-oic acid (**270**), *ent*-15β-isovalerayloxy-16-kauren-19-oic acid (**272**),

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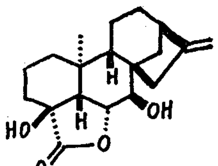
* See also section II, ref. 22, section X, refs. 144, 146, XI, refs. 174, 178, 181, 182, and 183.

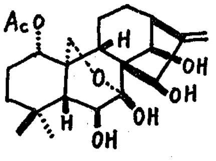
and *ent*-15-β-angeloyloxy-16-kauren-19-oic acid (**273**) together with several known *ent*-kaurane type diterpenes.[108)]

Eight *ent*-kaurane type diterpenes previously described were isolated from *Sideritis lagascana*.[109)]

On the basis of chemical and spectroscopic evidence, the structure of a new minor metabolite of *Gibberella fujikuroi* was determined as 4β,7β-dihydroxy-18-norkaurenolide (**274**).[110)]



(274)



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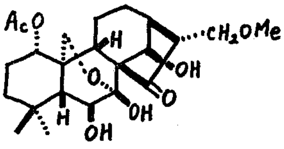
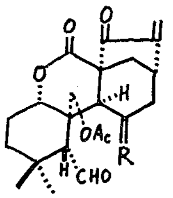


(276)

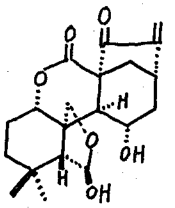
The structures of lasiokaurinol and lasiokaurinin, two novel diterpenoids of *Jsodon lasiocarpus*, were elucidated as **275** and **276**.[111)]

Seven diterpenoids were isolated from *Isodon japonicus*, and isodonal, trichodonin, and epinodosin were formulated as **277**, **278**, and **279**. Antimicrobial activity of these diterpenes was tested.[112)]

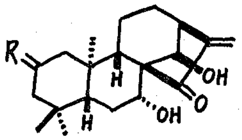


(277) R = α-OH, β-H

(278) R = α-H, β-OH



(279)

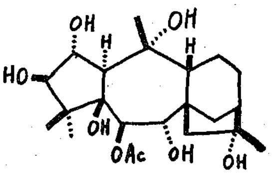


(280) R = α-H, β-OH

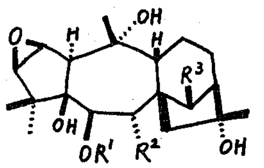
(281) R = O

Two new *ent*-kaurene type diterpenoids of *Isodon umbrosus*, umbrosin A and B were assigned the structures **280** and **281**.[113)]

A new toxic diterpene, lyoniol-D was isolated from *Lyonia ovalifolia var. elliptica* and the structure **282** was proposed on the basis of chemical and spectroscopic evidence and correlation with lyoniol-A (**283**).[114)]



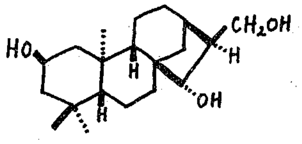
(282)



(283) R^1=Ac, R^2=OH, R^3=H

(284) R^1=R^2=H, R^3=OH

Rhodojaponin-III (**284**) was isolated from the flowers of *Tripetaleia paniculata*.[115] Five *ent*-kaurane type diterpenes, substances D (**285**), E (**286**), F (**287**), creticoside-C (**288**), and -E (**289**) were isolated from *Pteris cretica*.[116]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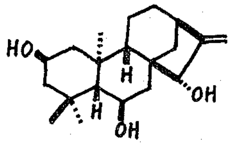
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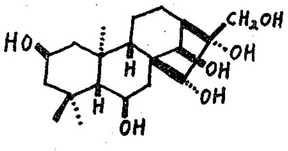
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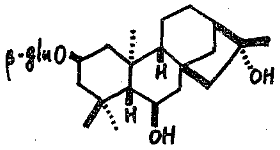
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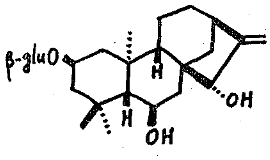
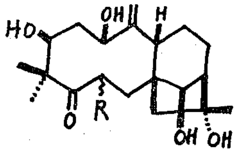
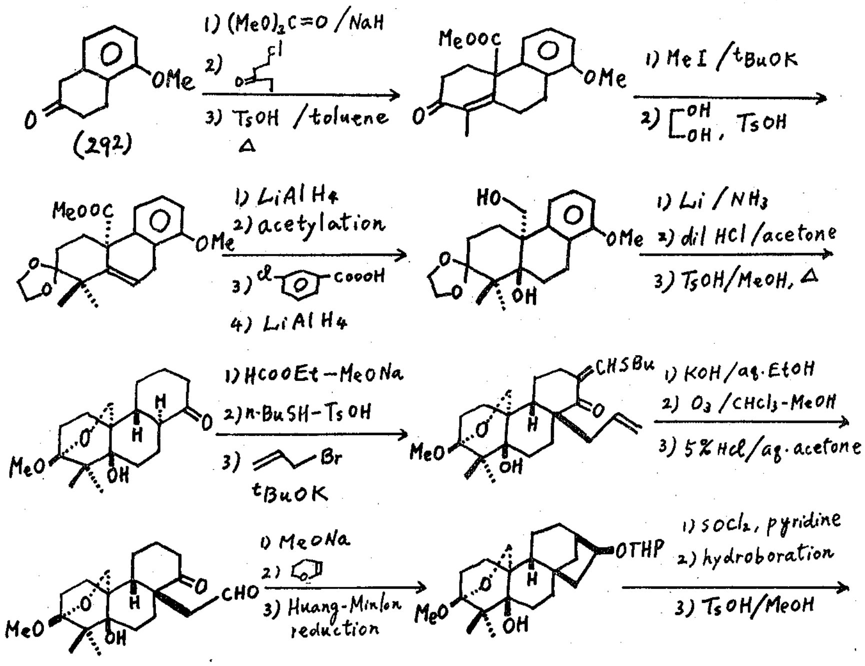

(289)


(290) R = β-OH

(291) R = α-OH

The stereochemistry of grayanol-A (**290**) and -B (**291**), new diterpenoids of *Leucothoe grayana*, was clarified using X-ray analysis of mono *p*-bromo benzoate of **291**.[117]

The stereoselective total synthesis of enmein (**294**) from 5-methoxy-2-tetralone (**292**) had been reported as a preliminary communication.[118] Now, its full paper was published.[119] The sequence is shown in Chart 8.



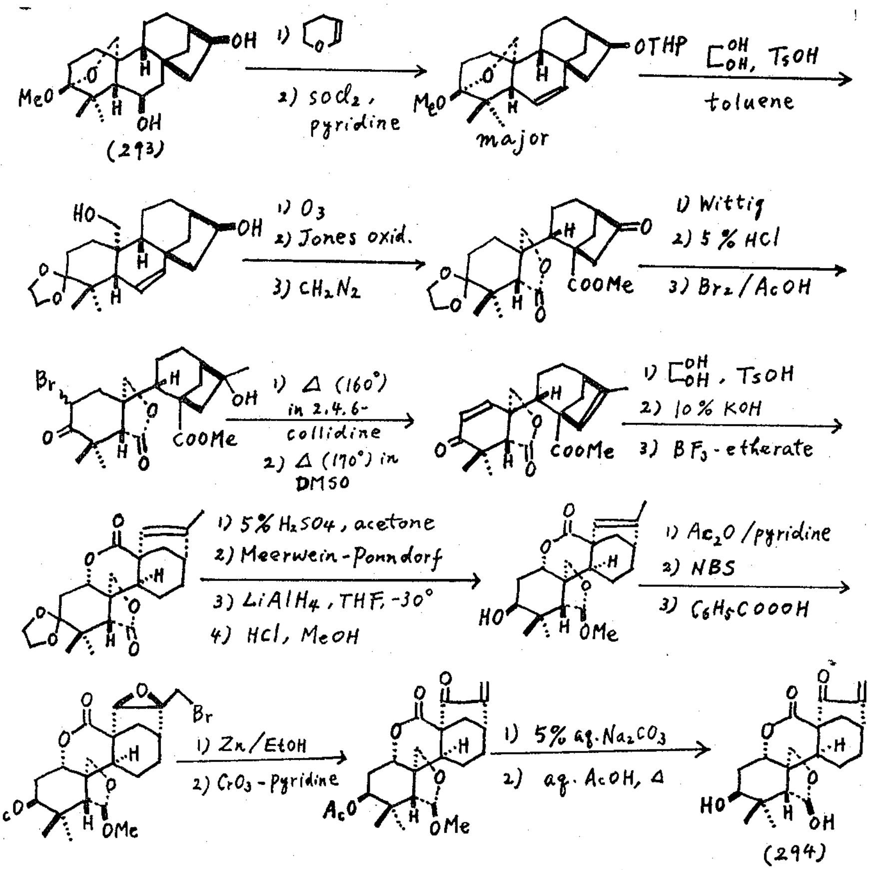


Chart 8

The chemical conversion of enmein (**294**) into an important relay compound (**293**) was also reported.[120] The outline is shown in Chart 9.

