

Review

## The Chemistry on Diterpenoids in 1972

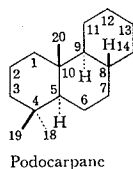
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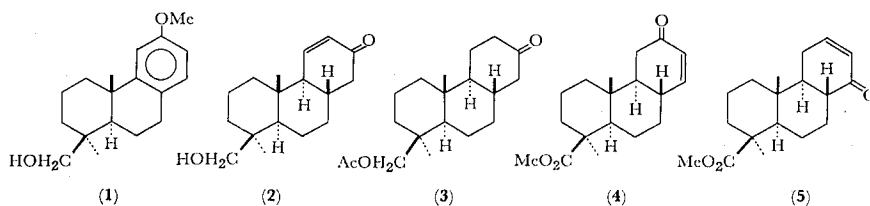
### I. INTRODUCTION

This is one of a series of annual reviews<sup>1~8)</sup> on diterpenoids chemistry. The classification is the same with that adopted in this series since 1969.

### II. PODOCARPANE DERIVATIVES\*\*



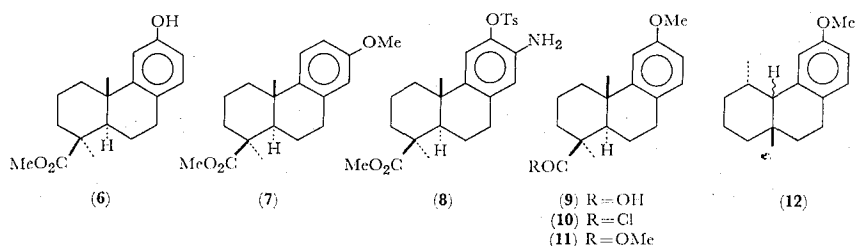
The ring-B conformations of some 6,-7-diacetoxy, 7-acetoxy-6-hydroxy, 6-dehydro, and 7-oxo derivatives of ring-C aromatic podocarpane derivatives were examined from a study of their NMR spectra.<sup>9)</sup> Birch reductions of compound **1** were investigated and the products were converted into the 13-oxo derivatives **2** and **3**. The C-14 ketone **5** was also prepared from the reduced derivative **4**.<sup>10)</sup>



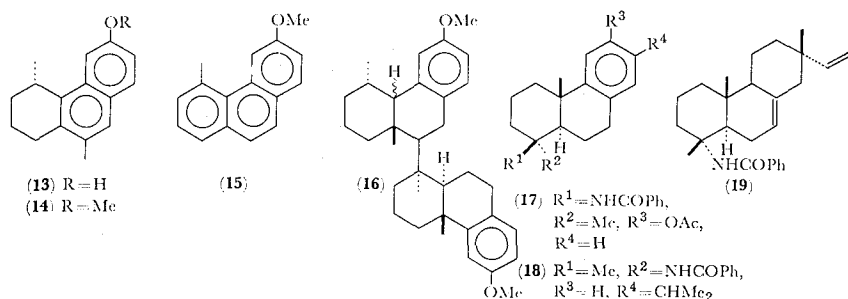
Conversion of compound **6** into the synthetically more useful compound **7** was investigated. In the most favorable case, the transformation was effected in ca. 57% yield by a five-stage sequence involving hydrogenolysis of the 13-amino-12-tosylate **8** with Raney nickel.<sup>11)</sup>

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\*\* See also III, ref. 29, VII, ref. 81, and IX, ref. 105.

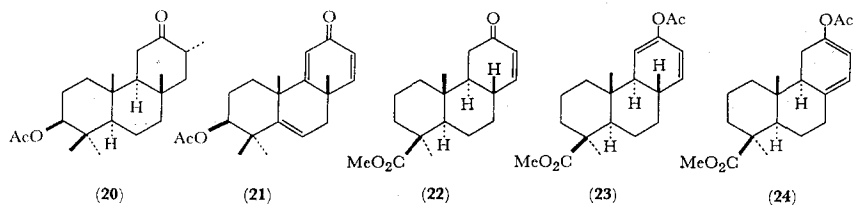


12-Methoxypodocarpa-8, 11, 13-trien-19-oi acid **(9)**, its acid chloride **10**, and its methyl ester **11** underwent a decarbonylation reaction on treatment with phosphoryl chloride. The products were proved to be octahydrophenanthrene **12**, tetrahydrophenanthrenes **13** and **14**, and the phenanthrene **15**. A minor product was tentatively assigned the dimeric structure **16**.<sup>12)</sup>



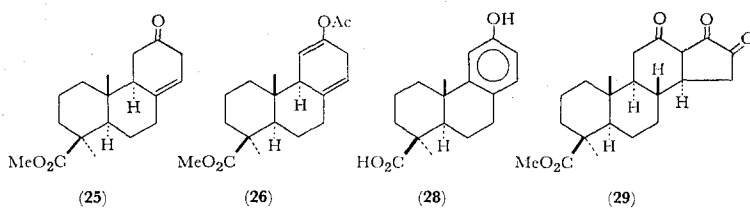
Reverse Ritter reaction was investigated with benzamides of steroids and diterpenoids. The benzamides, **17–19**, heated in benzene with P<sub>2</sub>O<sub>5</sub>, underwent a reverse Ritter reaction yielding C<sub>6</sub>H<sub>5</sub>CN and an *endo*- or *exo*- unsaturated compound. The distribution of the unsaturated compound depended on the reaction conditions.<sup>13)</sup>

Cyclization of some 2,6-dimethyl-9-(methoxyphenyl)nona-2,6-dienes and related compounds by polyphosphoric acid was investigated to synthesize dehydropodocarpene derivatives.<sup>14)</sup> Methyl 12-methoxy-7-oxopodocarpate on nitration in conc. H<sub>2</sub>SO<sub>4</sub> yielded 13-nitro-derivative (60 %) in addition to 11-nitro derivative (40 %). The photolysis of the former product was investigated.<sup>15)</sup> The syntheses of 3-acetoxy-8 $\beta$ , 13 $\alpha$ -dimethylpodocarp-12-one (**20**), the corresponding *D*<sup>13</sup>-ketone, and 3-acetoxy-8 $\beta$ -methyl-podocarpa-5,9 (**11**), 13-trien-12-one (**21**) were carried out.<sup>16)</sup>

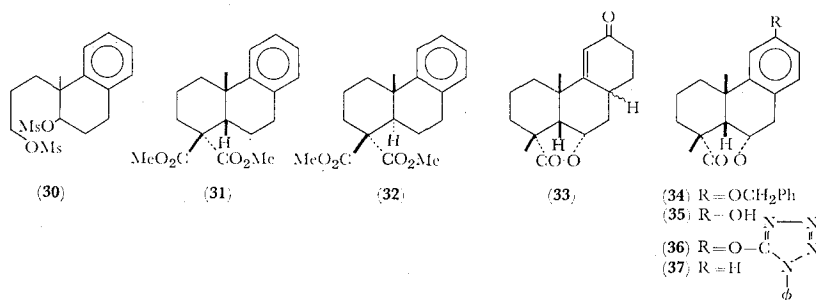


Enol acetylation of methyl 12-oxopodocarp-13-en-19-oate (**22**) was investigated. It gave mainly **23** and **24**. The factor causing the unexpected thermodynamic ratio

of 3:5 noted for **23** to **24** was concluded as the result of a delicate balance between double bond stabilities and steric interactions. Kinetically controlled enol acetylation of methyl 12-oxopodocarp-8(14)-en-19-oate (**25**) gave **26** (60 %) and **24** (25 %).<sup>17)</sup>

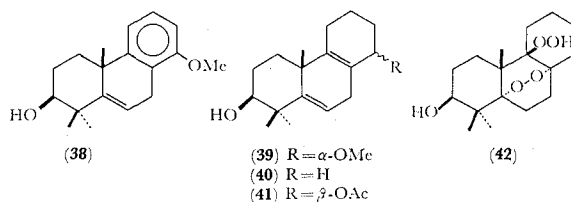


The conversion of podocarpic acid (**28**) to an 18-norsteroid **29** was accomplished.<sup>18)</sup> The dimesylate **30** of one of the epimers condensed with malonic ester to give a *cis*-product **31**, which on heating with palladized charcoal gave the *trans*-isomer **32**. A number of derivatives of the *cis*-fused products were prepared. A study of the NMR spectra of the cyclization products and some of their derivatives and other data clarified their conformation.<sup>19)</sup>

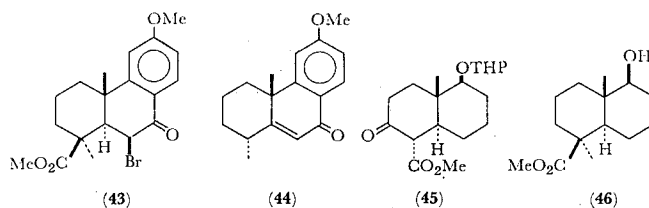


The compound **37** was prepared *via* **33**, **34**, **35**, and **36**, but conversion of this compound to the corresponding acid was not successful.<sup>20)</sup>

Birch reduction of the compound **38** was investigated, and product **39** and its hydrogenolysis product **40** were obtained. The methoxy group of compound **39** was readily displaced by acetoxy group with inversion of configuration by warming in acetic acid to give **41**. Compound **40** was highly sensitive to oxygen. It was autoxidized to **42** on exposing to the air.<sup>21)</sup> The conformations of the 14 $\alpha$ -methoxy-(**39**) and 14 $\beta$ -acetoxy-(**41**) derivatives of 3 $\beta$ -hydroxypodocarp-5,8-diene were studied by means of X-ray crystallographic analysis. As a result, it was found that, in the former substance, the ring-C had an unusually flattened conformation and showed an unusual thermal behavior.<sup>22)</sup>

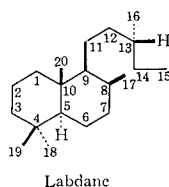


The one-step conversion of bromo-ketone **43** to the  $\alpha\beta$ -unsaturated ketone **44** by 1,5-diazabicyclo [4.3.0] nonene-5 (DBN) in *o*-xylene at reflux was reported. DBN was shown to be useful for the O-alkyl cleavage of methyl esters.<sup>23)</sup>

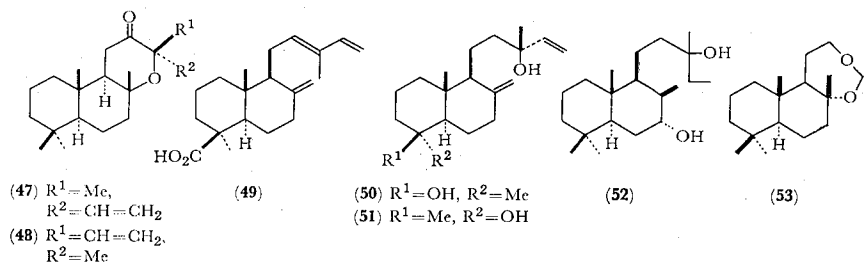


Compound **45** was converted into compound **46**, an attractive synthetic intermediate for a variety of podocarpic acid-type compounds, in a good overall yield.<sup>24)</sup>

### III. LABDANE DERIVATIVES\*



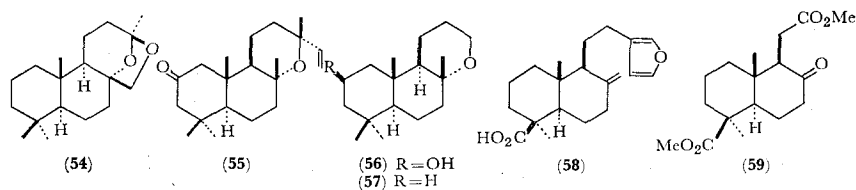
8,13-Epoxyabd-14-en-12-one (**47**) and its 13-epimer (**48**) were isolated from sun-cured Greek tobacco.<sup>25)</sup> From the acid fraction of the oleoresin from *Araucaria excelsa* were isolated communica acid (**49**), sandaracopimaric acid, abietic acid, cupressic acid, and its acetyl-derivative. From the neutral fraction of the same oleoresin were isolated manool, abietinal, abietinol, torulosal, torulosol, and two new nor diterpenes. The structures **50** and **51** were assigned to them.<sup>26)</sup>



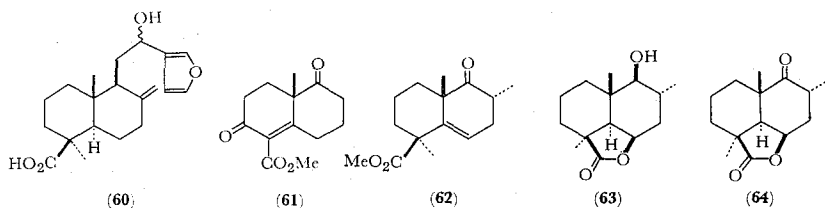
The tetrahydro-derivative **52** of the naturally occurring diterpene, 7 $\alpha$ -hydroxy manool, was synthesized.<sup>27)</sup> Utilization of manool oxide and related compounds for the preparation of compounds with ambergris-type odors was investigated. The acetal **53** prepared from sclareol was shown to have an ambergris-type odor of strength comparable to that of highly odoriferous acetal **54**. Attempts to convert 2-oxomanoyl

\* See also VI, ref. 79.

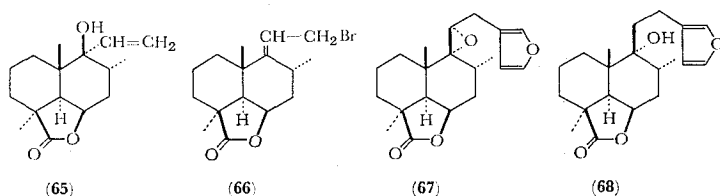
oxide **55** and manoyl oxide into the ethers **56** and **57** still retaining the original cyclic ether groups were also published.<sup>28)</sup>



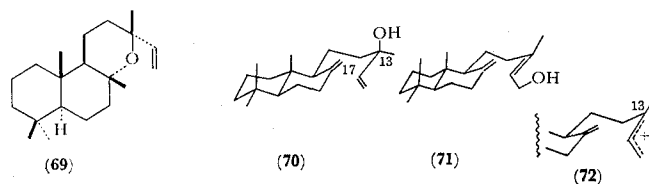
Lambertianic acid (**58**) synthesized starting from podocarpic acid. The central intermediate, diester-ketone **59**, was obtained by ozonolysis and hydrogenation, and the exocyclic methylene group in ring B was generated *via* a Reformatsky reaction. The furan ring was attached by nucleophilic attack of 3-lithiofuran and the 12-oxygen atom was removed by mesylation of the alcohols **60** and Li-liquid ammonia reduction.<sup>29)</sup>



The synthesis of marrubiin (**68**) was achieved starting from the keto lactone **64** which was prepared stereoselectively from the known keto ester **61** *via* **62** and **63**. The compound **64** on reaction with Li acetylide followed by reduction gave **65**, which gave **66** on treatment with  $PBr_3$  in pyridine. The bromide **66** was converted into furanoepoxide **67** by a reaction with 3-furanyl lithium followed by epoxidation. The final step, conversion of **67** into marrubiin (**68**) was achieved by reduction with lithium in ethylamine.<sup>30)</sup>

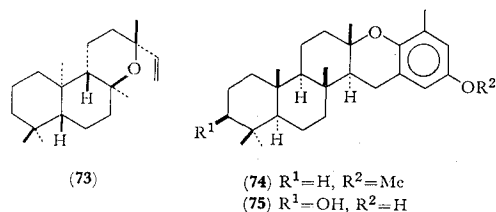


Dehydration of sclareol 8-acetate with  $POCl_3$ -pyridine yielded a mixture of acetates of iso- and trans-abienols, whereas pyrolysis of the 13-acetate by distillation proceeded through an ion pair forming mixed isoabienol, trans-abienol, 13-epimanoyl oxide and manoyl oxide (**69**).<sup>31)</sup>



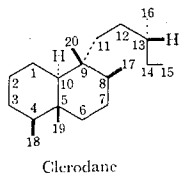
A bicyclic C-13 carbonium ion **72** was generated *in vitro* from manool (**70**) and  $\Delta^{13}$ -manool (**71**) and found to give, in refluxing AcOH, a 1:1 mixture of  $\Delta^{13}$ -manool acetate and olefins. Ring closures between C-13 and C-17 and between C-15 and C-17 were observed. The former cyclization gave approximately equal amounts of tricyclic  $\alpha$ -vinyl isopimaric and  $\beta$ -vinyl pimaric  $\Delta^7$ ,  $\Delta^8$ , and  $\Delta^{6(14)}$  dienes together with the products of backbone rearrangement. Under refluxing formic acid, formation of labdatrienes was precluded and yields of the initially cyclized pimaradienes and isopimaradienes, the backbone rearranged products and the product cyclized between C-15 and C-17 increased. The initial dienes and backbone rearranged products were interconverted by the reaction conditions showing that backbone rearrangement is reversible. A tetracyclic product, hiban-14 $\alpha$ -yl-formate, was also isolated and was formed quantitatively when the product formed by the cyclization between C-15 and C-17 possessing  $\Delta^8$  and  $\Delta^{13}$  was subjected to the reaction conditions. Deuterium labelling of  $\Delta^{13}$ -manool at C-14 showed that hiban-14 $\alpha$ -yl-formate was formed *via* such a carbon skeleton. Thus, the biogenesis of tetracyclic diterpenes was considered.<sup>32)</sup>

[15- $^3\text{H}$ ]*ent*-Labda-8(17), 13-dien-15-ol pyrophosphate was found to be specifically incorporated into *ent*-13-epimanoyl oxide (**73**) by *Gibberella fujikuroi*.<sup>33)</sup>



