The Chemistry on Diterpenoids in 1974

Eiichi Fujita, Kaoru Fuji, Yoshimitsu Nagao, Manabu Node, and Masahito Ochiai*

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I. INTRODUCTION

This is one of a series of our annual reviews1−10 on diterpenoids chemistry. The classification of the compounds is the same as that adopted in our reviews since 1969. In each section, the related compounds of similar structures are collected to form groups. In each group, isolations, structure determinations, and spectroscopic investigations are first described, syntheses and reactions are secondly, and biosyntheses and the others are finally followed. In each compound or sometimes in each group, the full paper(s) is first described and the short communication(s) is followed.

II. PODOCARPANE DERIVATIVES

Podocarpane

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

* I—±X, R1 A, I, A iE: Laboratory of Physiological Activity, Institute for Chemical Research, Kyoto University, Uji, Kyoto-Fu 611, Japan. Reprints requests should be addressed to E.F.
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The rule of maximum compactness was put forward as a guide for establishing the stereochemistry of catalytic hydrogenation in many cases. The catalytic hydrogenation of 4 afforded 5 as the major product which was more compact compound than 6.13)

\[ \text{(4)} \]
\[ \text{(5)} \]
\[ \text{(6)} \]

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

\[ \text{(7)} \]
\[ \text{(8)} \]
\[ \text{(9)} \]

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

\[ \text{(10)} \quad R = 0 \]
\[ \text{(11)} \quad R = \alpha^*-H, \beta^*-OH \]

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

\[ \text{(12)} \]
\[ \text{(13)} \]
\[ \text{(14)} \]
\[ \text{(15)} \]
\[ \text{(16)} \]
The formation of 15 in the reduction of podocarpanoic acid derivative 16 with zinc dust and AcOH presented an evidence for the intermediacy of an anion radical 17 during dissolving metal reduction in acidic medium.\(^{16}\)

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

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

Several methods for the introduction of a \(6\beta,19\) nitrogen bridge in podocarpane (496)
derivatives were reported. Attempted intramolecular N-alkylation in the 6a-bromo amide 31 gave ketol 32 via imino ether 33. The diosphenol 34 gave lactam 35, which was reduced to lactam 36.21)

![Chemistry on Diterpenoids in 1974](image)

The syntheses of steviol methyl ester (38a) and isosteviol methyl ester (38b) were carried out. The route is shown in Chart 1. The key reaction was the photoaddition of allene to 37.22) Attempts to synthesize 39, an important intermediate in the synthesis of diterpenoids and diterpene alkaloids, led ultimately to the isolation of 40.23)
Manool was isolated from *Salvia sclarea.*\(^{24}\) 13-Epimanool was isolated from *Abies alba.*\(^{25}\) ent-8(17),13(16),14-Labdatrien-18-oic acid (41) was isolated from *Hymenaea verrucosa.*\(^{26}\) From the roots of *Hermas villosa,* four diterpenic acids were obtained: *cis* and *trans* -Communic acid (42 and 43) and two further *cis, trans*-isomeric acids 44 and 45 with equatorial acid functions.\(^{27}\)

![Diagram of labdane derivatives](image)

Six diterpene acids of the labdane type were obtained from the oleoresin of *Araucaria bidwilli* and characterized as their methyl esters: 46, 47, 48, 49, 50 and 51.\(^{18}\) From the neutral fraction of *Larix decidua* bark, 13-epimanool, torulosyl acetate (52), torulosol (53), torulosal (54), and 19-acetoxylabda-12,14-dien-8-ol were isolated.\(^{29}\)
Labd-13-en-8-ol-15-oic acid (55) was isolated as the major component of the hardened trunk resin of *Hymenaea courbaril*. Two new acids 56 and 57 were isolated from *D. microzyga*.

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

From the acid fraction of the oleoresin of *Araucaria cunninghami* were isolated methyl communate, methyl isocupressate, and four new diterpenes. The structures 70, 71, 72, and 73 were assigned to them. From the neutral fraction of the same oleoresin were isolated five new diterpenes. The structures 74, 75, 76, 77, and 78 were assigned to them. The structure of gymnospermin, a new diterpene triol isolated from *Gymnosperma glutinosa* was determined to be 79.
In the diterpene ester, methyl sciadopate, the substituted butenediol side chain was shown to be trans (as 80) and not cis (81) as had previously been supposed.\(^{38,39}\) A new diterpene, isoagatholactone, isolated from \textit{Spongia officinalis}, is the first natural compound with the carbon skeleton of isoagathic acid (82), the acid-catalyzed cyclization product of agathic acid. The structure 83 was assigned to isoagatholactone on spectral grounds and chemical correlation with grindelic acid (84).\(^{40}\)

