

The Chemistry on the Diterpenoids in 1964

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The isolatin of the diterpenoids, the elucidation of their structures, and their syntheses in 1964 are summarized.

I. INTRODUCTION

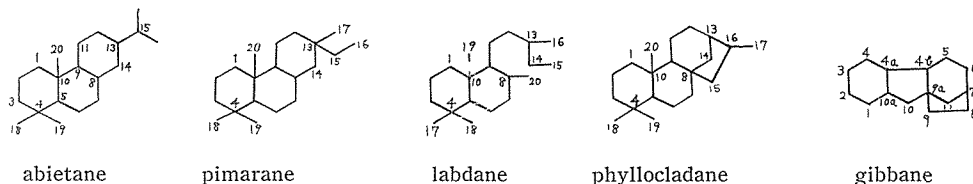
A general review on the diterpenoids was published by Tsutsui *et al.*¹⁾ in 1959. In 1961, a review on the synthesis of diterpenoids was published by Rogers and Barltrop²⁾, and very recently, another one on the same article by Kitahara *et al.*³⁾

There have been several older reviews on the diterpenoids by Simonsen and Barton⁴⁾, Barton⁵⁾, and de Mayo.⁶⁾

The chemistry of the diterpene alkaloids has been described in "The Alkaloids"⁷⁾ edited by Manske and in the book⁸⁾ of Boit, and other reviews by Marion⁹⁾, Pelletier¹⁰⁾ and Pinder¹¹⁾ have also been published.

The author wishes to treat the works of the chemistry on the diterpenoids published in 1964 in outline.

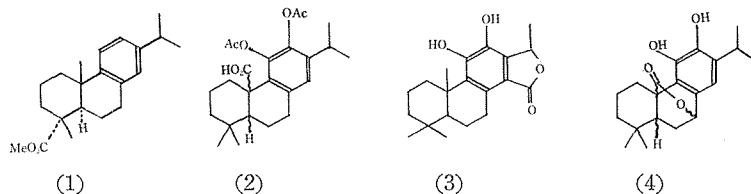
The classification will consist of abietane, pimarane, labdane, phyllocladane, gibbane and their related skeletons, diterpene alkaloids, and the others.



II. ABIETANE AND ITS RELATED SKELETON

From *Cistus labdaniferus*, methyl dehydroabietate (1) was isolated.¹²⁾

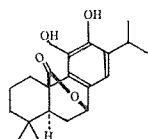
Linde¹³⁾ isolated a new diterpene carboxylic acid as diacetate, the structure of which proved to be (2). The compound was correlated to picrosalvin and structure (3)¹⁴⁾ previously proposed for the latter was revised to (4).



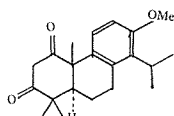
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Wenkert, *et al.*¹⁵⁾ proved the identity of carnosol, a bitter principle from *Salvia carnosol*, and picrosalvin from *S. officinalis*, *S. triloba* and *Rosmarinus officinalis* by the direct comparison, and proposed structure (5) for carnosol (picrosalvin), which was identical with that (4) of Linde.

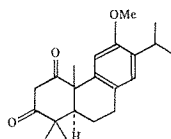
Mangoni and Belardini¹⁶⁾ isolated two crystalline compounds from *Cupressus sempervirens* oleoresin, and proposed structures (6) and (7) for compounds A and B, respectively.



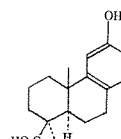
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(6)

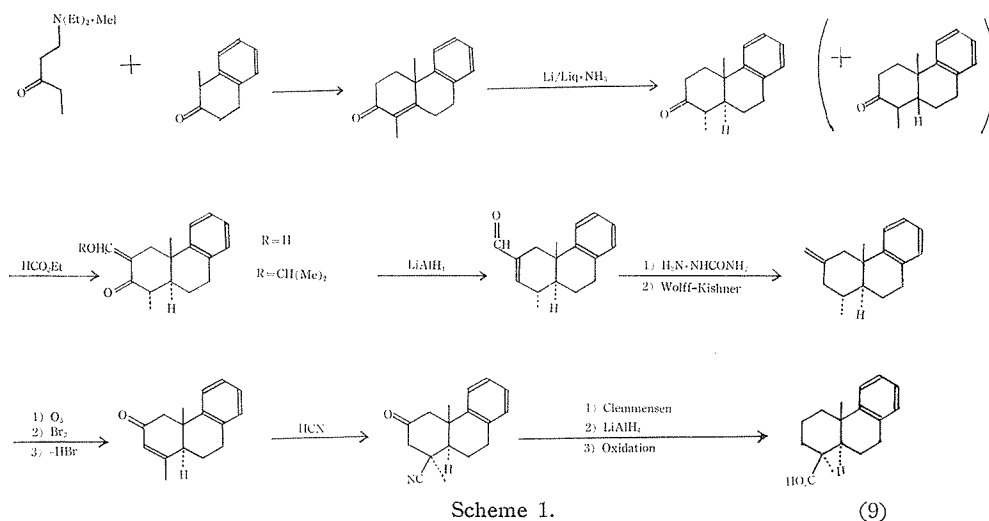


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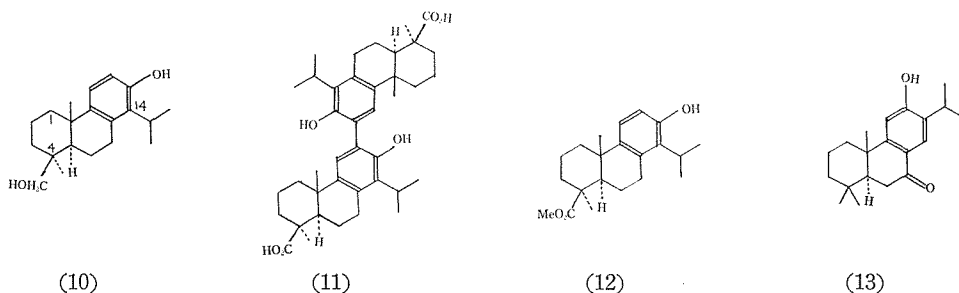
(8)

Meyer and Maheshwari¹⁷⁾ succeeded in a total synthesis of podocarpic acid (8) by a new route. They synthesized *d,l*-compound of structure (9) as shown in Scheme 1. Inasmuch as racemic acid has been resolved^{18a)} and *d*-desoxypodocarpic acid has been converted to *d*-podocarpic acid (8)^{18b)}, this work constitutes a total synthesis of podocarpic acid.



Day¹⁹⁾ reported the total syntheses of *d*-16-hydroxytotarol (10) and *d*-macrophylllic acid (11), a bisditerpenoid. The synthesis of compound (10) was carried out by a route in which agathene dicarboxylic acid was correlated. The synthesis of (11) was achieved by hydrolysis of dimethyl ester obtained by oxidative coupling of compound (12) with alkaline ferricyanide. The route would be parallel to the biosynthetic pathway.

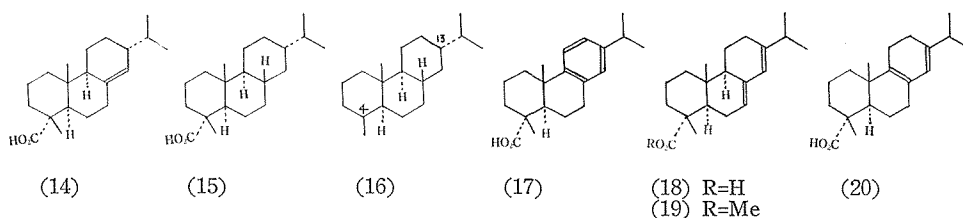
Totarol and sugiol (13) were isolated from a neutral fraction of the resin of *Tetracclinis articulata*.⁶⁵⁾



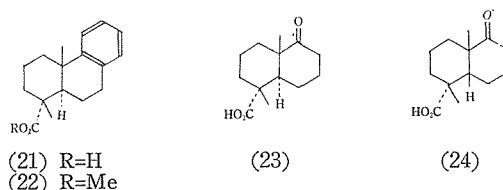
Burgstahler and Marx²⁰⁾ synthesized fichtelite from all-*trans*-tetrahydroabietic acid (15) which was prepared *via* several steps from compound (14). The latter is converted from abietic acid, neoabietic acid, or levopimaric acid. The synthesis of fichtelite established its stereochemistry as shown in (16), especially the stereochemistry of C-4 and C-13 being confirmed.

Burgstahler and Worden²¹⁾ carried out the syntheses of abietic acid (18) and palustric acid (20) from dehydroabietic acid (17).

Abietic acid (18) was isolated from *Agathis australis* fossil resin.⁶⁵⁾

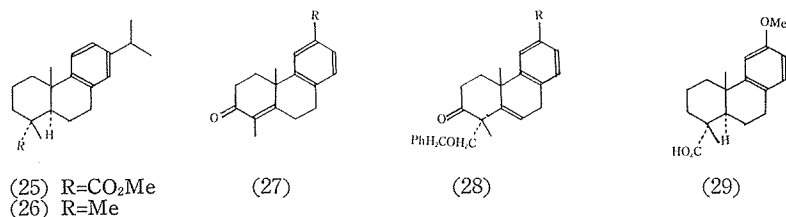


Spencer *et al.*²²⁾ synthesized *d,l*-methyl dehydradeisopropylabietate (22). As the starting material for the synthesis, a bicyclic Keto-acid (23) was used. Compound (23) proved to be different from the substance which was assigned to be (23) by Mathew and Dutta.^{23a)} The Indian workers^{23b)} reinvestigated and recognized that the compound assigned as (23) by themselves was actually A/B *cis* isomer (24), and they clarified palladium-charcoal induced isomerization in the course of the synthesis, in which compound (22) was previously converted from (24), showing several examples.