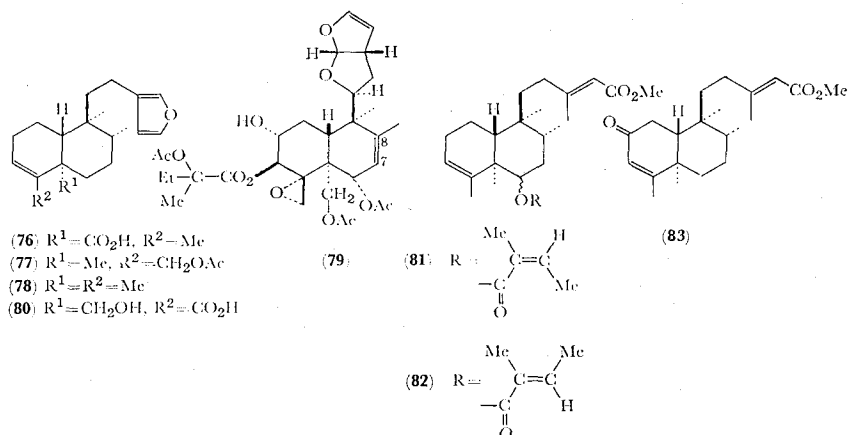
Desoxytaondiol methyl ether (**74**), a derivative of taondiol (**75**) previously isolated from *Taonia atomaria*, was synthesized from manool (**70**) by two steps of reactions.<sup>34)</sup>

#### IV. CLERODANE DERIVATIVES



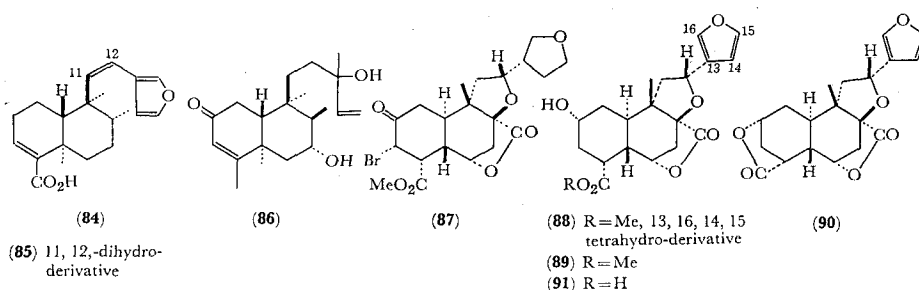
The absolute stereochemistry of maingayic acid was established as **76** by correlating it with hardwickiol acetate (**77**). The furano-olefin **78** derived from maingayic

acid was identical with the product obtained by hydrogenation of **77** in ethanol-triethylamine over palladium charcoal at 20°. <sup>35)</sup>



Clerodendrin A (**79**) and B were isolated from *Clerodendron tricotomum*. They showed the antifeeding activities for the tobacco cut worm. Clerodendrin B has a planar structure of 7,8-dihydro-derivative of clerodendrin A, but its stereochemistries at C-8, -9, -11, -13, and -16 are unknown. <sup>36)</sup> From *Conyza ivaeifolia* (Compositae), a clerodane-type diterpene, hautriwaic acid (**80**), which had been isolated from *Dodonea attenuata* by Jefferies and Payne, <sup>37)</sup> was isolated. <sup>38)</sup>

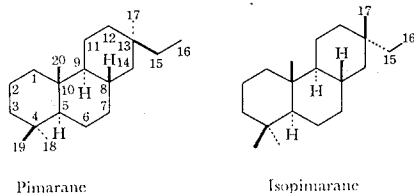
Acidic components of *Solidago altissima* roots were methylated with diazomethane and repeatedly chromatographed on silica gel to give two oily and one crystalline bitter principles. Their structures were elucidated as methyl 6-angeroyloxy- (**81**), 6-tygroyloxy- (**82**), and 2-oxokolavenate (**83**). <sup>39)</sup> Isolation of columbin from *Spirosperum penduliflorum* was reported. <sup>40)</sup> 11-Dehydro-*ent*-hardwickiic acid (**84**) and *ent*-hardwickiic acid (**85**) were isolated from *Croton oblongifolius*. <sup>41)</sup>



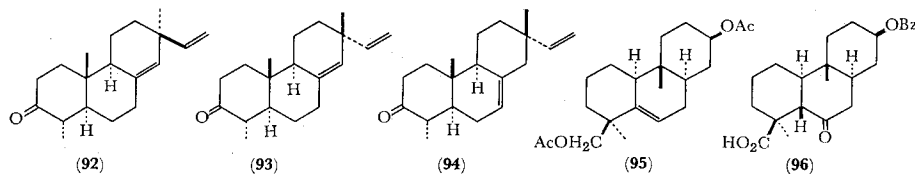
From *Teucrium chamaedrys* were isolated four bitter diterpenes, and their functional groups were characterized. <sup>42)</sup> The planar structure was assigned to stachysolone, a bitter substance from *Stachys annua*, on the basis of spectral and chemical evidence. <sup>43)</sup> Subsequently, the stereochemistry of stachysolone was investigated and formula **86** was given to it. <sup>44)</sup>

On the basis of the X-ray crystallographic study of 2-dehydro-3-bromo-tetrahydrodiosbulbin-A (**87**), the structure of tetrahydrodiosbulbin-A, diosbulbin-A, -B, and -C were revised to **88**, **89**, **90**, and **91**, respectively.<sup>45)</sup>

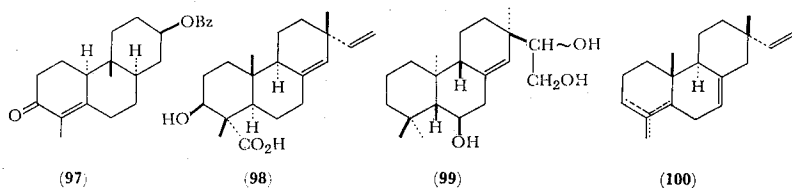
### V. PIMARANE AND ISOPIMARANE DERIVATIVES\*



The crystal structure of 12 $\beta$ -hydroxysandaracopimaric acid was determined from three-dimensional data collected on a single-crystal diffractometer with CuK $\alpha$  radiation.<sup>46)</sup> Three nor-diterpenes, 19-norpimara-8(14),15-dien-3-one (**92**), 19-nor-isopimara-8(14),15-dien-3-one (**93**), and 19-norisopimara-7,15-dien-3-one (**94**) were isolated from the bark of *Pinus silvestris*. Moreover, the following diterpenoids were characterized mainly by TLC and GLC: pimaral, isopimaral, dehydroabietal, pimaric acid, isopimaric acid, levopimaric acid, palustric acid, dehydroabietic acid, abietic acid, and neoabietic acid.<sup>47)</sup> Two new diterpenes, *ent*-pimara-8(14),15-dien-19-ol and *ent*-pimara-8(14),15-dien-19-al were isolated from *Aralia cordata*. Autoxidation of the latter was described.<sup>116)</sup>



Syntheses of **95**, **96**, and **97**, which were regarded as potential intermediates for the synthesis of *friedo*-pimarane type diterpene, were carried out.<sup>48,49)</sup>

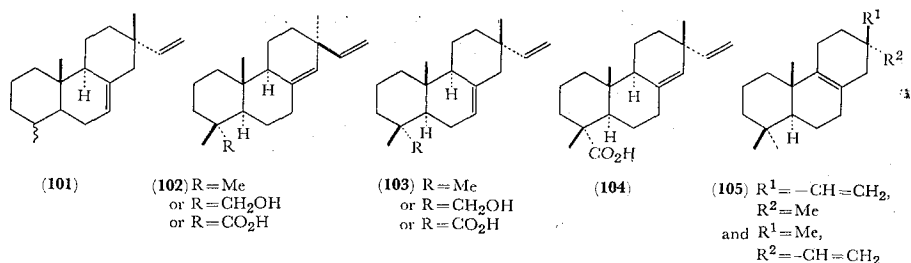


A new diterpene, 3 $\beta$ -hydroxysandaracopimaric acid (**98**), was isolated from *Juniperus rigida*.<sup>50)</sup> The structure of lagascatriol isolated from *Sideritis angustifolia* was proved to be **99**, on the basis of NMR spectral investigations and some reactions.<sup>51)</sup>

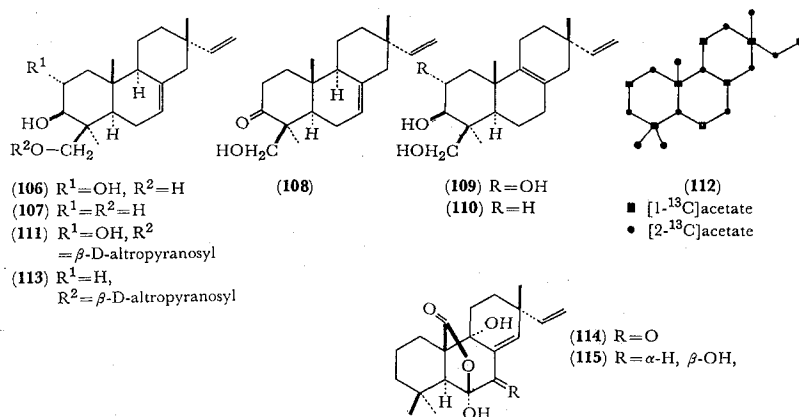
\* See also II, ref. 13, III, ref. 26, VI, refs 79 and 80, VII, ref. 83, and X, ref. 144.



Autoxidation of isopimaradienal was investigated and the formation of hydroperoxides was found. Additionally, a mixture of norditerpenoid hydrocarbons **100** and **101** were formed. Analogous results were obtained for dehydroabietinal and epitorulosal.<sup>52)</sup>



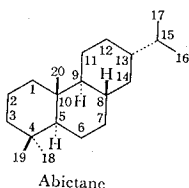
Carbon-13 NMR spectroscopy of pimaradienes was investigated. The chemical shift data for the pimaradienes, **102**, **103**, **104**, and **105**, were utilized for the determination of the otherwise difficultly assignable ring C conformation of the  $\Delta^{8(9)}$ -pimaradienes (**105**) as well as for the elucidation of the biosynthesis of the virescenosides, fungal isopimaradienic glycosides.<sup>53)</sup> These diterpene glycosides were isolated as the metabolites of mushroom *Oospora Virescens*. The biosynthesis of aglycones **106** and **107** was uncovered by carbon-13 NMR spectroscopy. The <sup>13</sup>C natural abundance NMR spectra of the aglycone alcohols, **106**, **107**, and **108** and their double bond isomers, **109** and **110**, obtained by acid hydrolysis of the glycosides, were recorded and their chemical shifts collected. Assignment of the  $\delta$  values was then carried out. Addition of sodium [1-<sup>13</sup>C] acetate to the mushroom culture medium, isolation of virescenoside A (**111**), hydrolysis to isovirescenol A (**109**), and inspection of the CMR spectrum of the latter revealed strong signal enhancement of the carbons depicted in **112**. Similar treatment of the culture with sodium [2-<sup>13</sup>C] acetate, isolation of virescenoside A (**111**) and B (**113**), conversion into isovirescencols A (**109**) and B (**110**), and perusal of the CMR spectra of the <sup>13</sup>C-enriched alcohols showed intense signal enlargement of the carbons portrayed in **112**. These results fit the present theory of the terpene biosynthesis.<sup>54)</sup>



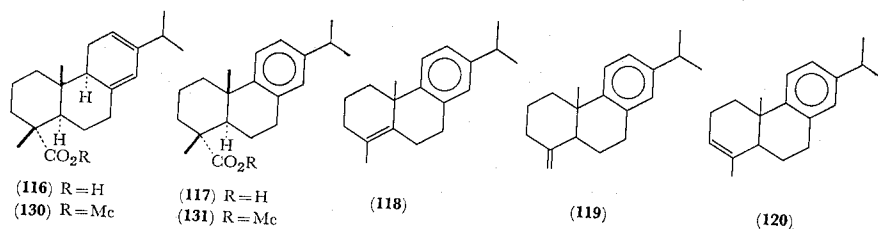
Two novel pimarane diterpenes LL-S491 $\beta$  (**114**) and - $\gamma$  (**115**) were isolated from fermentation of the fungus *Aspergillus chevalieri* (Lederls culture S491). LL-S491 $\beta$  displayed significant antibacterial activity against certain gram-positive organisms and LL-S491 $\gamma$  exhibited antiviral activity against *Herpes simplex*. Both compounds possess strong antiprotozoal activity against *Tetrachymena puriformis*. The structures of these antibiotics were elucidated.<sup>55)</sup>

Two short reviews on chemistry of pimaranes were published by Indian<sup>56)</sup> and Japanese authors.<sup>57)</sup>

## VI. ABIETANE DERIVATIVES\*



The crystal structure of levopimaric acid (**116**) was investigated. The acid was found to form a dimer by hydrogen bonding between the carboxyl groups of two independent molecules in the asymmetric unit.<sup>58)</sup>



The hot tube pyrolysis of dehydroabietic acid (**117**) at 400–500° was found to produce as major products the three possible ring A olefins, **118**, **119**, and **120** resulting from the elimination of the carboxylate moiety.<sup>59)</sup> The pyrolysis of abietic acid (**121**) and levopimaric acid (**116**) under identical conditions was found to yield ring-A olefins, isomerized products, dehydrogenation product **117**, and an elimination product *i.e.* deisopropyldehydroabietic acid (**122**). A mechanism was suggested for explanation of the formation of **122**.<sup>60)</sup> (Chart 1)

\* See also II, ref. 13, III, ref. 26, V, ref. 47, VI, ref. 80, and VII, ref. 83.

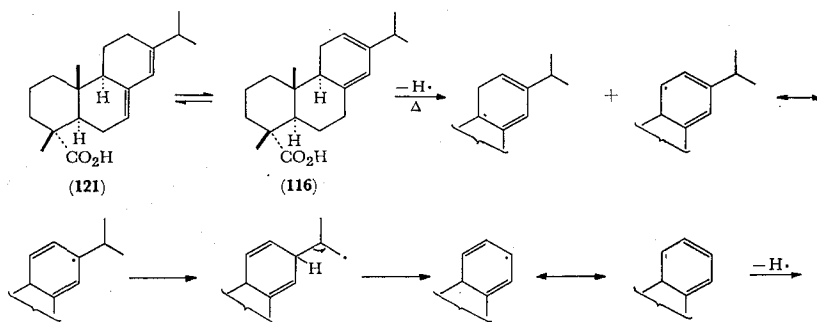
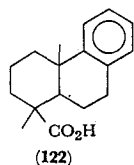
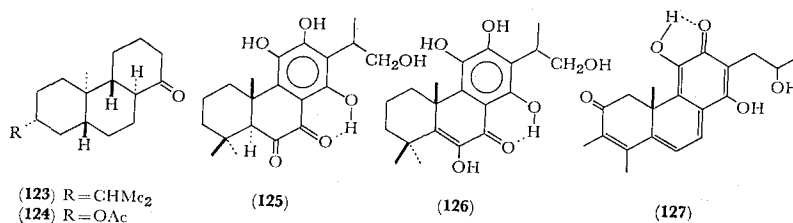


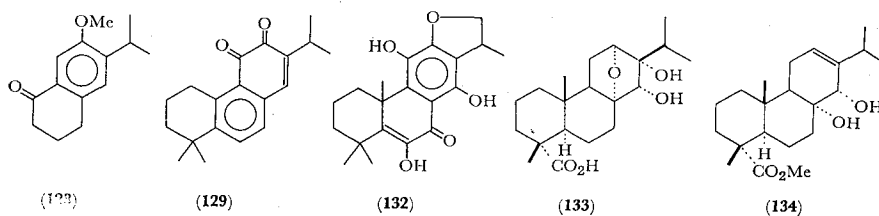
Chart 1



Conversion of abietic acid (121) to steroids was attempted and syntheses of the ketone compounds, **123** and **124**, were carried out. These compounds were regarded as the important intermediates in the synthesis of the skeleton of steroid antipodes.<sup>61)</sup>

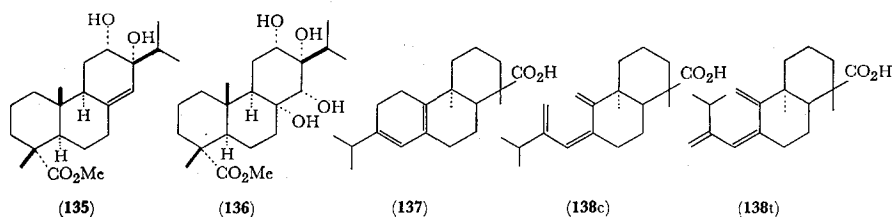


Coleon D, a new orange red diterpenoid hydroquinone, was isolated from the yellow glands on the leaves and inflorescences of *Coleus aquaticus* (Labiatae). The structure was determined as **125** which corresponded to a tautomer of coleon C **126**.<sup>62)</sup> Another new, very labile, deeply red colored quinone methide, coleon E, was isolated from the glands on the leaves of *Coleus barbatus*, *C. kilimandschari*, and a *Coleus* species, all of East African origin, and structure **127** was assigned to it.<sup>63)</sup>



Miltirone (**129**), a novel tricyclic diterpenoid quinone, was synthesized *via* 6-isopropyl-7-methoxy-1-tetralone (**128**).<sup>64)</sup> Methyl dehydroabietate (**131**) was prepared in a single step by dehydrogenation of methyl levopimarate (**130**) with  $\text{EtO}_2\text{C}\cdot\text{N}=\text{N}\cdot\text{CO}_2\text{Et}$  at  $25^\circ$ .<sup>65)</sup> A new yellow diterpenoid, lycoxanthol, was isolated from *Lycopodium lucidulum*, and its structure was suggested to be **132**.<sup>66)</sup>

