

The Chemistry on Diterpenoids in 1968

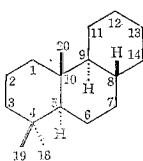
Eiichi FUJITA*

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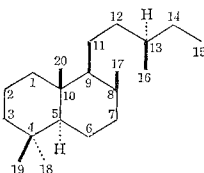
I. INTRODUCTION

The author has published a series of the reviews.^{1~4)} This review deals with an outline of the chemical works on diterpenoids in 1968.

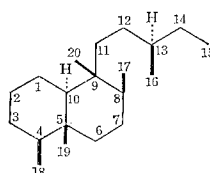
The classification consists of podocarpene, labdane, clerodane, pimarane, isopimarane, abietane, totarane, cassane, kaurane, gibberellane, atisane, aconane, beyerane, taxane, and the others, in accordance with a poposal** for systematic nomenclature subscribed to by most workers in this area.⁵⁾



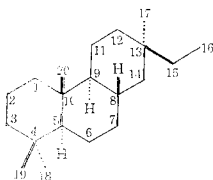
Podocarpene



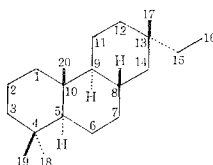
Labdane



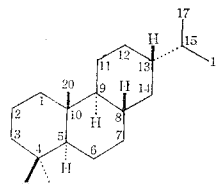
Clerodane



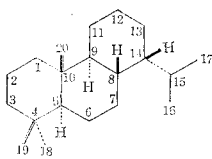
Pimarane



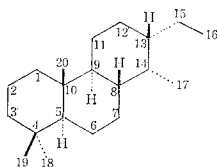
Isopimarane



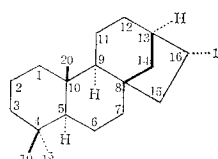
Abietane



Totarane



Cassane

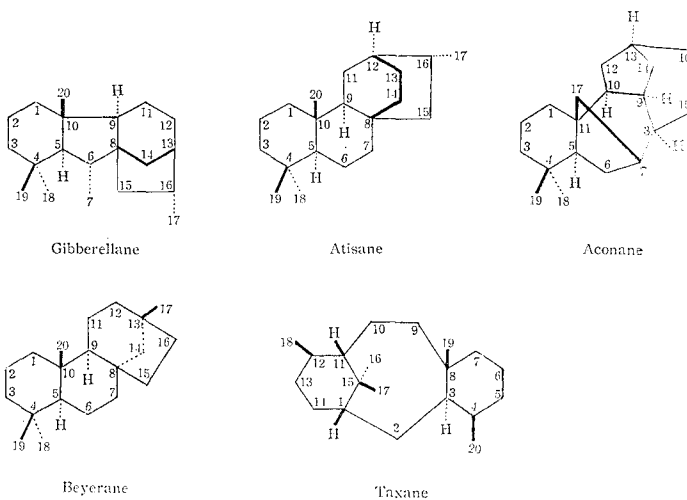


Kaurane

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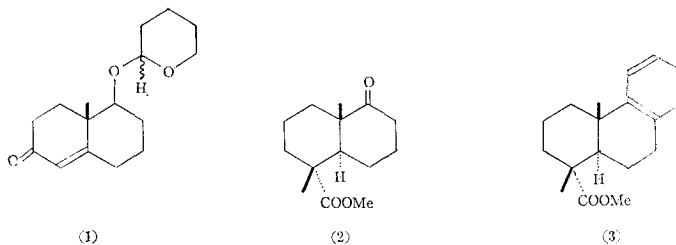
** The IUPAC Commission on the Nomenclature of Organic Chemistry has discussed these proposals and considered that they are as a whole in accordance with the general principles of the nomenclature of organic chemistry.

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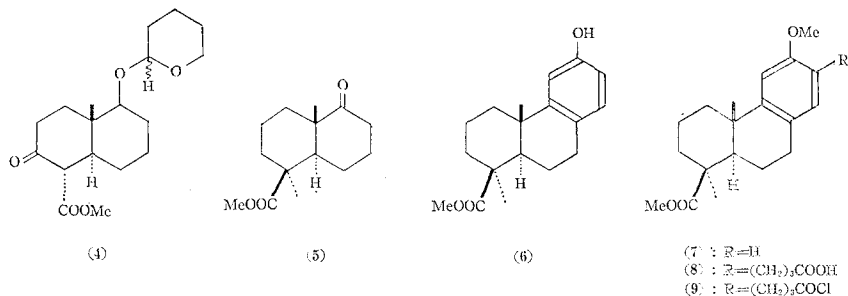


II. PODOCARPANE DERIVATIVES

Methyl *rac*-deisopropyldehydroabietate (3)^{*3} was derived from 1^{*3} *via* 2^{*3} by Spencer *et al.*⁶⁾ The synthesis was developed to that of podocarpic acid, that is,



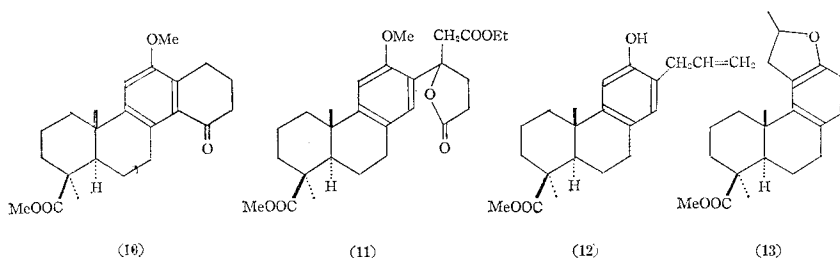
methyl *rac*-podocarpate (6)^{*3} was synthesized⁷⁾ from 4^{*3} *via* 5.^{*3} Methyl 12-methoxypodocarpa-8, 11, 13-trien-19-oate (7) was converted into 8. The corresponding acid chloride 9 was subjected to Friedel-Crafts cyclization to yield D-



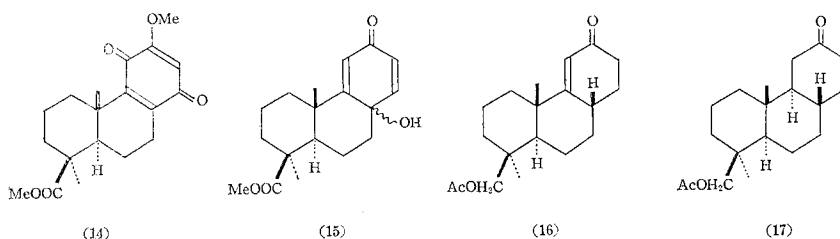
homosteroid 10. Lactone 11 was formed by Reformatsky reaction of 13-succinyl derivative. The rearrangement of C-12 O-allyl ether gave normal C-13 allyl

^{*3} Represented as one enantiomer.

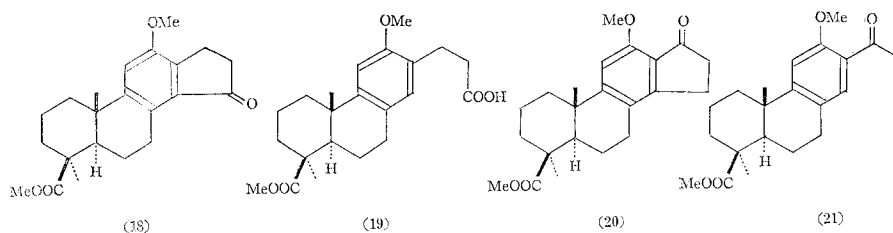
The Chemistry on Diterpenoids in 1968



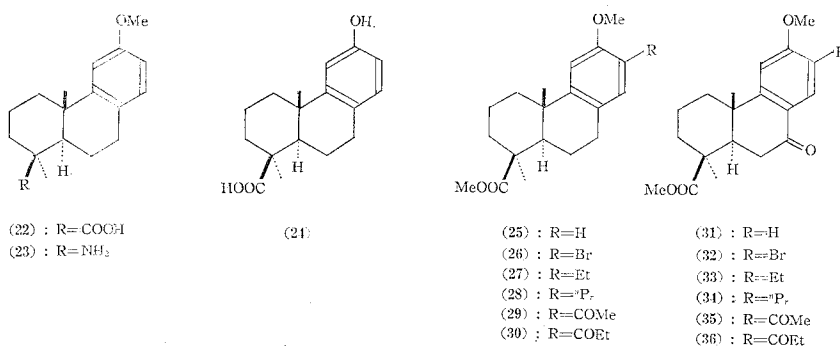
phenol **12** and coumaran **13**. Peracid oxidation of **7** gave the expected quinone **14** and hydroxy dienone **15**. Unsaturated ketone **16** on photolysis in methanol gave only the corresponding saturated ketone **17**.⁸⁾



Compound **18** was prepared from **19** in a fair yield, but attempted cyclization of compounds possessing a 1'-substituted-2'-carboxyethyl side chain at C-13 was unsuccessful. The C-17 ketone **20** was obtained in low yield from the 13-acrylyl

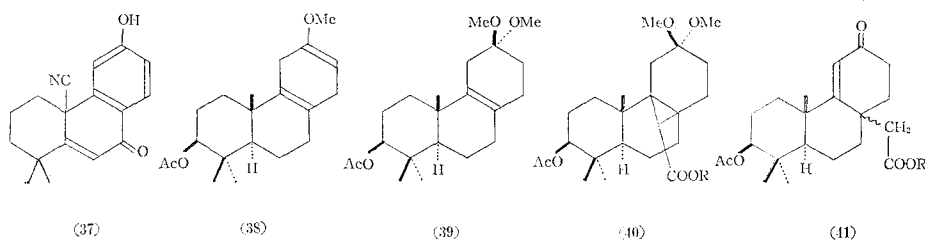


compound **21**.⁹⁾ The conversion of O-methylpodocarpic acid (**22**) into 12-methoxy-19-norpodocarpa-8, 11, 13-trien-4-amine (**23**) was investigated.¹⁰⁾ A variety



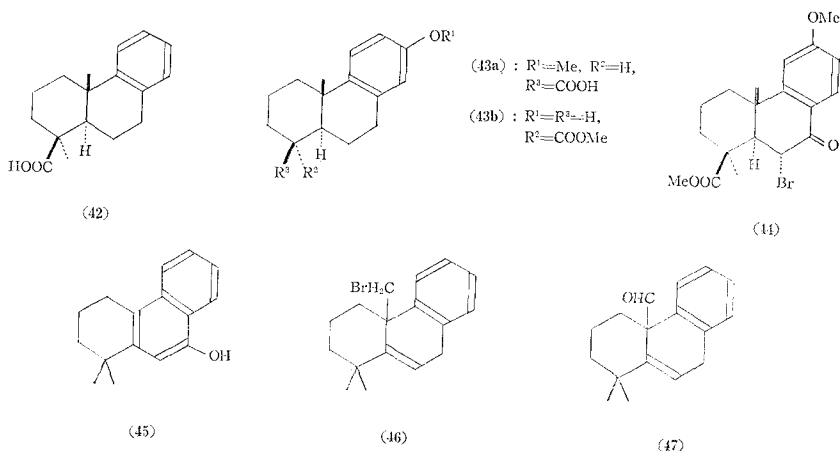
of derivatives of podocarpic acid (24), for instance, 25~30, gave their corresponding 7-oxo-compounds, 31~36 in moderate to good yield by a brief treatment with bromine in ether, preferably containing a free-radical initiator such as benzoyl peroxide, followed by hydrolysis.¹¹⁾

10-Cyano-12-hydroxy-7-oxo-20-norpodocarpa-5, 8, 11, 13-tetraene (37), a model for tricyclic C-aromatic diterpenoids, was synthesized.¹²⁾



Stipanovic and Turner¹³⁾ attempted to synthesize 41 from 38 *via* 39 and 40, but the reaction of diazoacetic ester on 39 was unsuccessful and 40 was not obtained. They examined the same reaction using more simple models.

A stereoselective synthesis of *rac*-desoxypodocarpic acid (as 42) and *rac*-13-methoxydesoxypodocarpic acid (as 43a) was reported by Ireland and Giarrusso.^{14a)} Methyl 13-hydroxydeisopropyldehydroabietate (43b) was synthesized by an Indian group.^{14b)} The stereochemistry of 6-bromo-7-oxo derivative 44 was established by X-ray analysis. Bromination of sugiyl methyl ether was examined.¹⁵⁾ Conformational analysis of 6-bromo-7-oxopodocarpic acid derivatives was tried by application of the Nuclear Overhauser Effect.¹⁶⁾ Okamoto *et al.*¹⁷⁾ published a

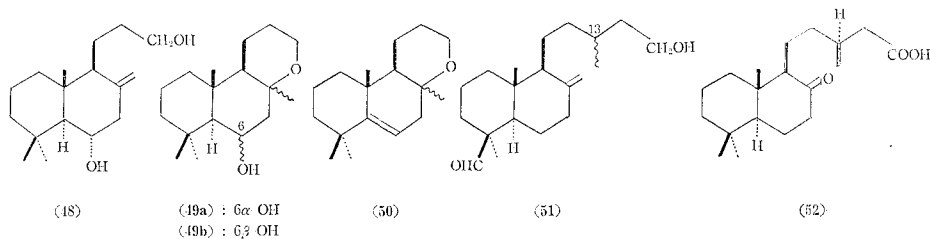


new method for angular formylation using Reimer-Tiemann's reaction. They prepared 47 *via* 46 starting from 45.