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

Nepetaefolinol, a new diterpenoid from \textit{Leonotis nepetaefolia}, was identified as 9,13-epoxy-6β-hydroxy-8α-labdane-16,15; 19,20-dilactone (86) on the basis of chemical and spectroscopic evidence. From the same plant, two new minor compounds, leonotinin (87) and 88 were isolated.\(^{43}\)
From the culture of *Acrostalagmus* NRRL-3481 were isolated three new C₁₆-terpenoids, acrostalidic acid (89), acrostalic acid (90), and isoacrostalidic acid (91), some of which were assumed to be biosynthetic intermediates for the lactone 92.⁴⁴)

\[
\text{HOOH} \quad \text{HO} \quad \text{HO} \quad \text{HOOH}
\]

From *Lasiocorys capensis* was isolated a new diterpenoid, lasiocoryin. Its structure was determined to be 93 by X-ray analysis,⁴⁷) and the structure of lagochilin, originally isolated from *Lagochilus nebrians*,⁴⁵,⁴⁶) was revised to 94 which was identical with the reduction product of 93.⁴⁷)

\[
\text{HO} \quad \text{HO} \quad \text{HO} \quad \text{HO}
\]

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

Mass spectra of the diterpenes; 4₁₂-cis- and 4₁₂-trans-abienol, isoabienol, 4₁₃-cis- and 4₁₃-trans-neoabienol were investigated.⁴⁹) The mass spectra of bisnorlabdanes 97, 98, 99, 100, and 101 were studied at both low and high resolution. All compounds gave characteristic C₁₃H₂₁ and C₁₆H₁₇ ions. Comparison of fragmentation patterns allowed ready distinction between isomeric acetals 97 and 98. The structure of 100 was assigned on the basis of its fragmentation pattern.⁵₀)

\[
\text{HO} \quad \text{HO} \quad \text{HO} \quad \text{HO} \quad \text{CH}_2\text{OH}
\]

In an attempt to establish the origin of the long range coupling in exocyclic epoxides, a series of 8,17-epoxylabdanes (102~115) were synthesized. All the α-epoxides (quasi-axial methylenes) unsubstituted in ring B exhibited long range coupling but the two β-epoxides 114 and 115 were not long range coupled.⁵¹)
The preparation and rearrangement with BF$_3$-Et$_2$O complex of a number of 8α,9α- and 8β,9β-epoxy-14,15-bisnor- and 14,15,16-trisnor-labdane derivatives were carried out to determine whether the clerodane diterpene skeleton could be obtained. A variety of rearranged carbon skeleton was obtained but not that of clerodane, probably because formation of this would involve the generation of a 1,3-diaxial interaction between the methyl groups of C-5 and C-9. A novel product from the bisnorlabdane epoxide 116 was the cyclodecenone 117.

IV. CLERODANE DERIVATIVES

Two diterpenes were obtained from the oleoresin of Araucaria bidwilli and characterized as their methyl esters; 118 and 119. A new diterpene was isolated from Olearia muelleri and structure 120 was assigned to it.
Annanone, a diterpenoid lactone isolated from *Stackys annua*, was shown to have structure 121. One known (122) and eight new (123, 124, 125, 126, 127, 128, 129, and 130) diterpenoids were isolated from *Solidago serotina*. The constitution and stereochemistry of the new compounds were deduced from their spectroscopic properties and chemical reactions.

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

On the basis of the results of an X-ray analysis and some chemical reactions, the structure of teucvin isolated from *Teucrium viscidum var. Miquelianum* was shown to be 138. Eugarzasadone was obtained from *Teucrium cubense*, and structure 139 was assigned to it. But later this compound was proved to be identical with teucvin, and the structure was revised to 138.
Teucrin A, a diterpene lactone isolated from *Teucrium chamaedrys*, was shown to have absolute structure 140 according to its UV and IR spectra and its chemical reactions. Teucrins B, E, F, and G, new diterpenoids isolated from *T. chamaedrys*, were proved to have structure 141, 142, 143, and 144, respectively, according to their IR, CD, and NMR spectra and their acetylation products.

Caryoptinol (145) and dihydrocaryoptinol (146) were isolated as the minor components in *Caryopteris divaricata*. A new diterpenoid 3-epicaryoptin (147b) was isolated from *Clerodendron calamitosum*. This compound possessed antifeeding activity against the larvae of *Spodoptera litura*. The confirmation of the absolute configuration of caryoptin (147a) and 3-epicaryoptin (147b), and the noteworthy experimental results about the CD spectroscopy for these dibenzoate derivatives were reported. Six antifeeding active diterpenes clerodin (148), caryoptin (147a), dihydroclerodin, dihydrocaryoptin, clerodin hemiacetal (149), and caryoptin hemiacetal (147c) were isolated from *Caryopteris divaricata*. The survey of the presence of chemical resistant factors in...
plants against the larvae of *Spodoptera litura* was examined. In addition, the antifeed-
diterpenes were surveyed from thirteen species of plants that belong to Verbenaceae
family. Among thirteen antifeedants, caryoptin (145) and dihydrocaryoptin (146)
from *Caryopteris divaricata* and 3-epi-caryoptin (147b) from *C. calamitosum* are contained.