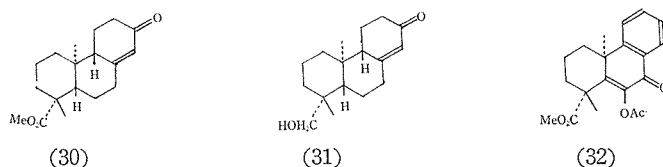
The treatment of methyl abietate (19) with mercuric acetate, followed by pyrolysis gave methyl Δ^6 -dehydro abietate (25). The oxidation reactions of (25) and Δ^6 -dehydroabietane (26), which was derived from (25), with several oxidizing agents, and several chemical reactions for the resulted oxidation products were investigated.²⁴⁾ In these reactions, some kinds of compounds oxygenated at C-6 or C-7 were gained.

Graham and McQuillin²⁵⁾ found that benzyloxymethylation of ketones of type (27) was highly stereospecific and gave α -substituted derivative (28). They made use of this reaction to synthesize dehydrodeisopropylabietic acid (21) and a stereoisomer (29) of podocarpic acid methyl ether.

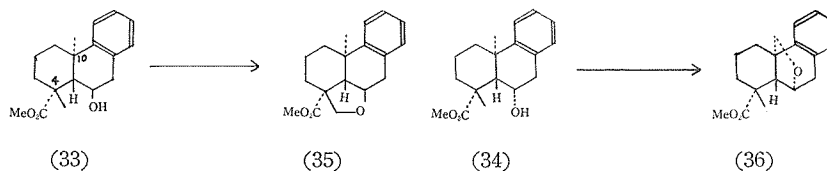


Wenkert *et al.*²⁶⁾ especially investigated the stereochemistry in the syntheses of some resin acids; they resolved racemic deisopropyldehydroabietic acid (21) and racemic desoxypodocarpic acid (9). Consequently, the total syntheses of four kinds of the optical active resin acids were accomplished.

Tahara *et al.*²⁷⁾ reported that compounds (30) and (31) derived from abietic acid (18) were useful as potential intermediates for the syntheses of the natural diterpenoids, and these compounds established the relationship between abietic acid (18) and agathic acid (71).



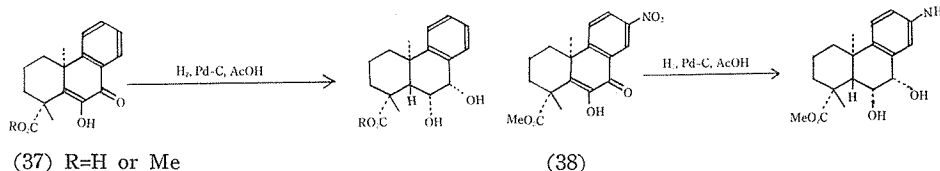
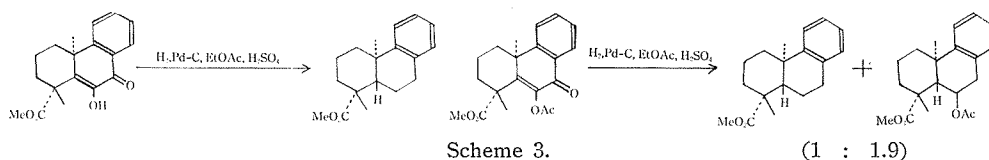
Tahara and Hirano²⁸⁾ prepared compounds (33) and (34) from compound (32) which was derived from abietic acid, and oxidized them with lead tetraacetate and iodine under irradiation with ultraviolet rays to yield compounds (35) and (36) as shown in Scheme 2.



Scheme 2.

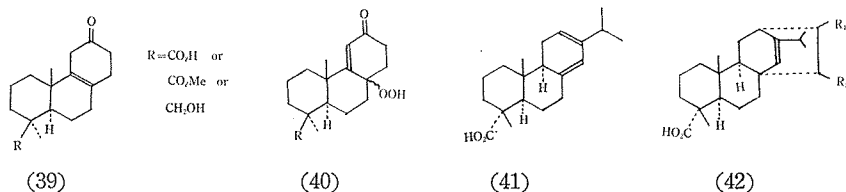
It was confirmed²⁹⁾ by n.m.r. data of many related compounds, particularly by the comparison of chemical shifts of their methyl protons at positions 4 and 10, that structures (35) and (36) were correct.

Tahara *et al.* also carried out a catalytic reduction of diosphenols (37) and (38) without sulfuric acid³⁰⁾, in comparison with hydrogenolysis (Scheme 3) previously reported²⁸⁾ in the presence of catalytic amounts of sulfuric acid. The results were shown in Scheme 4.



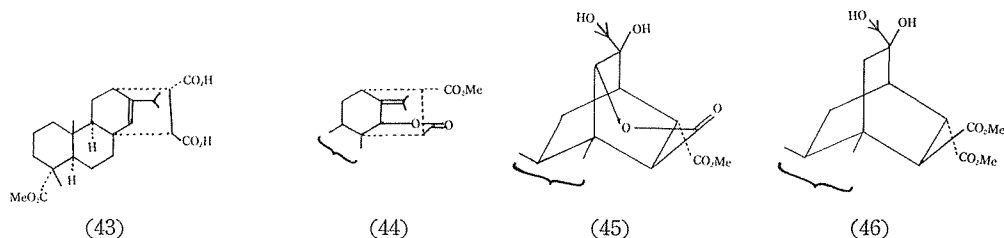
Scheme 4.

Rogers *et al.*³¹⁾ prepared compounds (39) from podocarpic acid (8) and passed oxygen through their ethereal solution for a few days, or irradiated their solution in carbontetrachloride with fluorescent lamp under passing oxygen to yield hydroperoxides of type (40).

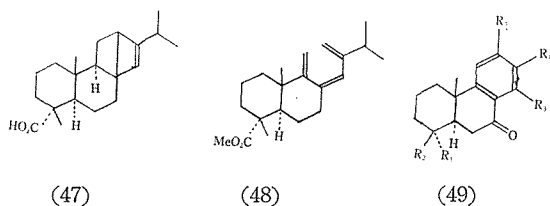


Herz *et al.*³²⁾ carried out the reactions of levopimaric acid (41) or rosin with β -propiolactone and acrylic acid, and isolated the Diels-Alder adducts of type (42).

Zalkow and Brannon³³⁾ prepared fumaric acid-methyl abietate Diels-Alder adduct (43) by heating fumaric acid and methyl abietate (19) at 200° in a nitrogen atmosphere, oxidized its methyl ester with permanganate, and got an unsaturated γ -lactone (44), a dihydroxylactone (45) and a diol (46).



Dauben and Coates³⁴⁾ clarified that the irradiation of ultraviolet rays gave a tetracyclic compound (47). The same authors³⁵⁾ also tried the photochemical transformation on methyl ester of palustric acid (20), and recognized the formation of photoequilibrium between the starting material and structure (48), which was supported by n.m.r. spectra.

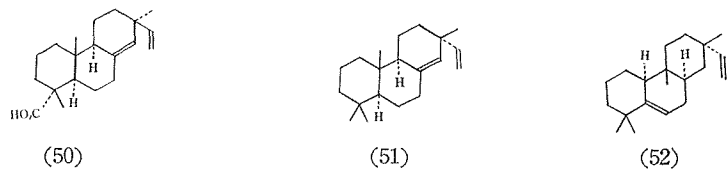


Cambie *et al.*³⁶⁾ studied ORD and CD spectra of several ketones conjugated with an aromatic ring. These compounds showed the Cotton effect curves with peaks near 350 m μ , and also weak maximum UV absorption in the isooctane solution at 320~350 m μ . Sugiol (13), 7-oxototarol (49: R₁=R₂=Me, R₃=i-Pr., R₄=OH, R₅=H), 7-oxopodocarpic acid (49: R₁=Me, R₂=CO₂H, R₃=R₄=H, R₅=OH) and 7-oxodehydroabietic acid (49: R₁=CO₂H, R₂=Me, R₄=i-Pr., R₃=R₅=H) *etc.* were used as the objects of measurement.

