<table>
<thead>
<tr>
<th>Title</th>
<th>The Chemistry on Diterpenoids in 1976</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author(s)</td>
<td>Fujita, Eiichi; Fuji, Kaoru; Nagao, Yoshimitsu; Node, Manabu; Ochiai, Masahito</td>
</tr>
<tr>
<td>Citation</td>
<td>Bulletin of the Institute for Chemical Research, Kyoto University (1978), 55(6): 494-538</td>
</tr>
<tr>
<td>Issue Date</td>
<td>1978-03-15</td>
</tr>
<tr>
<td>URL</td>
<td><a href="http://hdl.handle.net/2433/76756">http://hdl.handle.net/2433/76756</a></td>
</tr>
<tr>
<td>Type</td>
<td>Departmental Bulletin Paper</td>
</tr>
<tr>
<td>Textversion</td>
<td>publisher</td>
</tr>
</tbody>
</table>

Kyoto University
Review

The Chemistry on Diterpenoids in 1976

Eiichi Fujita*, Kaoru Fujii, Yoshimitsu Nagao, Manabu Node, and Masahito Ochial

Received November 2, 1977

I. INTRODUCTION

This is one of a series of our annual reviews on diterpenoids chemistry. The classification of the compounds is the same as that which has been used in our reviews since 1969.

II. PODOCARPANE DERIVATIVES

Rearrangement of deisopropyl phenacylidene type diterpene by means of aluminum chloride was investigated. Thus, the reaction of 1 with aluminum chloride in anhydrous benzene gave the rearranged ester 2, as a major product, in company

* BEM—, ± A%Aye, Irfm ,aIEl_.: Laboratory of Physiological Activity, Institute for Chemical Research, Kyoto University, Uji, Kyoto-Fu 611, Japan.
with the γ-lactone 3. On the other hand, the reaction of 4 afforded a large portion of the starting material in company with a small amount of the rearranged ester 5. Next, the reaction of the enol acetate 6 gave only the enol 7 in the company of deacetylation. Treatment of a phenol 8 with thallium (I) acetate and iodine gave a selective ortho-iodinated product 9,3)

N-Chloroacetylamine 10 on photolysis in methanol afforded the rearranged N-substituted glycine ester along with the unrearranged methyl ether.4)

A new stereocontrolled synthetic route to some intermediates (11a, b and 12a, b) for diterpenoid alkaloids and C₂₀ gibberellins was published. The synthetic approach contains a novel method of angular alkylation based upon a regioselective intramolecular α-oxocarbenoid insertion across the benzylic C-H (at C-10) bond in the copper-catalyzed carbenoid decomposition of the easily accessible α-diazomethyl ketone 13a and 13b to the corresponding bridged tetracyclic ketones 14a and 14b.5)
A facile regiospecific and stereocontrolled synthesis of a diterpene alkaloid intermediate from benzocyclobutenes was reported. Namely, thermolysis of 15 derived from methyl methylacetoacetate 16 in five steps gave phenanthrene derivative 17, which was converted into the epimer 18 by oxidation, bromination, dehydrobromination, and hydrogenation. Catalytic reduction of 18 gave the lactam 19, whose reduction with LiAlH₄ afforded imine 20. Similarly, compound 21 was synthesized.

![Chemical diagrams and reactions](attachment:image.png)

An efficient stereoselective synthesis of a tricyclic intermediate 22 for the synthesis of derivatives of abietic and podocarpic acid was reported. (Chart 2)

### III. LABDANE DERIVATIVES

11β-Hydroxymanoyl oxide (23) was isolated from Juniperus oxycedrus together with other diterpenes. From Cistus hirsutur, methyl ester 24 of 6β-acetoxyadenic acid was isolated. Labd-8(20), 13-dien-15-ol, (+)-manoyl oxide, epimanoyl oxide, cis-abienol, and 7α-hydroxydehydroabienol were isolated from the resin of
**Pinus koraiensis** and their identities confirmed by chemical and spectral methods.\(^{11}\)

A new diterpenoid, named vitexilactone, was isolated from the leaves of *Vitex cannabifolia* and its structure was established as 25 by the chemical and spectral examination.\(^{12}\)

Several new diterpenes, 26, 27, 28, 29, 30, and 31, were isolated from the plants of the genus *Brickellia*. Compound 27 is a new type of degraded diterpene which, however, is closely related to 26.\(^{13}\)

A new furanoid diterpene, potamogetonin (32), was isolated from seeds of *Potamogeton ferrugineus*. The structure was assigned on the basis of its spectral characteristics, particularly by NMR.\(^{14}\) Structure of ballotinone, a diterpenoid from *Ballota nigra*, was established on the basis of its \(^{13}\)C NMR spectrum to be 7-oxomarrubiin (33) \([15, 16\text{-epoxy-9-hydroxy-7-oxo-8\beta\text{H}-labda-13(16), 14-dien-19, 6\beta\text{-olactone}}]\).\(^{15}\) Giles and Schumacher\(^{16}\) had proposed structures 34 and 35 for \(\beta\)- and \(\alpha\)-levantenolide, respectively. However, it was reported that the C-12 stereochemistry of the \(\alpha\)-levantenolide, \([\alpha]_D^{{\Omega}}{+60.4}^\circ\), should be changed to 12 S and that of \(\beta\)-levantenolide, \([\alpha]_D^{{\Omega}}{-59.6}^\circ\), to 12 R on the basis of their \(^{13}\)C FT NMR spectra etc.\(^{17}\)

A furanoditerpene was isolated from *Hedychium spicatum*, and it was designated as 7-hydroxyhedychenone (36).\(^{18}\) Five *ent*-labdane diterpenes were isolated from the neutral fraction of the resin of *Araucaria bidwilli*. Two of the compounds were the already known methyl *ent*-8\(\beta\)-hydroxy-labd-E-13-en-15-oate (37) and *ent*-8\(\beta\), 15-labd-E-13-enediol (38). Three of them, previously unknown, were assigned the structures *ent*-15-acetoxy-labd-8, E-13-diene (39), *ent*-labda-8, E-13-dien-15-ol (40) and methyl *ent*-8\(\alpha\)-hydroxy-labd-E-13-en-15-oate (41).\(^{19}\)

A new diterpene galactoside, named acanthospermol-\(\beta\)-galactosidopyranoside, was isolated from *Acanthospermum hispidum* and its structure (42) was clarified.\(^{20}\) 13-Epimanool was isolated from *Pinus contorta* bark and *Tsuga heterophylla* wood. Southern pine (*Pinus* spp.) tall oil was found to contain a mixture of manool and 13-epimanool.\(^{21}\)
It was shown that tetrahydroabienol, which was obtained by hydrogenation of abienol (43), was a quasiracemic compound formed from C-13 epimers. Namely, the compound is a mixture of 44 and 45. The tetrahydroabienol (44 and 45) with phosphorus pentachloride smoothly gave the chloride 46 with less than 5% elimination to olefinic compounds. On the other hand, the C-8 epimeric alcohol 48 with phosphorus pentachloride gave a mixture comprising chloride 47 (40%), chloride 46, and olefin 49.