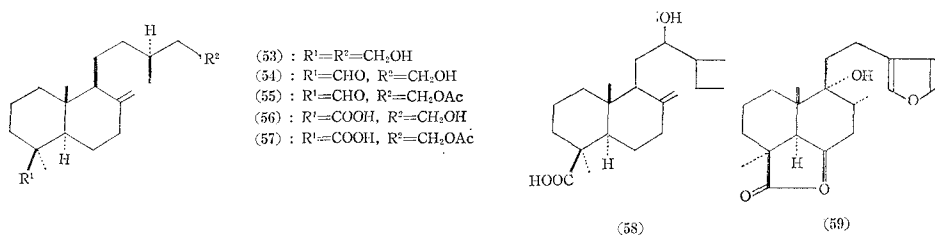
III. LABDANE DERIVATIVES

14, 15, 16-Trisnor-labd-8(17)-ene-6 α , 13-diol (48) was subjected to cyclization

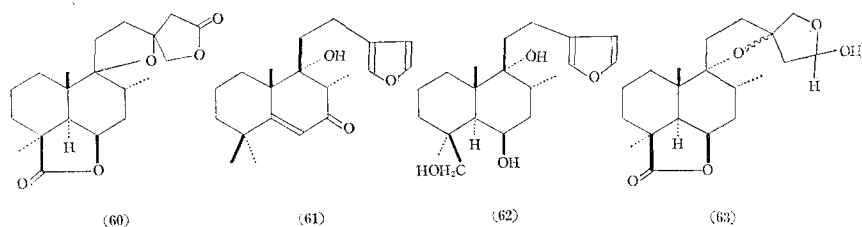
in the presence of p-toluenesulfonic acid to give 6 α - and 6 β -hydroxy-8,13-oxido-14,15,16-trisnorlabdane (49a, b), which were dehydrated to yield a same unsaturated product 50.¹⁸⁾ 19-Oxo-labd-8(17)-en-15-ol (51) (imbricatolal), from the



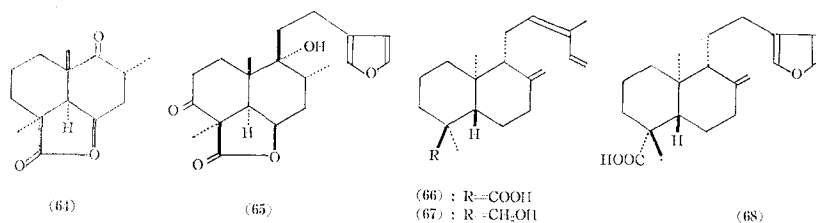
oleoresin of *Araucaria imbricata*, was converted into 17-nor-8-oxy-labdan-15-oic acid (52) by Bruns.¹⁹⁾ Thus, the S-configuration at C-13 in imbricatadiol (53), imbricatolal (51=54), imbricatolal-15-acetate (55), imbricatolic acid (56), and imbricatolic acid-15-acetate (57) was proved.



From *Juniperus phoenicea*, 12-hydroxylabd-8(17)-en-19-oic acid (58) was isolated.²⁰⁾ Mangoni and Adinolfi^{21,22)} established the stereochemistry of marrubiin, especially that of C-9 hydroxy group, as shown in formula 59. The structures of compounds X and Y, two labdane diterpenoids isolated together with marrubiin from *Leonotis leonurus*, were elucidated as shown in formulas 60 and 61, respectively.²³⁾ In the absence of pyridine dehydration of marrubiin with phosphorus trichloride appears to yield exclusively the $\Delta^9(11)$ -olefin whereas in its presence the Δ^8 -isomer predominates.²⁴⁾ From *Marrubium vulgare*, marrubenol (62) and the hemiacetal 63 were isolated besides marrubiin.²⁴⁾ A partial synthesis

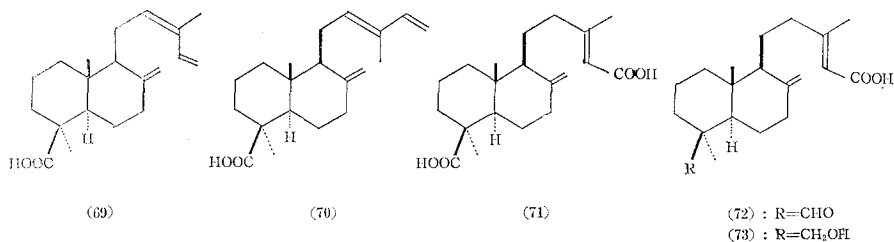


of marrubiin from compound 64 was carried out.²⁵⁾ From *Marrubium incanum* a new diterpenoid 65,²⁶⁾ whose physical properties correspond with those described by L. A. Salei *et al.*,²⁷⁾ was isolated. A full paper on the structure 66 of ozic

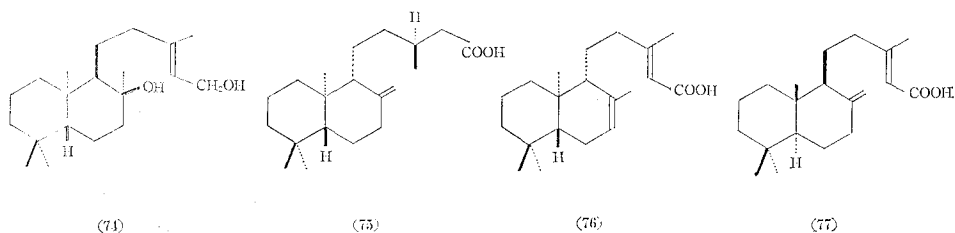


acid isolated from the wood of *Daniellia ogea* was published.²⁸⁾ The corresponding alcohol, ozol (67) was also isolated. From the wood of *D. oliveri* daniellic acid (68) was isolated. Chromic acid oxidation of sclareol was investigated and isolation of at least seven compounds was effected by chromatography of the methylated products. No pimarane derivatives were obtained.²⁹⁾

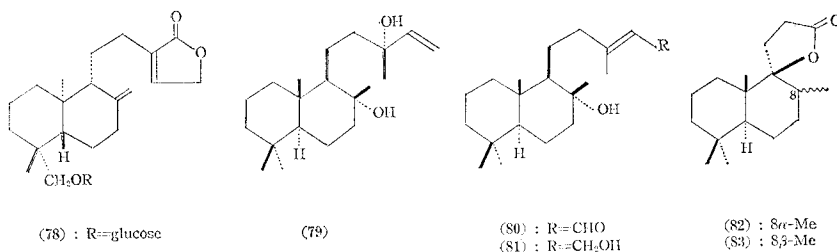
From oleoresin of black kauri *cis*- (69) and *trans*-communic acid (70), abietic acid, neoabietic acid, agathic acid (71), methyl agathate, and a new aldehydic carboxylic acid, agathalic acid (72) were isolated. The latter was reduced to agatholic acid (73) by sodium borohydride.³⁰⁾ From the dry leaves of *Aphana-*



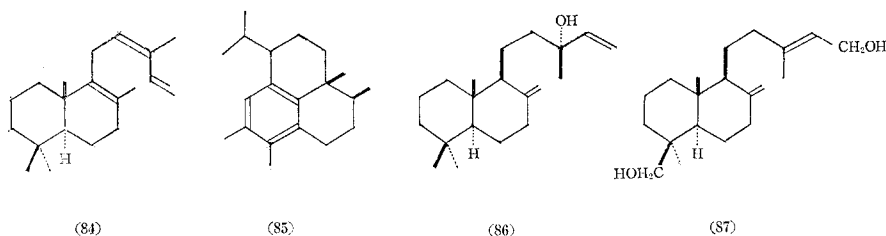
mixis polystachya aphanamixol (74) was isolated.³¹⁾ Eperuic acid (75), its Δ^7 -isomer, *ent*-7, 13-labdadien-15-oic acid (76), 8(17), 13-labdadien-15-oic acid (77), and the enantiomer (named "copalic acid") of 77 were isolated from *Oxystigma oxyphyllum*.³²⁾



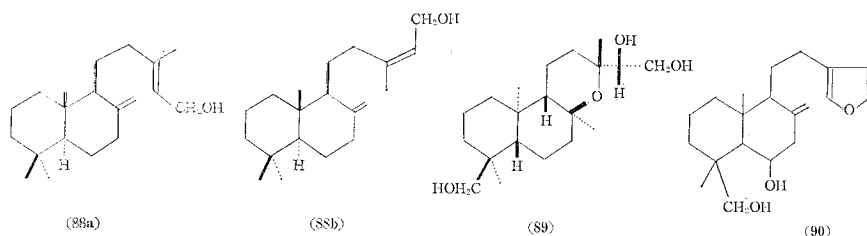
The structure 78 was proposed for neoandrographolide, a diterpene glucoside from *Andrographis paniculata*.³³⁾ Dehydration investigation of sclarealdehyde (80), a product from chromic acid oxidation of sclareol (79) was reported.³⁴⁾ The chromic acid oxidation product of sclareol, which was a mixture containing sclarealdehyde (80), was subjected to lithium aluminum hydride or sodium borohydride reduction. From the reaction mixture, diol 81 was isolated as acetate.³⁵⁾ Two new isoambreinolides, 82 and its 8-epimer 83, were synthesized and characteriz-



ed.³⁶⁾ Ruzicka and Janot³⁷⁾ treated sclareol (79) with β -naphthalenesulfonic acid at 190° and got a hydrocarbon C₂₀H₃₂, to which they assigned structure 84. Carman and Dennis³⁸⁾ reinvestigated the reaction and got a hydrocarbon C₂₀H₃₀, to which they assigned structure 85. They provided a rearrangement mechanism for the product formation. Manool (86) and agathadiol (87) cyclize in formic



acid to the 13-epimeric pimara-8, 15-dienes and 14 α -hydroxybeyerane derivatives. The mechanistic and biosynthetic implications of these results and the nuclear magnetic resonance spectra of relevant tricyclic and tetracyclic diterpenes were discussed.³⁹⁾ Manool (86), 13-epimanool, and the allylic primary alcohols 88a and 88b were subjected to acid-promoted dehydration [AcOH-H₂O-H₂SO₄ (83 : 10 : 7) at

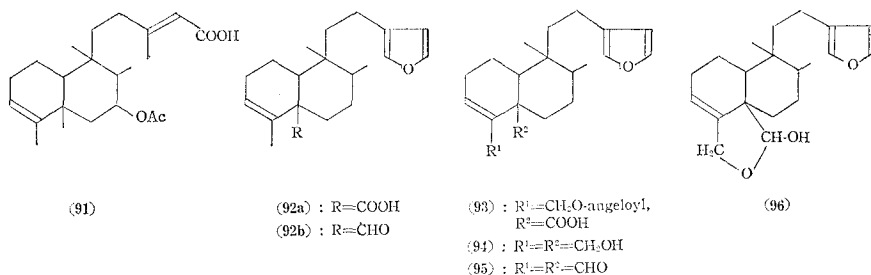


50°]. The four labdadienols gave product mixtures of essentially similar composition which varies with time. Their *in vitro* conversion into pimara- and rosa-dienes was discussed.⁴⁰⁾ A new diterpene triol was isolated from *Goodenia ramelii*, and structure 89 was assigned to it.⁴¹⁾ Extracts of the leaves of *Psiadia altissima* contained diterpenoid glycosides, the major aglycone of which is probably 90.^{81b)}

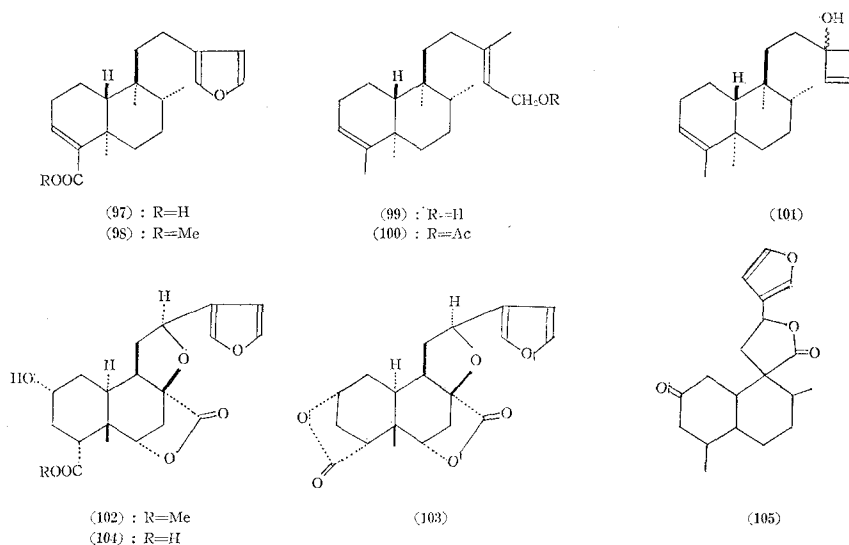
IV. CLERODANE DERIVATIVES

A bitter principle was isolated from the roots of *Solidago altissima* and named solidagonic acid, whose structure 91 was elucidated by Kotake *et al.*⁴²⁾ From

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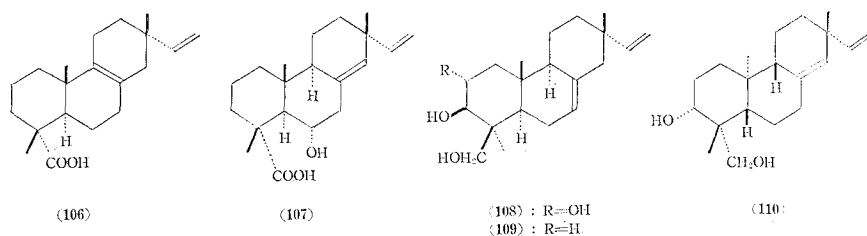
the roots of *Solidago serotina* furan-containing clerodane derivatives were isolated and structures 92 to 96 were tentatively assigned to them.⁴³⁾ The absolute configuration 97 was assigned to (-)-hardwickiic acid.^{44a)} Kolavelool (101) and methyl hardwickiate (98) were derived from kolavenol (99) and its acetate (100), respectively.^{44b)} Constitution and configuration of diosbulbin -A, -B, and -C were elucidated as 102, 103 and 104 by chemical and physical methods. They were



