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The Chemistry on Diterpenoids in 1969

Eiichi Fujita

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I. INTRODUCTION

The author has published a series of the reviews on diterpenoids chemistry.1,2,3,4 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.
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. 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 examination of the products from Pb(OAc)₄ oxidations of several compounds analogous to 1 and 2. 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 examined. 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). The route followed a modification of a sequence used by Zeiss and Martin 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-
4,8,11,13-tetraen-3-one (13). The lactone 14 was prepared by successive dehydration and hydrogenation of the 7α- and 7β-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 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.

Aldehyde 18 was subjected to the Wittig reaction followed by epoxidation to give the epoxide 19. The latter was treated with lithium aluminumhydride (LiAlH₄) to afford the 19S-ol, and then 7-ketoacetate 20 was prepared by its successive acetylation and oxidation.

The configuration and stereochemistry of methyl 11α-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.
The Chemistry on Diterpenoids in 1969

Methyl rac-13-methoxy-14-methylpodocarpa-8,11,13-trien-19-oate (25) and related compounds, e.g. 26, 27, and 28, were synthesized. Another synthesis of 25 via a similar way was also reported. The epoxy-olefin 29 was treated with BF₃-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 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.

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.
Angular methylolation was studied by Whitlock Jr. and Overman.\textsuperscript{19} The outline is shown in Chart 1.

Pelletier et al.\textsuperscript{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.\textsuperscript{21}
The Chemistry of Diterpenoids in 1969

The methoxy ester 25 and an \( \alpha,\beta \)-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.\(^{23}\)

\[
\text{Br} \quad \text{H} \\
\\
(45) \quad (46) \quad (47) : R' = \text{Me}, \quad R'' = \text{OH} \\
(48) : R' = \text{OH}, \quad R'' = \text{Me}
\]

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).

\[
\text{MeOOC} \quad \text{O} \\
\\
(49) : R = \text{H} \\
(50) : R = \text{NO}_2 \\
(51) \\
(52)
\]

Reactions of the bromo ketone 52 with nucleophiles were investigated. Three types of reactions afforded products 53, 54, and 55.\(^{25}\)

\[
\text{CH}_2\text{O} \quad \text{O} \\
\\
(53) : X = \text{NO}_2 \quad \text{CN} \quad \text{Ts} \\
(54) : X = \text{NMe}_2 \quad \text{NMMe}_2 \quad \text{OMe} \quad \text{OMe} \quad \text{OAc} \quad S-\text{CH}_2\text{Ph} \\
(55)
\]

Synthesis of \( \text{ent}-6\alpha\)-hydroxy-tetrahydro- (56) and \( \text{ent}-6\alpha\)-hydroxy-hexahydro-deoxypodocarpic acid (57) was investigated.\(^{26}\) Syntheses of \( \text{ent}-6\beta\)-hydroxy-tetrahydro- (58) and \( \text{ent}-6\beta\)-hydroxyhexahydro-deoxypodocarpic acid (59) via lactonization of 6\( \beta\) isomers were carried out.\(^{27}\) Temperature dependent PMR was used effectively for characterizing stereoisomers shown as types, 60, 61, and 62.\(^{28}\)
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.25a

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.10

* 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. 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.

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, $\beta$-sitosterol, torulosol, sandaracopimaradiene-3$\beta$,19-diol (74), and isopimaric acid. Two new diterpene alcohols isolated were shown to be 7$\alpha$-hydroxymanool (75) and 2$\beta$,3$\beta$-dihydroxymanoyl oxide (76).

The C-8 stereochemistry of "manool trihydrochloride" and other halogenated labdanes was reinvestigated and revised. 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, were revised to 8S structures 78 and 79, respectively.

A test of the mechanism of acid-catalyzed cyclization of manool to 14$\alpha$-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. (See Chart 3.)

