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The Chemistry on Diterpenoids in 1969

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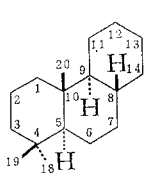
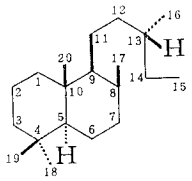
I. INTRODUCTION

The author has published a series of the reviews on diterpenoids chemistry.[1,2,3,4,5] This review deals with an outline of the chemical works on diterpenoids in 1969.

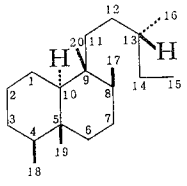
The classification** consists of podocarpane, labdane, clerodane, pimarane, isopimarane, abietane, totarane, cassane, kaurane, gibberellane, atisane, aconane, beyerane, taxane, and the others.



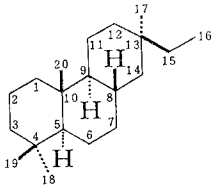
Podocarpane



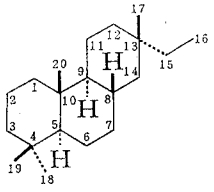
Labdane



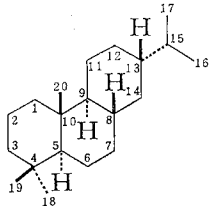
Clerodane



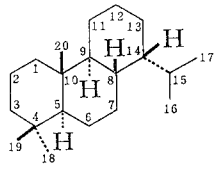
Pimarane



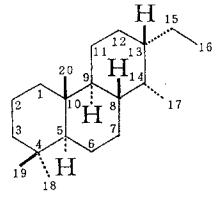
Isopimarane



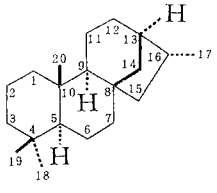
Abietane



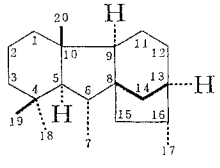
Totarane



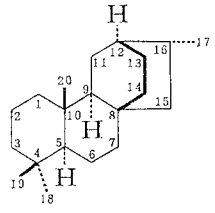
Cassane



Kaurane



Gibberellane



Atisane

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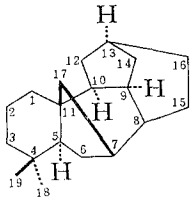
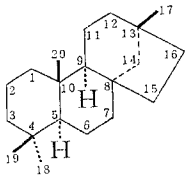
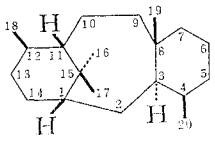
** See also ref. 5.



Aconane



Beyerane

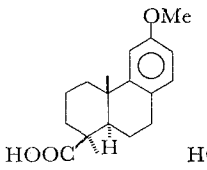


Taxane

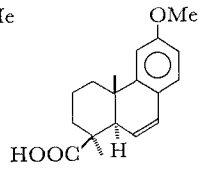
In each Section, the full papers were first described and the short communications followed. The order of the journals followed the alphabet of their names.

II. PODOCARPANE DERIVATIVES

Mass spectrometric studies on podocarpa-8, 11,13-triene esters, aldehydes, and alcohols with the oxygenated substituent at C-10 or at C-4 were reported.[6] A pathway involving the γ,δ-unsaturated acid **2** was suggested for the formation of lactones **3** and **4** from the oxidation of 12-methoxypodocarpa-8,11,13-trien-19-oic acid (**1**) with lead tetraacetate [$Pb(OAc)_4$]. Support for this suggestion was obtained from an examina-



(**1**)



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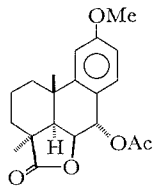

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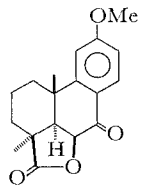
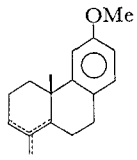


(**4**)

tion of the products from $Pb(OAc)_4$ oxidations of several compounds analogous to **1** and **2**.[7] Selective epoxidation of the methoxy alkenes mixture **5** from oxidative decarboxylation of **1** provided a method of obtaining a high yield of the exocyclic alkene **6** from the mixture. Methods for opening the epoxide ring of **7**, **8** and **9** were ex-



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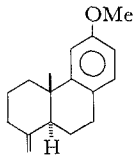

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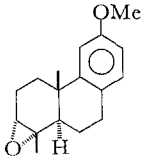

(**7**)

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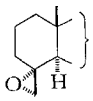
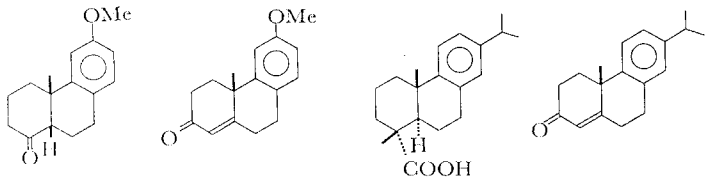


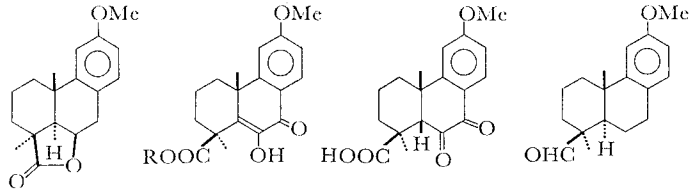
(**9**)

amined.[8] The acid **1** was converted into the 3-oxo compound **11** *via* the C-3 benzylidene derivative of 12-methoxy-18,19-bisnor-5β-podocarpa-8,11,13-trien-4-one (**10**).[9] The route followed a modification of a sequence used by Zeiss and Martin[10] to convert abieta-8,11,13-trien-18-oic acid (**12**) into a tricyclic steroid analog. The latter conversion was reinvestigated and modified to give a high yield of 18,19-bisnorabieta-



(10) (11) (12) (13)

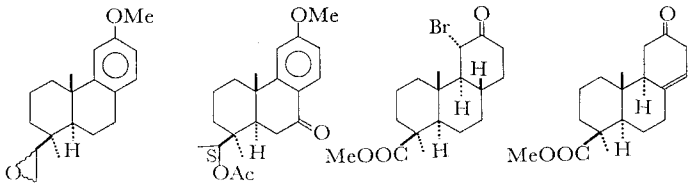
4,8,11,13-tetraen-3-one (**13**).[9] The lactone **14** was prepared by successive dehydration and hydrogenation of the 7 α- and 7 β-hydroxy lactones, and also by reduction of the 7-ketolactone with borane. Treatment of the 7-ketolactone with sodium hydroxide in methanol effected a fragmentation reaction to give the diosphenol **15**. Treatment



(**14**) (**15**): R=Me (**16**): R=H (**17**) (**18**)

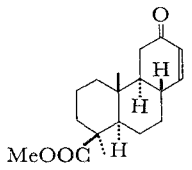
of the diosphenol **16** with potassium hydroxide afforded the *cis*-fused A/B ring diketo acid **17** rather than the product of an expected benzilic acid rearrangement.[11]

Aldehyde **18** was subjected to the Wittig reaction followed by epoxidation to give the epoxide **19**. The latter was treated with lithium aluminumhydride ($LiAlH_4$) to afford the 19S-ol, and then 7-ketoacetate **20** was prepared by its successive acetylation and oxidation.[12]



(**19**) (**20**) (**21**) (**22**)

The configuration and stereochemistry of methyl 11 α-bromo-12-oxopodocarpan-19-oate (**21**) were determined by application of the nuclear Overhauser effect. Then, the dehydrobromination of **21** with dimethyl acetamide—calcium carbonate resulted in a predominant 1,4-elimination process which for short reaction periods yielded the non-conjugated ketone **22** and for long reaction periods yielded the conjugated ketone **23**. The 1,2-elimination of hydrogen bromide was a minor process and took place to the extent of 20–22%. The ketone **22** was oxidatively cleaved to the keto-acid **24**, a valuable intermediate for the synthesis of bicyclic diterpenoids.[13]



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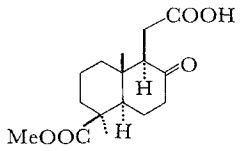

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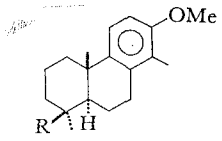
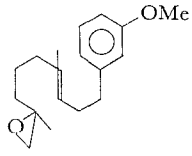


(25) : R=COOMe
(26) : R=Me
(27) : R=CH_2OH
(28) : R=CHO

Methyl *rac*-13-methoxy-14-methylpodocarpa-8,11,13-trien-19-oate (**25**) and related compounds, *e.g.* **26**, **27**, and **28**, were synthesized.[14] Another synthesis of **25** *via* a similar way was also reported.[15] The epoxy-olefin **29** was treated with BF_3-etherate to give two tricyclic alcohols, **30** and **31**, both of which had the *trans*-fused A/B ring system. On the other hand, the *cis*-isomer of **29**, *i.e.*, **32** on similar treatment



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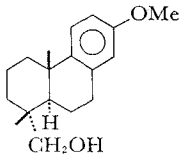

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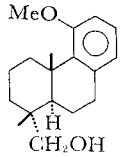

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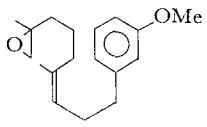
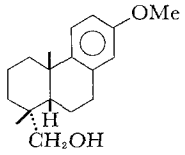


(32)

gave the A/B *cis*-fused alcohol **33**. These results suggest that the ring closure occurs not *via* a "nonstop" process, but rather *via* the intermediate cations having a rigid geometry.[16]



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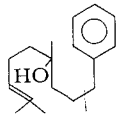

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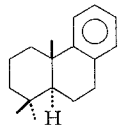

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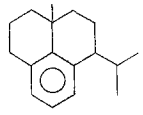

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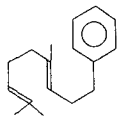
Reinvestigation of the ring closure of 4,8-dimethyl-1-phenylnon-7-en-4-ol (**34**) with polyphosphoric acid clarified that the main product was not **35** reported previously, but a hydrophenalene derivative **36**. The ring closure of diene **37** predominantly gave *trans*-podocarpatriene (**38**) accompanied by *cis*-isomer **39**. A nonconcerted mechanism was presented for this cyclization.[17]



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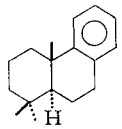

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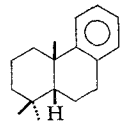

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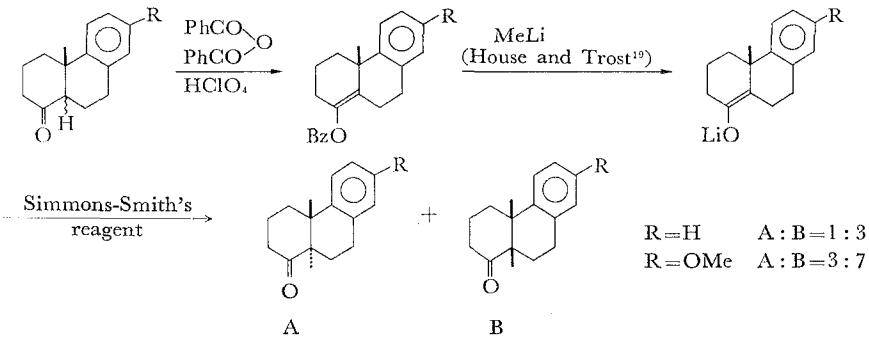


Chart 1

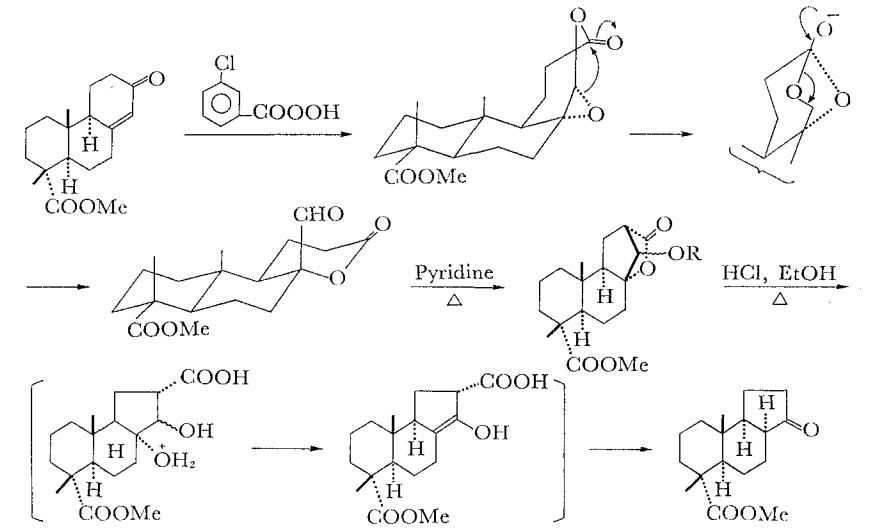
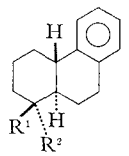


Chart 2

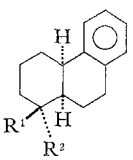
Angular methylalion was studied by Whitlock Jr. and Overman.[18] The outline is shown in Chart 1.

Pelletier *et al.*[20] investigated the transformation in the ring C of the resin acid degradation products. In Chart 2, a part of their work is shown.

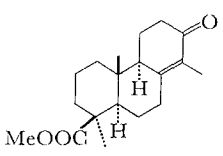
Synthesis and conformational analysis of tricyclic ring C aromatic 20-nor diterpenoid resin acid analogs, **40**, **41**, **42**, and **43** were reported by an Indian group.[21]



(**40**) : R^1=COOH, R^2=Me
(**41**) : R^1=Me, R^2=COOH



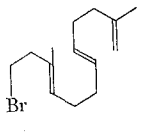
(**42**) : R^1=COOH, R^2=Me
(**43**) : R^1=Me, R^2=COOH



(**44**)

The methoxy ester **25** and an α,β-unsaturated keto ester **44** were synthesized as the promising intermediates for the diterpenes having the cassane skeleton.[22]

A biogenetic-like stereoselective olefin cyclization was studied: tetraene alcohol **46**, prepared from bromo-compound **45** *via* two steps, was treated with trifluoroacetic acid and then $LiAlH_4$ to give alcohols **47** (23%) and **48** (29%) accompanied by a hydrocarbon fraction.[23]



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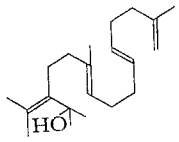

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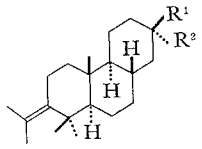
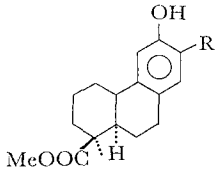
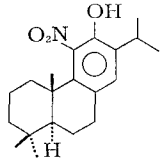


(47) : R^1=Me, R^2=OH
(48) : R^1=OH, R^2=Me

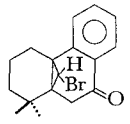
Nitration of phenols by silver nitrate on silica gel was reported. Thus, methyl podocarpate **49** was converted into 13-nitro derivative **50** by treating with silica gel impregnated with silver nitrate in refluxing benzene for 8 hr.[24] Ferruginol was also nitrated to 11-nitroferruginol (**51**).



(49) : R=H
(50) : $R=NO_2$

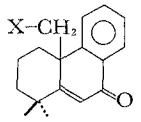


(51)

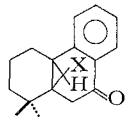


(52)

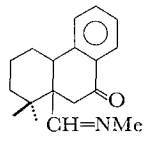
Reactions of the bromo ketone **52** with nucleophiles were investigated. Three types of reactions afforded products **53**, **54**, and **55**.[25]



(53) : $X=NO_2$
CN
Ts

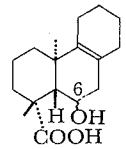


(54) : $X=N_3$
NMe_2
OMe
OAc
$S\text{-}CH_2Ph$

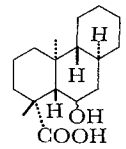


(55)

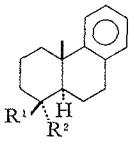
Synthesis of *ent*-6α-hydroxy-tetrahydro- (**56**) and *ent*-6α-hydroxy-hexahydro-deoxypodocarpic acid (**57**) was investigated.[26] Syntheses of *ent*-6β-hydroxy-tetrahydro- (**58**) and *ent*-6β-hydroxyhexahydro-deoxypodocarpic acid (**59**) *via* lactonization of 6β isomers were carried out.[27] Temperature dependent PMR was used effectively for characterizing stereoisomers shown as types, **60**, **61**, and **62**.[28]



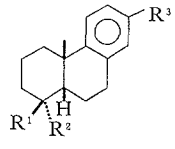
(**56**) : 6β-OH
(**58**) : 6α-OH



(**57**) : 6β-OH
(**59**) : 6α-OH

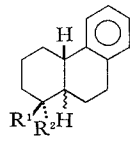


(**60**)

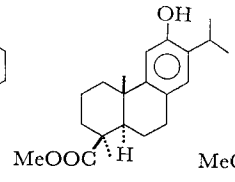


(**61**)

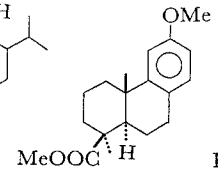
Methyl callitrisate was converted into the phenolic ester **63**, which was derived from methyl 12-methoxypodocarpa-8,11,13-trien-19-oate (**64**). Thus, a correlation of methyl callitrisate with a podocarpic acid derivative was accomplished which also confirmed structure **65** of callitrisic acid.[29a]



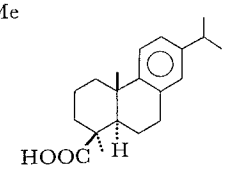
(**62**)



(**63**)



(**64**)

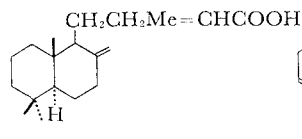


(**65**)

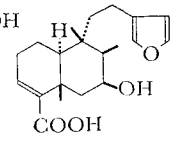
Analogs to racemic dehydroabietylamine and homodehydroabietylamine were synthesized. The isopropyl group was replaced by hydrogen, or by a methyl or methoxy group. The guanidinium salts were prepared from the corresponding amines. Further variations included the additional introduction of a hydroxy group and substitution of the amino or guanidinium group by a quaternary ammonium or isothiouronium group.[29b]

III. LABDANE DERIVATIVES*

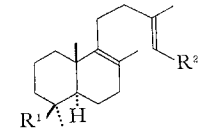
From the oleoresin of *Copaifera multijuga*, the known hardwickiic acid and two new diterpene acids, copaiferic acid and 7-hydroxy-hardwickiic acid, were isolated. The structures **66** and **67** of the latter two were determined by chemical and spectral examinations.[30]



(**66**)



(**67**)

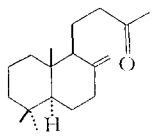


(**68**) : R^1=COOH, R^2=COOMe
(**69**) : R^1=R^2=COOMe
(**70**) : R^1=R^2=CH_2OH
(**71**) : R^1=CH_2OH, R^2=COOH

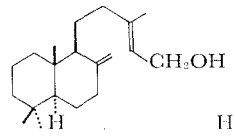
* See also Section V, ref. 62, Section VII, ref. 117 and Section XI, ref. 160a, b.