Allylic oxidation of exocyclic olefins with SeO₂/H₂O₂ was investigated and the mechanism was postulated: the reaction would proceed through the intermediacy of an oxaselenocyclobutane to a selenite ester which is solvated by competitive unimolecular (SN₁) and bimolecular (SN₂') processes.²⁴ (Chart 3)

† See another mechanism by H. P. Jensen and K. B. Sharpless (J. Org. Chem., 40, 264 [1975]).
In the synthesis of tertiary azides from scclareol 50 and dihydroscclareol 51, NH$_3$/BF$_3$-Et$_2$O was used. Stereoselective introduction of an azide group at C-8 was observed under appropriate conditions. Manoyl oxide 52 and 13-epimanoyl oxide 53 provided azide-ketone 54 by vinylic fragmentation with loss of C-14 and C-15.25)

The action of NaN$_3$-ICl or TIOAc-I$_2$ on labd-8(17)-en-13-ol 55 was investigated. The former reagent gave a mixture of 56 and 57, while the latter gave a mixture of 56 and 58.26)

Photochemical reaction of 15,16-dinorlabd-8(17)-en-13-on 59 was investigated. Namely, UV irradiation of 59 led to the fragmentation product 60 and its photocyclization product 61. Ethers 62 and 63 and $\beta,\gamma$-unsaturated alcohols 64 and 65 were formed via ketone 66.27) A partial synthesis of methyl lambertianate 67 from 13-keto degradation product 68 of methyl agathate was reported.28)

$\alpha$- and $\beta$-Levantenolide (34 and 35) were synthesized using functionalization at C-12 of labdanolic diterpene as shown Chart 4.29)
A synthesis of grindelic acid (69) from the easily available unsaturated (+)-ketone 66 was reported. The sequence is shown in Chart 5.

Isolation of labdane type diterpene from Pinus-pumila resin was reported, but the details are not known.

IV. CLERODANE DERIVATIVES

Six new diterpenoids, (70-75) were isolated from the roots of Solidago arguta, and their structures were deduced from their chemical and spectral properties. A new diterpene dialdehyde named linaridial was isolated from Linaria japonica, and the structure was established as 76 on the basis of the physicochemical evidence and the chemical correlation with the known furanoclerodane type compound 70. At the same time, two linaridial-analogs (77 and 78), which seem to be the artefacts formed secondarily from linaridial (76), were isolated from methanol extract of the same plant. Two lactones, mallotucin A and B, were isolated from Mallotus repandus. Mallotucin A was found to be identical with teucvin (79) isolated from Teucrium viscidum var. Miquelianum. Mallotucin B (80) was found to be the first diterpenoid with geminal methoxycarbonyl groups.

The structure and stereochemistry of corylifuran, a clerodane type diterpene from Croton corylifolius, have been determined as 81 by chemical and spectroscopic
data and X-ray crystallographic analysis. Methyl barbascoate (82), a major diterpenic component of the medicinal plant Croton californicus, was isolated and the structure determined by a combination of spectral and X-ray crystallographic studies. The structures of Ajugarin-I, II, and III (83, 84, and 85), which are insect antifeedants, isolated from Ajuga remota leaves, were determined.

A new clerodane type diterpene, floridiolic acid (86), was isolated from Evodia floribunda and the structure was confirmed by X-ray analysis of its methyl ester. Diterpene pentol 87, obtained by reduction of teucrin A with LiAlH₄, on treatment with 5% H₂SO₄ underwent an anisotropic rearrangement to give 88 identified by its acetates, acetonide, and oxidation products.

A review on the insect antifeedants found in plants was published. Several clerodane-type diterpenes were described in it.
V. PIMARANE AND ISOPIMARANE DERIVATIVES

Two diterpene acids, neothujic acid III and IV, were isolated from the fertilized female strobiles of thuja, *Thuja occidentalis*. The structure of neothujic acid III was determined as **89**. Four new pimarane type diterpene acids (**90**, **91**, **92**, and **93**) were isolated from *Dimorphotheca pluvialis* together with a beyerane type diterpene acid. The X-ray analyses of ent-3β-acetoxy-11α-bromoisopimar-8(14)-en-12-one (**94**) and its dihydroderivative (**95**) were reported.

(--)-Thermarol (**96**), a new ent-pimarane-type diterpene diol was isolated together with ent-pimara-8(14),15-dien-19-oic acid and ent-pimara-8(14),15-dien-19-ol from *Jungermannia thermarum*. Structure **97** of momilactone-C, a minor constituent of growth inhibitors in rice husk, was determined by X-ray analysis, which revealed that C-9, C-10 linkage of **97** was unusual cis configuration having a boat conformation of the ring A. The stereochemistry of C-9 of previously reported momilactone-A and B has been erroneously written and should now be revised to β-configuration (**98** and **99**) with respect to hydrogen atom as in momilactone-C.

A new pimaradiene carboxylic acid **100** was isolated from *Othonna cylindrica* as its methyl ester. The structure **101** for the γ-lactone derived from acid treatment of dihydroisopimarric acid (**102**) was revised to be **103** with a cis-A/B ring fusion, which was based on 13C NMR chemical shift data and spin-lattice relaxation time (T1) measurements. Constitutional effects in chemical ionization mass spectrometry of di- and tri-functional isopimarane type diterpens were reported.51
catalyzed reactions of \(7\alpha, 8\alpha\)-epoxy-isopimar-15-ene (104) and \(7\beta, 8\beta\)-epoxyisopimar-15-ene (105) were described. The epoxides were allowed to react with boron trifluoride etherate in dry benzene to give compounds 106, 107 and/or 108 with some miscellaneous products.