Treatment of a solution of daniellic acid (81) in EtOH with HCl gas gave illurinic acid (82). Monocyclofarnesyl-acetones were refluxed with LiAlH₄ in ether to give alcohols, which were acetylated. The acetates were treated with 100% H₂SO₄ in nitropropane at $-70^\circ$ to cyclize into bicyclofarnesol derivatives. Their stereochemistry was investigated. The hydrogenation and dehydration of epitorulosol were studied.
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 epimanoyle oxide, phyllocladene, cembrene, manool, epimanool, phyllocladanol and its 16β-isomer were separated by chromatography. A new diterpenoid 83 was isolated from *Marrubium vulgare*. It was supposed to be the major substrate from which marrubiin was generated as an artefact. Biogenetic implications were discussed. Psiadiol was isolated from *Psadia altissima* and structure 84 was given. It was converted into 85, 86, 87, and 88. Another new diterpenoid,
isopsiadiol was isolated from the same plant source (leaves) and structure 89 was assigned to this compound. The reaction of 6-deoxypsadiol (90) was also investigated. The constitution and stereochemistry of solidagenone (91) and the epimeric spiro ethers (92) isolated from Solidago canadensis were deduced on the basis of spectroscopic and chemical properties. Synthesis of isoabienol and trans-abienol from sclareol was reported. Dehydration of sclareol and 13-episclareol by dimethyl sulfoxide was investigated. Oxidation products of sclareol was investigated. Synthesis of labd-13-ene-8,15-diol from labda-8(17),13-dien-15-ol was reported.

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

\[
\begin{align*}
(93) & \quad R_1=R_2=COOMe \\
(94) & \quad R_1=R_2=COOMe \\
(95) & \quad R_1=CH_2OAc, R_2=COOMe \\
(96) & \quad R_1=CHO, R_2=COOMe \\
(97) & \quad R_1=CH_2OH, R_2=COOMe \\
(98) & \quad R_1=COOH, R_2=CH_2OAc \\
(99) & \quad R_1=COOH, R_2=H \\
(100) & \quad R_1=COOH, R_2=Ac \\
(101) & \quad R_1=CH_2OH, R_2=H \\
(102) & \quad R_1=CHO, R_2=H \\
(103) & \quad R_1=CHO, R_2=Ac \\
(104) & \quad R_1=CH_2OAc, R_2=Ac
\end{align*}
\]

8β-hydroxymarrubiin. 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. From Araucaria cunninghamii resin, some labdane derivatives—98–104—were isolated. Lagochilin was isolated from Lagochilus inebrians, and its structure was clarified to be

\[
\begin{align*}
(99) & \quad R_1=COOH, R_2=H \\
(100) & \quad R_1=COOH, R_2=Ac \\
(101) & \quad R_1=CH_2OH, R_2=H \\
(102) & \quad R_1=CHO, R_2=H \\
(103) & \quad R_1=CHO, R_2=Ac \\
(104) & \quad R_1=CH_2OAc, R_2=Ac
\end{align*}
\]

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
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. A norditerpene lactone, diosbulbine, was isolated from the tubers of Dioscorea bulbifera and structure 109 was presented by Indian workers, but this plane structure is identical with that of the known diosbulbin-B. The wood of Gossweilerodendron 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.

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, methyl 6-acetoxykolavenate (115), and methyl 6-angeloyloxykolavenate (116). In addition, kolavenol (108), kolavelool (117), 6-angeloyloxykolavelool (118), elon-
gatolide-A (119), -B (120), -C (121), -D (122), and -E (123) were isolated.\(^5\) 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.\(^6\) The absolute stereochemistry of plathyterpol\(^7\) at all centers except C-13 was defined to be 129.\(^8\)

From *Araucaria bidwilli* rosin, methyl kolavenate (methyl ester of 107) and ester 127 were isolated besides some labdane derivatives.\(^9\)

V. PIMARANE AND ISOPIMARANE DERIVATIVES

The isolation and characterization of two diterpenes from *Daedycium colensoi* as sandaracopimaradien-19-ol (128) and abeo-labdane derivative 129 was reported. The structure of carboxylic 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.\(^10\)

The neutral extractives from the bark of *Thuja plicata* contained, among other components, three alcohols. One was the known diterpene alcohol, isopimarinal (130), but the other two were the new \(\Delta^{8(14)}\),15-4\(\alpha\)-hydroxy-18-norisopimaradiene (131) and \(\Delta^{8(14)}\),15-4\(\beta\)-hydroxy-19-norisopimaradiene (132). The synthesis of these two alcohols were described. The greater amount of the \(4\alpha\) compound found in nature, and its relative ease of synthesis compared to \(4\beta\) isomer, showed it to be formed preferentially.\(^11\)