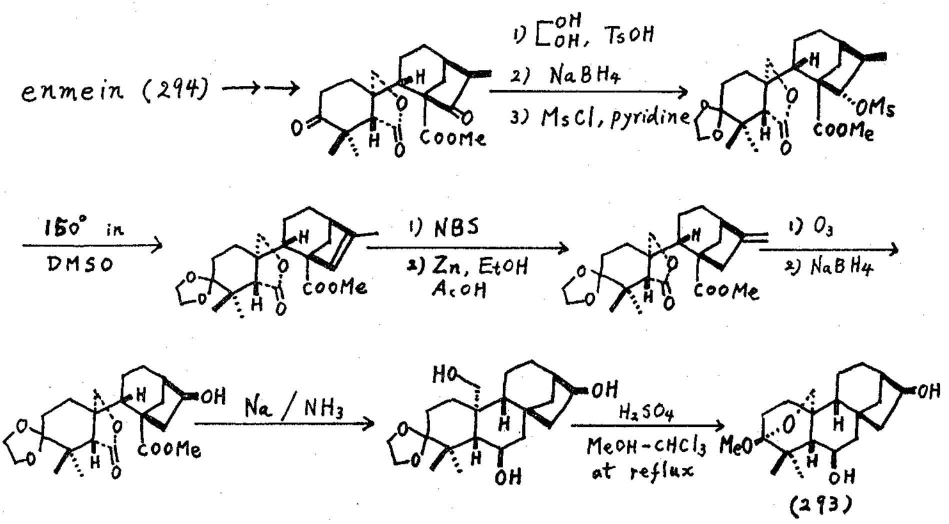


Chart 9

The total synthesis of the racemic compound **295**, a relay for the alkaloid napelline, was done through a route summarized in Chart 10, and the product was identified with the corresponding optically active derivative prepared from lucidusculine (**296**).[121]

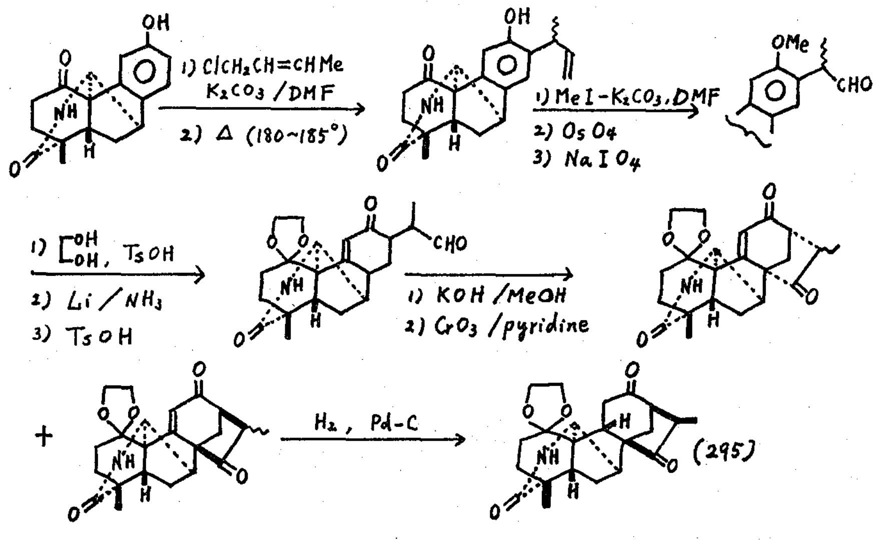


Chart 10

Lucidusculine (**296**) was converted into the lactame **295**, which was identical with the foregoing synthetic racemate. Then, napelline (**297**) was synthesized from **295**. The whole route from **296** to **297** is shown in Chart 11. Thus, the total synthesis of racemic napelline was accomplished.[122]

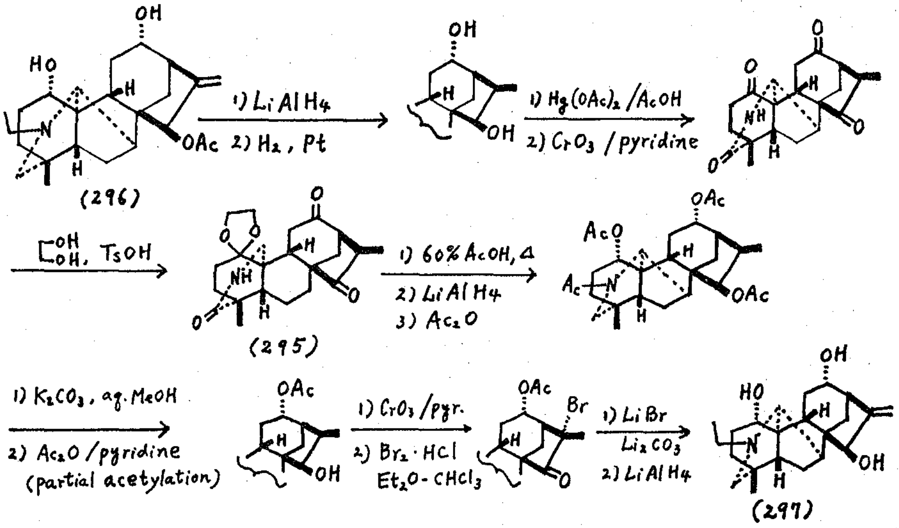
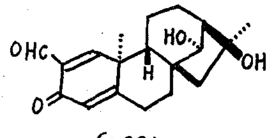
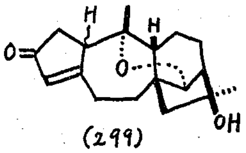


Chart 11

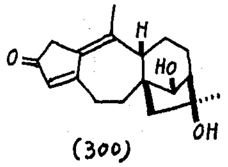
The compounds, **299** and **300**, having 4,4-bisnorgrayanotoxin skeleton were synthesized from the formylated cross-conjugated cyclohexadienones, **298** and its C-14 epimer, by a photochemical rearrangement. On the other hand, the nonformylated cyclohexadienone **301** gave the spiro compound **302** and the phenols, **303** and **304**, on photolysis in aqueous acetic acid.[123)]



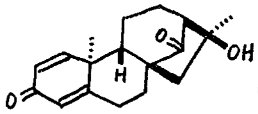
(298)



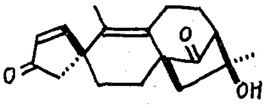
(299)



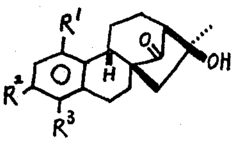
(300)



(301)



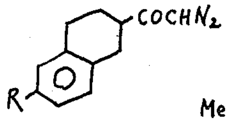
(302)



(303) $R^1 = Me, R^2 = OH, R^3 = H$

(304) $R^1 = OH, R^2 = H, R^3 = Me$

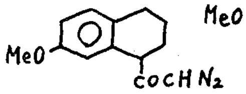
The acid-catalyzed reactions in weakly nucleophilic environments of several diazomethyl ketones, **305**, **306**, **307**, **308**, **309**, and **310**, were studied. Some of the obtained spirocyclohexa-2,5-dienone derivatives, **311**, **312**, and **313**, should be potential intermediates or models for the synthesis of tetracyclic diterpenes.[124)]



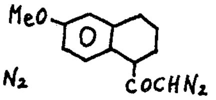
(305) R = H

(306) R = OH

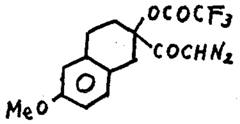
(307) R = OMe



(308)



(309)



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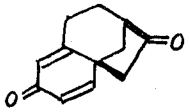
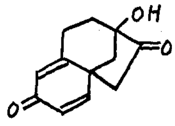
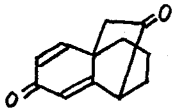


(311)

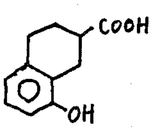


(312)

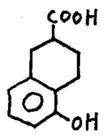


(313)

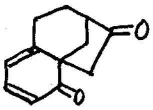
The diazoketones derived from compounds, **314** and **315**, were treated with trifluoroacetic acid to afford good yields of tricyclic ketones **316** and **317** incorporating a cyclohexa-2,4-dienone moiety.[125)]



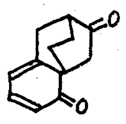
(314)



(315)

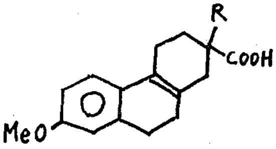


(316)

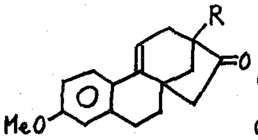


(317)

The 1,2,3,4,9,10-hexahydrophenanthrenecarboxylic acids **318**, **319**, and **320** were prepared and converted *via* their diazomethylcarbonyl derivatives to the 1,2,3,9,10,10$_a$-hexahydro-2,10$_a$-ethanophenanthren-12-one derivatives **321**, **322** and **323**, respectively, by short and efficient routes.[126)]



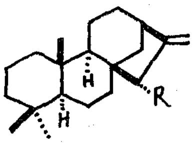
(318) R=H
(319) R=Me
(320) R=OH



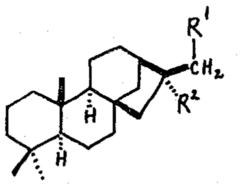
(321) R=H
(322) R=Me
(323) R=OH

Tosylation and LiAlH$_4$ reduction of some *ent*-17-norkaurane type alcohols, were studied, and the conformation of the ring B was discussed.[127)]

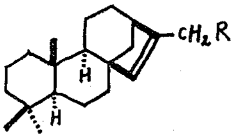
The reaction of phyllocladene (**324**) with thallium(I) acetate-iodine gave acetoxy products **325** and **326**, and its reaction with thallium(I) tosylate gave 17-iodoisophyllocladene **327**. Treatment of phyllocladene (**324**) or isophyllocladene (**328**) with thallium(I) benzoate-iodine gave benzoates **329** and **330**, which were also obtained using silver benzoate-iodine.[128)] In addition, the detailed reactions of thallium(I) carboxylates and iodine with many alkenes were reported.[129)]