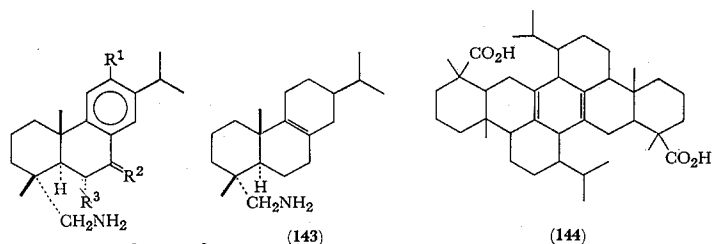
Structures were deduced for the products resulting from the  $\text{KMnO}_4$  and  $\text{OsO}_4$  oxidation of levopimaric acid (**116**). The major product of  $\text{KMnO}_4$  oxidation was an epoxydihydroxy carboxylic acid **133**. The products from  $\text{OsO}_4$  oxidation of methyl levopimarate (**130**) were diols, **134** and **135**, and tetraol **136**. The preparation of other enediols, epoxydiols, and tetraols derived from levopimaric acid was also reported.<sup>67)</sup>



It was found that a photostationary state of 50:50 exists between palustric acid (**137**) and the trienes **138c** and **138t**. The enhanced ring closure was explained on conformational grounds, noting that the isopropyl group destabilizes the transoid rotamer **138t** and hence increases the concentration of the cisoid rotamer **138c** which has the correct geometry for efficient ring closure. By evaluation of all related data, it was established that the photostationary state between diene and triene was controlled by the conformation of the triene.<sup>68)</sup>

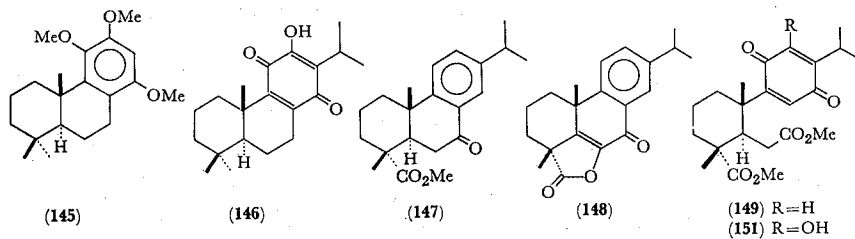
Benzene solutions of levopimaric acid, abietic acid, dihydroabietic acid, and methyl dehydroabietate were pyrolyzed at  $800^\circ$  on Vycor glass to yield tars containing the following general spectrum of products: toluene, styrene, indene, naphthalene, 2-methylnaphthalene, 2-vinylnaphthalene, acenaphthylene, phenanthrene, fluorene, and 2-phenylnaphthalene. The pyrolysis of methyl dehydroabietate in the absence of benzene indicated that toluene, styrene, indene, fluorene, and 2-phenylnaphthalene were the result of secondary reactions of pyrolysis products with phenyl radicals. Analysis of the products resulting from the pyrolysis of retene, under the same conditions, indicates that the high yield of naphthalene-related products obtained in the resin acid pyrolyzates must arise from A-ring cleavage in the parent molecule before complete aromatization occurs.<sup>69)</sup>

Dehydroabietylamine derivatives, *e.g.* **139–142**, were prepared in high yields by reduction of the corresponding amide derivatives with  $\text{LiAlH}_4$ . Analogously amine **143** was obtained from the corresponding amide.<sup>70)</sup>

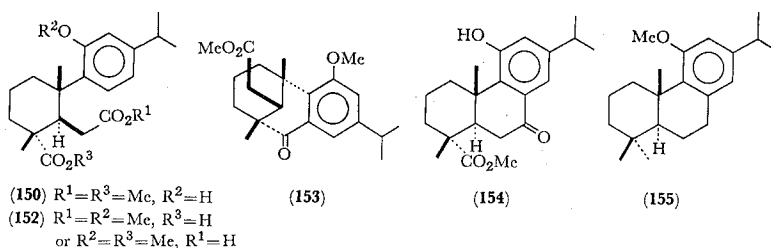
(139)  $R^1 = \text{Br}$ ,  $R^2 = \text{H}_2$ ,  $R^3 = \text{H}$ (140)  $R^1 = \text{Br}$ ,  $R^2 = \alpha\text{-H}$ ,  $\beta\text{-OH}$ ,  $R^3 = \text{H}$ (141)  $R^1 = R^3 = \text{Br}$ ,  $R^2 = \alpha\text{-H}$ ,  $\beta\text{-OH}$ (142)  $R^1 = R^3 = \text{Br}$ ,  $R^2 = \alpha\text{-OH}$ ,  $\beta\text{-H}$ 

Amber samples of different provenance were investigated by electron impact and field ionization mass spectrometry. Whereas electron impact mass spectra were not specific enough, field ionization spectra enabled one to identify amber from Baltic, Sicilian, Canadian, and Libanese areas. Very often the fragment peaks at  $m/e$  302 and  $m/e$  604 were observed. The former corresponds to a resin acid of abietic acid type ( $\text{C}_{20}\text{H}_{30}\text{O}_2$ ) and the latter to the diabietic acid type **144**<sup>71)</sup>.

*rac*-Royleanone (**146**) was synthesized from 5,7,8-trimethoxy-1-tetralone *via* podocarpane derivative **145**.<sup>72)</sup>



The oxidation of methyl 7-oxodehydroabietate (**147**) with perbenzoic acid and treatment of the crude product with methanol containing conc. HCl afforded a mixture of lactone **148**, quinone **149**, hydroxy ester **150**, and hydroxyquinone **151**. The intramolecular cyclization of half acid **152** derived from **150** gave two ketoesters **153** and **154**. The compound **154** was converted into 11-methoxydehydroabietane (**155**).<sup>73)</sup>

(150)  $R^1 = R^3 = \text{Me}$ ,  $R^2 = \text{H}$ (152)  $R^1 = R^2 = \text{Me}$ ,  $R^3 = \text{H}$ or  $R^2 = R^3 = \text{Me}$ ,  $R^1 = \text{H}$ 

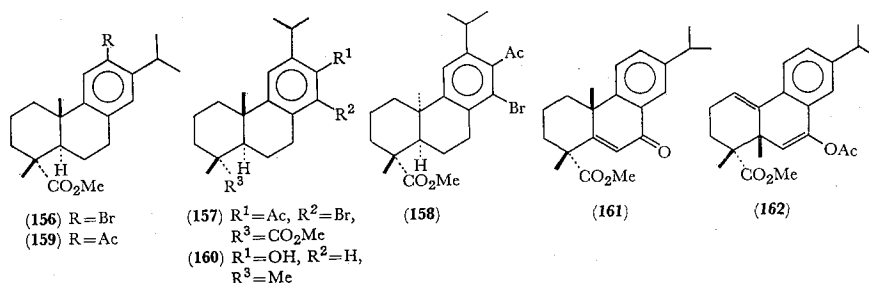
(153)

(154)

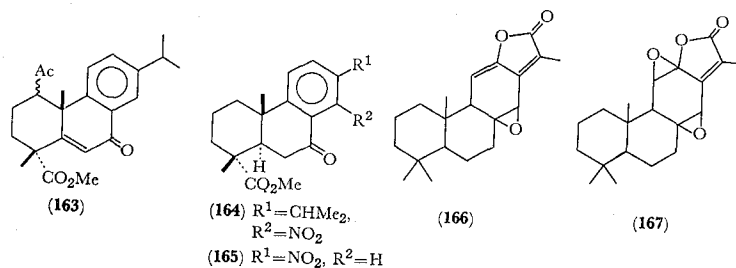
(155)

Friedel-Crafts reaction of methyl 12-bromodehydroabietate (**156**) with acetyl chloride afforded methyl 13-acetyl-14-bromo-12-isopropyldehydroabietate (**157**),

its *cis*-isomer (**158**), and methyl 12-acetyldehydroabietate (**159**). Conversion of **157** into semperviroil (**160**) was carried out and the absolute configuration of semperviroil was assigned.<sup>74)</sup>

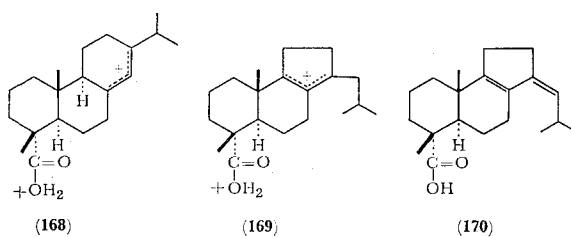


Benzonilidene compound **161** underwent rearrangement to **162** with 1,2-methyl migration and *vice versa*. Using the rearrangement, selective substitution at C-1 of dehydroabietic acid derivative was accomplished to give **163**.<sup>75)</sup>



Nitration of methyl 7-oxodehydroabietate (**147**) with fuming HNO<sub>3</sub> and conc. H<sub>2</sub>SO<sub>4</sub> (10:1) at 0–5° gave nitro compounds **164** and **165**.<sup>76)</sup>

From the fresh roots of *Euphorbia Jolkini* were isolated two new diterpenoids, jolkinolides A and B. Their structures were elucidated to be **166** and **167**, respectively.<sup>77)</sup> When a CH<sub>2</sub>Cl<sub>2</sub> solution of levopimaric acid (**116**) was dispersed in 96% H<sub>2</sub>SO<sub>4</sub> (5–10°), clear light orange solution of cation **168** was obtained. On quenching the cation solution in iced aq. Na<sub>2</sub>CO<sub>3</sub>, a near quantitative recovery of abietic acid resulted. Cation **168** at 25° (2 hours) in H<sub>2</sub>SO<sub>4</sub> underwent smooth rearrangement to **169** as evidenced by its UV spectrum and NMR spectrum. Quenching the cation **169** gave an unstable dienoic acid **170** in 80% yield and was purified through its methyl ester. The dienoic acid **170** regenerated cation **169** on dissolution in 96% H<sub>2</sub>SO<sub>4</sub>.<sup>78)</sup>

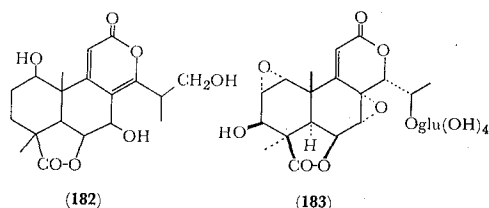




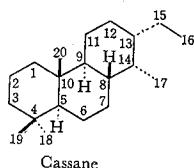
The plant-growth inhibitory activities of 12 kinds of compounds which were related to podolactones were determined using a pea-stem growth system.<sup>84)</sup> Podolactone E, isolated from *Podocarpus neriifolius* was the most active inhibitory compound. The structure **177** was assigned to this substance mainly on the basis of the NMR investigation. This substance is very likely a biogenetic precursor of inumakilactone B, which can be formed by epoxidation of the 7,8-double bond: hydration of the side chain of the latter compound may then lead to inumakilactone A.<sup>85)</sup>

The stereochemistry of nagilactone A and B was established by the spectral analyses and the X-ray method. The absolute configurations of both substances were also proposed as shown in **178** and **179**, respectively.<sup>86)</sup> The structures of two new norditerpenoid dilactones, nagilactone E and F, were proposed as **180** and **181**. A dual biological activity of nagilactones (inhibitory and promotive) for plant growth was also reported.<sup>87)</sup>

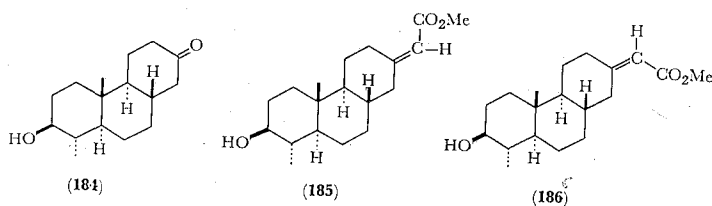
Further norditerpenoids of *Podocarpus macrophyllus* were investigated. The structures of inumakilactone E and inumakilactone A glucoside were elucidated as **182** and **183**. The latter was shown to be a potent inhibitor of the expansion and division of the plant cells.<sup>88)</sup>



### VIII. CASSANE DERIVATIVES

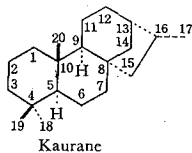


Syntheses of racemic, isomeric deoxo-4,14-didemethylcassaic acid derivatives, **185** and **186**, were carried out *via* **184**. From **185** and **186**, some derivatives were synthesized.<sup>89)</sup>

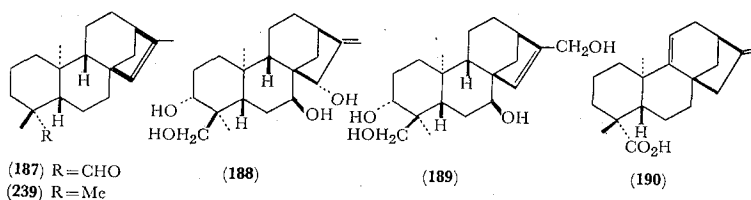




## IX. KAURANE DERIVATIVES\*

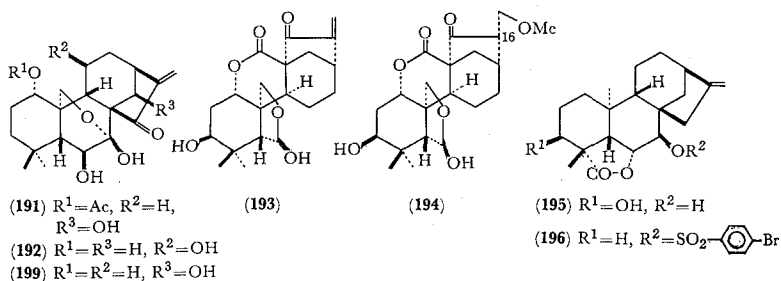


An aldehyde isolated from the Venezuelan plant *Espeletia weddellii* was identified by its crystal structure analysis to be *ent*-15-kauren-19-al (**187**).<sup>90)</sup> Two diterpenes, leucanthol (**188**) and isoleucanthol (**189**) were isolated from *Sideritis leucantha*, and their structures were determined.<sup>91)</sup>



Definitive evidence concerning the revised structure **190** for grandiflorenic acid, extracted from the resin of *Espeletia grandiflora*, was provided. The resin also contained the known kaurenic-type diterpenes, *ent*-16-kauren-19-oic acid, *ent*-16-kauren-19-al, and *ent*-16-kauren-19-ol.<sup>92)</sup>

On the basis of chemical and spectroscopic evidence, the structure and absolute configuration of the highly oxygenated diterpenes, lasiokaurin and lasiodonin isolated from *Isodon lasiocarpus* were shown to be **191** and **192**, respectively.<sup>93)</sup>



A sequence of sterically controlled reactions from enmein (**193**) gave naturally occurring isotrocin (**194**), and it established the absolute stereochemistry at C-16.<sup>94)</sup>

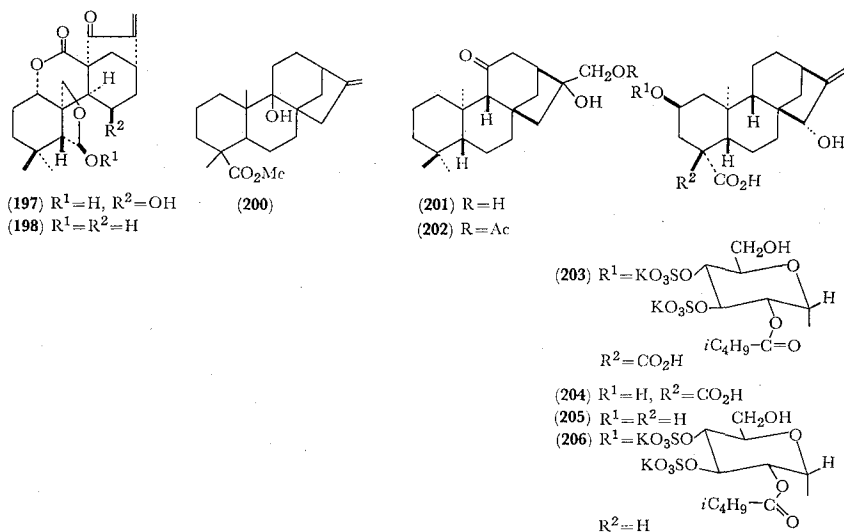
A new metabolite of *Gibberella fujikuroi* was isolated and shown to be 3 $\beta$ , 7 $\beta$ -dihydroxykaurenolide (**195**). It is the first time that the C-3 hydroxylated compound was isolated from the metabolite of this fungus. It suggests an alternative biosynthetic route to the gibberellins, in which 3-hydroxylation precedes ring contraction.<sup>95)</sup> The fact that ring A of the brosylate (**196**) of 7 $\beta$ -hydroxykaurenolide is distorted

\* See also X, ref. 145 and XI, ref. 173.

from ideal chair geometry while rings B and C adopt distorted twisted boat conformations was recognized by its three-dimensional X-ray analysis.<sup>96)</sup>

Six kinds of plants belonging to *Isodon* genus were checked for diterpenoid component. *I. longitubus* contained four known diterpenoids, nodosin (**197**), isodocarpin (**198**), oridonin (**199**), and lasiokaurin (**191**). Six new diterpenes were isolated and named isodomedin (from *I. shikokianus* var. *intermedius*), kamebanin, mebadonin (from *I. kameba*), inflexin (from *I. inflexus*), umbrosin (from *I. umbrosus*), and effusin (from *I. effusus*). Molecular formulae and spectral data indicated that all these compounds are tetra-cyclic diterpenoids.<sup>97)</sup>