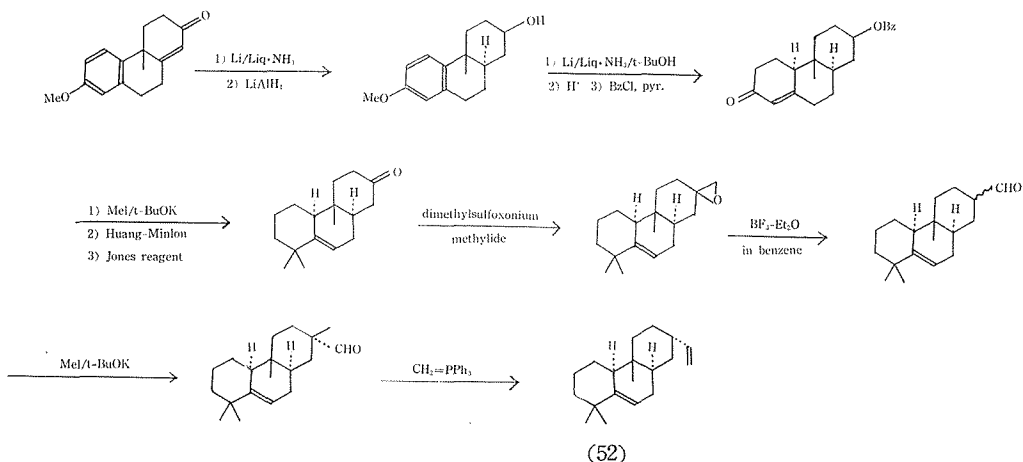
Sjoeborg and Sjoeborg³⁷⁾ found that dehydroabietylamine is available for easy resolution of *d,l*- γ -phenylpropylsuccinic acid and *d,l*- α -phenoxypropionic acid.

III. PIMARANE AND ITS RELATED SKELETON

Asselineau *et al.*³⁸⁾ investigated the hydrogenation under several conditions on pimarinic acid (50) and its some derivatives, for instance, $\Delta^{8(14)}$ -dihydropimaric acid and dihydropimaryl alcohol which was produced by reduction of $\Delta^{8(14)}$ -dihydropimaric acid with lithium aluminum hydride.



A diterpene hydrocarbon, rimuene, first isolated from the essential oil of *Dacrydium cupressinum* has been the subject of a number of structural investigations.



Scheme 5.

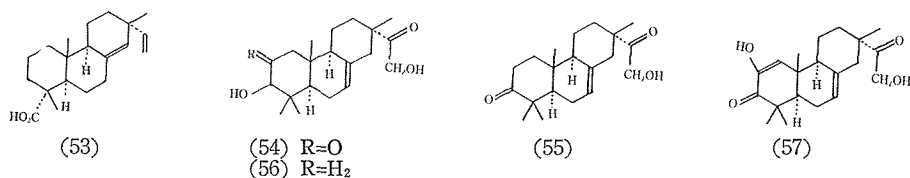
Structure (51) postulated by Briggs *et al.*³⁹⁾ has been shown to be incorrect, as Ireland and Schiess⁴⁰⁾ synthesized sandaracopimaradiene (51) and found that this compound was not identical with rimuene. Recently, the reinvestigation of the structure of rimuene was carried out by a couple of groups, that is, Corbett *et al.*⁴¹⁾ and Overton *et al.*⁴²⁾, and a completely same conclusion was introduced that the structure of rimuene should be represented by formula (52).

Ireland and Mander⁴³⁾ synthesized *d,l*-rimuene, and established the correctness of structure (52). The route of the synthesis will be summarized in Scheme 5.

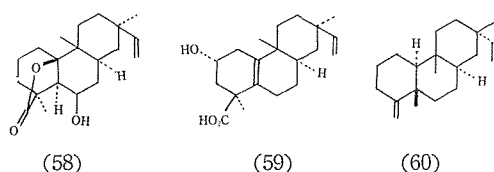
Sandaracopimaric acid (53) and 12 β -acetoxy derivative were isolated from the resin of *Tetraclinis articulata*⁶⁵⁾. Sandaracopimaric acid was also isolated from *Agathis australis* fossil resin.⁶⁵⁾

Nagahama⁴⁴⁾ reported a first isolation of sandaracopimarinol from the wood oil of *Cryptomeria japonica*. A diterpene hydrocarbon bearing a conjugated diene system was also isolated.

Enzell and Thomas⁴⁵⁾ investigated the constituents of kauri resin from *Agathis australis* in New Zealand and determined the chemical structures of araucarolone (54) (isopimar-7-ene-2,15-dione-3,16-diol), araucarone (55), araucarol (56) and araucarenolone (57).



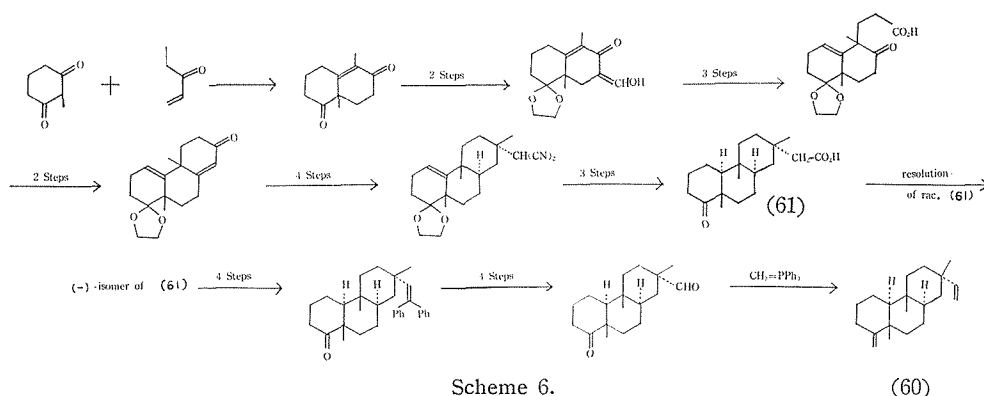
The structure and stereochemistry (58) of rosololactone, a new metabolite of *Trichothecium roseum*, were determined by Scott *et al.*⁴⁶⁾, and established also by X-ray diffraction studies of dibromorosololactone.



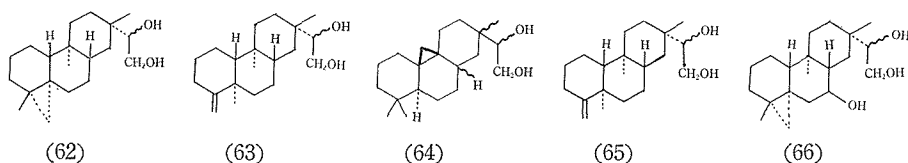
Isorosenolic acid, a minor acidic constituent of the fermentation was also isolated and its structure and stereochemistry (59) were determined.⁴⁷⁾

Yoshikoshi isolated a new diterpene, dolabradiene, and investigated its structure.^{48) 49)} Consequently, Kitahara and Yoshikoshi⁵⁰⁾ proposed formula (60) including its absolute configuration. Successively, Kitahara, Yoshikoshi *et al.*⁵¹⁾ accomplished the total synthesis of the optical active dolabradiene and established its structure and stereochemistry (60). The summarized route of the synthesis will be shown in Scheme 6.

Connolly *et al.*⁵²⁾ isolated erythroxydiol X, -Y, and -Z, as well as, triols, from petroleum ether extract of trunk wood of *Erythroxylon monogynum*, and proposed structures (62) and (63) for erythroxydiol X and -Y, respectively. Soman and Dev⁵³⁾

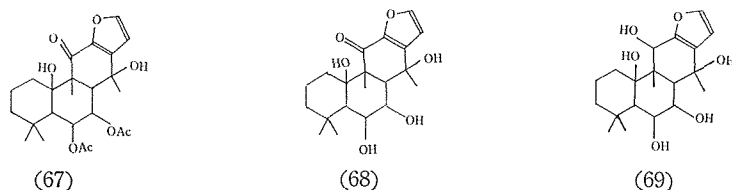


reported that the structure of devadarool from the same plant source was represented as (64). Connolly *et al.*, however, proposed the above-mentioned structure (62) for erythroxydiol X, which proved to be identical with devadarool, and denied formula (64).



As a result of reinvestigation, Dev *et al.*⁵⁴⁾ recognized that formula (64) proposed by themselves was incorrect and should be revised to (62). They also presented the presumed structures of allodevadarool (65) and hydroxydevadarool (66).⁵⁴⁾

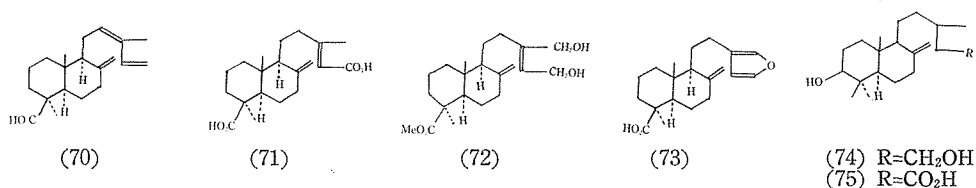
The bitter principles of the seeds of *Caesalpinia bonducella*, α -, β -, and γ -caesalpin, were isolated. The structures of α -caesalpin (67), β -caesalpin (68) and the hydrolyzed γ -caesalpin (69) were reported.⁵⁵⁾



IV. LABDANE AND ITS RELATED SKELETON

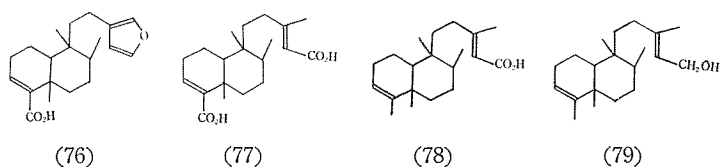
Communic acid (70) and levopimaric acid (41) were found in *Agathis robusta* oleoresin.⁵⁶⁾ The co-occurrence of these two acids is of biogenetic interest. The major constituent of *Agathis microstachya* oleoresin proved to be agathic acid (71).⁵⁷⁾

