

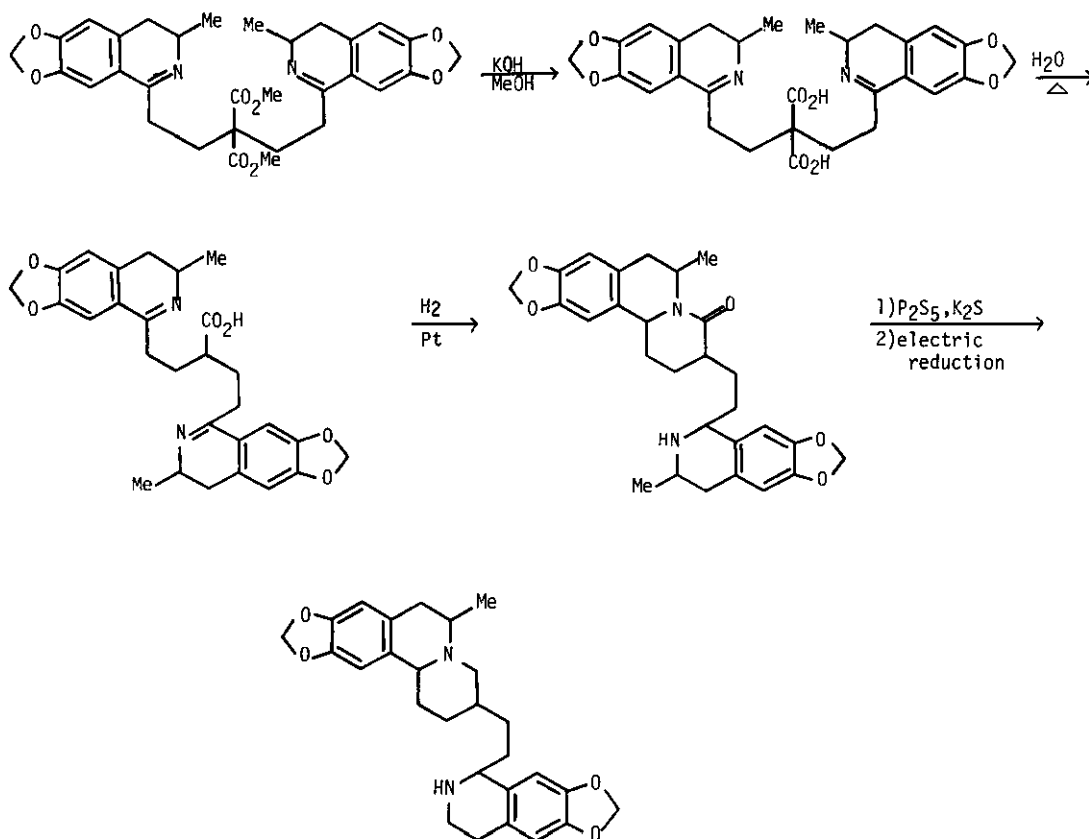
## SCIENTIFIC CONTRIBUTIONS OF PROFESSOR TETSUJI KAMETANI

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Professor Tetsuji Kametani was born in Tokyo on August 1, 1917, and graduated from the Pharmaceutical Institute, Medical Faculty, Tokyo Imperial University\* in August, 1943, which was the best academic place in Japan for organic chemists studying

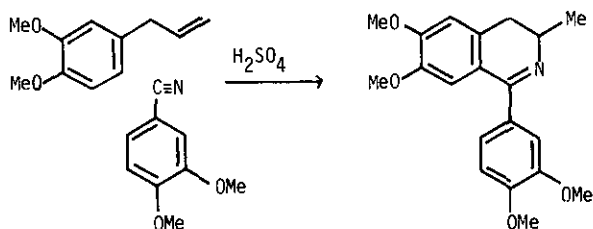
Chart 1



\* The name "Tokyo Imperial University" was changed to "University of Tokyo" after WW 2.

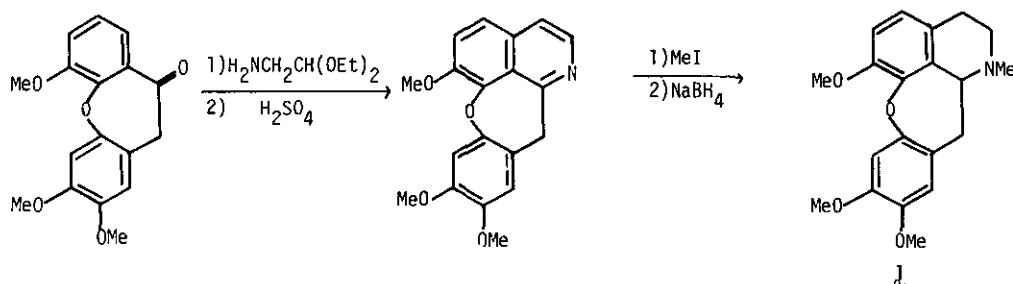
natural products at that time. His research career as an organic chemist started in 1942 at the above university under the guidance of Professor Shigehiko Sugawara, who is now an Honorary Editor of HETEROCYCLES, and he published his first paper entitled "A Synthesis of 4',5'-Methylenedioxy-6-[ $\beta$ -6'',7''-methylenedioxy-3''-methyl-py-tetrahydroisoquinolyl-1'']ethyl-3,4,5,6,7,8-hexahydro-(1',2';1,2-benzoquinolizidine) in *J. Pharm. Soc. Japan* [65, 372 (1945)]. This study aimed to synthesise an isoquinoline alkaloid, emetine, and greatly influenced his academic career. After returning from military service in 1945, Professor Kametani started afresh his studies at Tokyo College of Pharmacy, where he synthesised many heterocyclic compounds with fused isoquinoline ring systems and papaverine-like compounds in the development of new medicines. He obtained his Ph.D. from Tokyo University in 1951 in the field of isoquinoline alkaloids and then moved to the Pharmaceutical Institute, Osaka University. His research work in this university was divided into three parts; the development of new reactions, synthesis of imidazo- and pyrimidoisoquinolines, and medicinal chemistry. During these studies he discovered a new synthetic route to the isoquinoline ring system as shown in the following chart [*J. Pharm. Soc. Japan*, 72, 1090 (1952)] and a new method for the reduction of alcohols to alkanes, and also succeeded in the development of a strong analgesic. Before leaving Osaka University in 1959 he had published 50 papers.

Chart 2



Professor Kametani's work in the Pharmaceutical Institute, Tohoku University, started in 1959, on synthetic studies on the isoquinoline alkaloids. He accomplished a total synthesis of ( $\pm$ )-cularine (1) in 1963 (*J. Chem. Soc.*, 1963, 4289), which work was his first successful example in the total synthesis of natural products.

Chart 3



After success in the above synthesis, his interest in synthetic studies expanded to natural products, heterocyclic compounds and new medicines, and he published more than 800 papers in this University. Professor Kametani obtained the Academic Prize of the Pharmaceutical Society of Japan in 1969, and in 1980, he was conferred the Fujihara Prize for "Synthetic Studies on Physiologically Active Natural Products". He also obtained the Medal of Honor with Purple Ribbon (Shiju Hosho) in 1979 for "Synthesis of Natural Products and Development of New Medicines".

In 1974, he developed an effective method of analysis for designing synthetic approaches, based on fragmentation processes in mass spectrometry, and named this "Retro Mass Spectral Synthesis" [Accounts Chem. Res., 9, 319 (1976)]. Using this method, he has synthesised many types of natural products in the last five years. For this outstanding work, he was conferred the "Award of the Japan Academy" in 1980, which is one of the highest awards in Science in this country.

As it is impossible to list here all of his numerous publications, I would like to outline his main research work on the basis of the following classification.

- 1 Biomimetic-type Synthesis of Natural Products
- 2 Modified Pschorr Reaction
- 3 Photochemical Reaction
- 4 Benzyne and Nitrene Reactions
- 5 Phenolic Cyclisation
- 6 Ring Transformation — Ring Expansion and Contraction
- 7 Natural Product Synthesis via Enamines
- 8 Retro Mass Spectral Synthesis
- 9 Thermolysis of Benzocyclobutenes — Electrocyclic and Cycloaddition Reactions

## 10 Total Synthesis of Indole Alkaloids

## 11 Medicinal Chemistry

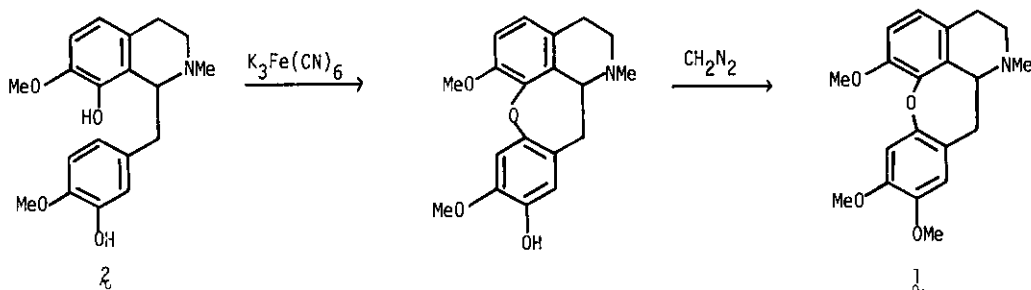
### 1 Biomimetic-type Synthesis of Natural Products

Some types of natural products, especially isoquinoline alkaloids such as morphine, are biosynthesised via oxidative coupling. Professor Kametani thought that one of the most reasonable ways for designing a synthetic route was to follow the biogenetic pathway of the natural product. During the 1960's he achieved total synthesis of many natural products by the phenolic oxidation method [Synthesis 1972, 657; Bioorg. Chem., 3, 430 (1974); Bioorg. Chem., Vol.II, 153 (1978)], and more recently by oxidation with singlet oxygen and by using selenium derivatives as follows.

#### 1.1---Phenolic Oxidation

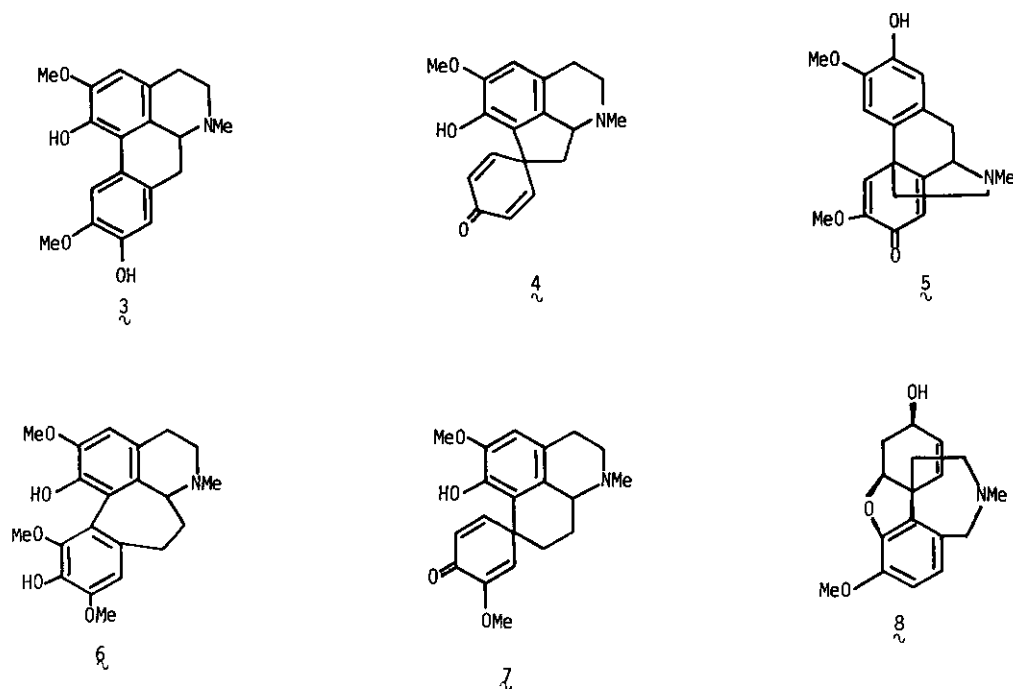
A. Chemical Oxidation: Cularine (1) and related alkaloids may be biosynthesized via phenolic oxidation of a 7,8-dioxygenated 1,2,3,4-tetrahydroisoquinoline followed by methylation of the coupling product. Professor Kametani has mimicked this sequence and succeeded in the total synthesis of cularine (1) from the diphenolic isoquinoline (2).

Chart 4



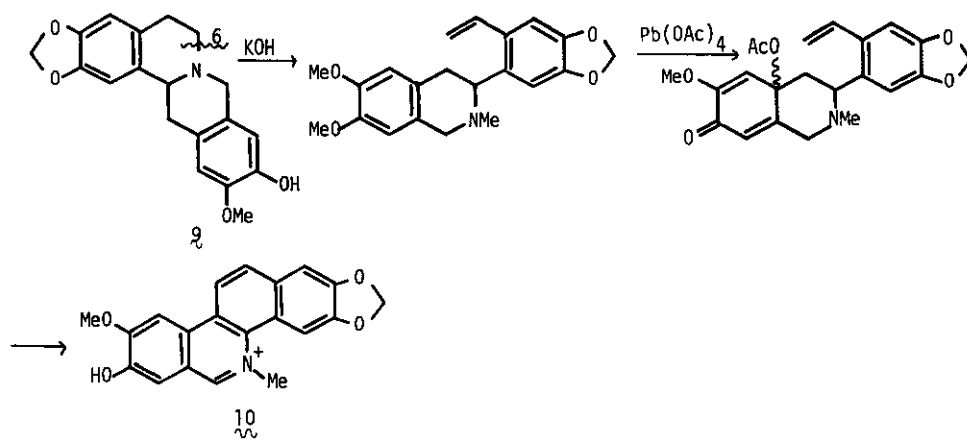
A similar type of oxidative coupling was observed in Nature in the biogenesis of aporphines (isoboldine 3), proaporphine (glaziovine 4), morphine (pallidine 5) homoaporphine (multifloramine 6), homoproaporphine (kreysiginone 7) and Amaryllidaceae (galanthamine 8) alkaloids, and he has synthesised about 50 alkaloids along their biogenetic pathways by oxidation of the appropriate phenolic isoquinolines with potassium ferricyanide.

Chart 5

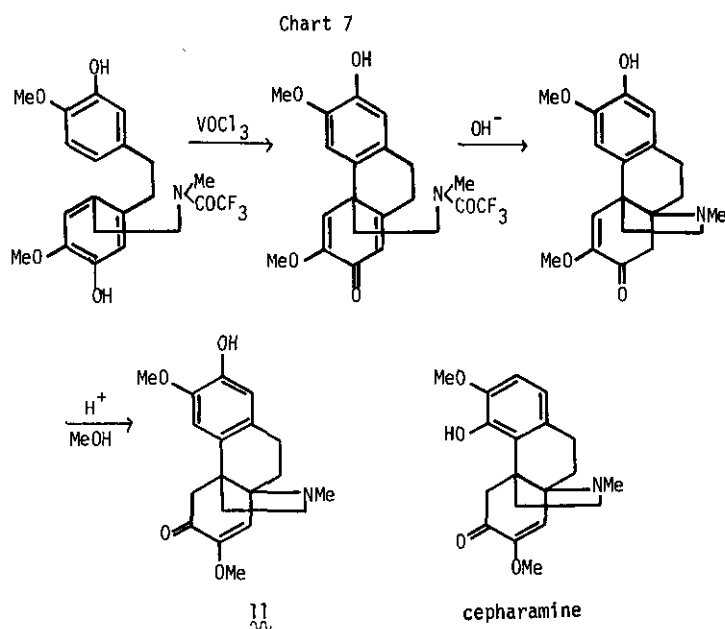


Professor Kametani also carried out a biogenetic synthesis of the benzophenanthridine alkaloid nitidine (10) from the berbine (9), by cleavage of the C<sub>6</sub>-N bond in 9 followed by oxidative coupling using lead tetraacetate as follows.

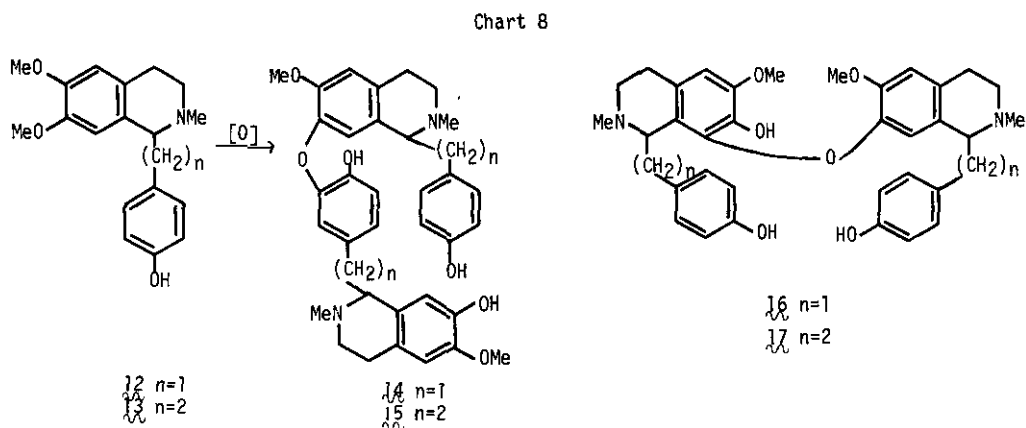
Chart 6



He has also used phenolic oxidation in non-biomimetic synthesis of natural products. For example, he has applied this oxidation reaction to a synthesis of the compound (11) with the hasubanan ring system.



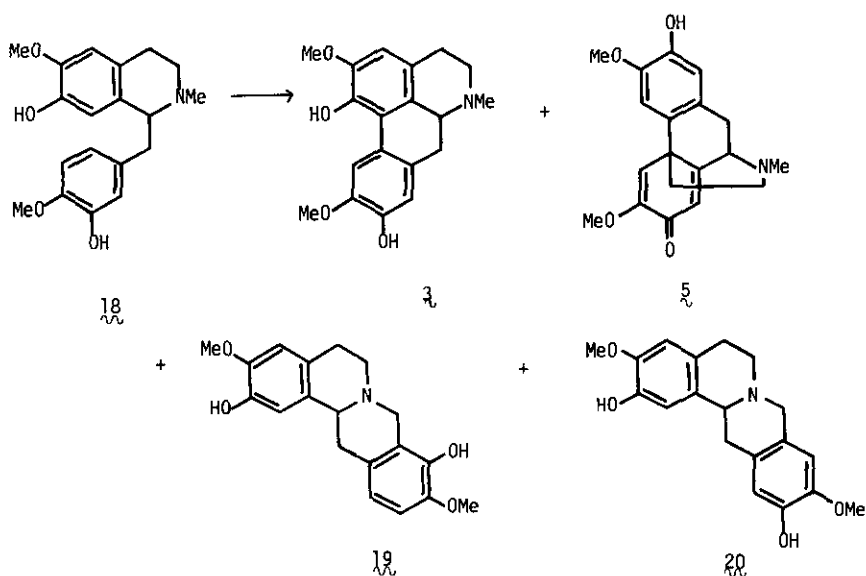
B. Enzymic Oxidation: After synthesis of many kinds of alkaloids by phenolic oxidative coupling using chemical reagents, Professor Kametani investigated phenolic



oxidation with enzymes in order to determine whether it was possible to induce new types of coupling in phenolic isoquinolines. Firstly, he examined the oxidation of coclaurine (12) and homococlaurine (13) with potato peelings in the presence of hydrogen peroxide at an appropriate pH, and obtained the head-to-tail coupling products (14) and (15) respectively. Similar oxidation with horseradish gave the head-to-head coupling products (16 and 17), and thus he showed the plant enzymes to have site selectivity in the coupling reactions.

He subsequently investigated the oxidation of racemic and optically active reticuline (18) with animal enzymes, and revealed that this enzymic system lacked stereoselectivity in the coupling reactions, and that molecular oxygen and NADPH played important roles. Moreover, he discovered the important fact that the berberine bridge could be formed chemically by oxidation of the N-methyl group.

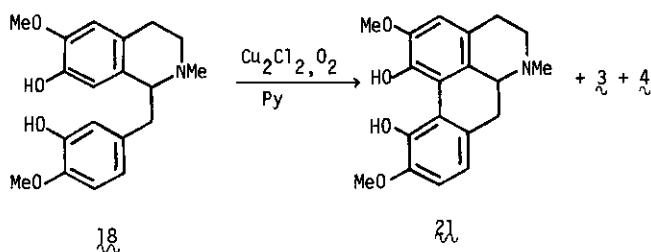
Chart 9



C. Enzymic Model: On the grounds that oxydases such as laccase and tyrosinase contain a copper ion, as the coenzyme, Professor Kametani assumed that a  $\text{Cu}_2\text{Cl}_2\text{-O}_2$  system would show enzymic action. He investigated the oxidation of reticuline (18) with this system in pyridine under mild conditions. Interestingly, he found that this oxidation proceeded smoothly to afford corytuberine (21) as the main product, in addition to isoboldine (3) and pallidine (4). The first product (21) is the

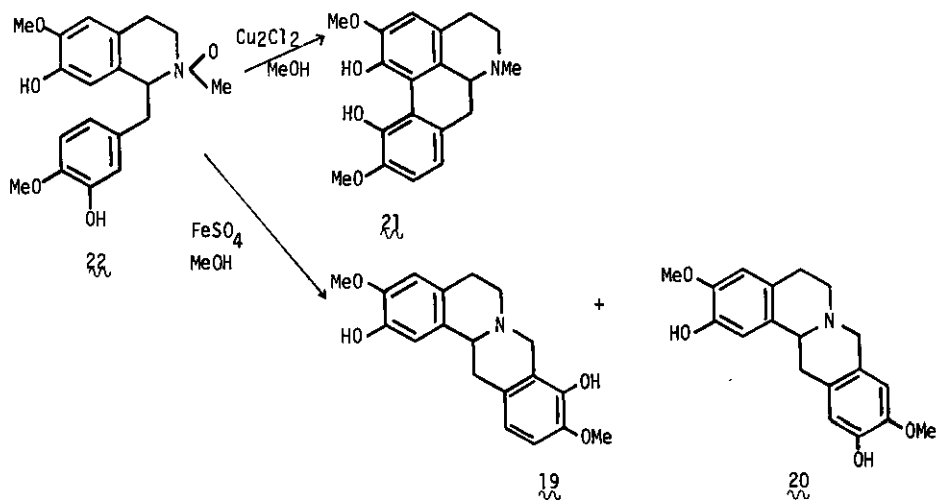
ortho-ortho coupling one that could not be formed by other chemical and enzymic oxidations. He also obtained successful results in the oxidation of orientaline, homoreticuline and homoorientaline by this system, and proposed a reaction mechanism for the oxidation.