The diene-ester 150 on heating underwent an intramolecular Diels-Alder reaction via the intermediate 151. The β-alkyl furan moiety in 151 reacts as the dienophile adding to the cyclohexadiene unit to give 152 as shown in Chart 2.

![Chart 2](image)

**V. PIMARANE AND ISOPIMARANE DERIVATIVES**

Sandalacopimaradienol was isolated from *Araucaria cooki*. GLC of the methylated resin of *Calocedrus decurrens* showed the peak of methyl sandaracopimaret. Isopimarol, isopimaric acid, and sandaracopimaric acid were isolated from *Podocarpus ferrugineus*. Chromatography of a cyclohexane extract of commercial "dragon's blood" resin (obtained from the exudate of the fruits of *Daemonorops draco*) yielded a fraction containing pimamic, isopimamic, and sandaracopimamic acids.

The investigation of the mass spectra of twelve naturally occurring isopimarane derivatives with three oxygen functions showed that constitution as well as configuration were important for the special fragmentation pattern. Raman spectral absorption bands were correlated with tri- and tetra-substituted double bonds in methyl \( \Delta^{7(9),13} \)-isopimarate (153) and methyl \( \Delta^{8(9),13} \)-isopimarate (154).

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

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

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

Esterification of maleopimaric acid by EtC(CH₂OH)₃ was investigated. It proceeded in two steps, and their rate constant, apparent activation energy and entropy were calculated.
VI. ABIETANE DERIVATIVES

Abieta-8,11,13-triene and abieta-8,11,13-trien-7-one were obtained from *Abies alba*. Abietinal (168) and abietic acid (169) were found in the oleoresin of *Araucaria cooki*. Abietic acid (169) and dehydroabietic acid (173) were isolated from a cyclohexane extract of commercial "dragon’s blood" resin (obtained from the exudate of the fruits of *Daemonorops draco*). Calocedrus decurrens was shown to contain dehydroabietic acid (173) and 7-oxodehydroabietic acid (174). The structures of suaveolic acid (175) and suaveolol (176), diterpenes in *Hyptis suaveolens* (Labiatae), were reported. Several abietane type diterpenes were isolated from the bark of *Podocarpus ferrugi-*
neus. They were ferruginol (177), sugiol (178), sugiyl methyl ether (179), xanthoperol (180), royleanone (181), 6-dehydroroyleanone (182), cryptojaponol (183), 5β-hydroxy-6-oxasugiyl methyl ether (184), 2-ketoferuginol (185), and 2β-acetoxy-sugiyl methyl ether (186), respectively. 

\begin{align}
(177) & \quad R^1 = R^2 = R^3 = R^4 = H, R^5 = OH \\
(178) & \quad R^1 = R^2 = R^3 = R^4 = H, R^5 = OH \\
(179) & \quad R^1 = R^2 = R^3 = R^4 = H, R^5 = OMe \\
(180) & \quad R^1 = R^2 = R^3 = R^4 = H, R^5 = OH \\
(181) & \quad R^1 = R^2 = R^3 = R^4 = H, R^5 = OH \\
(182) & \quad R^1 = H, R^2 = R^3 = R^4 = H, R^5 = OMe \\
(183) & \quad R^1 = R^2 = R^3 = R^4 = H, R^5 = OH \\
(184) & \quad R^1 = R^2 = R^3 = R^4 = H, R^5 = OMe \\
(185) & \quad R^1 = O, R^2 = R^3 = R^4 = H, R^5 = OH \\
(186) & \quad R^1 = H, R^2 = R^3 = R^4 = H, R^5 = OMe
\end{align}

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

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

\begin{align}
(188) & \quad \Delta^6
\end{align}

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

\begin{align}
(191) & \quad \Delta^6
\end{align}
In an effort to explore the stereochemistry of 6-ketoabieta-8,11,13-trienes, the related compounds, 193, 194, 195, and 196 were prepared.83)

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

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

Dehydroabietic acid (173) was chemically transformed, via 18 steps of reactions, into ketone 204 and 205 which are convenient starting materials for the preparation of 14a-methylsteroids.86) 3-Oxo-17β-acetoxy-14α-methyl-Δ4-8α,9β,10α,13α-estrene (206) was successively synthesized from 205.87)

The nitration of 207 gave 14-nitro (208) and 13-nitro ester (209), in ca. 1 : 1 ratio. The similar nitration of some methyl 7-oxo-derivatives having a substituent in 12 position (210, 211, 212, and 213) smoothly took place to yield selectively the corresponding 13-nitro-deisopropyl ester. In the case of 14-substituted ester (214), a mixture consisting of three compounds was obtained. A nitration of 215, however, gave only 14-nitro
product 216. Compound 217 on nitration gave an addition product 218 to the double bond.89)