(324) R=H
(330) R=OCOPh

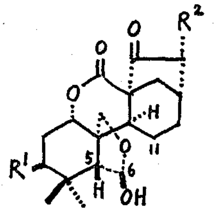


(325) R^1=I, R^2=OAc
(326) R^1=OAc, R^2=OH

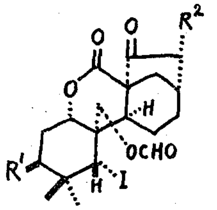


(327) R = I
(328) R = H
(329) R = OCOPh

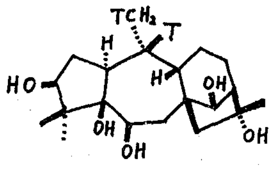
The hypoiodite reactions with dihydroisodocarpin (**331**), dihydroenmein 3-acetate (**332**) and isodotricin 3-acetate (**333**) were attempted in hopes of the oxygen-functionalization at C-11 of these compounds. However, it was observed that the reactions resulted in the formation of the 5-iodinated 5–6 cleaved products, **334**, **335**, and **336**, respectively.[130)]



(331) R^1=H, R^2=Me
(332) R^1=OAc, R^2=Me
(333) R^1=OAc, R^2=CH$_2$OMe



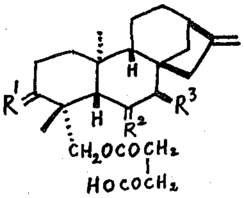
(334) R^1=H, R^2=Me
(335) R^1=OAc, R^2=Me
(336) R^1=OAc, R^2=CH$_2$OMe



(337)

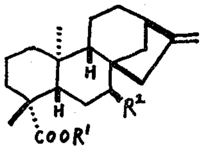
α-Dihydrograyanotoxin II was labeled with tritium at the C-10 and C-19 positions by catalytic hydrogenation of grayanotoxin II. Palladium-catalyzed hydrogenation in THF produced the α-form **337** exclusively, with specific activity 1.21 Ci/m mole and with 99% radiochemical purity.[131]

Metabolic transformations of some *ent*-kaurenes in *Gibberella fujikuroi* were reported. The conversion of *ent*-16-kaurenes to gibberellic acid in *G. fujikuroi* is blocked by A-ring modifications. Thus *ent*-3β-hydroxy-16-kauren-19-yl succinate (**338**) gives the 7β-hydroxy derivative **339** in good conversion (46%). The 3β-epimer **340** is converted to the 7β- (**341**) or the 6α-hydroxy derivative (**342**), and the former occurs for 3-oxo analog. The succinoyloxy function acts as a less efficient block and *ent*-16-kauren-19-yl succinate (**343**) is converted to 7β-hydroxy- (**344**) and 6β,7β-dihydroxy- (**345**) derivatives along with gibberellic acid. Of the pair of hydrolyzed 7β, 19-diol and 6β,7β,19-triol, only the former was effectively metabolized to gibberellic acid in *G. fujikuroi*.[132]

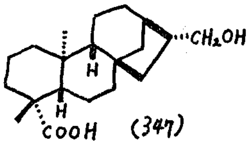


(338) $R^1=\alpha\text{-}OH,\beta\text{-}H$, $R^2=H_2$, $R^3=H$
(339) $R^1=\alpha\text{-}OH,\beta\text{-}H$, $R^2=H_2$, $R^3=OH$
(340) $R^1=\alpha\text{-}H,\beta\text{-}OH$, $R^2=H_2$, $R^3=H$
(341) $R^1=\alpha\text{-}H,\beta\text{-}OH$, $R^2=H_2$, $R^3=OH$
(342) $R^1=\alpha\text{-}H,\beta\text{-}OH$, $R^2=\alpha\text{-}OH,\beta\text{-}H$, $R^3=H$
(343) $R^1=R^2=H_2$, $R^3=H$
(344) $R^1=R^2=H_2$, $R^3=OH$
(345) $R^1=H_2$, $R^2=\alpha\text{-}H,\beta\text{-}OH$, $R^3=OH$

A partial synthesis of kaurenoic acid (**346**) from the hydroxy acid **347** was carried out. The hydroxylation of compound **348** by *Gibberella fujikuroi* was utilized for the synthesis of 7β-hydroxykaurenoic acid (**349**). An alternative synthesis of **349** was provided by the microbiological conversion of **347** to the 7β-hydroxy derivative by *Calonectria decora*.[133]

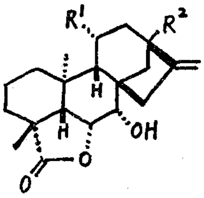


(346) $R^1=R^2=H$
(348) $R^1=(CH_2)_2COOH$, $R^2=H$
(349) $R^1=H$, $R^2=OH$

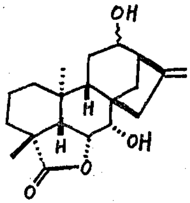


(347)

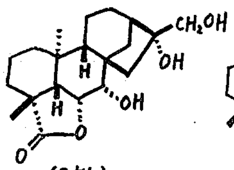
The ¹³C nuclear magnetic resonance spectra of some kaurenolides were investigated. Changes in the spectra were used to show that microbiological hydroxylation of 7α-hydroxykaurenolide (**350**) by *Rhizopus* afforded four compounds, **351**~**354**. 7β-Hydroxy-



(350) $R^1=R^2=H$
(351) $R^1=OH$, $R^2=H$
(353) $R^1=H$, $R^2=OH$



(352)



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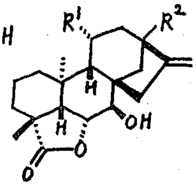
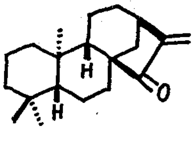


(355) $R^1=R^2=H$
(356) $R^1=OH$, $R^2=H$
(357) $R^1=H$, $R^2=OH$

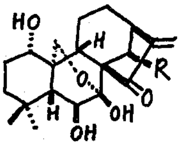
kaurenolide (**355**) afforded **356** and **357**.[134]

A systematic classification of 30 *Isodon* diterpenoids, structures of which had been elucidated already, on the basis of biogenetic consideration was published in Japanese.[135]

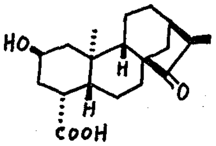
Incorporation of *ent*-16-kauren-15-one (**358**) into enmein (**294**) and of 14-deoxyoridonin (**359**) into oridonin (**360**) were demonstrated by tracer experiments using *Isodon japonicus*.[136]



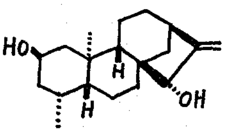
(358)



(359) R = H
(360) R = OH



(361)



(362)

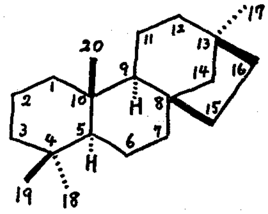
In a Japanese review related to the relationship between taste and chemical structure, *Isodon* diterpenoids were introduced.[137]

The structure-activity relationship of lyoniol-A (**283**) and the related compounds in association with the excitatory effect on muscle spindle afferents was reported.[138]

Compound **361** had been previously isolated from human urine.[139] Now, atractyligenin (**362**) was found in coffee bean as its glycoside.[140] The glycoside of **362** must be transformed to that of **361** in most part in the human body.[140]

The investigation of antimicrobial activity test of several *Isodon* diterpenoids was reported. The diterpenes having an exocyclic methylene conjugated with cyclopentanone in the molecule showed a highly specific activity against gram positive bacteria.[141]

X. BEYERANE DERIVATIVES*



Beyerane

Isolation of six known beyerane derivatives from *Sideritis valverdei* was reported.[109] Jativatriol (**363**) and conchitriol (**364**) were isolated from *S. angustifolia*.[142] *S. grandiflora* was proven to contain a new diterpene, tartessol (**365**)[143a] as well as *ent*-7α-acetoxy-15-beyerene-14β,18-diol.[143b]

Acid catalyzed rearrangement of compound **367** drived from sideridiol (**366**) gave diacetate **368** and monoacetate **369**, which constituted a partial synthesis of pusillatriol (**370**).[144]

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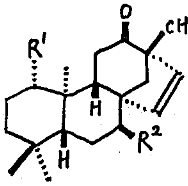
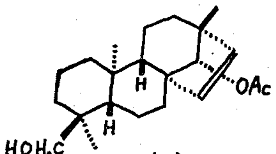
* See also section II, ref. 22.