Methyl sciadopate (72) was isolated by Sumimoto *et al.*⁵⁸⁾ from the heart wood of *Sciadopitys verticillata*, being correlated to agathic acid (71), and structure (72) was provided. It was also correlated to communic acid (70) and daniellic acid (73) by Miyasaka.⁵⁹⁾

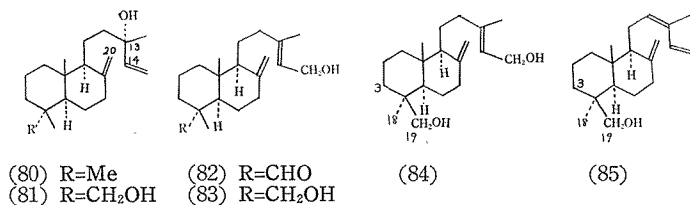


Labd-8(20)-ene-3 β ,15-diol (74), 3 β -hydroxylabd-8(20)-en-15-oic acid (75) and the corresponding 15-aldehyde were isolated from petroleum ether extract of the bark of *Araucaria imbricata* and characterized.⁶⁰⁾

Dev *et al.*⁶¹⁾ isolated the new diterpenoids from *Hardwickia pinnata* oleoresin. They were hardwickiic acid (76), kolavic acid (77), kolavenic acid (78) and kolavenol (79). The structures were postulated by chemical reactions mainly including dehydrogenation and hydrogenation, data of n.m.r. and biogenetic consideration.



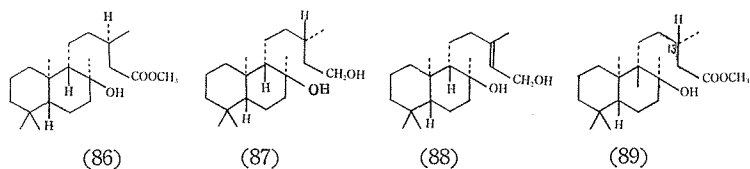
Rowe and Scroggins⁶²⁾ isolated 13-epimanool ($\Delta^{8(20),14}$ -labdadien-13 α -ol) (80), hydroxy-epimanool (81), contortolal (82) and contortadiol (83).

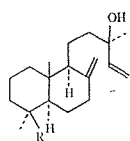


In the study of n.m.r. spectra of agathadiol (84) and communol (85), spin-spin coupling through four single bonds between one proton of C-19 methylene and C-3 α (axial) proton, and between another proton of C-19 methylene and C-18 methyl protons, was observed⁶³⁾.

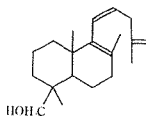
Isolation of the methylated resin acids of *Dodonaea lobulata* by Jefferies *et al.*⁶⁴⁾ gave a crystalline hydroxy ester, which was shown to be antipode (86) of methyl labdanolate. They also got from *Ricinocarpus muricatus* some bicyclic diterpenes of the labdane group, which were diols (87) and (88), and methyl enantio-13-*epi*-labdanolate (89). Compound (87) was correlated to compound (89).

Gough⁶⁵⁾ isolated communic acid (70), torulosic acid (90), manool (91), torulosol

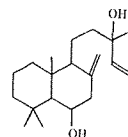




- (90) $R=CO_2H$
 (91) $R=Me$
 (92) $R=CH_2OH$
 (93) $R=CH_2OAc$



(94)

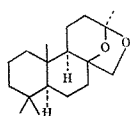


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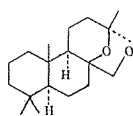
(92) and torulosyl monoacetate (93) from *Tetraclinis articulata* (N. African Sandarac), and elliotinol (94) from *Pinus elliotii*.

Some diterpenoids were isolated from *Larix sibirica* resin. One of them was larixol (95)⁶⁶⁾.

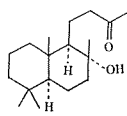
Semi-industrial production of odorous oxides (96) and (97) from manool (91) was successful in the selective epoxidation followed by ozonolysis.⁶⁷⁾



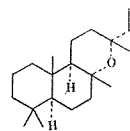
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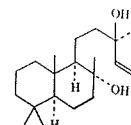
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(98)



(99)

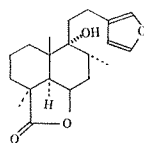


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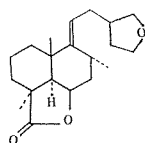
Mongoni *et al.*⁶⁸⁾ synthesized manoyl oxide (99) from 8α -hydroxy-15,16-bisnorlabdan-13-one (98).

The stereochemistry of a major oxidation product of sclareol (100) was established in the correlation with manoyl oxide (99)⁶⁹⁾.

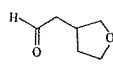
The isolation of marrubiin (101) from *Marrubium vulgare*⁷⁰⁾ and *Leonotis leonurus*⁷¹⁾ was reported.



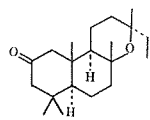
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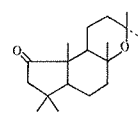
(102)



(103)



(104)



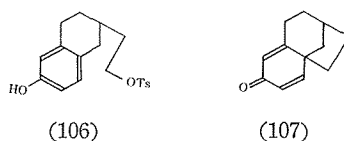
(105)

3-Tetrahydrofurylacetaldehyde (103), one of the degradation products which were obtained by ozonolysis of anhydrotetrahydromarrubiin (102), was synthesized and identified⁷²⁾.

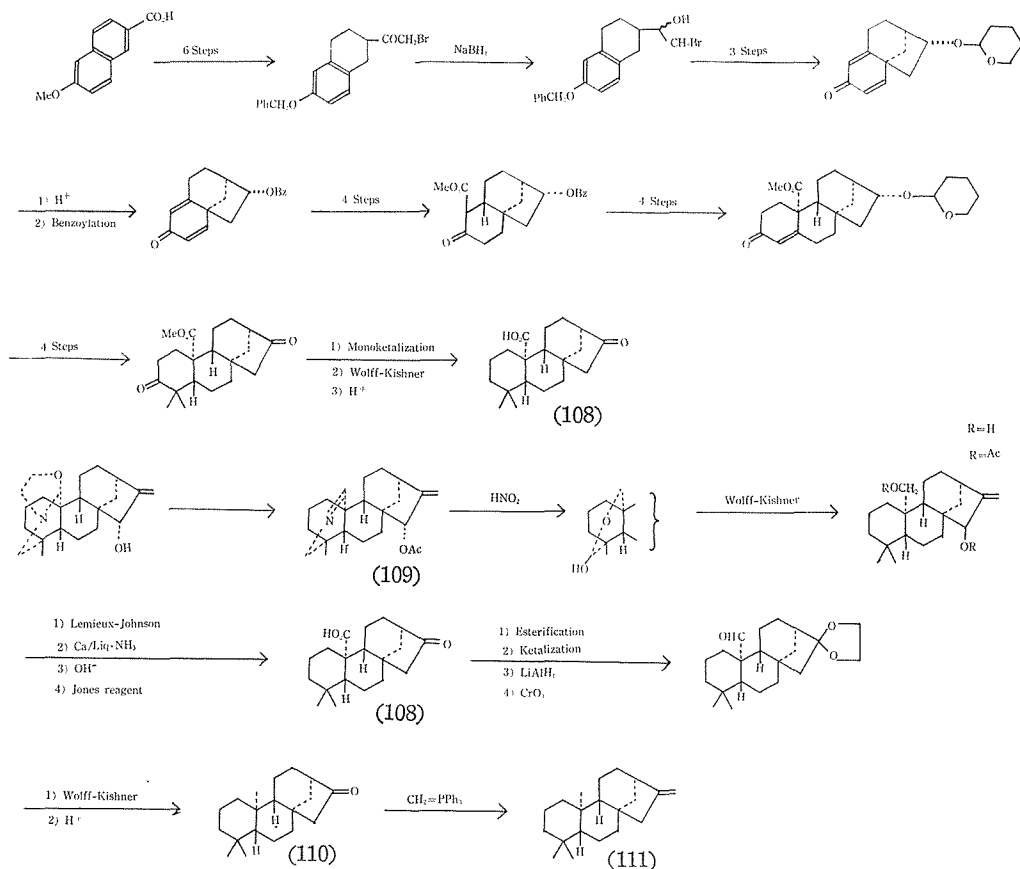
Colensan-1-one (105), an isomer of the naturally occurring norditerpene, colensan-14-en-2-one, was synthesized by Grant and Hill⁷³⁾ from 2-oxo-manoyl oxide (104).

V. PHYLLOCLADANE AND ITS RELATED SKELETON

Previously, Masamune got a dienone (107)⁷⁴⁾ by the treatment of compound (106) with a base. He applied this reaction and synthesized *d,l*-compound of a tetracyclic intermediate (108)⁷⁵⁾. Successively, he got (-)-isomer of compound (108) in good yield by degradation of natural veatchine (173), and from this material he synthesized an optical active compound (110)⁷⁶⁾. As this compound has been



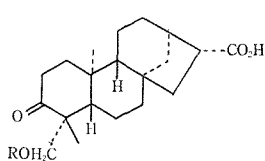
already converted to (-)-kaurene (111), the synthesis corresponds to a total synthesis of (-)-kaurene. Moreover, it is the first example of the transformation of a diterpene alkaloid to a naturally occurring diterpene, and now the direct correlation between two groups of natural products is accomplished. The synthetic route will be shown in Scheme 7.