Some chemistry of the \(\alpha\)- (133) and \(\beta\)-epoxides (134) derived from methyl pimarate was investigated. The \(\alpha\)-epoxide was found to be a very reactive species leading, by an intramolecular process, to a hydroxy-\(\gamma\)-lactone even on standing in hexane solution. The \(\beta\)-epoxide undergoes a cleavage reaction with Lewis acid to give a “backbone” rearrangement product, although a non-rearranged compound was observed in minor yield.\(^12\)

\*See also Section III, ref. 33 and Section XI, ref. 160a, b.
The oxymercuration-demercuration procedure was explored for methyl pimarate (135) and methyl sandaracopimarcate (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)

Virescenside A (139) and virescenside 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 roseum. The labelling pattern from [2-2H, 2-14C, (4R)-4-3H, 2-13C and 5-3H2, 2-14C]-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)

As a potential method for the construction of the lactone ring of rosenonolactone (142), an application of Pb(OAc)4-I2 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
The Chemistry on Diterpenoids in 1969

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. The isolation of rosenololactone (152) as a minor terpenoid from *Trichothecium roseum* was reported.

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

The dehydration of sandaracopimar-15-en-8β-ol (153) by thionyl chloride or by formic acid gave the dehydration products (4829), 48(14) and 4827) and a rearranged product 154, but no expected tetracyclic diterpenes.

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.

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

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.

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.

* See also Section IX.
Chart 4
The Chemistry on Diterpenoids in 1969

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

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

![Chemical structures](163, 164, 165, 166, 167)

salts and 2-dehydroabietylaminopyrimidine.** 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 octahydropyrene molecule were used.**

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.**

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

![Chemical structures](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

\[ \text{HOOC} \quad \text{HOOC} \]
\[ \text{(172)} \quad \text{(173)} \]

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

\[ \text{COOH} \quad \text{COOH} \]
\[ \text{(177)} \quad \text{(178)} \]

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-Cyanomethyl-12-hydroxyabietonitrile (180), 12-aminomethyl-12-hydroxyabietylamine (181), and 12-[(β-aminoethyl)dihydroxyabietylamine (182) were synthesized using the readily available 12-hydroxymethyl-12-hydroxyabietic 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
The Chemistry on Diterpenoids in 1969

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.

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

Structures 195 and 196 assumed previously for so-called “dihydrochloride” and “dihydrobromide” of abietic acid, were revised to 197 and 198, respectively.

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.

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

\[ (183) : X=H, Y=Z=O \]
\[ (184) : R=OH \]
\[ (185) : R=Cl \]
\[ (186) : R=CH₂N₂ \]
\[ (187) : R=CH₂OAc \]
acetylenedicarboxylic ester was used. A number of unusual reactions were observed.\textsuperscript{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).\textsuperscript{95)

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).\textsuperscript{96)

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
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.\(^\text{97}\)

Methyl 12\(\alpha\)-hydroxy-13\(\beta\)-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 \( \alpha,\beta \)-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.\(^\text{98}\)

![](image1.png)

Methyl 13\(\beta\)-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-13\(\beta\)-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-13\(\beta\)-abiet-8(9)-en-18-oate (226) with Li in liquid ammonia gave the less stable B/C cis-fused methyl 11-oxo-8\(\alpha\),13\(\beta\)-abietan-18-oate (227). The same reaction with methyl 7-oxo-13\(\beta\)-abiet-8(9)-en-18-oate (228) gave B/C cis-fused methyl 7-oxo-8\(\beta\),9\(\beta\),13\(\beta\)-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.\(^\text{100}\)

![](image2.png)
Two novel diterpenoid quinone methide tumor inhibitors, toxodine (230) and taxodone (231), were isolated from *Taxodium distichum* and their structures were assigned as shown.\textsuperscript{101}

The diene reaction of levopimaric acid with cyclopentenone afforded an endo, \textit{cis} adduct as major product and an \textit{exo}, \textit{cis} adduct in small quantity. The reaction of levopimaric acid with 1-cyclopentene-3,5-dione afforded a mixture of enolic \textit{endo}, \textit{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.\textsuperscript{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\textsubscript{3}.\textsuperscript{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.\textsuperscript{104} Some reactions of dehydroabietic acid were investigated.\textsuperscript{105}