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

A transformation of l-abietic acid (169) to a compound 222 having a benzohydroazulene skeleton was reported. The outline is shown in Chart 3.90)

Intramolecular functionalizations of 11-oxygenated abietanes were published. Hypoiodite reaction and oxidative cyclization of C-11 epimeric alcohols 223 and 224 resulted in functionalization at C-1 or C-20, as shown in Chart 4.14)
The structures 226 and 227 of the products resulting from photochemically induced hydrogen transfers in the levopimaric acid methyl ester-cyclopentadione adduct 225 were established by X-ray analysis of a heavy-atom derivative 228.91,92)

Compound 217 on photo-sensitized oxidation yielded unsaturated ketone 215.18) Oxidation of methyl abietate (229) by CrO₃ in AcOH at 80° gave methyl 7-oxodehydroabietate (207) (17%), methyl 6,12-dioxoabietate (230) (12.5%), and oxoaldehyde 231 (~3%). Treatment of 229 with kMnO₄ in pyridine afforded 45% of 207 and ~23% of 230.93)

Methyl levopimarate (232) was autoxidized in daylight to give compounds 233~239. Peroxide 240, which was formed in the initial stage of the photooxidation, gave 233~235 when exposed to light.94)
In concentrated sulfuric acid at 0° all-trans-tetrahydroabietic acid (241) was shown to rearrange to optically inactive 7-(1,1-dimethyl-tetradecahydrophenanthryl) dimethylacetic acid (242). A mechanism of the novel rearrangement was presumed as shown in Chart 5.

Phenol 219, derived from 7-abiatic acid, was oxidized with benzoyl peroxide to obtain 243, which was transformed into natural taxodione (244) and compound 245.

6a-Hydroxy-7-oxoabieta-8,11,13-triene (246), converted from 7-oxoabieta-8,11,13-triene, was treated with p-toluenesulfonyl chloride and then heated at 200°C to afford a
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$\beta$-naphthol derivative 247,

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

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

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

The benzonilidene ester 215 was readily brominated (NBS, Ac$_2$O-H$_2$SO$_4$, r.t., 6 hr.) to yield $\beta$-bromide 254 (85% yield), which was successively converted to terideadiol (255). The synthetic sequence is shown in Chart 7.
VII. TOTARANE DERIVATIVES

The X-ray analysis of compound 256 was carried out. Photo-sensitized oxidation of 13-methoxy-totara-6,8,11,13-tetraene (257) gave a hydroperoxide 258, which underwent
a facile rearrangement to a naphthyl derivative 259 in the presence of acid.\textsuperscript{18}

\begin{center}
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\end{tabular}
\end{center}

Nagilactone C (260) was isolated from \textit{Podocarpus purdieanus}.\textsuperscript{102}
The lactone 261 obtained from the culture of \textit{Acrostalagmus NRRL-3481} showed a strong inhibitory activity on the growth of an Avena coleoptile section.\textsuperscript{44}

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\end{center}

Some chemical transformations of sellowin-A (262), B (263), and C (264), norditerpene dilactones from \textit{Podocarpus sellowii}, were carried out.\textsuperscript{103}

\section*{VIII. CASSANE DERIVATIVES}

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The structures of norerythrostachamine (265) and norcassaidide (266), new alkaloids from the bark of \textit{Erythrophleum chlorostachys}, were chemically determined. The known
alkaloids, cassainine, cassamidine, and norerythrophlamide were also isolated.\textsuperscript{104}

Cassaine mustard (267) was prepared. Hydrolysis of cassaine (268) with HCl yielded the acid 269 which was converted \textit{via} the NH\textsubscript{4} salt into the Ag salt. This reacted with MeN(CH\textsubscript{2}CH\textsubscript{2}Cl\textsubscript{2}) to give 29\% of 267. The pharmacological properties of 267 were discussed.\textsuperscript{103}

The structure-cardiotoxic activity relationships of cassaine (268) and the related semisynthetic analogs were studied.\textsuperscript{106}

**IX. KAURANE DERIVATIVES*\textsuperscript{*}

A new diterpene, \textit{ent}-17-hydroxy-15-kauren-19-oic acid (270) and the known \textit{ent}-15\beta-hydroxy-16-kauren-19-oic acid (271) (=grandifloric acid) were isolated as the minor constituents from the roots of \textit{Aralia cordata}.\textsuperscript{107}

The petroleum ether extract of \textit{Enhydra fluctuans} yielded three new diterpenes, \textit{ent}-17-hydroxy-15-kauren-19-oic acid (270), \textit{ent}-15\beta-isovaleroyloxy-16-kauren-19-oic acid (272), and

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

(516)
and ent-15-β-angeloyloxy-16-kauren-19-oic acid (273) together with several known ent-kaurane type diterpenes.108)