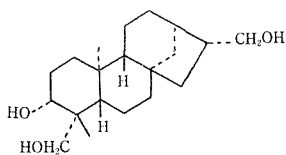
Scheme 7.

Jefferies *et al.*⁷⁷⁾ isolated three new diterpenes from *Beyeria brevifolia*, the structures of which were determined as (112), (113) and (114). The triol (114) was converted to β -dihydro-kaurene (16 α -dihydrokaurene) (115) through a series of reactions. Four kauranoid diterpenes were isolated from ethereal extract of *Ricinus carpus stylosus* and characterized⁷⁸⁾.

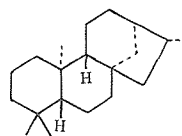
They were 16 α -(-)-kauran-17,19-dioic acid (116), 19-hydroxy-16 α -(-)-kauran-17-oic acid (117), (-)-kauran-16 α -17,19-triol (118) and (-)-kaur-16-en-19-oic acid



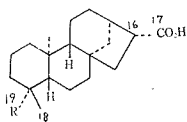
(112) R=H
(113) R=Ac



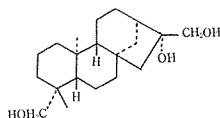
(114)



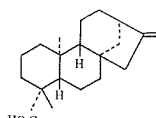
(115)



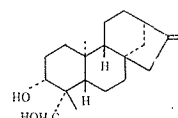
(116) R=CO₂H
(117) R=CH₂OH



(118)



(119)

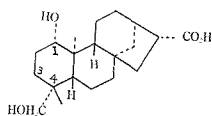


(120)

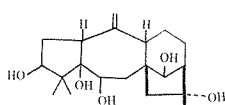
(119). The n.m.r. correlation of these diterpenoids were discussed.

Jefferies *et al.*⁷⁹⁾ isolated a new diterpene diol and the above-mentioned 16 α -(-)-kauran-3 α ,17,19-triol (114), correlated the former with the latter and proved the new compound to be (-)-kaur-16-ene-3 α ,19-diol (120).

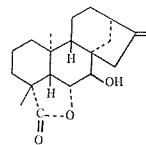
Another work by Henrick and Jefferies⁸⁰⁾ was the isolation of a new diterpene carboxylic acid, 1 α , 19-dihydroxy-16 α -(-)-kauran-17-oic acid (121). It is interesting that this structure corresponds to a biosynthetic precursor of the grayanotoxin skeleton. The configuration of the grayanotoxin skeleton, for instance grayanotoxin-II (122), may be rationalized as arising by a Wagner-Meerwein rearrangement of a 1 α -hydroxy-(-)-kaurane. The validity of such a process has been demonstrated recently in the triterpene series⁸¹⁾.



(121)



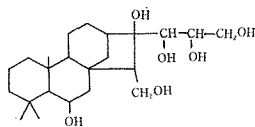
(122)



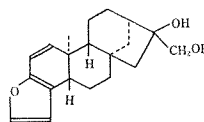
(123)

Galt and Hanson⁸²⁾ converted 7-hydroxykaurenolide (123) to (-)-kaur-16-en-19-oic acid (119) by chromic acid oxidation, hydrogenolysis with calcium in liquid ammonia and Wolff-Kishner's reduction.

Turbicoryn, a new glucoside was isolated from the seeds of *Turbina corymbosa* and structure (124) of its aglucone "turbicorytin" was postulated by the Mexican school⁸³⁾.



(124)

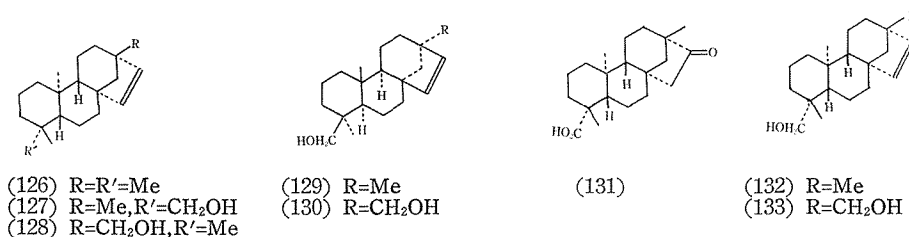


(125)

The constitution of kahweol, one of the constituents of the unsaponifiables of fats in Coffee beans, was represented as (125)⁸⁴⁾.

Scott *et al.*⁸⁵⁾ discussed the structure and stereochemistry of some polycyclic diterpenoids in view of biogenetic analysis.

Murray and McCrindle⁸⁶⁾ isolated stachene (126), 19-hydroxystachene (127) and 17-hydroxystachene (128) from the wood of *Erythroxylon monogynum*, and identified them.

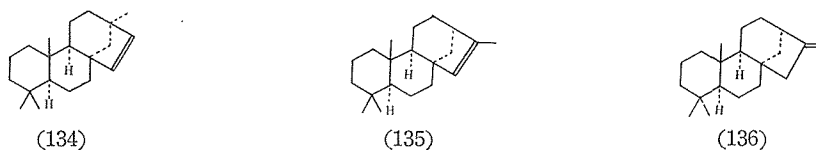


Kapadi and Dev⁸⁷⁾ isolated six new diterpenoids from the wood of the same plant, and studied the structure of monogynol, a major component. Consequently, they postulated formula (129) to monogynol. They also proposed structure (130) for another component, hydroxymonogynol.

Hanson⁸⁸⁾ carried out a partial synthesis of monogynol from isosteviol (131), the result of which showed that absolute configuration (129) suggested by Dev *et al.*⁸⁷⁾ corresponds to enantiomer of natural monogynol, accordingly, monogynol should be represented by (132).

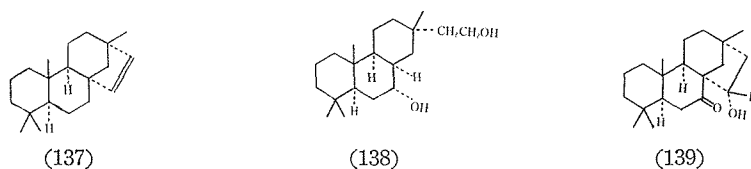
Successively, Kapadi and Dev⁸⁹⁾ revised the absolute configuration of monogynol and hydroxymonogynol to formulas (132) and (133), respectively.

Kitahara and Yoshikoshi⁹⁰⁾ established structure (134) of hibaene, a diterpene isolated from essential oil of the leaves of *Thujopsis dolabrata*



It was shown by gaschromatographic investigation that cupressene originally isolated from *Cupressus macrocarpa* was a mixture of isophyllocladene (135) (32%), phyllocladene (136) (trace) and a major diterpene hydrocarbon (67%). Although the latter could not be isolated in a completely pure state, it proved to be identical with hibaene (134) by several chemical evidences⁹¹⁾.

Wenkert *et al.*⁹²⁾ carried out a partial synthesis of isohibaene (137) from isopimaric acid. A strong Jones oxidation of diol (138), an intermediate, gave compound



(139). The pyrolysis of the acetate of (139) introduced a double bond in D ring. Wolff-Kishner reduction of C-7 carbonyl group of the product yielded isohibaene (137).

They provided the discussions on the stereochemistry of stachenone and beyerol, the related diterpenic substances.

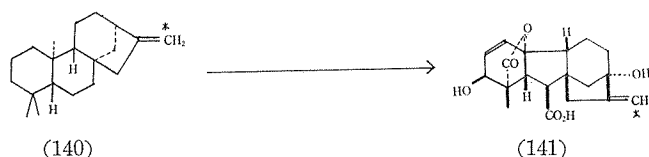
Kitahara and Yoshikoshi⁹³⁾ tried assignment of the methyl proton signals in the n.m.r. spectra of hibaene (134), dihydrohibaene, isophyllocladene (135) and phyllocladene (136).

Kapadi and Dev⁸⁹⁾ isolated *d*-hibaene, that is, stachene (126), its epoxide and a new diterpenoid from the wood of *Erythroxylon monogynum*.

VI. GIBBANE AND ITS RELATED SKELETON

In addition to gibberellins A₁, A₅, A₆ and A₈ which were previously isolated from *Phaseolus coccinens*, gibberellin A₃ and five new gibberellin-like substances, "Phaseolus α, β, γ , and ϵ ", were found.⁹⁴⁾ "Phaseolus ϵ " proved to be a gibberellin bound to carbohydrates and ninhidrin-positive compounds.

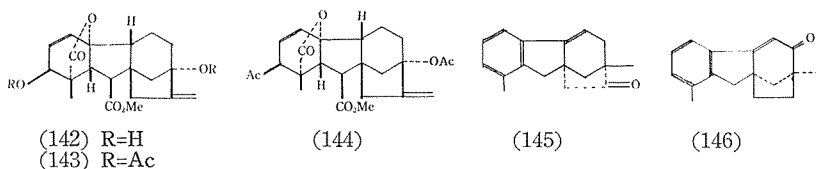
Cross *et al.*⁹⁵⁾ began the work on biosynthesis of gibberellins. They prepared (-)-[17-¹⁴C]-kaurene (140) and ¹⁴C-labelled gibberellin A₃ and investigated their metabolism by cultures of *Gibberella fujikuroi*. Consequently, it was found that (-)-kaurene (111) was a precursor of gibberellic acid (141). (Scheme 8)



Scheme 8.