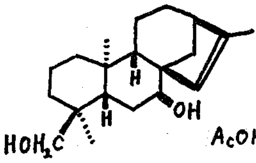


(363) R^1=OH, R^2=H

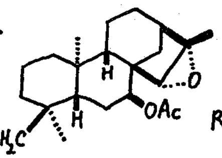
(364) R^1=H, R^2=OH



(365)



(366)



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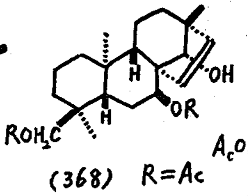
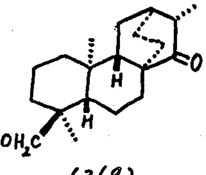


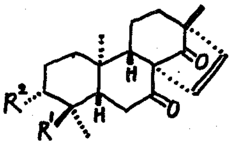
(368) R=Ac

(370) R=H



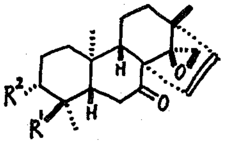
(369)

Unusual action of CH_2N_2 on the keto-esters **371** and **372** giving the oxiranes **373** and **374** was described.[145)]



(371) R^1=COOH, R^2=H

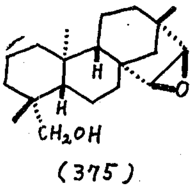
(372) R^1=CH_2OAc, R^2=OAc



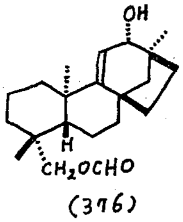
(373) R^1=COOMe, R^2=H

(374) R^1=CH_2OAc, R^2=OAc

Acid catalyzed rearrangements of beyerane, kaurane, and atisane type diterpenoids were investigated, and it was shown that the product mixture contains mostly beyerane derivatives in each case.[146)] Another work on the acid catalyzed rearrangement of beyerane derivative **375** was published. Thus, formic acid treatment of **375** gives rise to allylic alcohol **376** and a mechanism of the rearrangement is proposed involving a novel 1,4-hydride shift in the bicyclo [3:2:1] octane C/D ring system on the basis of deuterium labelled experiment.[147)]



(375)



(376)

Acid catalyzed rearrangements of **377** and **378** into **379** and **380** (Chart 12) published in 1972[148)] were cited as examples of the 1,2-vinyl shift followed by a 1,2-alkyl shift in an review concerning acid catalyzed rearrangements of β,γ-unsaturated ketones.[149)]

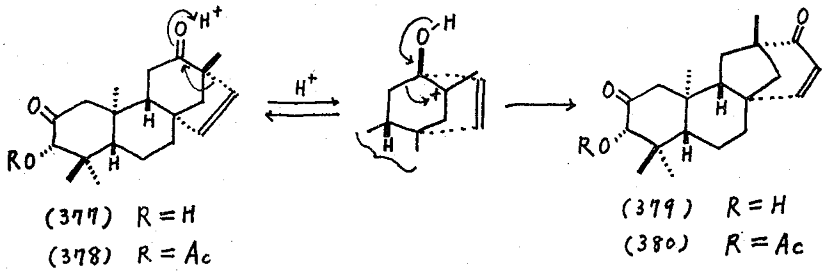
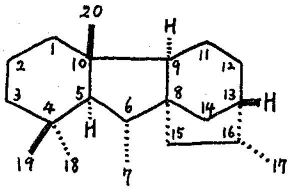


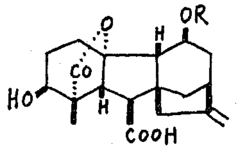
Chart 12

XI. GIBBERELLANE DERIVATIVES*



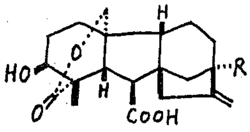
Gibberellane

A new gibberellin, gibberellin A_{35}(GA_{35}), and its glucoside were isolated from immature pods of *Cytisus scoporius* and their structures were elucidated as **381** and **382**, respectively.[150] The change of endogenous gibberellin in the germinated seeds of *Phaseolus vulgaris* was investigated and the isolation of GA_1, GA_8, GA_8 glucoside, and glucosyl esters of GA_1, GA_4, GA_{37} (**383**) and GA_{38} (**384**) were reported.[151]



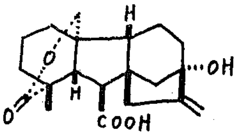
(381) R = H

(382) R = β-glucosyl



(383) R = H

(384) R = OH



(385)

From the immature seeds of *P. vulgaris,* GA_1, GA_8, GA_{38}, and GA_8 glucoside were isolated, and GA_4, GA_5, GA_6 and GA_{37} were identified by GC or GC-MS. In the etiolated seedlings glucosyl esters of GA_1 and GA_{38} were identified by GC and GA_8 glucoside was shown to be present by the histograms.[152]

Gibberellins were isolated from the mangrove plant; A_1 and A_3 from *Sonneratia apetala*; A_3, A_5, and A_9 from *Rhizophoria mucranata*; and A_3, A_4 and A_7 from *Bruguriera gymnorhiza.* Biological activity of these gibberellins were examined using three bioassays.[153]

The identification and determination of gibberellins A_1 and A_9 in seeds of *Corylus avellana* were reported.[154]

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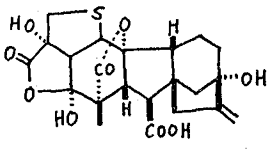
* See also section IX, ref. 132.

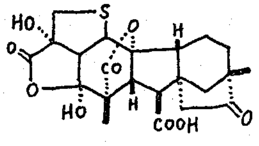
In addition to the previously identified[155] GA_{20} and GA_{29} in immature seeds of *Pisum sativum*, GA_9, GA_{17}, GA_{38} (**384**), and a new gibberellin A_{44} (**385**) were identified and quantitative analysis of these gibberellins was carried out.[156]

Structure of pharbitic acid, a gibberellin-related diterpenoid, was determined as **386** by X-ray crystallographic analysis of its derivative (**387**) obtained by acid treatment.[157]

Use of Copper hexafluoroacetylacetonate for the determination of the absolute configuration of alcohols **388** and **389** was reported.[158]



(386)



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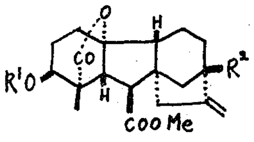
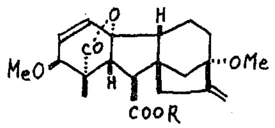


(388) $R^1 = Ac, R^2 = OH$

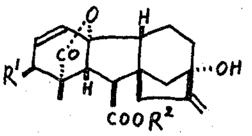
(389) $R^1 = R^2 = H$

Photolabile protection of the carboxyl group of gibberellins was published. Namely, photolysis of gibberellin derivative **390** derived from GA_3 gave a carboxylic acid **391** (42%) in EtOH at 30°.[159]



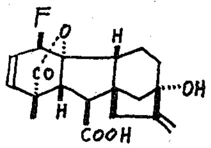
(390) $R = -CH_2CO-C_6H_4-OMe$

(391) $R = H$



(392) $R^1 = OH,\ R^2 = Me$

(393) $R^1 = F,\ R^2 = H$



(394)

It was described that reaction of 2-chloro-N,N-diethyl-1,1,2-trifluoroethylamine with gibberellic acid ester **392** gave the corresponding esters of 3β- and its allylic isomer 1β-fluorogibberellins (**393** and **394**). The fluoro-acids themselves (**393** and **394**) were

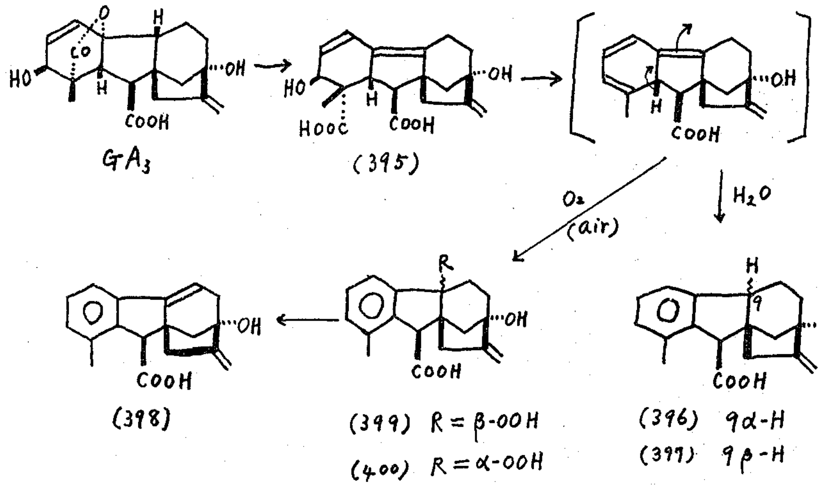


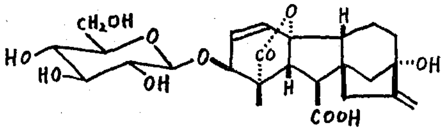
Chart 13

obtained by de-esterification of the corresponding *p*-bromophenacyl esters.[160]

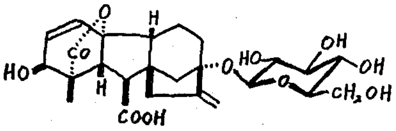
The decomposition pathway of GA_3 in aqueous solution was investigated. Decomposition of gibberellenic acid (**395**) in deuterium oxide gave 9-labelled products, **396** and **397**, and unlabelled acid **398**. Two partially characterized hydroperoxides **399** and **400** were detected as intermmediates in the oxidative transformation of GA_3 through **395** to **398**. The sequences are shown in Chart 13.[161]

Synthesis of GA_3-β-D-glucopyranosides (**401** and **402**) was reported.[162]

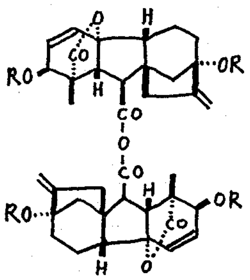
The 7-ol derivative **405** of GA_3 was synthesized from GA_3-anhydride (**403**) and its acetate (**404**).[163]



(401)

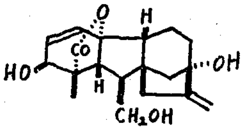


(402)