Chart 10



In 1978, Professor Kametani proposed a new hypothesis in isoquinoline alkaloid biogenesis, in which 1,2,3,4-tetrahydroisoquinoline N-oxides intervene in the oxidative coupling sequence, and then realised this in the laboratory as follows. Reticuline N-oxide (22) was treated with cuprous chloride or ferrous sulfate to form corytuberine (21) or protoberberines (19 and 20) respectively, in good yield. Investigation of this type of coupling was also carried out on orientaline N-oxide, homoreticuline N-oxide, and homoorientaline N-oxide.

Chart 11



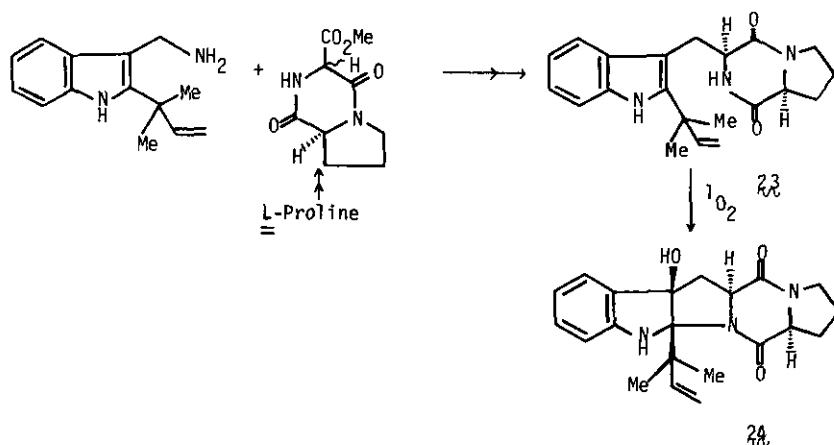


1.2--Oxidation with Singlet Oxygen

It is well known that singlet oxygen, derived from oxygen by photolysis, is an active species and a very useful reagent for some types of oxidation. Professor Kametani has used this species in a biogenetic-type synthesis of indole alkaloids.

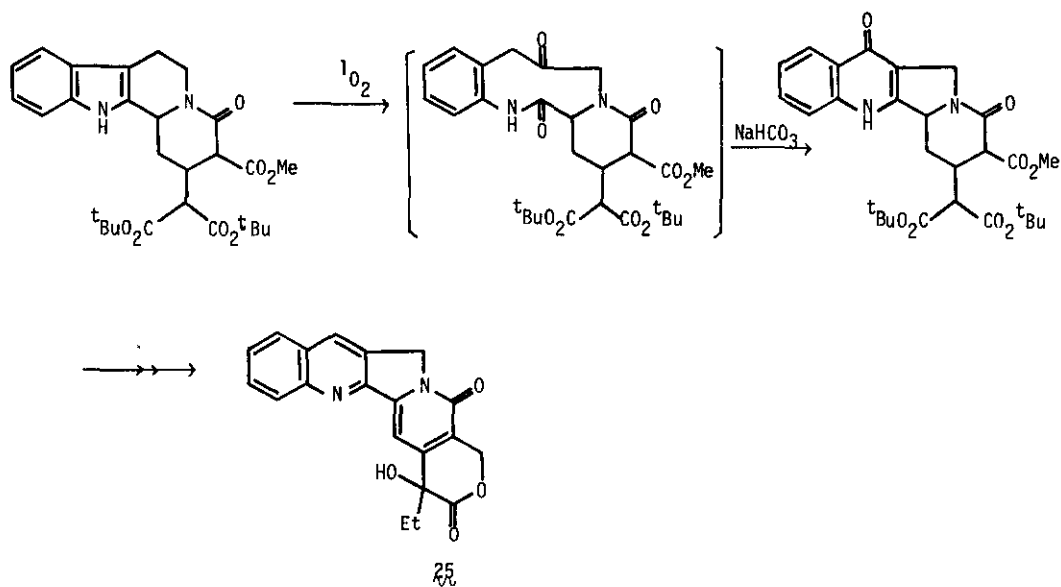
A Chiral Synthesis of (-)-Brevianamide E: Brevianamide E (24) is biosynthesised from deoxybrevianamide E (23) by an oxidative coupling, and he has used singlet oxygen to realise this step in the laboratory. Thus (-)-deoxybrevianamide E (23), prepared from a gramine and a diketopiperazine, was treated with singlet oxygen to yield (-)-brevianamide E (24). This work also proved the structure of the alkaloid to be as represented by formula 24 [J. Amer. Chem. Soc., 102, 3974 (1980)].

Chart 12



B. Total Synthesis of Camptothecin: Camptothecin (25), an anticancer alkaloid, is biosynthesised from an indole derivative, and the key step in this biogenesis is the transformation of the indole ring into a quinoline system. Professor Kametani has succeeded in this conversion by using singlet oxygen as shown in the following chart. This product was then converted into camptothecin (25). (±)-10-Methoxycamptothecin was also synthesised in the same way [Heterocycles, 14, 951 (1980)].

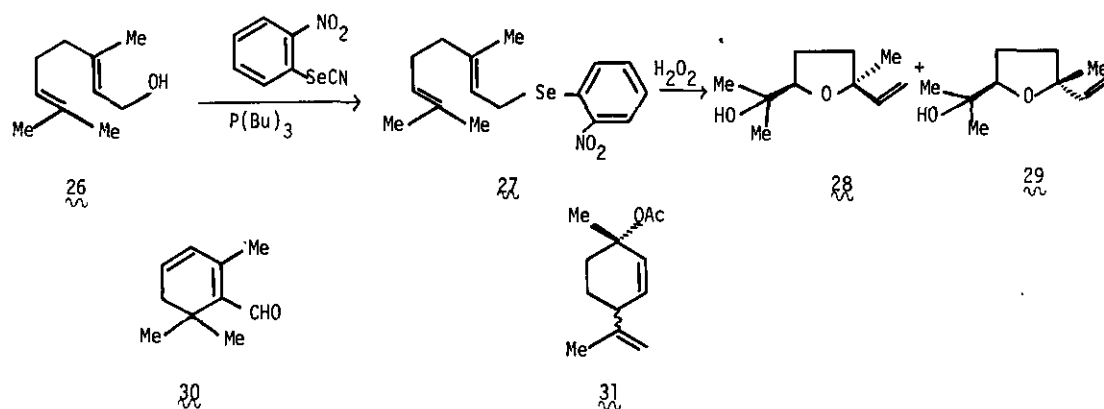
Chart 13



### 1.3 Oxidative Coupling via Organic Selenium Compounds

Recently, organic selenium compounds have been widely used as reagents for the modification of functional groups in organic synthesis, but there are not many examples of their use in the formation of carbon-carbon bonds. Professor Kametani has developed a new type of carbon-carbon bond formation by oxidation with a selenium

Chart 14



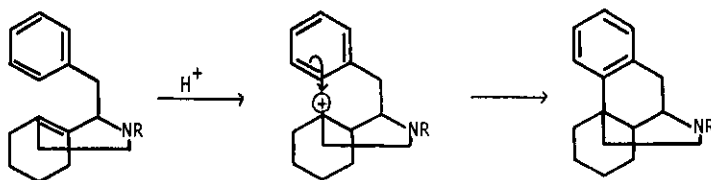
compound and by a route through a selenium intermediate, and has accomplished the total synthesis of some monoterpenes along the biogenetic pathway. For example, cis and trans-linalyloxides (28 and 29) were prepared from geraniol (26) by oxidation of the selenide (27) with 30 % hydrogen peroxide [Bioorg. Chem., 7, 215 (1978)], and safranal (30) and trans-p-menthan (31) were obtained by similar reactions.

## 2 Modified Pschorr Reaction

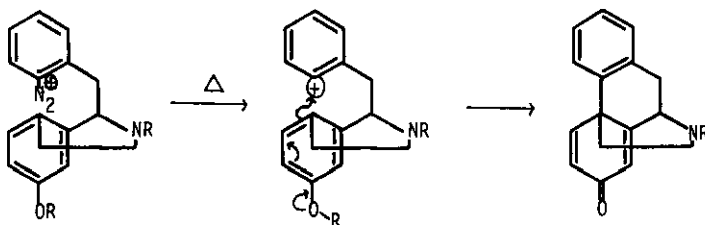
Phenolic oxidation provides a facile route to certain isoquinoline alkaloids. However, its utility is limited since intermolecular coupling also occurs to generate polymers. Moreover, intramolecular coupling always takes place at positions ortho and para to the phenolic hydroxyl group, showing that phenolic oxidation lacks siteselectivity. Furthermore, phenolic oxidation can not be employed in the synthesis of certain alkaloids which have hydroxyl groups meta to the coupling site. Since coupling occurs preferentially at the position para rather than ortho to the hydroxyl group, reticuline (18) can be converted into isoboldine (3) and pallidine (5), but not into salutaridine (38) and corytuberine (21). In view of these inherent limitations associated with phenolic oxidation, and in connection with the development of a general method for the synthesis of morphinan-

Grewé Cyclisation

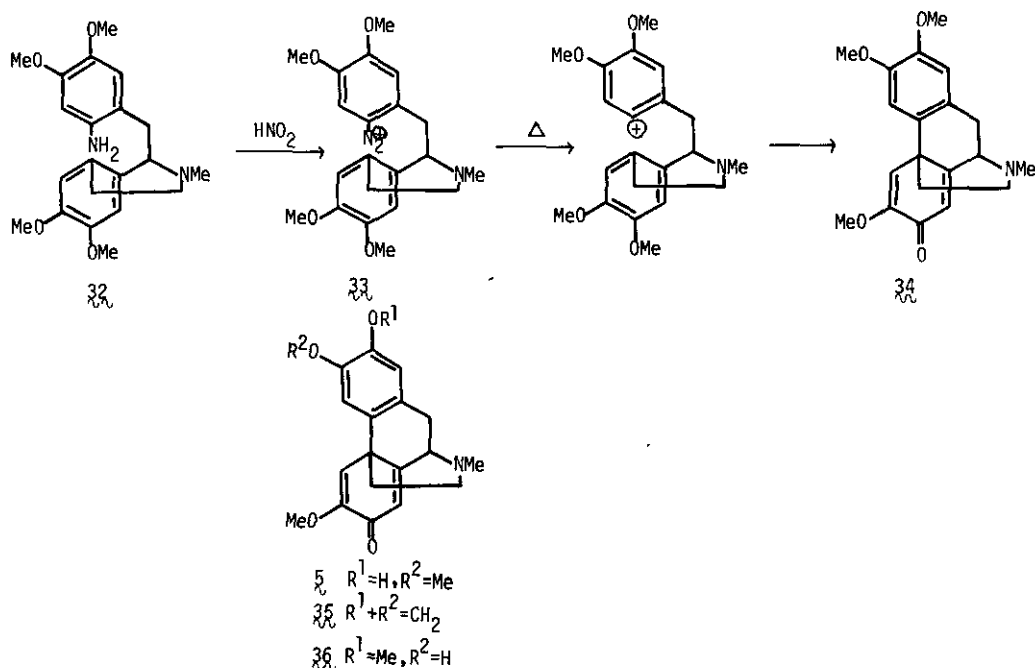
Chart 15



Kametani Cyclisation

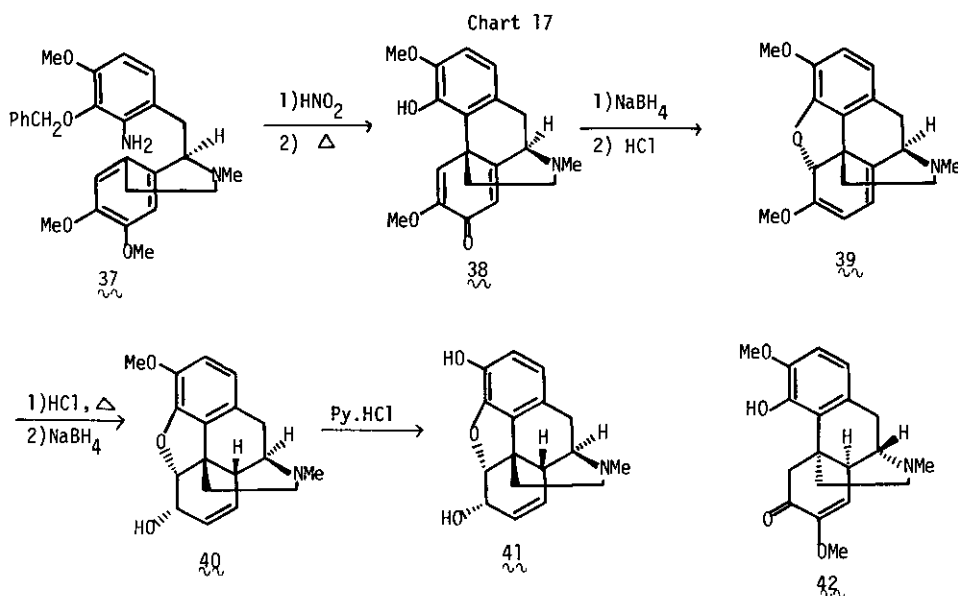


Based on the observation that Grewe cyclisation proceeds by nucleophilic attack of an aromatic ring on the carbonium ion generated by protonation of an olefinic system, Professor Kametani supposed that if the angular carbon of the isquinoline ring is activated by an appropriate substituent, this carbon would nucleophilically attack an aromatic cation generated in situ to form a morphinandienone-type compound. In order to generate the aromatic cation, he selected the decomposition of an aromatic diazonium salt, in which the position of the cation is fixed at the position occupied by the diazonium group, so that the reaction should proceed with high siteselectivity. On this consideration, 2'-aminolaudanidine (32) was diazotised with a slight excess of sodium nitrite in sulfuric acid, and the resulting diazonium salt (33) was decomposed thermally without a metal catalyst to form the morphinandienone (34) as the major product. Thus he discovered a general synthetic method for preparing morphinandienone-type alkaloids and synthesised amurine (35), pallidine (5) and flavinantine (36) by this method.



This reaction is particularly useful for the synthesis of morphinandienones which can not be prepared by phenolic oxidation, such as amurine (35) and flavinantine (36) [J. Heterocyclic Chem., 8, 341 (1971)].

Based on this method, Professor Kametani has achieved a total synthesis of morphine (41), one of the most interesting and complicated isoquinoline alkaloids. Thus, the R-(-)-2'-aminobenzylisoquinoline (37) was diazotised with sodium nitrite and sulfuric acid and the resulting diazonium salt was decomposed thermally without a catalyst to give salutaridine (38), which on reduction with sodium borohydride followed by dehydration in the presence of hydrochloric acid furnished thebaine (39). Since thebaine (39) had previously been converted into morphine (41) via codeine (40), the total synthesis of morphine and related alkaloids was achieved.



In a similar manner, he synthesised sinoacutine, an antipode of salutaridine (38), and converted it into (+)-thebaine which had already been correlated to sinomenine (42).

### 3 Photochemical Reaction

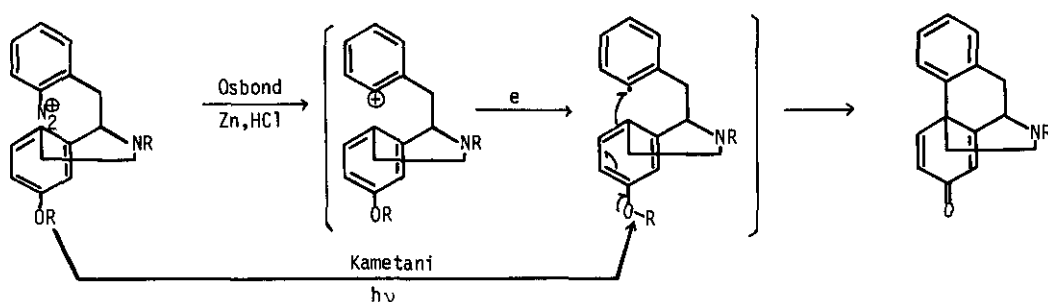
#### 3.1 Photo-Pshorr Reaction

Osbond reported that the diazonium salts derived from 2'-aminobenzylisoquinolines were transformed into morphinandienones by treatment with zinc and hydrochloric acid, after Professor Kametani had accomplished the total synthesis of morphine by the

modified Pschorr Reaction. He supposed that morphinandienone formation in Osbond's work proceeded via a radical mechanism, i.e. that the aromatic cation derived from the diazonium salt is reduced with zinc to form the aromatic radical which is then attacked by the second aromatic nucleus.

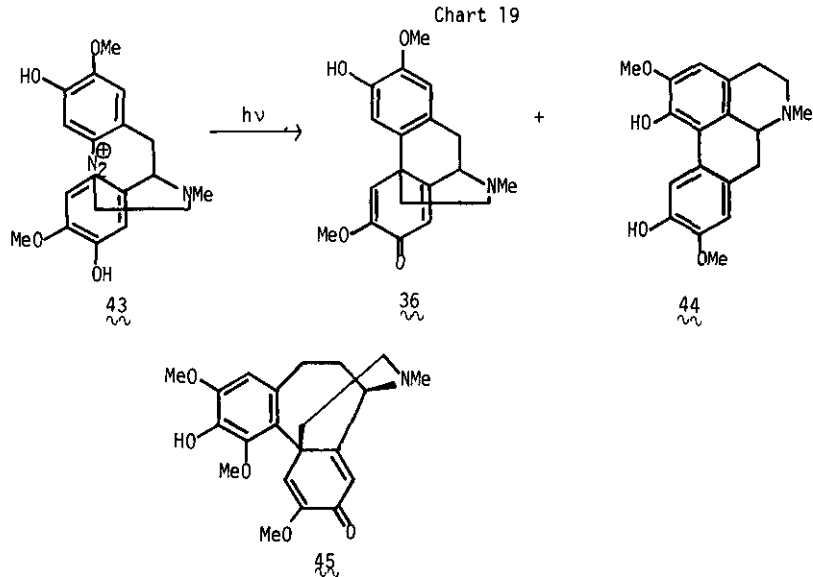
Based on this idea, he assumed that photolysis of a diazonium salt would be a more efficient way of effecting homolysis of the carbon-nitrogen bond to form the postulated radical intermediate.

Chart 18



He found in practice that irradiation of the diazonium salt (43), derived from 6'-

Chart 19

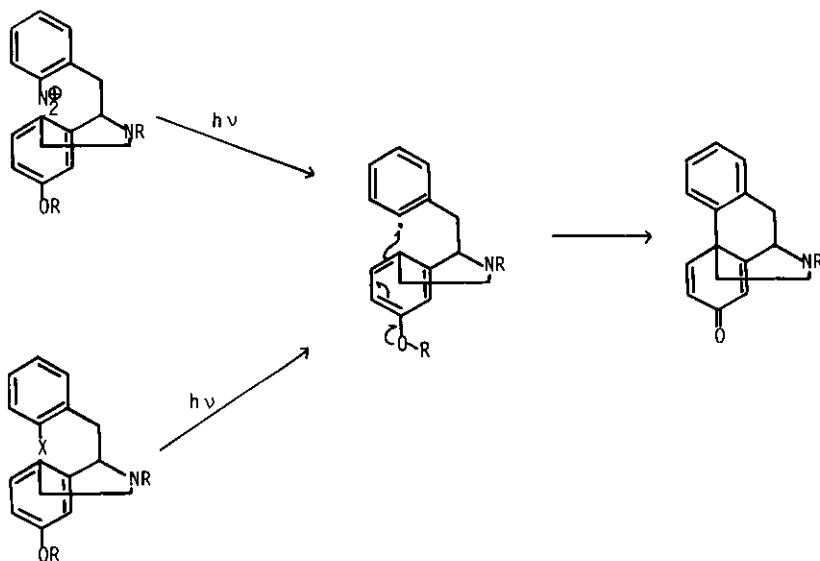


aminoorientaline by diazotisation in dilute sulfuric acid at  $5 - 10^{\circ}$  afforded flavinantine (36) and bracteoline (44) in moderate yields, and went on to synthesise many isoquinoline alkaloids using this photolysis [Accounts Chem. Res., 5, 219 (1972)]. Professor Kametani has applied the photo-Pschorr reaction to the phenethylisoquinoline series, and accomplished the total synthesis of androcymbine (45) under the same conditions as in the benzyloisoquinoline systems.

### 3.2 Photolytic Cyclodehydrohalogenation

It is well known that photolysis of aromatic halides results in the formation of biphenyl derivatives by reaction of the aryl radicals produced by homolytic cleavage of the carbon-halogen bond. Since the key intermediate in the photo-Pschorr reaction is probably the aromatic radical, it appeared likely that the latter could also be generated by radical formation from the  $C_2$ -halo-substituted benzyloisoquinoline to also afford the dienone. Based on this consideration, Professor Kametani investigated the potential utility of photolytic cyclodehydrohalogenation in the synthesis of dienone and aporphine alkaloids.

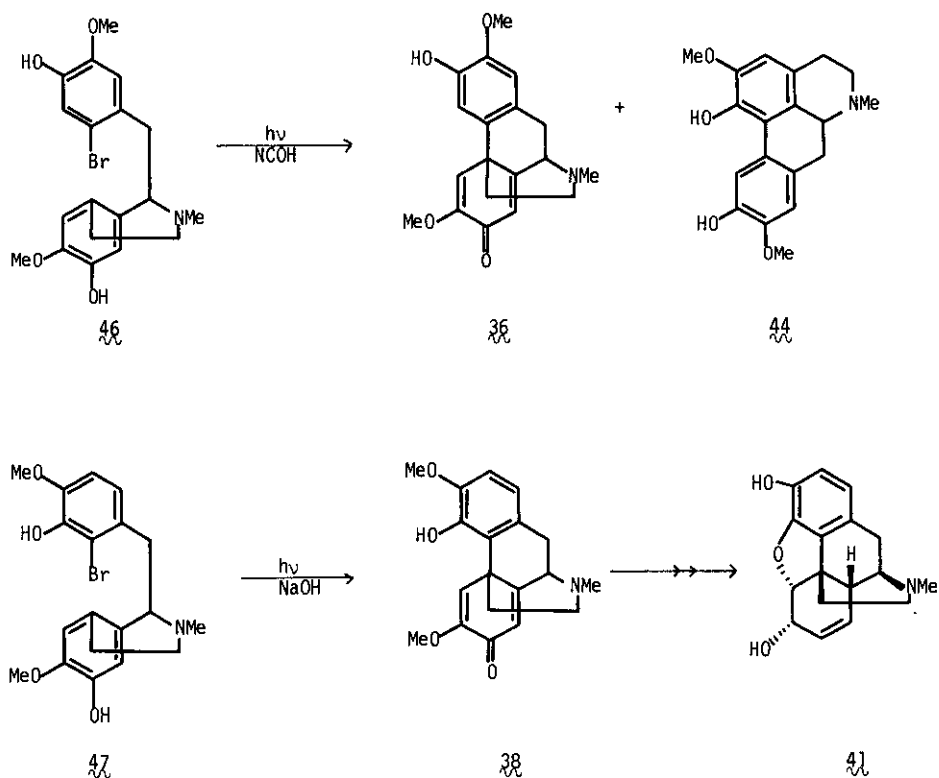
Chart 20



He firstly attempted a synthesis of aporphine and morphinandienone alkaloids; irradiation of 6'-bromoorientaline (46) in the presence of sodium hydroxide afforded bracteoline (44) and flavinantine (36) in moderate yields. By this route he obtained

many aporphine and morphinandienone alkaloids. Among these studies, the synthesis of salutaridine (38) from 2'-bromoreticuline (47) provided a formal total synthesis of thebaine (39), codeine (40) and morphine (41), because salutaridine (38) had already been converted into these alkaloids.