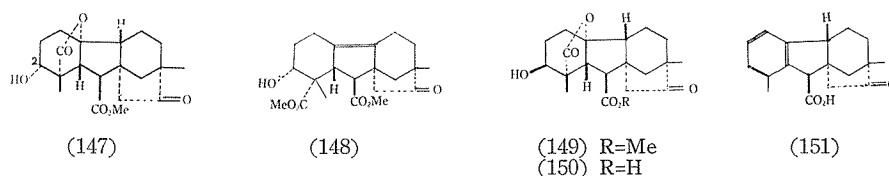
Tidd⁹⁶⁾ reported the dissociation constants of several gibberellins and their derivatives.

Jones *et al.*⁹⁷⁾ found a new substitution reaction in which the treatment of methyl gibberellate (142) or 2,7-di-O-acetyl derivative (143) with zinc and boiling acetic anhydride yielded methyl 7-acetoxy-2-acetyl-1-carboxy-4a-hydroxy-1-methyl-8-methylene-gibb-3-ene-10-carboxylate 1→4a lactone (144). The reaction mechanism of this new reaction was discussed.

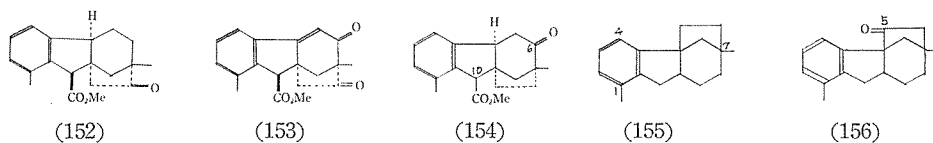


Sumiki *et al.*⁹⁸⁾ confirmed by synthesis that the structure of a ketone, C₁₇H₁₈O, which was afforded by pyrolysis of epigibberic acid (150) or by treatment of gibberone (145) with sulfuric acid, was 1,7-dimethyl-6-keto-gibba-A, 4b-tetraene (146).

They⁹⁹⁾ determined structure (148) of diester obtained from 2(eq.)-hydroxy epimer (147) of gibberellin C methyl ester by methanolysis, and got (147) from (148) by relactonization. The isomerization of the hydroxyl group to axial gave gibberellin C methyl ester (149), which was converted to gibberellin C (150) by acid-saponification. The reduction of carbonyl groups through thioketal was investigated.

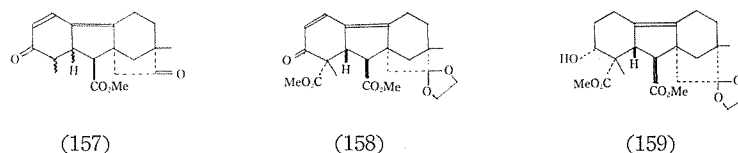


Huang-Minlon reduction of *d,l*-epigibberic acid (151) and desulfurization of natural methyl gibberate (152) thioketal were carried out. The stepwise desulfurization of *d,l*-methyl 6-oxo-dehydrogibberate (153) thioketal was investigated. Huang-Minlon reduction of methyl desoxo-6-oxo-gibberate (154) gave rise to epimerization at position C-10.¹⁰⁰⁾



They¹⁰¹⁾ synthesized 1,7-dimethylisogibba-A-triene (155) and 1,7-dimethyl-5-oxoisogibba-A-triene (156), both of which had isogibbane skeleton.

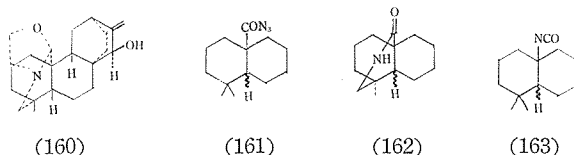
A partial synthesis of gibberellin C (150) was also carried out by Sumiki *et al.*¹⁰²⁾ Compound (157) was converted to compound (158) by ketalization, carboxylation, and esterification. The reduction with sodium borohydride and catalytic reduction of the latter gave compound (159). Boiling with dil. sulfuric acid, followed by esterification gave 2-hydroxy (eq.) epimer (147). The conversion of this substance to gibberellin C by base-catalyzed epimerization of 2-hydroxy group and acid hydrolysis, has been carried out as mentioned above.⁹⁹⁾



VII. DITERPENE ALKALOIDS

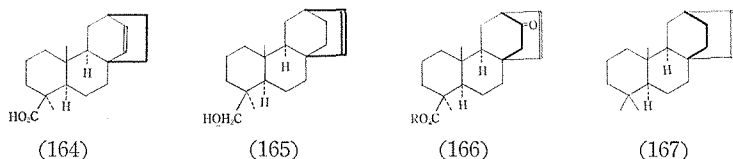
Pelletier¹⁰³⁾ described several unusual reactions of *Aconitum* and *Delphinium* alkaloids. These reactions are due to the polycyclic structure, particularly large number of bridged bonds. The reactions of imines and imminium salts of atisine and veatchine were discussed.

Dvornik and Edwards¹⁰³⁾ reported the structure and stereochemistry of atisine. They carried out a stereospecific hydration of exocyclic methylene group of atisine and degraded the product to a tetracyclic phenol. This enabled rigorous proof of the structure and relative and absolute stereochemistry (160) of atisine.



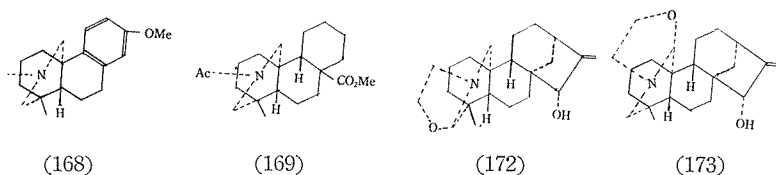
Brown¹⁰⁴⁾ prepared δ -lactam (*cis* and *trans*) (162), and isocyanate (163) *etc.* by photolysis of *cis*- and *trans*-1, 1-dimethyldecalin-10-carbonyl azides in cyclohexane. The yield of *trans* δ -lactam, however, was not good.

Zalkow and Girotra¹⁰⁵⁾ reported an approach to a synthesis of atisine (antipode) from podocarpic acid (8) which has already been synthesized by Wenkert and Tahara¹⁰⁶⁾. They attempted to get compound (164), but actually got (165), and this approach was not successful.



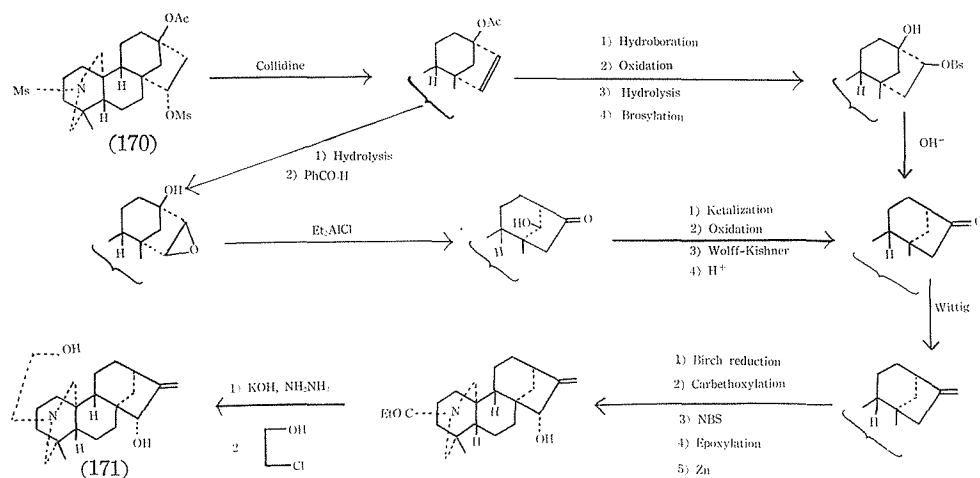
The same authors¹⁰⁷⁾ reached the synthesis of compound (167), which corresponded to the antipode of stisine's carbon skeleton, from compound (166) synthesized previously.

Ogiso and Iwai¹⁰⁸⁾ synthesized the racemate of compound (169), a degradation product of atisine and veatchine, from compound (168) synthesized previously by themselves.