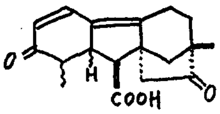
(403) R=H

(404) R=Ac

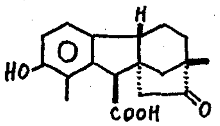


(405)

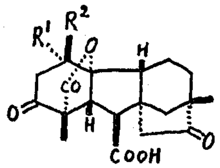
Reaction of GA_3 with 2N HCl at 90° for 4 hours afforded the compounds **406**~**409**. The main product was the dienone acid **406** resulting from decarboxylation and Wagner-Meerwein rearrangement of GA_3. Reaction of GA_3 with 2N HCl in THF (5 : 3 V/V) at 20° for 120 hours gave the 1-hydroxy-3-oxogibberellins **410** and **411** besides of com-



(406)

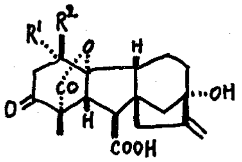


(407)



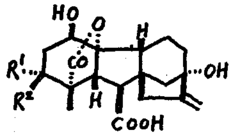
(408) $R^1=OH$, $R^2=H$

(409) $R^1=H$, $R^2=OH$



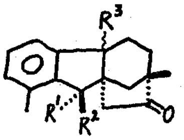
(410) $R^1=OH$, $R^2=H$

(411) $R^1=H$, $R^2=OH$



(412) $R^1=H$, $R^2=OH$

(413) $R^1=OH$, $R^2=H$



(414) $R^1=H$, $R^2=COOMe$, $R^3=α\text{-}H$

(415) $R^1=COOMe$, $R^2=H$, $R^3=α\text{-}H$

(416) $R^1=H$, $R^2=COOMe$, $R^3=β\text{-}H$

pound **409**. Subsequent Wagner-Meerwein rearrangement with trifluoro acetic acid for 50 hours at 20° transformed **410** and **411** to the corresponding hydroxydioxo acids **408** and **409**, respectively. Sodium borohydride reduction of **411** afforded **412** and **413** in a 3 : 1 ratio.164)

The mass spectra of the gibberic acid methyl esters (**414**～**416**) were examined. Fragmentation pathways were proposed on the basis of specific deuterium labelling at their 9 position and measurements at high resolution.165)

Stereoselective introduction of the methoxycarbonyl group into the tetrahydrofluoren-9-one (**417**) giving the 9β-methoxycarbonyl derivative (**418**) was achieved through a sequence shown in Chart 14.166)

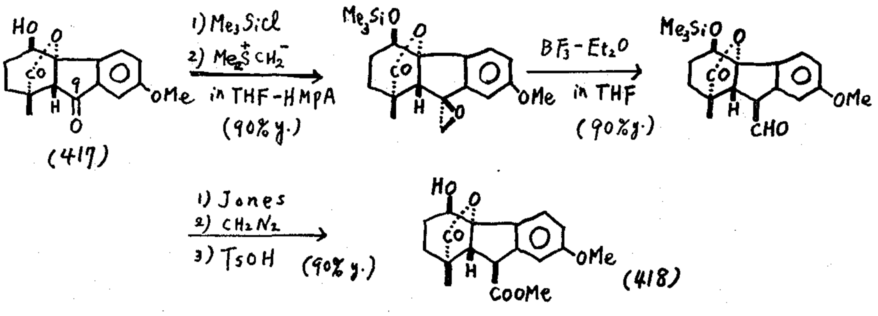


Chart 14

As model studies of the synthesis of the ring A of GA_3, alcohols **420** and **421** were synthesized from keto ester **419** as indicated in Chart 15.167)

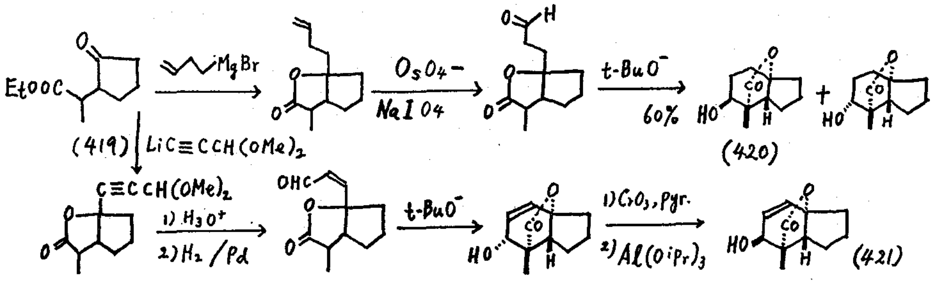
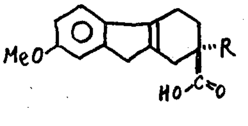


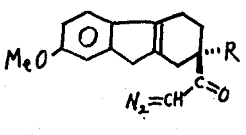
Chart 15

The 1,2,3,4-tetrahydrofluorene-2-carboxylic acids **422** and **423** were prepared and converted *via* their diazomethyl carbonyl derivatives **424** and **425** to tetracyclic compounds **426** and **427**, respectively.168)



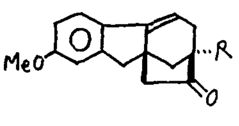
(422) R = H

(423) R = OH



(424) R = H

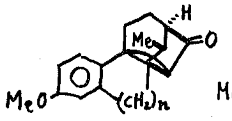
(425) R = OH



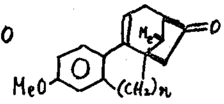
(426) R = H

(427) R = OH

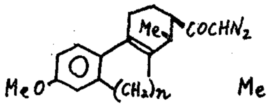
Stereocontrolled syntheses of ketones **428**, **429**, **430**, and **431** through intramolecular alkylation of γ,δ-unsaturated α'-diazomethyl ketones **432** and **433** were described. Catalytic hydrogenation of the cyclopropyl ketones (**428** and **429**) and of the unsaturated ketones (**430** and **431**) produced **434** and **435**.[169)]



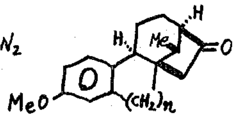
(428) n = 1
(429) n = 2



(430) n = 1
(431) n = 2

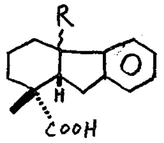


(432) n = 1
(433) n = 2

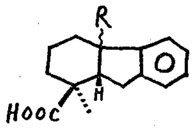


(434) n = 1
(435) n = 2

Stereoselective synthesis of the hydrofluorene derivatives **436**~**439** was reported and their conformational properties of their methyl esters were deduced from chemical and NMR spectral data.[170)]



(436) R = α-H
(439) R = β-H



(437) R = α-H
(438) R = β-H

Reaction of GA_3 with carrier-free tritium gas and 5% palladium on calcium carbonate as catalyst was shown to give a complex mixture of products including $[^3H]GA_3$, $[^3H]GA_1$, $[^3H]$tetrahydro GA_3, and $[^3H]$16,17-dihydro GA_3. The purified product $[^3H]GA_3$ likely arises from palladium catalyzed nonspecific exchange of GA_3 alkane hydrogen atoms with tritium. $[^3H]GA_1$ is also exchange labeled but most of its radioactivity is due to tritium addition to the C-1,2 olefinic bond of GA_3.[171)]

Tritium labelled GA_{20} (**440**), GA_5 (**441**), and GA_8 (**442**) were prepared *via* a route shown in Chart 16.[172)]

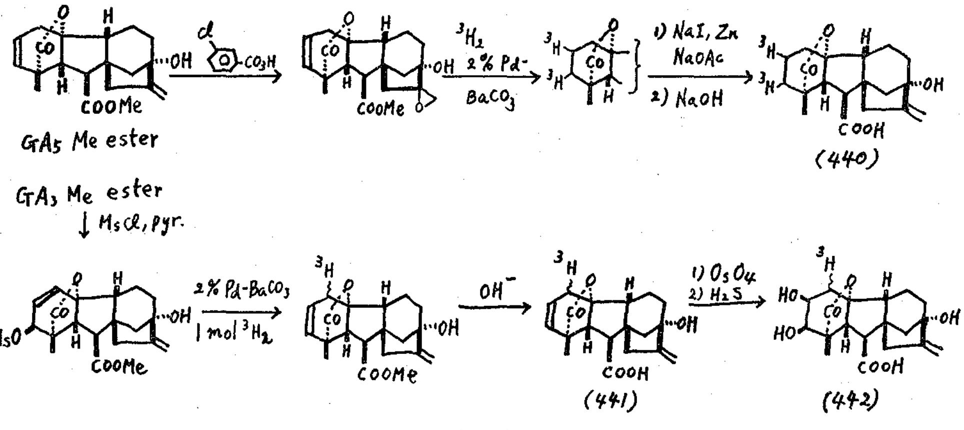
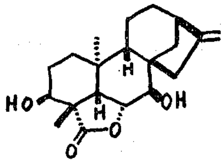
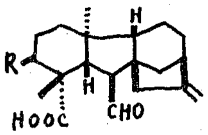
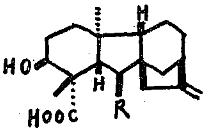


Chart 16

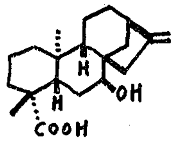
It was shown that GA_{14}-aldehyde (**444**), which had been derived[173)] from **443**, was formed from GA_{12}-aldehyde (**445**) in cultures of *Gibberella fujikuroi* and it was converted into fungal 3-hydroxylated gibberellins including GA_3 in the same culture. Gibberellin A_{14} (**446**) and its alcohol (**447**) were shown to be also metabolized to 3-hydroxy gibberellins, the former at a much lower rate. The biosynthetic pathway to gibberellins in the fungus was discussed in the light of these results.174)