Dioxygenated labdadienes, *e.g.*, **68**, **69**, **70** and **71**, were prepared and their optical rotation was compared.[31] Structure and optical rotation were correlated for some 8-oxo-17-norlabdanes which all had a negative rotation at the sodium D line and a negative Cotton effect. A correlation of communic acid with agathic acid was shown to be correct.[32]

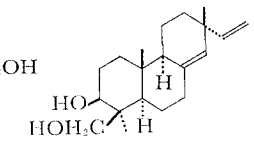
Examination of the heartwood of *Dacrydium kirkii* showed the presence of isopimaradiene, sclarene, *cis*-biformen, *trans*-biformen, manoyl oxide, 14,15-bisnorlabd-8(17)-en-13-one (**72**), labda-8(17),13-dien-15-ol (**73**), manool, isopimaradienol, β-



(**72**)

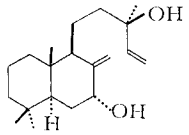


(**73**)

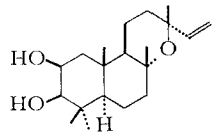


(**74**)

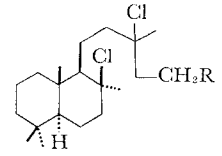
sitosterol, torulosol, sandaracopimaradiene-3β,19-diol (**74**), and isopimaric acid. Two new diterpene alcohols isolated were shown to be 7α-hydroxymanool (**75**) and 2β,3β-dihydroxymanoyl oxide (**76**).[33]



(**75**)



(**76**)

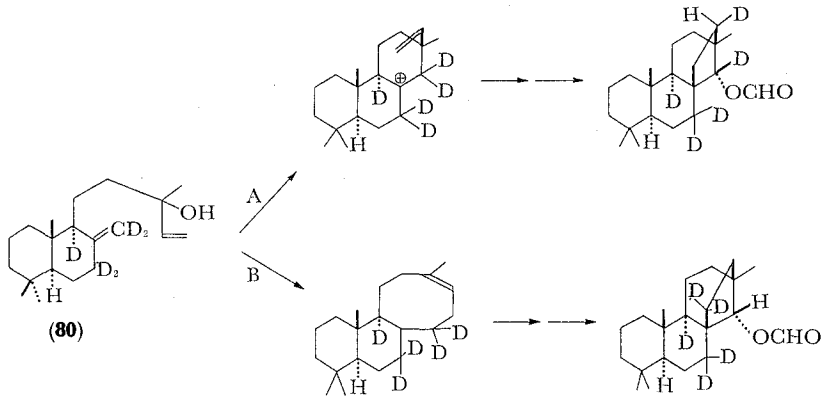


(**77**) : R=Cl
(**78**) : R=OAc
(**79**) : R=OH

The C-8 stereochemistry of "manool trihydrochloride" and other halogenated labdanes was reinvestigated and revised.[34] Thus, the structure and absolute configuration, 8S,13RS,16-trichlorolabdane (**77**), was assigned to "manool trihydrochloride". Similarly, dichloroacetate and dichloroalcohol, which were previously obtained and had been reported to have 8R configuration,[35] were revised to 8S structures **78** and **79**, respectively.

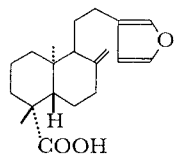
A test of the mechanism of acid-catalyzed cyclization of manool to 14α-hydroxybeyerane was achieved by synthesis and cyclization of 7,7,9,17,17-pentadeuteriomanool (**80**). The reaction involves initial formation of a cyclooctenyl cation, an unusual *in vitro* step, that is, it proceeds *via* the B route instead of the A route.[36] (See Chart 3.)

Treatment of a solution of daniellic acid (**81**) in EtOH with HCl gas gave illurinic acid (**82**).[37] Monocyclofarnesyl-acetones were refluxed with $LiAlH_4$ in ether to give alcohols, which were acetylated. The acetates were treated with 100% H_2SO_4 in nitropropane at −70° to cyclize into bicyclofarnesol derivatives. Their stereochemistry was investigated.[38] The hydrogenation and dehydration of epitorulosol were studied.[39]

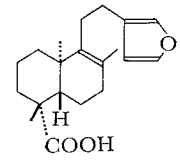


(80)

Chart 3

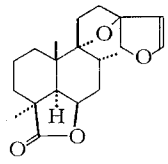


(81)

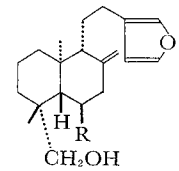


(82)

Fresh oleoresin from *Picea ajanensis* was treated with 1% NaOH and the neutral substance was extracted with ether. Distillation of the extract gave a diterpene residue (50.9%), from which epimanoyl oxide, phyllocladene, cembrene, manool, epimanool, phyllocladanol and its 16β-isomer were separated by chromatography.[40] A new diterpenoid **83** was isolated from *Marrubium vulgare*. It was supposed to be the major

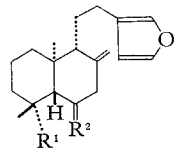


(83)

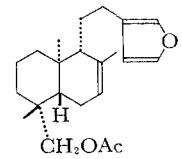


(84) : R=OH
(90) : R=H

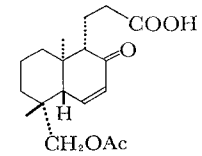
substrate from which marrubiin was generated as an artefact. Biogenetic implications were discussed.[41] Psiadiol was isolated from *Psiadia altissima* and structure **84** was given. It was converted into **85**, **86**, **87**, and **88**.[42] Another new diterpenoid,



(85) : R^1=CHO, R^2=O
(86) : R^1=CH_2OAc,
R^2=α-OH, β-H

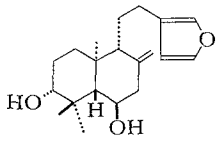


(87)

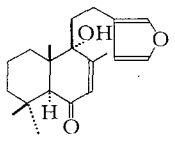


(88)

isopsiadiol was isolated from the same plant source (leaves) and structure **89** was assigned to this compound. The reaction of 6-deoxypsiadiol (**90**) was also investigated.[43] The constitution and stereochemistry of solidagenone (**91**) and the epimeric spiro ethers



(89)



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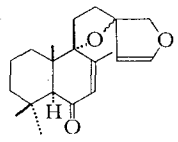
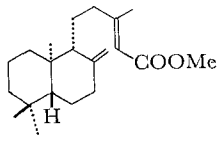


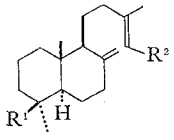
(92)

(**92**) isolated from *Solidago canadensis* were deduced on the basis of spectroscopic and chemical properties.[44] Synthesis of isoabienol and *trans*-abienol from sclareol was reported.[45] Dehydration of sclareol and 13-episclareol by dimethyl sulfoxide was investigated.[46] Oxidation products of sclareol was investigated.[47] Synthesis of labd-13-ene-8β,15-diol from labda-8(17),13-dien-15-ol was reported.[48]

The structure of leonotin, a novel furanoid diterpene, was determined to be

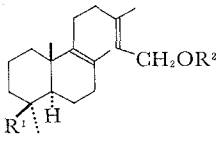


(93)

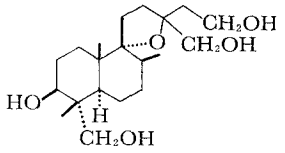


(**94**) : $R^1=R^2=COOMe$
(**95**) : $R^1=CH_2OAc$, $R^2=COOMe$
(**96**) : $R^1=CHO$, $R^2=COOMe$
(**97**) : $R^1=CH_2OH$, $R^2=COOMe$
(**98**) : $R^1=COOH$, $R^2=CH_2OAc$

8β-hydroxymarrubiin.[49] Methyl *enantio*-labda-8(17),13-dien-15-oate (**93**) was isolated from *Araucaria bidwilli* resin. In addition, **94**, **95**, **96**, and **97** were also isolated.[50] From *Araucaria cuninghamii* resin, some labdane derivatives—**98**~**104**—were isolated.[51] Lagochilin was isolated from *Lagochilus inebrians*, and its structure was clarified to be **105**.[52]



(**99**) : $R^1=COOH$, $R^2=H$
(**100**) : $R^1=COOH$, $R^2=Ac$
(**101**) : $R^1=CH_2OH$, $R^2=H$
(**102**) : $R^1=CHO$, $R^2=H$
(**103**) : $R^1=CHO$, $R^2=Ac$
(**104**) : $R^1=CH_2OAc$, $R^2=Ac$

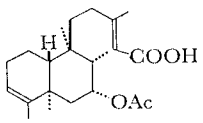


(105)

IV. CLERODANE DERIVATIVES*

A new bitter principle, solidagonic acid, isolated from the roots of *Solidago altissima*, was investigated and the structure **106** was proposed on the basis of chemical and

* See also Section III, ref. 30.



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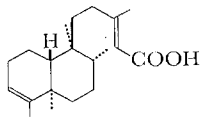

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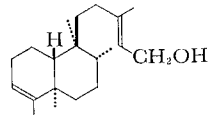

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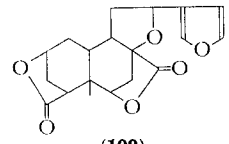
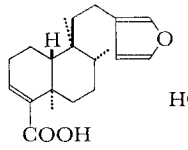


(109)

spectroscopic evidences. Moreover, kolavenic acid (**107**) and kolavenol (**108**) were isolated and related chemically to **106**. Their absolute configuration was determined by application of the octant rule for the ORD curves of their ketone derivatives.[53] A norditerpene lactone, diosbulbine, was isolated from the tubers of *Dioscorea bulbifera* and structure **109** was presented by Indian workers,[54] but this plane structure is identical with that of the known diosbulbin-B.[55] The wood of *Gosswеilerodendron balsamiferum* afforded five diterpenes. These were (−)-hardwickiic acid (**110**) together with the new diterpenes, agbaninol (**111**), agbanindiols A (**112**) and B (**113**), and monomethyl ester **114** of the known kolavic acid.[56]



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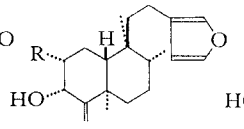
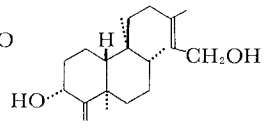
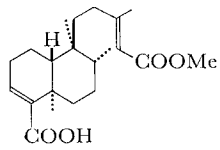


(111) : R=H
(113) : R=OH

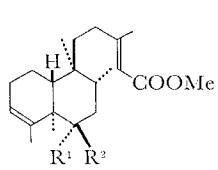


(112)

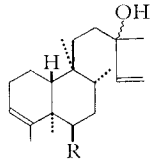


(114)

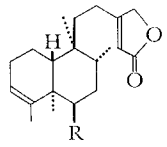
From the roots of *Solidago elongatea*, several oily diterpenoids were isolated by careful column and thin layer chromatography. Methylation of the polar fractions from the column with diazomethane gave three diterpenoid methyl esters, methyl kolavenate,



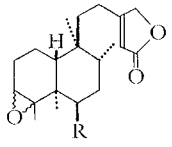
(115) : R^1=H, R^2=OAc
(116) : R^1=H, R^2=OAng



(117) : R=H
(118) : R=OAng

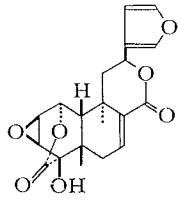


(119) : R=OH
(120) : R=OAc
(121) : R=OAng

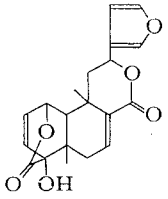


(122) : R=OAc
(123) : R=OAng

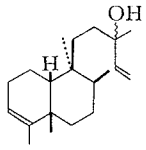
methyl 6-acetoxykolavenate (**115**), and methyl 6-angeloyloxykolavenate (**116**). In addition, kolavenol (**108**), kolavelool (**117**), 6-angeloyloxykolavelool (**118**), elon-



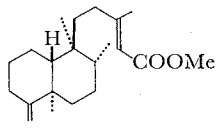
(124)



(125)



(126)



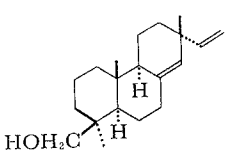
(127)

gatolide-A (**119**), -B (**120**), -C (**121**), -D (**122**), and -E (**123**) were isolated.[57] From the extract of *Fibraurea chloroleuca*, the known fibraurin (**124**) and a new furanoid diterpene, fibleucin, were isolated. The structure **125** was presented to the latter.[58] The absolute stereochemistry of plathyterpol[59] at all centers except C-13 was defined to be **129**.[60]

From *Araucaria bidwilli* rosin, methyl kolavenate (methyl ester of **107**) and ester **127** were isolated besides some labdane derivatives.[50]*

V. PIMARANE AND ISOPIMARANE DERIVATIVES

The isolation and characterization of two diterpenes from *Dacrydium colensoi* as sandaracopimaradien-19-ol (**128**) and *abeo*-labdane derivative **129** was reported. The structure of caroxylic acid **129** was confirmed by the synthesis of the methyl ester from 2-oxomanoyl oxide *via* acetoxylation followed by a benzilic acid-type rearrangement. In addition, ferruginol was isolated from the extract.[61]



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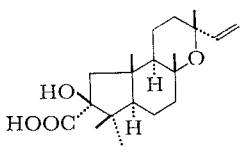

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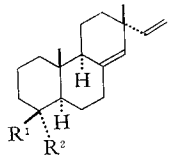
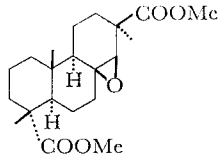


(130) : R^1=Me, R^2=CH_2OH
(131) : R^1=Me, R^2=OH
(132) : R^1=OH, R^2=Me

The neutral extractives from the bark of *Thuja plicata* contained, among other components, three alcohols. One was the known diterpene alcohol, isopimarinol (**130**), but the other two were the new $\Delta^{8(14),15}$-4α-hydroxy-18-norisopimaradiene (**131**) and $\Delta^{8(14),15}$-4β-hydroxy-19-norisopimaradiene (**132**). The synthesis of these two alcohols were described. The greater amount of the 4α compound found in nature, and its relative ease of synthesis compared to 4β isomer, showed it to be formed preferentially.[62]

Some chemistry of the α- (**133**) and β-epoxides (**134**) derived from methyl pimarate was investigated. The α-epoxide was found to be a very reactive species leading, by an intramolecular process, to a hydroxy-γ-lactone even on standing in hexane solution. The β-epoxide undergoes a cleavage reaction with Lewis acid to give a "backbone" rearrangement product, although a non-rearranged compound was observed in minor yield.[63]



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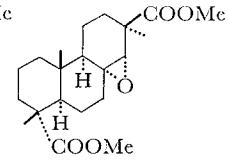

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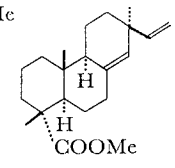

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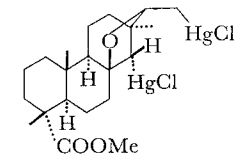
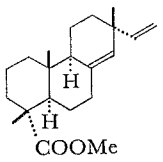


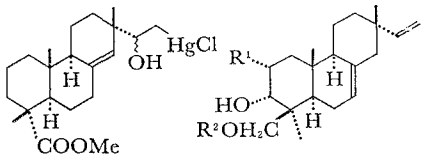
(136)

* See also Section III, ref. 33 and Section XI, ref. 160a, b.

The oxymercuration-demercuration procedure was explored for methyl pimarate (**135**) and methyl sandaracopimarate (**137**). In the first case, a dimercurialmonoether **136** was obtained yielding a cyclic ether on demercuration. In the second, a monomercuriol **138** was obtained arising from attack on the vinyl group only, and demercuration gave a mixture of alcohols.[64]



(137)



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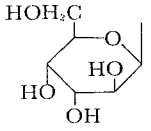
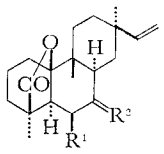


(139) : R^1=OH, R^2=

(140) : R^1=H, R^2= 〃

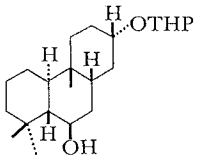
Virescenoside A (**139**) and virescenoside B (**140**), new altroside metabolites of *Oospora virescens*, were isolated and characterized.[65]

Geranylgeraniol was shown to be a precursor of rosenonolactone (**142**) in *Tricothecium reseum*. The labelling pattern from [2-$^3H_2$, 2-^{14}C, (4R)-4-^{3}H, 2-^{14}C and 5-$^3H_2$, 2-^{14}C]-mevalonate proved the hydride shift from C-9 to C-8. Desoxorosenonolactone (**141**) was shown to act as a precursor to rosenonolactone (**142**) and rosololactone (**143**)[66].