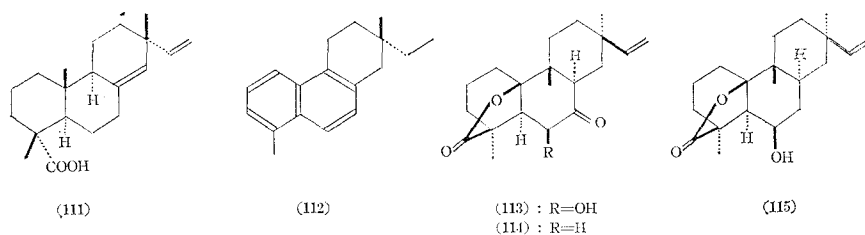
isolated from Dioscoreaceous plants.⁴⁵⁾ The full paper of the assignment of structure 105 to crotonin, a norditerpene from *Croton lucidus*, was published.⁴⁶⁾

V. PIMARANE AND ISOPIMARANE DERIVATIVES

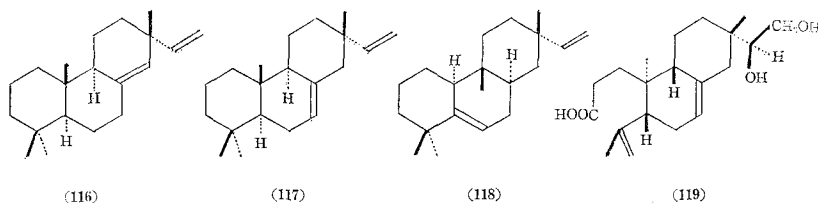
8, 15-Isopimaradien-18-oic acid (106) was isolated as methyl ester from balsam of *Pinus peuce*.⁴⁷⁾ From the acidic fraction of the extract of *Juniperus phoenicea* a new hydroxyacid diterpene was isolated and characterized as 6 α -hydroxysandaracopimaric acid (107).⁴⁸⁾ The structures of virescenol A and B, metabolites of *Oospora virescens*, were elucidated as shown in formulas 108 and 109, respectively.⁴⁹⁾ They readily undergo an acid-catalyzed isomerization to afford isovirescenol A and B, which have $\Delta^{8(9)}$ instead of Δ^7 . Isolation and constitution of oblongifolol, a new diterpene of *Croton oblongifolium*, was reported. Its structure was



shown to be *ent*-3 β ,19-dihydroxypimara-8(14),15-diene (110).⁵⁰⁾ Sandaracopimaric acid (111) was synthesized starting from testosterone acetate *via* 14 steps.⁵¹⁾ As catalytic dehydrogenation product of sandaracopimaric acid (111), compound 112 had been obtained. Now, this optically active compound was synthesized from R-($-$)-methylethylsuccinic acid (mono methyl ester) and 5-methylnaphthylmagnesium bromide.⁵²⁾ Isolation and structure of a new diterpene lactone from *Trichothecium roseum* was published. The substance was formulated as 6 β -hydroxyrosenonolactone (113) on the basis of chemical and spectroscopic evidence.



Circular dichroism data on lactones possessing the same skeleton were discussed.⁵³⁾ Biosynthesis of rosenonolactone was studied. Geranylgeraniol was incorporated in rosenonolactone (114). In the course of biosynthesis the hydride shift from C-9 to C-8 should be involved. This proposal was proved to be correct by feeding of doubly-labelled 4R-[4³H: 2-¹⁴C] mevalonic acid lactone. Deoxorosenonolactone was incorporated into rosenonolactone (114) and rosololactone (115).⁵⁴⁾



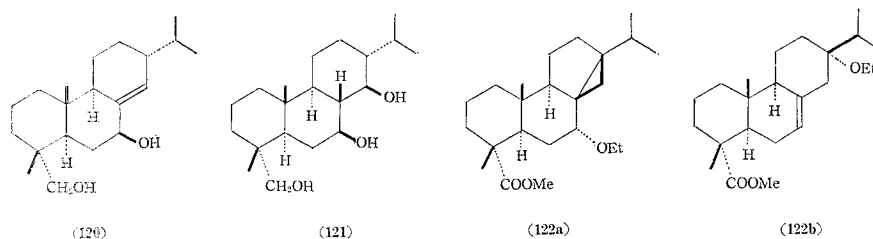
Manool (86) was treated with formic acid in chloroform to give three pimarane and isopimarane derivatives and a beyerane derivative. From the products sandaracopimaradiene (116), isopimaradiene (117), and rimuene (118) were derived chemically.⁵⁵⁾ The similar experiments on cyclization of manool were reported.^{39,40)}

A new acid was isolated from *Beyeria brevifolia*, and its structure was eluci-

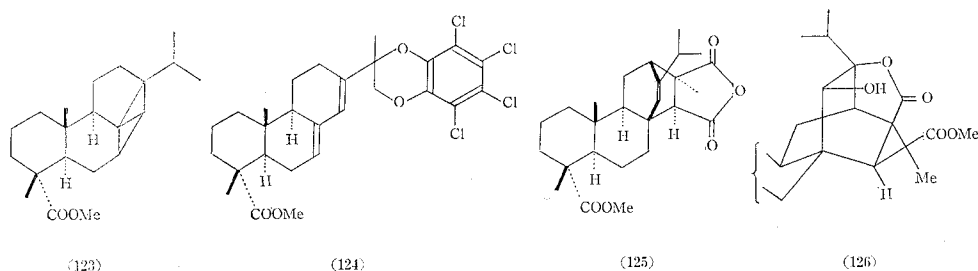
dated as shown in 119.⁵⁶⁾

VI. ABIETANE AND TOTARANE DERIVATIVES

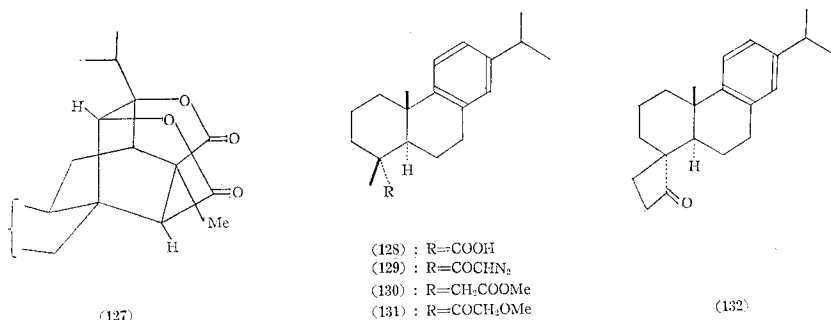
Monohydroboration-oxidation of abietic acid and methyl abietate with both diborane and *t*-2, 3-dimethylbutylborane led to preferential attack on the 7, 8-double bond to give 7-hydroxy-8(14)-enes, *e.g.*, 120. Dihydroboration-oxidation with these reagents yielded mainly 7 β , 14 β -dihydroxy derivatives, *e.g.*, 121, with smaller



amounts of the 7 α , 14 α -dihydroxy-compounds and a third 7, 14-diol of unknown stereochemistry.⁵⁷⁾ Abietic acid in absolute ethanol was irradiated for 96 hours with 2537Å light in the absence of oxygen and then esterified with diazomethane. Chromatography of the crude product on silica gel gave 122a and 122b. The formation of 122a involves the bicyclobutane intermediate 123.⁵⁸⁾ Treatment of



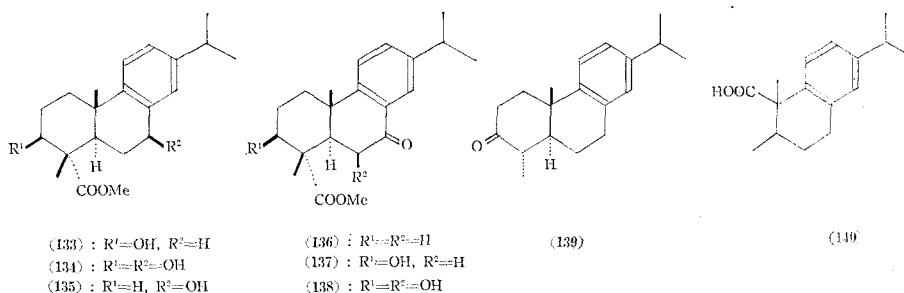
methyl abietate with tetrachloro-*o*-benzoquinone in xylene gave a solid adduct, to which structure 124 was assigned on the basis of spectroscopic investigation.⁵⁹⁾ Diels-Alder adducts of citraconic anhydride and methyl resinates were investigated. An adduct 125 was converted into the epoxide, which was subjected to acidic methanolysis to give 126. The latter was transformed into dilactone 127.⁶⁰⁾ Oxi-



dation of methyl abietate by monoperphthalic acid was investigated.⁶¹⁾ Methyl 12-acetyldehydroabietate was subjected to potassium borohydride reduction to give two kinds of alcohols, which were regarded as rotational isomers between two large substituents at C-11 and C-12. Similarly, lithium aluminum hydride reduction of the same material yielded two kinds of diols.⁶²⁾

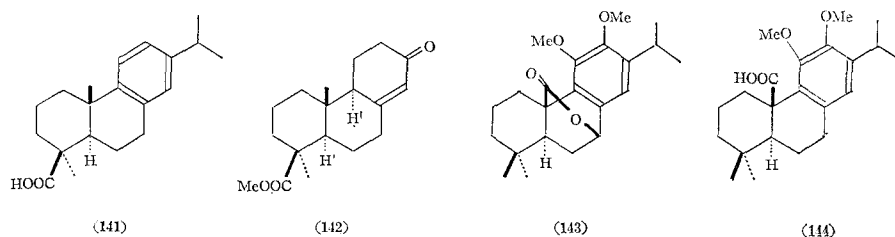
Treatment of the diazomethyl ketone **129**, derived from dehydroabietic acid (**128**), with a suspension of silver oxide in methanol afforded methyl homodehydroabietate (**130**) (55 %), a liquid ketone **131** (20 %), and a ketone **132** (22 %).⁶³⁾ Methyl 12- ω -bromoacetyldehydroabietate was heated with thiourea in EtOH to yield methyl 12-(2-amino-5-thiazolyl)-dehydroabietate. Methyl 12-(α -bromopropionyl)-dehydroabietate was treated with thiourea to afford methyl 12-(2-amino-4-methyl-5-thiazolyl)-dehydroabietate.⁶⁴⁾

Incubation of methyl dehydroabietate (methyl ester of **128**) with *Corticium sasakii* yielded methyl 3β -hydroxydehydroabietate (**133**) and methyl $3\beta,7\beta$ -dihydroxydehydroabietate (**134**). Both of 3β -hydroxy **133** and 7β -hydroxy-derivative **135** on incubation with *C. sasakii* gave diol **134**. Incubation of methyl 7-oxode-



hydroabietate (**136**) afforded methyl $3\beta,6\beta$ -dihydroxy-7-oxodehydroabietate (**138**) via 3β -intermediate **137**. Hydroxylation appears to occur first in the C-3 β position, then in the C-6 β or C-7 β position of the dehydroabietanes. Oxygenation of dehydroabietanes at C-3, C-6, or C-7 by this fungal oxidase is analogous to the position of oxygenation of dehydroabietanes obtained from *Juniperus* trees.⁶⁵⁾ Degradation of dehydroabietic acid by bacteria (*Flavobacterium resinovorius*) to 3-oxo-19-nor-dehydroabietane (**139**) and the proposed pathway were reported.⁶⁶⁾ Methyl dehydroabietate was subjected to microbial degradation by *Arthrobacter* sp. isolated from lodgepole pine to give dehydroabietic acid, methyl 3-oxodehydroabietate, and compound **140** (as methyl ester).⁶⁷⁾

An investigation on the resins of several *Callitris* species (Cupressaceae) led



to isolation of callitrisic acid (141), a new diterpenoid.⁶⁸⁾ The *rac*-callitrisic acid was synthesized from an intermediate 142.^{69a,b)} *rac*-Carnosol dimethyl ether (as 143) and *rac*-carnosic acid dimethyl ether (as 144) were synthesized.⁷⁰⁾ β -Keto-sulfoxide was effectively used for condensation in the synthesis as shown in Chart 1.