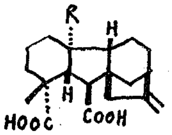

(443)

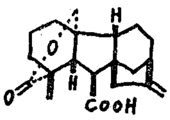

(444) R=OH
(445) R=H

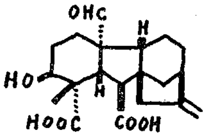

(446) R=COOH
(447) R=CH_2OH

Biosynthesis of gibberellins A_{12}, A_{15}, A_{24}, A_{36} and A_{37} by a cell-free system from *Cucurbita maxima* was investigated. Namely, GA_{12}-aldehyde (**445**) obtained from mevalonate *via ent*-7α-kaurenoic acid (**448**) was converted to GA_{12} (**449**). When Mn^{2+} was omitted from the system, GA_{12}-aldehyde and GA_{12} were converted to GA_{15} (**450**), GA_{24} (**451**), GA_{36} (**452**), GA_{37} (**383**), and so on.175)


(448)


(449) R=Me
(451) R=CHO


(450)


(452)

It was shown that 17-tritium labelled GA_{14} (**446**) applied to seedlings of dark grown dwarf pea (*Pisum sativum*) was converted to six gibberellins. The sequence of their interconversion (except GA_{28}) was shown as indicated in Chart 17.176)

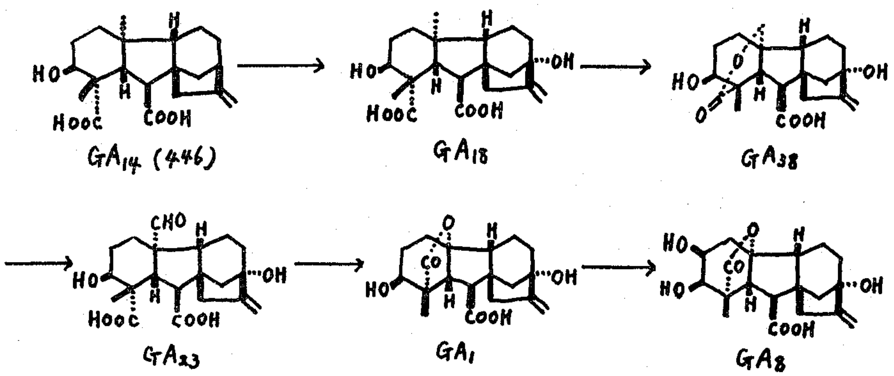
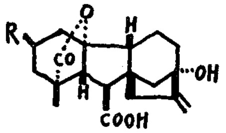
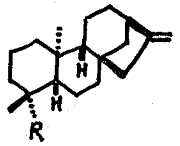


Chart 17

Furthermore, tritium labelled GA_{20} (**453**) applied to etiolated seedlings and germinating seeds of dwarf pea (*Pisum sativum*) was demonstrated to be converted to GA_{29} (**454**).177)

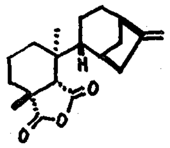
Mutant B1–41a, obtained by UV-irradiation of *Gibberella fujikuroi* strain GF-1a, was shown to be blocked for gibberellin synthesis at the step from *ent*-kaurenal (**455**) to *ent*-kaurenoic acid (**456**). In addition, a method of preparing *ent*-16-kaurene, labelled at C-15 and C-17 by deuterium and tritium was described.[178]

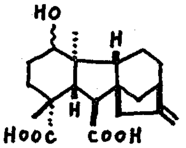

(453) R=H
(454) R=OH


(455) R=CHO
(456) R=COOH

Translocation and intracellular distribution of tritiated GA$_3$ in *Phaseolus vulgaris* were reported.[179] From *P. vulgaris* treated with radioactive GA$_3$, 3-O-β-glucosyl GA$_3$, 3-O-β-glucosyl-iso GA$_3$, 3-O-β-glucosyl gibberellenic acid and the β-glucoside of an unknown gibberellin-like substance were isolated and their interconversion was also reported.[180]

Detailed analysis of metabolites from *G. fujikuroi* was reported. The metabolites from 2-[^{3}H]-mevalonic acid lactone were separated by partition chromatography and characterized by GC directly linked to radio-counting and MS. From one fermentation, 72 compounds were detected. Of these, 25 known diterpenes including 15 gibberellins, were identified and 7 new products (**457**~**463**) were assigned tentative structures.[181]


(457)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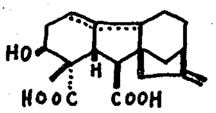
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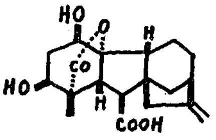
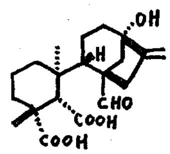
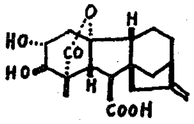
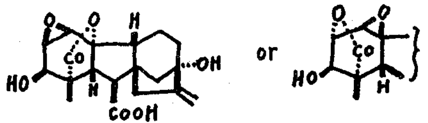

(460)

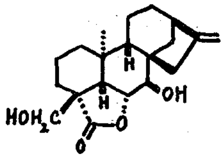

(461)

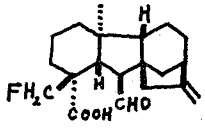

(462)



(463)

Fluorogibberellin A$_{12}$ aldehyde (**465**) derived from dihydroxy kaurenolide (**464**) was shown to be converted by *G. fujikuroi* into fluoro gibberellic acid (**466**) and fluorogibberellin A$_9$ (**467**).[182]


(464)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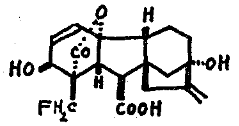
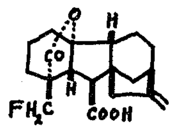
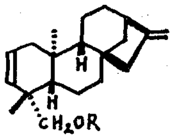

(466)

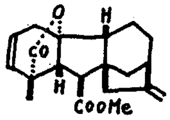

(467)

As the gibberellin metabolites from *ent*-kaura-2,6-dien-19-ol (**468**) and its succinate (**469**) in *G. fujikuroi* were found two C$_{19}$ and five C$_{20}$ gibberellins. They were characterized as their methyl esters (**470**~**476**).[183]

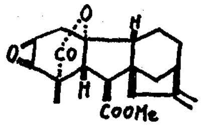


(468) R = H

(469) R = CO(CH₂)₂COOH



(470)



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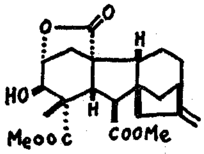
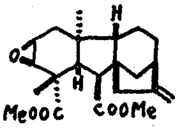


(472)



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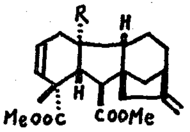
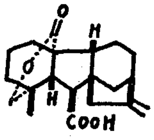


(474) R = Me

(475) R = COOMe

(476) R = CHO

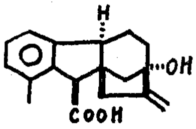


(477)

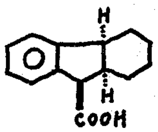
Activities of (±)-GA$_{15}$ (**450**) and (±)-GA$_{15}$-isolactone (**477**) which were obtained by total synthesis[184)] and GA$_{15}$ synthesized by interconversion[185)] of enmein (**294**) were assayed by the rice seedling test. As expected, (±)-GA$_{15}$ showed half the activity of natural GA$_{15}$. E-GA$_{15}$ which has a natural configuration showed the same activity as natural GA$_{15}$, while (±)-iso-GA$_{15}$ was almost inactive.[186)]

Four gibberellin (GA$_1$, GA$_3$, GA$_4$ and GA$_{37}$) glucosyl esters were synthesized and found to be as active as their respective free acids in the rice seedling bioassay. The rapid hydrolysis of the glucosyl esters was demonstrated by feeding experiments with glucosyl esters of [^{3}H] GA$_1$ and [^{3}H] GA$_4$.[187)]

Inhibition of flowering by hexahydrofluorene-9-carboxylic acids related to allogibberic acid (**478**) was investigated. Compound **479** was found to produce inhibition, and the stereochemical requirements for this type of biological activity were deduced.[188)]



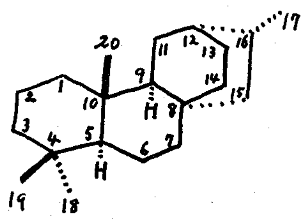
(478)



(479)

Effects of gibberellic acid on mevalonate activation in germinating *Corylus avellana* seeds[189)] and on sterol production in *C. avellana* seeds[190)] were reported.

XII. ATISANE DERIVATIVES*



Atisane

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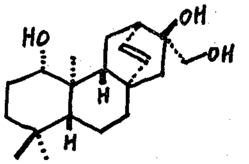
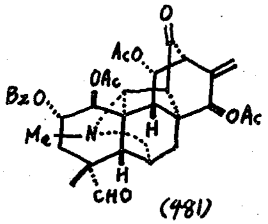
* See also section X, refs. 144 and 146.