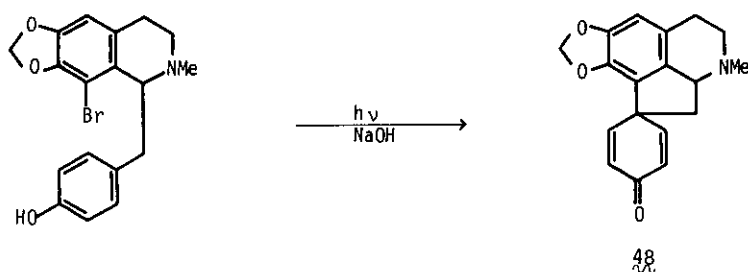
Chart 21



Having demonstrated the feasibility of preparing morphinandienones by photocyclo-dehydrohalogenation, he then successfully extended this study to a synthesis of proaporphine alkaloids as shown by the preparation of mecambrine (48) in the following chart.

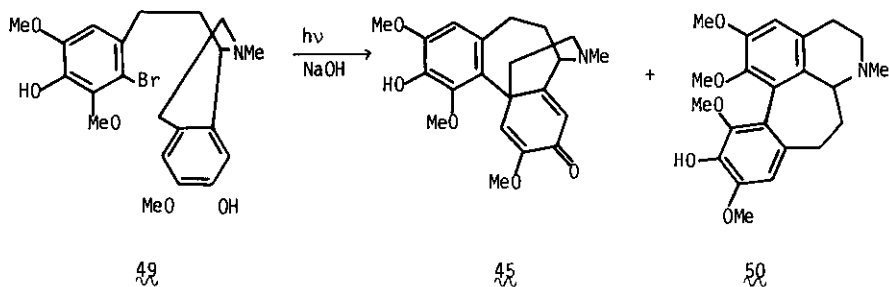


Chart 22



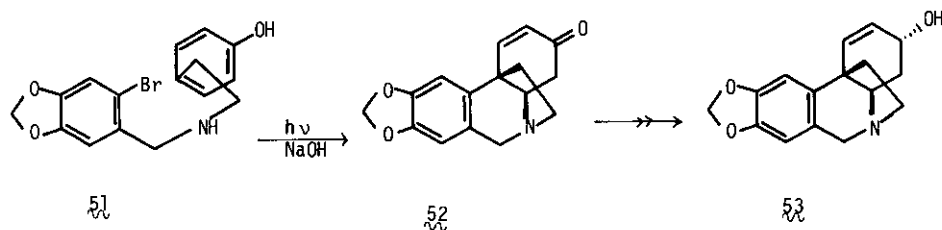
In addition to the conversion of phenolic bromobenzylisoquinolines into aporphine, morphinandienone, and proaporphine alkaloids, he has applied this photolysis to synthesis of the corresponding "homo" alkaloids. For example, photolytic cyclization of the bromophenol (49) gave androcymbine (45) and multifloramine (50).

Chart 23



Finally, the spirodienone synthesis by photolytic cyclisation was also used in the

Chart 24

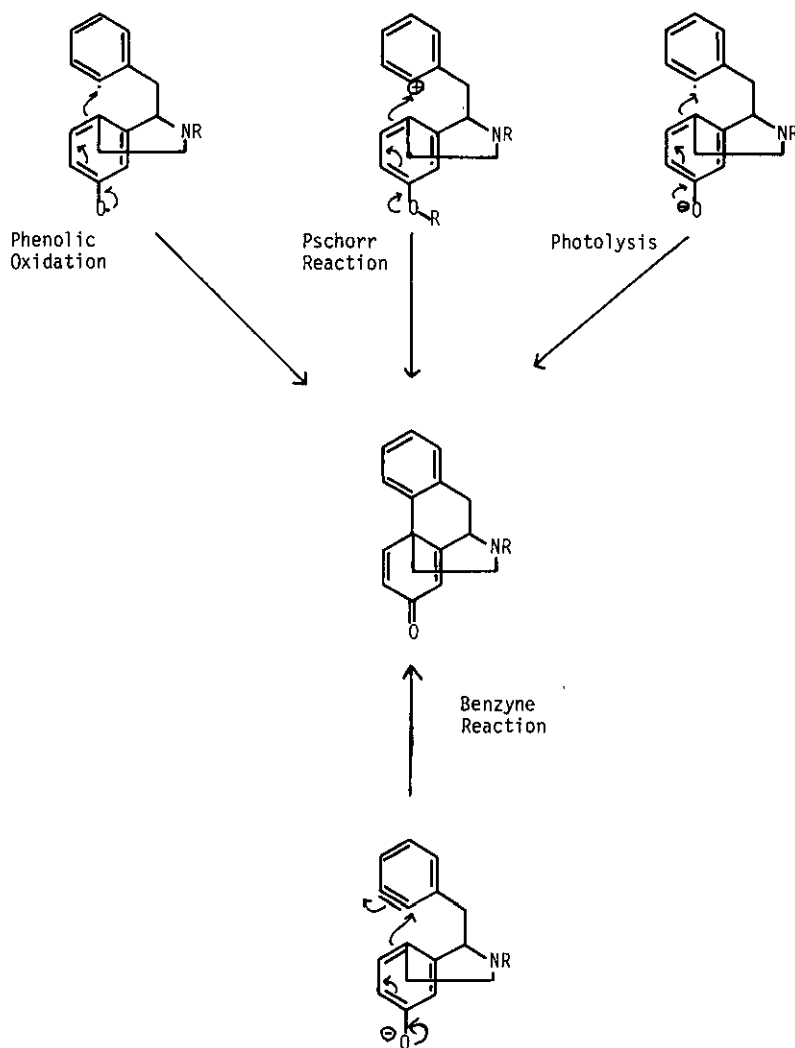


total synthesis of certain Amaryllidaceae alkaloids. Thus, irradiation of the phenolic bromoamine (51) afforded the enone (52), which had already been correlated to crinine (53). By a similar method, galanthamine (8) was obtained from the appropriate bromoamide.

#### 4 Benzyne and Nitrene Reactions

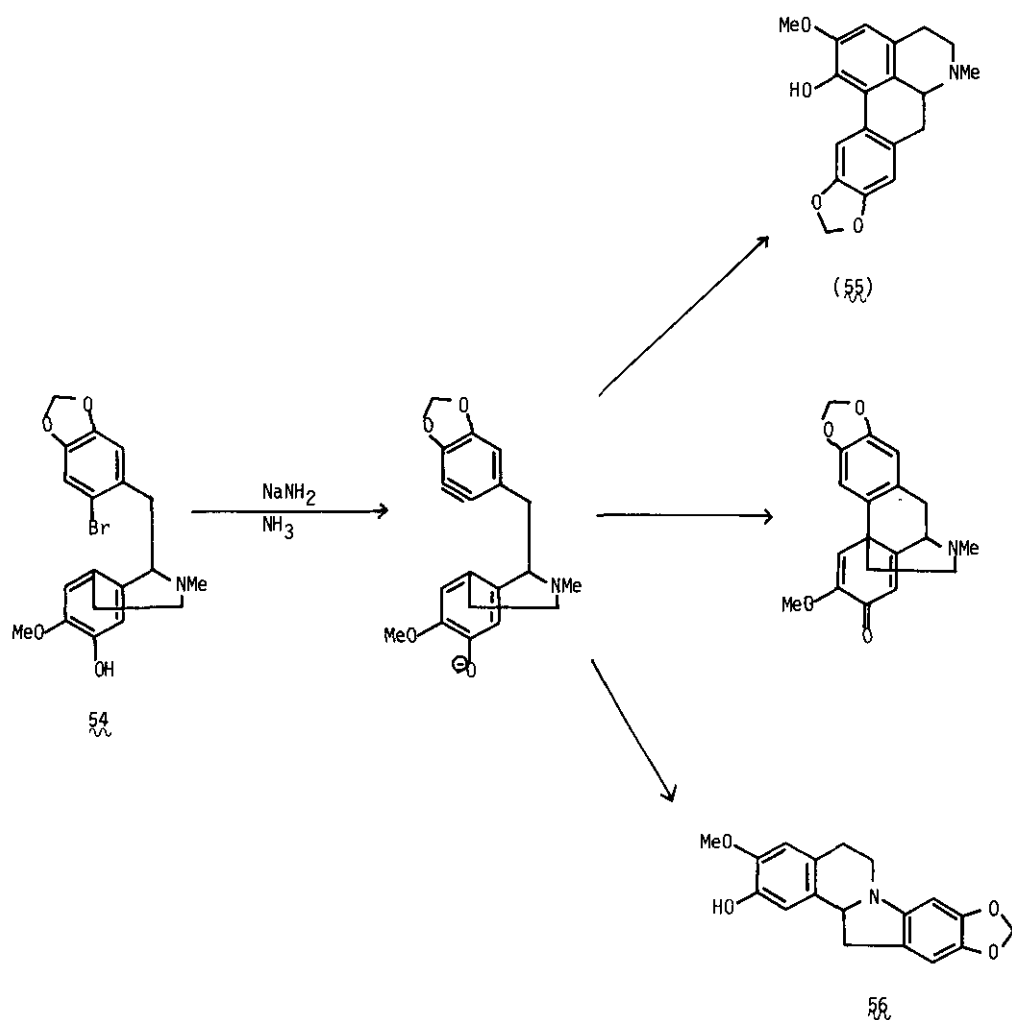
As a fourth approach to the total synthesis of isoquinoline alkaloids, Professor Kametani explored the utility of the benzyne reaction, which involves a mechanism in the substitution on an aromatic ring which is different from that in the ionic reaction in Pschorr synthesis and the radical reaction in phenolic oxidation and photolysis.

Chart 25



2'-Bromoisoquinoline (54) was treated with sodium amide in liquid ammonia to give domesticine (55), amurine (35) and cryptowoline (56). Proof that this type of reaction proceeded via a benzyne intermediate was provided by the observation of cine-substitution in the case of a 3'-bromoisoquinoline.

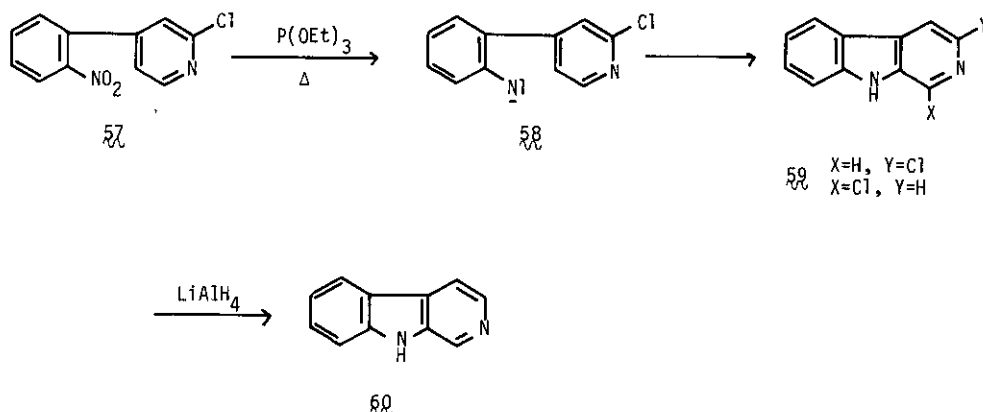
Chart 26



After the synthesis of natural products via benzyne, Professor Kametani achieved the total synthesis of indole alkaloids by using another unstable intermediate, nitrene [Heterocycles, **2**, 209 (1974)], which showed as high reactivity as found for benzyne. Thus, heating the nitro compound (57) in triethyl phosphite gave the

cyclisation products (59), via the nitrene (58), which were converted into the alkaloid harman (60).

Chart 27



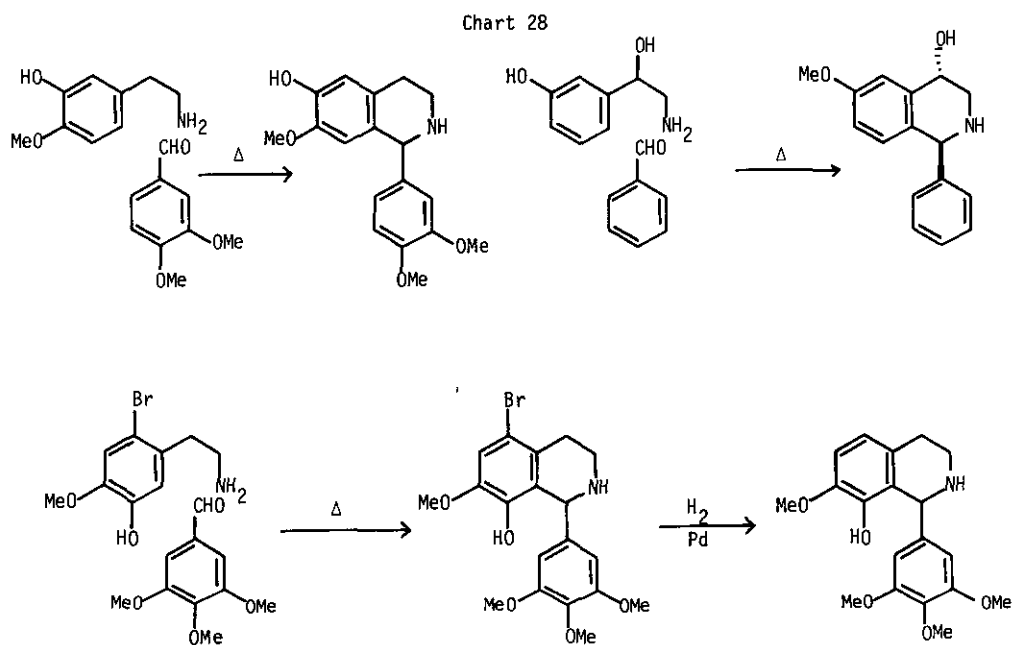
## 5 Phenolic Cyclisation

Many types of reaction are available for the preparation of the isoquinoline ring system, and the most important and widely used syntheses involve Bischler-Napieralski and Pictet-Spengler reactions. In these syntheses however, ring formation occurs usually in strong acidic media, and these methods can therefore not be applied for the synthesis of compounds sensitive to acid. Moreover, isoquinoline alkaloids could be biosynthesised by Pictet-Spengler type reaction from the phenolic phenethylamines and suitable aldehydes, but the ring formation in Nature occurs under milder conditions than the strong acidic conditions used in the laboratory. Professor Kametani investigated a general synthesis of the isoquinoline ring system from phenethylamines under mild conditions which corresponded to those of Nature.

In 1968, he developed a new synthetic reaction to form 1,2,3,4-tetrahydro-7-hydroxy-isoquinolines in neutral medium (without acid) from various 3-hydroxyphenethylamines and carbonyl compounds by a modification of the Pictet-Spengler reaction. He proposed that this type of non-acidic reaction be called "Phenolic Cyclisation", because the phenolic hydroxyl group in the phenethylamine apparently played an important role, with nonphenolic phenethylamines not affording any cyclisation products, i.e. isoquinolines [Heterocycles, **3**, 311 (1975)].

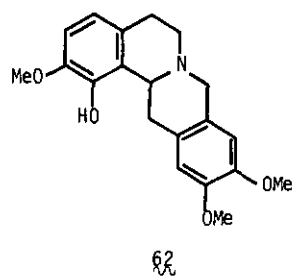
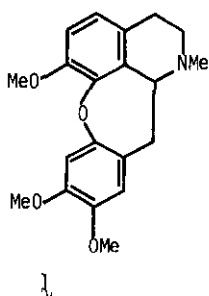
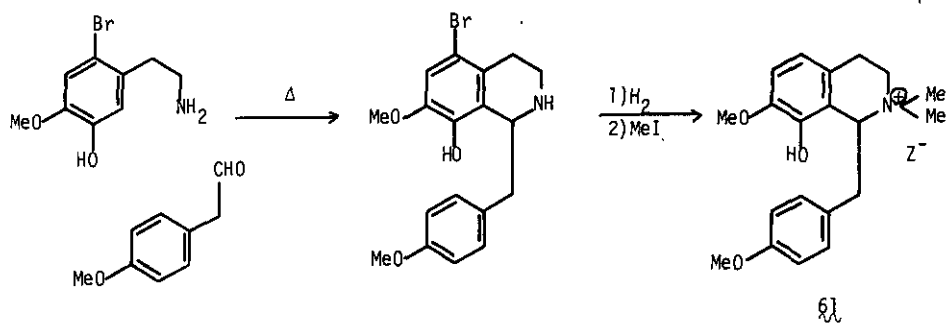
Later, he found that this cyclisation proceeded in basic medium, and also reported a simple synthesis of 4-hydroxylated isoquinolines which were difficult to prepare by the usual methods.

After developing a new and general synthesis of the isoquinoline nucleus he attempted to obtain the 7,8-dioxygenated isoquinolines by this method. He subjected the phenolic phenethylamines, whose para-cyclisation site was protected with a bromine atom, to phenolic cyclisation in order to get 7,8-dioxygenated isoquinolines. In this reaction, he presumed that cyclisation at the ortho-position to the hydroxyl group would proceed smoothly because the reactivity of the benzene ring was increased by the presence of the phenolic hydroxyl group in the amine. Some successful results are shown in the following chart.



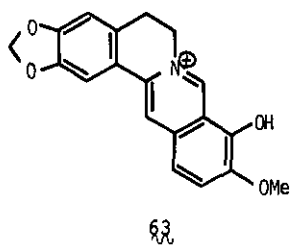
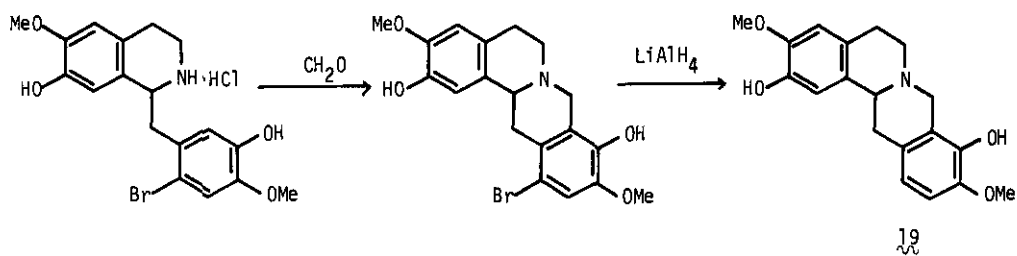
On the basis of the above knowledge, Professor Kametani attempted a synthesis of 7,8-dioxygenated isoquinoline alkaloids, and achieved a total synthesis of petaline (61) with phenolic cyclisation as the key reaction, and then cularine (1) and caseadine (62) by phenolic cyclisation and further reactions.

Chart 29



The same idea has been applied to the total synthesis of the 9,10-dioxygenated berbine alkaloids, scoulerine (19) and berberine (63), and moreover, Professor

Chart 30



Kametani has developed a synthetic reaction to 9,10-dioxygenated berbines under the conditions of controlled pH in the cyclisation step.

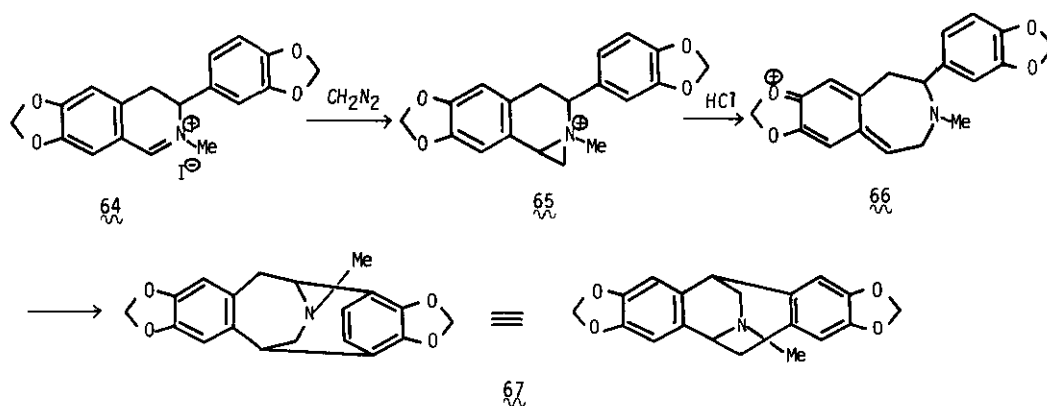
## 6 Ring Transformation — Ring Expansion and Contraction

### 6.1 Isopavine Synthesis

Ring expansion reaction is an effective method for the synthesis of seven-membered compounds from cyclohexane derivatives because the latter are readily available. Professor Kametani has developed a new type of isopavine synthesis by a ring expansion reaction involving a one-step ring opening and ring closure which resulted from application of the ring expansion method through the aziridinium intermediate formed by diazomethane-iminium insertion.

Treatment of the 3,4-dihydroisoquinolinium salt (64) with diazomethane afforded the aziridinium salt (65) which was treated with hydrochloric acid to give reframidine (67) through a transient quinonoid intermediate (66).

Chart 31



Although few isoquinolines have been prepared by this route, this novel method provides a general route to the isopavine alkaloids.

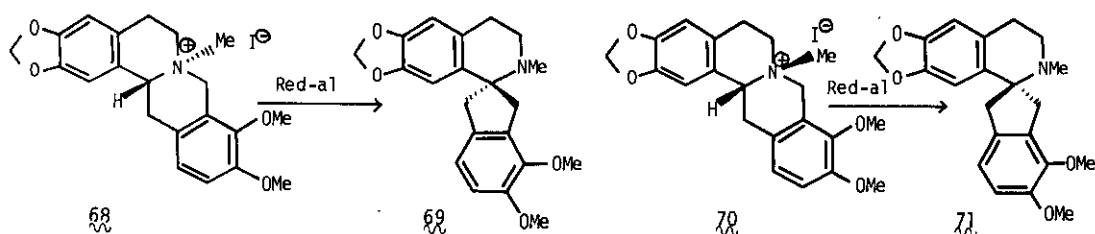
### 6.2 Ochotensane Synthesis

Ochotensine-type alkaloids could be biosynthesised from berbines although the exact route remains unclear. Many chemists have tried this type of conversion in the laboratory, but only Shamma has realised this step while others have given up in failure. Professor Kametani also examined the conversion of berbine into ocho-

tensanes and succeeded in finding two routes; one is a direct method and the other is the route through rheadan which is described in 6.3.