Eight ent-kaurane type diterpenes previously described were isolated from Sideritis lagascana.100)

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

The structures of lasiokaurinol and lasiokaurinin, two novel diterpenoids of Isodon lasiocarpus, were elucidated as 275 and 276.111)

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

Two new ent-kaurene type diterpenoids of Isodon umbrosus, umbrosin A and B were assigned the structures 280 and 281.113)

A new toxic diterpene, lyoniol-D was isolated from Lyonia ovalifolia var. elliptica and the structure 282 was proposed on the basis of chemical and spectroscopic evidence and correlation with lyoniol-A (283).114)
Rhodojaponin-III (284) was isolated from the flowers of *Tripetaleia paniculata*.\(^{115}\)

Five *ent*-kaurane type diterpenes, substances D (285), E (286), F (287), creticoside-C (288), and -E (289) were isolated from *Pteris cretica*.\(^{116}\)

The stereochemistry of grayanol-A (290) and -B (291), new diterpenoids of *Leucothoe grayana*, was clarified using X-ray analysis of mono \(\rho\)-bromo benzoate of 291.\(^{117}\)

The stereoselective total synthesis of enmein (294) from 5-methoxy-2-tetralone (292) had been reported as a preliminary communication.\(^{118}\) Now, its full paper was published.\(^{119}\) The sequence is shown in Chart 8.
The chemical conversion of enmein (294) into an important relay compound (293) was also reported. The outline is shown in Chart 9.

Chart 8

Chart 9

(519)
The total synthesis of the racemic compound 295, a relay for the alkaloid napelline, was done through a route summarized in Chart 10, and the product was identified with the corresponding optically active derivative prepared from lucidusculine (296).121)

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

The compounds, 299 and 300, having 4,4-bisinorgrayanotoxin skeleton were synthesized from the formylated cross-conjugated cyclohexadienones, 298 and its C-14 epimer,
by a photochemical rearrangement. On the other hand, the nonformylated cyclohexa-
dienone 301 gave the spiro compound 302 and the phenols, 303 and 304, on photolysis
in aqueous acetic acid.122)

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

The diazoketones derived from compounds, 314 and 315, were treated with trifluoro-
acetic acid to afford good yields of tricyclic ketones 316 and 317 incorporating a cyclohexa-
2,4-dienone moiety.128)
The 1,2,3,4,9,10-hexahydrophenanthrene carboxylic acids 318, 319, and 320 were prepared and converted via their diazomethylcarbonyl derivatives to the 1,2,3,9,10,10a-hexahydro-2,10a-ethanophenanthren-12-one derivatives 321, 322, and 323, respectively, by short and efficient routes.\(^\text{126}\)

Tosylation and LiAlH\(_4\) reduction of some ent-17-norkaurane type alcohols, were studied, and the conformation of the ring B was discussed.\(^\text{127}\)

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

The hypoiodite reactions with dihydroisodocarpin (331), dihydroenmein 3-acetate (332) and isodotricin 3-acetate (333) were attempted in hopes of the oxygen-function-alization at C-11 of these compounds. However, it was observed that the reactions resulted in the formation of the 5-iodinated 5–6 cleaved products, 334, 335, and 336, respectively.\(^\text{130}\)
α-Dihydrograyanotoxin II was labeled with tritium at the C-10 and C-19 positions by catalytic hydrogenation of grayanotoxin II. Palladium-catalyzed hydrogenation in THF produced the α-form 337 exclusively, with specific activity 1.21 Ci/m mole and with 99% radiochemical purity.131)

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

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

The 13C nuclear magnetic resonance spectra of some kaurenolides were investigated. Changes in the spectra were used to show that microbiological hydroxylation of 7α-hydroxykaurenolide (350) by Rhizopus afforded four compounds, 351 〜 354. 7β-Hydroxy-
kaurenolide (355) afforded 356 and 357.\textsuperscript{134}

A systematic classification of 30 Isodon diterpenoids, structures of which had been elucidated already, on the basis of biogenetic consideration was published in Japanese.\textsuperscript{139}

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

\[
\begin{align*}
\text{(358)} & \quad R = H \\
\text{(359)} & \quad R = H \\
\text{(360)} & \quad R = OH \\
\text{(361)} & \quad R = OH \\
\end{align*}
\]

In a Japanese review related to the relationship between taste and chemical structure, Isodon diterpenoids were introduced.\textsuperscript{137}

The structure-activity relationship of lyoniol-A (283) and the related compounds in association with the excitatory effect on muscle spindle afferents was reported.\textsuperscript{133}

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

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

X. BEYERANE DERIVATIVES*  

Isolation of six known beyerane derivatives from Sideritis valverdei was reported.\textsuperscript{109}

Jativatriol (363) and conchintriol (364) were isolated from S. angustifolia.\textsuperscript{142} S. grandiflora was proven to contain a new diterpene, tartessol (365)\textsuperscript{142a} as well as ent-7a-acetoxy-15-beyerene-14\beta,18-diol.\textsuperscript{142b}