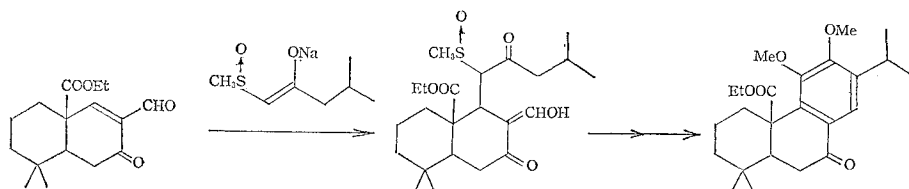
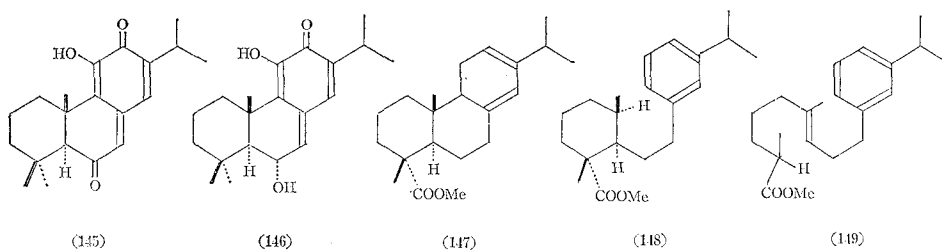
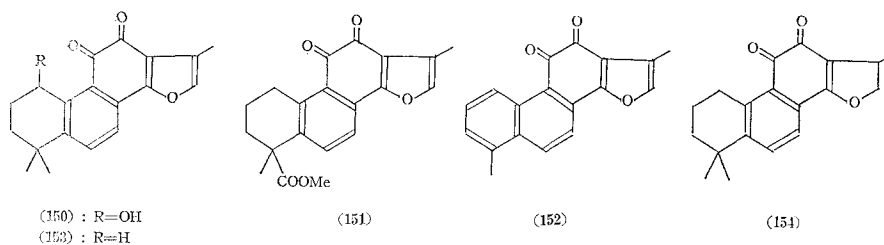


Chart 1

Two novel diterpenoid quinone methides, taxodione (145) and taxodone (146), were isolated from *Taxodium distichum*. Each showed significant inhibitory activity against the Walker carcinosarcoma 256 in rats, at 40 and 25 mg/kg, respectively.⁷¹⁾ Novel ring openings in methyl levopimarate (147) were investigated at 200° in the presence of catalytic amount of KOH. The products were found to be 148, 149, and *cis* isomer of 149.⁷²⁾ From dried red roots of *Salvia miltior-*



rhiza, two novel pigments, hydroxytanshinone (150) and methyl tanshinonate (151) were isolated.⁷³⁾ Total syntheses of tanshinone-I (152), -II (153), and cryptotanshinone (154) were published by two groups.^{74a,b)} Another short-step syn-



theses were also reported.⁷⁵⁾ A stereoselective formation of a tricyclic system and the total synthesis of *rac*-fichtelite (as 155) was reported by Johnson *et al.*⁷⁶⁾ The outline is shown in Chart 2.

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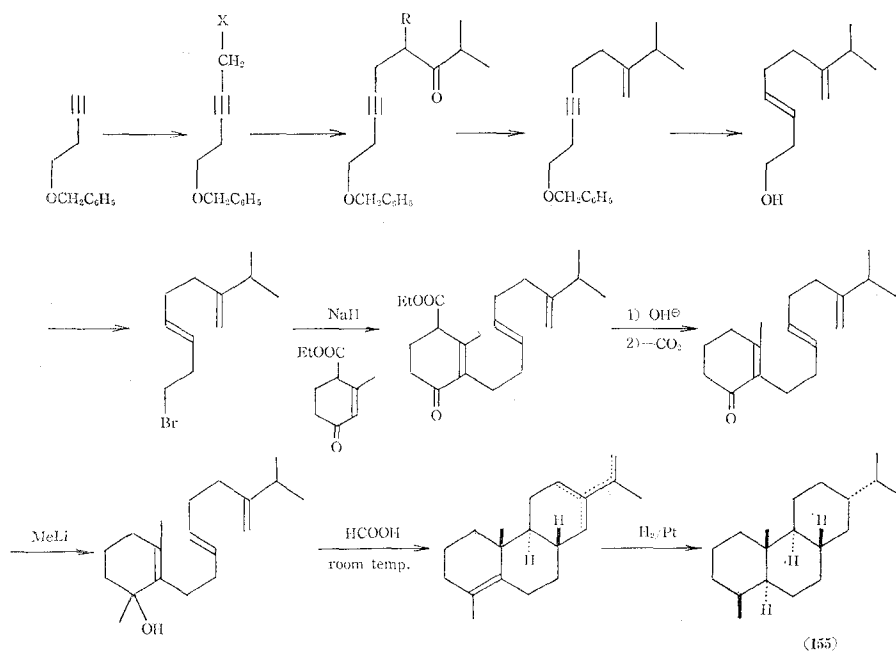
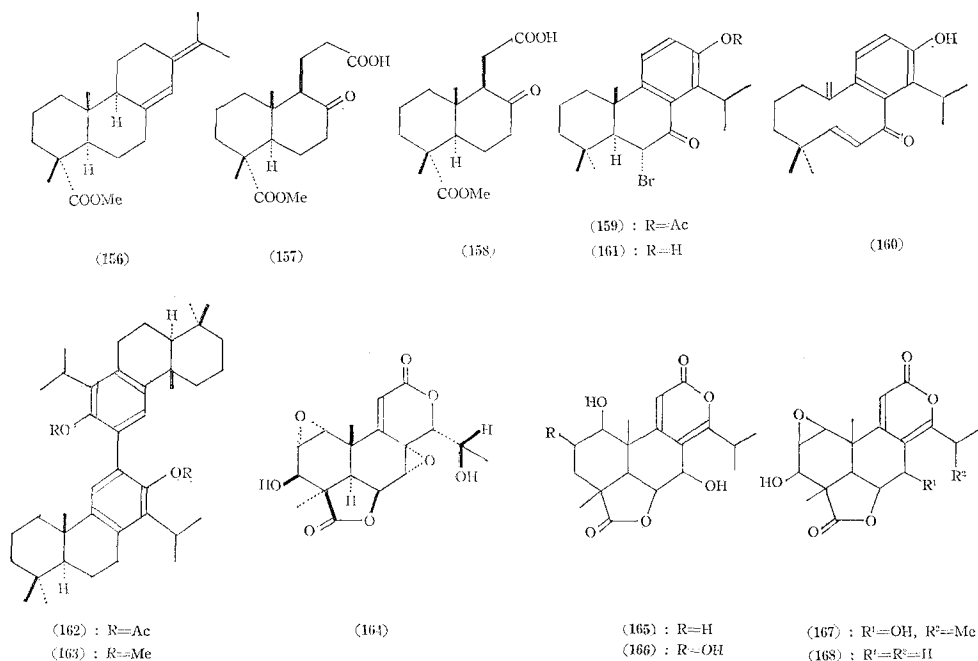


Chart 2

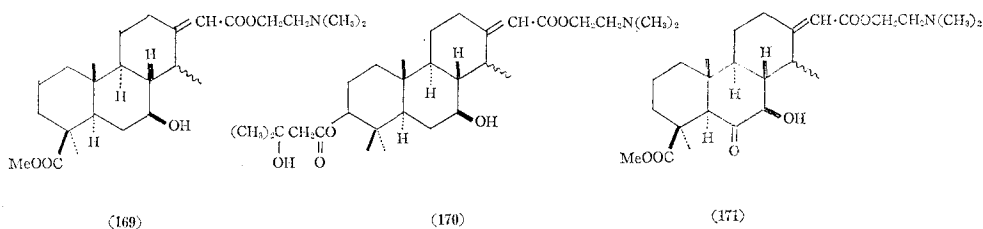
Deamination of 18-nor-4-amino-abieta-8, 11, 13-triene was investigated.⁷⁷⁾ Oxidative degradation of methyl neoabietate (156) and methyl levopimarate (147) yielded 157 and 158, respectively, both of which can be used as good intermediates for synthesis of diterpenoids.⁷⁸⁾



6 α -Bromo-7-oxototaryl acetate (159) was treated with NaHCO₃ in DMSO to give α , β -unsaturated ketones (4⁵) (60 %) and a secoditerpenoid 160 (5 %). The high yield (80 %) of 160 was achieved when 6 α -bromo-7-oxototarol (161) was used.⁷⁹⁾ A nuclear magnetic resonance study of hindered rotation in biphenyls was carried out using podototarol diacetate (162) and podototarol dimethyl ether (163).⁸⁰⁾ The structure 164 was assigned to inumakilactone A, a bitter bisnorditerpenoid, isolated from the wood of *Podocarpus macrophyllus*.⁸¹⁾ Structures of nagilactone, A (165), B (166), C (167), and D (168), novel nor- and bisnor diterpenoids isolated from *Podocarpus Nagi*, were elucidated.⁸²⁾

VII. CASSANE DERIVATIVES

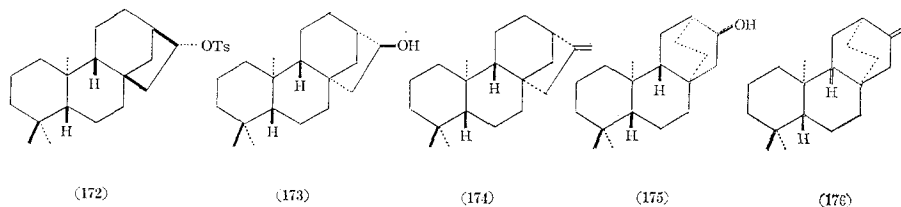
Three new alkaloids were isolated from the bark of *Erythrophleum guineense* syn. *E. suaveolens*. Chemical and spectroscopic data provided evidence for the structure of two of them, cassamidine (169) and coumidine (170), and strongly



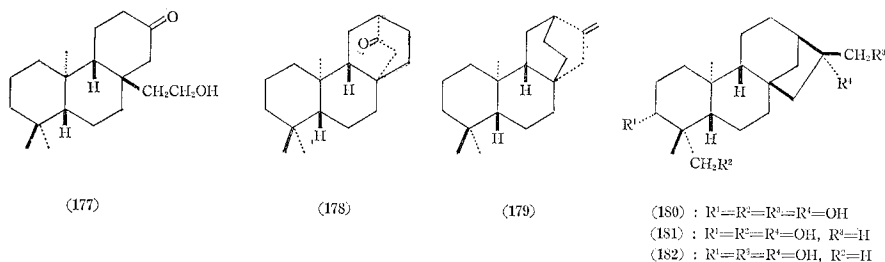
suggested that the third alkaloid, erythrosuamine is represented by 171.⁸³⁾ From the seeds of *Caesalpinia bonducella*, α -, β -, and γ -caesalpin were isolated.⁸⁴⁾

VIII. KAURANE AND BEYERANE DERIVATIVES

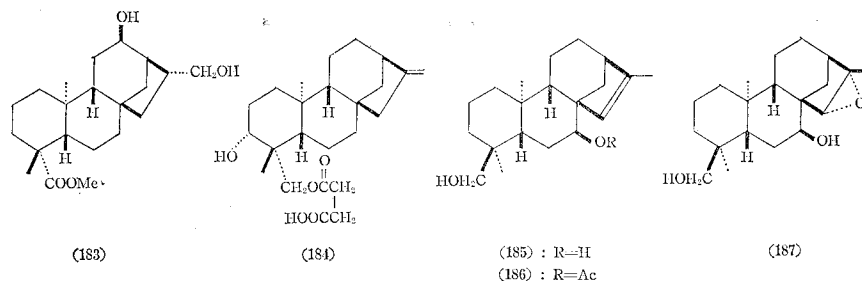
Foliage from *Cryptomeria japonica* was analyzed for diterpenoid hydrocarbons by Overton *et al.*⁸⁵⁾ Samples grown from some seed sources furnished *ent*-kaurene ((-)-kaurene) as the sole product of this type, whilst those from other sources yielded only phyllocladene. These observations were found to be seasonally independent and it was concluded that *C. japonica* exists in two chemically distinct forms. Combined gas chromatography-mass spectrometry was effectively applied to quantitative analysis of mixtures of diterpene-hydrocarbons.⁸⁶⁾ *ent*-17-Nor-16 β -tosyloxykaurane (172) was heated at reflux with HOAc in the presence of NaOAc to give a mixture of acetates (ca. 90 % yield), from which, after treatment with LiAlH₄ alcohol 173 was isolated in 5 % yield. The latter was convert-



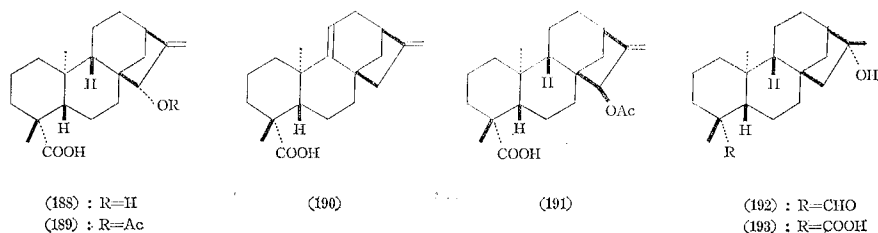
ed into *ent*-phyllocladene (174) via oxidation followed by Wittig reaction. Similarly, alcohol 175 was isolated from the above mixture in 25 % yield. The same treatment of the alcohol yielded atisirene (176). *ent*-17-Noratisan-13-one (178) was prepared from *ent*-kaurene via the ketol (177). Neoatisirene (179) was derived from 178 by Wittig reaction.⁸⁷⁾ Structures were established for three new diter-