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 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.\textsuperscript{106}

A full paper of the chemical conversion of enmein into enantio-abietane and total synthesis of abietane was published.\textsuperscript{107}
The Chemistry of Diterpenoids in 1969

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 monoperanaphthalic 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 abiet-7,13-dien-19-oate (methyl 4-epiabietate) (Me ester of 172) and methyl abiet-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 abiet-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 with Pb(OAc)\(_4\), and by thermolysis of diazomethyl ketone 246, as shown in Chart 5.\(^{111}\)

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-
ponents, isotanshinone-I (247), -II (248), and isocryptotanshinone (249) were characterized as shown.\(^\text{113}\)

A sample of amber was investigated and the constitution was assumed to be dimerization product of abietic acid, as shown in 250.\(^\text{114}\)

VII. TOTARANE DERIVATIVES

6α-Bromo-13-hydroxytotara-8,11,13-trien-7-one (251) was treated with DMSO-\(\text{NaHCO}_3\) to give a secoditerpenoid 252. The monoepoxide derivative 253 of secoditerpenoid methyl ether was treated with sulfuric acid in acetone to afford a naphthalenic aldehyde 254 by transannular cyclization and heterolytic fragmentation reactions, as shown in Chart 6.\(^\text{115}\)

The methyl group attached to an aromatic ring was functionalized by decomposition of hypobromite of a tertiary benzylic alcohol in the \textit{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.\(^\text{116}\)

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.\(^\text{117}\)
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.\(^{119}\)

\[
\text{(256) } R = \text{isopropyl} \\
\text{(257) } R = \text{Et}
\]

**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-
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 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. KAUERANE DERIVATIVES**

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

The succinate 266 was esterified by diazomethane, then, treated with POCl₃ 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.

(318)
and 277, respectively, on the basis of chemical and spectroscopic methods, especially of the IR spectra of their various derivatives.\textsuperscript{123}

Kaurenoic acid was isolated from \textit{Enhydra fluctuans}.\textsuperscript{124}

On the basis of the NMR and the mass spectra, the structure 278 was assigned to songoramine, a diterpene alkaloid.\textsuperscript{125}

The crude glycosides from \textit{Atractylis gummifera} were esterified with diazomethane and chromatographed on neutral alumina column to yield atracyligenin methyl ester (279) as a major product and 2-O-methylatracyligenin methyl ester (280) as a minor product.\textsuperscript{126}

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

Geranylgeraniol (282) and \textit{ent}-labda-8(17),13-dien-15-ol (283) pyrophosphate were shown to act as the precursors to \textit{ent}-kaurene, the kaurenolides, and gibberellic acid. The possibility that \textit{ent}-pimara-7,15-diene or \textit{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-\textsuperscript{3}H]- and 2-[\textsuperscript{3}H\textsubscript{2}]-mevalonic acid with \textit{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 \textit{via} decarboxylation of the
\( \beta,\gamma \)-unsaturated carboxylic acid, that is, \( \alpha^1, \alpha^2 \) or \( \alpha^{1(1)} \)-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 7a-hydroxy-kaurenolide (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\(_4\) gave ent-7,8-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-

Oxokaurenoic acid 285 on Meerwein-Ponndorf reduction gave 7\( \beta \)- (290) and 7\( \alpha \)-ol (286), which were separated by the preparative thin layer chromatography. The 7\( \beta \)-ol 290 on ozonolysis followed by Wittig reaction using the isotope gave 17-radioactive 290.\(^{130}\)

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. The preliminary communications had been published in 1967*. The reduction of ketone 293 with lithium tri-\( t \)-butoxy-aluminum hydride

* See ref. 4.
The Chemistry on Diterpenoids in 1969

[LiAl \((t-BuO)\_3H\)] in absolute tetrahydrofuran (THF) gave alcohols 294 and 295, while the reduction of ketone 293 with NaBH\(_4\) in THF-H\(_2\)O 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 \((t-BuO)\_3H\) in anhydrous solvent to give alcohol 299, while it was reduced with 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 \(\beta\)-OH group at C-15 were shown to be more easily adsorbed than compounds possessing an \(\alpha\)-OH group at C-15. The unfavorable influence of C-16/\(\beta\) methyl group for adsorption was recognized. The most favorable effect for adsorption was proved by C-3 \(\alpha\) equatorial OH among the compounds of Group 2.132