(141) : R^1=H, R^2=H_2
(142) : R^1=H, R^2=O
(143) : R^1=OH, R^2=H_2

As a potential method for the construction of the lactone ring of rosenonolactone (**142**), an application of $Pb(OAc)_4$-I_2 transannular oxidation was explored. Lactone **145** derived from 6β-alcohol **144** was tried to isomerize into **146** under an acidic condition, but the attempt was not successful. The ether **147** derived from the same compound (**144**) by oxidation with only $Pb(OAc)_4$ was cleaved by its treatment with



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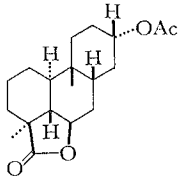
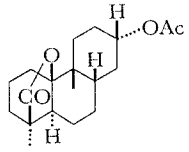


(145)



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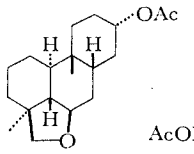

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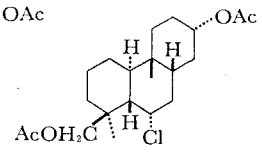

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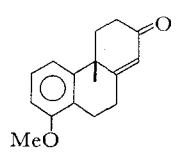

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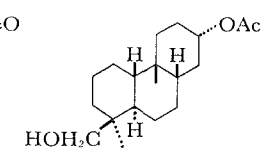
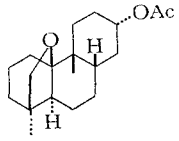


(150)

pyridine hydrochloride in acetic anhydride to form **148**. The similar compound **150** which was synthesized from **149** was subjected to photooxidation with $Pb(OAc)_4$ and I_2 to yield the desired oxygen bridge **151** in 28% yield.[67] The isolation of rosenololactone (**152**) as a minor terpenoid from *Trichothecium roseum* was reported.[68]



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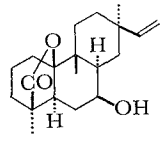

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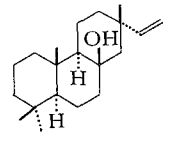

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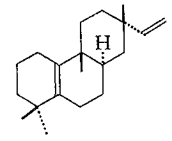


(154)

Isotopic incorporation and production/time studies confirmed that desoxorosenonolactone (**141**) was oxidized to rosenonolactone (**142**) and rosololactone (**143**) by cultures of *Trichothecium roseum*.[69]

The dehydration of sandaracopimar-15-en-8β-ol (**153**) by thionyl chloride or by formic acid gave the dehydration products ($\Delta^{8(9)}$, $\Delta^{8(14)}$ and $\Delta^{8(7)}$) and a rearranged product **154**, but no expected tetracyclic diterpenes.[70]

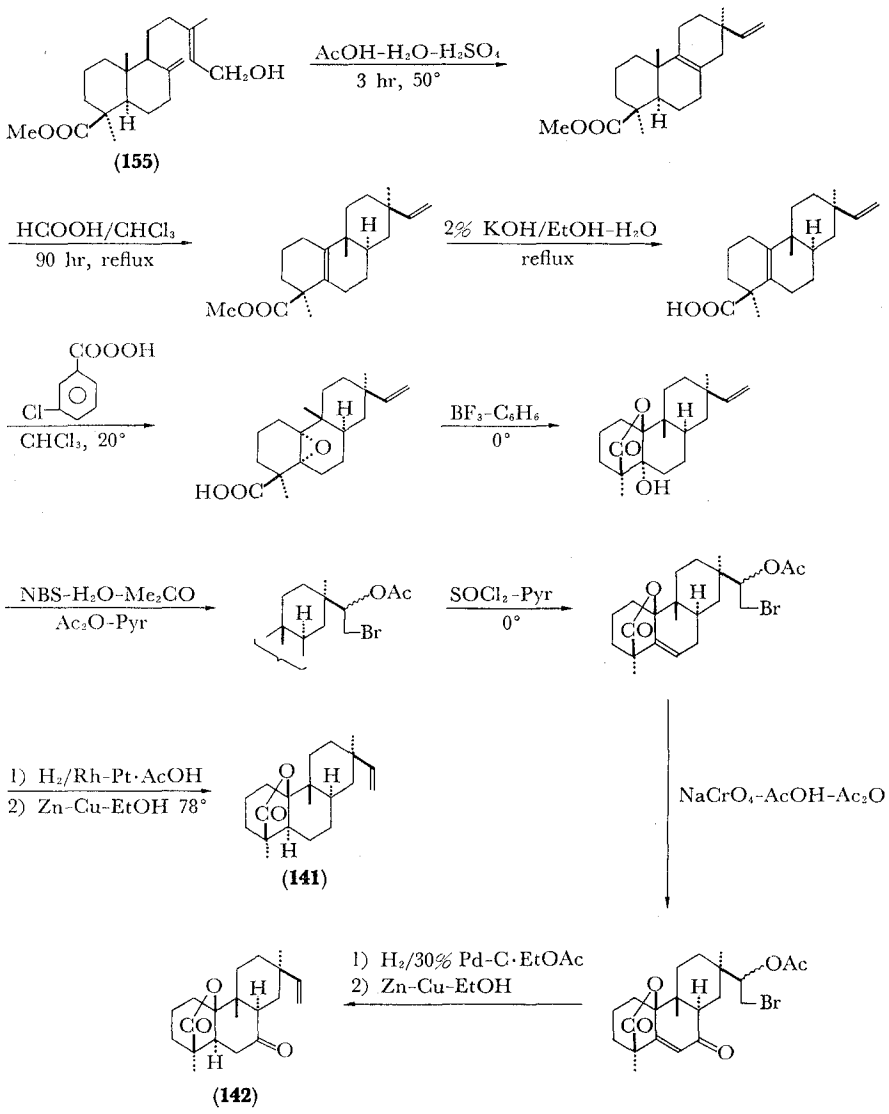
The mevalonoid hydrogen was incorporated in the C-1, C-5, and C-6 of rosenonolactone (**142**), thus the possibility of the formation of any unsaturated intermediates involving these centers during the biosynthesis was excluded. Since the migrating methyl group (C-10 → C-9) is *cis* to the lactone ring, a concerted lactonization is unlikely and hence it would seem likely on the basis of these results that an α-oriented C-10 enzyme or C-10-hydroxy bond is formed which is displaced with inversion when the lactone ring is formed.[71]

Rosenonolactone (**142**) and desoxorosenonolactone (**141**) were synthesized, modelled on their biosynthetic pathway, from methyl isocupressate (**155**), as shown in Chart 4.[72]

A new norditerpenoid hydrocarbon, 18-norisopimara-4(19),7,15-triene (**156**), was isolated as a minor component from the heartwood of *Dacrydium biforme*, and characterized. Isopimara-7,15-diene was the major diterpene.[73]

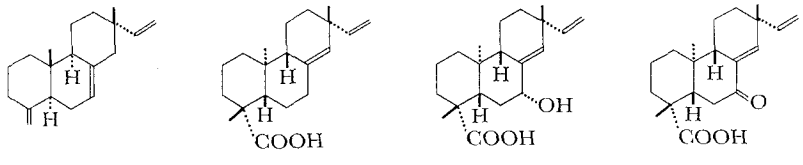
Investigation of the stems and leaves of *Aralia cordata* and *A. racemosa* showed the presence of several diterpenes. Both plants contained *ent*-kaur-16-en-19-oic acid and *ent*-pimara-8(14),15-dien-19-oic acid (**157**). From the acidic fraction of the ether extract of the roots of *A. cordata*, three *ent*-pimarane derivatives, **158**, **159**, and **160** were isolated. In addition, an alcohol **161** and an *ent*-kaurane derivative* were isolated.[74]

* See also Section IX.

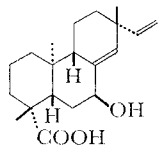


(155) **(141)** **(142)**

Chart 4



(156) **(157)** **(158)** **(159)**



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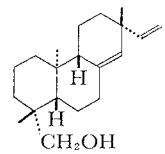

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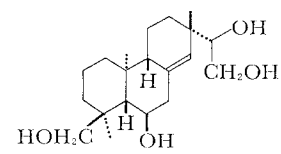
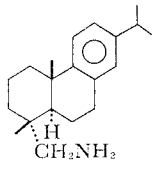


(162)

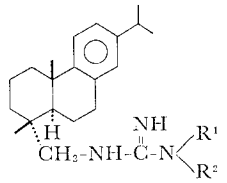
From *Siegesbeckia pubescens,* a new neutral compound (**162** or its mirror image) and the known kaurane derivative* were isolated.[75]

VI. ABIETANE DERIVATIVES**

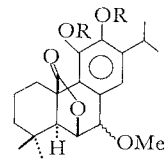
In order to investigate the antimicrobial activity, various derivatives of dehydroabietylamine (**163**) were prepared. They included *N*-monoalkyl derivatives, *N,N*-dialkyl derivatives, dehydroabietylguanidines **164**, dehydroabietylurea, -thiourea, -salts of dehydroabietylisourea and -isothiourea, quaternary dehydroabietylammonium



(163)



(164)
(165) : $R^1=R^2=H$

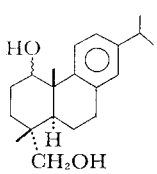


(166) : R=H, with 7β OMe
(167) : R=Me, with 7α OMe

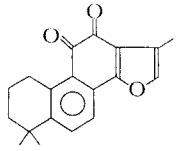
salts and 2-dehydroabietylaminopyrimidine.[76] The partial syntheses of the derivatives of dehydroabietylamine (**163**) and dehydroabietylguanidine (**165**), which were modified at positions 6, 7, 10, 12, 13, and 14, were reported. Benzylic oxidation, substitution of the aromatic nucleus, and benzylic epimerization of the octahydrophenanthrene molecule were used.[77]

In the leaves of Rosemary two new derivatives of carnosic acid were found : the 7β-methyl ether **166** of the γ-lactone and after methylation of the resin the 7α-methyl ether **167** of the same lactone with methylated phenolic groups. The phenolic group of carnosol, neighbored to the isopropyl group of this compound, can only be methylated with dimethylsulfate, not, however, with diazomethane.[78]

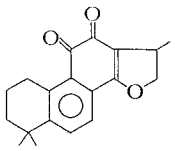
Teideadiol (**168**), a new diterpene, was isolated from *Nepeta teydea.*[79] The total



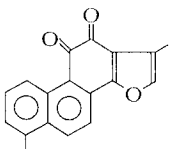
(168)



(169)



(170)



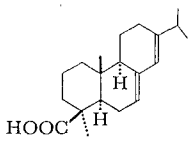
(171)

* See also Section IX.

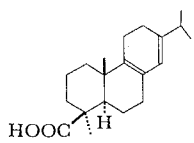
** See also Section II, refs. 9, 10, 24, and 29 and Section V, ref. 61.

syntheses of tanshinone-II (**169**), cryptotanshinone (**170**), and tanshinone-I (**171**) were reported.[80]

4-Epiabietic acid (**172**) and 4-epipalustric acid (**173**) were isolated from the acid fraction of *Juniperus phonicea*.[81] The Diels-Alder addition of methyl levopimarate (**174**) with maleic anhydride afforded **175** (not **176**).[82]



(172)



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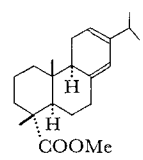
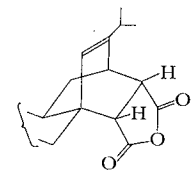
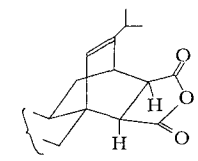


(174)

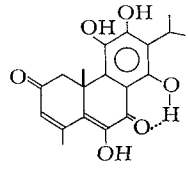


(175)

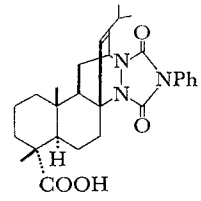


(176)

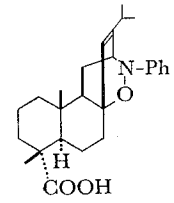
A yellow pigment, coleon B, was isolated from *Coleus igniarius* (Labiatae), and structure **177** was assigned to this. The absolute configuration was determined by its conversion into 19-nordihydroroyleanone trimethyl ether and its comparison with dihydroroyleanone trimethyl ether.[83]



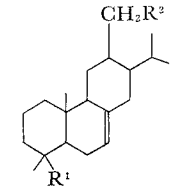
(177)



(178)



(179)



(180) : $R^1=R^2=CN$
(181) : $R^1=CH_2NH_2$, $R^2=NH_2$
(182) : $R^1=R^2=CH_2NH_2$

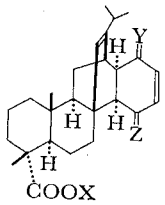
Diels-Alder reactions of levopimaric acid with several azodienophiles were investigated. On reaction with 4-phenyl-1,2,4-triazoline-3,5-dione it furnished a diazabicyclo[2, 2, 2]octane derivative **178**. Base hydrolysis of this adduct furnished dehydroabietic acid and levopimaric acid in poor yields. Cycloaddition of nitrosobenzene to levopimaric acid was shown to give a 1 : 1 adduct. On the basis of NMR data and chemical reactions the structure of this adduct was established as **179**.[84]

12-Cyanomethyldihydroabietonitrile (**180**), 12-aminomethyl-dihydroabietylamine (**181**), and 12-(β-aminoethyl)dihydroabietyl-amine (**182**) were synthesized using the readily available 12-hydroxymethyldihydroabietic acid (derived from levopimaric acid).[85]

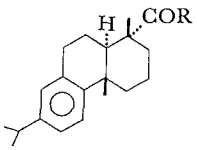
Quinone-levopimaric acid adduct ("quinopimaric acid") (**183**), and its several derivatives (modified at X, Y, and Z) were synthesized and characterized.[86]

Analogs of deoxycorticosteroids based on the skeleton of dehydroabietic acid (**184**) were prepared *via* **185**～**187**.[87]

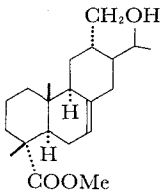
The isomerization of the methyl esters of conjugated dienoic resin acids (levopimaric, palustric, and neoabietic) of pine gum in the presence and absence of base, as well as in the presence of added carboxylic acid, was examined.[88]



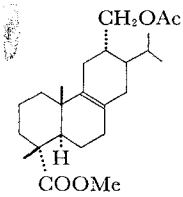
(**183**) : X=H, Y=Z=O



(**184**) : R=OH
(**185**) : R=Cl
(**186**) : R=CH_2N_2
(**187**) : R=CH_2OAc



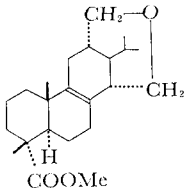
(**188**)



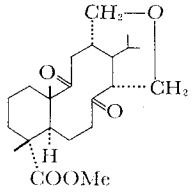
(**189**)

Methyl 12-α-hydroxymethyl 13β-abiet-7,8-enoate (**188**) in an acetic acid-sulfuric acid mixture was acetylated and isomerized, giving methyl 12-α-acetoxymethyl 13β-abiet-8,9-enonate (**189**). This was converted into the 7-keto enone by chromic acid oxidation. Methyl 12,14-(2-oxapropano)-13β-abiet-8,9-enoate (**190**) reported previously was converted to a 1,6-diketone **191** and a 1,2-diol **192** by ruthenium tetroxide oxidation of the 8,9 double bond.[89]

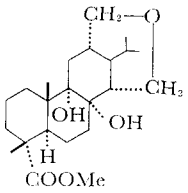
The osmylation of abietic acid gave diol **193** accompanied by a small amount of tetraol **194**.[90]



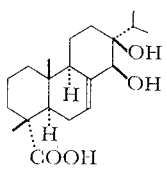
(**190**)



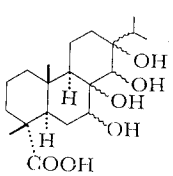
(**191**)



(**192**)

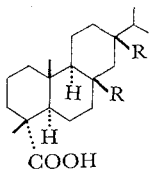


(**193**)

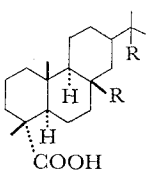


(**194**)

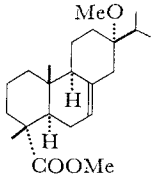
Structures **195** and **196** assumed[91] previously for so-called "dihydrochloride" and "dihydrobromide" of abietic acid, were revised to **197** and **198**, respectively.[92]



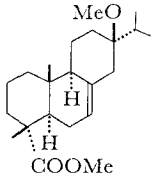
(**195**) : R=Cl
(**196**) : R=Br



(**197**) : R=Cl
(**198**) : R=Br



(**199**)



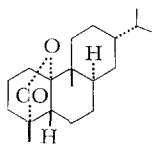
(**200**)

Irradiation of methyl abietate in methanol or benzene-methanol gave two epimeric ethers **199** and **200** accompanied by the products of decarboxylation, disproportionation, isomerization, and polymerization.[93]

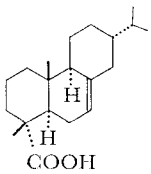
For the purpose of preparing the suitable intermediates for the synthesis of polycyclic molecules, the oxidation of some Diels-Alder adducts of levopimaric acid was investigated. As the model compound, the adduct of levopimaric acid and

acetylenedicarboxylic ester was used. A number of unusual reactions were observed.[94]