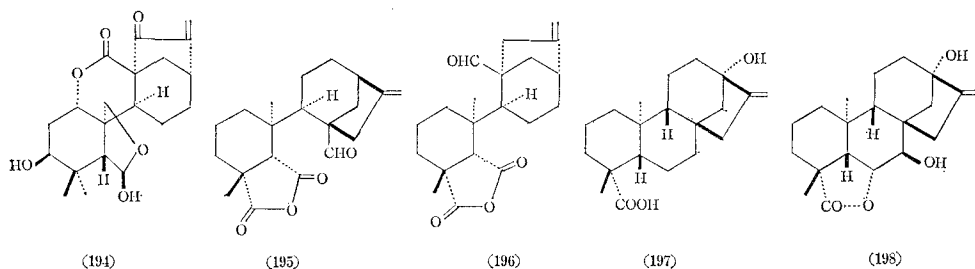
penes, *ent*-kaurane-3 β , 16, 17, 19-tetraol (180), *ent*-kaurane-3 β , 16, 19-triol (181) and *ent*-kaurane-3 β , 16, 17-triol (182), which were obtained from *Beyeria latifolia*.⁸⁸⁾ *ent*-12 α , 17-Dihydroxy-16 β -kauran-19-oic acid was isolated as methyl ester 183 from *Beyeria leschenaultii*. Four known kauranes were also isolated.⁸⁹⁾ Isolated of the known kauranes and beyeranes from *Beyeria brevifolia* was reported.⁵⁵⁾ A succinate 184 was isolated from *Goodenia strophiolata* accompanied by the known



diol.⁹⁰⁾ The same diterpenoid was also isolated from *G. ramelii*.⁴¹⁾ From *corols* of *Sideritis sicula*, two new diterpenes, sideridiol and siderol were isolated. Structures 185 and 186 were assigned to them. The absolute configuration was established by correlation with *ent*-isokaurene.⁹¹⁾ Further investigation led to isolation of third diterpene, sideroxol, whose structure was elucidated as shown in formula 187.⁹²⁾ On the basis of chemical and spectroscopic evidence, structure 188 was assigned to grandiflorolic acid extracted from the resin of *Espeletia grandiflora*.⁹³⁾ Similar diterpenoids 189 and 190 were isolated together with 188



from *E. schultzei*.⁹⁴⁾ The structure **191** was assigned to xylopic acid, a new diterpenic acid isolated from *Xylopia aethiopica*.⁹⁵⁾ *ent*-16 β -Hydroxykauran-19-al (**192**) and *ent*-16 β -hydroxykauran-19-oic acid (**193**) were isolated among other metabolites from a large-scale fermentation of *Fusarium moniliforme*.⁹⁶⁾ Recently the bitter principles of the *Isodon* species have been shown to be kauranoid diterpenes. Induced amongst these are a number of compounds of which enmein (**194**) is the best known, where ring B of the kaurene skeleton has been cleaved. Fujenal (**195**) from *Gibberella fujikuroi* represents another example of this series. Cleav-



age between C-6 and C-7 permits rotation about the 9-10 bond. Molecular models suggest that this rotation is probably hindered and it was of interest to distinguish between the two possible rotamers of fujenal (**195** and **196**). The investigation by Hanson and White⁹⁷⁾ gave an evidence for the prevalence of the rotamer **195** in the ground state of fujenal. The transformation of steviol (**197**) into *ent*-6 β , 7 α , 13-trihydroxykaur-16-en-19, 6 β -olide (**198**) by *Gibberella fujikuroi* was reported by the same authors.⁹⁸⁾ Doubly-labelled 4R-[4³H and 2-¹⁴C]-mevalonic acid lactone was fed to *Gibberella fujikuroi*. 7, 18-Dihydroxy-kaurenolide and gibberellic acid were isolated. Whereas the kaurenolide retained all the tritium of the parent mevalonate, the gibberellic acid had lost one tritium atom. From this result and degradation experiment the following conclusions could be drawn. i) The C-9-hydrogen atom of the tetracyclic diterpenes remains throughout the cyclization stages including the formation of ring D, and a $\Delta^{8(9)}$ -pimaradiene is excluded at this stage. ii) During the elimination of a C-20 substituent and the formation of the lactone ring of the gibberellins a $\Delta^{10(9)}$ or $\Delta^{10(5)}$ olefin is precluded, because both the 9 and 5-tritiums are retained. iii) Cyclization of a geranylgeranylpyrophosphate derived from 4R-[4³H]-mevalonic acid lactone would be expected to produce an axial tritium atom at position 3 in a kauranoid precursor. Since this atom is retained in gibberellic acid, inversion must have taken place at this center on hydroxylation.⁹⁹⁾

The total synthesis of *rac*-kaur-16-en-19-oic acid (as **199**), *rac*-monogynol (as **200**) and some oxygenated kauranes, chemically and biologically interesting tetracyclic diterpenes, was accomplished by Mori and Matsui¹⁰⁰⁾ as shown in Chart 3. Preparation of some lactones of podocarpane and kaurane series from tricyclic or tetracyclic resin and analogs was described by the same authors.¹⁰¹⁾ A tetrahydrofurano-hydrophenanthrene derivative was synthesized in the synthetic studies on cafestol.¹⁰²⁾ *ent*-19-Nor-16 β -kaurane (**201**) and *ent*-19-nor-kaurane (**202**)

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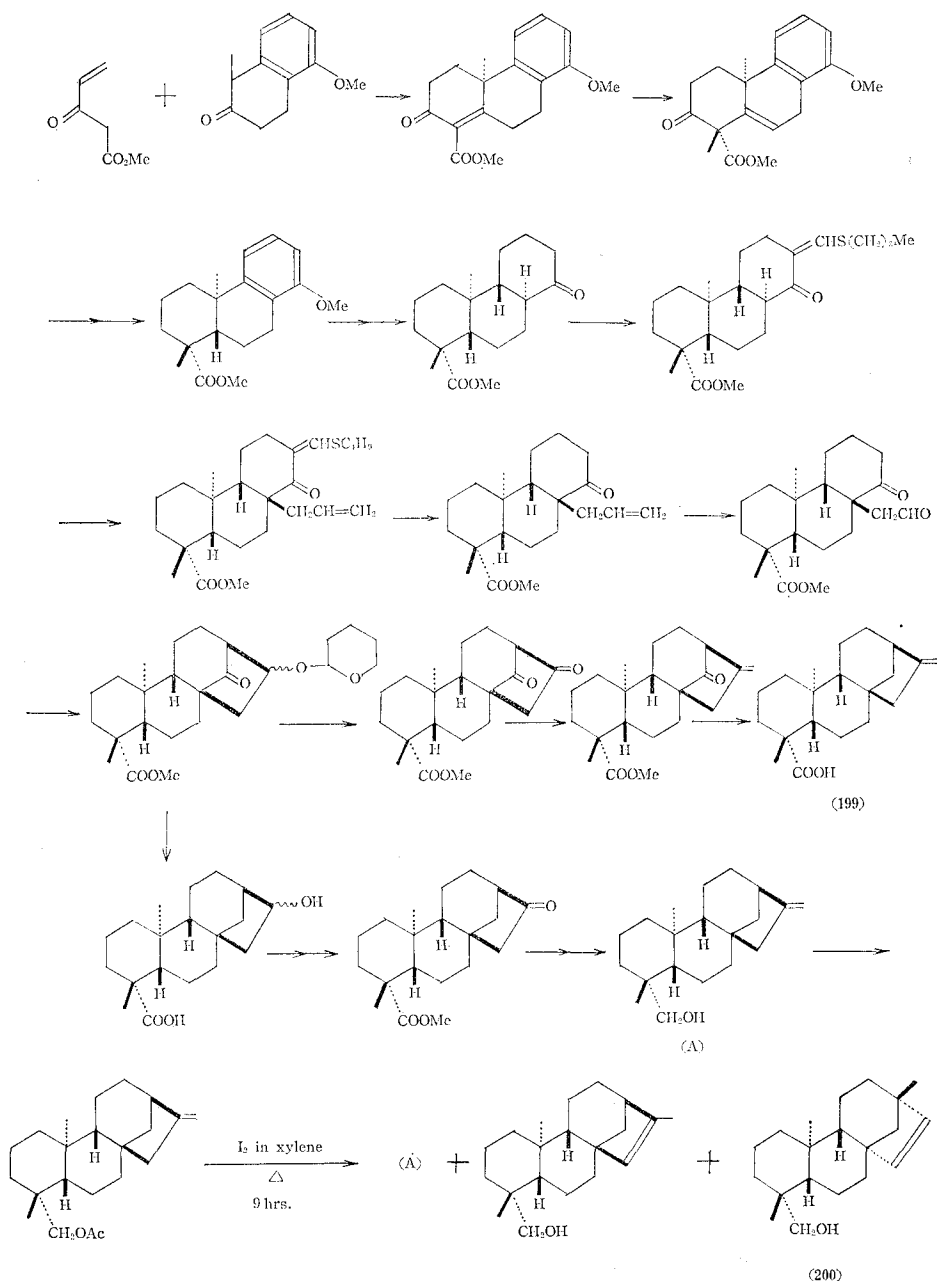
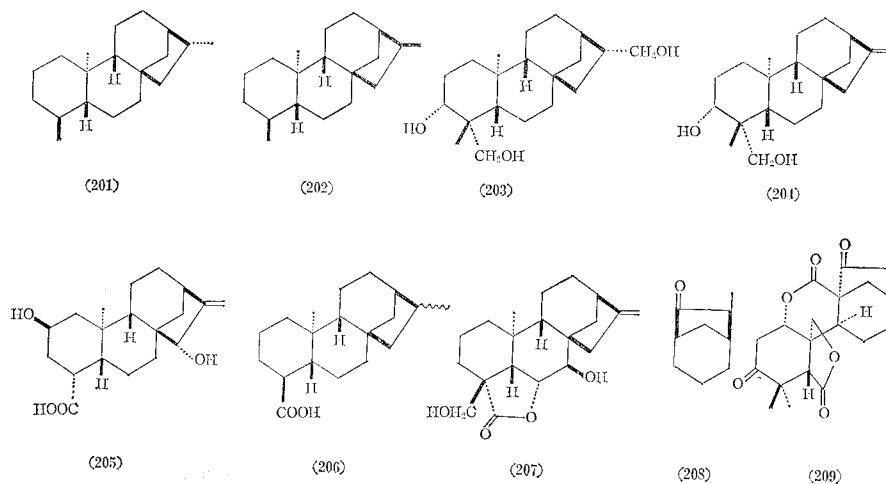


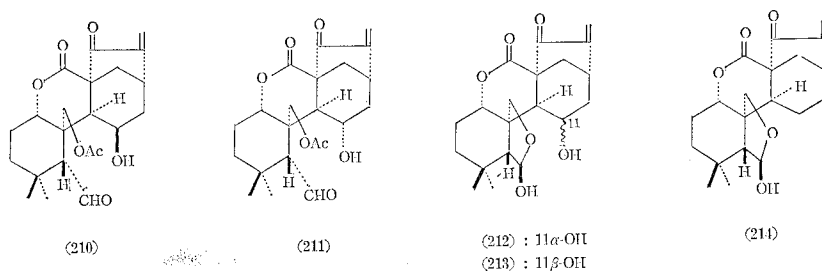
Chart 3

were prepared from *ent*-16 β -kaurane-3 β , 17, 19-triol (203) and *ent*-16-kaurene-3 β , 19-diol (204) through unambiguous route, and the products were proved to be identical with the samples derived from atractyligenin (205).¹⁰³⁾ The stereochemistry, especially that of C-9, of atractylanic acid (206),¹⁰⁴⁾ which was derived from atractyligenin, was confirmed by a partial synthesis from 7, 18-dihydroxykaurenolide (207).¹⁰⁴⁾ A full paper on the synthesis of (–)-6-methyl-7-oxo-bicyclo [3, 2,

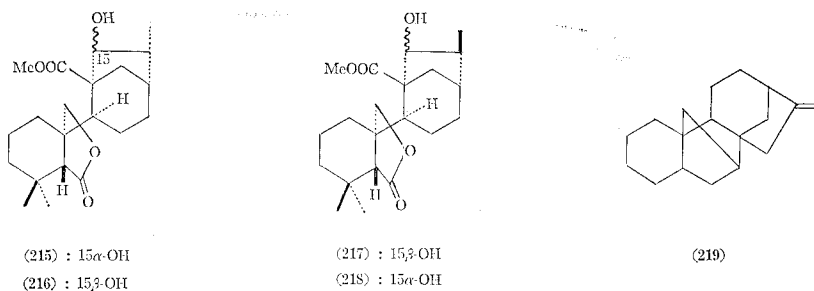
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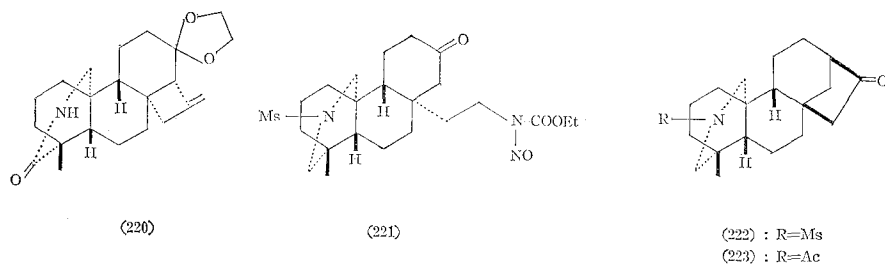
1] octane (208), the antipodal substance of a pyrolysis product of bisdehydrodihydroenmein (209), was published by Uyeo *et al.*¹⁰⁵⁾ On the basis of spectral data and biogenetic considerations the structure 210 had been deduced by Fujita *et al.*¹⁰⁶⁾ for trichodonin isolated from *Isodon trichocarpus*. Kubota and Kubo¹⁰⁷⁾ isolated the same compound from *I. japonicus* and confirmed unambiguously this



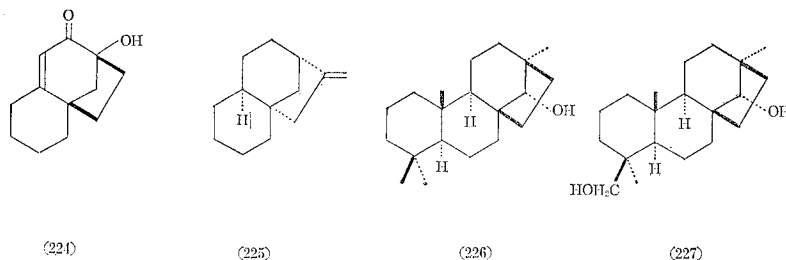
structural assignment by correlating trichodonin with isodonal (211) which is also present in *I. japonicus*. They also isolated a new diterpenoid epinodosin (212), which is the C-11 epimer of the known nodosin. The full papers which deal with the structure and absolute configuration of nodosin (213)¹⁰⁸⁾ and isodocarpin (214)¹⁰⁹⁾ were published by Fujita *et al.* Four possible epimeric alcohols 215~218