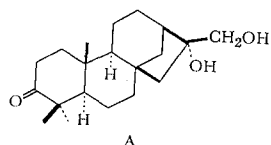
A new diterpene, stenolobin, was isolated from *Viguiera stenoloba* and the structure was elucidated as **200**.<sup>98)</sup> Calliterpenone (**201**) and calliterpenone monoacetate (**202**) were isolated from the aerial parts of *Callicarpa macrophylla* and their structures and stereochemistry were reported on the basis of spectral data and their conversions to *ent*-17-norkaurane.<sup>99)\*</sup>

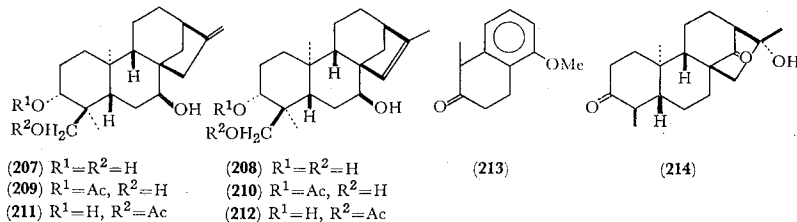


A new sulfated glycoside, carboxyatractyloside (**203**) was isolated from the rhizomes of *Atractylis gummifera*. The structure of the aglycone, carboxyatractyligenin (**204**), was determined by means of spectroscopic as well as chemical data and confirmed by correlation with the known atractyligenin (**205**). The structure of the glycoside was determined by correlation with atractyloside (**206**).<sup>102)</sup>

Six diterpenes, foliol (**207**), isofoliol (**208**), sidol (**209**), isosidol (**210**), linearol (**211**), and isolinearol (**212**), were isolated from *Sideritis leucantha*. *S. linearifolia* yielded foliol (**207**), sidol (**209**), and linearol (**211**) only.<sup>103)</sup>

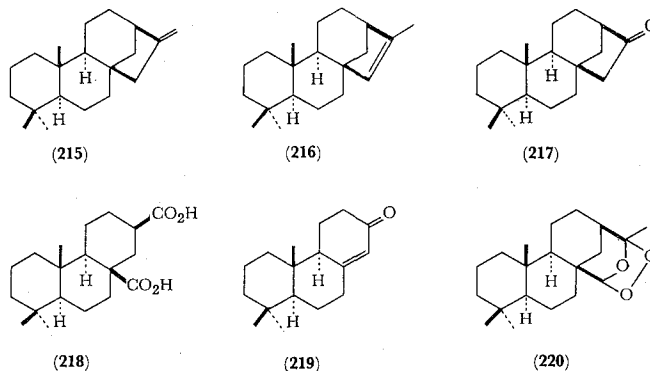
\* Recently, however, the structure of calliterpenone was revised to  $13\beta$ -kauran-3-one- $16\alpha,17\beta$ -diol (**A**) by Ahmad and Zaman.<sup>100)</sup> The correctness of the structure **A** was reconfirmed by the joint work<sup>101)</sup> of the author's (E. F.) group and Chatterjee's group.



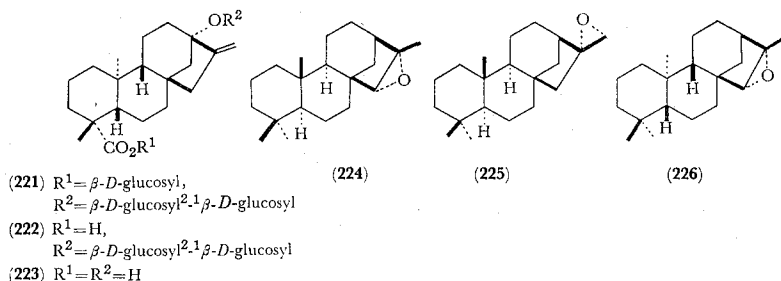


Total syntheses of a kaurane derivative **214** and related compounds which are potential intermediates for the synthesis of highly oxygenated diterpenes such as grayanotoxins, were accomplished from **213**.<sup>104)</sup>

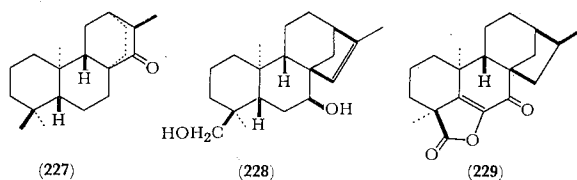
Oxidative degradations of phyllocladene (**215**) and isophyllocladene (**216**) were carried out. Several routes from phyllocladene (**215**) into the diacid **218** via norketone **217** were demonstrated. On a series of reactions including ozonolysis, isophyllocladene (**216**) was converted into podocarp-8-(14)-en-13-one (**219**), an optically active relay which is useful in syntheses. It is of interest that the ozonide **220** of isophyllocladene was isolated and characterized.<sup>105)</sup>



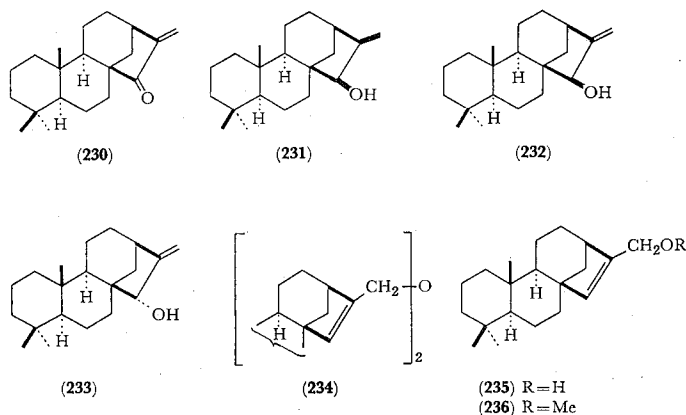
An interesting hydrolysis of glucoside bond in stevioside (**221**) by a soil bacterial strain (YSB-9, unidentified) was reported. It gave steviolbioside (**222**) as a major product and steviol (**223**) as a minor.<sup>106)</sup>



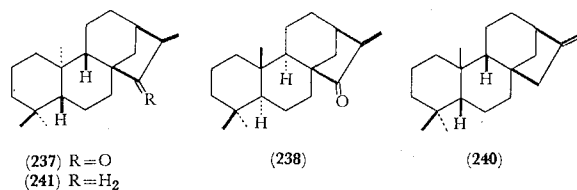
Some chemistry concerning the epoxides of phyllocladene (**215**), isophyllocladene (**216**), and kaurene-phyllocladene type compounds was described. The products from, and the effect of solvent on the ring-opening of  $15\alpha$ , 16-epoxyphyllocladane (**224**) and of  $16\alpha$ , 17-epoxyphyllocladane (**225**) with boron trifluoride as well as other Lewis acids were examined. Treatment of *ent*-15 $\beta$ , 16-epoxykaurane (**226**) with boron trifluoride-ether complex results rearrangement, giving *ent*-atisan-15-one (**227**). Photo-oxygenation of phyllocladene (**215**) and isophyllocladene (**216**) was also studied.<sup>107)</sup>



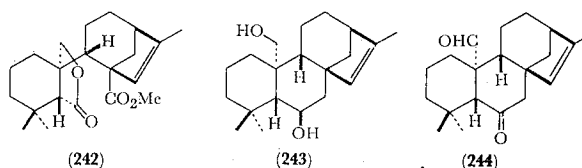
The secondary hydroxy-group of sidoriol (**228**) was confirmed as being in the 7- rather than the 12-position by conversion of the former into *ent*-7-oxokaur-5-en-18, 6-olide (**229**).<sup>108)</sup> Some reactions in ring D of  $13\beta$ -kaurane (phyllocladane) derivatives were reported. Metal hydride reduction of  $13\beta$ -kaur-16-en-15-one (**230**) afforded tetrahydro-derivative **231**, but none of the expected 1,2-reduction product **232**. Treatment of  $13\beta$ -kaur-16-en-15 $\alpha$ -ol (**233**) with aqueous acid in methanol yielded a dimeric ether **234** in addition to 17-hydroxy-(**235**) and 17-methoxy- $13\beta$ -kaur-15-ene (**236**).<sup>109)</sup>



The enolization-ketonization of the *ent*-kauran-15-ones and  $13\beta$ -kauran-15-ones was reported. At temperature below  $100^\circ$  the rates of enolization of *ent*-kauran-15-one (**237**) and  $13\beta$ -kauran-15-one (**238**) were much greater than those of the 16S-epimers, and the enols were exclusively ketonized to the 16R-epimers. Reasons for this kinetic control were discussed in terms of steric hindrance, torsional strain, and stereoelectronic factors.<sup>110)</sup>



Enmein (**193**) was converted into *ent*-15-kaurene (**239**), *ent*-16-kaurene (**240**), and *ent*-kaurane (**241**). Thus, acyloin condensation of lactone ester **242** derived from enmein (**193**) by several steps afforded a key intermediate **243**. On Jones oxidation followed by Huang-Minlon reduction, diol **243** gave **239**, **240**, and **241**, via keto aldehyde **244**. On the other hand, Nagata's modification of Wolff-Kishner reduction on **244** afforded *ent*-kaurane (**241**) as a sole product.<sup>111)</sup> Hydrogenation of the double bond during the Nagata's modification of Wolff-Kishner reduction was studied in detail using *ent*-16-kaurene (**240**) as a reference compound and the possible mechanisms were discussed.<sup>112)</sup>



The stereochemistry of hydroboration, osmylation, and epoxidation of some kaur-6,7-enes was investigated. The attack of the reagents takes place exclusively from  $\beta$ -side of the molecule to give a variety of substances suitably functionalized for study in gibberellin biosynthesis.<sup>113)</sup>

*rac.*-Steviol (**223**), tetracyclic diterpene with a substituent at the bridgehead C-13 position, was synthesized starting from the known keto ester **245** through the sequence shown in Chart 2.<sup>114)</sup> Conversion of **246** into steviol (**223**) had been accomplished by the same authors in 1971.<sup>115)</sup>

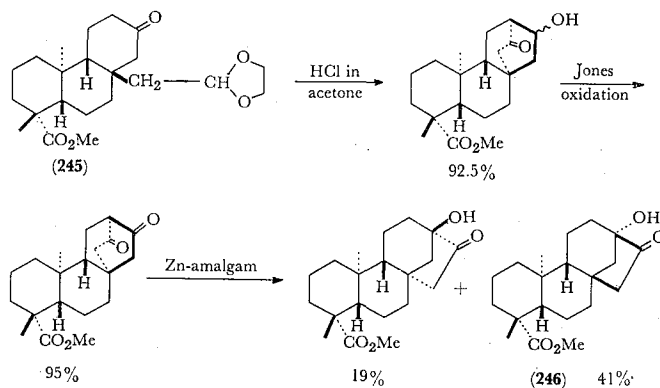
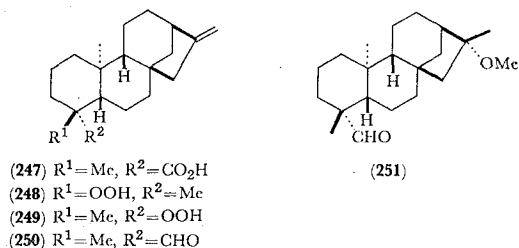


Chart 2

Kaurenoic acid (**247**) and epimeric hydroperoxides **248** and **249** were obtained by autoxidation of *ent*-kaur-16-en-19-al (**250**). Extensive studies on autoxidation of *ent*-16-methoxy-kauran-19-al (**251**) were carried out and a suggestion that some 4-hydroxynorditerpenes isolated from natural sources so far are probably artifacts was provided.<sup>116)</sup>



Diol **252** derived from enmein (**193**) was transformed into enmein through the sequence of the reactions shown in Chart 3. Thus the first total synthesis of enmein was accomplished since the diol **252** was synthesized from 2,5-dihydroxynaphthalene.<sup>117)</sup>

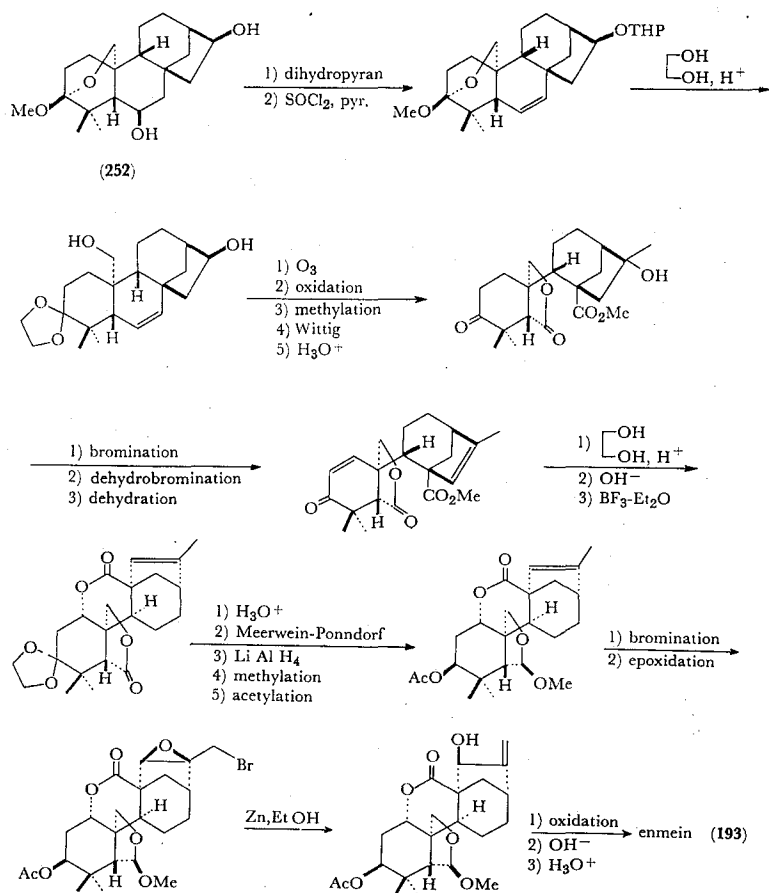
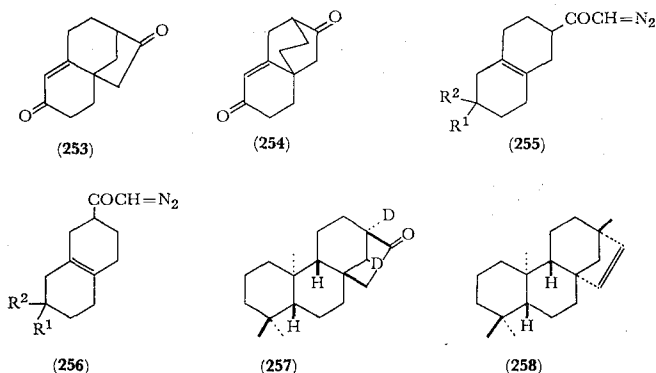


Chart 3

The copper-catalyzed decomposition of the diazomethyl ketones **255** and **256** followed by simple chemical reactions offered a new method for the preparation of tricyclic compounds **253** and **254** containing the 3,2,1- and 2,2,2-bicyclooctane ring systems which are envisaged as intermediates in a "BC+D+A" total synthesis of tetracyclic diterpenoids.<sup>118)</sup>



Very rare example of bridgehead enolization was demonstrated in *ent*-kaurene derivative.<sup>119)</sup> The deuterated ketone **257** with 36–47% deuterium at C-14 and virtually 100% deuterium at C-13, prepared from *ent*-beyer-15-ene (**258**) through a series of reactions, was shown to lose almost all of deuterium at C-13 on treatment with *t*-BuOK and *t*-BuOH at 172° for 72 hr. in a sealed tube.