An intermediate 109 in the synthesis of erythroxydiol X was prepared by methylation of 110 via its enamine derivative. Thus, the pyrrolidine enamine on treatment with diazomethane to give the cyclopropaphenanthrene 111 which was hydrolyzed to 109 by heating in aq. MeOH. Furthermore, alkylation of 109 with ClCO\(_2\)Et gave the ester 112 which was converted to the acid 113 by Clemmensen reduction followed by hydrolysis. The perhydrophenanthrenol 114 was prepared from 110 in 9 steps. Formulae 109-114 represent their racemate, respectively.

In a review on the biosynthetic studies with \(^{13}\)C labeled precursors, virescenol B (115) was exemplified.

**VI. ABIETANE DERIVATIVES**
From *Hyptis fructicosa*, 14-methoxytaxodione (116) was isolated together with the known horminone (117) and its structure was determined on the basis of spectroscopic data and by chemical correlations.\(^{57}\) Two new diterpenoid quinones, conacytone (118) and icetexone (119) were isolated from *Salvia ballotaeflora*. Their structures were determined by the X-ray analyses.\(^{58,59}\) The acentric crystal structure of cis-coleon D (120) was established by the X-ray analysis (by direct methods). The absolute configuration was determined from the known chirality of the A/B ring junction.\(^{60}\) Isolation of stemolide (121), a novel diterpene bisepoxide, from the leaves of *Stemodia maritima* was reported. The structure was determined by X-ray analysis.\(^{61}\) Two alcohols isolated from *Nepeta granatensis* were identified as 7α, 18-dihydroxy-14-abietene and 14α, 18-dihydroxy-7-abietene by their chemical reaction.\(^{62}\)

\[\text{HO} \quad \text{HO} \quad \text{OH} \quad \text{HO} \quad \text{OH} \]
\[(116) \quad (117) \quad (118) \quad (119) \quad (120) \quad (121)\]

Kinetics of the thermal isomerization of abietic acid in the presence of air at 200° into palustic and neoabiestic acid was investigated.\(^{63}\) Iodine catalyzed disproportionation of abietic acid gave dihydroabiesticates or dehydroabiesticates. E.s.r. meas-
measurements suggested the intermediacy of free radicals.\textsuperscript{64} Acid treatment in acetic anhydride of blocked cyclohexadienone derivatives \textsuperscript{122} and \textsuperscript{123} gave \textsuperscript{124} and \textsuperscript{125}, respectively, through Wagner-Meerwein rearrangement of the angular methyl group. On the other hand, under similar conditions, \textsuperscript{126} and \textsuperscript{127} were transformed into \textsuperscript{128} and \textsuperscript{129}, respectively, as the result of an abnormal dienone phenol rearrangement.\textsuperscript{65}

Direct introduction of bromine into the ring A of phenacylidene derivatives of \textit{l}-abietic acid was developed and it was applied to the conversion of abietic acid into teideadiol (\textsuperscript{130}) having a hydroxy group on the ring A of its abietane skeleton.\textsuperscript{66}

\begin{itemize}
\item \textsuperscript{Chemistry on Diterpenoids in 1976}
\end{itemize}

Photo-oxidation of tanshinone II (\textsuperscript{131}) was published. Thus, UV irradiation of \textsuperscript{131} in the presence of air afforded 9-hydroxy-tanshinone (\textsuperscript{132}), anhydride \textsuperscript{133}, and lactone \textsuperscript{134}. The formation of these compounds was explained in terms of an intermediate \textsuperscript{135}, derived from tanshinone II by photoenolization and oxygenation.\textsuperscript{67}

Oxidation of ferruginol \textsuperscript{136} with benzoyl peroxide gave 12-benzoyloxy-11-hydroxyabieta-8, 11, 13-triene (\textsuperscript{137}) which was converted into taxoquinone (\textsuperscript{138}), 7\textalpha--acetoxyroyleanone (\textsuperscript{139}), dehydroroyleanone (\textsuperscript{140}), horminone (\textsuperscript{117}), 7-oxoroy-
leanone (141), and inuroyleanone (142).  
Transformation of dehydroabietic acid (145) to a key intermediate for the synthesis of steroids was examined. 13-Isopropyl-18, 19-bisnor-5β-podcarpa-8, 11, 13-trien-3-one (143) was synthesized from 145 via the ketone 144. In addition, methyl 14-oxo-podocarpan-18-oate 146 was synthesized from 122.

A potential synthetic intermediate 147 of rac-carnosic acid 148 was synthesized as shown in Chart 7.

![Chart 7](image)

![Chart 8](image)
Chemistry on Diterpenoids in 1976

The total syntheses of rac-carnosic acid dimethyl ether (149) and rac-carnosol dimethyl ether (150) were achieved.72) The outline is shown in Chart 8.

rac-Royleanone (151) was prepared in 16 steps from 2,3,6-trimethoxybenzoic acid via the trimethoxy intermediate 152.73)

A short and highly stereoselective total synthesis of rac-callitrisic acid (153) was described.74) The sequence is shown in Chart 9.

Stereo-selective isopropyl-methyl migration in l-abietic acid derivative was investigated, and was applied to synthesis of 15-beyerene (l-hibaene) (154) from l-abietic acid as shown in Chart 10.75)
Synthesis of deuterium and tritium labeled derivatives (155 and 156) of moleo-
pimaric acid was reported.\textsuperscript{76}

\[
\begin{align*}
\text{(155)} & : R^1 = 2H \text{ or } 3H, \\
& : R^2 = O \\
\text{(156)} & : R^1 = 2H \text{ or } 3H, \\
& : R^2 = \text{NCH}_2\text{CH}_2\text{OH}
\end{align*}
\]

Effects of hydrofluorene and hydrophenanthrene compounds derived from dehydroabietic acid (145) on the second leaf sheath growth of rice seedlings were examined in the presence and absence of gibberellic acid.\textsuperscript{77}

A review on the synthetic chemistry starting from abietic acid was published.\textsuperscript{78}

\section*{VII. TOTARANE DERIVATIVES}

Three new C\textsubscript{16} terpenoids, which may lie on the biosynthetic pathway for the antifungal metabolite LL-Z 1271\textalpha{} (157), were isolated from an \textit{Acrostalagmus} fungus, and assigned the structures 158, 159, and 160.\textsuperscript{79} The compound 157 has been assumed to be derived from diterpene biogenetically.\textsuperscript{80}
The previously published structure 161 of sellowin B was revised to 162 on the basis of the X-ray crystallographic study of its bromohydrin acetate 163. Treatment of 164 with thallium (I) acetate and iodine gave 165.