The route developed by Professor Kametani involves a Stevens rearrangement and has merit in that ochotensane could be obtained stereoselectively and that racemisation did not occur in this rearrangement. Thus Red-al treatment of the (+)-trans-berbine methiodide (68) gave the ochotensane (69), and the (+)-cis isomer (70) was converted into the ochotensane (71), a spiro-isomer of 69, by the same reaction.

Chart 32



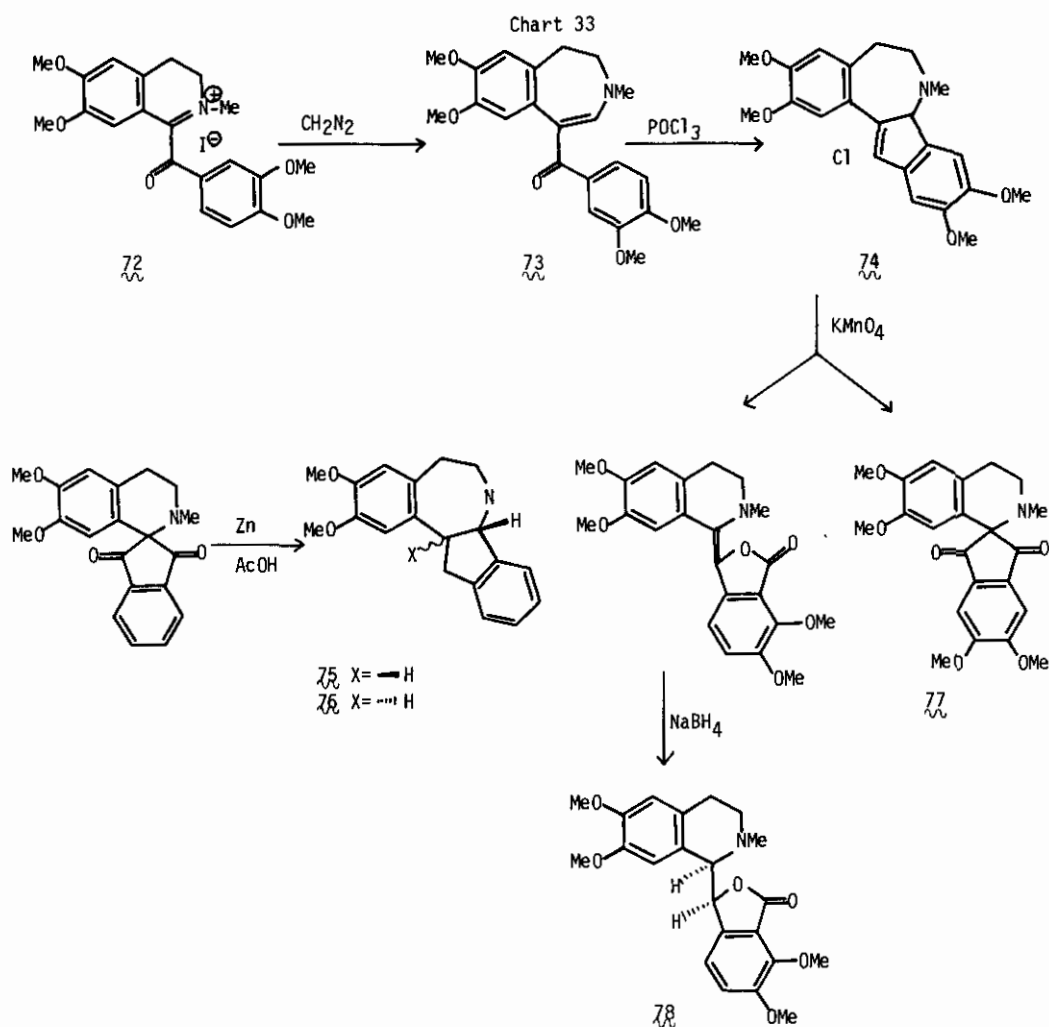
This is an effective route for the synthesis of ochotensine-type compounds because berbines are readily obtained by synthesis.

### 6.3 Rheadan Synthesis

Although rheadans have a benzazepine ring system, these alkaloids belong to the isoquinoline series as they are biosynthesised from 1-benzyltetrahydroisoquinolines via phthalideisoquinolines. On account of this, Professor Kametani has examined the conversion of benzylisoquinolines and phthalideisoquinolines into rheadans and has developed new synthetic routes to rheadans using a ring expansion method.

The first method is similar to the isopavine synthesis described above: insertion of carbene, derived from diazomethane, to the 1-benzoyl-3,4-dihydroisoquinolinium salt (72) gave the azepine derivative (73) which was converted into the rheadan (74). By this method, he synthesised many rheadan derivatives. The second is a one-step synthesis of rheadan from 1-spirobenzylisoquinoline by a dissolving metal reduction as shown for the formation of the benzindanoazepines (75 and 76).



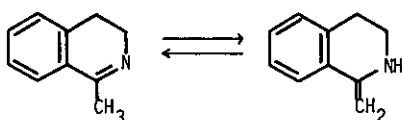


Furthermore, he transformed the rheadan (74) into the phthalideisoquinoline (78) and the spirobenzylisoquinoline (77), which corresponds to the reverse process of biogenesis of rheadan alkaloids.

### 7 Natural Product Synthesis via Enamines

It is well known that the  $\beta$ -carbon atom in an enamine system shows a strong affinity for an electron-poor center such as a carbonium cation or a benzyne system. Professor Kametani found in 1958 that 3,4-dihydro-1-methylisoquinolines behave as enamines, i.e. 1,2,3,4-tetrahydro-2-methyleneisoquinolines. In the mid 1970's, he achieved the total synthesis of some benzoquinolizidine natural products from 3,4-dihydro-1-methylisoquinolines by making use of this enamine character.

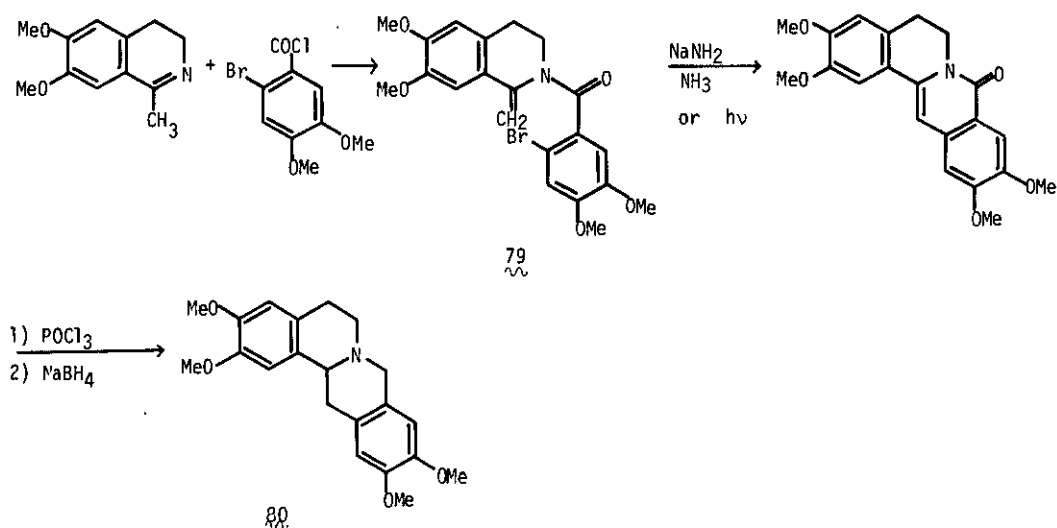
Chart 34



### 7.1. Protoberberine Synthesis

As 2'-bromobenzylisoquinolines readily generate a benzyne on treatment with sodium amide in liquid ammonia as described in Section 4, Professor Kametani assumed that reaction of 2-(2'-bromobenzoyl)-1-methyleneisoquinolines with sodium amide would give protoberberines via cyclisation, i.e. by reaction of the enamine moiety of the molecule with the benzyne system initially generated. On this assumption, the 2'-bromobenzoylisoquinoline (79) was treated with sodium amide, and he obtained the expected xylopinine (80) in good yield as shown in the following chart. Moreover, he investigated a synthesis of berbines by photolysis of 79 and found the same result as in the case of benzyne reaction. By these methods, many kinds of berbine were synthesised.

Chart 35

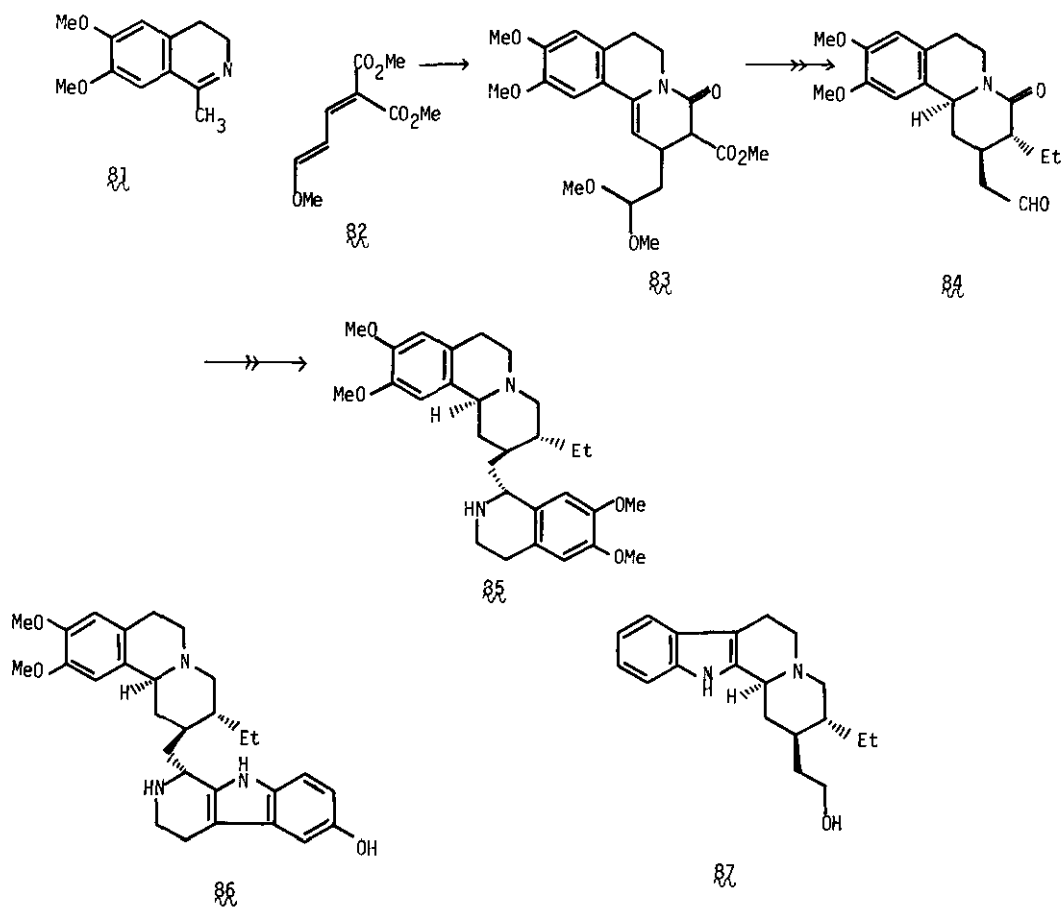


During the above synthesis he developed a new method for the reduction of an amide to an amine in which the former was treated with phosphorous oxychloride, followed by sodium borohydride reduction of the resulting chloride.

### 7.2 Ipecac Alkaloid Synthesis

Professor Kametani has found an enamine annelation whereby 3,4-dihydro-1-methylisoquinolines are converted to benzo[a]quinolizines by Michael addition to  $\alpha,\beta$ -unsaturated esters, and has synthesised emetine (85) by use of this reaction. Thus, reaction of the 3,4-dihydro-1-methylisoquinoline (81) with the ester (82) gave, in one step, the enamide (83) which was stereoselectively converted into the aldehyde (84). This was subjected to Pictet-Spengler reaction with homoveratrylamine to give

Chart 36



emetine (85). I believe this to be the shortest route to emetine. In the same way, tubulosine (86) and dihydrocorynantheol (87) were synthesised stereoselectively. The key intermediate for a total synthesis of camptothecin (25) was also prepared from 3,4-dihydro- $\beta$ -carboline by enamine annelation.

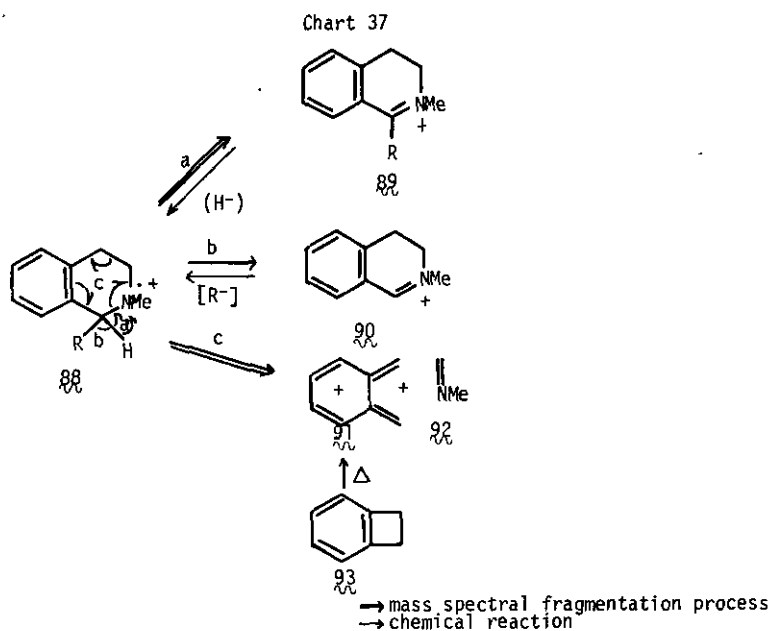
#### 8 Retro Mass Spectral Synthesis

In 1974, Professor Kametani proposed a new and effective synthetic design that he called "Retro Mass Spectral Synthesis" [Accounts Chem. Res., 9, 319 (1976)]. This analysis is based on fragmentation processes in mass spectrometry, and he has synthesised many kinds of natural products along the routes determined by this method. He discovered this analysis for the design of a synthetic route from the following assumption. Since fragmentation in the mass spectrometer is a chemical process that results in bond breaking, fragmentation of a compound is sometimes very similar to chemical degradation reaction. For example, cyclohexene produces butadiene ion radical and ethylene in its fragmentation, a process which is also observed in chemical reaction. On the other hand, cyclohexenes can be obtained from butadienes and ethylene derivatives by Diels-Alder reaction. These facts indicate that some mass spectral fragmentations parallel chemical degradation processes and therefore also parallel retroprocesses of synthetic reactions of organic compounds. To determine whether this analysis could be used as a synthetic design, he firstly examined a simple compound.

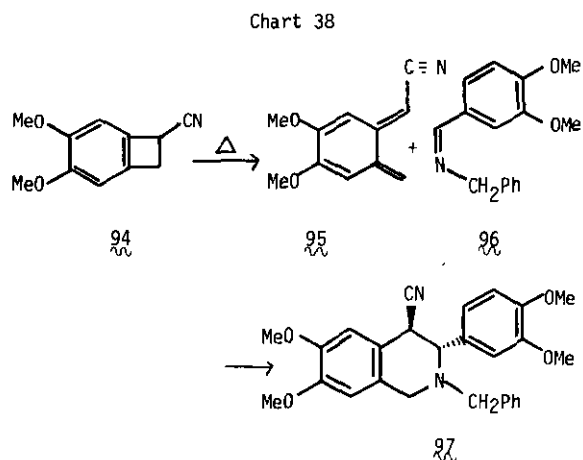
In the mass spectra of a series of 1-monosubstituted 1,2,3,4-tetrahydro-2-methyl-isoquinolines (88), fragment ions (89 and 90) formed by loss of the C-1 substituent or C-1 hydrogen are observed, in addition to an  $M^+ - 43$  ion (91) derived by retro-Diels-Alder reaction of 88.

Reduction of 1-substituted 3,4-dihydroisoquinolines (89) is the most common method for the synthesis of 1-monosubstituted 1,2,3,4-tetrahydroisoquinoline derivatives (88). Another method is the alkylation of 1-unsubstituted 3,4-dihydroisoquinoline (90) with Grignard reagents.

On comparison of these syntheses with the mass spectra of isoquinolines, it is seen that the reduction method corresponds to a retrograde of the formation of the 3,4-dihydroisoquinolinium ion 89 from the molecular ion 88, and the alkylation method to a retrograde of the formation of ion 90 from 88 in its mass spectrum. These phenomena suggested that the fragmentation processes in the mass spectrometer indicate an effective method of retrosynthesis and that their observation might also lead to useful synthetic routes to target compounds.



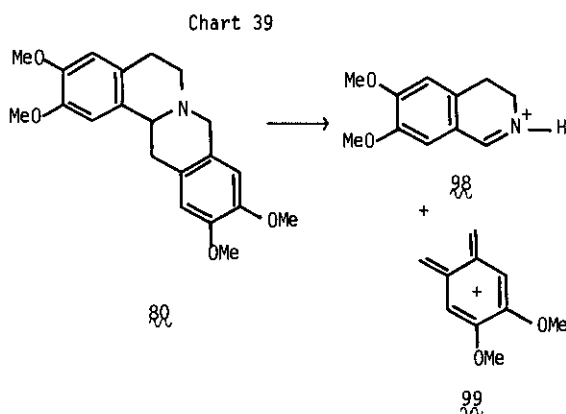
Professor Kametani therefore examined a synthesis of 1,2,3,4-tetrahydroisoquinoline from the compounds which correspond to the ion 91 and the fragment 92 formed by retro-Diels-Alder reaction of the molecular ion. He selected the benzocyclobutene 94 as



the chemical equivalent of ion 91, because benzocyclobutene 93 readily produces *o*-quinodimethane 91 on heating. Reaction of 94 with the Schiff base 96, the synthon corresponding to ion 92, at 150 - 160°, afforded the 1,2,3,4-tetrahydroisoquinoline 97 in both regio- and stereospecific manner by cycloaddition of the *o*-quinodimethane 95 to the Schiff base. Thus, he succeeded in developing a new synthesis of 1,2,3,4-tetrahydroisoquinolines by applying Retro Mass Spectral Synthetic Analysis.

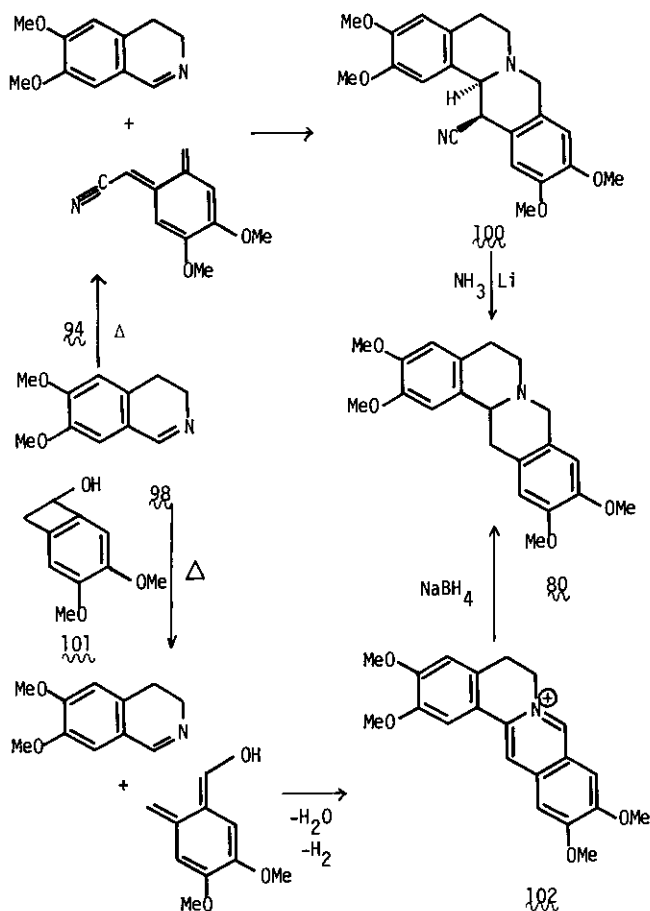
#### 8.1 Protoberberine Alkaloid Synthesis

The mass spectrum of xylopinine (80) shows an ion 99 having an *o*-quinodimethane system, together with a 3,4-dihydroisoquinolinium ion (98). This fragmentation process suggested that a combination of synthons corresponding to these two ions (98 and 99) would produce xylopinine (80) by Retro Mass Spectral Synthesis.



On the basis of this consideration, Professor Kametani examined the total synthesis of xylopinine using 1-cyano- and 1-hydroxybenzocyclobutenes as shown in the following chart.

Chart 40

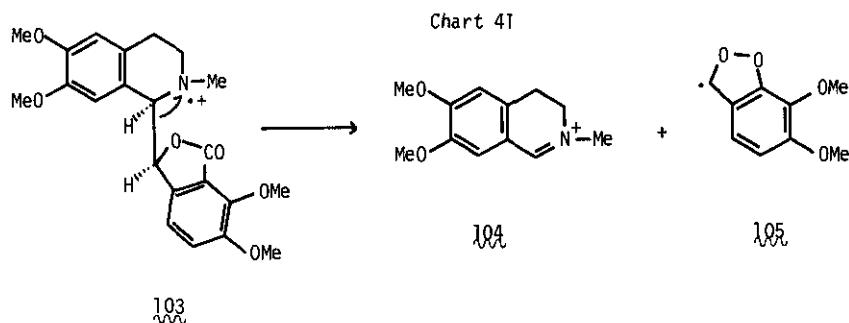


Heating 1-cyanobenzocyclobutene (94) with the 3,4-dihydroisoquinoline (98) at 150 - 160° gave 13-cyanoprotoberberine (100). Reductive decyanation with lithium in liquid ammonia afforded xylopinine (80). Similarly, a mixture of the benzocyclobutenol (101) and 98 was heated to give the expected protoberberine (102), which was reduced with sodium borohydride to afford xylopinine (80).