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

* See also section II, ref. 22.
Unusual action of CH$_2$N$_2$ on the keto-esters 371 and 372 giving the oxiranes 373 and 374 was described.$^{145}$

\[
\begin{align*}
(371) & \quad R^1 = \text{COOH}, \quad R^2 = \text{H} \\
(372) & \quad R^1 = \text{CH}_2\text{OAc}, \quad R^2 = \text{OAc}
\end{align*}
\]

Acid catalyzed rearrangements of beyerane, kaurane, and atisane type diterpenoids were investigated, and it was shown that the product mixture contains mostly beyerane derivatives in each case.$^{148}$ Another work on the acid catalyzed rearrangement of beyerane derivative 375 was published. Thus, formic acid treatment of 375 gives rise to allylic alcohol 376 and a mechanism of the rearrangement is proposed involving a novel 1,4-hydride shift in the bicyclo [3:2:1] octane C/D ring system on the basis of deuterium labelled experiment.$^{147}$

\[
\begin{align*}
(375) & \quad \text{CH}_2\text{OH} \\
(376) & \quad \text{CH}_2\text{OCHO}
\end{align*}
\]

Acid catalyzed rearrangements of 377 and 378 into 379 and 380 (Chart 12) published in 1972$^{148}$ were cited as examples of the 1,2-vinyl shift followed by a 1,2-alkyl shift in an review concerning acid catalyzed rearrangements of $\beta,\gamma$-unsaturated ketones.$^{149}$

(525)
XI. GIBBERELLANE DERIVATIVES*

A new gibberellin, gibberellin A₃₅(GA₃₅), and its glucoside were isolated from immature pods of *Cytisus scoporius* and their structures were elucidated as 3₈₁ and 3₈₂, respectively. The change of endogenous gibberellin in the germinated seeds of *Phaseolus vulgaris* was investigated and the isolation of GA₁, GA₈, GA₈ glucoside, and glucosyl esters of GA₁, GA₄, GA₇ (3₈₃) and GA₈₈ (3₈₄) were reported.

From the immature seeds of *P. vulgaris*, GA₁, GA₈, GA₈₈, and GA₈ glucoside were isolated, and GA₄, GA₅, GA₇ and GA₇ were identified by GC or GC-MS. In the etiolated seedlings glucosyl esters of GA₁ and GA₈ were identified by GC and GA₈ glucoside was shown to be present by the histograms.

Gibberellins were isolated from the mangrove plant; A₁ and A₃ from *Sonneratia apetala*; A₃, A₅, and A₇ from *Rhizophoria mucranata*; and A₅, A₄ and A₇ from *Bruguriera gymnorrhiza*. Biological activity of these gibberellins were examined using three bio-assays.

The identification and determination of gibberellins A₁ and A₅ in seeds of *Corylus avellana* were reported.

* See also section IX, ref. 132.
In addition to the previously identified\textsuperscript{155} GA\textsubscript{20} and GA\textsubscript{29} in immature seeds of \textit{Pisum sativum}, GA\textsubscript{9}, GA\textsubscript{17}, GA\textsubscript{28} (384), and a new gibberellin A\textsubscript{44} (385) were identified and quantitative analysis of these gibberellins was carried out.\textsuperscript{156}

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

Use of Copper hexafluoroacetylacetonate for the determination of the absolute configuration of alcohols 388 and 389 was reported.\textsuperscript{158}

Photolabile protection of the carboxyl group of gibberellins was published. Namely, photolysis of gibberellin derivative 390 derived from GA\textsubscript{3} gave a carboxylic acid 391 (42\%) in EtOH at 30°.\textsuperscript{159}

It was described that reaction of 2-chloro-N,N-diethyl-1,1,2-trifluoroethylamine with gibberellic acid ester 392 gave the corresponding esters of 3β- and its allylic isomer 1β-fluorogibberellins (393 and 394). The fluoro-acids themselves (393 and 394) were
obtained by de-esterification of the corresponding p-bromophenacyl esters.\textsuperscript{160)}

The decomposition pathway of GA\textsubscript{3} in aqueous solution was investigated. Decomposition of giberrellenic acid (395) in deuterium oxide gave 9-labelled products, 396 and 397, and unlabelled acid 398. Two partially characterized hydroperoxides 399 and 400 were detected as intermediates in the oxidative transformation of GA\textsubscript{3} through 395 to 398. The sequences are shown in Chart 13.\textsuperscript{161)}

Synthesis of GA\textsubscript{3}-\beta-D-glucopyranosides (401 and 402) was reported.\textsuperscript{162)}

The 7-ol derivative 405 of GA\textsubscript{3} was synthesized from GA\textsubscript{3}-anhydride (403) and its acetate (404).\textsuperscript{163)}