The chemistry of biologically active norditerpene dilactones isolated from Podocarpus species was discussed.

**VIII. CASSANE DERIVATIVES**

Cassane

19-Nor-4-dehydrocassaidine (166) was isolated from the bark of Erythrophleum couminga and its structure was determined by spectral data. Investigation of diterpenoids in four species of Pterodon was carried out. From P. pubescens, the new ester 167 was isolated. From P. emarginatus, compounds 168, 169, 170, and 171 were isolated. The diterpenoids 169 and 170 were isolated also from P. polygalaeiflorus. The compound 170 was further isolated from P. apparicioi.

From cassaine (172), several analogs, (173-179) were prepared. From 3-dehydrocassaic acid (180), derivatives 181 and 182 were made.
Compounds 183, 184, and 185 were prepared from the known derivatives of cassenic acid, and 183 and 185 were shown to have cardiotonic activity.86)

IX. KAURANE DERIVATIVES

From Sideritis paulii, sideridiol (186), isofoliol (187), and a new diterpene, epoxyisofoliol (188) were isolated.87) A new diterpenoid, epoxyisosidol (189) was isolated from Sideritis biflora.88) Four new hydroxylated ent-kauran-19-oic acids, 190, 191, 192, and 193 were isolated from Eupatorium album.89)

From Pteris dispar, 191 and four new diterpenes, 193, 194, 195, and 196 were isolated.90) Eight new diterpenes, rastronols A (197), B (198), C (199), D (200), E (201), F (202), G (203), and H (204), were isolated from Englerstrum scandens.91)
ent-Kaur-16-en-19-oic acid (205) was isolated as its methyl ester from Othonna cylindrica. The root bark of Annona senegalensis is used by Nigerian herbalists to treat cancer. From the root bark of this plant, six crystalline materials were isolated. They were found to be ent-kauran-16β-ol, ent-kaur-16-en-19-oic acid (205), methyl ent-16α-kauran-19-al-17-oate (206), methyl ent-19-nor-16α-kauran-4β-ol-17-oate (207), compound 208, and 209 or 210.

The root and overground part of Verbesina angustifolia were found to contain diterpenic acids 205 and 211. The root of V. oncophora also contained these two acids and ent-kauran-13-ol.

A new diterpenic acid 212 was isolated from Melampodium perfoliatum. The "coffee atractylosides" 213 and 214 were isolated from Coffea arabica.

The enzymatic hydrolysis of the glycosides fraction of the leaves of Stevia paniculata gave four aglycones and their structures were elucidated as 190, 191, 215, and 216. Two new diterpene-glycosides, microlepin and 16-epimicrolepin, were isolated from the overground part of Microlepia marginata and assigned the structures 217 and 218. The structures of paniculosides, I, II, and III, three new diterpene-glycosides of Stevia Paniculata, were determined as 219, 220, and 221.
From the leaves of *Stevia rebaudiana*, two new sweet glucosides, rebaudiosides A and B, were isolated besides the known glucosides, stevioside and steviolbioside. On the basis of IR, MS, $^1$H and $^{13}$C NMR as well as chemical evidence, the structures 222 and 223 were assigned to rebaudiosides A and B, respectively. Isolation and identification of the hypoglycemic agent, carboxyatractylate (224), from *Xanthium strumarium* were reported.

Anopterine was isolated from the leaf and bark of *Anopterus macleayanus* and bark of *A. glandulosus*, and its structure was determined to be represented as 225. Hydrolysis of anopterine and oxidation with potassium ferricyanide gave an unusual product 226, whose structure was confirmed by the X-ray analysis. To two new minor alkaloids of *A. macleayanus*, anopterimine and anopterimine N-oxide, were assigned the structures 227 and 228, and the partial structures of two other new alkaloids, hydroxyanopterine and dihydroxyanopterine were also reported.

The structures of grayanotoxins XVI and XVII, two physiologically active diterpenoids of *Leucothoe grayana*, were elucidated as 229 and 230. On the basis of the
results of an X-ray analysis the stereochemistry of pieristoxin G (231) was discussed.\textsuperscript{105)\textsuperscript{107)}\textsuperscript{108} The \textsuperscript{13}C NMR spectra of some kauranoid diterpenes have been assigned. The application of the results to the determination of the sites of hydroxylation in this series was discussed.\textsuperscript{106)\textsuperscript{108} The X-ray analyses of 232\textsuperscript{107)}\textsuperscript{108} and 233\textsuperscript{108)} were reported. The reaction of the keto esters 234 and 235 with Na in liquid ammonia afforded mixtures of \textit{ent}-kaurane, \textit{ent}-beyerane, and dimeric products.\textsuperscript{109)\textsuperscript{110)}}

The synthesis of steviol (236) (Chart 11) and two A-ring modified analogs 237 and 238 was reported.\textsuperscript{110)\textsuperscript{111)}\textsuperscript{112)} The full details of the synthesis of phyllocladene (239) from abietic acid was published.\textsuperscript{111)\textsuperscript{112}} The synthesis of \textit{ent}-kaur-16-ene-11\textalpha,\textalpha\textalpha-diol (240) and \textit{ent}-kaur-16-\textit{en}-15-on-11\textalpha-ol (241) from \textit{ent}-kaur-16-ene was performed. The outline is shown in Chart 12.\textsuperscript{112)}}
Buffered formolysis of ent-12α-p-tolysulfonyloxykaurane (242) followed by hydrolysis gave chiefly the corresponding alcohol 243, smaller amounts of the epimeric ent-atisan-13-(244 and 245) and 16-ols (246 and 247), together with traces of ent-kauran-12β-ol (248) and the ent-14(13→12)abeo-kauran-13α-ol (249).113