The preparation from *Gibberella fujikuroi* of a cell-free system that converts mevalonate into *ent*-kaurene (**240**) was reported. The system was used to show that a pimaradiene intermediate is not involved in the biosynthesis of *ent*-kaurene by *Gibberella fujikuroi*. However, an enzyme-bound pimarane with, for example, a stabilized C-8 carbonium ion system or the direct cyclization of pyrophosphate **259** illustrated in Chart 4 are possible alternatives.<sup>120)</sup>

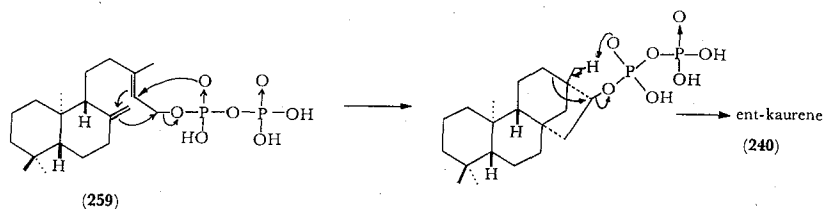
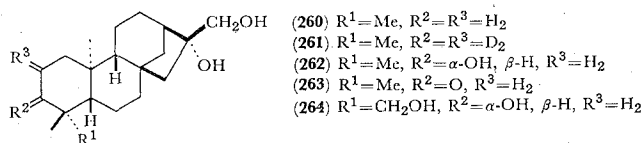


Chart 4

As a preliminary experiment of the biosynthesis, changes in the quantity of major diterpenoids, enmein (**193**), oridonin (**199**), and isodocarpin (**198**) were examined every ten days by GC and GC-MS. Enmein (**193**) and oridonin (**199**) were found to increase markedly in June and July.<sup>121)</sup>

Mass spectra of five kaurane derivatives, **260–264**, were studied by Russian workers.<sup>122)</sup>

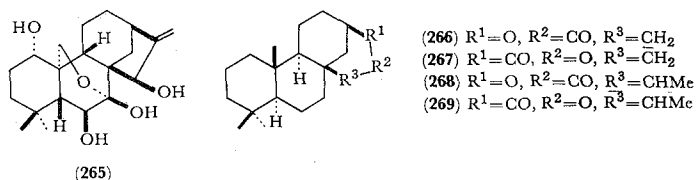
Chemistry on Diterpenoids in 1972



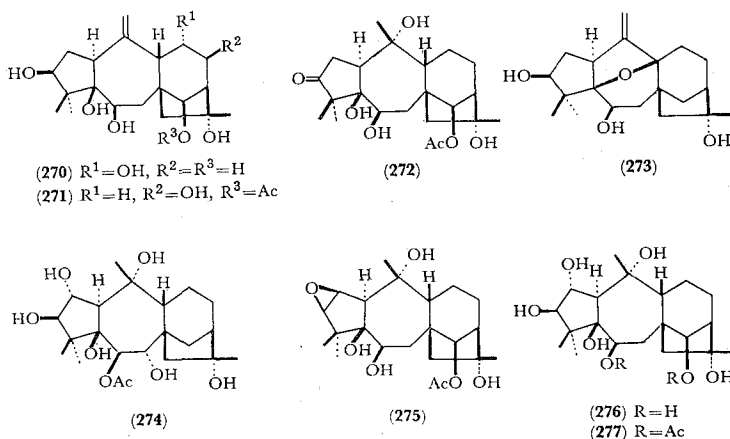
An interesting method was presented by which the specific radioactivity of [ $^{14}\text{C}$ ]-labeled compounds can be determined using MS data for GLC-MS. The specific activity of [ $^{14}\text{C}$ ]-labeled *ent*-kaurene (240), *ent*-7 $\alpha$ -hydroxykaurenoic acid, *ent*-kaurenoic acid, and gibberellin  $A_{12}$ -aldehyde were determined by this method. These compounds were thus shown to be derived from 2-[ $^{14}\text{C}$ ]-MVA without significant dilution of the label in a cell-free enzyme system from *Cucurbita pepo*.<sup>123)</sup> Mass spectra of [ $^{17-^{13}\text{C}}$ ] kaurene, [ $^{17-^{13}\text{C}}$ ] 6-hydroxykaurene, and [ $^{17-^{13}\text{C}}$ ] kaurane were reported and discussed.<sup>124)</sup>

Interproton allylic spin-spin coupling involving exocyclic groups was extensively studied for 55 compounds including lasiokaurin (191) and 1-epienmerol (265).<sup>125)</sup> The  $J_{15,16}$  values for the stereoisomeric *ent*-kauran- and 13 $\beta$ -kauran-15-ols indicate a twist envelope conformation for ring D in all except the (16S)-15 $\beta$ -ols. The chemical shifts of the C-15 protons confirm the stereochemical assignments.<sup>126)</sup>

Lactone rings in 266, 267, 268, and 269 were shown to exist in chair conformation by ORD curves and solvent shift in NMR spectra.<sup>127)</sup>



Eight A-nor-B-homo-kaurane type diterpenes were isolated. They are grayanotoxins-XII (270)<sup>128)</sup>, -XIII (271)<sup>128)</sup>, -XIV (272)<sup>129)</sup>, and -XV (273)<sup>129)</sup> from *Leucothoe grayana*, lyoniol-D (274)<sup>130)</sup>, from *Lyonia ovalifolia* var. *elliptica*, rhodojaponins-V (275)<sup>131,132)</sup> -VI (276)<sup>132)</sup>, and -VII (277)<sup>131)</sup> from *Rhododendron japonicum*.





Grayanotoxin II (**278**) was converted to 20-nor-kaurane derivatives (**279**) and (**280**) through a sequence shown in Chart 5.<sup>133)</sup>

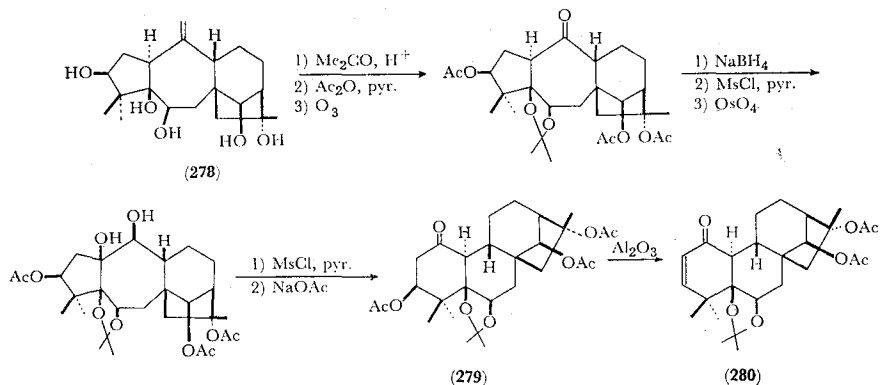


Chart 5

Partial synthesis of grayanotoxin-II (**278**) from its degradation product **281** was reported.<sup>134)</sup> The route is shown in Chart 6.

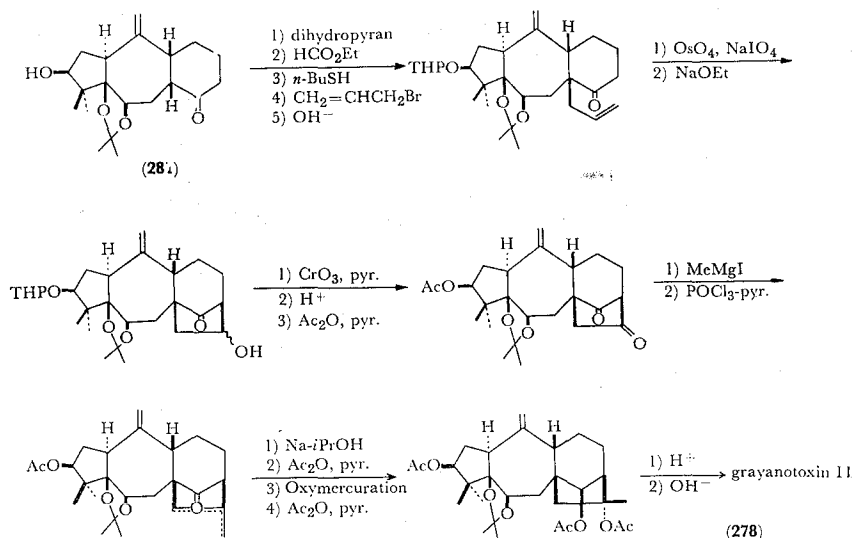
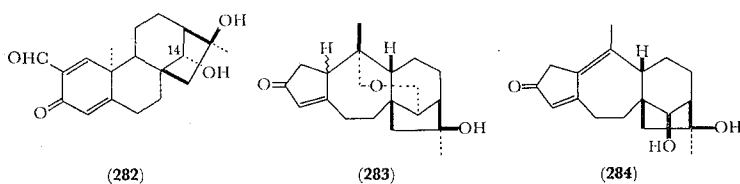
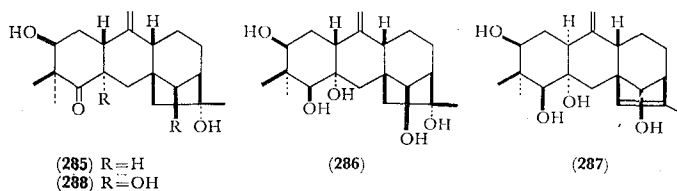


Chart 6

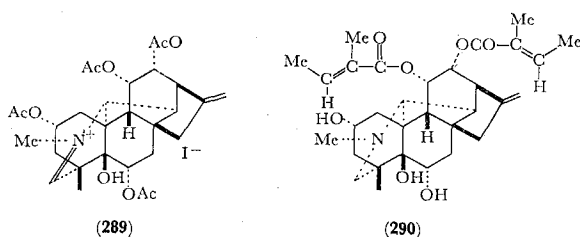
The compounds **283** and **284** with grayanotoxin skeleton were prepared by photochemical reaction of the synthesized compound **282** and its C-14 epimer.<sup>135)</sup>



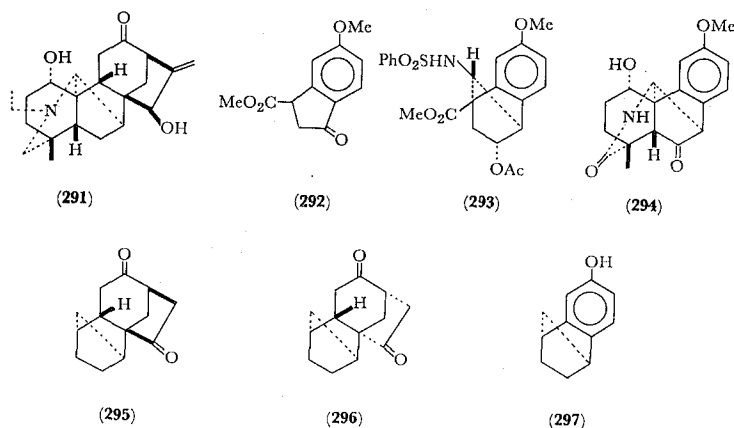
The first isolation of anthraditerpenoid, leucothol A from *Leucothoe grayana* was reported and the structure was determined as **285** by means of X-ray crystallographic analysis.<sup>136)</sup> Other three diterpenoids in this class were additionally found in this year. They are leucothols B (**286**),<sup>137,138)</sup> C (**287**),<sup>137)</sup> and D (**288**).<sup>138)</sup>



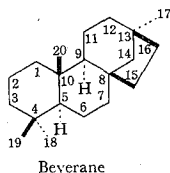
On the basis of the structure **289** of the product of a reaction between  $O,O,O,O$ -tetraacetylanopteryl alcohol and methyl iodide, the parent alkaloid, anopterine, isolated from *Anopterus macleanus* and *Anopterus glandulosus* was shown to have the structure **290**. The structure **289** was determined by an X-ray analysis.<sup>139)</sup>



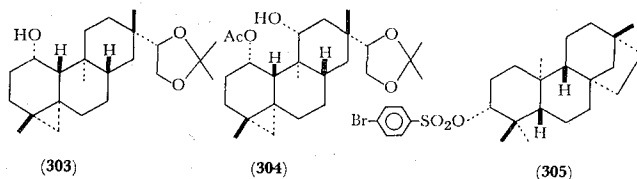
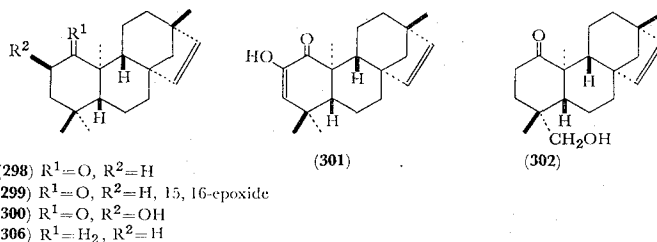
An approach to the total synthesis of songorine (**291**) has been tried by Wiesner's group. A ketoester **292** was stereoselectively converted to a crucial intermediate **293**<sup>140)</sup> which was further converted to the pentacyclic keto lactam **294** by a series of reactions.<sup>141)</sup> The syntheses of diketones **295** and **296** from phenol **297** had been reported by Wiesner *et al.* in 1970.<sup>142)</sup> In view of the considerable synthetic value of these ketones an X-ray analysis of **295** was carried out to confirm their structure.<sup>143)</sup>



## X. BEYERANE DERIVATIVES\*



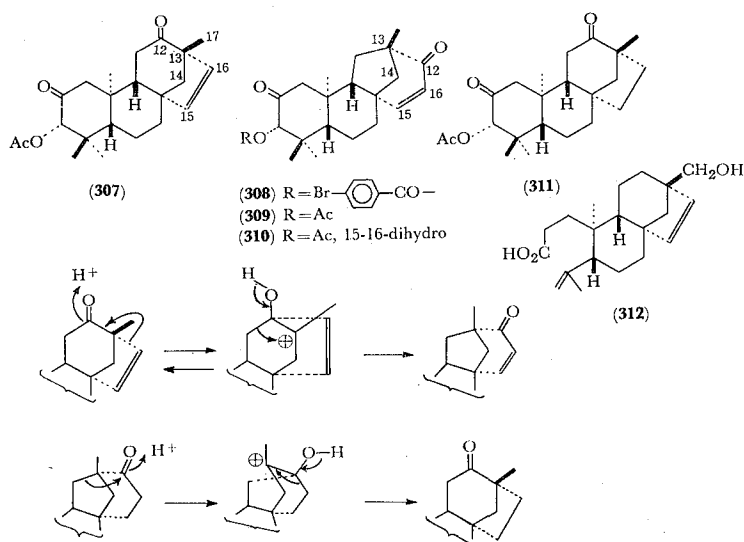
The structures of seven new diterpenoids **298**–**304** from the root wood of *Erythroxylon australe* were assigned on the basis of chemical and spectroscopic evidence. Two of them were isolated as isopropylidene acetals, **303** and **304**, by treatment with acetone and copper sulfate.<sup>144)</sup> Six known compounds including *ent*-15-beyerene (**306**)<sup>145)</sup> were also isolated.



The crystal structure of the *p*-bromobenzenesulfonate of *ent*-beyeran-3 $\beta$ -ol (**305**) was elucidated by three-dimensional X-ray method. In (**305**), rings A, B, and C have chair conformations.<sup>96)</sup>

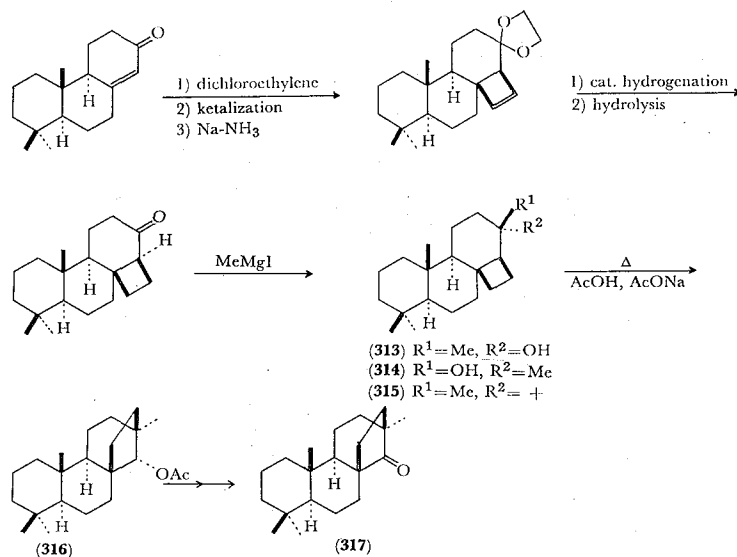
A recently isolated new naturally-occurring compound<sup>146)</sup> of a 12-oxo-beyer-15 (16)-ene system was confirmed to undergo a double 1,2-rearrangement across the 12, 13-single bond in acid medium<sup>147)</sup>, because the structure of the *p*-bromo-benzoate of the acid rearranged compound was established as **308** by X-ray crystal structural analysis.<sup>148)</sup> Namely, **307** induced high yield rearrangement to **309** with various acids. Furthermore, addition of acid to an acetic acid-acetic anhydride solution of the dihydro-derivative **310** afforded **311**. The easy rearrangement of this system was proposed as indicated in the Chart 7.<sup>147)</sup>

\* See also III, ref. 32.



From biosynthetic study of diterpenes in *Beyeria leschenaultii*, beyerene and beyeren-19-ol was indicated to serve as precursors of beyerol, 17,19-dihydroxybeyer-15-en-3-one and the 3,4-secobeyerene acid **312** but only beyerene was incorporated into 6 $\beta$ ,17-dihydroxybeyer-15-en-3-one, the major component. The significance of beyerene and beyeren-19-ol as precursors of **312** is discussed with reference to possible mechanism for its formation.<sup>149)</sup>

Synthesis of (+)-14-hibaone (**317**) from  $\Delta^{8(14)}$ -podocarpin-13-one was accomplished as shown in Chart 8, which included a photochemical reaction with dichloroethylene and a direct conversion of the tetracyclic epimeric alcohols **313** and **314**, precursors of the biogenetic intermediate **315** postulated by Edwards, into 14 $\alpha$ -hibyl acetate **316**.<sup>150)</sup>



Erythroxydiol A (**318**) was synthesized *via* a route in Chart 9<sup>144</sup> from the steviol methyl ester synthesized already.