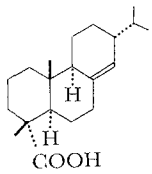
The catalytic hydrogenation products of abietic, neoabietic, and levopimaric acid were correlated with the products from the reduction with Li in liquid ammonia. Structural and stereochemical assignments were presented to all the known and many of the new dihydroabietic acids. The new characterized compounds are as follows: 9,5-friedoabietan-18:10-olide (**201**), 7-abieten-18-oic acid (**202**), 8(14)-abieten-18-oic acid (**203**), 13-abieten-18-oic acid (**204**), 8-abieten-18-oic acid (**205**), 8,13(15)-abietadien-18-oic acid (**206**), and 13(15)-abieten-18-oic acid (**207**).[95]



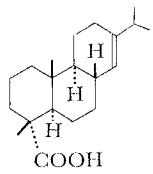
(**201**)



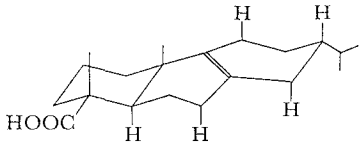
(**202**)



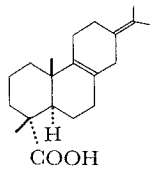
(**203**)



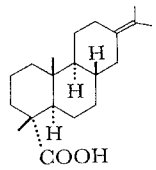
(**204**)



(**205**)

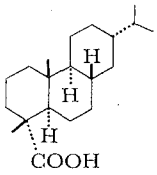


(**206**)

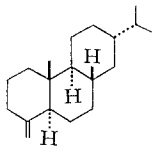


(**207**)

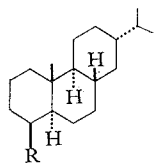
Abietan-18-oic acid (**208**) was converted into 19-nor-4(18)-abietene (**209**), which was hydrogenated or was subjected to hydroboration followed by reduction to yield fichtelite (**210**) as a major product. On the other hand, the hydroboration product was oxidized to 18-norabietan-19-al (**211**), which was subjected to epimerization followed by reduction to afford 19-norabietane (**212**).[96]



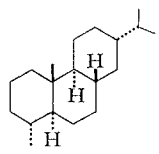
(**208**)



(**209**)

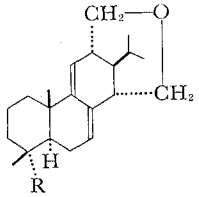


(**210**) : R=Me
(**211**) : R=CHO

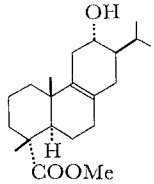


(**212**)

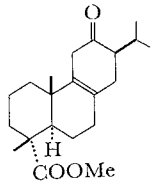
Methyl 12,14-(2-oxapropano)-13β-abiet-8(9)-enoate (**190**) was treated with NBS to give a heteroannular diene (**213**). The same compound **190** was allowed to



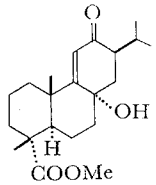
(**213**) : R=COOMe
(**214**) : R=CH_2OH



(**215**)



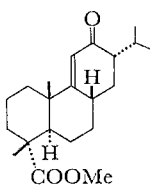
(**216**)



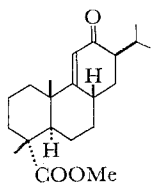
(**217**)

react with *m*-chloroperbenzoic acid to give the 8,9-epoxide in a low yield. 7-Keto derivative of **190** was treated with $LiAlH_4$ to yield alcohol **214**.[97]

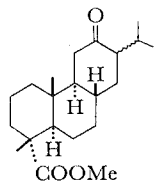
Methyl 12α-hydroxy-13β-abiet-8(9)-en-18-oate (**215**) was oxidized with Jones' reagent to yield **216** accompanied by a minor product **217**. The main product **216** was treated with base or acid-washed alumina to afford epimeric α,β-unsaturated ketones, **218** and **219**, which were converted into the dihydro derivatives, **220** and **221**, respectively. The minor product **217** was hydrogenated to the B/C *cis*-fused keto alcohol **222**.[98]



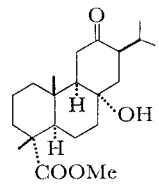
(218)



(219)



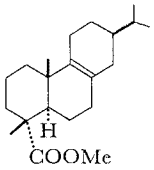
(220) : 13α isopropyl
(221) : 13β isopropyl



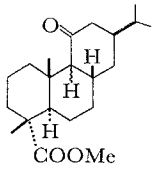
(222)

Methyl 13β-abiet-8(9)-en-18-oate (**223**) was oxidized by *t*-butyl chromate to give some products, the structure and stereochemistry of which were elucidated. Methyl 11-oxo-13β-abietan-18-oate (**224**) and its 9-epimer (**225**) were prepared. The hydroboration of **223** provided a simple route to the 7-oxygenated abietanes.[99]

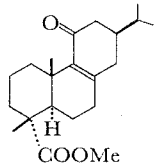
The reduction of methyl 11-oxo-13β-abiet-8(9)-en-18-oate (**226**) with Li in liquid ammonia gave the less stable B/C *cis*-fused methyl 11-oxo-8α,13β-abietan-18-oate



(223)



(224) : 9αH
(225) : 9βH



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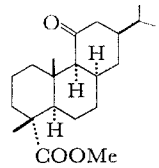
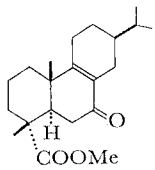
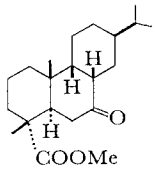


(227)

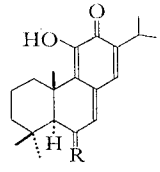
(**227**). The same reaction with methyl 7-oxo-13β-abiet-8(9)-en-18-oate (**228**) gave B/C *cis*-fused methyl 7-oxo-8β,9β,13β-abietan-18-oate (**229**). The absence of the parallelism between the reduction of these abietanes and their steroidal analogs is attributed to the lack of the ring D in the formers. The formation of **229** appears to come from the protonation of the most stable carbanion intermediate.[100]



(228)



(229)



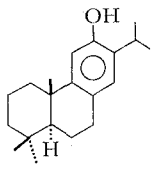
(230) : R=O
(231) : R=β-H, α-OH

Two novel diterpenoid quinone methide tumor inhibitors, toxodine (**230**) and taxodone (**231**), were isolated from *Taxodium distichum* and their structures were assigned as shown.[101]

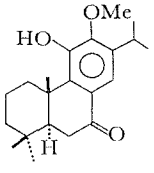
The diene reaction of levopimaric acid with cyclopentenone afforded an endo, *cis* adduct as major product and an exo, *cis* adduct in small quantity. The reaction of levopimaric acid with 1-cyclopentene-3,5-dione afforded a mixture of enolic endo, *cis* adducts. The structure and stereochemistry of these adducts were determined by photolytic methods and by correlating them with the product of a novel Favorskii reaction on the epoxide of the known levopimaric acid-benzoquinone adduct.[102]

Dehydroabietinol acetate was isolated for the first time from the neutral high boiling resins of ordinary pine trees by chromatography on silica gel with 12% $AgNO_3$.[103]

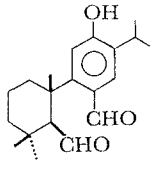
From the non steam volatile fraction of the methanol extract from the wood of *Juniperus rigida,* ferruginol (**232**), cryptojaponol (**233**), and a new diterpene aldehyde (**234**) were isolated.[104] Some reactions of dehydroabietic acid were investigated.[105]



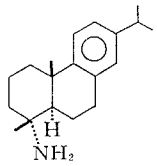
(**232**)



(**233**)

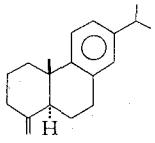


(**234**)

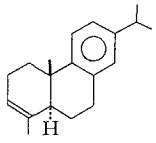


(**235**)

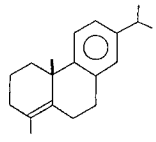
Deamination reaction of 19-norabieta-8,11,13-trien-4-amine (**235**), derived from dehydroabietic acid, with sodium nitrite in aqueous acetic acid afforded the products,



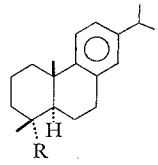
(**236**)



(**237**)

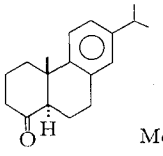


(**238**)

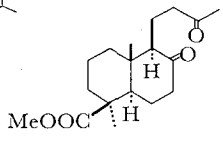


(**239**) : R=OAc
(**240**) : R=OH

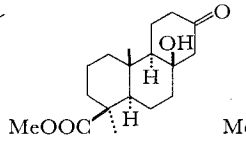
236 to **240**. A mixture of **236**, **237**, and **238** was treated with osmium tetroxide and sodium metaperiodate to yield the ketone **241**, which will be available for steroidal synthesis.[106]



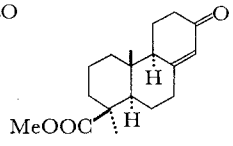
(**241**)



(**242**)



(**243**)



(**244**)

A full paper of the chemical conversion of enmein into enantio-abietane and total synthesis of abietane was published.[107]

The carbonyl and non-carbonyl fractions from the neutral part of the oleoresin of *Larix europaea* were separated. Chromic acid oxidation of the former fraction yielded dehydroabietic, isopimaric, pimaric, abietic, and neoabietic acids. In the latter fraction, 13-epi-manool was identified as its 3,5-dinitrobenzoate.[108]

The reaction of methyl abietate with monopernaphthalic acid in ether gave methyl 13,14-epoxyabietate, methyl 13,14-dihydroxy-7-oxoabietate, methyl 7,8,13, 14-tetrahydroxyabietate, and the new compounds, methyl 13,14-*trans*-dihydroxyabietate and methyl 7,8-epoxy-13,14-*trans*-dihydroxyabietate.[109]

Ozonolysis of dimethyl agathate (**94**) gave the diketone **242**, which was cyclized with base to give **243**. The ketol **243** on dehydration gave **244**. Reaction of **244** with isopropyl-magnesium bromide in ether and column chromatography of the product gave methyl abieta-7,13-dien-19-oate (methyl 4-epiabietate) (Me ester of **172**) and methyl abieta-8,13-dien-19-oate (methyl 4-epipalustrate) (Me ester of **173**). Dehydrogenation of the crude Grignard product, or dehydrogenation of mixtures of methyl 4-epiabietate and methyl 4-epipalustrate, gave methyl abieta-8,11,13-trien-19-oate, that is, methyl 4-epidehydroabietate.[110]

The functionalization of the isopropyl group of dehydroabietic acid was achieved by intramolecular cyclization of 12-carboxy-derivative **245**[111] with $Pb(OAc)_4$ and by thermolysis of diazomethyl ketone **246**, as shown in Chart 5.[112]

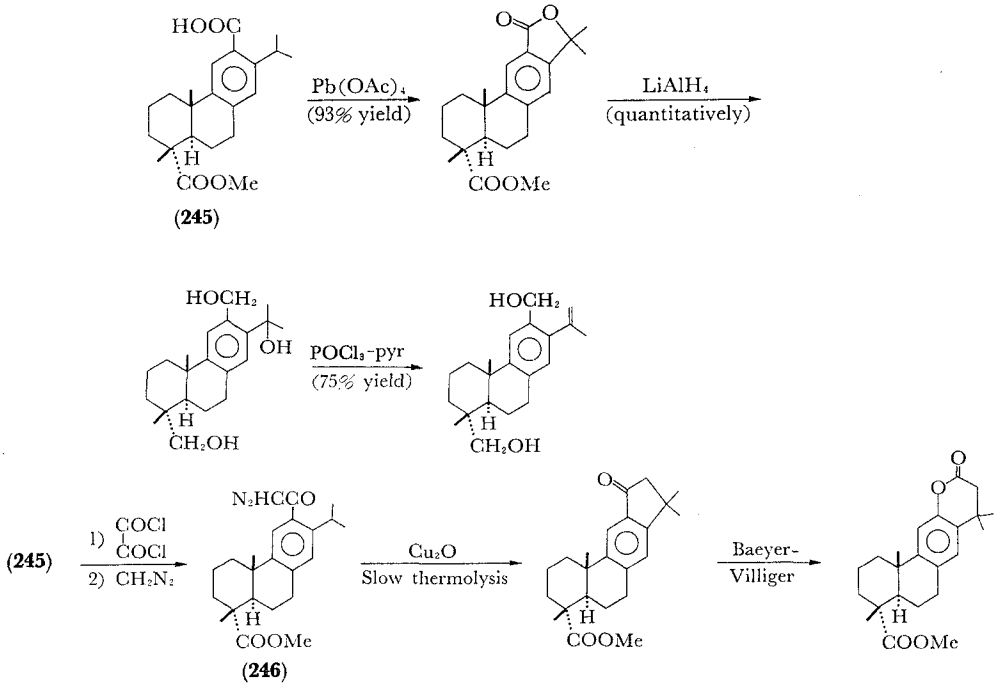
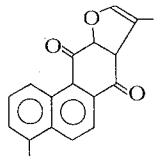
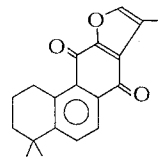


Chart 5

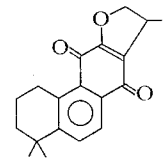
From the Chinese drug "tan-shen", the dried root of *Salvia miltiorrhiza*, tanshinone-I, -II, and cryptotanshinone had been isolated and characterized. Now, new com-



(247)



(248)



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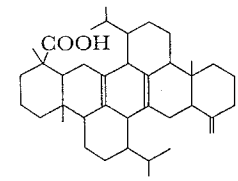


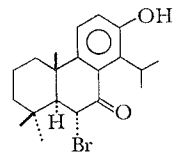
(250)

ponents, isotanshinone-I (**247**), -II (**248**), and isocryptotanshinone (**249**) were characterized as shown.[113]

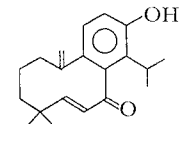
A sample of amber was investigated and the constitution was assumed to be dimerization product of abietic acid, as shown in **250**.[114]

VII. TOTARANE DERIVATIVES

6α-Bromo-13-hydroxytotara-8,11,13-trien-7-one (**251**) was treated with DMSO-$NaHCO_3$ to give a secoditerpenoid **252**. The monoepoxide derivative **253** of secoditerpenoid methyl ether was treated with sulfuric acid in acetone to afford a

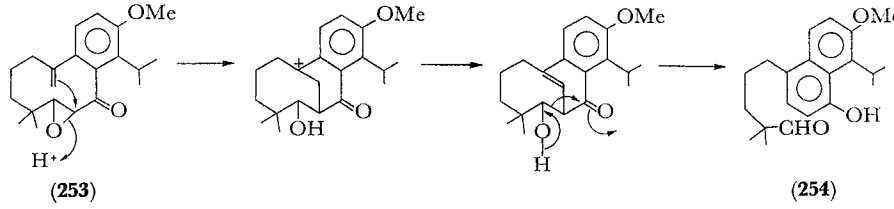


(251)



(252)

naphthalenic aldehyde **254** by transannular cyclization and heterolytic fragmentation reactions, as shown in Chart 6.[115]



(253) (254)

Chart 6

The methyl group attached to an aromatic ring was functionalized by decomposition of hypobromite of a tertiary benzylic alcohol in the *ortho* position to the methyl group to yield a cyclic ether. The examples are shown in Chart 7. The isopropyl group in totarane derivative **225** was not functionalized.[116]

The carbon-13 nuclear magnetic resonance (NMR) spectroscopy of naturally occurring substances was investigated, and the chemical shift data of non-protonated sites of terpenoids including totarol acetate, manool, and sclareol were described.[117]

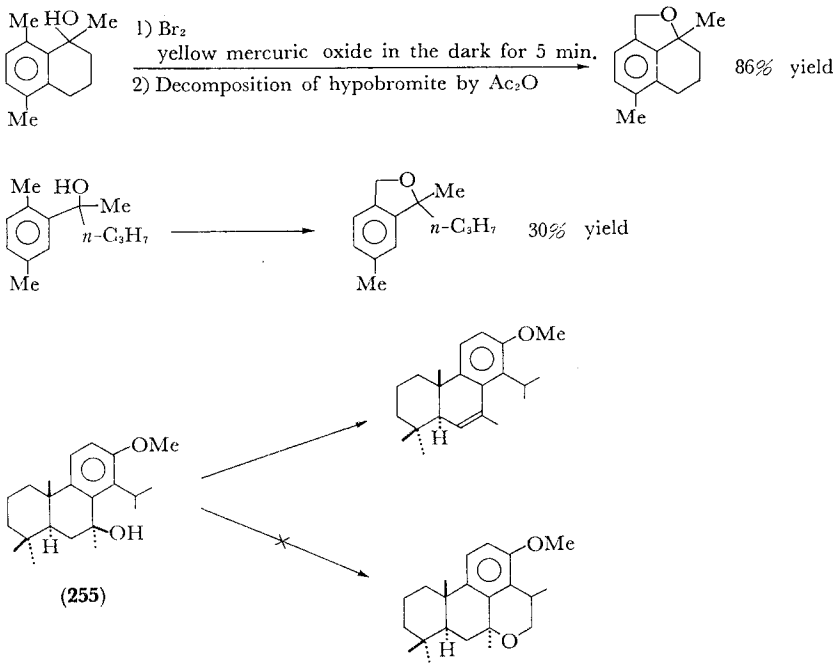
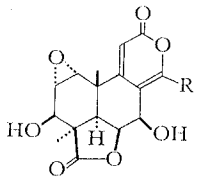


Chart 7

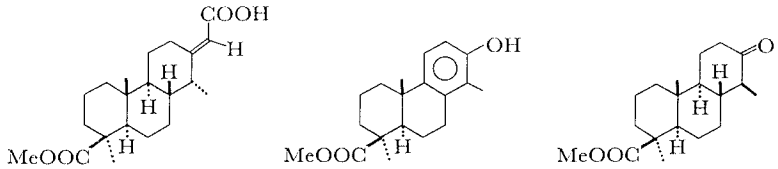
Nagilactones A, B, C, and D were isolated from *Podocarpus Nagi*. The seeds and leaves of *P. macrophyllus* yielded nagilactones A and C and inumakilactones. The structures, **256** and **257**, were assigned to nagilactones C and D, respectively.[118]



(**256**) : R=isopropyl
(**257**) : R=Et

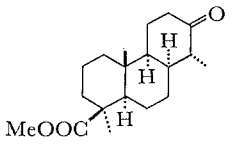
VIII. CASSANE DERIVATIVES*

The synthesis of the epimers of *rac*-7-desoxocassamic acid (**258**) (at C-8 and at C-14) was reported. The catalytic hydrogenation of the aromatic ring of methyl *rac*-13-

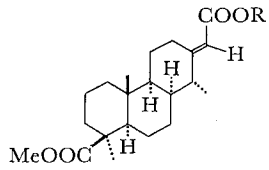


* See also Section II, ref. 22.