The first reported oxygenated diterpenoid of the *ent*-atisane class, sideritol (**480**) was isolated from *Sideritis angustifolia*.[191] The structure of vakognavine was determined as **481** based on an X-ray analysis.[192]

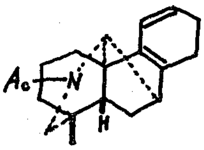


(480)

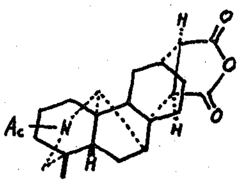


(481)

The Diels-Alder reaction of maleic anhydride with diene **482** afforded the adduct **483** stereoselectively. The causes of the stereoselectivity and its implication for the synthesis of diterpene alkaloids were discussed.[193]

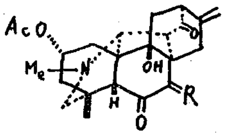


(482)



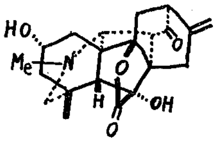
(483)

Miyaconitine (**484**) and miyaconitinone (**485**) on alkaline hydrolysis gave rise to miyaconine (**486**) and apomiyaconine (**487**).[194]

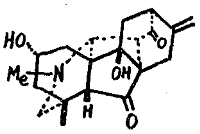


(484) R = α-OH, β-H

(485) R = O

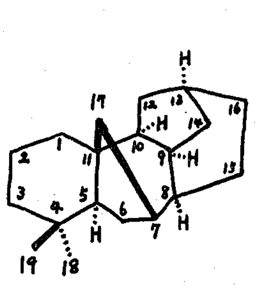


(486)



(487)

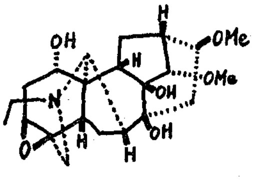
XIII. ACONANE DERIVATIVES



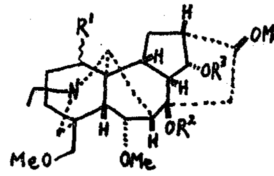
Aconane

The complex structures of two alakloids, excelsine (**488**) and delphisine (**489**), were determined by X-ray analyses.[195,196] The correlation of delphisine (**489**) with neoline

(**490**) accomplished to demonstrate that original structural assignment **490** for neoline was correct and that the revised structure **491**[198] was erroneous. Thus, the structures of chasmanine and homochasmanine must be revised to **492** and **493**, respectively.[199]



(488)



(489) $R^1=\alpha$-OH, $R^2=R^3=Ac$

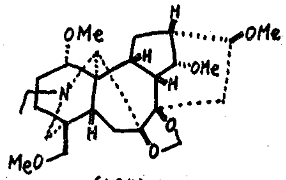
(490) $R^1=\alpha$-OH, $R^2=R^3=H$

(491) $R^1=\beta$-OH, $R^2=R^3=H$

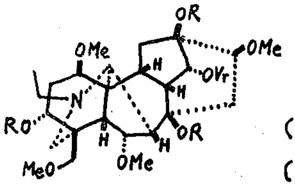
(492) $R^1=\alpha$-OMe, $R^2=R^3=H$

(493) $R^1=\alpha$-OMe, $R^2=Me$, $R^3=H$

The structure of deoxydelcorine isolated from *Delphinium corumbosum*, was assigned as **494**.[200] Two new alkaloids, veratroyl pseudaconine (**495**) and diacetyl pseudaconine (**496**), were isolated from *Aconitum ferox* along with known diterpene alkaloids.[201]



(494)



Vr = Veratroyl

(495) $R = H$

(496) $R = Ac$

The first total synthesis of talatisamine (**497**) was carried out as shown in Chart 18.[202] Thus, pentacyclic intermediate **498** was converted into the potential intermediate **499** whose structure was confirmed by an X-ray analysis.[203] Skeletal rearrangement of (**499**) followed by $LiAlH_4$ reduction afforded the relay **500**, which was converted into talatisamine (**497**) through **501**.

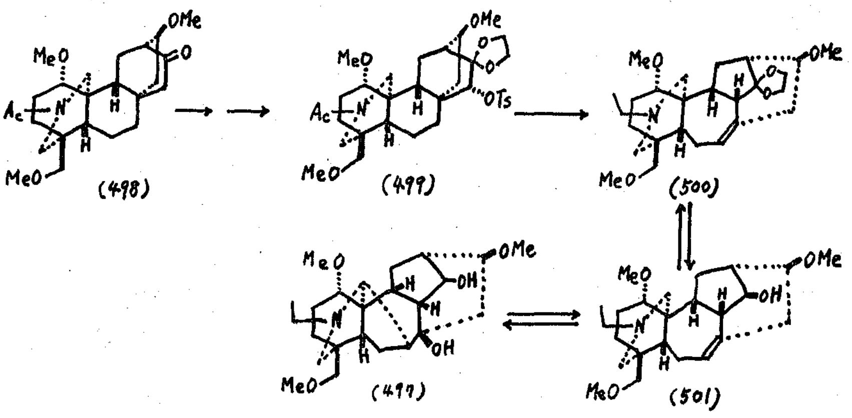
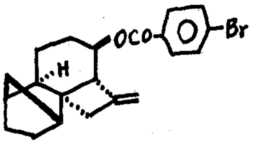


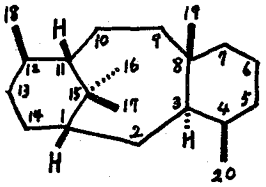
Chart 18

An X-ray analysis of the synthetic compound **502** being part of the skeleton of the aconite alkaloids was carried out.[204]



(502)

XIV. TAXANE DERIVATIVES



Taxane

There are no papers on the title topics which appeared in 1974.

XV. THE OTHERS

An improved stereoselective synthesis of all *trans*-geranyl-geraniol (**503**) was reported.[205] The route is outlined in the Chart 19.

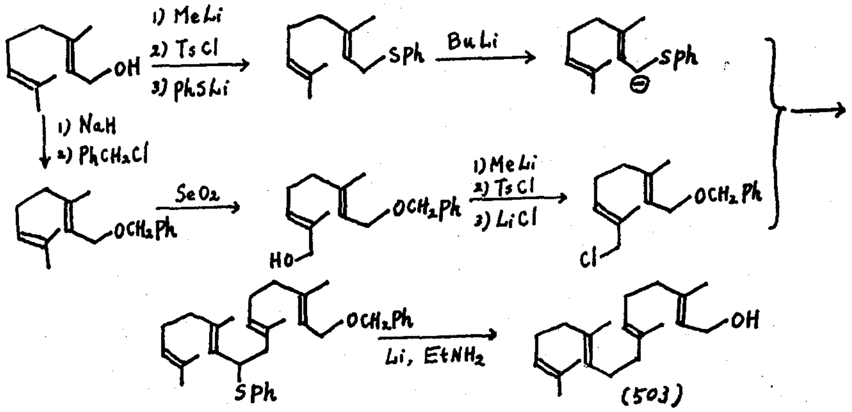
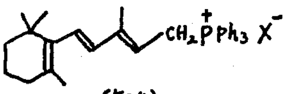
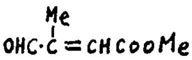


Chart 19

The Wittig reaction of **504** with **505** gave tretinoin methylester (**506**). A formulation for a tretinoin (**507**)-containing cream useful against acne was reported.[206]

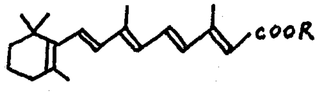


(504)



$$OHC{\cdot}\overset{\overset{\displaystyle Me}{|}}{C}{=}CHCOOMe$$

(505)



(506) R = Me
(507) R = H

A total synthesis of cembrene (**508**) was accomplished through a series of reactions as shown in Chart 20. Thus, the crucial intermediate **509** was cyclyzed by nickel tetracarbonyl in N-methylpyrrolidone to give a cyclic compound **510** which was further transformed to cembrene (**508**).[207]

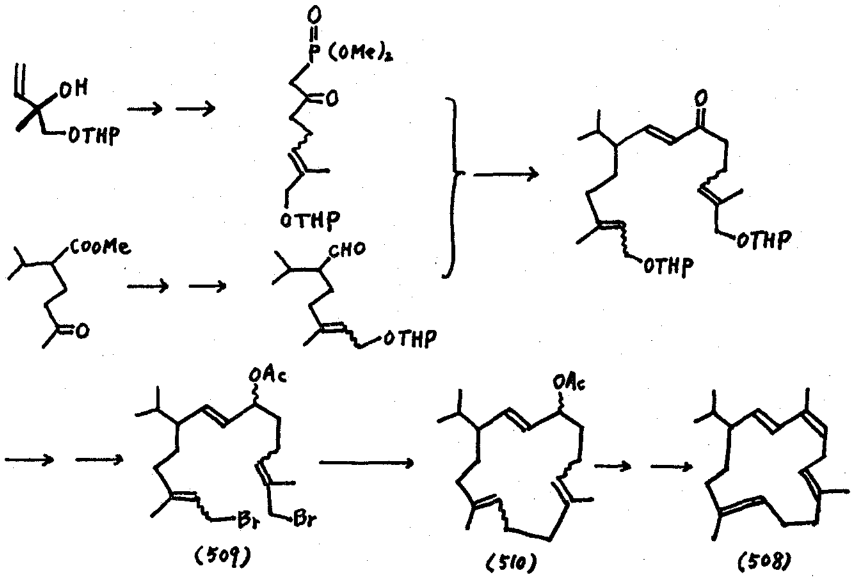
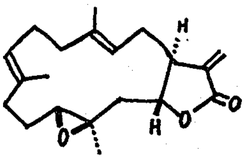
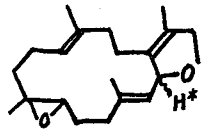