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-7\(\alpha\)-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 \(A_5\) 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
were elegantly synthesized by Beames and Mander.\textsuperscript{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 \textit{via} 314. Quite similarly, 316 was converted into 317. Catalytic hydrogenations of 315 and 317 were also carried out.\textsuperscript{136}
Asebotoxin-I and -II, toxins of *Pieris japonica*, were investigated and structures, **318** and **319**, were presented, respectively.\(^{137}\)

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.\(^{139}\) Now, further five kaurane diterpenes—ent-kauran-16\(\beta\)-ol, ent-16-kauren-19-oic acid, ent-15\(\alpha\)-hydroxy-16-kauren-19-oic acid, ent-kaurane-16\(R\), 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.\(^{140}\)

In the stems and the leaves of *Aralia cordata*, as well as in the roots, ent-16-kauren-19-oic acid was contained.\(^{141}\)

Previously, enmein (325) was converted into ent-kaurane.\(^{142}\) 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
silica gel containing 2.5% of silver nitrate. On the other hand, the Nagata's modification of Wolff-Kishner reduction of 327 gave \textit{ent}-kaurane.\textsuperscript{14}\textsuperscript{1}

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-

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 \textit{ent}-kaurene, atisine, garryine, and veatchine, a formal chemical conversion of enmein into the latter diterpenoids was performed.\textsuperscript{14}\textsuperscript{3}

A chemical evidence for the configuration of C-1 \textalpha{}-hydrogen and C-5 \textbeta{}-hydroxy group in grayanotoxin-II was presented, as shown in formula 337.\textsuperscript{14}\textsuperscript{3} This communication described the chemical conversion of grayanotoxin-II (337) into 338 and its tetra-acetate.

A synthesis of a \textit{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.\textsuperscript{14}\textsuperscript{4}

From \textit{Siegesbeckia pubescens}, the known \textit{ent}-16,17-dihydroxy-kauran-19-oic acid (341) was isolated.\textsuperscript{14}\textsuperscript{3}
X. BEYERANE DERIVATIVES

The toluene-\(\beta\)-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-14\(\alpha\)-ol formate 349. This finding is compatible with only scheme B mechanism in Chart 10.\(^{146}\)

\(\text{Chart 10}\)
The quite same conclusion was presented by another group on the basis of an experiment using \textit{348} labelled by D at C-14.\textsuperscript{147}

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

\begin{center}
\begin{tabular}{ccc}
\textit{350} & \textit{351} & \textit{352} \\
\end{tabular}
\end{center}

\section*{XI. GIBBERELLANE DERIVATIVES\textsuperscript{*}}

Two novel gibberellins, \textit{GA}_{21} and \textit{GA}_{22}, were isolated from immature seeds of sword bean, \textit{Canavalia gladiata}. The isolation procedure of these substances as well as their growth-promoting effects on dwarf maize mutants \textit{d_{1}} and \textit{d_{5}}, rice, cucumber and dwarf peas (Progress No. 9) were described.\textsuperscript{149}

\begin{center}
\begin{tabular}{ccc}
\textit{353} & \textit{354} & \textit{355} & \textit{356} \\
\end{tabular}
\end{center}

The structures of two new gibberellins, \textit{GA}_{21} and \textit{GA}_{22}, isolated from immature seeds of sword bean, were determined as \textit{353} and \textit{354}, respectively, on the basis of chemical and physicochemical studies.\textsuperscript{150}

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

\begin{center}
\begin{tabular}{ccc}
\textit{357} & \textit{358} & \textit{359} & \textit{360} \\
\end{tabular}
\end{center}

\begin{center}
\begin{tabular}{ccc}
\textit{361} & \textit{362} & \textit{363} & \textit{364} & \textit{365} \\
\end{tabular}
\end{center}

\textsuperscript{*} See also Section IX, refs. 128, 134, and 136.
and successive ring closure of the latter. Subsequently, 358 was converted into a C-aromatic hydrofluorene derivative 363 via 359, 360, 361, and 362.