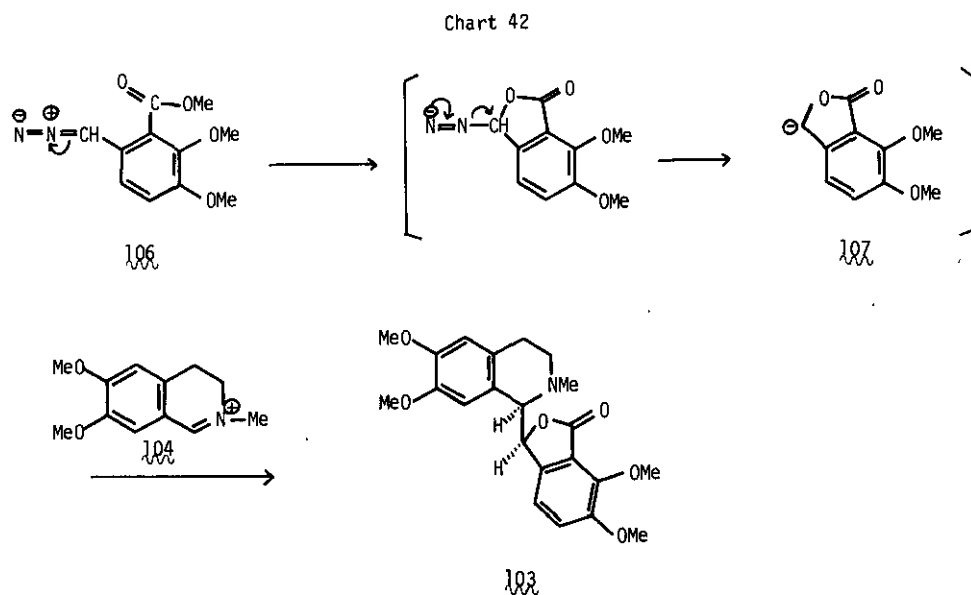
This method provided a new and convenient synthetic route to protoberberine alkaloids and has merit in that it can be used to prepare easily the berbines which could not be obtained by the usual methods.

## 8.2 Phthalideisoquinoline Alkaloid Synthesis

The base peak in the mass spectrum of cordrastine (103) is assigned to ion 104. The partner ion of 104 is the phthalide radical (105).



In the case of Retro Mass Spectral Synthesis of this type of alkaloid, Professor Kametani used methyl 6-diazomethyl-2,3-dimethoxybenzoate (106) as the chemical equivalent of the phthalide radical (105), because the 6-diazomethyl compound readily generates a reactive ion (107) which has a similar structure to that of 105. Treatment of the 6-diazomethyl compound (106) with 3,4-dihydro-6,7-dimethoxy-2-methylisoquinolinium iodide (104) in methanol-chloroform solution gave cordrastine (103) stereoselectively. Hydrastine was obtained by the same method. Thus, he developed a simple synthetic method for phthalideisoquinoline alkaloids.

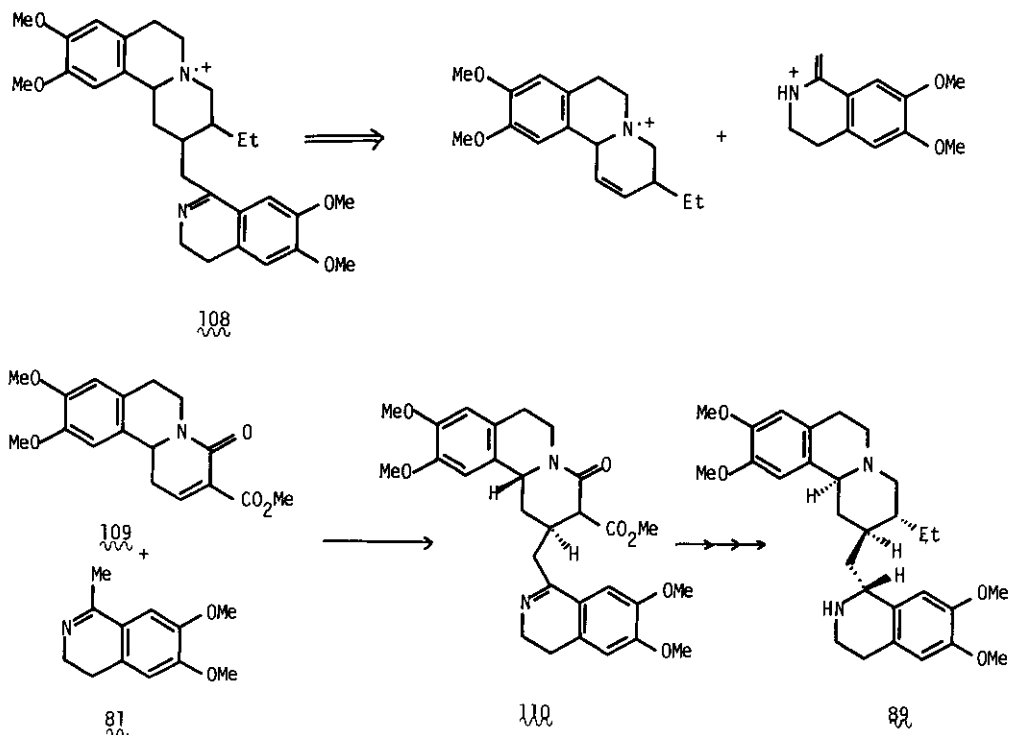




### 9.3 Emetine Synthesis

Retro Mass Spectral Synthesis has also been applied to develop a practical and efficient route to the ipecac alkaloid emetine (85). It had been observed that the main mass spectral fragmentation process for the emetine base (108) is as shown in the following chart.

Chart 43



Professor Kametani therefore assumed that utilisation of the feasible synthetic equivalents of these mass spectral fragments, the  $\alpha,\beta$ -unsaturated ester (109) and the 3,4-dihydro-1-methylisoquinoline (81), in a Michael reaction would enable a synthesis of emetine via the Retro Mass Spectral adduct (110). With this then as the key step, a synthesis of emetine was undertaken as follows.

The  $\alpha,\beta$ -unsaturated ester (109) was treated with 3,4-dihydro-1-methylisoquinoline (81) in dry methanol to give stereoselectively the adduct (110) as a single product, which was transformed into emetine (85) by ethylation, decarboxylation, reduction and epimerisation.

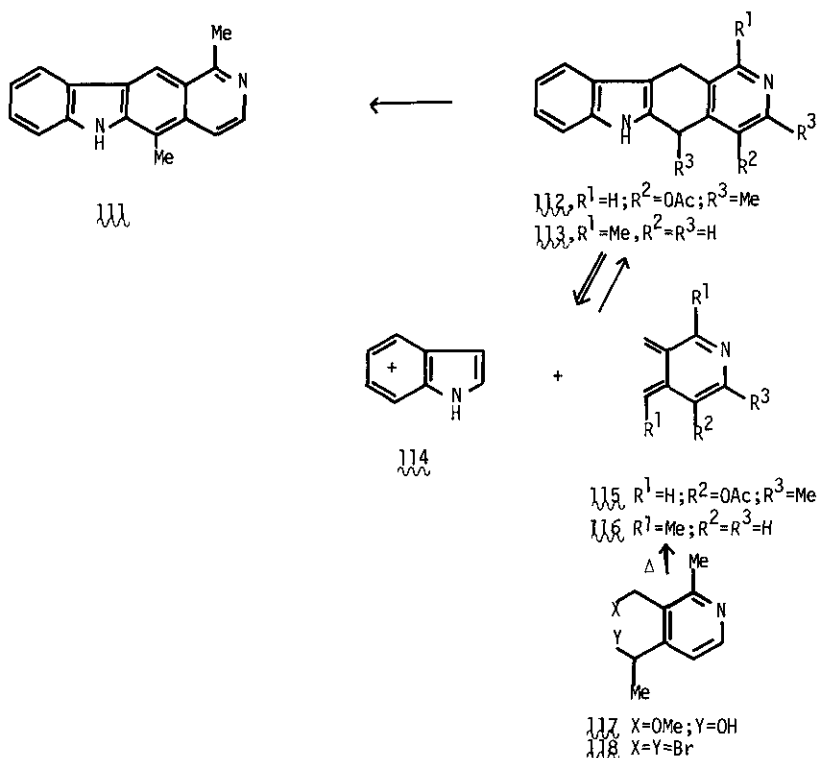
Thus the Retro Mass Spectral Method provided a simple and efficient route for the synthesis of emetine and related alkaloids.

#### 8.4 Olivacine Synthesis

The mass spectrum of olivacine (111) shows no characteristic ions other than the molecular ion. However, the dihydropyridocarbazole (112) reveals two ions (114) and (115) formed by opening of ring C. Professor Kametani thought that dihydro-olivacine (113) would generate an indole ion (114) and an analogous *o*-quinodimethane-pyridine ion (116) in its mass fragmentation process. Therefore, olivacine synthesis from indole (114) and the dibromomethylpyridine (118), which is a chemical equivalent of the *o*-quinodimethane-pyridine (116), was examined.

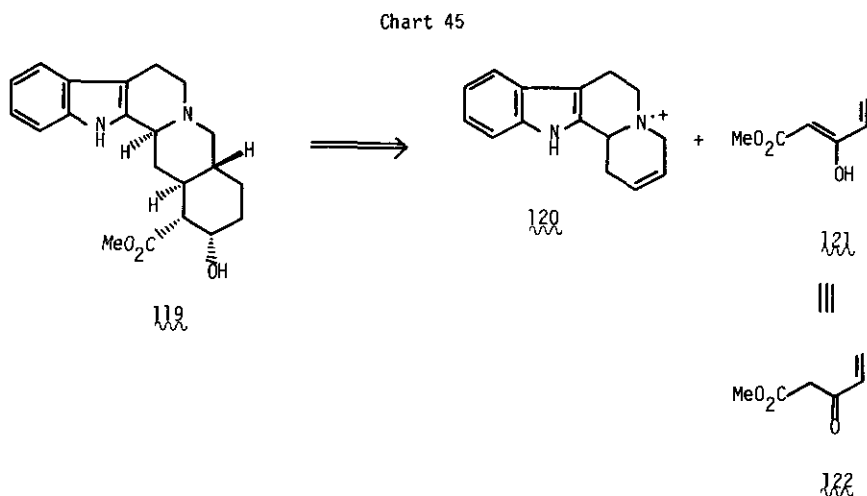
Refluxing 4-(1-hydroxyethyl)-3-methoxymethyl-2-methylpyridine (117) in 47 % hydrobromic acid gave the corresponding dibromide (118), which was condensed with indole by heating to afford olivacine (111) in one step.

Chart 44



8.5 Yohimbine Synthesis

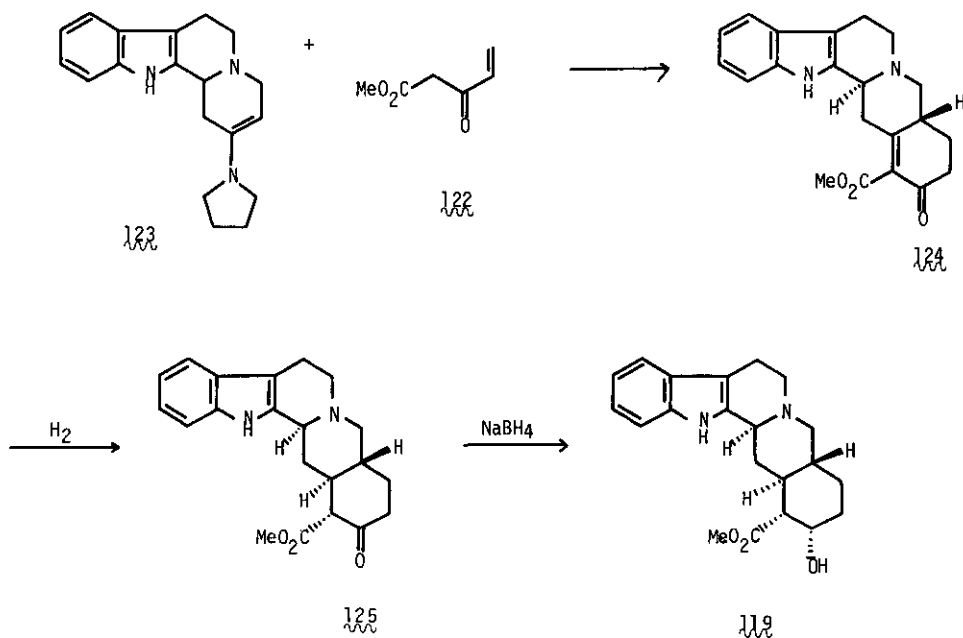
Professor Kametani examined a total synthesis of yohimbine (119) along the route designed by Retro Mass Spectral Analysis. A characteristic ion (120) in the mass spectrum of yohimbine is formed by cleavage of ring E. The partner of ion 120 is the hypothetical ion 121.



A Retro Mass Spectral Synthesis would employ the enamine (123) and methyl 3-oxo-4-pentenoate (122), which are chemical equivalents of, or synthons for, ions 120 and 121.

Reaction of the pyrrolidine enamine (123) of indolo[2,3-*a*]quinolizin-2-one with methyl 3-oxo-4-pentenoate (122) gave 15,16-dehydroyohimbinone (124). Catalytic hydrogenation of 124 on 30 % palladium on carbon gave (±)-yohimbinone (125), which was converted into (±)-yohimbine (119) in addition to β-yohimbine by sodium borohydride reduction. Thus, a total synthesis of (±)-yohimbine (119) was accomplished along the Retro Mass Spectral route.

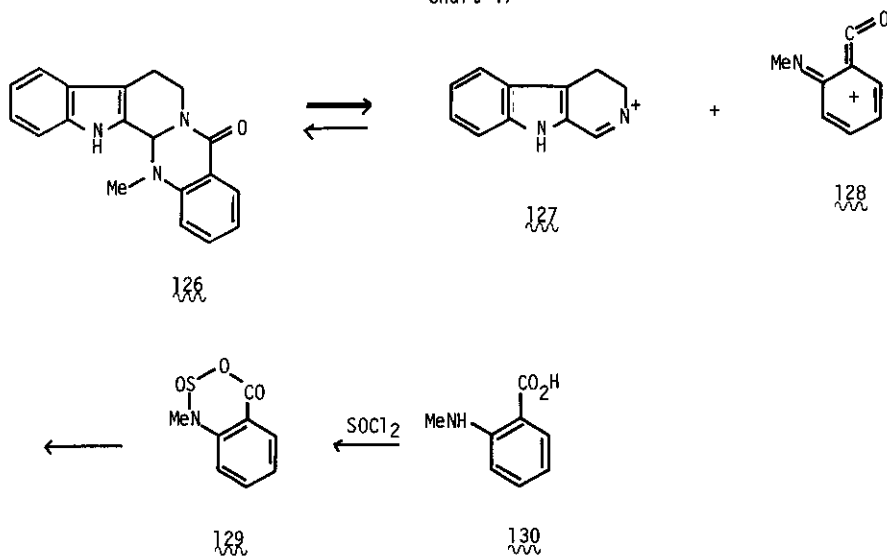
Chart 46



### 8.6 Quinazolinone Alkaloid Synthesis

Evodiamine (**126**), a typical member of the quinazolinocarboline alkaloids, showed

Chart 47



two characteristic ions in its mass spectrum, (127) and (128), formed by retro-Diels-Alder reaction of ring D. This behaviour indicates that evodiamine (126) could be synthesised from 3,4-dihydro- $\beta$ -carboline (127) and the iminoketene (128). Firstly, Professor Kametani investigated a method for generation of the unstable intermediate iminoketene (128) and found 128 to be generated in situ from the sulfinamide anhydride (129) obtained by reaction of N-methylantranilic acid (130) with thionyl chloride. On this finding, he attempted a synthesis of evodiamine (126) as follows.

Heating N-methylantranilic acid (130) with thionyl chloride produced an unstable sulfinamide anhydride (129), which was treated with 3,4-dihydro- $\beta$ -carboline (127) in dry benzene at room temperature to afford evodiamine (126) regioselectively. In this reaction, the sulfinamide anhydride (129) was converted into the iminoketene (128), which reacted regioselectively with 3,4-dihydro- $\beta$ -carboline (127) by cycloaddition to form evodiamine.

By similar methods, Professor Kametani has synthesised many quinazalone and quinazolinocarboline alkaloids.

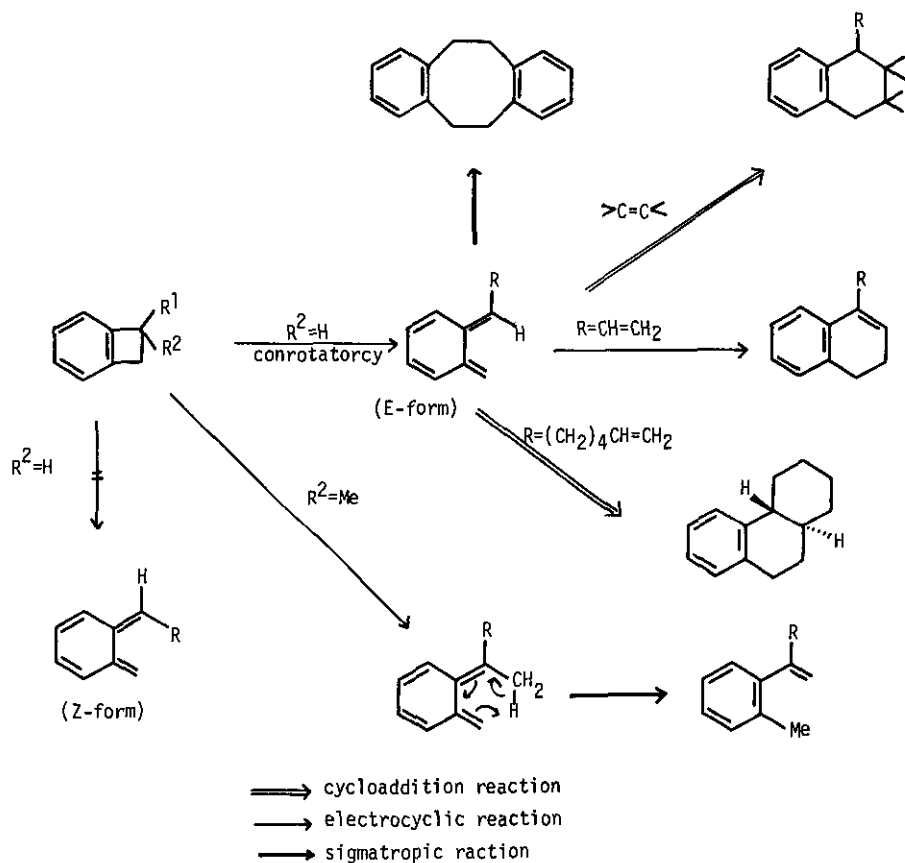
#### 8.7 Miscellaneous

In addition to the work described above, the Retro Mass Spectral Method has been applied to the synthesis of a wide range of compounds in which the key reaction is the thermolysis of a benzocyclobutene, as already mentioned in the synthesis of xylopinine (8.1). As Professor Kametani has energetically investigated the total synthesis of natural products via benzocyclobutene thermolysis, I would like to describe this Retro Mass Spectral Synthesis work, e.g. synthesis of steroids, yohimbanes, and ochotensanes, under a separate heading.

### 10 Thermolysis of Benzocyclobutenes — Electrocyclic and Cycloaddition Reactions

In his research work on Retro Mass Spectral Synthesis, Professor Kametani has used benzocyclobutenes as the synthetic equivalents of some kind of chemical species in the key step of natural product total synthesis, e.g. as described in xylopinine synthesis. He also investigated the chemical behaviour of benzocyclobutenes, and found that o-quinodimethanes, derived from benzocyclobutenes by heating, proceeded to react in a regio- and stereoselective manner via three types of pericyclic reaction as shown in the following chart. Among these reactions, he has employed cycloaddition and electrocyclic reactions in the key steps of the total synthesis of natural products as follows.

Chart 48

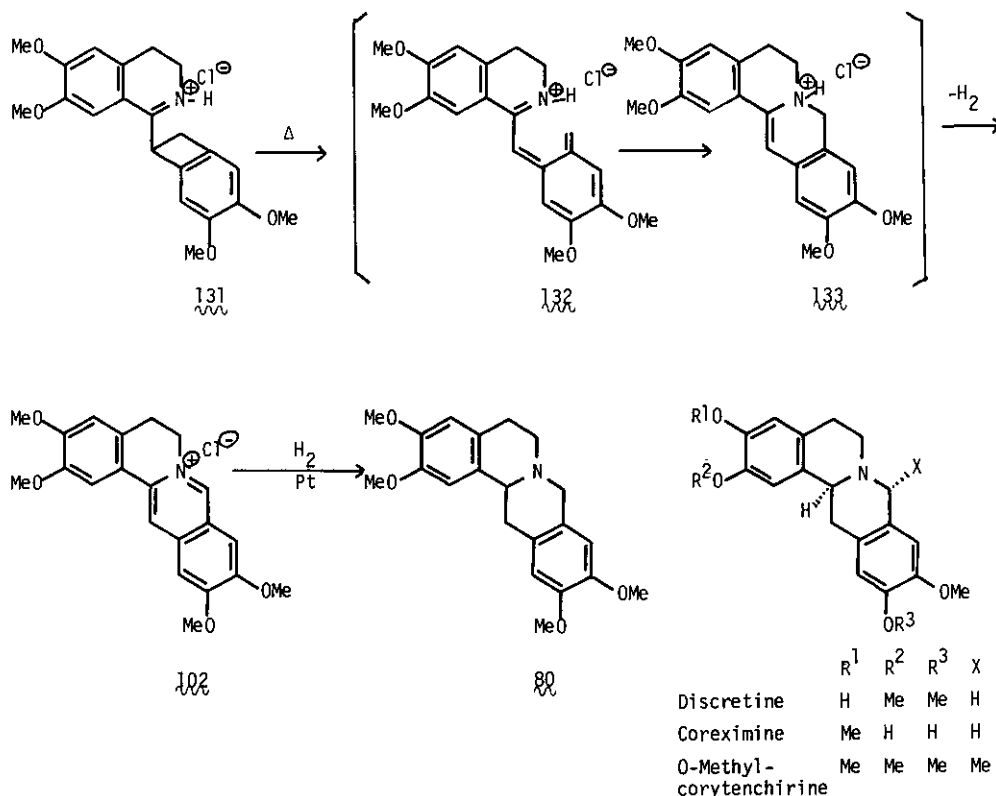


### 9.1.1. Protoberberine Synthesis

Since *o*-quinodimethanes can readily form cyclisation products by electrocyclic reaction as shown in the above chart, Professor Kametani firstly investigated protoberberine synthesis by this reaction.

Thermolysis of the 1-benzocyclobutenyl-3,4-dihydroisoquinoline hydrochloride (131) at 160 - 180° gave in good yield the protoberberine (102) via electrocyclic reaction of the initially formed *o*-quinodimethane (132) followed by dehydrogenation of the cyclised product (133). Hydrogenation of 102 in the usual manner afforded xylopinine (80). He synthesised discretine, coreximine and *O*-methylcorytenchirine in the same way. This route provided a general method for the synthesis of protoberberine alkaloids.