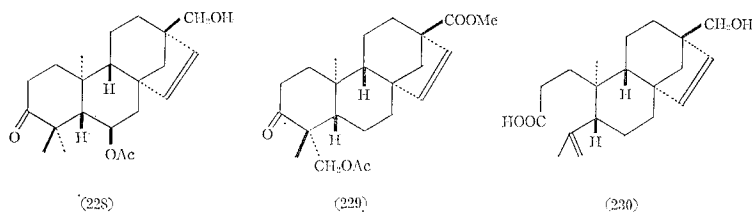
were partially synthesized, and the interesting epimerizations of **215** to **216** and of **217** to **218** were discussed.¹¹⁰⁾ A review on the diterpenoids of "Enmeiso" was published in Japanese.¹¹¹⁾ Another review about the chemistry on diterpenoids of *Isodon* species was published in English by Fujita.¹¹²⁾ The carbon skeleton **219** was deduced for vakognavine, an alkaloid of *Aconitum palmatum*.¹¹³⁾ A new simple synthesis of veatchine from **220** was reported by Wiesner *et al.*¹¹⁴⁾ The



compound **220** was converted into **221**, which was treated with sodium ethoxide in refluxing ethanol to give **222**. The latter was transformed through a series of reactions into **223**, which had been converted into veatchine. A conjugated ketone **224** was synthesized, then the compound was transformed into **225**.¹¹⁵⁾



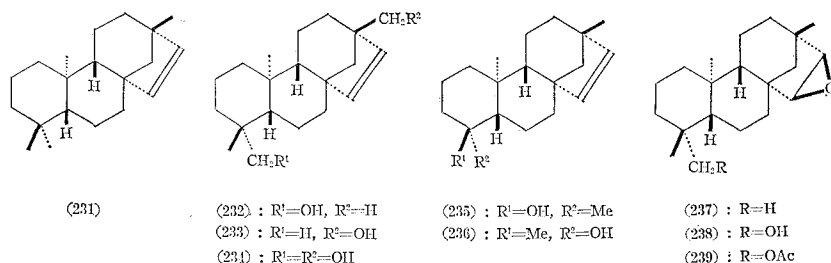
Manool and agathadiol cyclize in formic acid to 14 α -hydroxybeyerane derivatives **226** and **227** besides pimarane derivatives.^{39, 55)*} Three new diterpenes, which were correlated with beyerol and were shown to be modified *ent*-beyer-15-enes **228**, **229**, and **230**, were yielded from a variety of *Beyeria leschenaultii*.¹¹⁶⁾ The



structure and stereochemistry of *ent*-hibaene (231), erythroxyol A (232), erythroxyol B (233), and erythroxydiol A (234) were assigned on the basis of spectroscopic properties and chemical reactions.¹¹⁷⁾ Erythroxydiol A (234) was

* See also section III.

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converted into erythroxyol A (232), and erythroxyol A (monogynol) (232) and B (233) were converted into *ent*-hibaene (231). Two norditerpenoid tertiary alcohols, 235 and 236, and three diterpenoid epoxides, 237, 238, and 239, were isolated from *Erythroxyton monogynum*.¹¹⁸⁾ Compound 241, a potential intermediate for synthesis of gibberellins, was derived from 240 through a route shown in Chart 4 by Mori, Matsui *et al.*¹¹⁹⁾ The biogenetic-like rearrangements of isosteviol de-

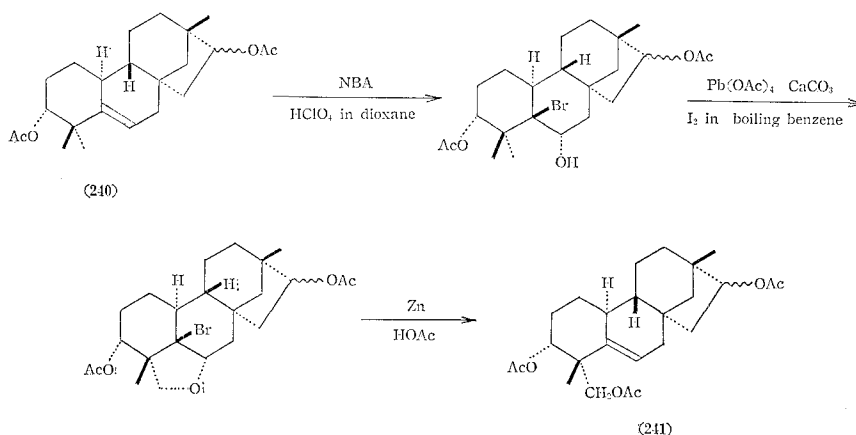
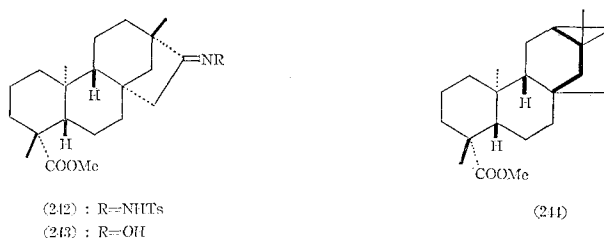
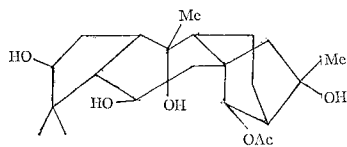


Chart 4

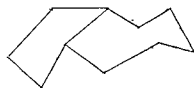
rivatives 242 and 243 were carried out to give several products, among which methyl trachyloban-19-oate (244) was found from the reaction of 242 (as its sodium salt) in 10 % ethylene glycol diethylcarbitol at 180~190°.¹²⁰⁾ Stereochem-



istry of grayanotoxin I was investigated more in detail and the stereochemical structure 245 with the 246 (not 247) type hydroazulene was presented.¹²¹⁾



(215)



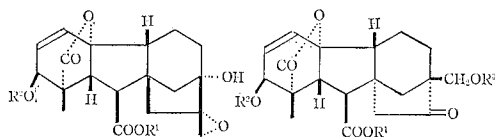
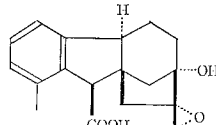
(216)



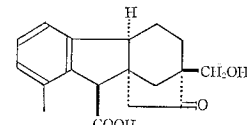
(247)

IX. GIBBERELLANE DERIVATIVES

Gibberellic acid 16 S, 17-epoxide (248) and its acetate (249) were converted by Wagner-Meerwein's rearrangement into hydroxymethyl derivatives 250 and 251, respectively. *Allo*-gibberic acid 16 S, 17-epoxide (252) was rearranged to 253.¹²²⁾ Gibberellin A₁₆, a new metabolite of *Gibberella fujikuroi*, was isolated as

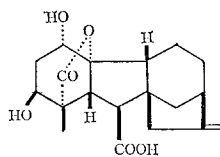
(248) : R¹=R²=H(249) : R¹=H, R²=Ac(250) : R¹=R²=R³=H(251) : R¹=R²=H, R³=Ac

(252)

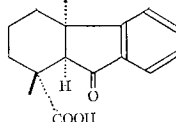


(253)

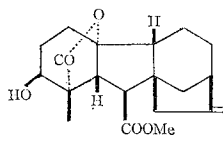
the methyl ester, and the structure (254) was elucidated.¹²³⁾ An intermediate (as 255) for synthesis of gibberellins was synthesized as racemic compound.¹²⁴⁾ Fragmentation patterns of gibberellin A₄ methyl ester (256) and its 3-keto-1-13-



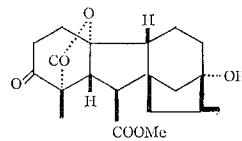
(254)



(255)

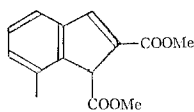


(256)

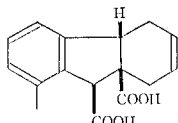


(257)

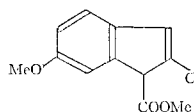
hydroxy-16, 17-dihydro analog (257) as well as mass spectra of some Δ^1 - and $\Delta^{1(10)}$ -unsaturated compounds of gibberellin series were investigated. Gibberellin derivatives unsaturated in the ring A gave different mass spectra, depending on the position of the double bond. This is useful for the determination of the position of double bond.¹²⁵⁾ 1,2-Dicarbomethoxy-7-methylindene (258) was synthesized. Its Diels-Alder reaction with butadiene yielded tetrahydrofluorene derivative 259.¹²⁶⁾ The double bond isomers of 1,2-dicarbomethoxy-6-methoxyindene, 260 and 261,



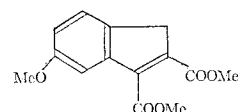
(258)



(259)

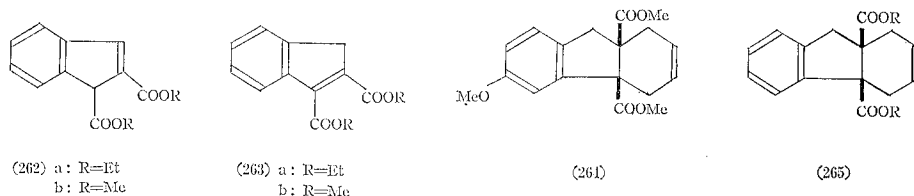


(260)



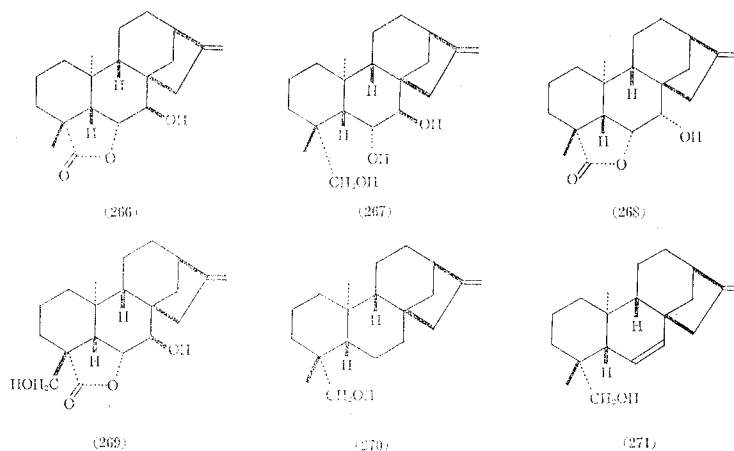
(261)

and another pair of 1, 2-dicarbomethoxyindene, 262 and 263, were synthesized. In each case, the less highly substituted double bond isomer 260 or 262 is the more stable. However, derivatives of each of these indenenes reacted with 1, 3-butadiene to give the Diels-Alder adduct (264 and 265) derived from the more



highly substituted double-bond isomer.¹²⁷⁾

None of 7-hydroxykaurenolide (266), its related triol (267) and 7 α -hydroxykaurenolide (268) was incorporated into gibberellic acid by *Gibberella fujikuroi*, but 7-hydroxykaurenolide (266) was converted into 7,18-dihydroxykaurenolide (269) in high yield. Incorporation of alcohol 270 into gibberellic acid was much higher than that of diene 271.¹²⁸⁾ Seven ¹⁴C-labelled compounds, including gibberel-



lins A₁₂, A₁₃ and A₁₄, were prepared and tested as precursors in the biosynthesis of gibberellic acid by *Gibberella fujikuroi*. It was suggested by Cross *et al.*¹²⁴⁾ that gibberellic acid is biosynthesized from *ent*-kaurene ((-)-kaurene) through 272 and gibberellin A₁₄ (274) or the corresponding 7-aldehyde 273. Gibberellin A₁₃ (275) was not thought to be a precursor of gibberellic acid. The biosynthetic pathway suggested by them is shown in Chart 5. Although several kaurene derivatives, 276, 277 and 278 having the 16-methylene group, undergo ring contraction to gibberellanes, *e. g.* 279, with base, those having a 16-keto-group, 280 and 281 do not. The fact was considered to be due to a long-range effect associated with the 16-keto-group.¹²⁹⁾ Methyl 3-dehydrogibberellate (282) was treated with zinc in acetic acid and then with aqueous sodium bicarbonate to give a reductive delactonized product 283.¹³⁰⁾ The presence of three water-soluble