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 confirmed the assumption to be correct. On the other hand, the catalytic hydrogenation of \(^{6}(\mathrm{H})\) 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.

A new rice seedling test for gibberellins, “microdrop method”, was described. A review on gibberellins in immature seeds of morning glory was published. (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.

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.

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...
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 LiAlH₄ in t-butanol and THF to give gibberellin A₁ (378) and its 3-epimer.¹⁵⁹

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 383.¹⁹³

Geranylgeraniol (282) and ent-labda-8(17),13-dien-15-ol (283) pyrophosphate were shown to act as precursors of ent-16-kaurene, the kaurenolides, and gibberellic acid. The labelling pattern from 4- (R)-[4-³H] and 2-[³H₂]-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 hydroxylatation 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

The known methoxyhexahydrofluorenone 388 was converted into acids 389 to 392. The selective lithium-hydrogen exchange and subsequent carbonation reactions were
effectively applied to introduce the carboxyl functions. Their examples are shown in Chart 11.\(^{163}\)

\[
\begin{align*}
\text{Chart 11}
\end{align*}
\]

A very short introduction on the biosynthesis of the kaurenilides and gibberellic acid was published in Japanese.\(^{163}\)

Addition of (2-chloroethyl)-trimethylammonium chloride and Amo-1618 \(2'-\text{isopropyl}-4'-(\text{trimethylammonium chloride})-5'-\text{methylphenylpiperidine-1-carboxylate}\) 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-hydroxykaurenilide, 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 \(\alpha\)-amylase formation in germinating barley were investigated.\(^{166}\)

Two new gibberellins A\(_{26}\) (393) and A\(_{27}\) (394) and their glucosides (395 and 396)
were isolated from the immature seeds of *Pharbitis nil*. They exhibited only slight growth-promoting activities on seedlings of rice, dwarf maize and cucumber.

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.

The formal total syntheses of some C19-gibberellins in racemic form were published in detail. 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 A4 (405) which had been transformed into gibberellins A2, A3, and A18.

![Chemical structures](image)

O(2)-β-D-Glucopyranosyl-gibberellin A1 methyl ester (406) was prepared from gibberellin A1 methyl ester and α-acetobromoglucose by Koenigs-Knorr synthesis followed by deacetylation. The reaction of gibberellin A3 with α-acetobromoglucose yielded tetraacetyl-β-D-glucopyranosyl ester 407.

The stereospecific labelling of the gibberellins and the kaurenolides with 2 (R) and 5 (R)-[3H] 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 initiates ring contraction possesses the 6β-stereochemistry.

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.
A facile route to cis-hexahydrofluorene-2,9-dione and its 7-methoxy analog was developed. The route is shown in Chart 12.\textsuperscript{173}

\begin{align*}
\text{HOCH}_2 & \xrightarrow{\Delta, N_2} \text{HOOC} \\
\text{HO} & \xrightarrow{\text{Zn, aq. HOAc}} \text{HOOC} \\
\text{R} & \xrightarrow{\text{PPA, 80°}} \text{HOOC}
\end{align*}

<table>
<thead>
<tr>
<th>R</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>90% yield</td>
</tr>
<tr>
<td>OMe</td>
<td>90% yield</td>
</tr>
<tr>
<td>H</td>
<td>85% yield</td>
</tr>
<tr>
<td>OMe</td>
<td>50% yield</td>
</tr>
</tbody>
</table>

Chart 12

XII. ATISANE DERIVATIVES\textsuperscript{*}

Spireine isolated previously from Spireae was shown by IR and NMR spectra and chemical evidence to be \textbf{410} or \textbf{411}.\textsuperscript{174}

\begin{align*}
\text{(410)} & : R^1, R^2 = \text{CH}_2, R^3 = \text{Me}, R^4 = \text{OH} \\
\text{(411)} & : R^1 = \text{Me}, R^2 = \text{OH}, R^3, R^4 = \text{CH}_2
\end{align*}