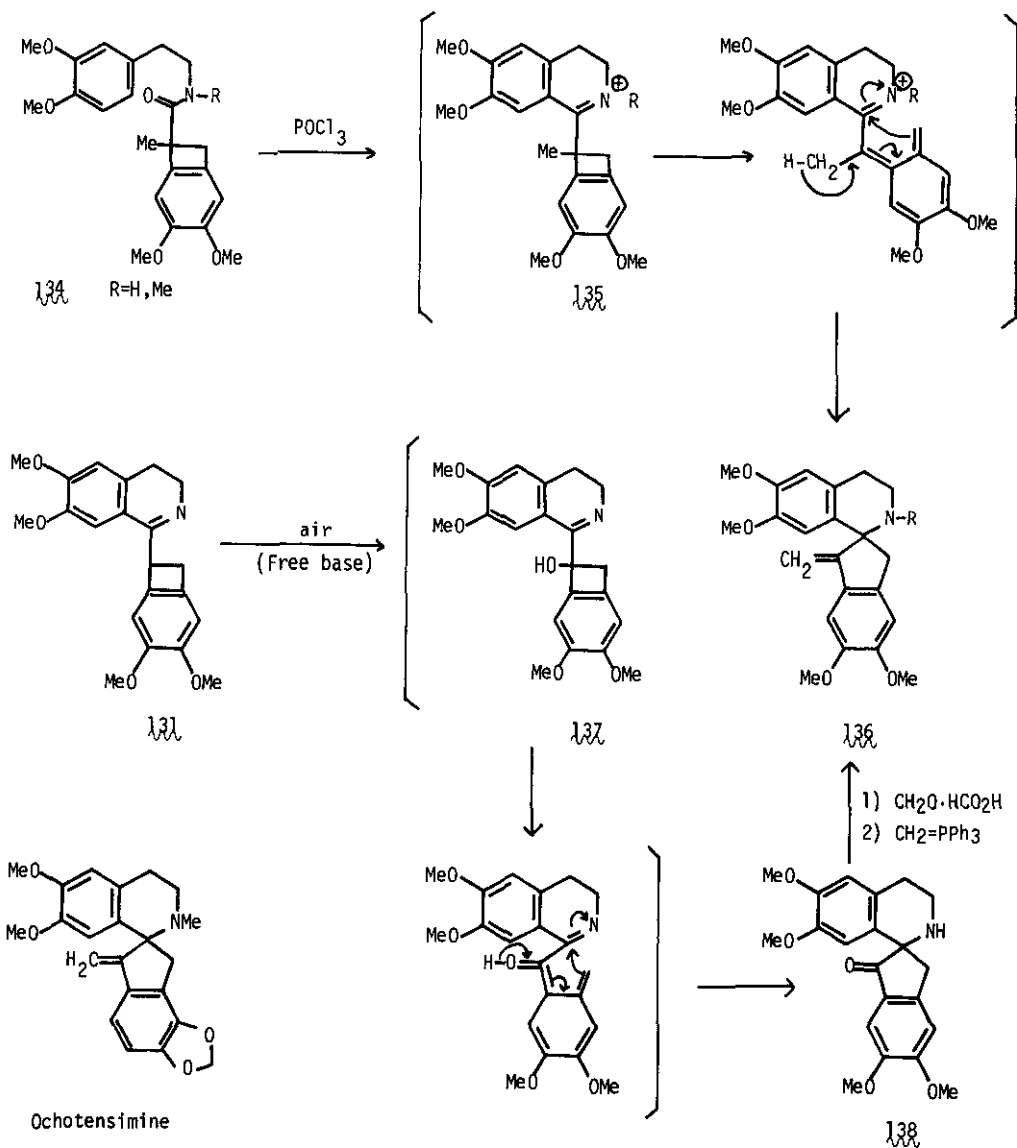
Chart 49



### 9.2. Spirobenzylisoquinoline Synthesis

In connection with protoberberine synthesis, Professor Kametani achieved a novel synthesis of spirobenzylisoquinolines. It was surprising that Bischler-Napieralski reaction of the amide (134) with phosphoryl chloride in refluxing benzene did not provide the expected 3,4-dihydroisoquinolinium salt (135). Instead, he obtained the spirobenzylisoquinoline (136), formed by the route shown in the following chart. Professor Kametani also observed the interesting fact that while the hydrochloride of the 1-benzocyclobutenyl-3,4-dihydroisoquinoline (131) is stable at room temperature, the free base is unstable in air. The free base (131) on standing in chloroform solution at room temperature was transformed into the ketospirobenzylisoquinoline (138) through the hydroxylated compound (137). He thus achieved a new synthesis of ochotensane-type compounds.

Chart 50



This work provided a more direct route to the ochotensimine-type alkaloids than the stepwise procedure theretofore reported.

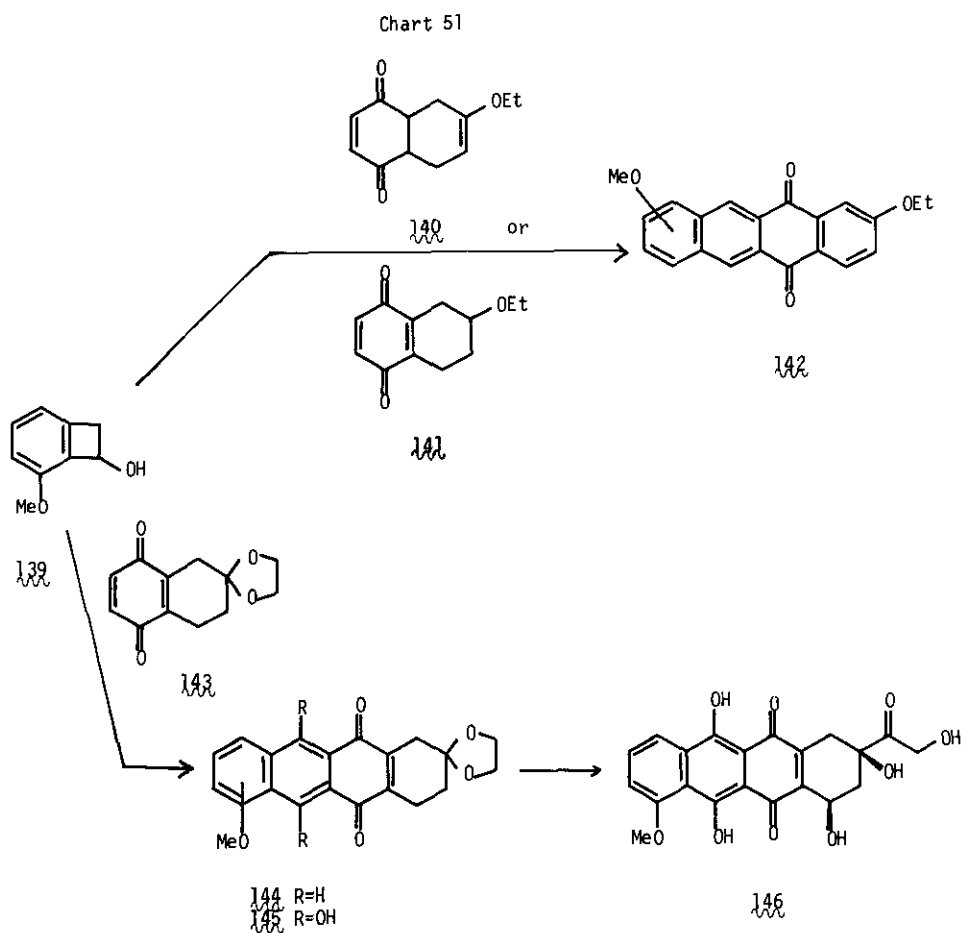
### 9.3. Tetracycline Synthesis

It is well known that naphthoquinones are effective dienophiles, and Professor Kametani therefore set out to develop a new and simple method for the synthesis of



tetracycline-type compounds, based on intermolecular cycloaddition reaction between *o*-quinodimethanes and naphthoquinones, and also investigated the total synthesis of adriamycinone (146).

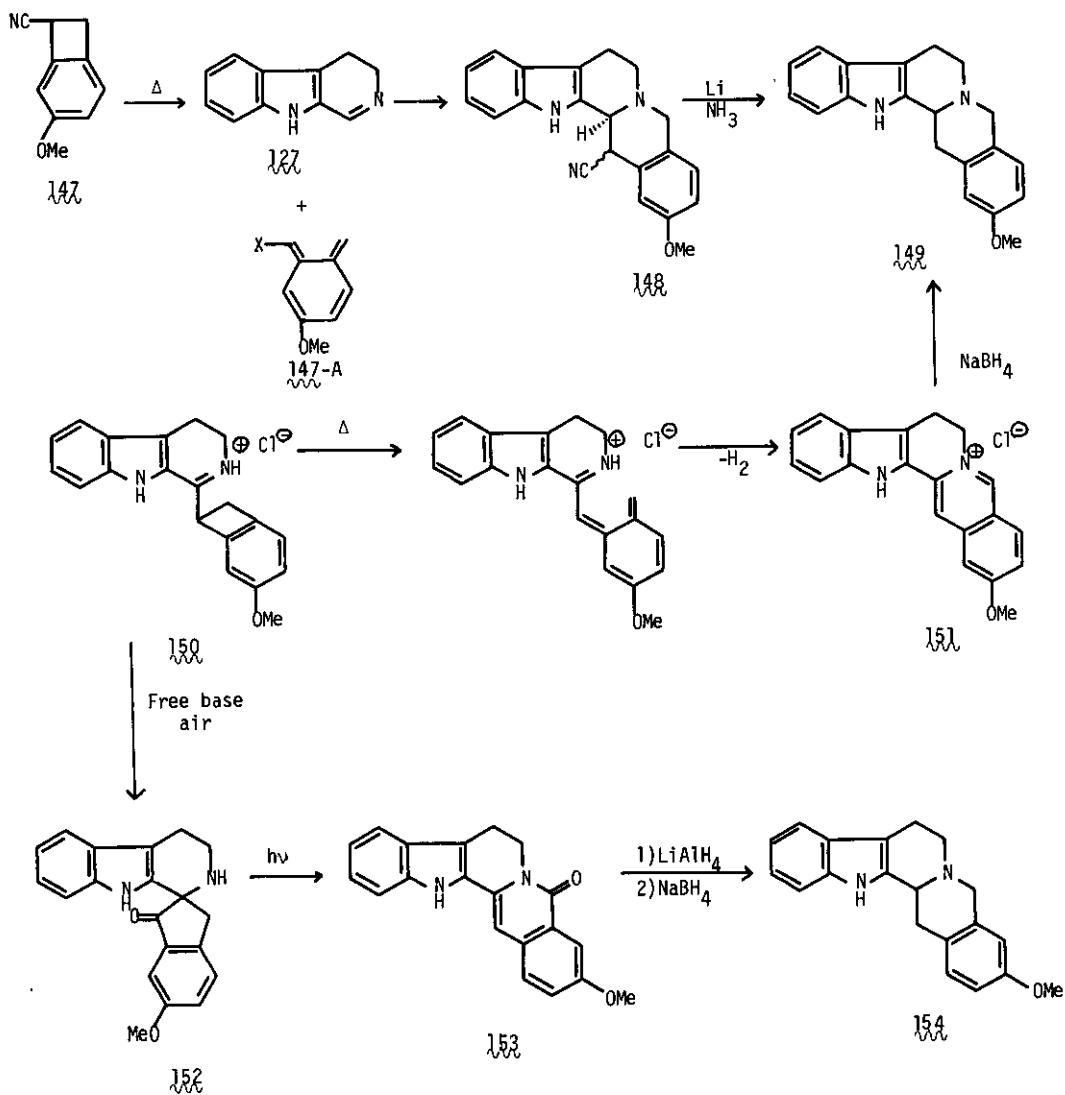
Reaction of 6-ethoxy-5,8,9,10-tetrahydronaphthoquinone (140) with 6-methoxycyclobutenol (139) at 150 - 160° afforded the tetracyclic compound (142), which was also obtained by treatment of the benzocyclobutenol (139) with 6-ethoxynaphthoquinone (141). Similarly, the benzocyclobutenol (139) was converted into the tetracyclic compound (144) by reaction with the quinone (143). This product can be considered to be a potential synthetic precursor to adriamycinone (146), because the related 6,11-dihydroxylated compound (145) has been converted into adriamycinone.



#### 9.4 Yohimbine Synthesis

On the basis of successful synthesis of protoberberine-type compounds from benzocyclobutenes by electrocyclic reaction and by intermolecular cycloaddition reaction (described in Retro Mass Spectral Synthesis), Professor Kametani assumed that the yohimbones, e.g. (157) possible intermediates to yohimbine (119), could be obtained

Chart 52



by reaction of the appropriate *o*-quinodimethanes with 3,4-dihydro- $\beta$ -carboline (127). He firstly investigated yohimbone synthesis as follows. Intermolecular cycloaddition between 1-cyanobenzocyclobutene (147) and 3,4-dihydro- $\beta$ -carboline (127) was effected at 150 - 160° to give regioselectively the 14-cyano-hexadehydroyohimbane (148), which was decyanated by treatment with metallic lithium in liquid ammonia in the presence of isopropyl alcohol to afford the hexadehydroyohimbane (149). This synthesis falls into the category of Retro Mass Spectral Synthesis, because the yohimbane (149) shows the two ions 127 and 147-A (X=H) in its mass spectrum.

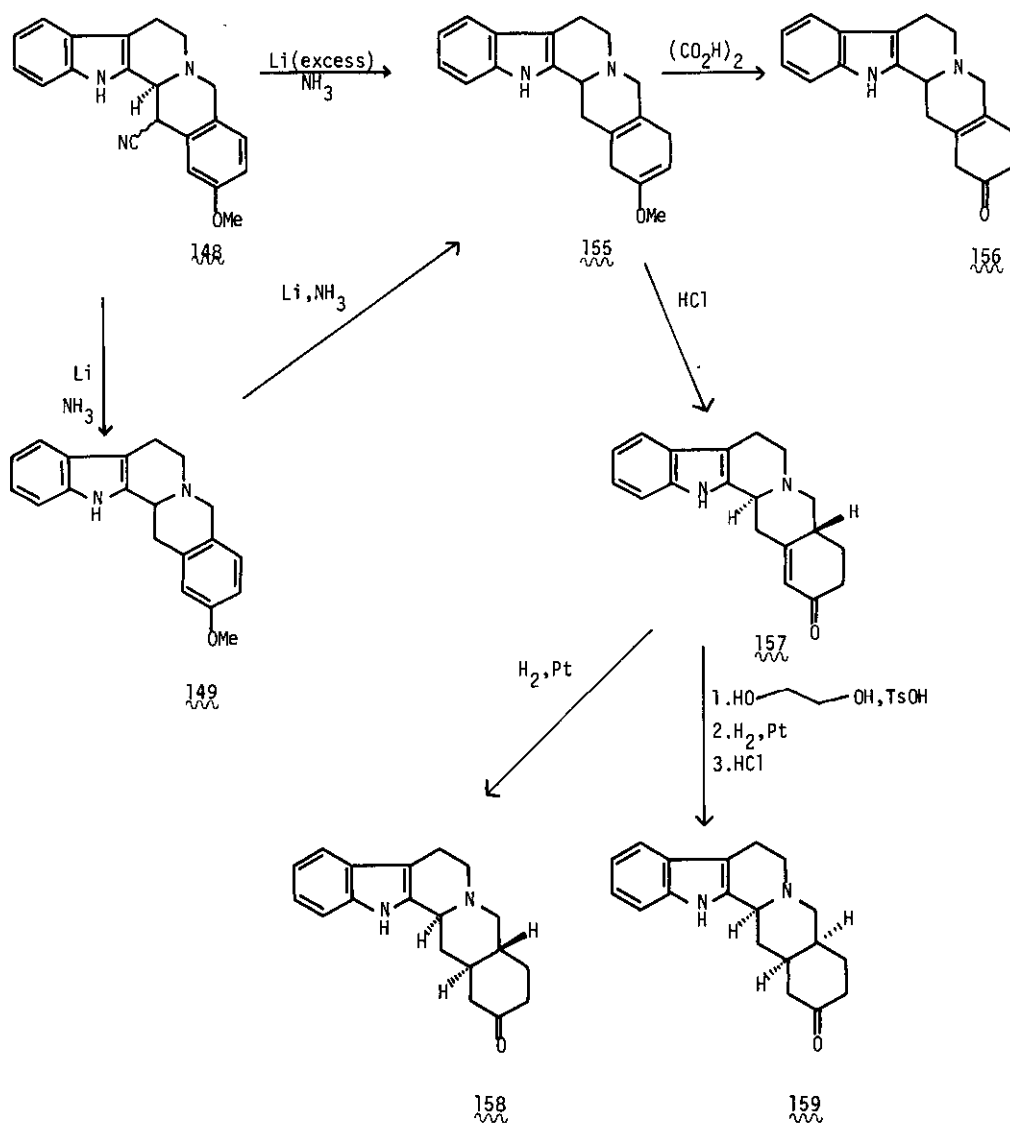
Moreover, thermolysis of 1-benzocyclobutenyl-3,4-dihydrocarboline (150) hydrochloride at 155° gave the expected decadehydroyohimbane (151) which was reduced with sodium borohydride to give the hexadehydroyohimbane (149).

In addition, Professor Kametani synthesised another type of hexadehydroyohimbane (154), differing only in the position of the methoxyl substituent, by utilising the difference in reactivities of the free base and the hydrochloride. Thus, the free base, the 1-benzocyclobutenyl-3,4-dihydrocarboline (150), rearranged on standing in chloroform at room temperature to the ketospirobenzyl- $\beta$ -carboline (152). Irradiation of this product in dry tetrahydrofuran at room temperature gave the lactam (153) which had already been converted into 18-methoxyyohimbane (154).

It is interesting to note that the same starting material gave rise to two yohimbanes which are positional isomers, as shown in the above chart.

Birch reduction of the hexadehydroyohimbane (149) with the lithium in liquid ammonia-isopropyl alcohol system gave the enol ether (155). The same enol ether was obtained by reduction of 14-cyanoyohimbane (148) with a large excess of lithium in liquid ammonia and isopropyl alcohol. Finally, treatment of the enol ether with oxalic acid gave the  $\beta,\gamma$ -unsaturated dehydroyohimbone (156), while reaction with hydrochloric acid by Swan's method afforded the dehydroyohimbone (157), which had already been converted into 158 and 159 as shown in the following chart. These methods would be particularly useful for the synthesis of yohimbanes and yohimbones with an electron-withdrawing group on ring E. This type of compound can not be obtained by the usual Mannich reaction of 1-benzyl-1,2,3,4-tetrahydro- $\beta$ -carboline with formalin, but in Professor Kametani's synthesis the key starting materials already have the "berberine bridge carbon" in the molecule.

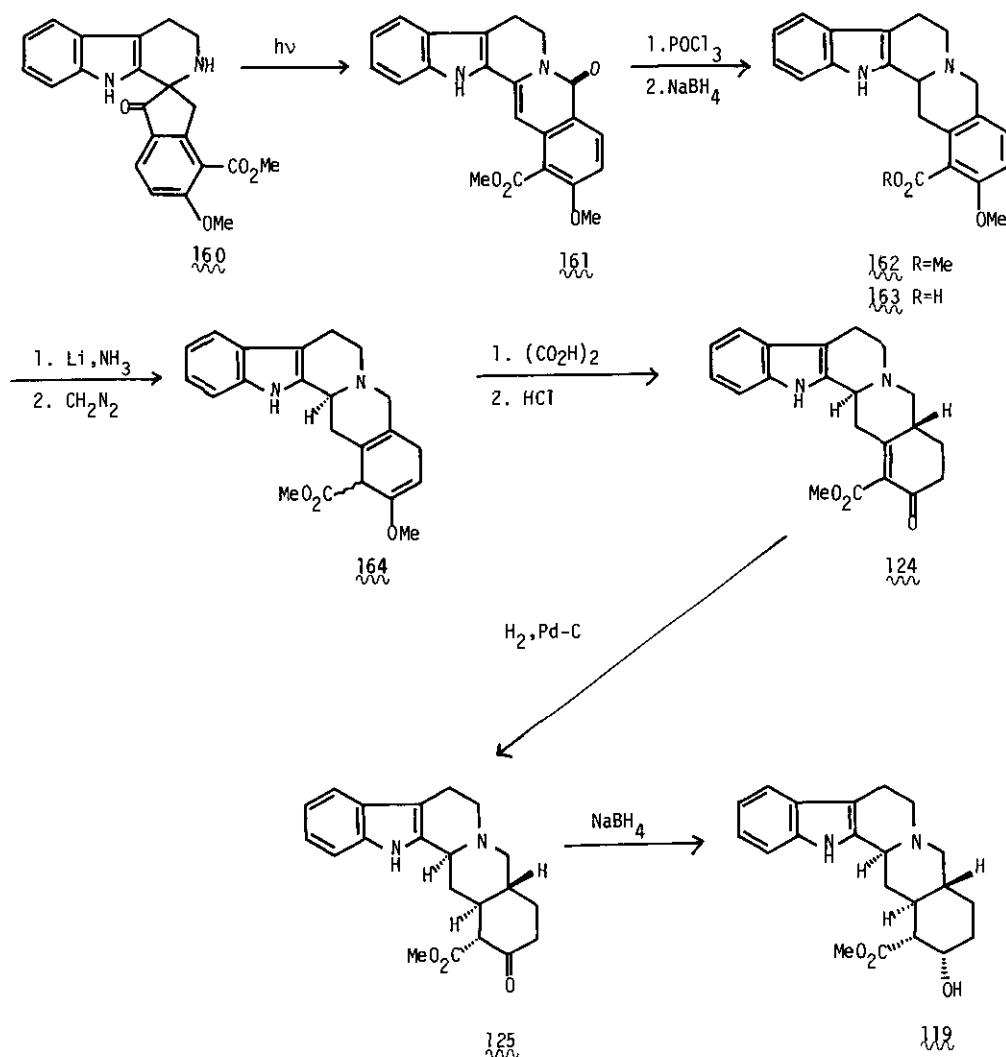
Chart 53



Based on the above model experiment, Professor Kametani accomplished a total synthesis of yohimbine (119) from the 1-spirobenzyl- $\beta$ -carboline (160). Photolysis of 160, followed by reduction of the rearranged product (161) gave O-methyl-hexadehydroyohimbine (162), the free carboxylic acid (163) of which was subjected

to Birch reduction followed by treatment with diazomethane to afford *O*-methyltetra-dehydroyohimbine (164). Reaction of the latter with oxalic acid followed by hydro-chloric acid treatment furnished dehydroyohimbine (124) which had already been transformed into yohimbine (119) as described in Retro Mass Spectral Synthesis. Thus, a total synthesis of yohimbine was accomplished by this new method developed by Professor Kametani.