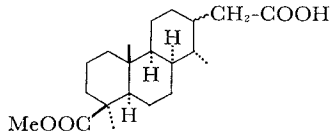
hydroxy-14-methyldesoxypodocarpate (**259**) gave the thermodynamically stable methyl *rac*-13-oxo-14β-methylpodocarpan-19-oate (**260**) and 13-oxo-14α-methyl-5α,8α,9α,10β-podocarpan-19-oate (**261**). The ketone **261** was treated with ethoxyethyne *via* a Grignard reaction and the corresponding ethoxyethynylcarbinol was isomerized



(261)



(262) : R=Et
(263) : R=H

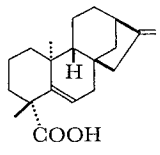


(264)

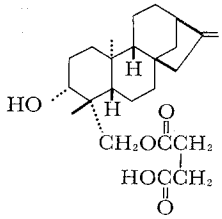
in the presence of dilute acid to give the ethyl ester **262**, whose alkaline hydrolysis afforded *rac*-7-desoxo-cassamic acid (**263**). Catalytic hydrogenation of **263** over Adams' platinum oxide in ethanol gave a new *rac*-7-desoxodihydrocassamic acid (**264**).[119]

IX. KAURANE DERIVATIVES*

From the flowers and leaves of *Espeletia schultzii*, grandifloric acid (**265**) was isolated.[120]



(265)



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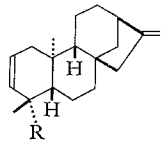


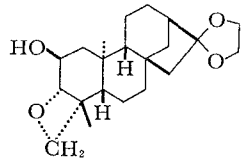
(267) : R=$CH_2OCOCH_2CH_2COOMe$
(268) : R=CHO
(269) : R=COOH
(270) : R=Me

The succinate **266** was esterified by diazomethane, then, treated with $POCl_3$ to give 2,16-diene **267**, which was converted into aldehyde **268** by a usual way. From the aldehyde (**268**), the carboxylic acid **269** and hydrocarbon **270** were derived. On the other hand, **267** was converted into *ent*-kaur-16-ene-2β,19-diol (**272**) *via* an oxetane **271**.[121]

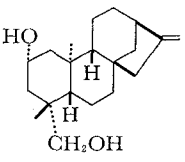
Three resin acids were isolated from *Espeletia Schultzii*, and their structures, **273**, **274**, and **275**, were clarified.[122]

Triketo-grayanotoxin-II and diketo-grayanotoxin-I, which were derived from grayanotoxins with chromic anhydride oxidation, were characterized as shown in **276**

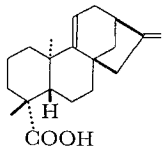
* See also Section III, ref. 40, Section VI, ref. 107 and Section XI, ref. 160a, b.



(271)



(272)



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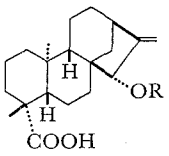
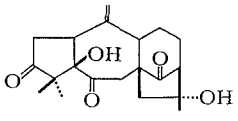
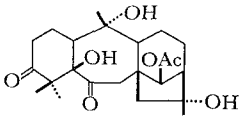


(274) : R=Ac
(275) : R=H

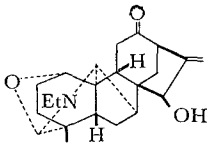
and **277**, respectively, on the basis of chemical and spectroscopic methods, especially of the IR spectra of their various derivatives.[123]



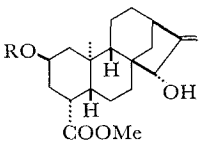
(276)



(277)



(278)



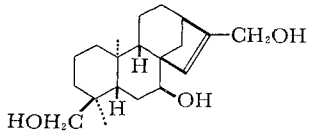
(279) : R=H
(280) : R=Me

Kaurenoic acid was isolated from *Enhydra fluctuans*.[124]

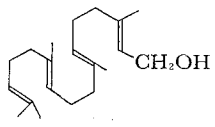
On the basis of the NMR and the mass spectra, the structure **278** was assigned to songoramine, a diterpene alkaloid.[125]

The crude glycosides from *Atractylis gummifera* were esterified with diazomethane and chromatographed on neutral alumina column to yield atractyligenin methyl ester (**279**) as a major product and 2-*O*-methylatractyligenin methyl ester (**280**) as a minor product.[126]

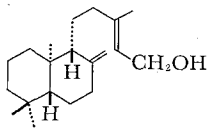
The residues of the petroleum ether and ether extracts of the corollas of *Sideritis sicula*, from which sideridiol, siderol, and siderosol had been separated previously, were chromatographed on activated alumina to give sideritriol (**281**).[127]



(281)



(282)

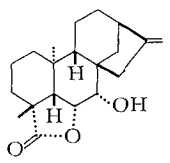


(283)

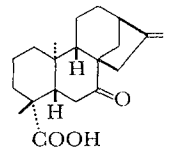
Geranylgeraniol (**282**) and *ent*-labda-8(17),13-dien-15-ol (**283**) pyrophosphate were shown to act as the precursors to *ent*-kaurene, the kaurenolides, and gibberellic acid. The possibility that *ent*-pimara-7,15-diene or *ent*-pimara-8(9),15-diene may act as a precursor to the foregoing diterpenoids was excluded by a biosynthetic experiment using 4-(R)-[4-^{3}H]- and 2-[$^3H_2$]-mevalonic acid with *Gibberella fujikuroi*. The hydroxylation of the ring A of gibberellins was shown to proceed under the retention of the original configuration. Moreover, it was shown that the loss of one carbon at C-20 in the formation of the C-19 gibberellins did not proceed *via* decarboxylation of the

β,γ-unsaturated carboxylic acid, that is, Δ^1-, Δ^5- or $\Delta^{9(11)}$- 20-carboxylic acid, but might probably occur *via* a Baeyer-Villiger-type oxidation of the C-20 carbonyl function.[128]

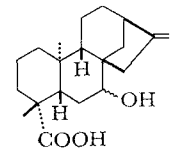
Sodium borohydride ($NaBH_4$) reduction of 7-oxokaurenolide afforded 7α-hydroxykaurenolide (**284**). Hydrogenolysis of 7-oxokaurenolide with calcium in liquid ammonia gave *ent*-7-oxo-16-kauren-19-oic acid (**285**), which on reduction with $NaBH_4$



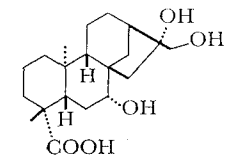
(**284**)



(**285**)



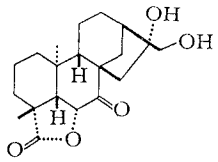
(**286**) : 7αOH
(**290**) : 7βOH



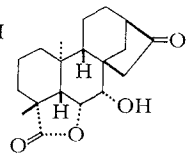
(**287**)

gave *ent*-7β-hydroxy-16-kauren-19-oic acid (**286**). Keto-acid **285** was treated with osmium tetroxide, then reduced with $NaBH_4$ to yield **287**, which was converted into 16-keto derivative by sodium metaperiodate.

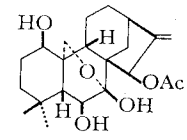
The Wittig reaction of the ketone also afforded **286**. Similarly, compound **288** on $NaBH_4$ reduction followed by sodium metaperiodate oxidation gave **289**. *ent*-



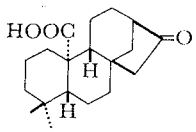
(**288**)



(**289**)



(**291**)

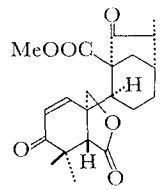


(**292**)

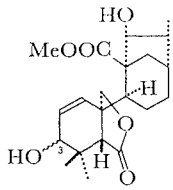
Oxokaurenoic acid **285** on Meerwein-Ponndorf reduction gave 7β- (**290**) and 7α-ol (**286**), which were separated by the preparative thin layer chromatography. The 7β-ol **290** on ozonolysis followed by Wittig reaction using the isotope gave 17-radioactive **290**.[129]

The structure and absolute configuration **291** of trichokaurin was established on the basis of chemical and spectroscopic evidence. The chemical conversion of trichokaurin into *ent*-16-oxo-17-norkauran-20-oic acid (**292**) was accomplished, which means the formal transformation of trichokaurin into *ent*-16-kaurene, atisine, garryine, and veatchine.[130] The preliminary communications had been published in 1967*.

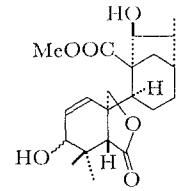
The reduction of ketone **293** with lithium tri-*t*-butoxy-aluminum hydride



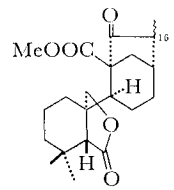
(**293**)



(**294**) : 3α-OH
(**295**) : 3β-OH



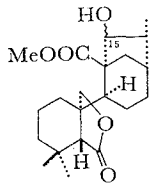
(**296**) : 3α-OH
(**297**) : 3β-OH



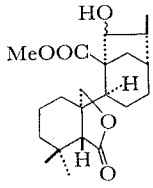
(**298**) : 16α-Me
(**303**) : 16β-Me

* See ref. 4.

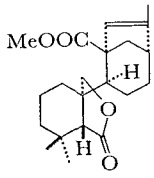
[LiAl (t-BuO)$_3$H] in absolute tetrahydrofuran (THF) gave alcohols **294** and **295**, while the reduction of ketone **293** with $NaBH_4$ in THF-H_2O gave an alcohol **296**. Alcohol **294** on weak alkaline treatment was epimerized to **296**. Similarly, alcohol **295** was epimerized to **297** under similar conditions. Ketolactone ester **298** was reduced with LiAl (t-BuO)$_3$H in anhydrous solvent to give alcohol **299**, while it was reduced with



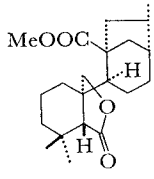
(**299**) : 15α-OH
(**300**) : 15β-OH



(**301**) : 15β-OH
(**302**) : 15α-OH



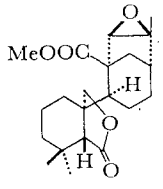
(**304**)



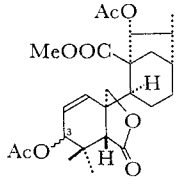
(**305**)

$NaBH_4$ in aq. methanol to give alcohol **300**. Alcohol **299** was epimerized to **300** in weak alkaline conditions. Two other epimeric alcohols **301** and **302** were derived from **300** *via* a series of reactions. Alcohol **301** was epimerized to **302** by treatment with weak alkali, although the reaction was much slower.[131]

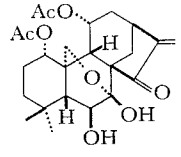
Silica gel thin-layer chromatography of several epimeric enmein derivatives, (that is, Group 1 : **299**, **300**, **301**, **302**, **298**, **303**, **304**, **305**, **306**; Group 2 : **296**, **297**, **294**, **295**, **293**, **307**, and **308**) was investigated. Compounds possessing a β-OH group at C-15 were shown to be more easily adsorbed than compounds possessing an α-OH group at C-15. The unfavorable influence of C-16β methyl group for adsorption was recognized. The most favorable effect for adsorption was proved by C-3 α equatorial OH among the compounds of Group 2.[132]



(**306**)



(**307**) : 3β-OAc
(**308**) : 3α-OAc

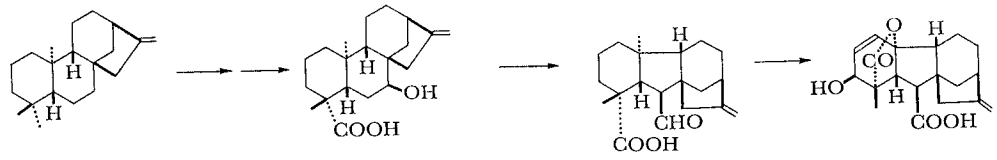


(**309**)

Two bitter diterpenes were isolated from *Isodon shikokianus*. One of them was the known oridonin, and the other was a new kaurene derivative **309** and named shikokianin.[133]

Dilution analysis method recognized the incorporation of *ent*-16-kaurene into *ent*-7α-hydroxy-16-kauren-19-oic acid (**290**) in *Gibberella fujikuroi*. The incorporations of **290** into the aldehyde **310** was also recognized by the dilution analysis. Moreover, **290** was incorporated after 5 days into gibberellin A_3 in a high ratio. Thus, the biosynthetic route shown in Chart 8 was supported.[134]

The key intermediates, **311** and **312**, in the total synthesis of tetracyclic diterpenes



(290) **(310)**

Chart 8

were elegantly synthesized by Beames and Mander.[135] The outline is shown in Chart 9.

The similar synthetic approach to tetracyclic diterpenoids was reported. This report was also based on the intramolecular carbene insertion reaction and subsequent cleavage of the cyclopropane ring. Thus, diazoketone **313** was converted into **315** *via* **314**. Quite similarly, **316** was converted into **317**. Catalytic hydrogenations of **315** and **317** were also carried out.[136]

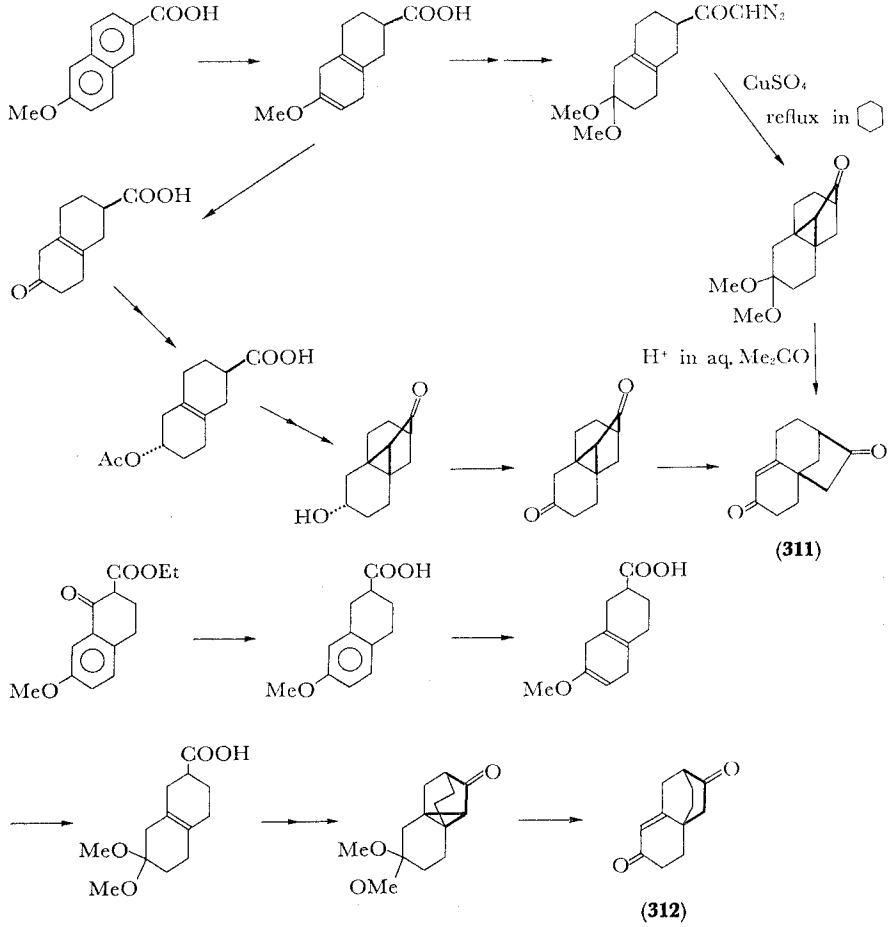
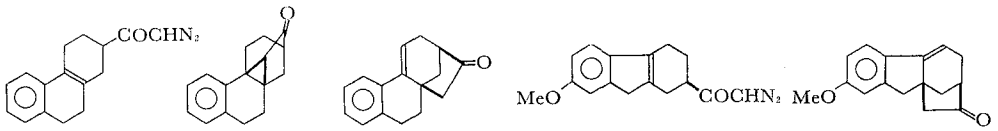
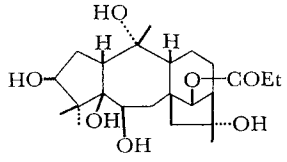


Chart 9

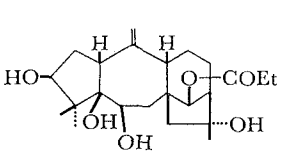


(313) (314) (315) (316) (317)

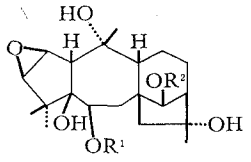
Asebotoxin-I and -II, toxins of *Pieris japonica*, were investigated and structures, **318** and **319**, were presented, respectively.[137]



(318)



(319)

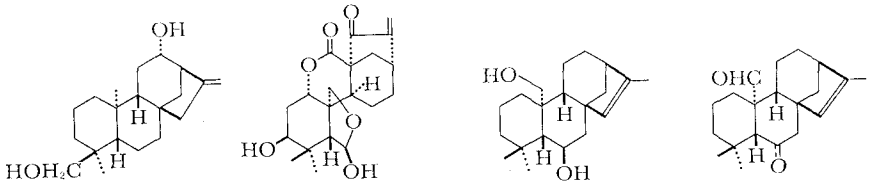


(320): $R^1=R^2=Ac$
(321): $R^1=Ac$, $R^2=H$
(322): $R^1=R^2=H$
(323): $R^1=H$, $R^2=C(=O)-CH(OH)-CH_3$

Structures of rhodojaponin-I, (**320**), -II (**321**), and -III (**322**), toxins of *Rhododendron japonicum*, and of Asebotoxin-III (**323**), a toxin of *Pieris japonica*, were clarified as shown.[138] They were correlated with each other.