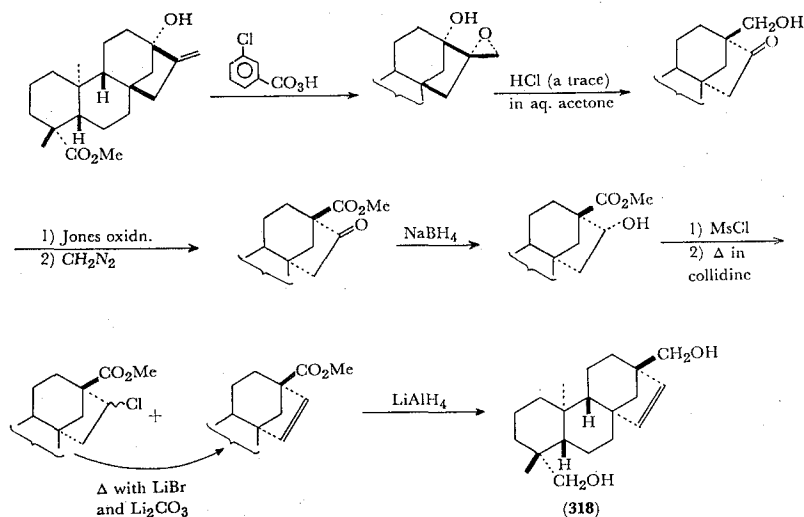
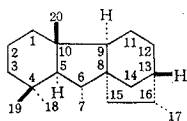


Chart 9

## XI. GIBBERELLANE DERIVATIVES



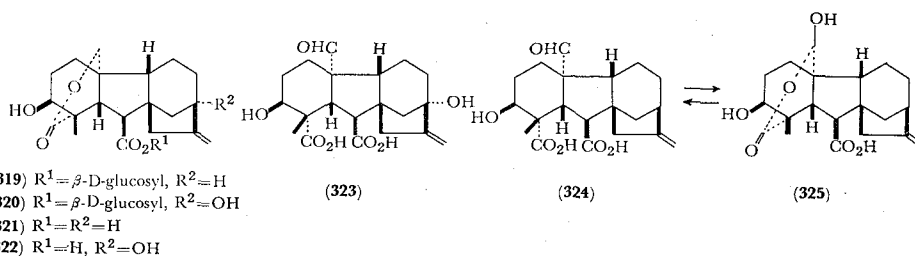
Gibberellane

From immature seeds of *Wistaria floribunda*, gibberellins  $A_{18}$  and  $A_{23}$  were isolated.<sup>151)</sup> Gibberellins  $A_9$  and  $A_{13}$  were isolated from *Enhydra fluctuans* and identified on the basis of m.p., m.m.p., IR, MS and co-chromatography.<sup>152)</sup>

A new naturally occurring tetrahydrogibberellin  $A_3$  was isolated from the leaves of *Sonneratia apetala*,<sup>153)</sup> but the identification was questioned by MacMillan and Takahashi<sup>154)</sup> on the basis of the reported m.p., UV, and NMR spectra. Therefore, this gibberellin, m.p. 280–285°, was re-isolated and conclusively identified<sup>155)</sup> by direct comparison with tetrahydrogibberellin  $A_3$ , m.p. 285–290°.

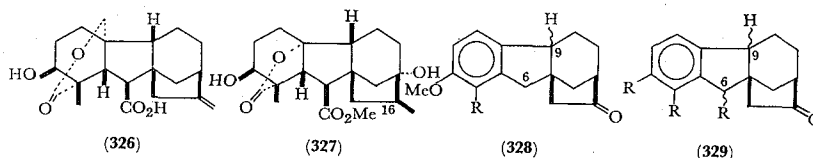
Glucosyl esters **319** and **320** of  $GA_{37}$  (**321**) and  $GA_{38}$  (**322**) together with free  $GA_1$  and glucosyl ester of  $GA_4$  were isolated from mature seeds of *Phaseolus vulgaris*.<sup>156)</sup>

Full paper about structure of gibberellin  $A_{23}$  (**323**) isolated from the immature fruits of *Lupinus luteus* was published.<sup>157)</sup> A new gibberellin,  $GA_{36}$  (**324**–**325**) was isolated from the culture filtrates of *G. fujikuroi*. Confirmation of structure for  $GA_{36}$  was obtained by reduction with sodium borohydride to  $GA_{37}$  (**326**).<sup>158)</sup>



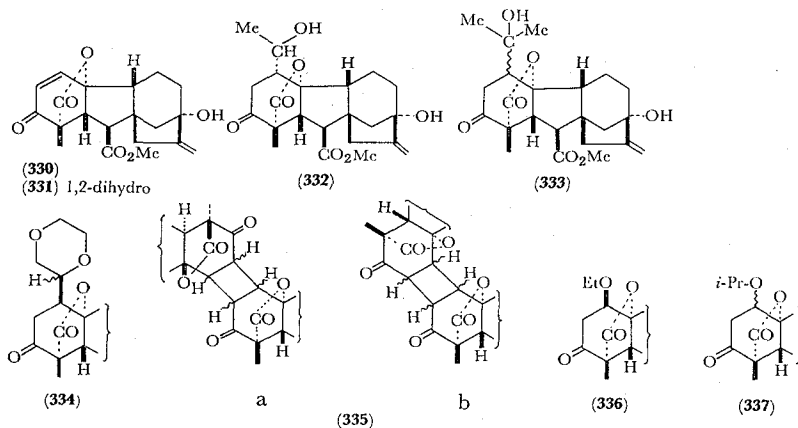
A short review on recent progress in chemistry of gibberellins was published in Japanese.<sup>159)</sup>

Stereochemistry at C-16 of dihydrogibberellin A<sub>1</sub> methyl ester (327) and its 16-epimer was elucidated<sup>160)</sup> by NMR analysis employing a shift reagent, Eu(thd)<sub>3</sub> or Eu(fod)<sub>3</sub>.

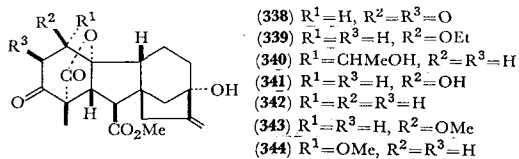


Spectroscopic methods for assignment of C-9 stereochemistry in gibbanes, 328 and 329, were presented. Namely, in the C-9 $\alpha$  gibbanes the respective C-6 methylene protons resonate at higher field than those of the isomeric C-9 $\beta$  gibbanes. In gibban-16-ones having ester functionality at C-4 or C-6 there is a tendency for C-9 $\alpha$  isomer to exhibit C-16 carbonyl absorption in the infrared near 1740  $\text{cm}^{-1}$  whereas C-9 $\beta$  isomers absorb near 1730  $\text{cm}^{-1}$ .<sup>161)</sup>

The photochemistry of GA<sub>3</sub> derivative 330 in ethanol, isopropanol and dioxan was investigated. In all three cases the following reaction types were found; (a) photoreduction of the  $\Delta^1$ -double bond leading to the saturated ketone 331; (b) C-addition of a solvent molecule to this bond leading to the corresponding 1-substituted ketones 332, 333, or 334; (c) photoaromatization of ring A; (d) extensive cyclodimerization leading to the products of type 335. In EtOH and iso-PrOH the formation of the O-adducts 336 and 337 also takes place.<sup>162)</sup>



The configurations at C-1 of gibberellin A<sub>3</sub> epoxy derivative **338** and its EtOH photoaddition products, **339** and **340**, were determined on the basis of their NMR spectra and by comparison of their CD curves with **341**, **342**, **343**, and **344**.<sup>163)</sup>



Gibberellanes in which ring A is aromatic react with DDQ giving allylic carbonium ions (via Δ<sup>9</sup>-enes) which then undergo Wagner-Meerwein rearrangement; in 13-hydroxy-compounds such as **345**, the 13,16-bond migrates to C-12 to give a 13-keton **346**, whereas in 13-deoxy-gibberellanes such as **347** or **348**, the 8,15-bond migrates to position 9 to give a 6,8-ene such as **349** or **350**,<sup>164)</sup> as shown in Chart 10.

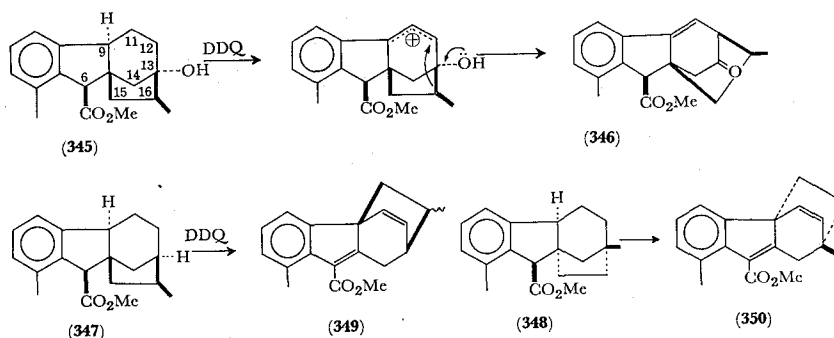
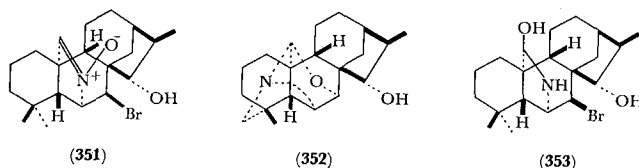


Chart 10

Functionalization of non-activated C-H bond by photolysis of some nitrones was studied. The nitron **351** derived from enmein (**193**) in 14 steps was photodecomposed under various conditions, and the products **352** and **353** were obtained in a favorable yield. The possible mechanisms (a and b) were presumed as shown in Chart 11. The compound **352** was then converted into gibberellin A<sub>15</sub> in 6 steps.<sup>165)</sup>



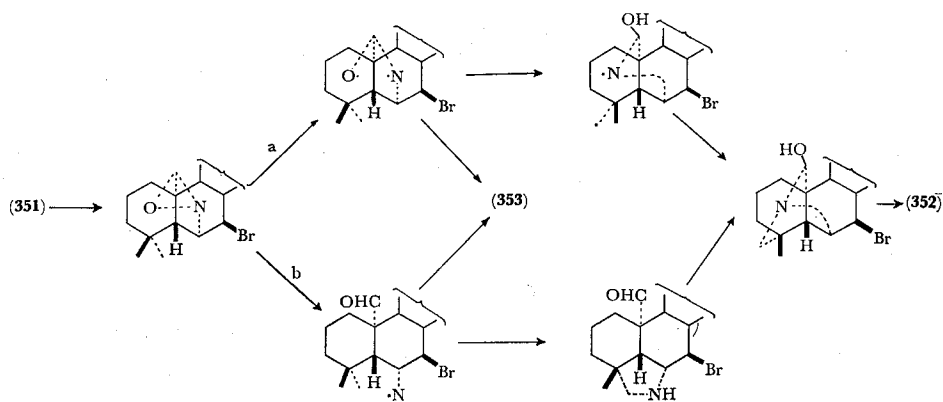


Chart 11

Partial synthesis of gibberellin A<sub>37</sub> by selective reduction of the hindered 10-carboxy-group in gibberellin A<sub>13</sub> was reported,<sup>166)</sup> as shown in Chart 12.

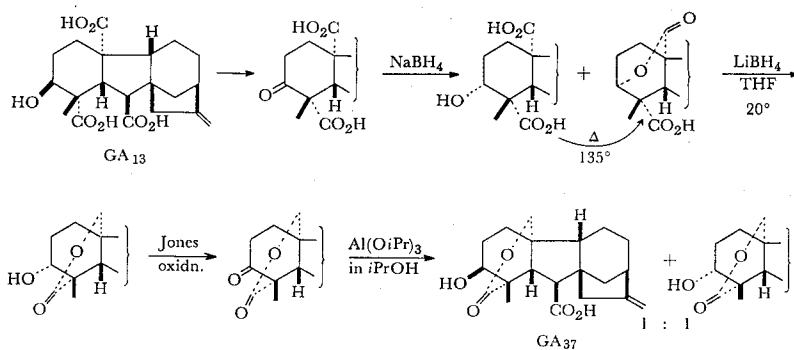
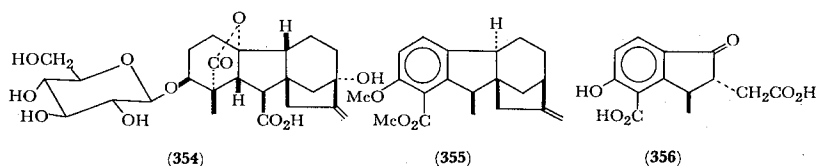


Chart 12

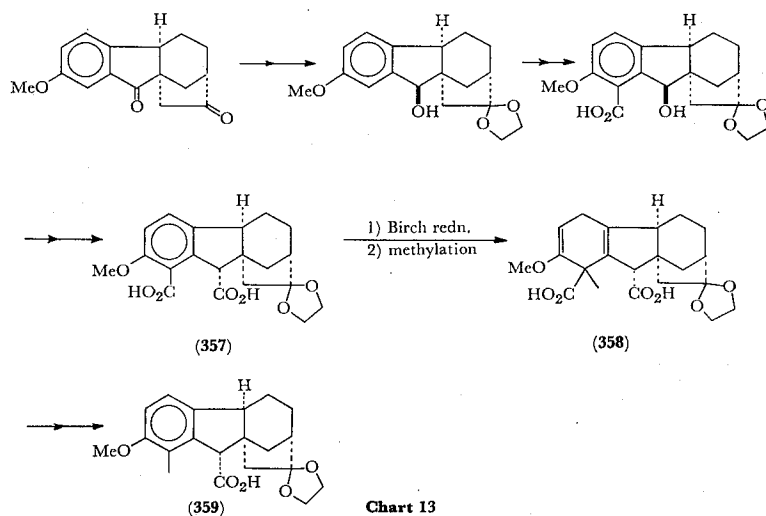
Gibberellin-A<sub>1</sub>-O(3) β-D-glucopyranoside (354) was prepared from gibberellin A<sub>1</sub> methyl ester and α-acetobromoglucose followed by demethylation and deacetylation.<sup>167)</sup>



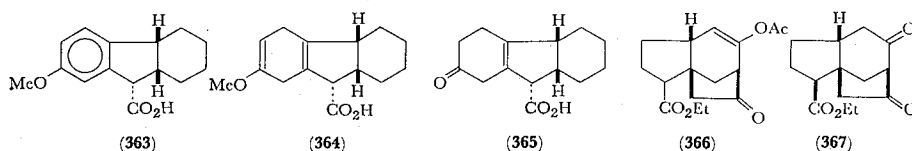
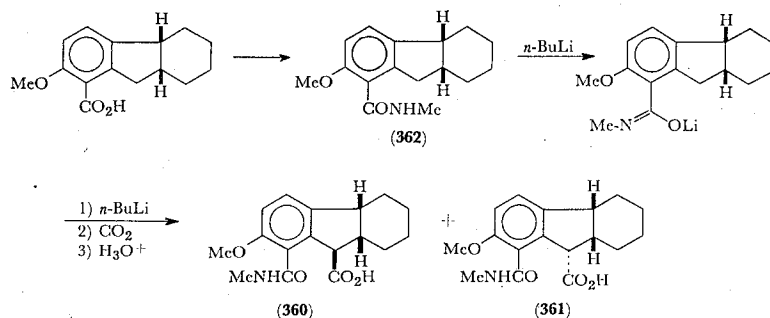
An aromatized ring-A gibberellane derivative 355 was synthesized from terracinoic acid (356) which was prepared from terramycin.<sup>168)</sup>

A stereospecific synthesis of compound 357 suitable for elaboration to gibberellin A<sub>4</sub> was reported, as shown in Chart 13. However, in preliminary investigation, it was shown that the compound 358 derived from 357 readily undergoes decarboxylation and oxidation to 359 under very mild conditions.<sup>169)</sup>





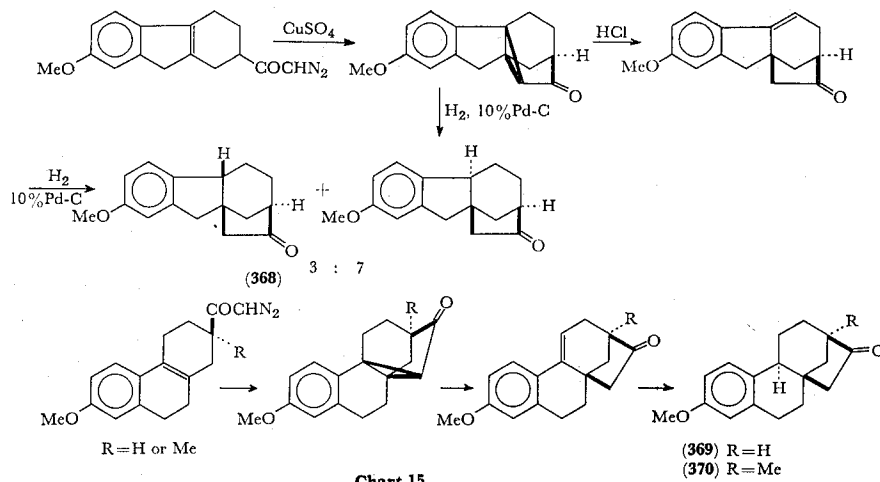
A useful synthetic route to the epimeric diacid derivatives **360** and **361** was provided by selective metalation and carbonation of *N*-methylamide **362**, as shown in Chart 14. The applicability of the Birch reduction to the conversion of the methoxy acid **363** to either enol ether **364** or the keto acid **365** was also demonstrated.<sup>170)</sup>



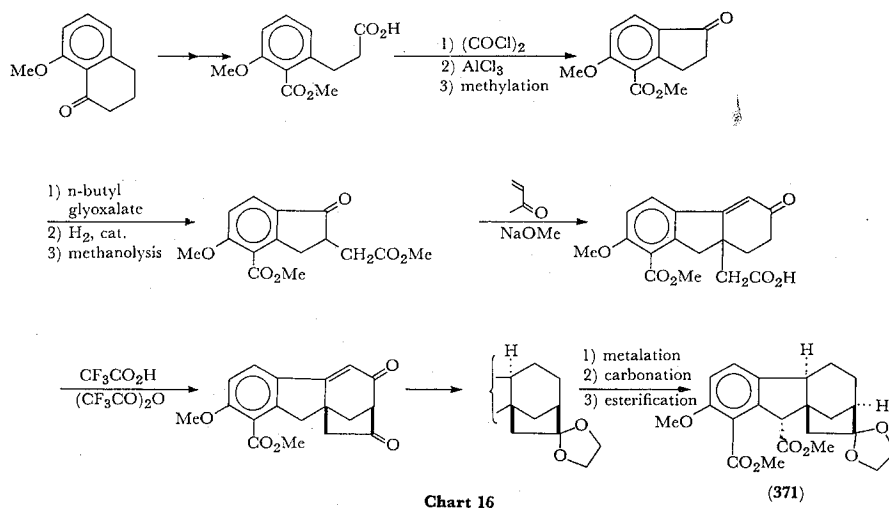
Tricyclic bridged compounds **366** and **367** related to gibberellinic diterpenes were synthesized.<sup>171,172)</sup>