The detailed investigation on the ring B contraction of kauranolides and related compounds into gibberellane-type compounds was carried out. The lactone 250
on treatment with base and subsequent methylation gave the gibberellane aldehyde 251 and the alcohol 252. The ester 253 gave a similar result. The lactone 254 on the same treatment afforded only the desired product 251 quantitatively. The ring B contraction did not proceed with the ester 255. The results are rationalized in terms of stereochemical considerations.\(^\text{114}\)

On the hypoiodite reaction, 17-norkauran-6\(\alpha\)-ols 256, 257, 258, 259, and 260 gave 261, 262, 263, 264, and 265, respectively. 17-Norkauran-6\(\beta\)-ols 266, 267, and 268 on the same reaction yielded 269, a mixture of 270 and 271, and 272, respectively. Thus, the O-functionalization of the inactive C-19 methyl group of 17-norkauran-6-ols was achieved.\(^\text{115}\)

Treatment of ent-16\(\alpha\)-methoxy-17-norkaurane (273) and lactone 274 with boron
trifluoride-ether complex in ethanedithiol gave the corresponding alcohols 275 and 276, respectively, with retention of the original stereochemistry.\textsuperscript{116} Demethylfuje-noic acid derivative 278 was synthesized from the key intermediate 277.\textsuperscript{117}

Reaction of sodium azide and iodine chloride with phyllocladene (239) gave the compound 279. On the same treatment, isophyllocladene (280) gave two major products, 281 and 282, and two minor products, 283 and 284.\textsuperscript{26}

Thioacetals 285-288 were dethioacetalized by the treatment with thallium (III) nitrate under mild conditions for a short time to recover the parent carbonyl compounds in good yields. The reaction mechanisms were also discussed.\textsuperscript{118}

Oridonin (289), lasiokaurin (290), enmein (291), enmein-3-acetate (292), and related compounds (293 and 294), all of which have \( \alpha \)-methylene cyclopentanone function in their molecule, were shown to have antitumor activity against Ehrlich ascites carcinoma inoculated into mice and specific activity against gram-positive bacteria. On the other hand, compounds 295 and 296, trichokaurin (297), and dihydroenmein (298) showed any activity neither against tumor nor against bacteria. Thus it was concluded that the \( \alpha \)-methylene-cyclopentanone system must be an important active center. Biomimetic reactions of oridonin and enmein with several thiols \textit{etc.} supported this conclusion.\textsuperscript{119,120}

Enzymatic cyclization of rac-14,15-oxidogeranylgeranyl pyrophosphate (299) to hydroxykaurenes 300 and 301 was reported.\textsuperscript{121} Conversion of geranylgeranyl pyrophosphate to \textit{ent}-kaurene in enzyme extracts of sonicated chloroplasts was reported.\textsuperscript{122} Incorporations of \textit{ent}-kaur-16-ene and \textit{ent}-kaur-16-en-15-one (302) into enmein (291) and oridonin (289) by \textit{Isodon japonicus} were demonstrated by tracer experiments with seven labeled \textit{ent}-kaurene derivatives. Furthermore, evidence was obtained that functionalization of \textit{ent}-kaur-16-ene at the allylic C-15 atom proceeds through direct oxygenation.\textsuperscript{123}

\textit{ent}-Kaur-16-en-19-oic acid (205) was transferred by \textit{Cunninghamellla blakesleeana}
Chemistry on Diterpenoids in 1976

\[ (299) \]

\[ (300) R^1=\text{OH}, R^2=\text{H} \]
\[ (301) R^1=\text{H}, R^2=\text{OH} \]

\[ (302) \]

\[ (303) R=\text{H} \]
\[ (304) R=\text{H} \]
\[ (305) R^1=R^2=\text{H} \]
\[ (306) R^1=\text{OH}, R^2=\text{H} \]
\[ (307) R^1=\text{OH}, R^2=\text{H} \]
\[ (308) R^1=\text{H}, R^2=\text{OH} \]

A series of hydroxylated derivatives, 216, 303, 204, and 305. Hydroxylation of \(3\beta,7\beta\)-dihydroxykaurenolide (306) by \textit{Rhizopus arrhizus} afforded 307 and 308.

**X. BEYERANE DERIVATIVES**

\[ \text{Beyerane} \]

A new beyerane type diterpenic acid 309 accompanied by some new pimaran type diterpenes was isolated from \textit{Dimorphotheca pluvialis}. The X-ray analysis of methyl
ent-16β-p-bromobenzylxyloxy-17(16→12)abeo-atisan-19-oate (311), a derivative of a formolysis product of methyl ent-12β-toluene-p-sulfonyloxybeyeran-19-oate (310), was reported.126)

A minor product in the reaction of jativatriol (312) with hydrochloric acid was elucidated as 313 by the X-ray analysis.127) The X-ray analysis of ent-3β-acetoxy-11α-bromobeyer-2,12-dione (314) was reported.128)

XI. GIBBERELLANE DERIVATIVES

A general method for the conversion of 3-hydroxygibberellins into the methyl esters of 2-hydroxygibberellins was published. Thus the structures of two new gibberellins, GA46 (315) from seed of Echinocystis macrocarpa and GA47 (316) from cultures of Gibberella fujikuroi (strain GF-1a), were determined by these partial syntheses.129)

The 13C-NMR study of several gibberellin derivatives was reported.130) The aminolysis of gibberellin-As-(N-hydroxy-succinimide)-ester (317) with benzylamine

\[
\begin{align*}
\text{(315)} && \text{(316)} && \text{(317)} R=O-N & \text{(318)} R=\text{NH-CH}_2\text{C}_6\text{H}_5 \\
\text{(319)} R=\text{O-NH-CO(CH}_2)_2\text{CONHCH}_2\text{C}_6\text{H}_5
\end{align*}
\]

The aminolysis of gibberellin-As-(N-hydroxy-succinimide)-ester (317) with benzylamine

\[
\begin{align*}
\text{THPOCH}_2\text{CHO} & \xrightarrow{\text{TiCl}_3, \text{LiAlH}_4, \text{THF}} \text{30%} \xrightarrow{\text{Mg(Hg)}\cdot \text{TiCl}_4} \text{90%} \xrightarrow{\text{complex of (C}_2\text{AlCl}_3)_2\text{Ti}} \text{good yield}
\end{align*}
\]
yielded gibberellin- \( \text{-A}_3 \)-benzylamide (318) and \( \text{O-} \text{(gibberelin-\text{-A}_3 \text{-oyl})-N-} \text{(benzyla-}
\text{mino)-succinoyl-hydroxy-amine (319)} \). \( ^{131} \) Three types of new reagents for the intramolecular pinacolic coupling of dicarbonyl compounds were developed. These are magnesium amalgam-titanium tetrachloride, cyclopentadienyltitanium trichloride-lithium aluminum hydride, and the hexamethylbenzene complex of the well-defined Ti (II) species (\( \text{Cl}_2 \text{AlCl}_2 \))\(_2 \)Ti. \( ^{132} \) These new pinacolic coupling reactions seem to be very effective for the construction of C-D ring system in synthesis of \( \text{A}_3 \)-type gibberellins. (Chart 13)