From the dried fruits of *Xylopia aethiopica*, xylopic acid had been isolated and its structure elucidated.[5] Now, further five kaurane diterpenes—*ent*-kauran-16β-ol, *ent*-16-kauren-19-oic acid, *ent*-15α-hydroxy-16-kauren-19-oic acid, *ent*-kaurane-16β, 19-diol, and *ent*-15-oxo-16-kauren-19-oic acid were isolated.[139]

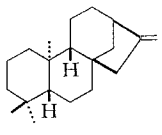
Isolation of candicandiol, a new diterpene, from *Sideritis candicans*, and the elucidation of its structure **324** were reported.[140]



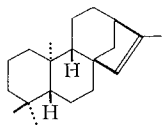
(324) (325) (326) (327)

In the stems and the leaves of *Aralia cordata*, as well as in the roots, *ent*-16-kauren-19-oic acid was contained.[74]

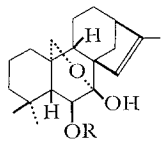
Previously, enmein (**325**) was converted into *ent*-kaurane.[2,3] Now, the former **325** was transformed into *ent*-15-kaurene (**329**) and *ent*-16-kaurene (**328**). The diol **326**, derived from enmein, on oxidation gave keto-aldehyde **327**, which was heated with anhydrous hydrazine and sodium to give a mixture of *ent*-16-kaurene (**328**) and *ent*-15-kaurene (**329**). They were effectively separated by a column chromatography on



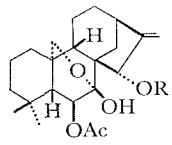
(328)



(329)



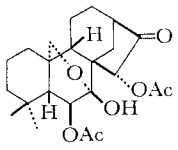
(330) : R=H
(331) : R=Ac



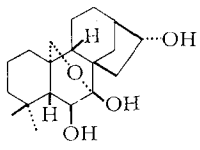
(332) : R=H
(333) : R=Ac

silica gel containing 2.5% of silver nitrate. On the other hand, the Nagata's modification of Wolff-Kishner reduction of **327** gave *ent*-kaurane.[141]

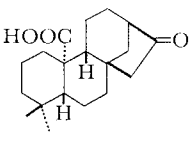
Subsequently, enmein (**325**) was converted into 7-hemiketal **330**, whose acetate **331** in pyridine was photo-chemically oxygenated with oxygen gas using haematoporphyrin as sensitizer to give an allyl alcohol **332**. The acetate **333** of the latter was subjected to ozonolysis to yield 16-ketone **334**, which was finally subjected to hydrogen-



(334)



(335)



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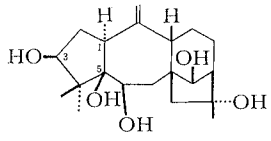
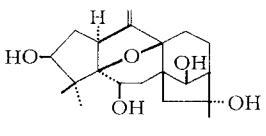


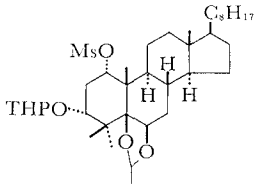
(337)

olysis with an excess amount of calcium in liquid ammonia to afford the known hemiketal diol **335**. This compound had been converted into the keto-acid **336**. Since **336** had further been converted into *ent*-kaurene, atisine, garryine, and veatchine, a formal chemical conversion of enmein into the latter diterpenoids was performed.[142]

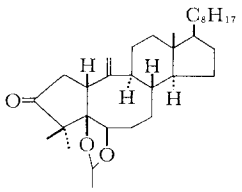
A chemical evidence for the configuration of C-1 α-hydrogen and C-5 β-hydroxy group in grayanotoxin-II was presented, as shown in formula **337**.[143] This communication described the chemical conversion of grayanotoxin-II (**337**) into **338** and its tetra-acetate.



(338)



(339)



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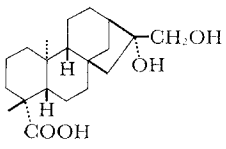


(341)

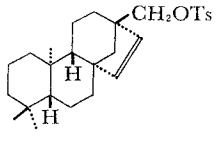
A synthesis of a *cis* perhydroazulene derivative **340** related to grayanotoxin from 4,4-dimethylcholest-1,5-dien-3-one *via* **339** through many steps of reactions was published.[144]

From *Siegesbeckia pubescens*, the known *ent*-16,17-dihydroxy-kauran-19-oic acid (**341**) was isolated.[75]

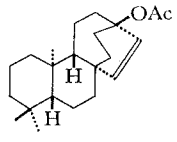
X. BEYERANE DERIVATIVES

The toluene-*p*-sulfonates, **342** and **345**, were solvolyzed in buffered acetic acid. The former **342** led to approximately equal amounts of bridgehead acetates **343** and **344**, while the latter **345** gave **346** and **347**. The rate of solvolysis of **345** was twelve times greater than that of neopentyl tosylate at 100°. The possible reaction paths were discussed.[145]

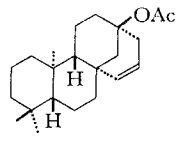
The formolysis of [14-^{14}C]-isomanool (**348**) was found to lead to [14-^{14}C]-beyeran-14α-ol formate **349**. This finding is compatible with only scheme B mechanism in Chart 10.[146]



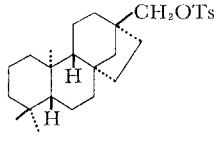
(**342**)



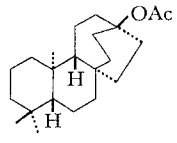
(**343**)



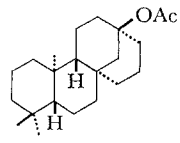
(**344**)



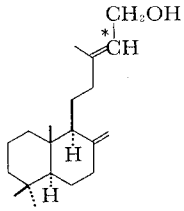
(**345**)



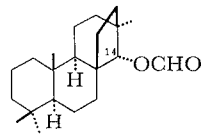
(**346**)



(**347**)



(**348**)



(**349**)

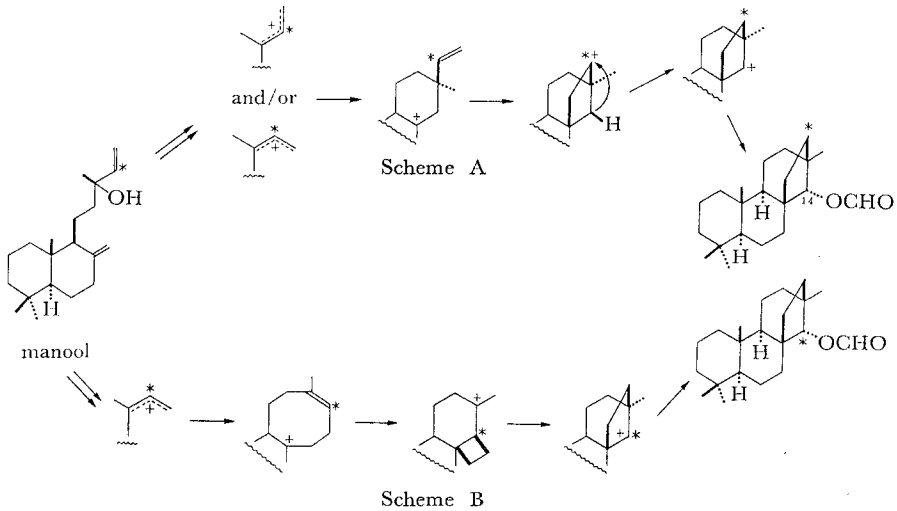
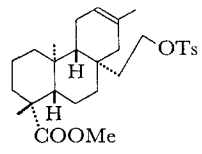


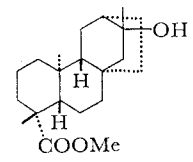
Chart 10

The quite same conclusion was presented by another group on the basis of an experiment using **348** labelled by D at C-14.[147]

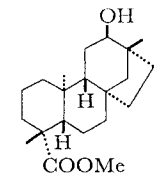
Solvolytic cyclization of the unsaturated tricyclic toluene-*p*-sulfonate **350** afforded the atisan-13-ol derivative **351**, which at higher temperature underwent Wagner-Meerwein rearrangement to the *ent*-beyeran-12-ol derivative **352**.[148]



(350)



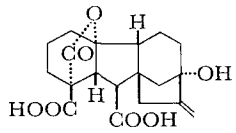
(351)



(352)

XI. GIBBERELLANE DERIVATIVES*

Two novel gibberellins, GA_{21} and GA_{22}, were isolated from immature seeds of sword bean, *Canavalia gladiata*. The isolation procedure of these substances as well as their growth-promoting effects on dwarf maize mutants d_1 and d_5, rice, cucumber and dwarf peas (Progress No. 9) were described.[149]



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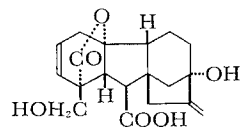
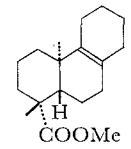
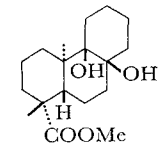


(354)



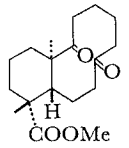
(355)



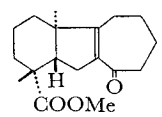
(356)

The structures of two new gibberellins, GA_{21} and GA_{22}, isolated from immature seeds of sword bean, were determined as **353** and **354**, respectively, on the basis of chemical and physicochemical studies.[150]

C-Homohydrofluorene **358** was synthesized by opening of the B/C ring juncture of $\Delta^{8(9)}$-unsaturated ester **355**, derived from abietic acid, *via* glycol **356** to diketone **357**



(357)



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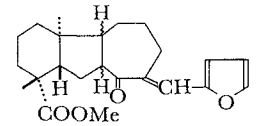
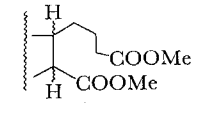


(359)



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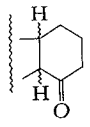
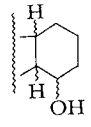
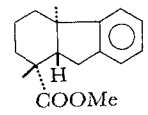


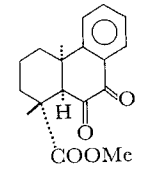
(361)



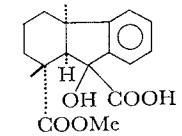
(362)



(363)



(364)

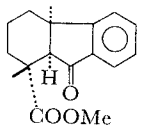


(365)

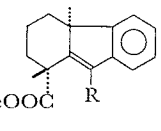
* See also Section IX, refs. 128, 134, and 136.

and successive ring closure of the latter.[151] Subsequently, **358** was converted into a C-aromatic hydrofluorene derivative **363** *via* **359**, **360**, **361**, and **362**.[152]

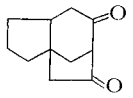
Hydrofluorene **365** previously derived from *cis*-dioxo ester **364** by its alkaline treatment had been assumed to have the *cis*-A/B-ring fusion without any reliable evidence. Now, comparison of this compound (**365**) and its derivative **366** with **363**



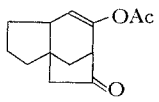
(366)



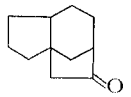
(367) : R=OAc
(368) : R=H



(369)



(370)



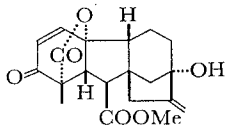
(371)

confirmed the assumption to be correct. On the other hand, the catalytic hydrogenation of $\Delta^{5(6)}$-hydrofluorenes, **367** and **368**, was investigated. The stereochemical analysis in hydrogenation was done and the ratio of the *cis*- and *trans*-products was examined under various conditions.[153]

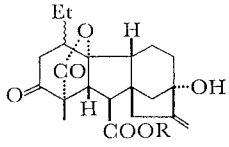
A new rice seedling test for gibberellins, "microdrop method", was described.[154] A review on gibberellins in immature seeds of morningglory was published.[155] (The both reviews were published in Japanese.)

Stereoselective synthesis of the tricyclic systems, **369**, **370**, and **371**, similar to the B/C/D rings in gibberellins, from 4-acetoxy-cyclohexanone was published.[156]

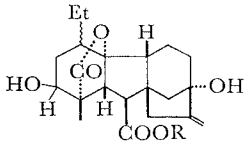
Treating triethylborane in THF with **372** in an inert atmosphere gave a mixture of **373** and **374**. Reduction of the mixture with $NaBH_4$ in aqueous dioxane gave the mixed diols, **375** and **376**, the former of which was isolated after separation on silica gel.[157]



(372)

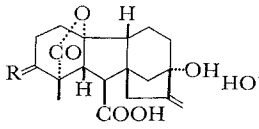


(373) : R=Me
(374) : R=Et

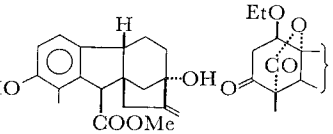


(375) : R=Me
(376) : R=Et

Methyl dehydrogibberellate (**372**) was reduced with $NaBH_4$ in aqueous dioxane to yield 3α-hydroxy- and 3α-hydroxy-1,2-dihydro-derivatives. Lithium borohydride reduction of **372** in dry THF at 0° yielded the latter derivative alone. Hydrogenation of methyl gibberellate and 3-epigibberellic acid over 15% Pb-C in ethyl acetate afforded

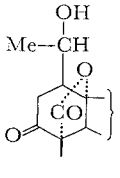


(377) : R=O
(378) : R=α-H, β-OH

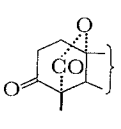


(379)

(380)



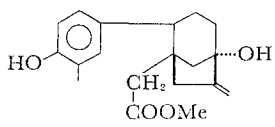
(381)



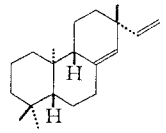
(382)

16,17-dihydro-derivatives of each compound. In both cases a pair of possible epimers was formed. 1,2-Dihydro-dehydrogibberellic acid (**377**) was treated with $LiAlH_4$ in *t*-butanol and THF to give gibberellin A_1 (**378**) and its 3-epimer.[158]

The UV illumination of **372** in benzene resulted in fairly slow reaction and formation of 14% of **379**, along with more polar products. The same product **379** was formed up to 16% yield after illumination of **372** in ethanol also, but in this case there were also formed 6% of **380** and 15% of **381**. Unlike this, **372** illuminated in benzylalcohol gave up to 15% of **382**, along with the main product (60%) secophenol **383**.[159]



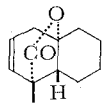
(383)



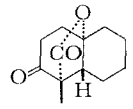
(384)

Geranylgeraniol (**282**) and *ent*-labda-8(17),13-dien-15-ol (**283**) pyrophosphate[160] were shown to act as precursors of *ent*-16-kaurene, the kaurenolides, and gibberellic acid. The labelling pattern from 4- (R)-[4-^{3}H]- and 2-[$^3H_2$]-mevalonic acid in these tetracyclic diterpenes was determined and this evidence was used to exclude *ent*-pimara-7,8- and- 8,9-dienes from the biosynthesis. *ent*-Pimara-8(14)-15-diene (**384**) was shown to be specifically incorporated into the kaurenolides and gibberellic acid. The stereochemistry of hydroxylation of ring A of gibberellins was shown to proceed with retention of configuration. The loss of angular C-20 atom in the formation of the C-19 gibberellins did not involve the decarboxylation of a 1-, 9(11)-, or 5-unsaturated acid.[128]

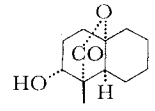
Analogs of ring A of the gibberellins, for instance **385**, **386**, and **387**, were synthesized.[161]



(385)

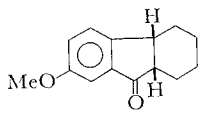


(386)

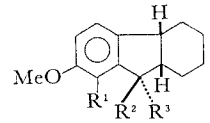


(387)

The known methoxyhexahydrofluorenone **388** was converted into acids **389** to **392**. The selective lithium-hydrogen exchange and subsequent carbonation reactions were



(388)



(389) : $R^1=R^2=H$, $R^3=COOH$
(390) : $R^1=R^3=H$, $R^2=COOH$
(391) : $R^1=R^3=COOH$, $R^2=H$
(392) : $R^1=R^2=COOH$, $R^3=H$

effectively applied to introduce the carboxyl functions. Their examples are shown in Chart 11.[162]