Full report on new synthetic routes to tetracyclic bridged-bicyclo[3.2.1]octane intermediates **368**, **369**, and **370** by intramolecular alkylation reactions through  $\alpha$ -diazomethyl ketones of hydroaromatic  $\gamma$ ,  $\delta$ -unsaturated acids was published.<sup>172)</sup>

This route is shown in Chart 15. A portion of this work had been reported in a preliminary communication.<sup>173)</sup>



A fully functionalized tetracyclic gibberellin intermediate **371** was synthesized *via* a route shown in Chart 16.<sup>174)</sup>



A-ring functionalization of hydrofluorene compound **372** derived from abietic acid was accomplished by hypiodite reaction, as shown in Chart 17.<sup>175)</sup>

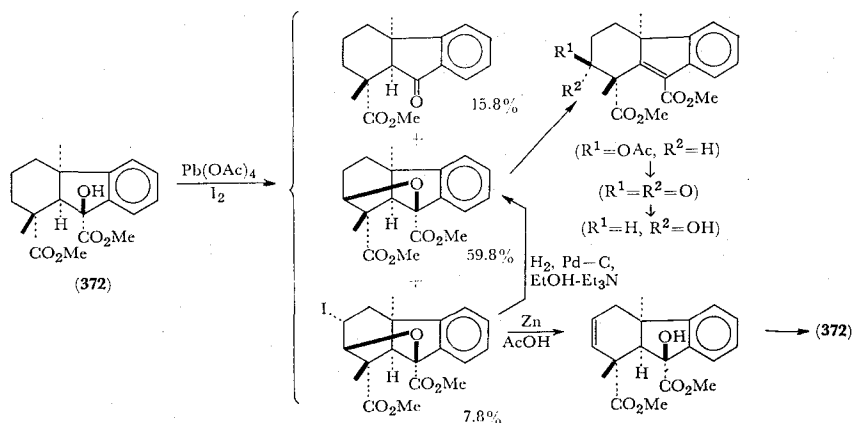
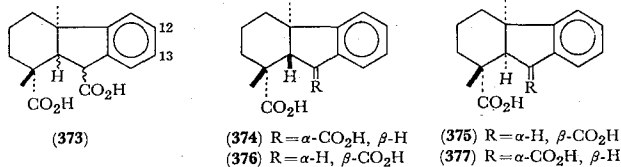


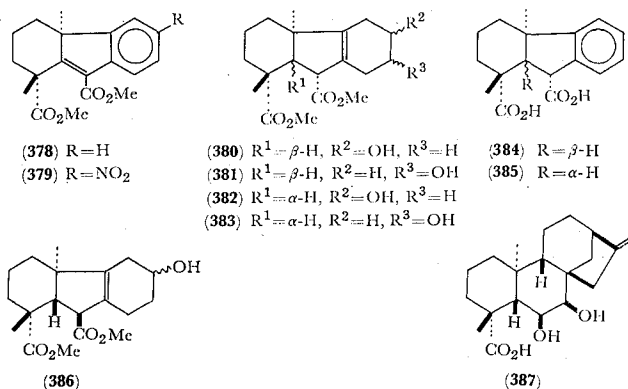
Chart 17

For the synthesis of the gibberellin skeleton, the four possible stereoisomers **374**, **375**, **376**, and **377** and their esters were prepared<sup>176)</sup> from **373** which had been synthesized from abietic acid.



Furthermore, nitration of diesters of above four compounds gave only 13-nitro compounds, and, in contrast, its dehydro-derivative **378** was nitrated to give only 12-nitro compound **379**.<sup>177)</sup>

Syntheses of 12- and 13-hydroxy diesters (**380**, **381**, **382**, and **383**) regarded as important intermediates for the formation for D-ring in gibberellin, were accomplished in the *trans* (**384**) and *cis*-A/B-ring fused isomer (**385**) by reduction in lithium-*liq.* ammonia system and then by hydration with mercuric acetate. The 12-hydroxy diester **386** obtained by epimerization at C-6 of the unstable form **380** has the same skeleton as in A- and B-rings of gibberellin A<sub>12</sub>.<sup>178)</sup>



The sequence of oxidation on ring B in kaurene-gibberellin biosynthesis was investigated. The results of incubation of  $[6\beta\text{-}^3\text{H}, 17\text{-}^{14}\text{C}]\text{-ent-7}\alpha\text{-hydroxy-16-kauren-19-oic acid}$  showed that  $6\beta\text{-hydrogen}$  atom is lost in the formation of gibberellic acid. However,  $\text{ent-6}\alpha, 7\alpha\text{-dihydroxy-16-kauren-19-oic acid}$  (**387**) was not incorporated into gibberellic acid. Experiments with  $[1\text{-}^3\text{H}_2, 1\text{-}^{14}\text{C}]\text{-geranyl pyrophosphate}$  suggested that the  $6\beta\text{-hydrogen}$  atom migrates to C-7 during ring contraction.<sup>179)</sup>

A significant specific incorporation of  $[^{14}\text{C}]\text{-gibberellin A}_{13}$  anhydride (**388**), which was prepared from  $7\beta\text{-hydroxy-kaurenolide}$  as shown in Chart 18, into gibberellic acid (0.14%) and gibberellin  $\text{A}_4/\text{A}_7$  fraction (0.07%) was recognized. However, there was no detectable incorporation into these substances from the  $[^{14}\text{C}]\text{-gibberellin A}_{13}$  (**389**).<sup>180)</sup>

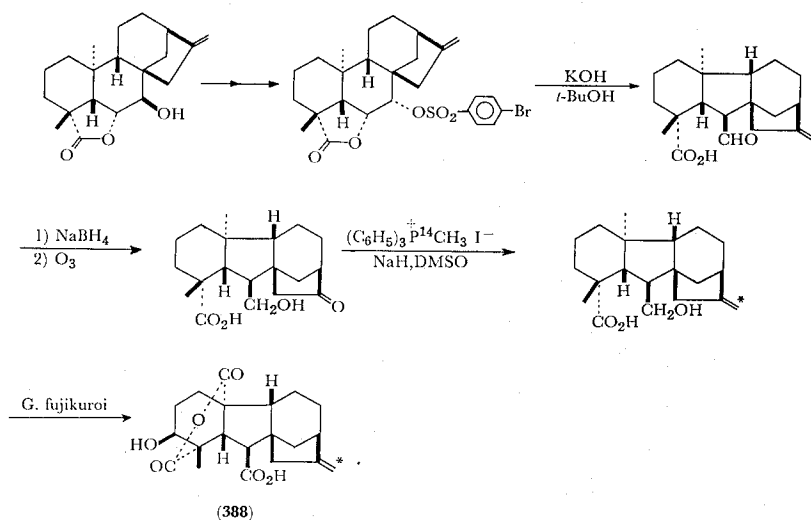
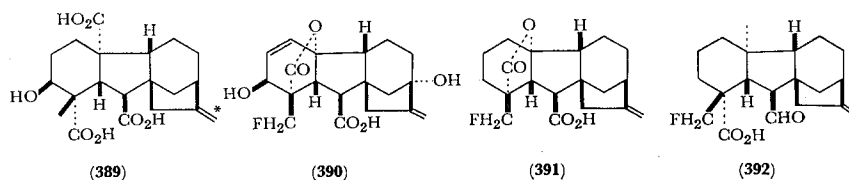
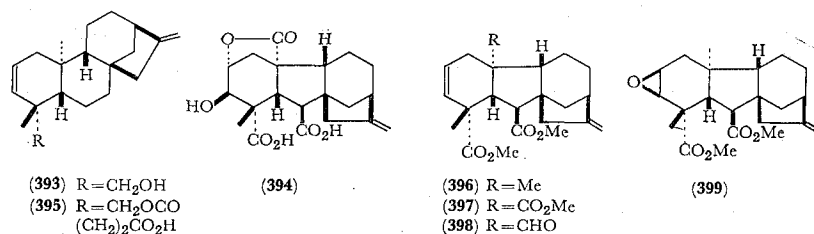


Chart 18

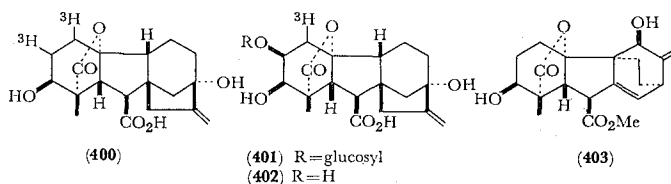
Fluorogibberellic acid **390** and fluorogibberellin  $\text{A}_9$  **391** were produced by a fermentation of *G. fujikuroi* to which  $\text{ent-4}\alpha\text{-fluoromethyl-16-gibberellen-7-al-19-oic acid}$  (**392**) had been added.<sup>181)</sup>



It had previously been reported that  $\text{ent-kaura-2,16-dien-19-ol}$  (**393**) is converted to gibberellane derivative **394** by *Gibberella fujikuroi*. Examination of the less polar methyl esters of the acidic metabolites derived from **393** or its hemisuccinate ester **395** gave four gibberellane derivatives, **396**, **397**, **398**, and **399**.<sup>182)</sup>



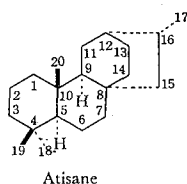
Tritium labeled gibberellin A<sub>1</sub> (**400**) synthesized from GA<sub>3</sub> was imbibed to seeds of *Phaseolus vulgaris*. Its radioactive metabolic products were [<sup>3</sup>H]-GA<sub>8</sub>-glucoside (**401**) and [<sup>3</sup>H]-GA<sub>8</sub> (**402**). The absence of radioactive GA<sub>3</sub> and GA<sub>3</sub>-glucoside was indicated.<sup>183)</sup>



It was demonstrated that species belonging to two genera of the same family elaborate different antheridiogens. Thus, the structural diversity of antheridiogens may reach the genus level. The question whether such diversity reaches the species level was investigated by comparing the structure of the recently characterized antheridiogen of *Anemia phyllitidis* with that of *A. hirsuta*, which showed that both substances are the same and have structure **403**.<sup>184)</sup>

In a review on evolution and biosynthesis of terpenoid pheromons and hormones, gibberellins A<sub>3</sub>, A<sub>5</sub>, and A<sub>15</sub> were described.<sup>185)</sup> In another review on the principles of promotion and inhibition of growth in plants, gibberellins were described.<sup>186)</sup>

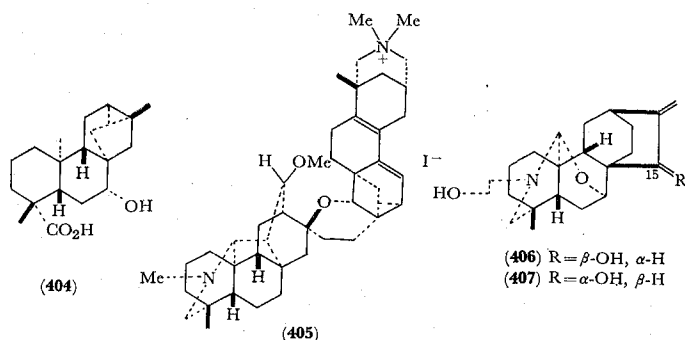
## XII. ATISANE DERIVATIVES\*



A new diterpene, 7 $\alpha$ -hydroxy-4-epitrichylobanic acid (**404**), was isolated from *Helianthus ciliaris*.<sup>187)</sup>

The structure of staphisine, a novel diterpene alkaloid dimer isolated by Jacobs and Craig<sup>188)</sup> in 1941 from the mother liquors accumulated during the isolation of delphinine from the seeds of *Delphinium staphisagria*, was established by a single-crystal X-ray structure determination of the monomethiodide (**405**).<sup>189)</sup>

\* See also IX, ref. 118.



The mass spectral studies of ajaconine from *Delphinium ajacis* seeds were carried out. The crystalline sample earlier identified as pure ajaconine was found to be a mixture of five compounds when analysed as their trimethylsilyl derivatives on a mass spectrometer-gas chromatograph. Structures **406** and **407** were assigned to gas-liquid chromatography peak 2 ajaconine and peak 3 ajaconine, respectively.<sup>190)</sup>

A new angular alkylation through intramolecular carbenoid insertion was performed to afford some key intermediates toward diterpene alkaloids and C<sub>20</sub>-gibberellins syntheses. The outline was shown in Chart 19.<sup>191)</sup>

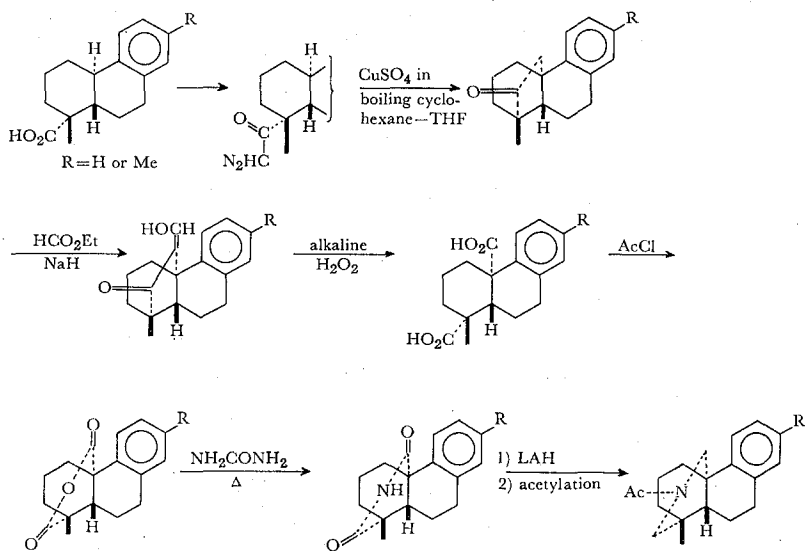
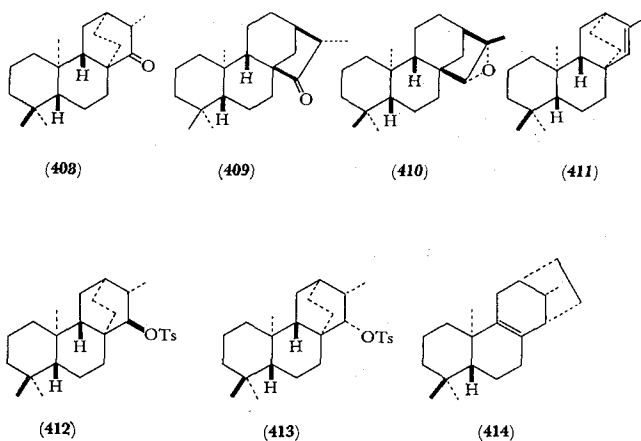


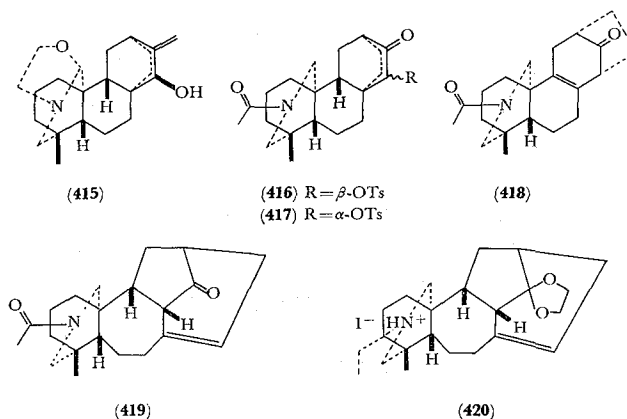
Chart 19

*ent*-(16R)-Atisan-15-one (**408**) and small amounts of *ent*-(16R)-kauran-15-one (**409**) were yielded by the treatment of *ent*-kaurane 15 $\beta$ , 16 $\beta$ -epoxide (**410**) with boron trifluoride-ether complex in benzene. In the conversion of **408** into *ent*-atis-15-ene (**411**), the 15-tosylates **412** and **413** of the epimeric *ent*-atisan-15-ols were found to rearrange to the olefin **414** in high yield.<sup>192)</sup>

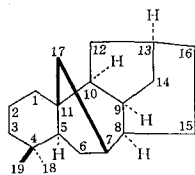


Atisine (**415**) had been converted into the epimeric toluene-*p*-sulfonates **416** and **417**. Acetolysis of **416** or **417** afforded the same 14(8→15)*abeo*-17-oxa-8-ene **418**. In contrast, whereas gas phase pyrolysis of **416** gave the olefin **418**, the isomer **417** gave a 9(8→15)*abeo*-17-oxa-8(14)-ene **419**.