Chart 20

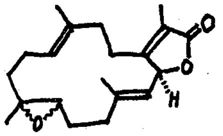
The structure of lobophytolide (**511**) isolated from marine invertebrate, the soft coral *Labophytum cristagalli* was determined by X-ray diffraction analysis.[208] Some new cembrane derivatives **512**∼**517** were isolated from marine source (*Sarophytum glaucum*).[209]



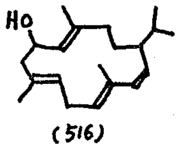
(511)



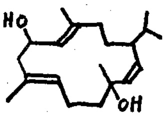
(512) (513)
(epimeric at H*)



(514) (515)
(a epimeric at epoxide)



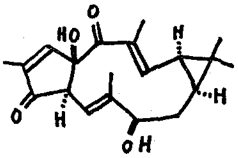
(516)



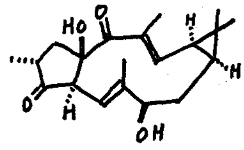
(517)
(tentative structure)

Two new diterpenes **518** and **519** related to bertyadionol (**520**) were isolated from *Bertya cuppresoida*.[210]

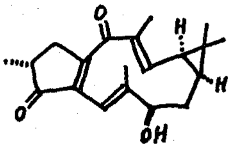
The leaves of *Fatsia japonica* was found to contain phytyl palmitate, linoleate, and phytol.[211] The structure **521** was assigned to 19-deoxydideacetyl-fusicoccin, a minor metabolite of *Fusicoccum amygdali*.[212] From the same source, 12-O-acetylfusicoccin (**522**) and 12-O-acetylisofusicoccin (**523**) were isolated.[213] Acid hydrolysis of fusicoccin



(518)



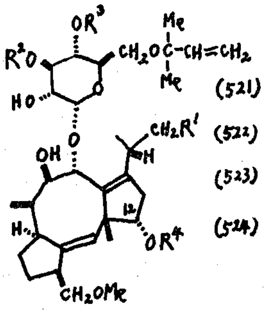
(519)



(520)

(**524**) afforded the deacetyl aglycon **525** whose structure was studied by NMR and mass spectroscopy.[214] The interpretation of the principal fragment ions of cotylenol (**526**) and its derivatives was reported.[215]

A synthesis of key intermediate **528** for portulal (**527**) was reported as outlined in Chart 21. The structure of **528** was established by correlating with a degradation product (**529**) of portulal (**527**).[216]

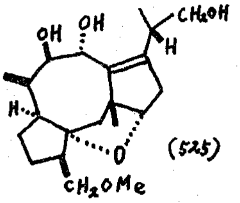


(521) $R^1=R^2=R^3=R^4=H$

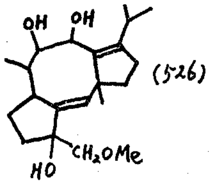
(522) $R^1=OAc, R^2=R^4=Ac, R^3=H$

(523) $R^1=OAc, R^2=H, R^3=R^4=Ac$

(524) $R^1=OAc, R^2=Ac, R^3=R^4=H$



(525)



(526)

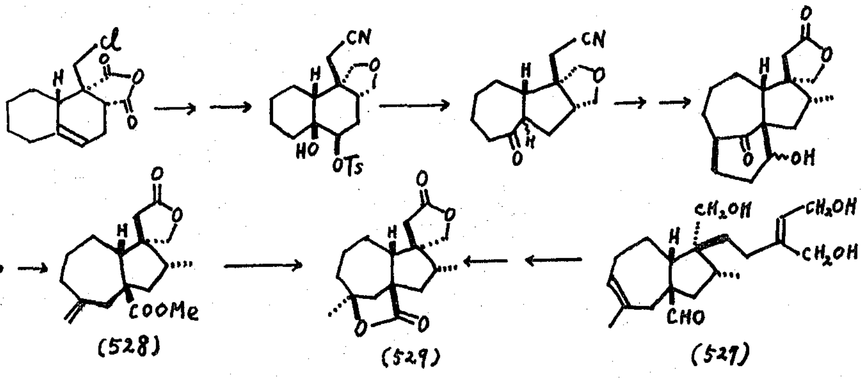
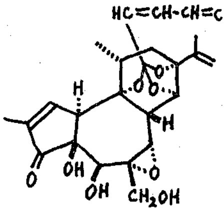
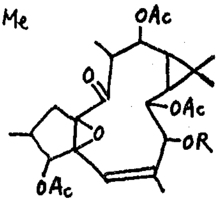


Chart 21

A piscicidal constituent **530** was isolated from *Excoecaria agallocha*.[217] Detailed investigation of *Euphorbia resinifera* resulted in separation of four new diterpenes **531**∼**534** and a mixture of ingenol (**535**)-3-esters of methyl substituted long chain fatty acids. Their irritant and cocarcinogenic activity were also described.[218] Other ingenol derivatives **536** and **537** were isolated from *Euphorbia ingens*.[219] A new diterpene, 5-deoxyingenol was isolated as its diacetate **538** from *Euphorbia biglandulosa*.[220] *Euphorbia kansui* was found to contain 20-deoxyingenol (**539**)[221] and the ester **540** of 13-oxyingenol.[222]

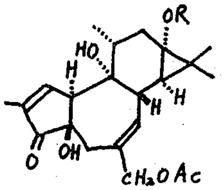


(530)



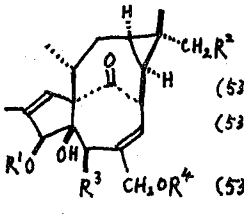
(531) $R = COCH_2Ph$

(532) $R = COCH_2$-⟨O⟩-OMe



(533) $R = CO\overset{Me}{C}=\overset{Me}{C}H$

(534) $R = COCH_2Ph$

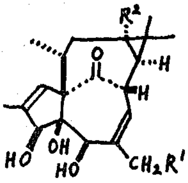


(535) $R^1 = R^2 = R^4 = H,\ R^3 = OH$

(536) $R^1 = 2,4,6$-decatrienoate,
$R^2 = OCO\overset{Me}{C}=\overset{Me}{C}H,\ R^3 = OH,\ R^4 = H$

(537) $R^1 = 2,4,6$-decatrienoate,
$R^2 = R^4 = H,\ R^3 = OH$

(538) $R^1 = R^4 = Ac,\ R^2 = R^3 = H$



(539) $R^1 = R^2 = H$

(540) $R^1 = OCO(CH_2)_4Me$,
$R^2 = O$-dodecanoyl

The compound **541** was served as a starting material for a synthesis of **542** through a sequence of reactions which appeared suitable for the synthesis of the system present in anhydroryanodol.[223] The outline is shown in Chart 22.

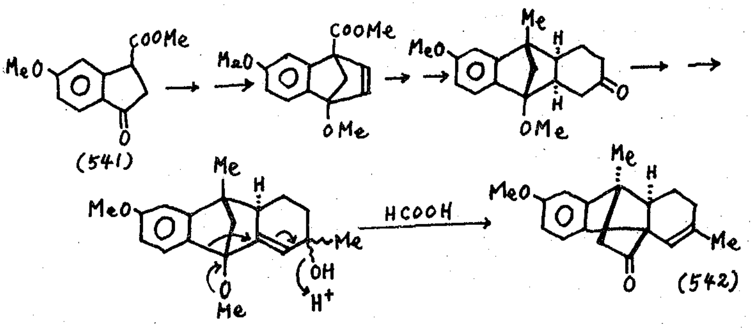
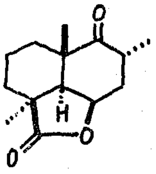
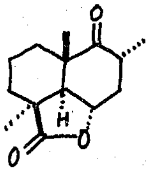


Chart 22

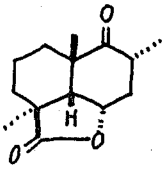
The full paper on the synthesis of terpenoid antibiotic LL-Z 1271α(**543**) was published in 1973.[224] The outline was reviewed in our previous article.[9] The transformations of the keto lactone **544**, a key intermediate for the synthesis of **543**, into keto lactones **545** and **546** were reported.[225] The second total synthesis of **543** starting from **547** was also reported.[226] The synthetic route is shown in Chart 23.



(544)



(545)



(546)

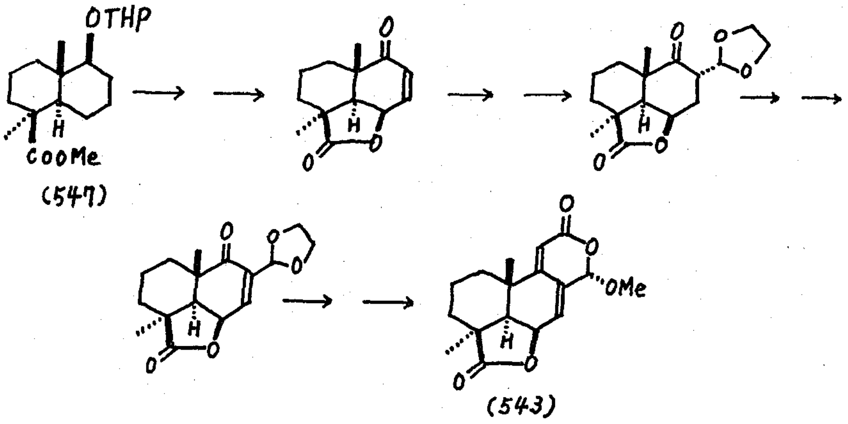


Chart 23

Minor diterpenoids were isolated from *Stachys annua*,²²⁷⁾ but no details are available yet.

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