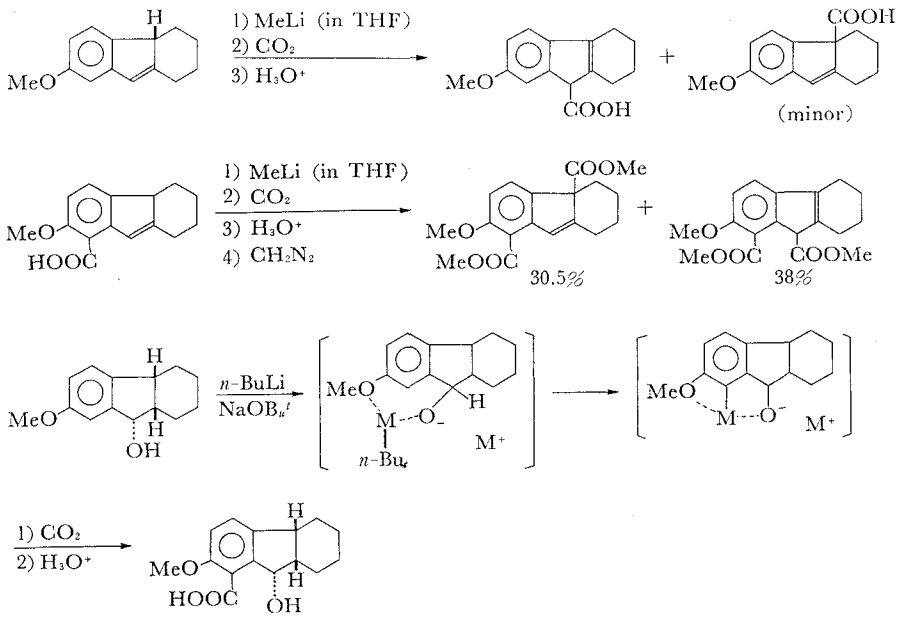


Chart 11

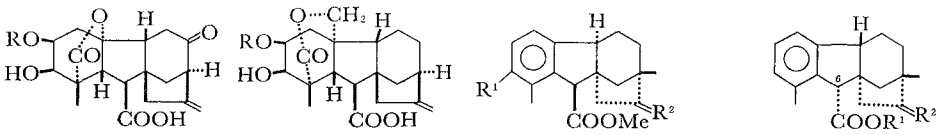
A very short introduction on the biosynthesis of the kaurenolides and gibberellic acid was published in Japanese.[163]

Addition of (2-chloroethyl)-trimethylammonium chloride and Amo-1618 [2′-isopropyl-4′-(trimethylammonium chloride)-5′-methylphenylpiperidine-1-carboxylate] to growing cultures of *Gibberella fujikuroi*, at the beginning of the gibberellic acid production phase, almost completely suppressed the biosynthesis of gibberellic acid and of the diterpenes *ent*-16-kaurene, 7-hydroxykaurenolide, and 7,18-dihydroxykaurenolide.[164]

Line diagrams of combined gaschromatography—mass spectrometry low resolution mass spectra were presented for the methyl esters of gibberellins A_1 to A_{24} and for the trimethylsilyl ethers of the methyl esters of the hydroxylated gibberellins A_1 to A_8, A_{10}, A_{13}, A_{14}, and A_{16} to A_{23}. These reference spectra allow conclusive identification of the presently known gibberellins without access to authentic specimens.[165]

Gibberellins and α-amylase formation in germinating barley were investigated.[166]

Two new gibberellins A_{26} (**393**) and A_{27} (**394**) and their glucosides (**395** and **396**)

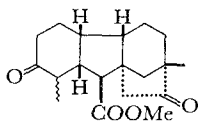


(**393**) : R=H (**394**) : R=H (**397**) : R^1=OH, R^2=O (**398**) : R^1=Me, R^2=O
(**395**) : R=β-glucosyl (**396**) : R=β-glucosyl (**399**) : R^1=H, R^2=H,H (**400**) : R^1=Me, R^2=H,H
(**401**) : R^1=H, R^2=O

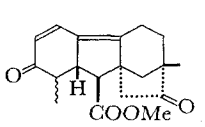
were isolated from the immature seeds of *Pharbitis nil*.[167a,b] They exhibited only slight growth-promoting activities on seedlings of rice, dwarf maize and cucumber.[167b]

Methyl 3-hydroxygibberate (**397**) was derived from methyl gibberate through nitration, reduction, diazotization and hydrolysis. The same sequence of reaction was applied to methyl *rac*-gibberate, the C-6 epimer (as **398**) of methyl *rac*-epigibberate, methyl deoxogibberate (**399**), and methyl *rac*-deoxoepigibberate (as **400**) to yield the corresponding 3-hydroxy derivatives. Catalytic hydrogenation of 3-hydroxy gibberellanes with aromatic ring A to saturated gibberellanes was also investigated.[168]

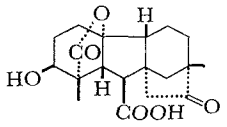
The formal total syntheses of some C_{19}-gibberellins in racemic form were published in detail.[169] They consisted of the following steps : (i) Synthesis of *rac*-epigibberic acid (**401**). (ii) Synthesis of a *rac*-dioxo-ester **402** from **401**. (iii) Conversion of optically active dioxo-ester **402** into dienone **403**. (iv) Partial synthesis of gibberellin C (**404**) from **403**. (v) Conversion of **404** into gibberellin A_4 (**405**) which had been transformed into gibberellins A_2, A_9, and A_{10}.



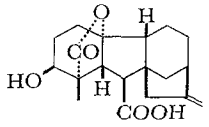
(402)



(403)

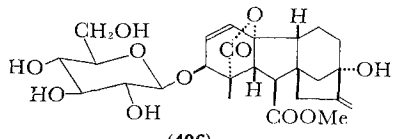


(404)

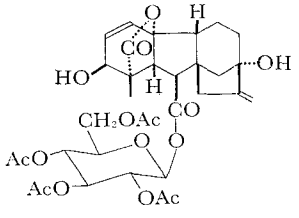


(405)

O(2)-β-D-Glucopyranosyl-gibberellin A_3 methyl ester (**406**) was prepared from gibberellin A_3 methyl ester and α-acetobromoglucose by Koenigs-Knorr synthesis followed by deacetylation. The reaction of gibberellin A_3 with α-acetobromoglucose yielded tetraacetyl-β-D-glucopyranosyl ester **407**.[170]



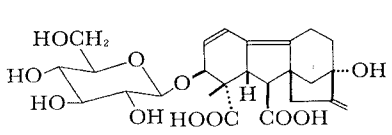
(406)



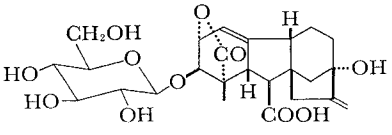
(407)

The stereospecific labelling of the gibberellins and the kaurenolides with 2(R) and 5(R)-[^{3}H] mevalonate led to the conclusion that the dehydrogenation of ring A was a *cis*-elimination of hydrogen from the α face of a saturated gibberellin and that hydroxylation of ring B to form the kaurenolides must take place with retention of configuration at C-6 and C-7 of the kaurene skeleton. The ring-contraction to form the gibberellins which takes place at the aldehyde oxidation level, results in the loss of 5(R)-mevalonoid hydrogen from C-6. This suggests that the leaving group which iniciates ring contraction possesses the 6β-stereochemistry.[171]

Structures of new gibberellin glucosides, F-II (**408**), F-III (**409**), F-IV (**396**), and F-VI (**397**), in immature seeds of *Pharbitis nil* were assigned as shown.[172]



(408)



(409)

A facile route to *cis*-hexahydrofluorene-2,9-dione and its 7-methoxy analog was developed. The route is shown in Chart 12.[173]

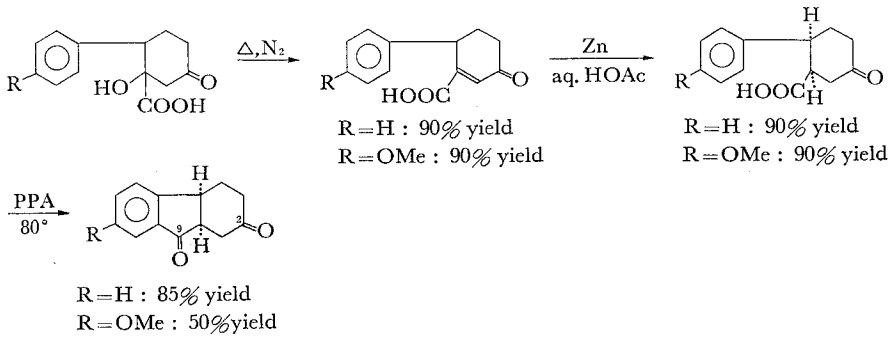
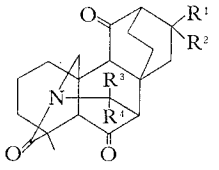


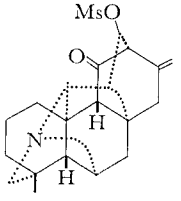
Chart 12

XII. ATISANE DERIVATIVES*

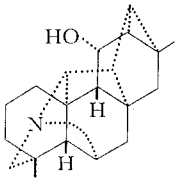
Spireine isolated previously from Spireae was shown by IR and NMR spectra and chemical evidence to be **410** or **411**.[174]



(**410**) : R^1,R^2=CH_2, R^3=Me, R^4=OH
(**411**) : R^1=Me, R^2=OH, R^3,R^4=CH_2

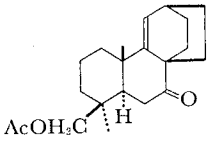


(412)

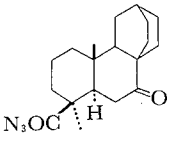


(413)

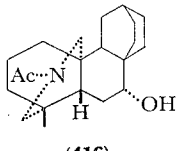
The reduction of a hetisine derivative **412** with $LiAlH_4$ yielded a novel rearrangement product, whose structure was determined to be **413** by single-crystal X-ray diffraction studies.[175]



(414)



(415)

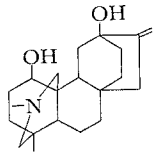


(416)

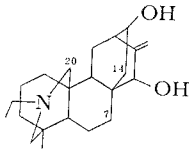
* See also Section X, ref. 148.

A degradation product **416** of ajaconine was synthesized from podocarpic acid *via* **414** and **415** through a series of reactions.[176]

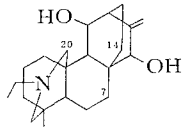
Denudatine was isolated and its structure **417** assigned previously by Singh *et al.*[177a]



(**417**)

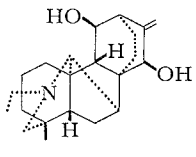


(**418a**) : $C_{20}-C_{14}$ or $C_{20}-C_7$

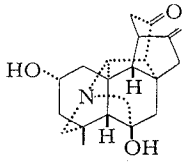


(**418b**) : $C_{20}-C_{14}$ or $C_{20}-C_7$

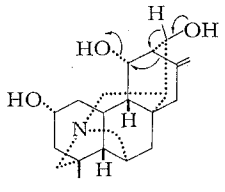
was revised by Wiesner *et al.*[177b] to **418a** or **418b**. The X-ray analysis by Brisse[178] determined its structure and absolute configuration to be **419**.



(**419**)



(**420**)

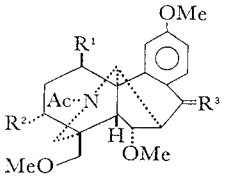


(**421**)

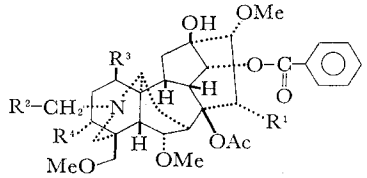
The X-ray crystal structure of delnudine, a novel alkaloid, was shown to be **420**.[179] This alkaloid was isolated from the seeds of *Delphinium denudatum* and characterized, and its biogenesis from hetisine (**421**) was assumed as shown.[180]

XIII. ACONANE DERIVATIVES

The compound **422** was synthesized as a model compound for the synthesis in the series of aconitine and delphinine.[181]



(**422**) : $R^1=R^2=H$, $R^3=O$
(**423**) : $R^1=OMe$, $R^2=OH$, $R^3=O$
(**424**) : $R^1=R^2=H$, $R^3=H,H$

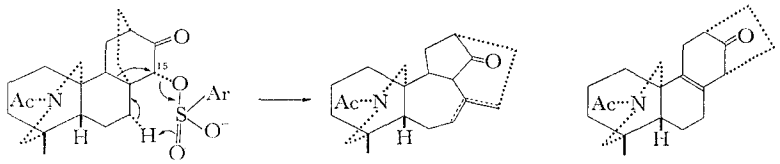


(**425**) : $R^1=OH$, $R^2=Me$, $R^3,R^4=OMe,OH$
(**426**) : $R^1=R^2=H$, $R^3,R^4=OMe,H$

Aconitine degradation product **423** was converted into the previously synthesized compounds **422** and **424**, thus providing a complete chemical proof of structures for aconitine (**425**) and delphinine (**426**).[182]

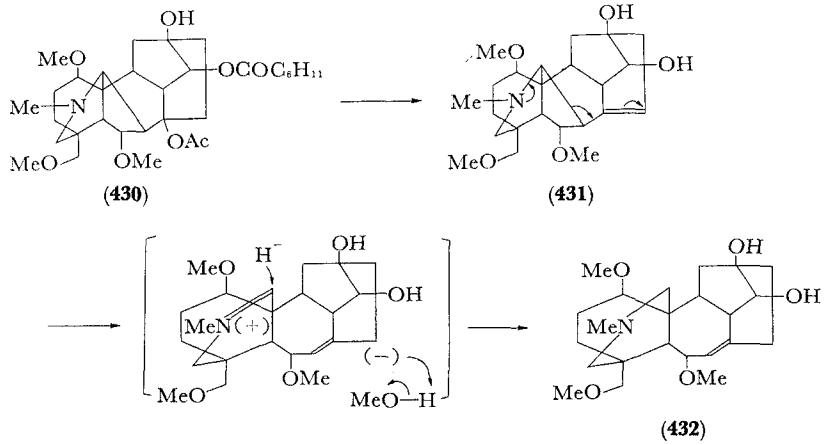
Stereospecific skeletal rearrangements during the pyrolysis of epimeric toluene-*p*-sulfonates were reported. The 15α-*O*-tosylate **427** of atisane skeleton was subjected

to pyrolysis to afford an aconane-type product **428**. On the other hand, 15β-*O*-tosylate on pyrolysis yielded **429**. Acetolysis of 15α- and 15β-*O*-tosylates gave a same product **429**.[183]



(427) **(428)** **(429)**

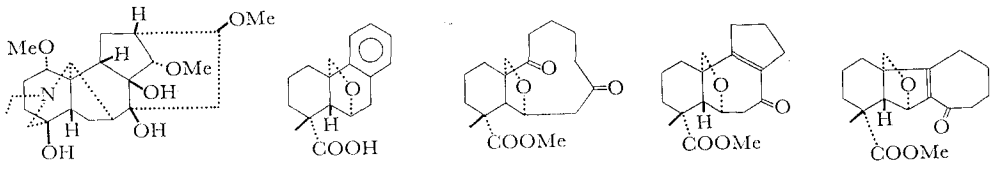
The product **431** derived from **430** by pyrolysis followed by alkaline hydrolysis, dissolved in methanol, was irradiated at 0° with quartz mercury vapor lamp in the presence of an excess of $NaBH_4$ to yield **432**. The mechanism was proposed as shown in Chart 13, which proved to be correct by $NaBD_4$ experiment.[184]



(430) **(431)** **(432)**

Chart 13

The characterization[185] of lappaconine, an aconane alkaloid, and the X-ray structure analysis[186] of its crystalline hydrobromide led to a final elucidation of structure and absolute configuration **433**.



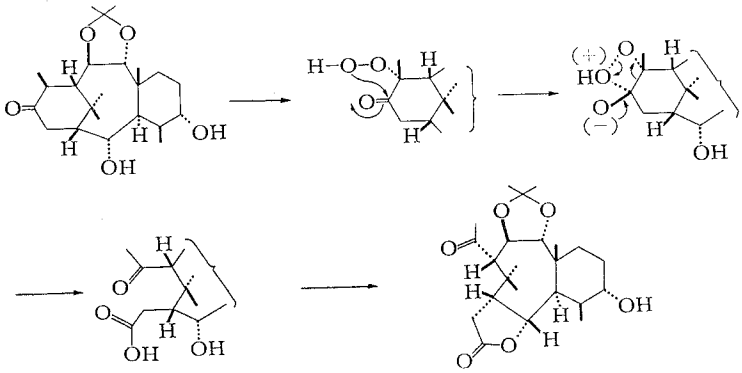
(433) **(434)** **(435)** **(436)** **(437)**

Skeletal transformation of a podocarpane derivative into an aconane-like derivative was attempted. The compound **434**, derived from abietic acid, was converted into

435, which on acidic treatment gave **436** and **437** in a ratio of 4 to 1. The *cis* β-dihydro derivative was prepared from **436** by hydrogenation.[187]

XIV. TAXANE DERIVATIVES

The stereochemistry of isopropylidene dihydrotaxinolactone, a novel autooxidation product of isopropylidenedihydrotaxinol, was proposed to be represented as **438**. The mechanism was presented as shown in Chart 14.[188]

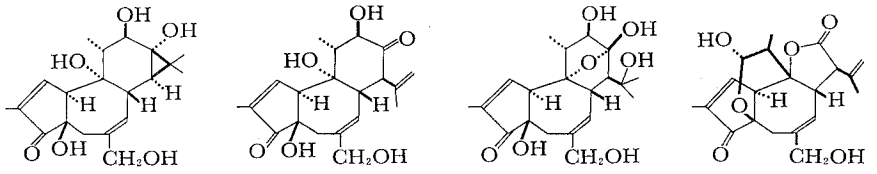


(438)

Chart 14

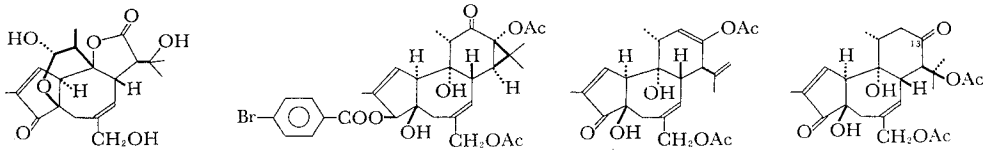
XV. THE OTHERS

Oxidation of phorbol (**439**) with one mole of sodium periodate in aqueous solution yielded tiglophorbol, bisdehydrophorbol (**440**), and hydroxybisdehydrophorbol-hemiketal (**441**) as the main products. Together with tiglophorbol, **442** and **443** were endproducts of the oxidation of phorbol with two moles of sodium periodate.[189]