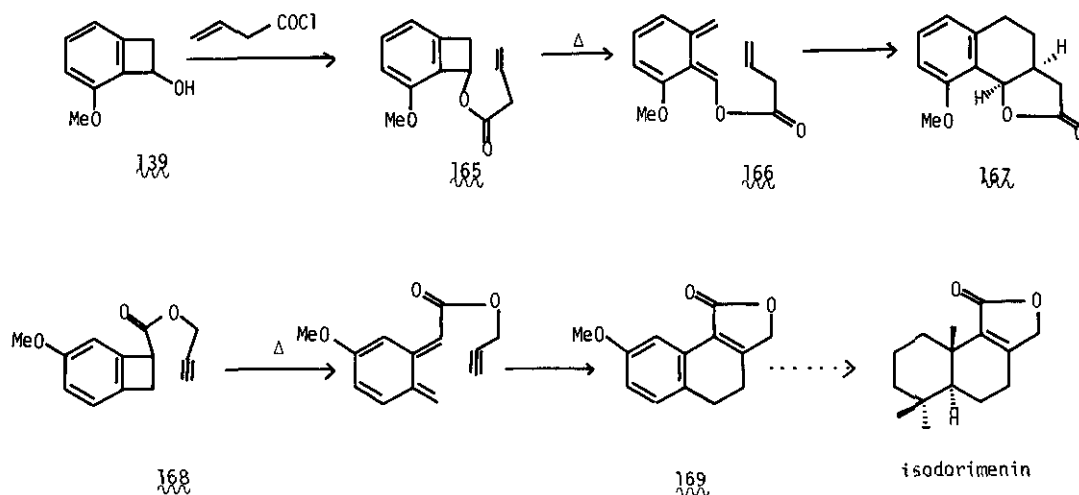
Chart 54



### 9.5 Sesquiterpene Synthesis

Although the cycloaddition mentioned above is an intermolecular reaction, Professor Kametani found that polycyclic systems are obtained regio- and stereoselectively in excellent yield on heating benzocyclobutenes that carry, on C-1, a chain of five or six atoms with a terminal multiple bond. Moreover, he discovered that this type of intramolecular cycloaddition proceeded smoothly even with unreactive dienophiles such as isolated C=C and C≡C bonds. With this knowledge, he developed a general synthetic route to basic tricyclic sesquiterpene ring systems, the eudesman- (167) and driman- (169) type terpenes, by intramolecular cycloaddition as follows. The ester (165) was heated at 190 - 200° to give the tricyclic compound (167) via the *o*-quinodimethane (166). Similarly, the driman-type lactone (169) was obtained from benzocyclobutene (168). These routes are among the most convenient ones for preparation of these types of sesquiterpene ring systems.

Chart 55

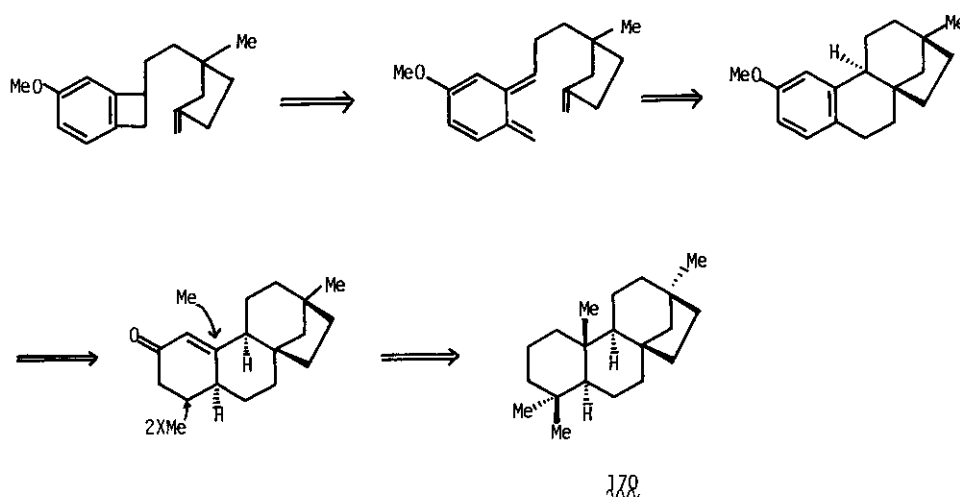


### 9.6 Diterpene Synthesis

A Total Synthesis of Hibaol: The bridged bicyclo[3.2.1]octane moiety found in hibaene is an integral part of the structure of a large class of tetracyclic diterpenes. One of the most difficult synthetic steps in the preparation of such tetracyclic diterpenes is to build the bicyclo[3.2.1]octane system from hydrophenanthenes. As described earlier, Professor Kametani has developed a synthetic route to the hydrophenanthrene ring, using intramolecular cycloaddition of an olefinic benzocyclobutene, and so he thought that it should be possible to synthesise, in one step, the hibaene ring system if a benzocyclobutene substituted by a methylenecyclopentane unit is subjected to

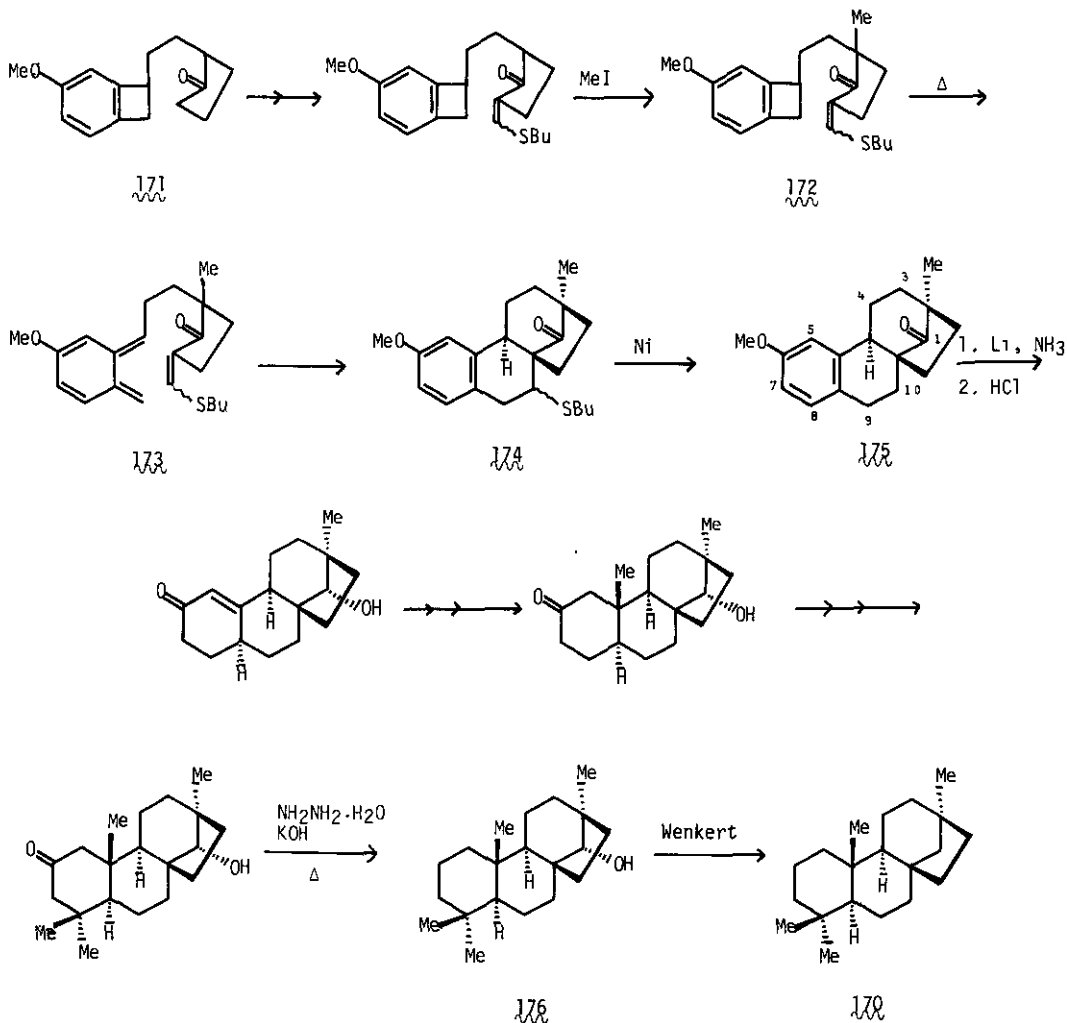
thermolysis. Based on this consideration, he planned a synthesis of dihydrohibaene (170) as shown in the following chart.

Chart 56



Along these lines, he investigated a total synthesis of dihydrohibaene (170) and hibaol (176) from 2-benzocyclobutenylethylcyclopentanone (171). Prior to introducing the methyl group to the C<sub>2</sub>-position of the cyclopentanone ring, the C<sub>5</sub>-position was blocked by a protecting group which would later function as the dienophile. A methyl group was then introduced to the C<sub>2</sub>-position by reaction with methyl iodide in tert-butanol in the presence of potassium tert-butoxide to give the key intermediate (172). Heating the latter in o-dichlorobenzene at 180° for 13 h afforded the tetracyclic compound (174) in a regioselective and stereoselective manner via the o-quinodimethane (173). Desulfurisation of this product with Raney nickel in ethanol gave the potential intermediate (175). Thus, he established a novel and short synthesis of the tetracyclic moiety which constitutes the framework of hibaene.

Chart 57



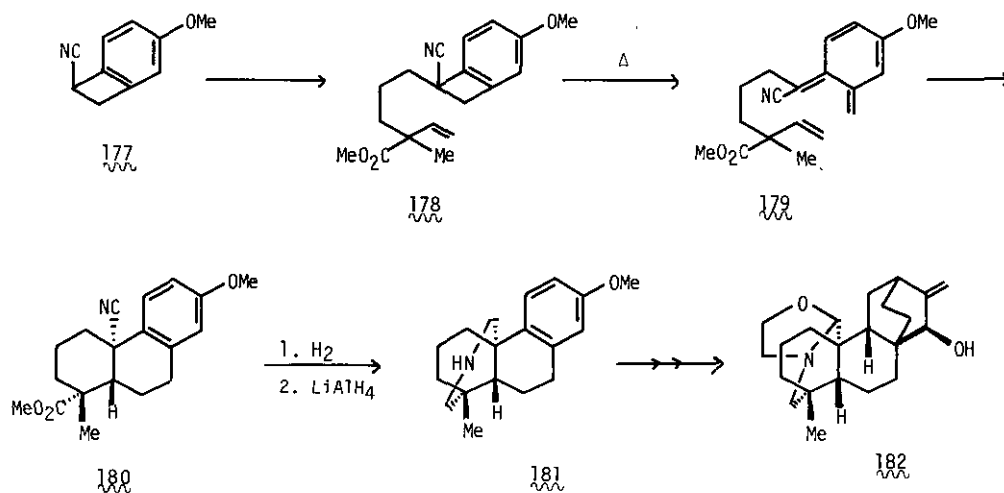
After conversion of the tetracyclic compound (175) into the Birch reduction product, the latter was transformed into hibaol (176) by the following series of reactions, Eschenmoser cleavage, introduction of methyl group to C<sub>10</sub>-position, cyclisation, introduction of two methyl groups to C<sub>4</sub>-position, and finally Wolff-Kishner reduction. As hibaol (176) had already been correlated with dihydrohibaene (170) by Wenkert, this work constituted a total synthesis of hibaol and dihydrohibaene.

B. Diterpene Alkaloids: Nagata had achieved total synthesis of the diterpene alkaloids,



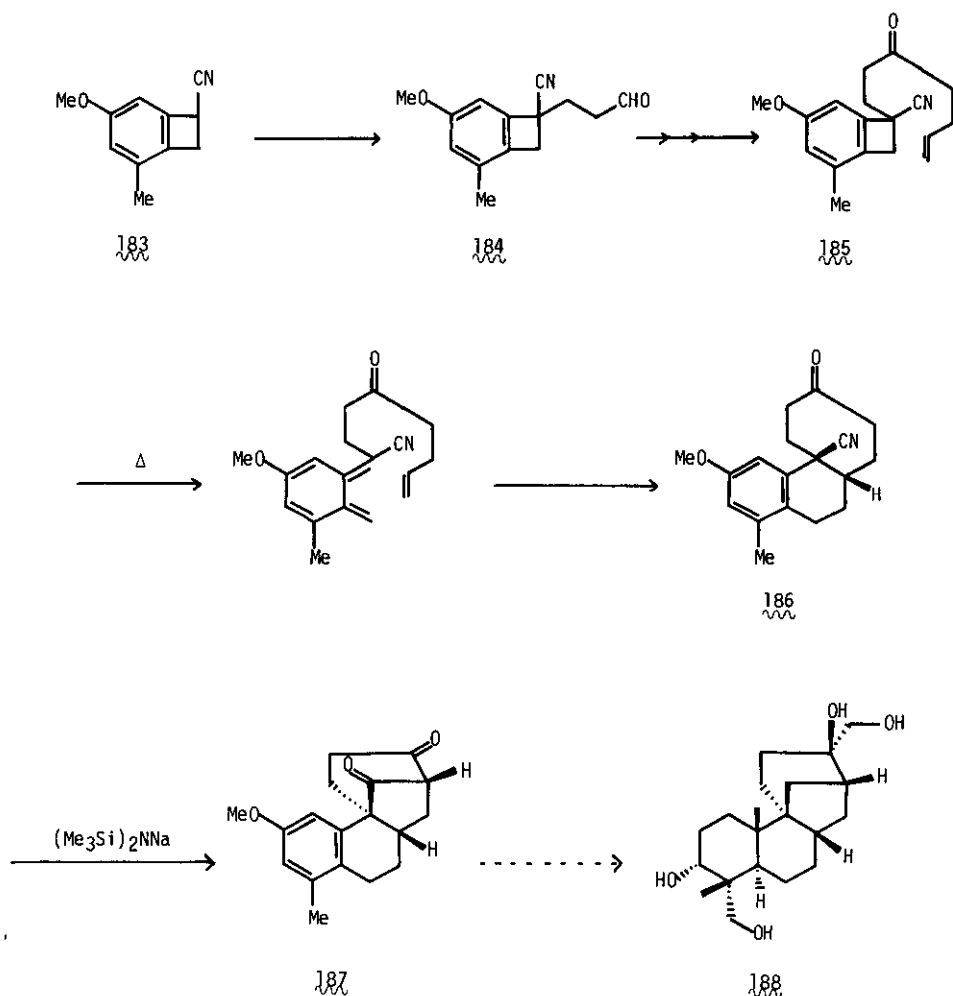
atisine (182), veatchine and garryine, during 1964 - 1967. In these syntheses the key and common intermediate was 16,17-imino-13-methoxy-5 $\beta$ ,10 $\alpha$ -podocarpene-8,11,13-triene (181), which Nagata prepared in many steps. Professor Kametani attempted a simple synthesis of 181 by intramolecular cycloaddition of *o*-quinodimethane. The olefin (178), prepared straightforwardly from the benzocyclobutene (177), was heated at 230° to give the tricyclic compound (180), in addition to its stereoisomer through the *o*-quinodimethane (179). Hydrogenation of the product (180) followed by lithium aluminium hydride reduction of the resulting lactam, afforded Nagata's intermediate (181). Thus, he achieved a simple and short synthesis of 181 by using the intramolecular cycloaddition reaction. Moreover, since this product had been correlated to atisine (182), veatchine and garryine, by Nagata, this work constituted formal total synthesis of these alkaloids.

Chart 58



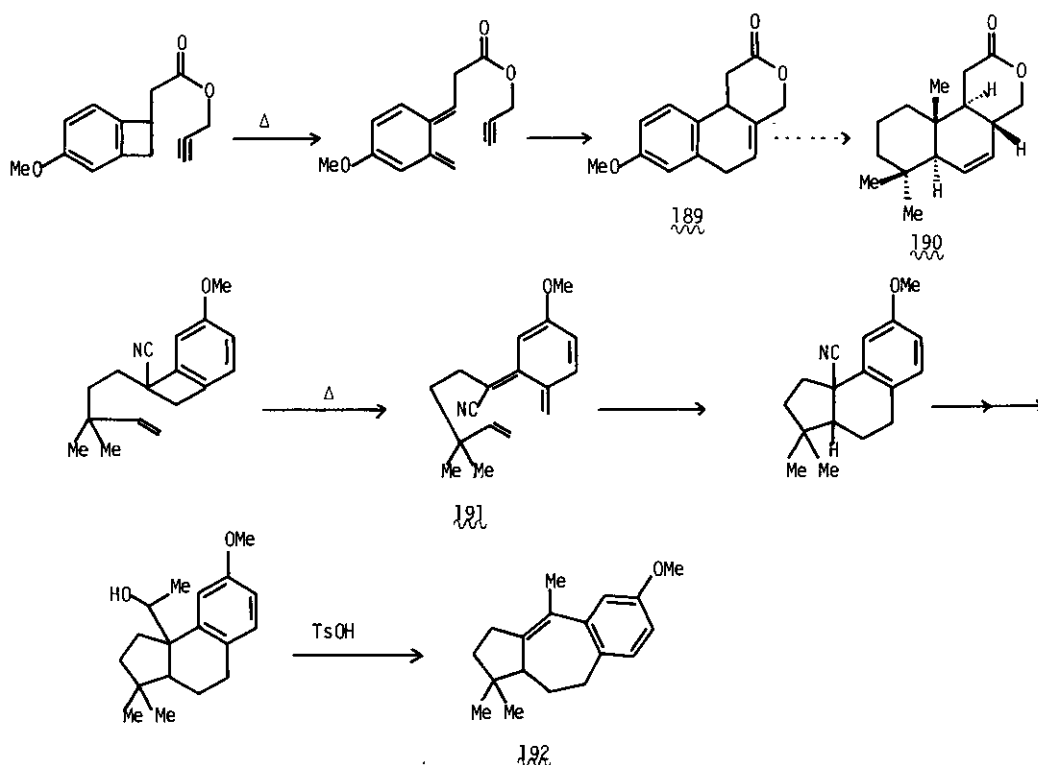
C. Aphidicolan: A new and stereoselective synthetic route to the main skeleton (187) of aphidicolin (188), involving intramolecular cycloaddition as the key reaction, was established by Professor Kametani. He firstly made the tricyclic seven-membered ring compound (186) from the benzocyclobutene (185), derived from the cyanobenzocyclobutene (183) via the aldehyde (184), and bridged it by an aldol condensation to produce the aphidicolan system (187).

Chart 59



D. Miscellaneous: The basic skeleton (189) of abietane-type diterpene (190) was synthesised by a route similar to that used for the driman-type compound described above. The A, B, and C rings (192) of acebotoxine were obtained by intramolecular Diels-Alder reaction of the o-quinodimethane (191) followed by molecular rearrangement of the cycloaddition product as summarised in the following chart.

Chart 60

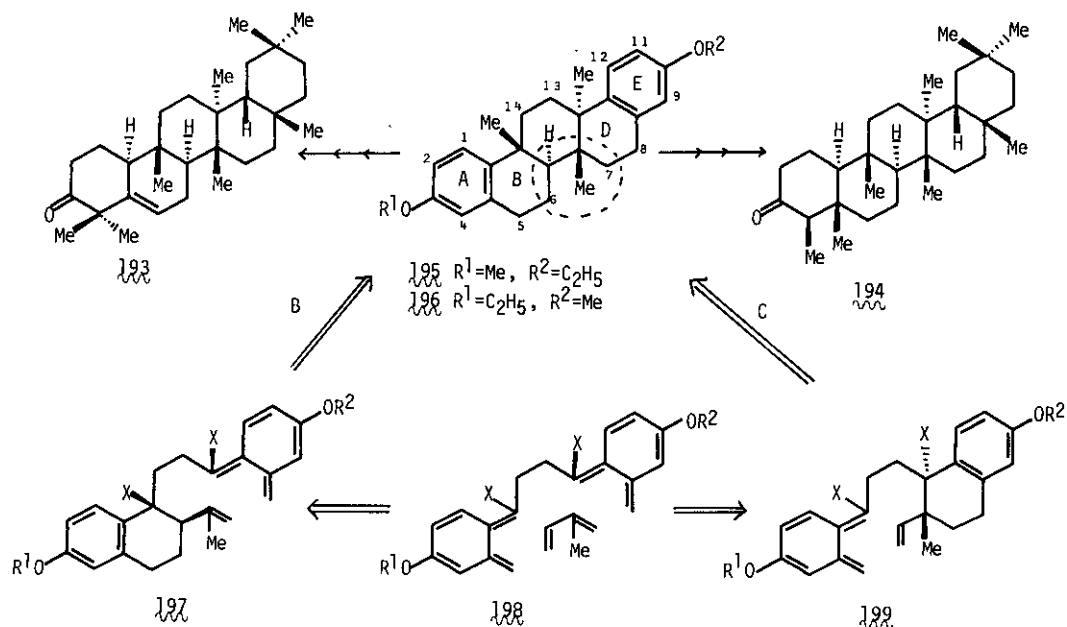


### 9.7 Triterpene Synthesis

The pentacyclic aromatic diethers (195 and 196), with trans,anti,trans-BCD ring structure and the correct array of angular methyl groups, are important intermediates in the total synthesis of the pentacyclic triterpenes, as seen in the total synthesis of alnusenone (193) and friedelin (194) by Ireland. A crucial step in the synthesis of these pentacyclic diethers is the introduction of the methyl groups at the angular positions with the required stereochemistry.