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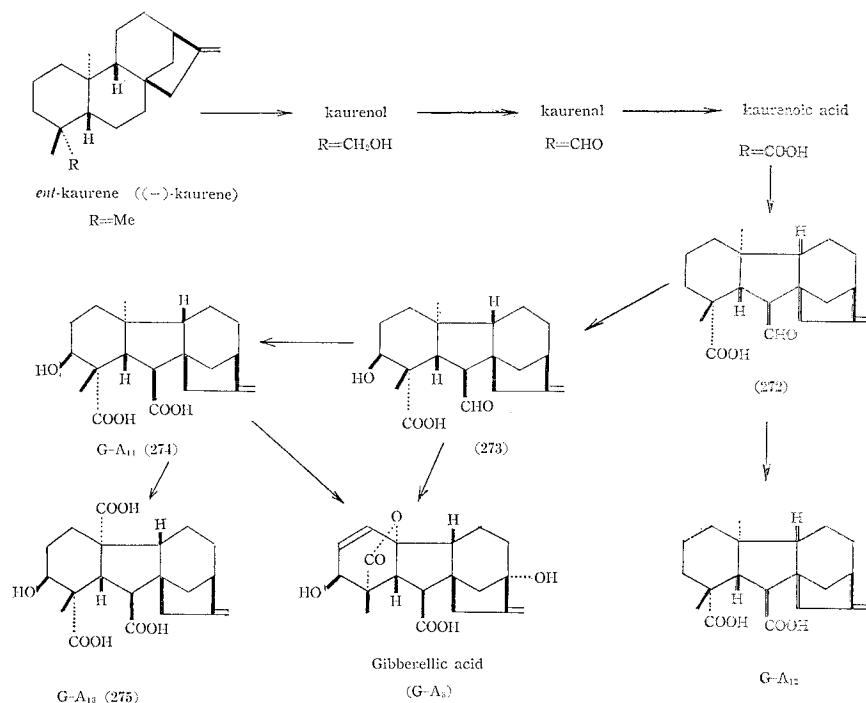
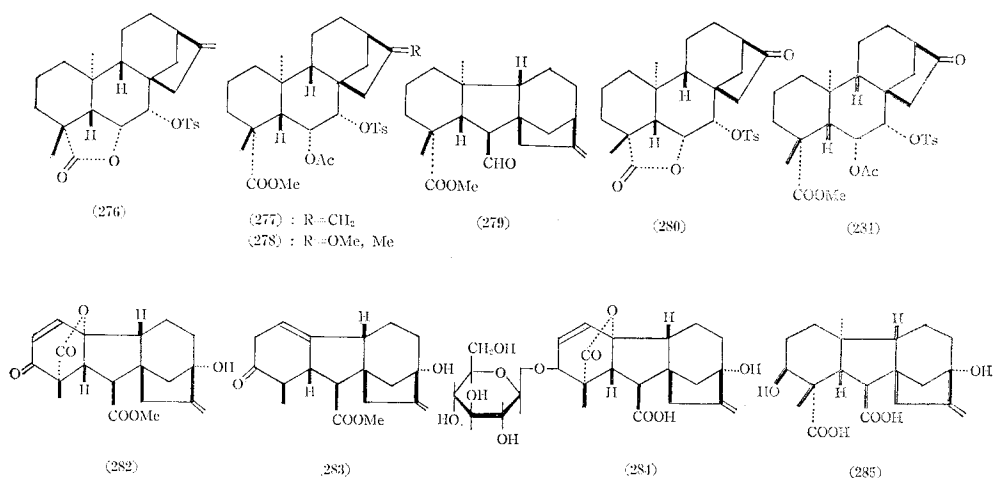


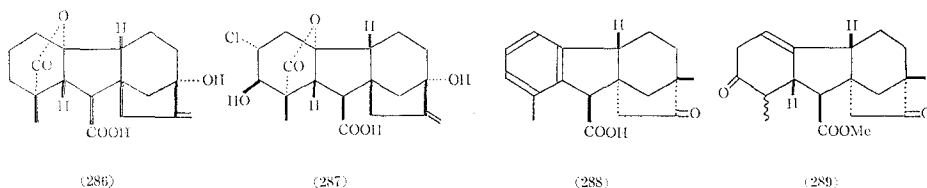
Chart 5



gibberellins was confirmed in immature seeds of morning glory (*Pharbitis nil*). The structure of the main component was elucidated as 3-*O*- β -glucosyl-gibberellin A₃ (284).¹³¹⁾ A short review about isolation of new gibberellins from higher plants and their biological activity was published. It is concerned with Bamboo gibberellin, *Pharbitis* gibberellin, gibberellin A₃ glucoside (284), and *Canavalia* gibberellins I and II.¹³²⁾ A new gibberellin, tentatively called *Lupinus* gibberellin I, was isolated from young yellow lupin seeds (*Lupinus luteus*). It was shown

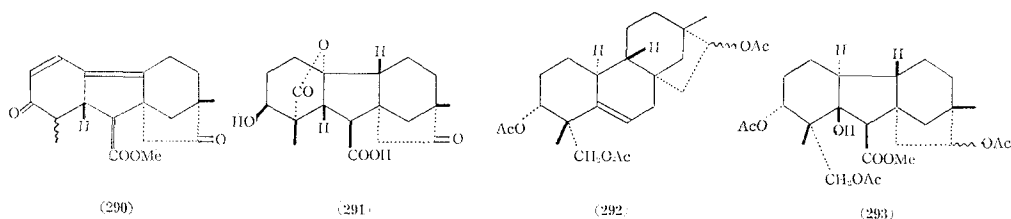
to have structure (285).¹³³⁾

A new nomenclature of gibberellins was proposed.¹³⁴⁾ According to this, *Lupinus* gibberellin-I, Bamboo gibberellin, *Pharbitis* gibberellin, *Canavalia* gibberellin-I and -II were named gibberellins A₁₈, A₁₉, A₂₀, A₂₁ and A₂₂, respectively. A review on the isolation techniques of plant growth substances was published, in which purification of bamboo gibberellin by counter-current distribution and isolation of gibberellins A₁ and A₃ by partition chromatography were described.¹³⁵⁾ Gibberellin A₂₃, that is, gibberellin A₃ glucoside (284) was isolated from immature seeds of *Lupinus luteus*.¹³⁶⁾ Investigations of gibberellins in *Phaseolus multiflorus* by combined gas chromatography-mass spectrometry have been carried out by MacMillan *et al.* They¹³⁷⁾ reported the detection of gibberellin A₂₀ (*Pharbitis* gibberellin) (286) in extracts of young seed of the plant and some observations on the structures of compounds *a* and *b*, previously isolated from seeds of *P.*

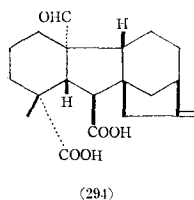


multiflorus by Jones.¹³⁸⁾ The investigation provided strong support for the structure 287, originally suggested for compound *b* by Jones.

Mori, Matsui, Sumiki, *et al.*^{139,140)} converted *rac*-epigibberic acid (as 288), which had been synthesized by themselves, into 290 *via* an important intermediate 289. Since the ketone 290 had been converted into gibberellin C (291) by



them,¹⁴¹⁾ this completed total synthesis of *rac*-gibberellin C. Gibberellin C had been transformed into gibberellin A₄,¹⁴²⁾ which had been converted into gibberellins A₂¹⁴³⁾ and A₉.¹⁴⁴⁾ Conversion of gibberellin A₉ into A₁₀ had also been reported.¹⁴⁵⁾ Thus, the foregoing work constituted the formal total synthesis of *rac*-gibberellins A₂, A₄, A₉ and A₁₀. The same group¹⁴⁶⁾ reported the synthetic sequence for the conversion of compound 292 into 293. Gibberellin A₂₄ (294), a new aldehydic



gibberellin was isolated from *Gibberella fujikuroi*.¹⁴⁷⁾ Circular dichroism of some C₁₉ gibberellins and their methyl esters, and some other related compounds at wave length of 200~300 mμ was investigated and the application of the lactone chromophore to their structural and stereochemical elucidation was described.¹⁴⁸⁾ The synthesis of perhydrofluorenone derivative 295 was reported by Kitahara *et al.*¹⁴⁹⁾ The outline of the route is shown in Chart 6.

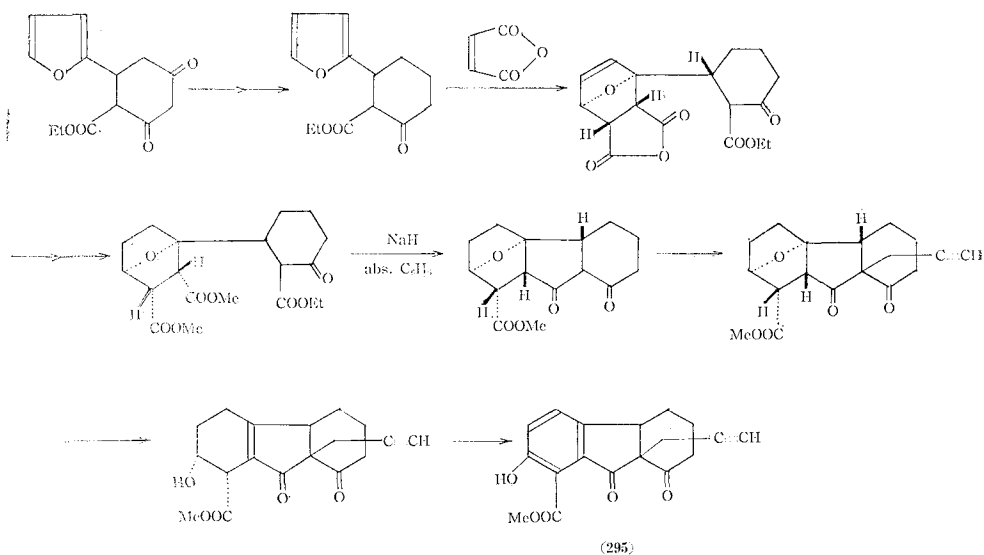
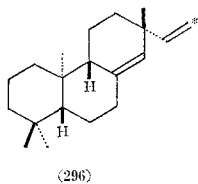


Chart 6

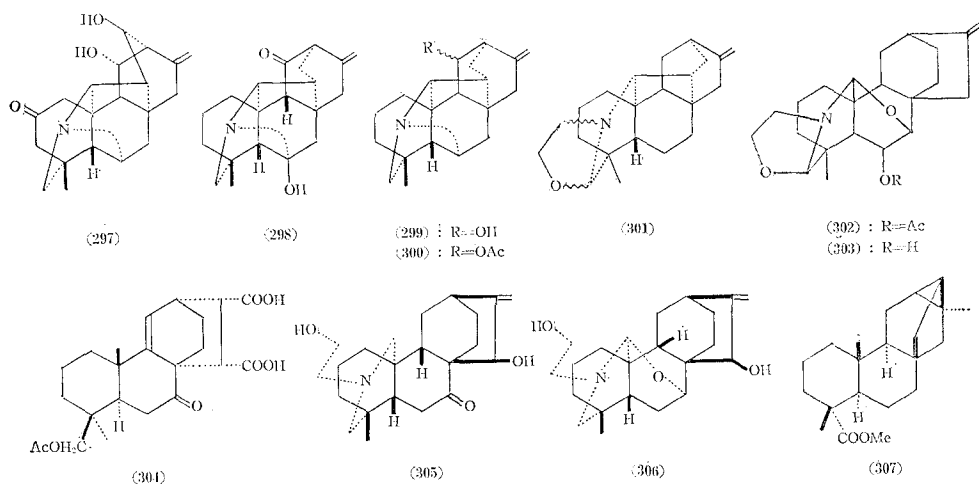
Cross and Stewart¹⁵⁰⁾ reported that addition of the labelled *ent*-pimara-8(14), 15-diene (296) to a fermentation of *Gibberella fujikuroi*, and isolation of the metabolites produced, gave labelled methyl gibberellate (incorporation 0.05 %) and labelled 7-hydroxykaurenolide. Hanson and White¹⁵¹⁾ proved by feeding [2-³H₂, 2-¹⁴C] mevalonic acid lactone to *Gibberella fujikuroi* that *ent*-pimara-8(14), 15-diene (296) is a precursor for *ent*-kaurene, 7-hydroxykaurenolide, and 7, 18-



dihydroxykaurenolide. They also prepared labelled *ent*-pimara-8(14), 15-diene (296) (¹⁴C and ³H), and carried out feeding experiments to *Gibberella fujikuroi*. Its very low incorporation (0.02 %) to gibberellic acid was observed. Decarboxylation of C₂₀ gibberellin to C₁₉ gibberellin was discussed on the basis of multiple labelled mevalonate experimental results. Subsequently, Cross and Stewart¹⁵²⁾ revised their foregoing report. They described that pimaradiene and pimaradienol are not incorporated into gibberellic acid, on the basis of the degradation experiments.

X. ATISANE DERIVATIVES

The tentative structure **297** previously proposed for an alkaloid isolated from *Delphinium cardinale* was confirmed.¹⁵³⁾ The alkaloid is identical with hetisinone, which was first obtained as the transformation product of hetisine and later isolated from *D. denudatum*. Ten alkaloids were isolated from *Spiraea japonica* and the structure **298** of spiradine A was elucidated by X-ray analysis. The structures **299** and **300**, were assigned to spiradine B and C, respectively, based on the chemical correlation with A.¹⁵⁴⁾ Subsequently, spiradine D isolated from the same plant source proved to be represented as **301**.¹⁵⁵⁾ The plane structures, **302** and **303**, were proposed for spiradines F and G, respectively.¹⁵⁶⁾ A key intermediate **304** in the synthesis of atidine (**305**) and ajaconine (**306**) was prepared.¹⁵⁷⁾



The synthesis of methyl 13, 16-cycloatisan-18-oate (methyl *anti*-trachylobanate) (**307**) from methyl levopimarate was reported by Herz *et al.*^{158,159)} The compound **308** which was derived from the starting material *via* Diels-Alder reaction was converted into **309** by the mesylation, and the latter was transformed into the final product as shown in the Chart 7.