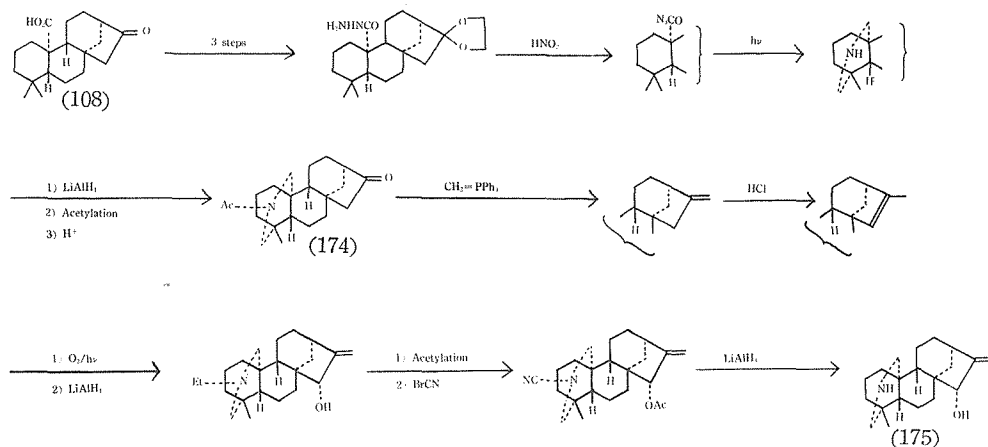


Nagata *et al.*¹⁰⁹⁾ have already accomplished the first excellent total synthesis of *d,l*-atisine. Now, they¹¹⁰⁾ synthesized *d,l*-dihydroveatchine (171) from compound (170), which they already synthesized, *via* a route shown in Scheme 9. Since the transformation of compound (171) to garryine (172) and also to veatchine (173) has already been accomplished, this means a completion of the total syntheses of *d,l*-garryine and *d,l*-veatchine.

On the other hand, Masamune¹¹¹⁾ accomplished a total synthesis of the optically active garryine (172). He got compound (175) from the above-mentioned (-)-16-keto-10-carboxy-17,20-bisnorkaurane (108) *via* a series of reactions shown in Scheme



Scheme 9.



Scheme 10.

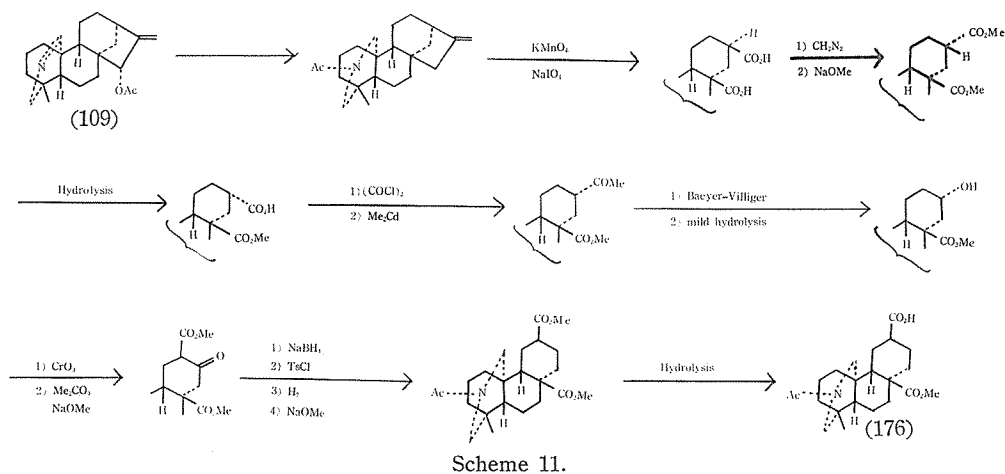
10. As the alkylation of this compound (175) to dihydroveatchine (171) has already been reported, this means a total synthesis of natural garryine.

Subsequently, Masamune¹¹²⁾ succeeded in the conversion of veatchine (173) to compound (176). The route will be shown in Scheme 11. Since product (176) has already been derived to atisine (160) by Pelletier *et al.*, this work means an accomplishment of the transformation from veatchine (173) and garryine (172) to atisine (160).

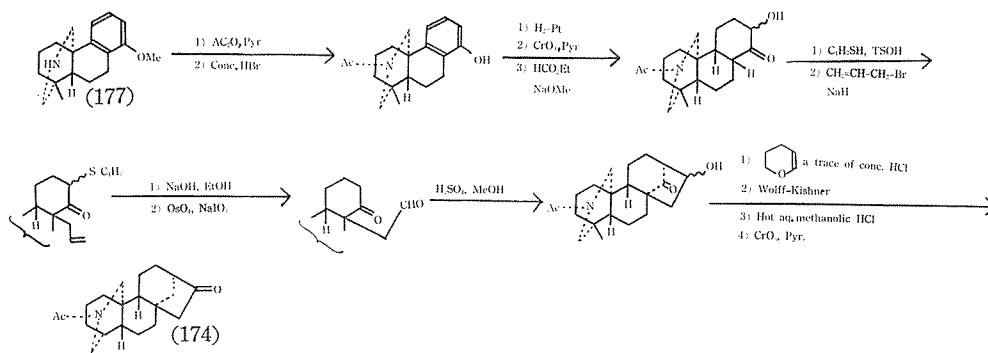
Wiesner *et al.*¹¹³⁾ synthesized racemic compound (174) from *d,l*-amine (177), which they have already synthesized. This compound can be converted to garryine (172) and veatchine (173), as mentioned above. Accordingly, this means the third achievement of the total synthesis of garryine and veatchine. The synthesis will be summarized in Scheme 12.

Okamoto *et al.*¹¹⁴⁾ investigated isohypnognavine, an alkaloid in *Aconitum majimai*

The Chemistry on the Diterpenoids in 1964



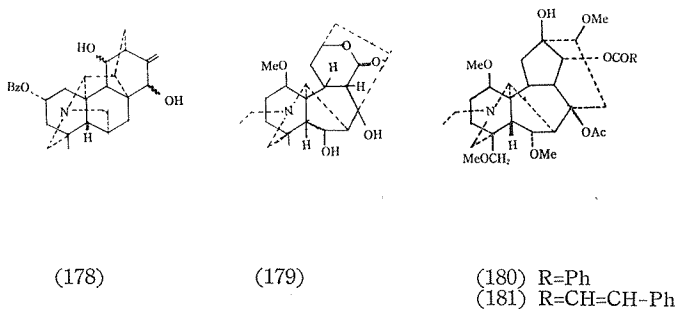
Scheme 11.



Scheme 12.

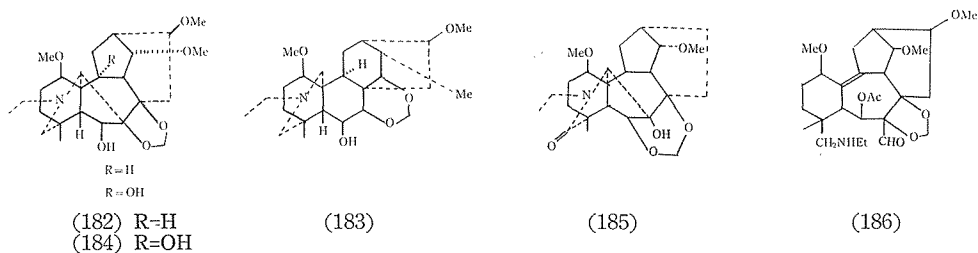
and *A. japonicum*, and gave it structural formula (178) on the basis of various kinds of reactions.

The structure of heteratisine, an alkaloid of a modified lycotconine-type skeleton, was investigated by Edwards and Ferrai¹¹⁵⁾ and by Aneja and Pelletier.¹¹⁶⁾ The same structure (179) was suggested by both of schools, provided that the configuration of the methoxyl group was not confirmed by Pelletier *et al.* The conclusion coincided with the result of X-ray analysis¹¹⁷⁾ of heteratisine hydrobromide monohydrate.



Achmatowicz and Marion¹¹⁸⁾ found two new lycoctonine type alkaloids, chasmanitine (180) and chasmanthine (181), for which the structures shown were given.

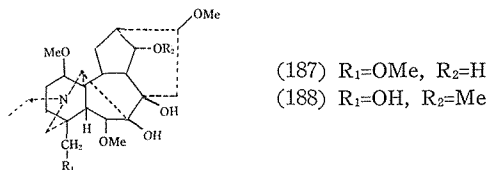
Crabb and Cookson¹¹⁹⁾ compared n.m.r. data of various methylenedioxy protons, and found that the coupling constant of both protons showed 0~2 c.p.s. in five membered ring, while it showed 6 c.p.s. in six membered ring. Since methylene protons of methylenedioxy group in delphenine and its derivatives have low coupling constant, a five membered methylenedioxy ring should be contained in these alkaloids. Accordingly, the structure of delphenine prefers (182) to (183) and also deltamine (eldelidine) should be represented as (184). Moreover, the similar protons in isooxodelphenine have a larger coupling constant (4.3 c.p.s.), and therefore, the alkaloid will contain a six membered methylenedioxy ring as shown in (185).



Khaimova *et al.*¹²⁰⁾ isolated lappaconitine from *Aconitum ranunculifolium*, degraded it in various ways and suggested its partial structure.

Wiesner *et al.*¹²¹⁾ investigated structure (186) of isoeldeline and its reactions.

Benn and May¹²²⁾ observed the incorporation of mevalonic acid-2-¹⁴C, acetate 1-¹⁴C and acetate-2-¹⁴C into browniine (187) and lycoctonine (188), and found that their biosynthesis is similar with other terpenes.



VIII. THE OTHERS

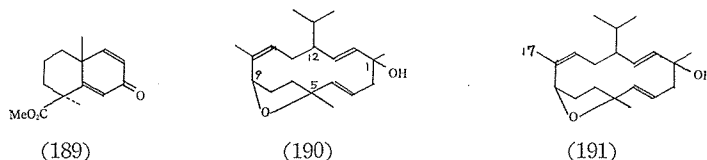
Spencer *et al.*¹²³⁾ studied the synthesis of resin acid intermediates; they got a small yield of dienone by the condensation of 2,6-dimethyl-2-carbomethoxy-6-formylcyclohexanone and acetone, and synthesized 8 α ,10 β -dimethyl-8 β -carbomethoxy- $\Delta^{1,9;3,4}$ -hexahydronaphthalone-2 (189).