(439) **(440)** **(441)** **(442)**

Nine kinds of heavy atom-bearing derivatives of phorbol were prepared. Single crystal for X-ray structural analysis was obtained from 3-*O*-(*p*-bromobenzoyl)-

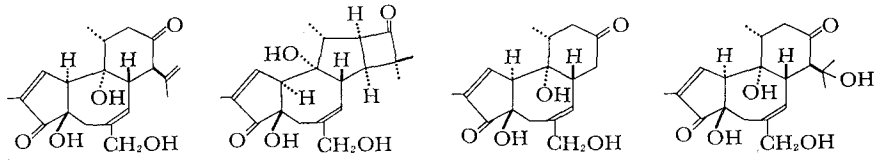


(443) **(444)** **(445)** **(446)**

neophorbol-13,20-diacetate (**444**). The structure **439** of phorbol was derived from the structure and absolute configuration of **444** as revealed by X-ray analysis on the basis of the known chemistry of the functional groups and on NMR data.[190]

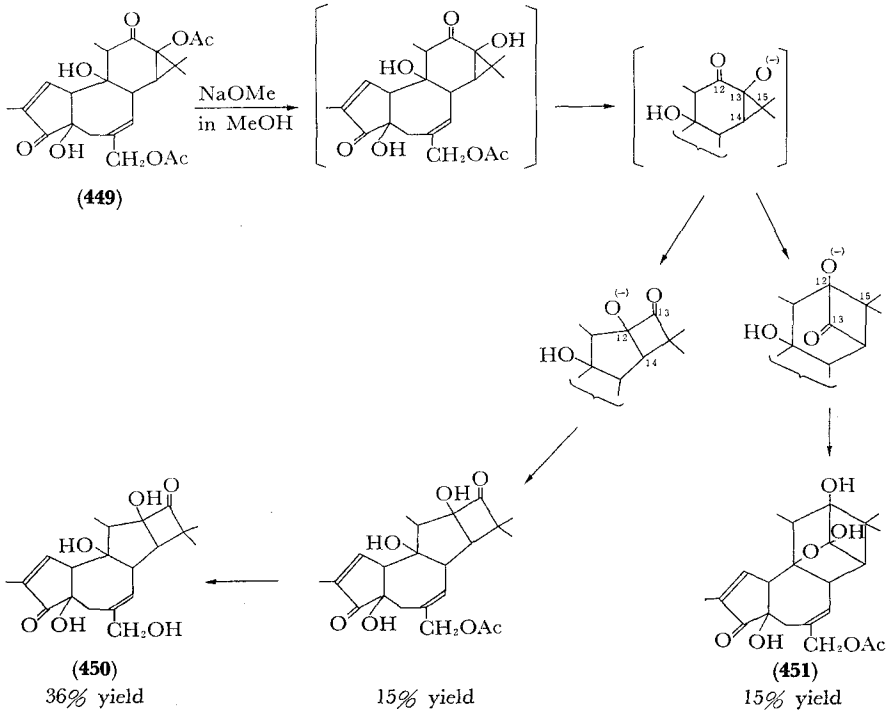
Reaction of phorbol-13,20-diacetate with mesyl chloride in pyridine induced a homoallyl rearrangement of the α-(acetoxy-cyclopropyl)-carbinol group yielding crotophorbolone-enol-13,20-diacetate (**445**) and acetoxy-crotophorbolone-20-acetate (**446**). The latter was generated from the former by an intramolecular migration of acetyl group in 13-position. By base catalyzed transesterification **445** was converted to crotophorbolone (**447**).[191]

Dehydration of phorbol-20-monoacetate or phorbol-20-tritylether with phosphoryl chloride in pyridine yielded phorbobutanone-20-monoacetate or -20-tritylether, re-



(447) **(448)** **(452)** **(453)**

spectively. From tritylether, phorbobutanone (**448**) was prepared. Phorbobutanone is one of the products obtained from phorbol (**439**) with 0.02 N sulfuric acid. Its structure and stereochemistry **448** was derived from NMR- and CD-measurements of



(449)

(450) 36% yield

15% yield

(451) 15% yield

Chart 15

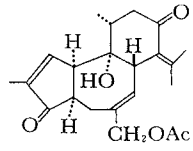
itself and its derivatives and from mechanistic considerations of the phorbol rearrangement involving the α-(hydroxycyclopropyl)-carbinol group.[192]

The formation of the rearranged acyloins, **450** and **451**, from 12-desoxy-12-oxophorbol-13,20-diacetate (**449**) was reported. The mechanism is shown in Chart 15.[193]

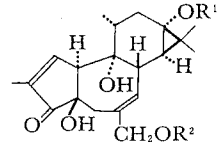
Reaction of phorbol with boiling 0.02 N H_2SO_4 (Flaschenträger-reaction) essentially yielded four products in an over all yield of 78% and acetone. These are crotophorbolone (**447**), phorbobutanone (**448**), **452**, and **453**.[194]

The diterpene parent of the tumor promotors from *Croton* oil was shown to be phorbol and the structure determination of its solvate was reported.[195]

On the basis of spectral data and subsequent correlation studies, structure **454** was established for a diterpene acetate isolated from *Croton rhamnifolius*. The C-20-acetoxy group was introduced by acetylation during the isolation procedure, so this compound could exist in the plant as the parent alcohol or as a fatty acid ester.[196] The compound **454** had been derived from phorbol (**439**) or bisdehydrophorbol (**440**) by the reaction with zinc in acetic acid by Hecker *et al.*[194]



(454)



(455a) : R^1 = –C(=O)–CH(Me)(Me), R^2 = Ac

(455b) : R^1 = –C(=O)–CH(Me)(Me), R^2 = H

(456a) : R^1 = –C(=O)–C(H)=C(Me)–Me, R^2 = Ac

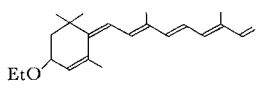
(456b) : R^1 = –C(=O)–C(H)=C(Me)–Me, R^2 = H

(457a) : R^1 = –C(=O)–CH(Me)–CH_2–Me, R^2 = Ac

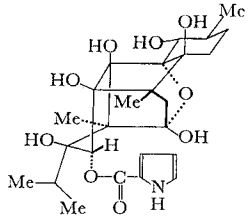
(457b) : R^1 = –C(=O)–CH(Me)–CH_2–Me, R^2 = H

Two irritant and tumor promoting fractions were isolated from the latex of *Euphorbia triangularis* by the application of the multiplicative distribution methods and adsorption chromatography. Mass spectra suggested that each fraction consisted of three esters. They were shown to be **455a** to **457b**.[197] In a review "150 years of Croton Oil Research", there was described about phorbol.[198]

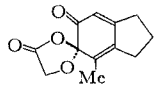
Treatment of dehydroretinol with hydrochloric acid in light petroleum or *p*-toluenesulfonic acid in benzene produced an unknown substance. Treatment of



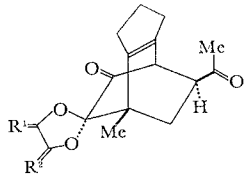
(458)



(459)



(460)

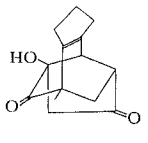


(461) : R^1 = H,H, R^2 = O

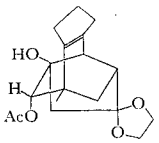
(462) : R^1 = O, R^2 = H,H

dehydroretinol with hydrochloric acid in ethanol produced, besides 3-ethoxy-anhydroretinol (**458**), same compound as above.[199]

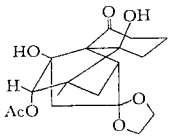
The key steps for the synthetic approach to ryanodine (**459**) were the preparation of *O*-spirodienone lactone **460**, its reaction with methylvinyl ketone which gave **461** and **462**, and the conversion of **461** and **462** into compound **463** by base. Finally ozonolysis of **464** followed by internal condensation gave compound **465**.[200]



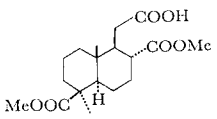
(463)



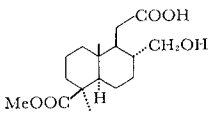
(464)



(465)



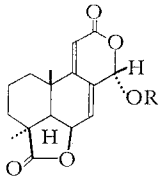
(466)



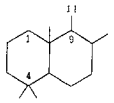
(467)

The rate of reduction of representative methyl esters with sodium trimethoxyborohydride decreases in the order primary > secondary > tertiary. Sodium trimethoxyborohydride reduced with 100% selectivity the secondary ester group in the alicyclic diester acid **466** and gave alcohol **467**. In the reduction of methyl abietate by sodium trimethoxyhydride, time required for the complete reduction was eight times longer than that in the reduction of **466**.[201]

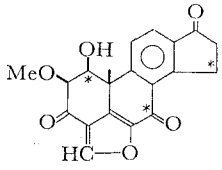
The syntheses of *trans, trans, trans*-2,6,10-geranylgeraniol and *trans, trans, trans*-2,6,10-geranyllinalool were performed.[202] The structure **468** was assigned to a new antifungal and biogenetically significant mold metabolite LL-Z 1271α, a C_{17} terpenoid, obtained from an unknown *Acrostalagmus* species known as culture LL-Z 1271. A minor metabolite, LL-Z 1271γ, was shown to be the corresponding lactol **469**. It remains uncertain, whether these metabolites are formed from a C_{20} precursor by microbiological degradation or from a C_{15} precursor **470** by addition of one C_1 unit at C-11.[203]



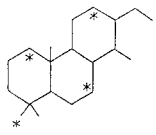
(468) : R=Me
(469) : R=H



(470)



(471)



(472)

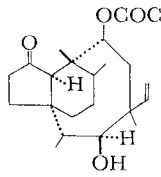
[^{14}C]Viridin (**472**) derived from [2-^{14}C]mevalonate has a labelling pattern (shown by an asterisk in **471**) which corresponds to the biogenesis of the tail-to-tail condensation of two farnesyl residues. Thus, another biogenesis from cassane (having the labelling pattern shown in **472**) is excluded.[204]

A short introduction on pleuromutilin (**473**), an antibacterial metabolite of *Pleurotus mutilus*, was published in Japanese.[205]

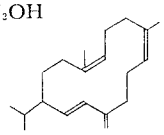
A new diterpene, stachysolon, was isolated from *Stachys annua*, and it was shown to be a bicyclic α,β-unsaturated ketone possessing a secondary and a tertiary hydroxy group.[206]

Two new diterpenes, isocembrene (**474**) and isocembrol (**475**), were isolated from *Pinus sibirica.*[207]

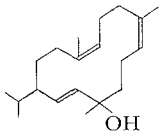
A phytochemical and biological review of the genus *Croton* was published.[208]



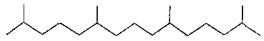
(473)



(474)



(475)



(476)

A review in Japanese on the synthesis of natural products applying a new hydrocyanation reaction was published by Nagata.[209]

Spectroscopic evidence was presented to prove the identity of a norditerpene hydrocarbon, isolated from Bute Inlet wax, as pristane (2,6,10,14-tetramethylpentadecane) (**476**).[210]

The production of phytol in greening callus cultures of *Kalanchoë crenata* was studied. There were only trace quantities of phytol in dark-grown callus but the amount of phytol markedly increased on exposure of the callus to light. This increase in phytol occurred before chlorophyll could be detected in the callus and was correlated with plastid naturation. A nonsaponifiable component of coconut milk was detected in dark-grown but not in light-grown cells. (Chlorophyllide a + phytol $\rightleftharpoons$ chlorophyll a).[211]

A review on the biosynthesis of isoprenoid was published in Japanese.[212]

Selective introduction of diterpenoid chromene residue was achieved by the scheme shown in Chart 16.[213]

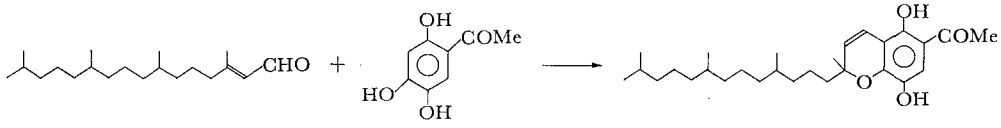
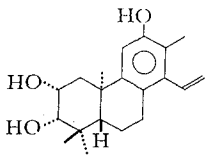


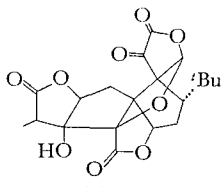
Chart **16**

A novel diterpene, cleistanthol, was isolated from *Cleistanthus schlechteri.* Its structure **477** presents a new type of diterpene skeleton.[214]

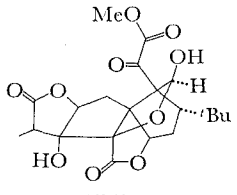
Dehydroginkgolide A (**478**), dissolved in methanol, was allowed to stand for thirty minutes to form a mixture of ester hemiacetal **479** and ester aldehyde **480** in a



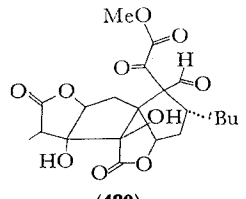
(477)



(478)

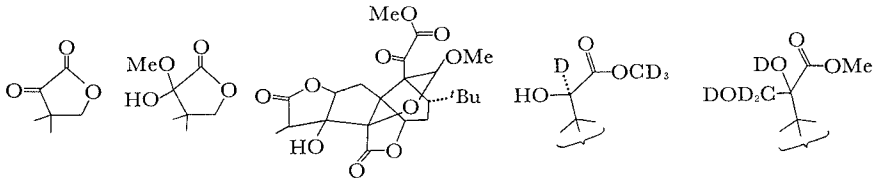


(479)



(480)

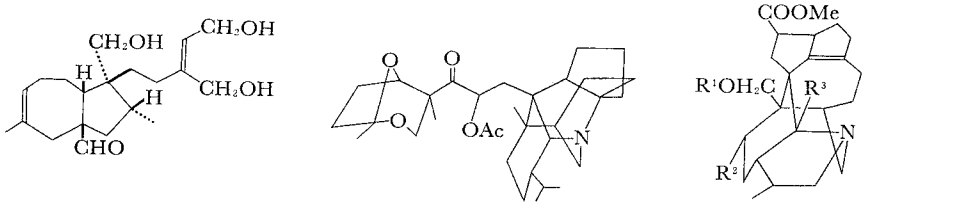
ratio of 4 to 1. On the other hand, 3,3-dimethyl-2-oxo-γ-butyrolactone **481** was rapidly changed to **482** by addition of methanol. These phenomena were followed by UV- and CD-measurements.[215]



(481) **(482)** **(483)** **(484)** **(485)**

Non-enolizable α-keto-ester **483** derived from dehydroginkgolide A on irradiation in perdeuteriomethanol yielded a reduction product **484** by an intramolecular hydrogen abstraction and an adduct **485** by an intermolecular hydrogen abstraction.[216]

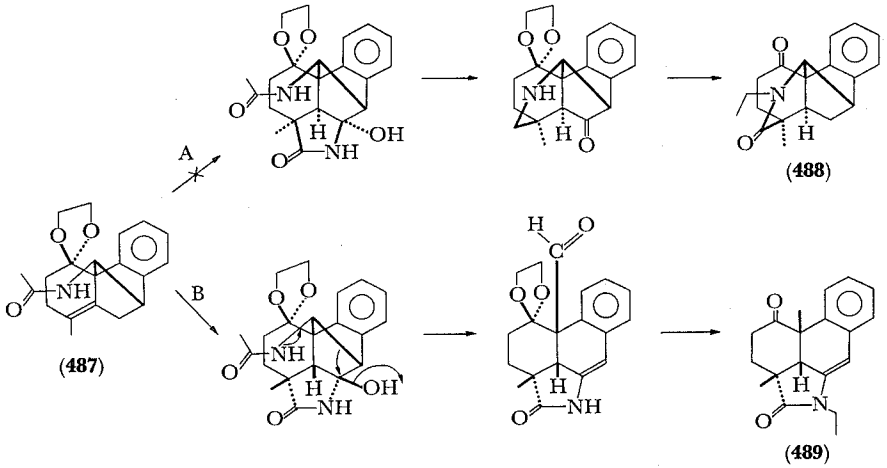
A neutral component, portulal, isolated from *Portulaca grandiflora* has the unique plant growth regulating activities. Its structure and absolute configuration was established to be **486** by a three-dimensional X-ray diffraction study of *p*-bromophenylsulfonylhydrazone.



(486) **(490)**

(491) : R^1=Ac, R^2=OAc, R^3=OH
(492) : R^1=R^2=R^3=H
(494) : dihydro-derivative of **491**

The conversion of the tetracyclic compound **487** into **488** was tried through the course A, but actually the reaction proceeded unexpectedly through the course B and

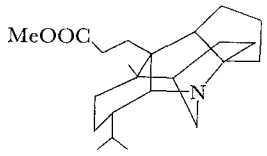


(487) **(488)** **(489)**

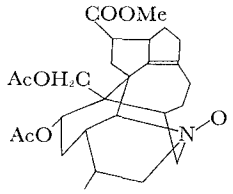
Chart 16

gave an undesired product **489**, whose structure was determined by the X-ray analysis. The outline is shown in Chart 16.[218]

From the methanol extract of the fruits of *Daphniphyllum macropodum*, five kinds of alkaloids were isolated. They are daphniphylline (**490**), yuzurimine (**491**), yuzurimine B (**492**), methyl homosecodaphniphyllate, and a new alkaloid. The new alkaloid was identical with methyl homodaphniphyllate (**493**) which was derived *via* 7 steps of reactions from daphniphylline.[219]



(493)



(495)

Previously, structure **494** was proposed for dihydro-derivative of macrodaphnine isolated from the bark of *Daphniphyllum macropodum*, but the structure for macrodaphnine itself was revised to **495** on the basis of the X-ray analysis data.[220]

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