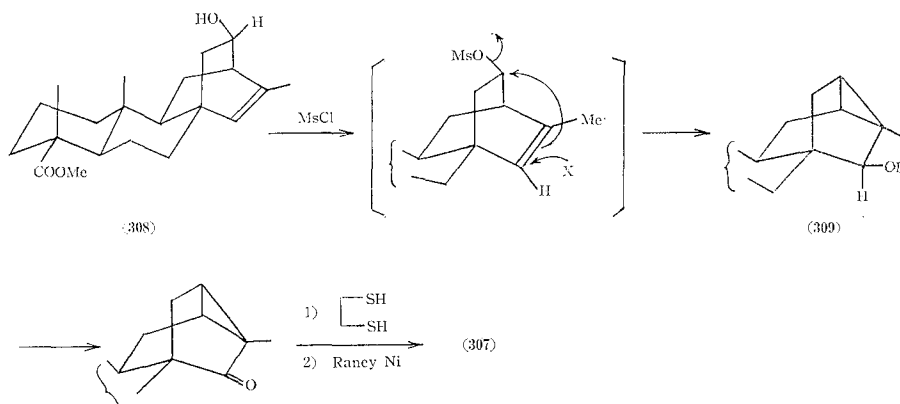
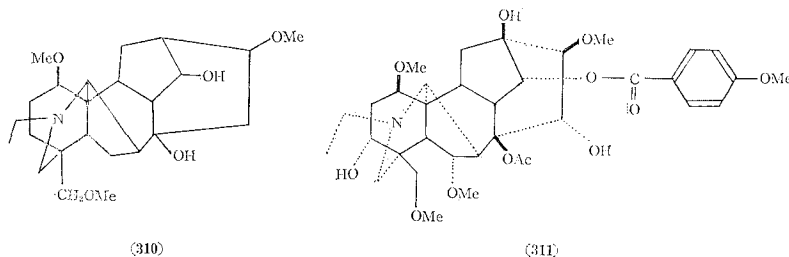


Chart 7

XI. ACONANE DERIVATIVES

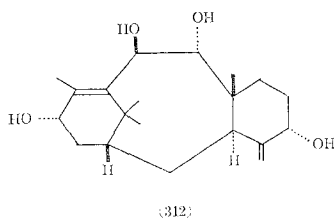
On the basis of mass spectrometry, the NMR data of acetylbenzoyl derivative, and the NMR data of the product prepared from pyrolysis of diacetyl derivative, the formula **310** was proposed for talatizamine.¹⁶⁰⁾ The structure of jesaconitine



isolated from *Aconitum* species was elucidated as **311**, on the basis of the NMR data of the alkaloid and its pyrolysis products. The pyrolysis was carried out in an NMR tube, and continuously monitored by NMR spectroscopy to provide evidence for the elimination product. This method of pyrolysis constituted a rapid and convenient way of establishing the presence of certain C-8 ester groups in these diterpene alkaloids using small amounts of material.¹⁶¹⁾

XII. TAXANE DERIVATIVES

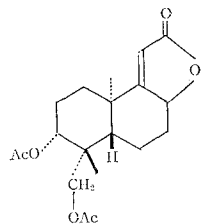
A constituent of the heartwood of *Taxus cuspidata* was isolated and named taxusin.¹⁶²⁾ Hydrolysis of taxusin gave tetraol **312**, which had been isolated from *T. baccata* by English workers.¹⁶³⁾ The application of Mills' rule gave same conclusion on the absolute configuration of C-13 hydroxy group. Taxusin corresponds to tetraacetate of **312**.¹⁶²⁾



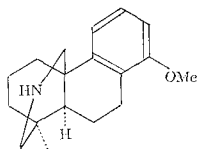
XIII. THE OTHERS

Johnson¹⁶⁴⁾ published a review on nonenzymic biogenetic-like olefinic cyclizations. The ORD curves of many diterpenecarboxylic acids and related compounds were taken and examined by English workers.¹⁶⁵⁾ Discussions on preferred conformations of carboxylic acids and carboxyl sector rule were described. The NMR investigation on forty four kinds of diterpene alkaloids and related compounds was published.¹⁶⁶⁾ On the basis of the NMR data of C-4 methyl group in a series of atisine and veatchine, the conformation of ring E was discussed. The relationship between the chemical shift of C-4 methyl protons and nitrogen

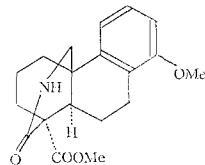
atom was also discussed. The conformation of the primary hydroxy group at C-18 or C-19 in many diterpenoids was discussed on the basis of the chemical shift of C-4 methyl protons' signal in the NMR spectra.¹⁶⁷⁾ Similarly, the conformation of C-4 axial and equatorial carboxylic acids, esters, and aldehydes in diterpenoids was discussed on the basis of NMR data of C-10 methyl group.¹⁶⁸⁾ The NMR spectra and conformations of some lactones of octa- and decahydro-8-hydroxynaphthoic acids were discussed,¹⁶⁹⁾ on relation to synthesis of diterpenoid acids. A ten-step stereoselective synthesis of racemic andrographolide lactone (as 313), which had been obtained previously in optically active form by degradation of triacetylandrographolide, was published.¹⁷⁰⁾



(313)



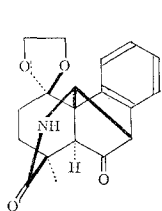
(314)



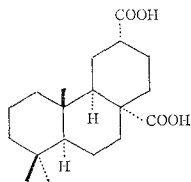
(315)

Turner *et al.*¹⁷¹⁾ published procedures for the synthesis of tetracyclic intermediates—*e.g.* 314 and 315—incorporating the bridged nitrogen-containing ring common to many of the diterpene alkaloids.

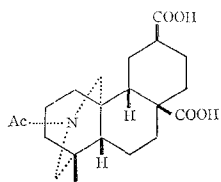
Wiesner *et al.*¹⁷²⁾ carried out a stereoselective synthesis of pentacyclic intermediate 316 during the synthesis in the series of diterpene alkaloids. Stereoselective synthesis of racemic tricyclic dicarboxylic acid (as 317), a synthetic model for the N-acetyl-dicarboxylic acid 318, was reported by Pelletier *et al.*¹⁷³⁾ Stereoselective synthesis of racemic perhydrophenanthrene derivative (as 319) was



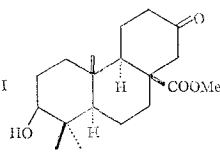
(316)



(317)

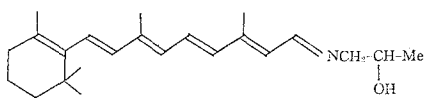


(318)

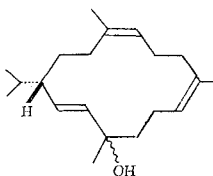


(319)

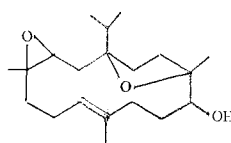
reported by Dutta *et al.*¹⁷⁴⁾ Spectral properties of Schiff bases of retinal were investigated. 1-(Retinylideneamino)-2-propanol (320) and its 11-*cis* isomer were prepared by condensing retinal with 1-amino-2-propanol in dry acetonitrile, and



(320)

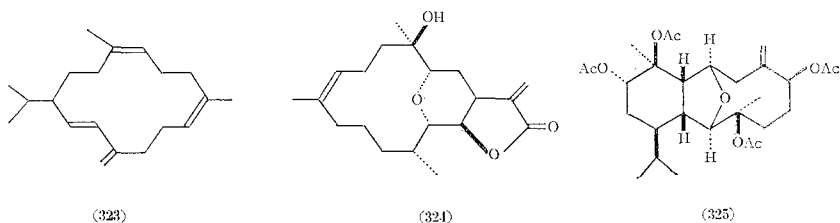


(321)

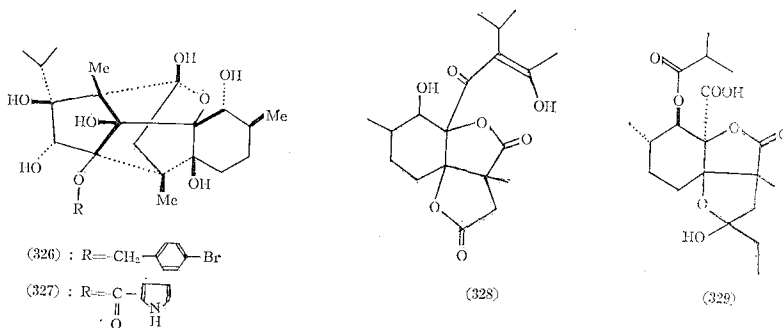


(322)

λ_{max} in non polar solvent was discussed.¹⁷⁵⁾ Thunbergol, a new macrocyclic diterpene alcohol, was isolated from the oleoresin of *Pseudotsuga menziesii*, and structure 321 was assigned to this.¹⁷⁶⁾ A new diterpene, incensole-oxide (322), was isolated from the resin produced by *Boswellia carteri*. Chemical and physico-chemical data showing the position of the oxirane ring supported the structure.¹⁷⁷⁾ The new diterpenes, isocembrene (323) and isocembrol, were isolated from oleo-



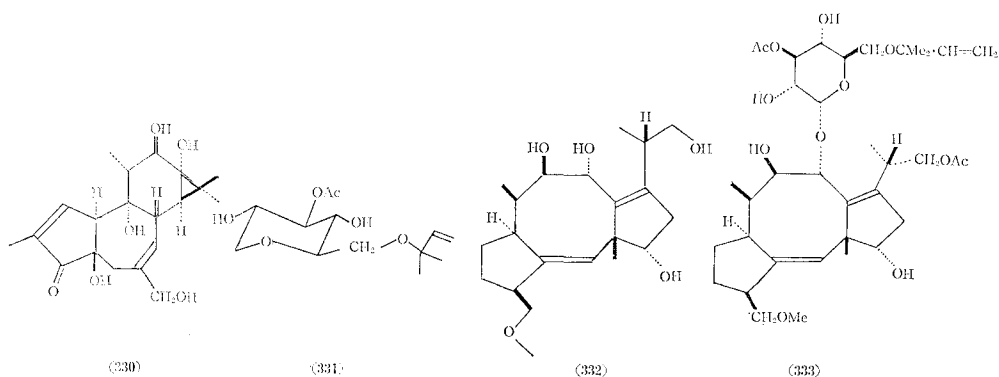
resin of *Pinus sibirica*.¹⁷⁸⁾ The plane structure of the latter is identical with 321. The antibacterial marine diterpene eunicin was isolated from *Eunicea mammosa* and characterized,¹⁷⁹⁾ and structure 324 was assigned to it. The assignment was fully substantiated by the X-ray crystallographic study of its iodoacetate.¹⁸⁰⁾ From the petroleum ether extract of dried *Eunicella strica*, a new diterpenoid, eunicellin was isolated. The structure 325 was presented on the basis of chemical evidence and an X-ray analysis of dibromide.¹⁸¹⁾ The molecular structure of ryanodol *p*-bromo benzyl ether was elucidated as 326 on the basis of X-ray analysis.¹⁸²⁾ The structure was identical with that proposed by Wiesner *et al.*¹⁸³⁾ except that the configuration of the carbon atom carrying the isopropyl group in the five-membered ring is reversed. An article, which represents the English version of the second



part of a lecture on the structure of ryanodine (327) delivered by Wiesner¹⁸⁴⁾ in 1967, in the auditorium of the Institute for Org. Chem. and Biochemistry, Czechoslovak Academy of Sciences, was published. Ryanodol was treated with excess periodate and then alkali to give a C₁₉ compound, whose structure 328 was proposed on the basis of the several reactions.¹⁸⁵⁾ The structure 329 was proposed for a C₁₉ acid obtained together with the foregoing ketone in the periodate oxidation of ryanodol.¹⁸⁶⁾

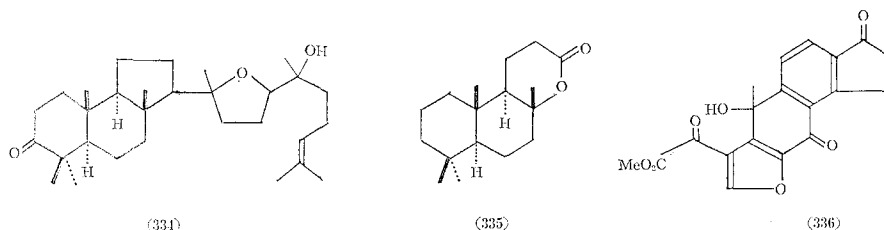
Hecker *et al.* published a series of the reports on the chemistry of phorbol. They were concerned with polybenzoate and polyacetate of phorbol and phorbol-3-ol, functional derivatives of allyl-group of phorbol,¹⁸⁷⁾ ether derivatives of

phorbol,¹⁸⁸⁾ derivatives of phorbol-12-one and their circular dichroism,¹⁸⁹⁾ the α , β -unsaturated tertiary 1,2-ketogroup in phorbol,¹⁹⁰⁾ and the oxidation of phorbol with leadtetraacetate.¹⁹¹⁾ Another report on the chemistry and structure of phorbol was published by Crombie *et al.*¹⁹²⁾ The structure and absolute configuration 330 have been established by the X-ray analysis of its bromine-containing derivative.¹⁹³⁾



Characterization of the oxygen substituents of fusicoccin (fusicoccin A), $C_{35}H_{58}O_{13}$, a highly phytotoxic metabolite of *Fusicoccum amygdali*, led to a partial structure 331.¹⁹⁴⁾ Crystallographic studies of two mercuribromide derivatives prepared from fusicoccin and its deacetyl aglycone resulted in the presentation of the structure and relative stereochemistry 332 for deacetyl aglycone.¹⁹⁵⁾ On the basis of chemical works and X-ray data, Barton *et al.*¹⁹⁶⁾ presented the complete structure 333 including absolute configuration. These results were completely identical with those of the independent work on fusicoccin A by Ballio and his colleagues.¹⁹⁷⁾ They carried out an X-ray determination of the structure of the iodobenzenesulfonate of fusicoccin with supporting chemistry.

d-Malabaricol (334) was converted into *d*-ambreinolide (335).¹⁹⁸⁾ A biosynthetic study with viridin (336), an active antifungal metabolic product of *Gliocladium*



virens, led to a conclusion that the metabolite is biosynthesized from mevalonic acid lactone by way of farnesyl pyrophosphate, squalene epoxide, and lanosterol, and excluded the possibility that the compound might be derived from mevalonic acid *via* geranylgeranyl pyrophosphate and a tricyclic diterpenoid (cassane type skeleton).¹⁹⁹⁾ The biosynthesis of pleuromutilin, a metabolite from *Pleurotus mutilus*, was described by Arigoni.²⁰⁰⁾

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