A new stereocontrolled synthesis of some intermediates 11a and 11b for \( \text{C}_{20} \) gibberellins were published. \( ^{5} \) The reductive methylation of each epimeric diacid 320 and 321 was investigated by successive reaction with lithium in THF-liquid ammonia followed by methyl iodide. In each case, the diacid product (322 from 320 and 323 from 321) was formed by introduction of the C-4 methyl group from the side of the molecule opposite to the carboxyl group at C-6. \( ^{133} \)

Various methods for the introduction of a carboxyl group into the benzylic position of compounds, 324, 325, and 326 were investigated. Among them, the best was found to involve deprotonation of these acetal esters with lithium N-cyclohexyl-N-tert-butylamide, followed by carboxylation, which was highly stereoselective. \( ^{134} \)

The hypoiodite reactions on the 7-norgibberellane derivatives were studied. The reaction with 7-nor-6-on-20-ol 328 derived from compound 327 afforded a high yield of 3,20-ether 329. The second hypoiodite reaction with the \( \alpha \)-ol 330 performed between C-6 and C-20 and yielded compound 331, whose oxidation with the Jones reagent gave ketolactone 332. \( ^{115} \)
Ring B contraction of kauranoids and related compounds into gibberellane-type compounds was investigated in detail.\textsuperscript{114} (See section IX.)

A formal total synthesis of rac-gibberellin A\textsubscript{12} (340) mimicking the biogenetical pattern was achieved by employing methyl rac-7,16-dioxo-17-norkauran-19-oate (337) as a relay compound.\textsuperscript{135,136} The outline is shown in Chart 14. Thus, compound 333 was converted into 337 via 7-en-13-ol 334, 7-keto-13-al 335, and a key intermediate 336 for ring D closure. Conversion of 337 into diketolactone 338 had been done.\textsuperscript{137} Then the 16-oxo compound 338 was transformed into the 16-ene 339, whose conversion into GA\textsubscript{12} (340) had been performed.\textsuperscript{137,138}

The photochemical [2+2]-cycloaddition of ethylene and tetramethylethylene to 3-dehydrogibberellin A\textsubscript{5} (341) under \( n \rightarrow \pi^* \)-excitation conditions was investigated. The reaction lead to a 3:1 ratio of the cis-fused \( \alpha \)- and \( \beta \)-cyclobutane annelated epimers 342 and 343 as well as 344 and 345 in 70 and 86\% yield, respectively. Reduction of the annelated products with NaBH\textsubscript{4} was also discussed.\textsuperscript{139}

The structure and molecular packing of the cyclobutane annelated pseudogibberellin A\textsubscript{1} derivative 346, prepared by trifluoroacetic acid catalyzed Wagner-Meer-
wein rearrangement of 347, was established by X-ray analysis.\(^{140}\) The oxidative lactonization and oxidative decarboxylation of gibberellin A\(_1\) (348) and A\(_7\) (349) with neutral manganese dioxide were investigated. The reaction with GA\(_1\) gave compounds, 350, 351, and 352 and that with GA\(_7\) produced 353 and 354.\(^{141}\)
E. Fujita, K. Fuji, Y. Nagao, M. Node, and M. Ochiai

The synthesis of 2,3-(3H)-GA9 with a specific activity of 47 Ci mmole⁻¹ was reported. The chemical conversion of GA13 (355) into GA4 (356) was accomplished. The route is shown in Chart 15.

The synthesis of gibberethione (357) isolated from seed of Pharbitis nil as a catabolic product of GA3 was carried out by the direct coupling of 3-dehydro-GA3 (341) and mercaptopyruvic acid. The uniformly 3H-labeled gibberellin A3 amides, 358 and 359, were prepared by amidation of the mixed anhydride of uniformly 3H-labeled GA3 and inactive GA3 with H₂N(CH₂)₄NH₂ (n=4 and 5).

The synthesis of neutral and amino-substituted amides of the gibberellin A₃ and A₁ series via aminolysis of the corresponding gibberellin carboxylic acid anhydrides was published. The mass spectra and ¹H-NMR data of these compounds are also discussed. The synthesis of gibberellin-A₃-oyl-2-¹⁴C-glycine (360) was reported. Gibberellin A₁-(7)-alcohol (361) and gibberellin-A₁-(7)-aldehyde (362) were prepared from GA₁ (348).

GA₁₃ (363), on treatment with Pb(OAc)₄-dimethylformamide (DMF) at 18°C, afforded a mixture (60:40) of the known GA₄ (364), identified by g.l.c.-mass spectrometry of the methyl ester, and the new isomeric lactone 365; minor amounts of the corresponding 3-ketones 366 and 367 were also formed. This is the first chemical correlation of C₂₀ gibberellin to C₁₉ gibberellin. A rearrangement of compounds 368 and 369 with triethylxonium fluoroborate in CH₂Cl₂ into the corresponding bridged ketones 370 and 371 was published. Their transformation to some key hydrofluorene synthons 372 and 373 towards the C₂₀ gibberellins was also reported.

The photolysis of 3-dehydro-gibberellin A₁ (374) followed by methylation gave Δ⁴-3,4-secoaldehyde 377 via acid 376. The initial methylation of 374 followed by photolysis also gave 377. The tetrahydro-compound 378 derived from 376 was treat-
ed with alkali to yield epimeric alcohols 379 and 380. Thus, this reaction should be a good evidence for the retro-aldol mechanism to epimerization of the 3-hydroxy-group of GA1 under the basic condition.

A formal synthesis of gibberellin A12 (340) was accomplished starting from l-abiatic acid. The synthetic route is summarized in Chart 16.