The reduction of a hetisine derivative \textbf{412} with LiAlH\textsubscript{4} yielded a novel rearrangement product, whose structure was determined to be \textbf{413} by single-crystal X-ray diffraction studies.\textsuperscript{175}

\begin{align*}
\text{O} & \xrightarrow{\text{MsO}} \\
\text{HO} & \xrightarrow{\text{HO}} \\
\text{AcO} & \xrightarrow{\text{N}}
\end{align*}

* 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.\textsuperscript{17d}

Denudatine was isolated and its structure 417 assigned previously by Singh et al.\textsuperscript{17a}

\[
\text{HOCH}_2\text{OH, } \text{C}_{20}\text{-C}_{14} \text{ or } \text{C}_{20}\text{-C}_7
\]

was revised by Wiesner et al.\textsuperscript{17b} to 418a or 418b. The X-ray analysis by Brisse\textsuperscript{17c} determined its structure and absolute configuration to be 419.

The X-ray crystal structure of delnudine, a novel alkaloid, was shown to be 420.\textsuperscript{17d} This alkaloid was isolated from the seeds of Delphinium denudatum and characterized, and its biogenesis from hetisine (421) was assumed as shown.\textsuperscript{180}

XIII. ACONANE DERIVATIVES

The compound 422 was synthesized as a model compound for the synthesis in the series of aconitine and delphinine.\textsuperscript{181}

\[
\text{OMeOH OMe}
\]

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).\textsuperscript{181}

Stereospecific skeletal rearrangements during the pyrolysis of epimeric toluene-\textit{p}-sulfonates were reported. The 15\textalpha-\textit{O}-tosylate 427 of atisane skeleton was subjected
The Chemistry on Diterpenoids in 1969

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 429.18'

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 NaBH₄ to yield 432. The mechanism was proposed as shown in Chart 13, which proved to be correct by NaBD₄ experiment.184

The characterization19 of lappaconine, an aconane alkaloid, and the X-ray structure analysis185 of its crystalline hydrobromide led to a final elucidation of structure and absolute configuration 433.

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

435, which on acidic treatment gave 436 and 437 in a ratio of 4 to 1. The cis \( \beta \)-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.\(^{188}\)

![](chart14.png)

**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.png)

(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.png)  (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.  

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).

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

![Chart 15](335)
itself and its derivatives and from mechanistic considerations of the phorbol rearrangement involving the \( \alpha \)-(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 \( \text{N} \) \( \text{H}_2\text{SO}_4 \) (Flaschenträger-reaction) essentially yielded four products in an overall 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.\(^{194}\)

\[
\begin{align*}
\text{Crotophorbolone (447)} & \quad \text{Phorbobutanone (448)} & \quad 452 & \quad 453
\end{align*}
\]

\[
\begin{align*}
(455a) : R^1 = \text{-C-CH-Me} & & R^2 = \text{Ac} & \quad (455b) : R^1 = \text{-C-CH-Me} & & R^2 = \text{H}
\end{align*}
\]

Two irritant and tumor promoting fractions were isolated from the latex of \textit{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 \( \rho \)-toluenesulfonic acid in benzene produced an unknown substance. Treatment of
The Chemistry on Diterpenoids in 1969

dehydroretinol with hydrochloric acid in ethanol produced, besides 3-ethoxy-anhydroretinol (458), same compound as above.149)

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)

\[
\text{(463)} \quad \text{(464)} \quad \text{(465)} \quad \text{(466)} \quad \text{(467)}
\]

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 C17 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 C20 precursor by microbiological degradation or from a C15 precursor 470 by addition of one C1 unit at C-11.203)

\[
\text{(468)} : R=\text{Me} \\
\text{(469)} : R=\text{H}
\]

[14C]Viridin (472) derived from [2-14C]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*.

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

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

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).

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 \( \rightarrow \) chlorophyll a).

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

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

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

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
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.

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.

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.

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
E. Fujita
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), yuzuri-
mamine 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)

\[
\begin{align*}
&\text{MeOOC} \quad \text{MeOOC} \\
&\text{COOMe} \quad \text{AcOH.C} \\
&(493) \\
&\text{MeOOC} \quad \text{AcO} \\
&(495)
\end{align*}
\]

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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The Chemistry on Diterpenoids in 1969

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The Chemistry of Diterpenoids in 1969


The Chemistry on Diterpenoids in 1969