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

\begin{align*}
(401) & \quad (402) \\
(403) & \quad (404) \\
(405) & \quad (406) \quad (407) \\
(408) & \quad (409) \\
(410) & \quad (411) \\
(412) & \quad (413) \\
(414) & \quad (415) \\
(416) & \quad (417)
\end{align*}
pound 409. Subsequent Wagner-Meerwein rearrangement with trifluoro acetic acid for 50 hours at 20° transformed 410 and 411 to the corresponding hydroxydioxo acids 408 and 409, respectively. Sodium borohydride reduction of 411 afforded 412 and 413 in a 3:1 ratio.164)

The mass spectra of the gibberic acid methyl esters (414~416) were examined. Fragmentation pathways were proposed on the basis of specific deuterium labelling at their 9 position and measurements at high resolution.166)

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

As model studies of the synthesis of the ring A of GA₂₆, alcohols 420 and 421 were synthesized from keto ester 419 as indicated in Chart 15.167)

The 1,2,3,4-tetrahydrofluorene-2-carboxylic acids 422 and 423 were prepared and converted via their diazomethyl carbonyl derivatives 424 and 425 to tetracyclic compounds 426 and 427, respectively.168)
Stereocontrolled syntheses of ketones 428, 429, 430, and 431 through intramolecular alkylation of γ,δ-unsaturated α'-diazomethyl ketones 432 and 433 were described. Catalytic hydrogenation of the cyclopropyl ketones (428 and 429) and of the unsaturated ketones (430 and 431) produced 434 and 435.\(^{166}\)

![Structural formulas](image)

Stereoselective synthesis of the hydrofluorene derivatives 436–439 was reported and their conformational properties of their methyl esters were deduced from chemical and NMR spectral data.\(^ {170}\)

![Structural formulas](image)

Reaction of GA3 with carrier-free tritium gas and 5% palladium on calcium carbonate as catalyst was shown to give a complex mixture of products including \[^{6}\text{H}]\text{GA}_3, \[^{3}\text{H}]\text{GA}_1, \[^{3}\text{H}]\text{tetrahydro GA}_3,\) and \[^{3}\text{H}]\text{16,17-dihydro GA}_3.\) The purified product \[^{3}\text{H}]\text{GA}_3 likely arises from palladium catalyzed nonspecific exchange of GA3 alkane hydrogen atoms with tritium. \[^{3}\text{H}]\text{GA}_1\) is also exchange labeled but most of its radioactivity is due to tritium addition to the C-1,2 olefinic bond of GA3.\(^ {171}\)

Tritium labelled GA20 (440), GA5 (441), and GA8 (442) were prepared via a route shown in Chart 16.\(^ {172}\)

![Reaction pathways](image)

It was shown that GA14-aldehyde (444), which had been derived\(^ {173}\) from 443, was formed from GA19-aldehyde (445) in cultures of Gibberella fujikuroi and it was converted...
into fungal 3-hydroxylated gibberellins including GA$_3$ in the same culture. Gibberellin A$_{14}$ (446) and its alcohol (447) were shown to be also metabolized to 3-hydroxy gibberellins, the former at a much lower rate. The biosynthetic pathway to gibberellins in the fungus was discussed in the light of these results.$^{174}$

Biosynthesis of gibberellins A$_{12}$, A$_{15}$, A$_{24}$, A$_{36}$ and A$_{37}$ by a cell-free system from Cucurbita maxima was investigated. Namely, GA$_{12}$-aldehyde (445) obtained from mevalonate via ent-7a-kaurenoic acid (448) was converted to GA$_{12}$ (449). When Mn$^{2+}$ was omitted from the system, GA$_{12}$-aldehyde and GA$_{12}$ were converted to GA$_{16}$ (450), GA$_{24}$ (451), GA$_{36}$ (452), GA$_{37}$ (383), and so on.$^{176}$

It was shown that 17-tritium labelled GA$_{14}$ (446) applied to seedlings of dark grown dwarf pea (Pisum sativum) was converted to six gibberellins. The sequence of their interconversion (except GA$_{28}$) was shown as indicated in Chart 17.$^{176}$

Furthermore, tritium labelled GA$_{20}$ (453) applied to etiolated seedlings and germinating seeds of dwarf pea (Pisum sativum) was demonstrated to be converted to GA$_{29}$ (454).$^{177}$
Mutant B1-41a, obtained by UV-irradiation of Gibberella fujikuroi strain GF-1a, was shown to be blocked for gibberellin synthesis at the step from ent-kaurenal (455) to ent-kaurenoic acid (456). In addition, a method of preparing ent-16-kaurene, labelled at C-15 and C-17 by deuterium and tritium was described.178)

Translocation and intracellular distribution of tritiated GA3 in Phaseolus vulgaris were reported.179) From P. vulgaris treated with radioactive GA3, 3-O-β-glucosyl GA3, 3-O-β-glucosyl-iso GA3, 3-O-β-glucosyl gibberellenic acid and the β-glucoside of an unknown gibberellin-like substance were isolated and their interconversion was also reported.180)