The n→π* photolysis of gibberellin C (381) and its methyl ester (382) was performed by Norrish I cleavage to form secoaldehydes 383 and 384, respectively. The subsequent intramolecular [2+2] cycloaddition of these secoaldehydes gave oxetane products 385 and 386.

Isosteviol (387) and steviol acetate (388) were efficiently metabolized by cultures of resuspended mycelium of Gibberella fujikuroi, mutant B1-41a. Isosteviol was exclusively converted into ring-CD-rearranged derivatives (389-392) of gibberellins A17, A18, A20, and 13-hydroxygibberellin A12. Steviol acetate was mainly trans-
formed into the 7β-hydroxy- and 6β, 7β-dihydroxy-derivatives and to the 13-acetates (393 and 394) of gibberellins A17 and A20.155

Microbiological hydroxylation of gibberellin A9 (395) and its methyl ester was investigated employing Gibberella fujikuroi, mutant B1-41a. Gibberellin A9 was principally metabolized into gibberellins A20 (396) and A40 (397). Other metabolites were detected by g.l.c.-mass spectrometry. Gibberellin A9 was partially metabolized by cultures of Rhizopus nigricans to give only gibberellin A10 (398). Gibberellin A9 methyl ester, however, was converted into the methyl esters of the 16α- and 16β-epimers (399 and 400) of 16,17-dihydro-16,17-dihydroxygibberellin A9, GA20 (396), GA40 (397), GA45 (401), and a monohydroxygibberellin A9 (possibly 402).156

Origin of the oxygen atoms in the lactone bridge of C19-gibberellins was studied. [18O]-Label in the 19-oic acid of the C20 gibberellins, GA12 (340) and GA12-alcohol (403), was incorporated without loss into C19-gibberellins by cultures of Gibberella fujikuroi, mutant B1-41a.157 Biological activities of fluorogibberellins and interactions with unsubstituted gibberellins were examined.158 A Japanese review,
Chemistry on Diterpenoids in 1976

whose title is “Recent advances of biosynthetic study of gibberellins”, was published.\textsuperscript{159} In a Japanese review on the inhibitors against isoprenoids biosyntheses, a biosynthetic route of gibberellin A\textsubscript{3} was briefly illustrated.\textsuperscript{160} A review “Studies on gibberellins in higher plants” was published in Japanese.\textsuperscript{161}

XII. ATISANE DERIVATIVES

The structures of staphigine (404) and staphirine (405), two novel bisditerpene alkaloids from \textit{Delphinium staphisagria}, were established utilizing \textsuperscript{13}C and \textsuperscript{1}H NMR spectroscopy.\textsuperscript{162} The structure elucidation of three novel alkaloids from \textit{D. staphisagria}, staphidine (406), staphinine (407), and staphimine (408), was accomplished.\textsuperscript{163} Staphisagnine (409) and staphisagrine (410), two new bis-diterpene alkaloids, were isolated from the mother liquors of the same plant.\textsuperscript{164}

The molecular structure of a minor product of oxidative cleavage of methyl ent-trachyloban-19-oate (411) with thallic acetate was determined as 412 by the X-ray analysis of the corresponding diol 413.\textsuperscript{165}
E. Fujita, K. Fuji, Y. Nagao, M. Node, and M. Ochiai

The construction of the substituted denudatine system by diene addition was reported. The outline is shown in Chart 17.

Two papers which were interesting for synthesis of atisane type diterpene alkaloids were published.

XIII. ACONANE DERIVATIVES

A new alkaloid, delphisine (414) was isolated from Delphinium staphisagria. Neoline (415) was prepared from delphisine (414) by several routes. Thus, 1α-hydroxy group of neoline was supported, and the revised structure 416 assigned by Marion...
et al. was proved to be in error. On the basis of other well-established chemical correlations, the structures of chasmanine and homochasmanine must also be revised to 417 and 418, respectively. Furthermore, the structure of chasmanine was established by an X-ray analysis of chasmanine 14α-benzoate (419) hydrochloride.

A new alkaloid whose structure was elucidated as 416 was isolated from the same plant source. Structure 420 was assigned to alkaloid A isolated from Delphinium bicolor by the examination of its 13C NMR spectrum. The structure and absolute configuration of excelsine (421) was determined by an X-ray analysis of its hydroiodide. The X-ray analysis of the compound 422 which was synthesized from atisine was reported.

An important intermediate 423 for the total synthesis of chasmanine (417) was synthesized as shown in Chart 18.

In a review article titled "the diterpenoid alkaloids of Delphinium staphisagria" was described the chemistry of aconane type alkaloids together with other alkaloids.

XIV. TAXANE DERIVATIVES

No papers have been published on the title topics in 1976.

XV. THE OTHERS

New diterpenes, flexibilene (424), 6-hydroxysinulariolide (425), 11-dehydro-sinulariolide (426), (E)-(−)-cembrene A (427), and 3, 4:11, 12-diepoxycecmbrine A (428) were isolated from the soft coral, Sinularia flexibles, as the minor diterpenoids.
Duva-4, 8, 13-triene-1, 3-diol (429) found in the leaf wax of *Nicotiana tobacum* was shown to have highest concentration in the wax from young leaves and quantitatively decrease in importance with leaf age. Absolute stereochemistry of mukulol (430) was determined by chemical correlation with cembrene A (427) and (+)-cis-piperitol (431). The biogenetic type cyclization of geranylgeranic acid chlorid (432) followed by a series of reactions via rac-mukulol (430) afforded rac-cembrene (433). Incensole (434) was also synthesized from rac-mukulol (430). A total synthesis of casbene (436) from methyl rac-cis-chrysanthemate (435) was accomplished. The outline is shown in Chart 19.

Jones oxidation of cembrene (433) has been carried out and the products were analyzed in detail. The conformation and relative stereochemistry of ovatiodiolide (437) isolated from *Anisomeles ovata* were studied by $^1$H NMR spectroscopy. X-ray analyses were also done to confirm the structures of ovatiodiolide (437) and acid cyclization product 438. The molecular structure and absolute configuration of jatrophone (439), $p$-iodobenzoate (440) of jeunicin isolated from *Eunicea mammosa*, and new thunberganoid 441 were determined by the X-ray analysis.
Four new diterpenes, jolkinols A (442), B (443), C (444), and D (445), were isolated from *Euphorbia jolkini*. The structures of dictyol A (446) and B (447) isolated from the brown alga, *Dictyota dichotoma*, were determined on the bases of spectroscopic and chemical evidence. These diterpenes were also isolated from the digestive gland of the molluscs, *Aplysia depilans*. Independent examination of the constituents of the red alga, *Sphaerococcus coronopifolius*, by two groups led to the isolation of closely related diterpenes, sphaerococcenol A (448) and bromosphaerocol (449).