Bory and Fetizon¹²⁴⁾ found an empirical relationship between infrared spectra and stereochemistry about di- and triterpene esters.

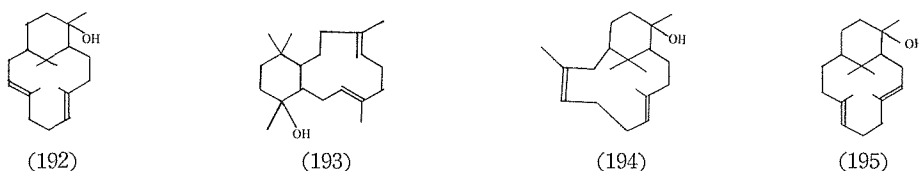
Brieskorn and Grosseckettler¹²⁵⁾ isolated some diterpenoids together with triterpenes, phytosterols and monoterpenes from pollen of *Salvia officinalis*.

Smith *et al.*¹²⁶⁾ studied the cyclization of farnesylacetone stereoisomers and their monocyclic analogs.

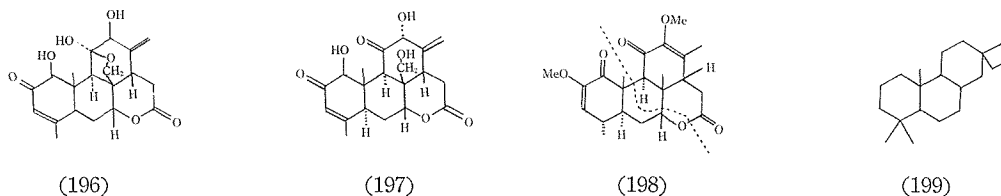
Rowland *et al.*¹²⁷⁾ showed that macrocyclic diterpene hydroxyethers isolated from Tobacco and Cigarette smoke were two diastereoisomers of 12-isopropyl-1,5,9-trimethyl-5,8-oxido-3,9,13-cyclotetradecatrien-1-ol (190) and 12-isopropyl-1,5-dimethyl-9-methylene-5,8-oxido-3,13-cyclotetradecadien-1-ol (191).



Erdtman, Sumimoto *et al.*¹²⁸⁾ investigated the structure of verticillol which was isolated from the wood of *Sciadopitys verticillata* and suggested formula (192). On the other hand, Ishikawa *et al.*¹²⁹⁾ preferred formula (193) to (192), but they also recognized the possibility of formulas (194) or (195) with less probability. It has not yet been clarified, which is correct.



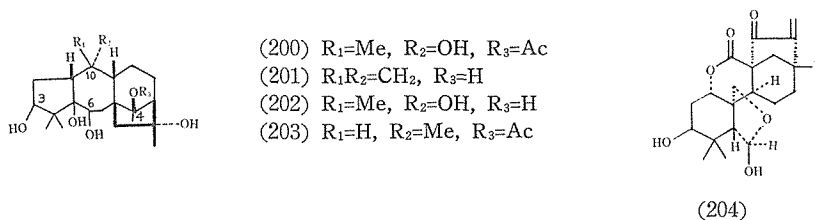
Polonsky and Fourrey¹³⁰⁾ isolated four crystalline components from *Ailanthus altissima* and suggested a hemiketal structure (196) of ailanthone, a major component, while Casinovi *et al.*¹³¹⁾ isolated ailanthone as a principle bitter component of *Ailanthus glandulosa* and proposed a keto alcohol structure (197). Another difference between both structures is the steric configuration of the hydroxyl group at C-12.



Since the structures of several bitter principles and their derivatives have been clarified, their biogenesis is being discussed. In the discussion of biogenesis of quassin (198), Thomas¹³²⁾ and Valenta *et al.*¹³³⁾ suggested dimerization scheme of C₁₀-units, that is, a hypothesis of an oxidative coupling between the same two C₁₀ units separated by a dotted line in (198). Moreover, the latter authors pointed out that quassin may be produced from a diterpenoid pimarane skeleton (199) by a series of rearrangements by 1,2-shifts.

Recently, Bredenberg¹³⁴⁾ and Dryer¹³⁵⁾ suggested a third pathway in which the C₂₆ terpenoids may be precursors of the C₂₀ bitter principles.

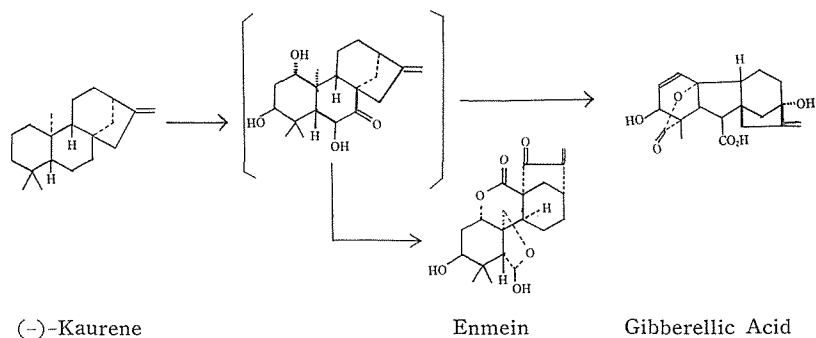
Nakanishi *et al.*¹³⁶⁾ provided the evidence for the elucidation of full stereochemistry on grayanotoxin-I, -II, and -III, the toxic components of *Leucothoe grayana*. They are shown as (200), (201 = 122), and (202), respectively.



A short review of their structures by Kakisawa¹³⁷⁾ is available.

Tallent¹³⁸⁾ investigated the products from the reaction of acetylanhydromedol (=grayanotoxin-I) and 10-desoxyacetylanhydromedol (203) with cupric sulfate in acetone.

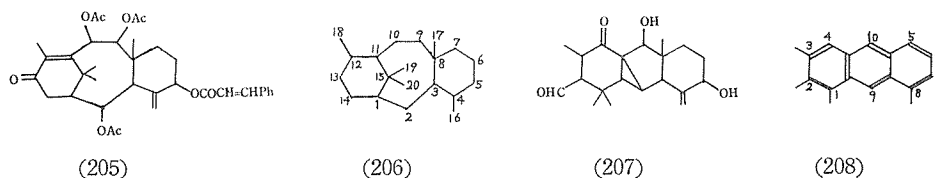
The structure elucidation of enmein, a bitter principle of *Isodon trichocarpus*, was accomplished by the co-operation of many Japanese schools, and the excellent results were published. The structure and stereochemistry of enmein were established as (204) on the basis of many kinds of chemical and physical evidences. At the same time, X-ray study¹⁴⁰⁾ of acetyl bromoacetyldihydroenmein confirmed the structure. The biogenesis of enmein is very interesting in relation to metabolites of *Gibberella fujikuroi*. Enmein may be considered as a diterpene of (-)-kaurene homolog, and it is the first example of naturally occurring diterpenes formed by the cleavage of carbon linkage in the B ring. A rough biogenesis will be shown in Scheme 12.



Scheme 12.

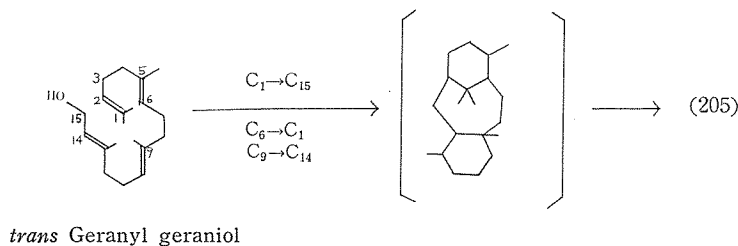
The plane structure of taxinine, a desdimethylamino derivative of taxine, an alkaloid in *Taxus baccata*, was already determined as (205) in 1963. A part of the work which constituted an earlier study was published by Uyeo *et al.*¹⁴¹⁾ Now, the name "Taxane" was suggested for skeleton (206).¹⁴²⁾

Uyeo *et al.*¹⁴³⁾ determined structure (207) of anhydrotaxininol, which was gained by hydrolysis of taxinine. They also discussed the reaction mechanism. Taga got 1,2,3,8-tetramethyl anthracene (208)¹⁴⁴⁾ by selenium-dehydrogenation, the structure



of which was confirmed by synthesis.¹⁴⁵⁾

The biogenesis of taxinine (205) was discussed in relation with that of verticillol by Sumimoto *et al.*¹²⁸⁾ and Ishikawa *et al.*¹²⁹⁾ as shown in Scheme 13.



Scheme 13.

The stereochemistry of taxinine, taxinol and anhydrotaxininol was discussed in the 8th. Symposium of Natural Organic Compounds in Japan.¹⁴⁶⁾

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SUPPLEMENT

- IV. The isolation of abienol from Canada Balsam was reported.¹⁴⁷⁾ Communic acid, cupressic acid, and isocupressic acid were isolated from *Cupressus sempervirens* resin.¹⁴⁸⁾
- VII. Hypaconitine proved to be deoxymesaconitine and the absolute stereochemistry was shown to be same with aconitine.¹⁴⁹⁾
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