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

Fluorogibberellin A12 aldehyde (465) derived from dihydroxy kaurenolide (464) was shown to be converted by G. fujikuroi into fluoro gibberellic acid (466) and fluorogibberellin A9 (467).182)

As the gibberellin metabolites from ent-kaura-2,6-dien-19-ol (468) and its succinate (469) in G. fujikuroi were found two C19 and five C20 gibberellins. They were characterized as their methyl esters (470~476).183)
Activities of (±)-GA15 (450) and (±)-GA15-isolactone (477) which were obtained by total synthesis\textsuperscript{184} and GA15 synthesized by interconversion\textsuperscript{185} of enmein (294) were assayed by the rice seedling test. As expected, (±)-GA15 showed half the activity of natural GA15. E-GA15 which has a natural configuration showed the same activity as natural GA15, while (±)-iso-GA15 was almost inactive.\textsuperscript{186}

Four gibberellin (GA1, GA3, GA4 and GA37) glucosyl esters were synthesized and found to be as active as their respective free acids in the rice seedling bioassay. The rapid hydrolysis of the glucosyl esters was demonstrated by feeding experiments with glucosyl esters of [\textsuperscript{3}H] GA1 and [\textsuperscript{3}H] GA4.\textsuperscript{187}

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

Effects of gibberellic acid on mevalonate activation in germinating Corylus avellana seeds\textsuperscript{189} and on sterol production in C. avellana seeds\textsuperscript{190} were reported.

**XII. ATISANE DERIVATIVES**

* See also section X, refs. 144 and 146.
The first reported oxygenated diterpenoid of the ent-atisane class, sideritol (480) was isolated from *Sideritis angustifolia*. The structure of vakognavine was determined as 481 based on an X-ray analysis.

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

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

XIII. ACONANE DERIVATIVES

The complex structures of two alakloids, excelsine (488) and delphisine (489), were determined by X-ray analyses. The correlation of delphisine (489) with neoline...
(490) accomplished to demonstrate that original structural assignment 490 for neoline was correct and that the revised structure 491 was erroneous. Thus, the structures of chasmanine and homochasmanine must be revised to 492 and 493, respectively.

![Chemical structures](image)

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

![Chemical structures](image)

The first total synthesis of talatisamine (497) was carried out as shown in Chart 18. Thus, pentacyclic intermediate 498 was converted into the potential intermediate 499 whose structure was confirmed by an X-ray analysis. Skeletal rearrangement of (499) followed by LiAlH₄ reduction afforded the relay 500, which was converted into talatisamine (497) through 501.

![Chart 18](image)

An X-ray analysis of the synthetic compound 502 being part of the skeleton of the aconite alkaloids was carried out.
XIV. TAXANE DERIVATIVES

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

XV. THE OTHERS

An improved stereoselective synthesis of all \textit{trans}-geranyl-geraniol (503) was reported.\textsuperscript{205} The route is outlined in the Chart 19.

The Wittig reaction of 504 with 505 gave tretinoin methylester (506). A formulation for a tretinoin (507)-containing cream useful against acne was reported.\textsuperscript{206}
A total synthesis of cembrene (508) was accomplished through a series of reactions as shown in Chart 20. Thus, the crucial intermediate 509 was cyclized by nickel tetra-carbonyl in N-methylpyrrolidone to give a cyclic compound 510 which was further transformed to cembrene (508).207

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

Two new diterpenes 518 and 519 related to bertyadjonol (520) were isolated from Bertya cuppresoida.210

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

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

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

A piscicidal constituent 530 was isolated from Excoecaria agallocha.217) Detailed investigation of Euphorbia resinifera resulted in separation of four new diterpenes 531–534 and a mixture of ingenol (535)-3-esters of methyl substituted long chain fatty acids. Their irritant and cocarcinogenic activity were also described.218) Other ingenol derivatives 536 and 537 were isolated from Euphorbia ingens.219) A new diterpene, 5-deoxyingenol was isolated as its diacetate 538 from Euphorbia biglandulosa.220) Euphorbia kansui was found to contain 20-deoxyingenol (539)221) and the ester 540 of 13-oxygenol.222)
The compound 541 was served as a starting material for a synthesis of 542 through a sequence of reactions which appeared suitable for the synthesis of the system present in anhydroryanodol. The outline is shown in Chart 22.

The full paper on the synthesis of terpenoid antibiotic LL-Z 1271a(543) was published in 1973. The outline was reviewed in our previous article. The transformations of the keto lactone 544, a key intermediate for the synthesis of 543, into keto lactones 545 and 546 were reported. The second total synthesis of 543 starting from 547 was also reported. The synthetic route is shown in Chart 23.
Minor diterpenoids were isolated from *Stachys annua* but no details are available yet.

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