Uniquely different class of diterpenes were isolated from the marine animal
E. Fujita, K. Fuji, Y. Nagao, M. Node, and M. Oghai

sources. One of them was isolated from Dollabella californica and assigned structure 450,\textsuperscript{193} Dolatriol (451) and dolatriol 6-acetate (452) were isolated from Dollabella auriculata,\textsuperscript{194} The structure of jatrophastrione (453), a constituent of the chloroform extract of Jatropha macrorhiza, was determined by an X-ray analysis.\textsuperscript{195} It was found to possess inhibitory activity toward the P-388 lymphocytic leukemia test system. The structure of icetexone (454) isolated from Salvia ballotaeflorae was determined from diffractometer data by direct methods.\textsuperscript{196} Furthermore, X-ray analyses were effectively used for determination of several new diterpenes, 18-hydroxydecipia-2(4), 14-dien-1-oic acid (455) from Eremophila decipiens,\textsuperscript{197} gnidimacrin (456) and its 20-palmitate (457), macrocyclic antileukemic diterpenoid esters from Gnidia subcordata\textsuperscript{198}, cinnzeylanine (458) and cinnzeylanol (459) from Cinnamonum zeylanicum,\textsuperscript{199} and prostratin (460) from Pimelea prostrata.\textsuperscript{200}

![Chemical structures and diagrams](image-url)

Chemical evidence for prostratin (460) was given by Hecker et al.\textsuperscript{201} The new potent antileukemic principles, gnidilatin 20-palmitate (461), gnidilatidin 20-palmitate
Chemistry on Diterpenoids in 1976

(462), and gnidilatin (463), and the new toxic diterpenoids, gnidilatidin (464) and gnidiglaucin (465) were isolated from Gnidia species. Gnidilatidin (464) was independently isolated from Daphne odora as a nematicidal constituent named odoracin.

From the resin isolated from latex of Euphorbia poisonii in Nigeria, four diterpenoids, 466-469, were isolated. Among these, 467 and 468 were new natural products. The dried latex of the same plant was exhaustively extracted with acetone, from which compounds 470 and 471 were isolated. A new cryptic irritant and cocarcinogen 472 was isolated from seeds of Croton sparciflorus.

The structure of TG-2 (473), one of the major constituents of the soldier secretions of Tinervitermes gratiosus, was determined by an X-ray analysis. Five other congeners TG-1 (474), TG-3 (475), and TG-4 (476) from T. gratiosus, TB-1 (477) and TB-3 (478) from T. bettonianus, were isolated and their structures were elucidated from spectral studies. TG-1 was identical with TB-2 isolated from T. bettonianus.

Two new diterpenes, maritinol (479) and stemodinol (480), were isolated from Stemodia maritima. After the intraperitoneal administration of retinoic acid (481) to rats, three urinary metabolites 482, 483, and 484 were isolated and identified.
Biosynthetic studies of fusicoccin (485) and fusicoccin J (486) and H (487) using [3-\(^{13}\)C]-mevalonic acid lactone revealed that a polypropylenyl pyrophosphate precursor cyclizes in a manner different to that previously observed in the biosynthesis of the ophiobolins.\(^{211}\)

Ingenol 3, 20-dibenzoate (488) and phorbol 12-tiglate 13-decanoate (489) were isolated from *Euphorbia esula* and *Croton tiglium*, respectively and characterized as antileukemic components.\(^{212}\) A number of derivatives of pleuromutilin (490) were prepared\(^{213,214}\) and bactericidol activity of some derivatives were tested.\(^{213}\) The structural relationship of phorbol-12-myristate-13-acetate and cortisol was discussed and a possible mechanism for the tumor promoting activity of phorbol was presented.\(^{215}\)

Many kinds of diterpene resin acids were isolated from *Pinus densiflora* needles and cortex.\(^{216}\) Isolation of free cis- and trans-phytrol from the red alga *Gracilaria andersoniana* was reported.\(^{217}\)

In a review titled “Diterpenoids of Isodon and Teucrium Plants”, many kaurane- and clerodane-derivatives were described.\(^{218}\) In a review titled “Biosynthetic Studies with \(^{13}\)C-Labeled Precursors”, examples on some diterpenoids, e.g. virescenol B, gibberellic acid, aphidicolin, and fusicoccin, were described.\(^{56}\) Another review concerning the biosynthesis of isoprenoids appeared in Japanese.\(^{210}\)

**ADDENDUM TO III.**

The bled resin of *Araucaria imbricata* (*A. araucana*) was examined and nine labdane derivatives, 491-499, were isolated.\(^{220}\) Among them, compounds 492, 495, and 497 had been reported.
Chemistry on Diterpenoids in 1976

REFERENCES


H. Mizuno, T. Ohsawa, and A. Tahara, ibid., 24, 1527 (1976).
A. Tahara, Y. Harigaya, and M. Onda, ibid., 24, 1497 (1976).
Chemistry on Diterpenoids in 1976

34, 920 (1976).


(82) S. Ito and M. Kodama, Heterocycles, 4, 595 (1976).


(86) A. Cronlund, ibid., 13, 175 (1976).


(95) H. Obermann and G. Spitteller, ibid., 109, 3540 (1976).


E. Fujita, K. Fuji, Y. Nagao, M. Node, and M. Ochiai


(151) T. Nakata and the late A. Tahara, ibid., 1515 (1976).


(159) K. Wada and T. Ishida, ibid., 14, 748 (1976).


(170) S. W. Pelletier, N. V. Mody, A. J. Jones, and M. H. Benn, ibid., 3025 (1976).


(536)


(175) S. W. Pelletier and N. V. Mody, Heterocycles, 5 [Special Issue (Dec. 1)], 771 (1976).


E. Fujita, K. Fuji, Y. Nagao, M. Node, and M. Ochiai

(1976).


(218) E. Fujita, Y. Nagao, and M. Node, Heterocycles, 5 (Special Issue), 793 (1976).