Each conversion took place stereospecifically *via* a seven-membered transition state. The structure of olefin **419** was confirmed by an X-ray analysis of the derived ethylene acetal hydride (**420**).<sup>193)</sup>

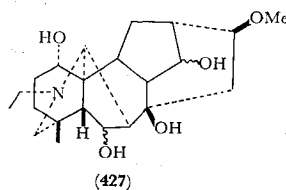
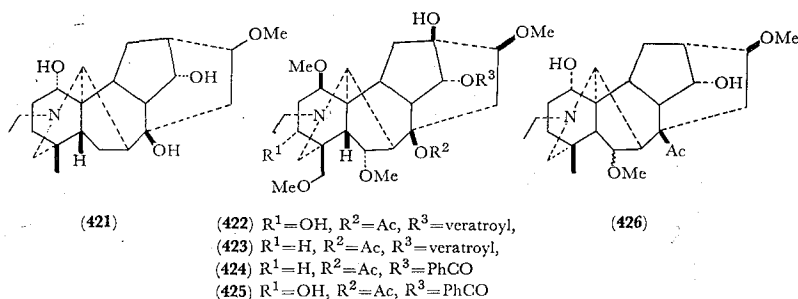


### XIII. ACONANE DERIVATIVES



Karacolone, a new diterpene alkaloid, was isolated from *Aconitum karacolicum*, and assigned structure **421**.<sup>194)</sup>

Adsorption chromatography of the mixture of alkaloids obtained from roots of the plant *Aconitum ferox* yielded four known alkaloids which were identified as pseudoaconitine (**422**), bikhaconitine (**423**), chasmaconitine (**424**), and indaconitine (**425**).<sup>195)</sup>

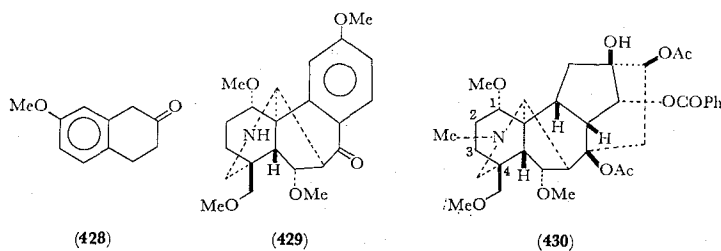


The structures for A (**426**) and B (**427**), two unknown alkaloids of *Delphinium bicolor*, and the utility of the carbon-13 magnetic resonance technique to the diterpene alkaloids were reported.<sup>196)</sup>

The mass spectra were examined in order to investigate splitting of ring A substituents of several lycoctonine alkaloids.<sup>197)</sup>

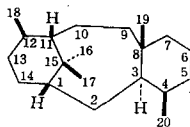
The optically active delphinine degradation product **429** was stereoselectively synthesized *via* several steps from methoxy tetralone (**428**). Thus, it was clarified that the configuration of the ring A methoxyl group in delphinine had to be reversed in comparison with the previously reported structure and this alkaloid had to be represented by the formula **430**. The compound **429** or its derivatives constituted an extremely favorable advanced relay for the synthesis of delphinine.<sup>198)</sup>

The details of an X-ray analysis of the acid oxalate of compound **429** were published, which confirmed the stereochemistry at C-1.<sup>199)</sup> This work had been reported in a preliminary communication.<sup>200)</sup>





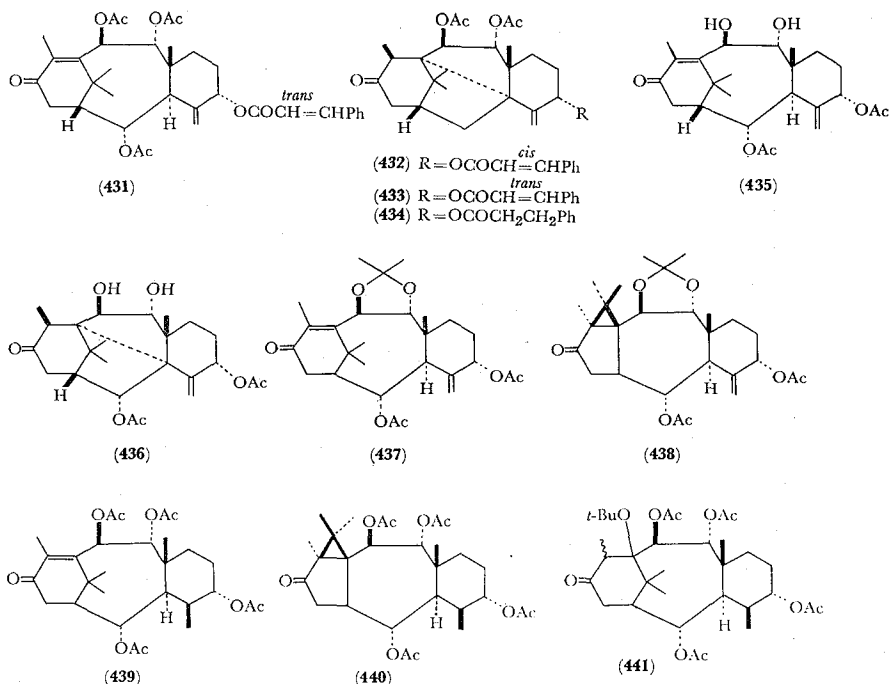
## XIV. TAXANE DERIVATIVES



Taxane

Photochemical behavior of taxinine (**431**) and its derivatives was investigated. Irradiation on **431** with a 450-W high-pressure Hg lamp in dioxane for 15 min afforded quantitatively a nonseparable 1:1 mixture of transannular products **432** and **433**, which upon hydrogenation over Pd/C-AcOEt gave the single dihydro compound **434**. Analogously, irradiation on **435** gave the transannular product **436** in quantitative yield.<sup>201)</sup> On the other hand, irradiation on **437** for 5 hr in dioxane yielded 48% of cyclopropyl ketone **438**<sup>201,202)</sup> and 8% of transannular ketone **436**, with recovery of 38% of the starting material.

Irradiation on **439** in *t*-BuOH for 10 hr gave, after the separation, 65% of the isomeric cyclopropyl ketone **440** and 32% of the solvent adduct **441**.<sup>201)</sup>

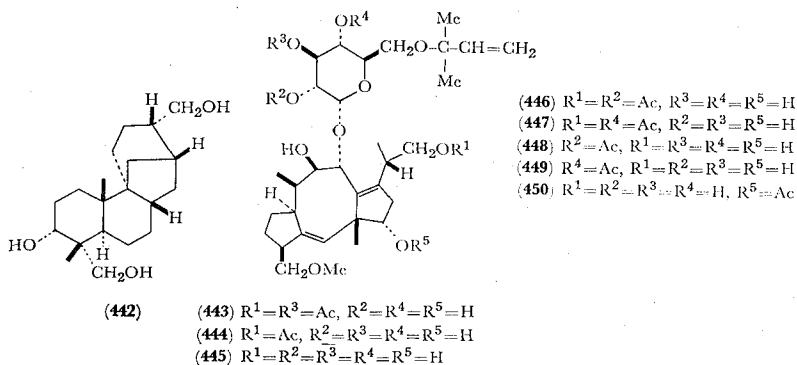


## XV. THE OTHERS\*

It was established by chemical and spectroscopic evidence, and an X-ray analysis of the bis-acetonide that aphidicolin, an antibiotic produced by *Cephalosporium*

\* See also VI, ref. 79.

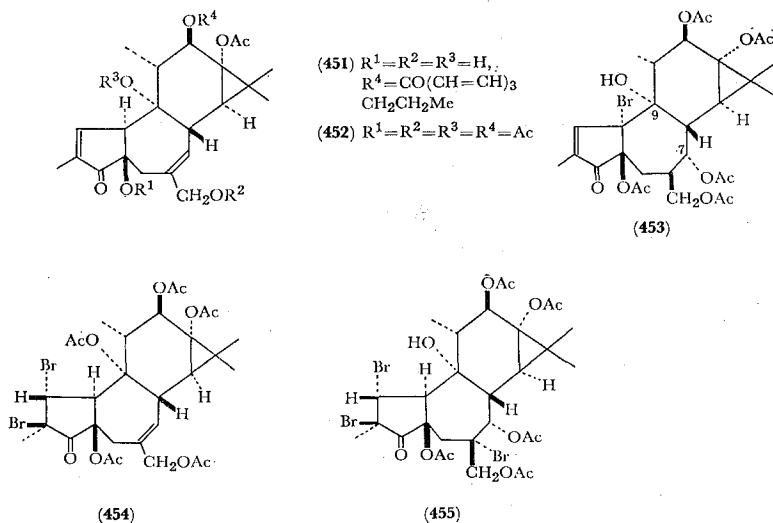
*aphidicola*, was shown to contain a novel tetracyclic diterpenoid ring system and to have structure **442**.<sup>203)</sup>



Besides fusicoccin (**443**), a highly phytotoxic compound, culture filtrates of *Fusicoccum amygdali* contain a number of by-products. Four of them were also produced when fusicoccin was incubated. They might be derived non-enzymically from fusicoccin in the process of the fermentation. The structures of two of these compounds, monodeacetylfusicoccin (**444**) and dideacetyl-fusicoccin (**445**), had been established. The other two products, allofusicoccin and isofusicoccin were characterized and assigned structures **446** and **447**, respectively.<sup>204)</sup>

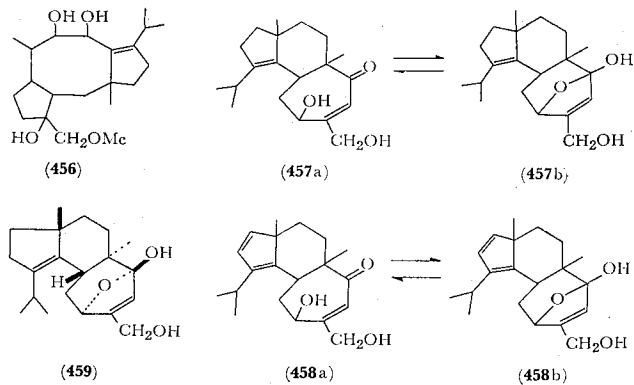
Three isomers of monodeacetylfusicoccin, monodeacetylallofusicoccin (**448**), monodeacetylisofusicoccin (**449**) and 12-O-acetyl-dideacetylfusicoccin (**450**) were also isolated from the culture filtrates of *F. amygdali* as minor co-metabolites.<sup>205)</sup>

From the benzene extract of *Sapium japonicum* twigs and bark, a piscicidal diterpene was isolated. Its structure was determined as **451** on the basis of its UV, IR, PMR, and mass spectra and those of its derivatives. The piscicidal activity of this substance is 4 times that of rotenone.<sup>206,207)</sup>



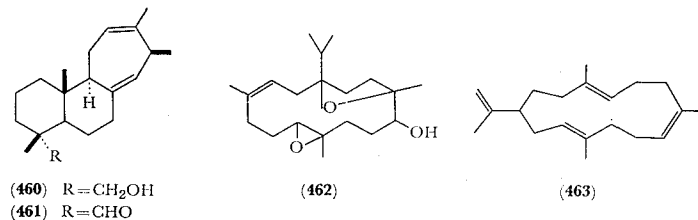
Bromination reactions of phorbol pentaacetate (**452**) were investigated. Four types of brominations, after column chromatographic separations, afforded **453**, **454**, and **455**. The compounds, **453** and **455**, might be formed by intramolecular acetyl migration ( $C_9\text{-OAc} \rightarrow C_7$ ) of each primary labile  $C_7$ - $\beta$ -bromo product during chromatographic purification.<sup>208)</sup>

The structure elucidation of cotylenol (**456**), a new metabolite produced by a fungus strain 501-7W, was published. Cotylenol was found to be the aglycone of the leaf growth substances cotylenins A and B.<sup>209)</sup>



The structures of cyathin  $A_3$  and allocyathin  $B_3$ , metabolites of the bird's nest fungus *Cyathus belenae*, were reported. The former was shown to have the equilibrium structure between **457a** and **457b** in the solution, and the latter was assigned structure **458**. Single crystal of cyathin  $A_3$  was, however, established to have structure **457b** by the X-ray analysis. Its relative configuration **459** was also clarified.<sup>210)</sup> Cyathin  $A_3$  and allocyathin  $B_3$  are new diterpenes having novel carbon skeleton.

Some diterpenes, strobol (**460**), strobol (**461**), manoyl oxide, and *cis*- and *trans*-abienols, were isolated as major constituents of the extract of *Pinus strobus* cortex tissue.<sup>211)</sup>

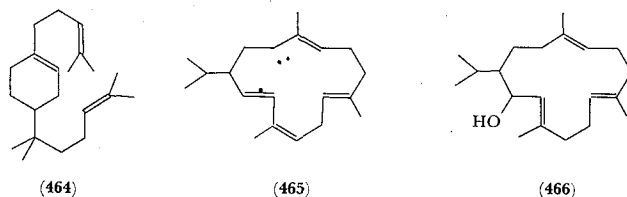


A new macrocyclic diterpene, isoincesole-oxide (**462**), was isolated from Frankincense in very small amount. The structure was deduced on the basis of the chemical and physicochemical data.<sup>212)</sup>

Neocembrene A, a trail pheromone of *Nasutitermes*, was shown to be the cembrene analogue 12-isopropyl-1,5,9-trimethylcyclotetradeca-1,5,9-triene (**463**) by degradation, by comparison of its perhydro-derivative with perhydrocembrene, and by

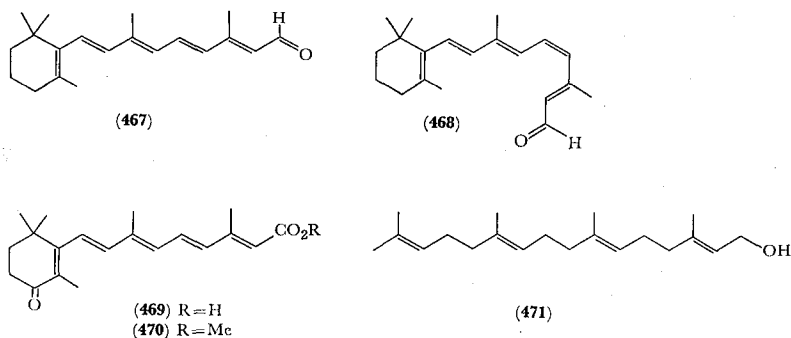
isomerization with sodium methylsulfinylmethanide followed by degradation. The configurations of the double bonds are unknown.<sup>213)</sup>

The monocyclic diterpenes,  $\alpha$ -camphorene (**464**), cembrene (**465**), and allylcembreol (**466**) were isolated from gum resin of *Commiphora mukul*.<sup>214)</sup>



The crystal structure of all-*trans* retinal was determined by an X-ray analysis as **467**.<sup>215)</sup>

An X-ray analysis of 11-*cis*-retinal (**468**) was independently executed, and reported.<sup>216)</sup> The details of geometry of all-*trans* and 11-*cis* retinals are considerably interested in explanation of the photoreceptor process.



4-Oxoretinoic acid (**469**) was prepared from methyl retinoate by oxidation with  $MnO_2$  and hydrolysis of the resulting keto ester **470**. Sodium borohydride reduction of **469** or **470**, followed by dehydration and hydrolysis afforded vitamin A<sub>2</sub> acid. Compounds **469** and **470** showed lower vitamin A activity than retinoic acid in rats.<sup>217)</sup>

It was clarified that the bacteriochlorophylls isolated from *Chromatium vinosum* and *Rhodospseudomonas spheroides* are esters of phytol and the bacteriochlorophyll isolated from *Rhodospirillum rubrum* (Athiorhodaceae) is esterified at the propionic acid side chain by all-*trans*-geranylgeraniol (**471**).<sup>218)</sup>

The terpenoid antibiotic LL-Z 1271 $\alpha$  (**473**) was synthesized from the (+)-ketolactone **472** obtained by degradation of marrubiin. The synthetic route is shown in Chart 20.<sup>219)</sup>

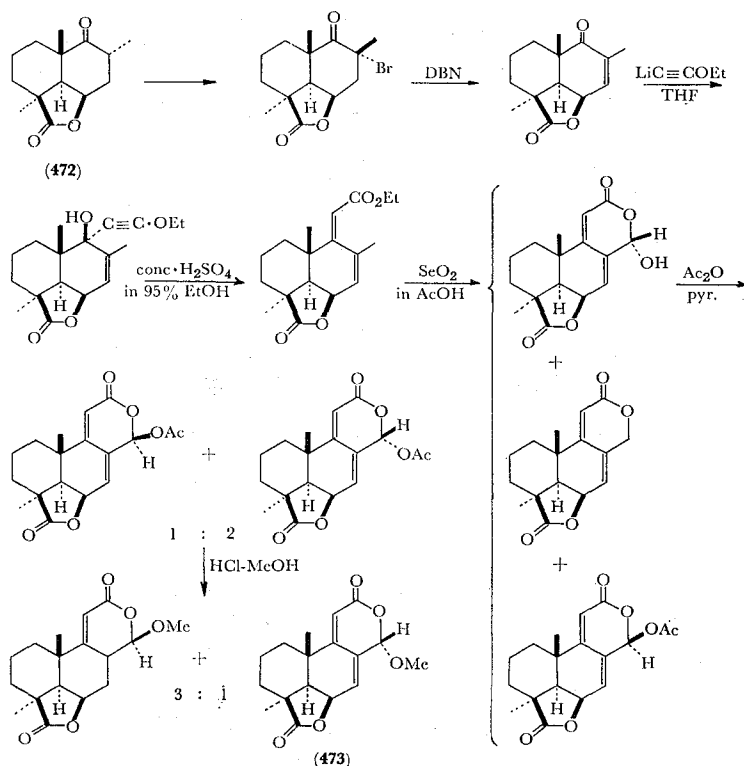


Chart 20

A comparison of the NMR and mass spectra of bilobalide  $C_{15}H_{18}O_8$  and of the ginkgolides  $C_{20}H_{24}O_{9-11}$  was described.<sup>220)</sup>

Three reviews "the structures and syntheses of natural products" were published in Japanese, in which pimarane type and tetracyclic diterpenes were described.<sup>221,222,223)</sup>

In a Japanese review on the rooting promotor and rooting inhibitor, portulal isolated from *Portulaca grandiflora*, was described.<sup>224)</sup>

A brief list of the references on plant physiological substances was published, in which the references of gibberellin  $A_{37}$  and  $A_{38}$  glucosyl ester were shown.<sup>225)</sup> In a Japanese review "active constituents of piscicidal plants", callicarpone, maingayic acid, huratoxin, and some other diterpenes were described.<sup>226)</sup>

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## Chemistry on Diterpenoids in 1972

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