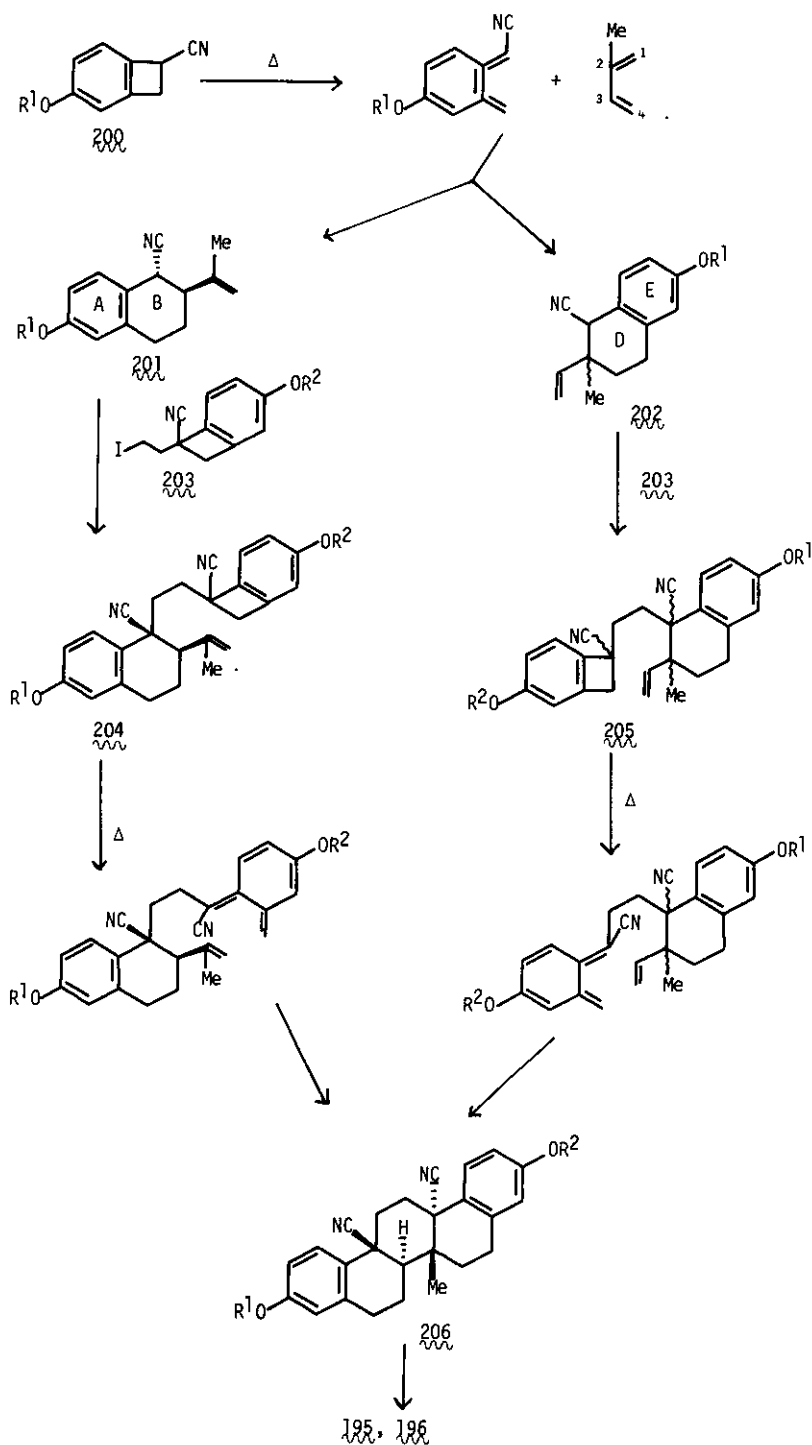
Since Professor Kametani found that intramolecular cycloaddition of an o-quinodimethane in the synthesis of diterpenes could proceed stereoselectively as already described above, he investigated a simple stereoselective synthesis of the key intermediates for triterpenoid synthesis by this method. His ideas were based on observation that the  $C_6$ - $C_{6a}$ - $C_{6b}$ - $C_7$  unit of the target molecule corresponds to isoprene, and the remainder to the bis-o-quinodimethane, as shown by 198. On this consideration, he tried approaches to the pentacyclic compounds (195 and 196) by an intermolecular (route A) and two intramolecular (routes B and C) cycloaddition reactions.

Chart 61



His first attempt was a one-step synthesis of the pentacyclic compound by a double intermolecular cycloaddition of the bis-o-quinodimethane to isoprene (route A). However, attempted preparation of the pentacyclic compound by heating the bisbenzo-cyclobutene with an excess of isoprene gave instead the 1 : 2 adduct, a bistetralin derivative, so he turned his attention to a stepwise synthesis of the pentacyclic aromatic diether. He selected 4-alkoxy-1-cyanobenzocyclobutene (200) as starting material for the stepwise synthesis (routes B and C). Heating 200 (R<sup>1</sup>=Me) with isoprene gave, in good yield, a mixture of the tetralins (201 and 202) in the ratio of 1 : 1. Condensation of the former (201) with benzocyclobutenylethyl iodide (203, R<sup>2</sup>=Et), in the presence of sodium amide, proceeded stereoselectively to give the key intermediate (204) with the 1-cyano and 2-vinyl groups in a cis relationship. Thermolysis of 204 at 210 - 215° provided the pentacyclic compound (206) stereoselectively, via o-quinodimethane. This product was reduced with DIBAL followed by Wolff-Kishner reduction to yield the expected 6b,12b,14a8-trimethylated pentacyclic compound (195), identical to that obtained by Ireland. By analogous reactions, using 1-cyano-4-ethoxybenzocyclobutene (200, R<sup>1</sup>=Et) and 1-

Chart 62



cyano-1-(2-iodoethyl)-4-methoxybenzocyclobutene (203,  $R^2=Me$ ), the pentacyclic aromatic diether (196), which had been converted into friedelin by Ireland, was synthesised as shown in the following chart.

Moreover, Professor Kametani also used the initial intermolecular cycloaddition by-product (202) for synthesis of the pentacyclic compounds (195 and 196). Thus, condensation of 202 with the iodide (203) gave the key compound (205), thermolysis of which afforded the pentacyclic dicyanide (206). This route, however lacked stereoselectivity.

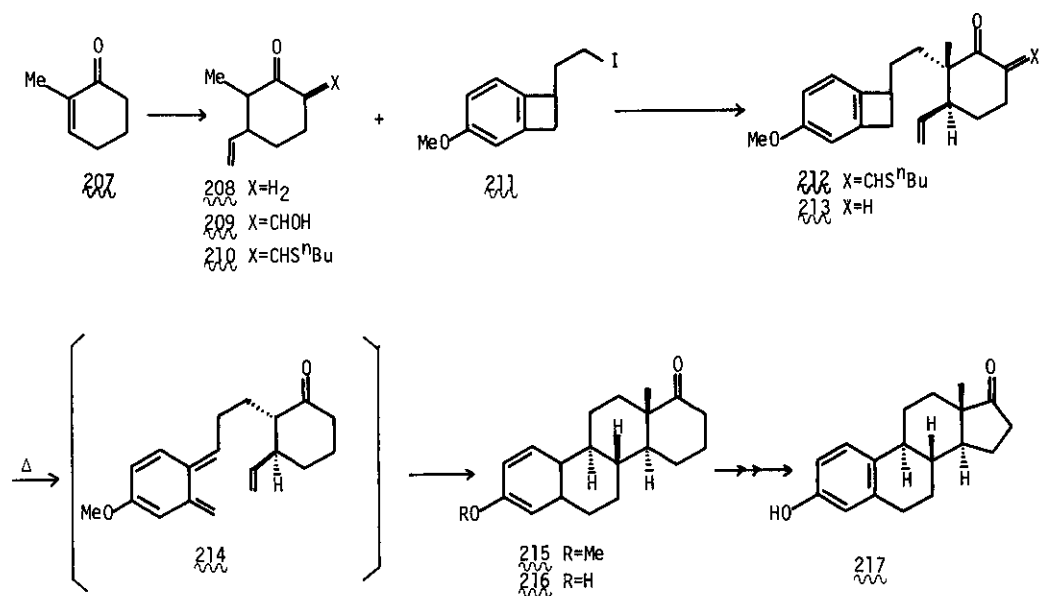
Thus, he obtained the key compounds which have been correlated with the triterpenoids, alnusenone and friedelin, in a simple stereoselective way, providing an effective method for the synthesis of pentacyclic diethers.

### 9.8 Steroid Synthesis

In connection with an interest in the synthetic development of cycloaddition or electrocyclic reaction starting from *o*-quinodimethanes, based on benzocyclobutenes, Professor Kametani investigated the synthesis of pharmacologically active steroids.

A Estrone: With the above knowledge of benzocyclobutene thermolysis, Professor Kametani firstly designed a novel synthesis of D-homoestrone (216), which had been correlated to estrone (217), from the benzocyclobutene (213) via *o*-quinodimethane

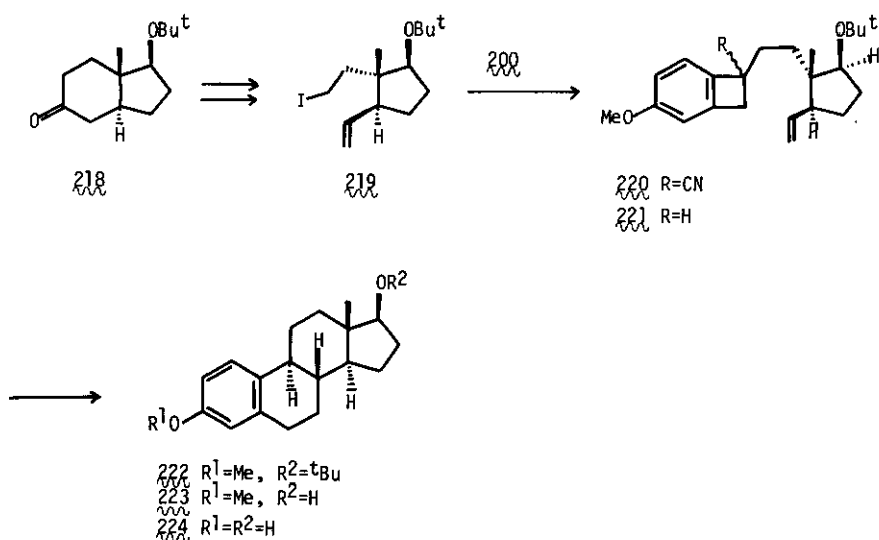
Chart 63



(214). Preparation of the requisite benzocyclobutene (213) was straightforward. Thus, condensation of thiomethylenecyclohexanone (210), which was derived from 2-methylcyclohexanone (207), through (208) and (209), with benzocyclobutenylethyl iodide (211) afforded the 1,1-disubstituted cyclohexanone (212) which was hydrolysed to give the key intermediate (213). This compound was smoothly and stereoselectively converted, in boiling *o*-dichlorobenzene for 4 h, to *O*-methyl-D-homoestrone (215). Thus he provided a new and general approach to estrone (217), and it was confirmed that the cycloaddition reaction of *o*-quinodimethane (214) preceeded along the reaction pathway proposed in following chart, namely, that the configuration of substituents on the cyclohexanone ring controlled the stereochemistry of the B, C ring junction in the product (215), and that the stereochemistry of the butene ring in 213 did not affect that of the product.

Asymmetric Synthesis of Estradiol: Based on the highly stereoselective cycloaddition reaction described above, thermolysis of the optically active olefinic benzocyclobutene (221) was expected to give an optically active steroid (222) by asymmetric induction, and this was found to be the case. The optically active olefinic benzocyclobutene (221) was obtained from reaction of the benzocyclobutene[200, R=Me] with optically active cyclopentane (219), derived from (1S,3aS,7aS)-1-*tert*-butoxy-3a,4,7,7a-

Chart 64

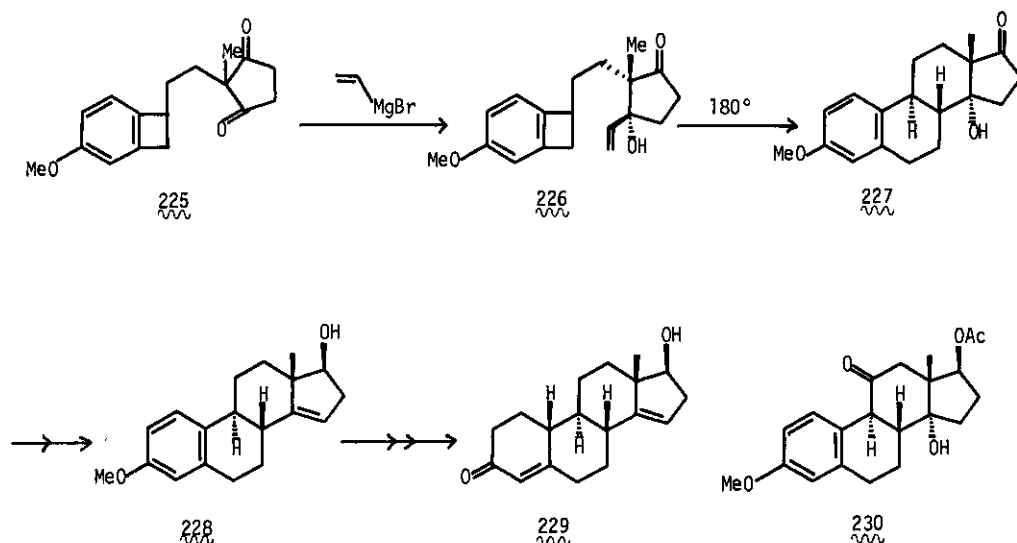


tetrahydro-7a-methyl-5-(6H)-indanone (218) in several steps. Thermolysis of (221) gave 17-O-tert-butyl-3-O-methylestradiol (222) in 83.8 % yield. Compound (222) thus obtained was converted to 3-O-methylestradiol (223), the optical purity of which was determined to be 96.8 %, i.e. 1:d = 98.4:1.6, comparison with the optical rotation of an authentic sample derived from natural estradiol (224). Finally, removal of the protecting group at C<sub>3</sub>-position gave (+)-estradiol (224). Thus, he developed new methodology for the synthesis of optically active steroidal hormones.

C, 14-Dihydro-19-nortestosterone: As described above, Professor Kametani developed a new synthetic method for A-ring aromatic steroids, and so he then attempted a synthesis of 14-dihydro-19-nortestosterone (229), which shows one hundred times as much androgenic activity as testosterone, by using a stereo- and regioselective o-quinodimethane cycloaddition.

The benzocyclobutenylcyclopentadione (225), derived from 1-cyano-4-methoxycyclobutene and 2-formylmethyl-2-methylcyclopentane-1,3-dione, reacted with vinylmagnesium bromide to give the olefinic compound (226) stereoselectively, which on thermolysis yielded the tetracyclic compound (227) as a single product. This was then converted into the olefinic alcohol (228) which had already been transformed into 229. Thus this work constituted a total synthesis of 14-dehydro-19-nortestosterone (229). Using an analogous reaction sequence, 17-O-acetyl-14 $\alpha$ -hydroxy-3-methyl-11-oxo-estradiol (230), which could be an important precursor in the synthesis of 11-oxidised steroids, was prepared.

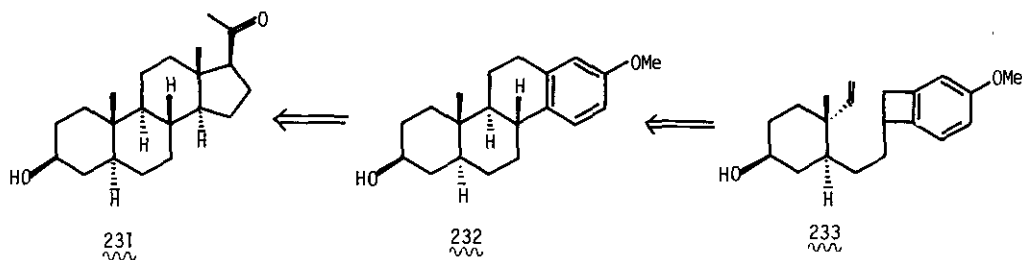
Chart 65





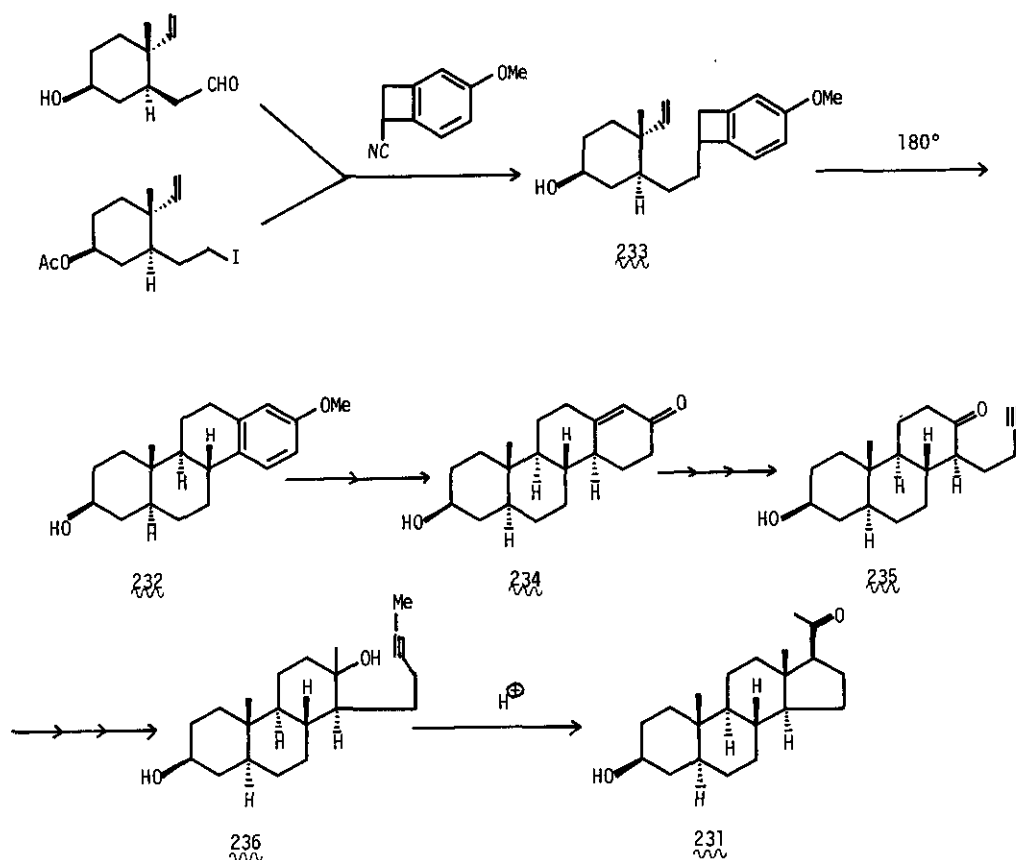
D. Pregnane-Type Steroids: Pregnane-type steroids not only constitute an important class of steroid hormones but could also be key intermediates in the synthesis of other types of steroid hormones. Professor Kametani therefore planned a total synthesis of (+)-5 $\alpha$ -dihydropregnenolone (231), a known metabolite of progesterone, the acetate of which is an important synthetic intermediate for cholesterol, via the D-ring aromatic steroid (232), as outlined in the following chart.

Chart 66



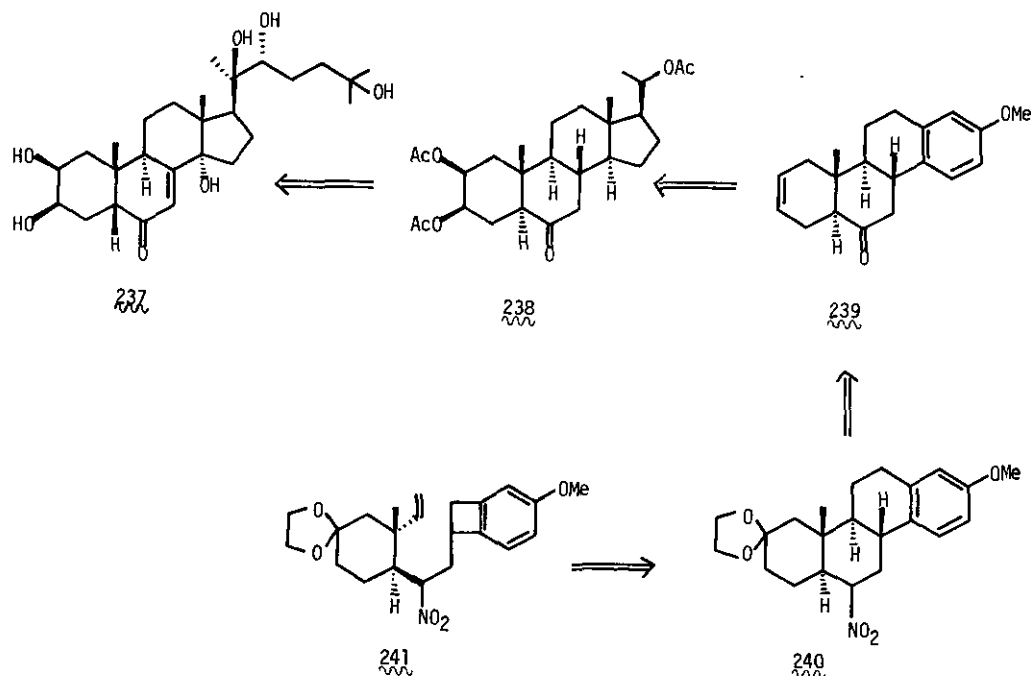
The optically active olefinic benzocyclobutene (233), prepared from 1-cyano-4-methoxybenzocyclobutene, was subjected to thermolysis to afford the D-ring aromatic steroid (232) stereoselectively, which was then converted into the enone (234) by Birch reduction followed by acid treatment. Although the transformation of 234 into the pregnane-type steroid had already been reported, he carried out the following sequence of reactions in order to obtain a more efficient conversion. The acetylenic ketone (235), resulting from Eschenmoser ring opening reaction of the corresponding epoxide of 234, was converted into the acetylenic alcohol (236) by successive treatment with methyllithium, and methyl iodide in the presence of sodium amide in liquid ammonia. Cyclisation of (236) was effected using trifluoroacetic anhydride and trifluoroacetic acid to furnish (+)-5-dihydropregnenolone (231), the optical purity of which was found to be 91.4 %.

Chart 67



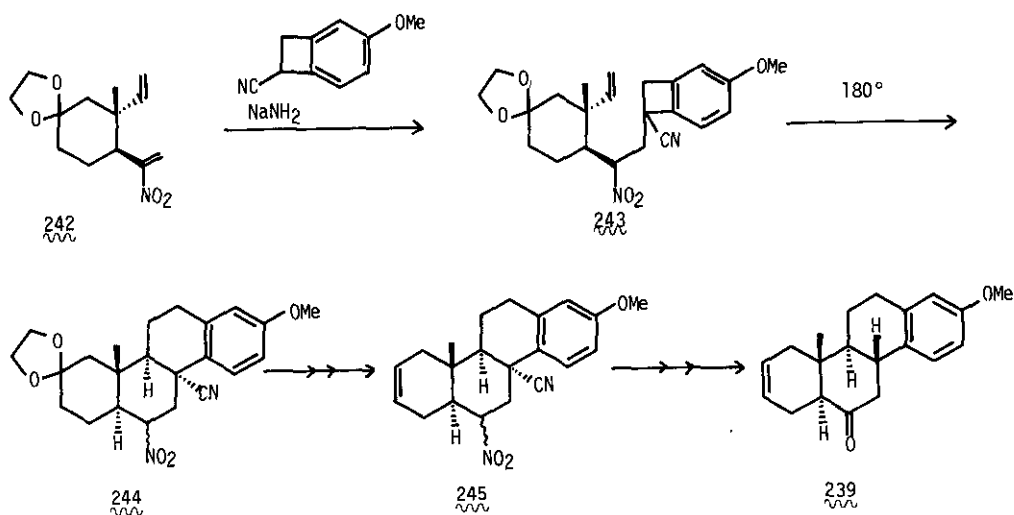
D- $\beta$ -Ecdysone: With an effective synthesis of D-ring aromatic steroids, and an efficient procedure for their conversion to pregnane-type steroids in hand, Professor Kametani planned a stereoselective total synthesis of  $\beta$ -ecdysone (237), via 238 and 239, the latter of which could be derived by thermolysis of benzocyclobutene via 240.

Chart 68



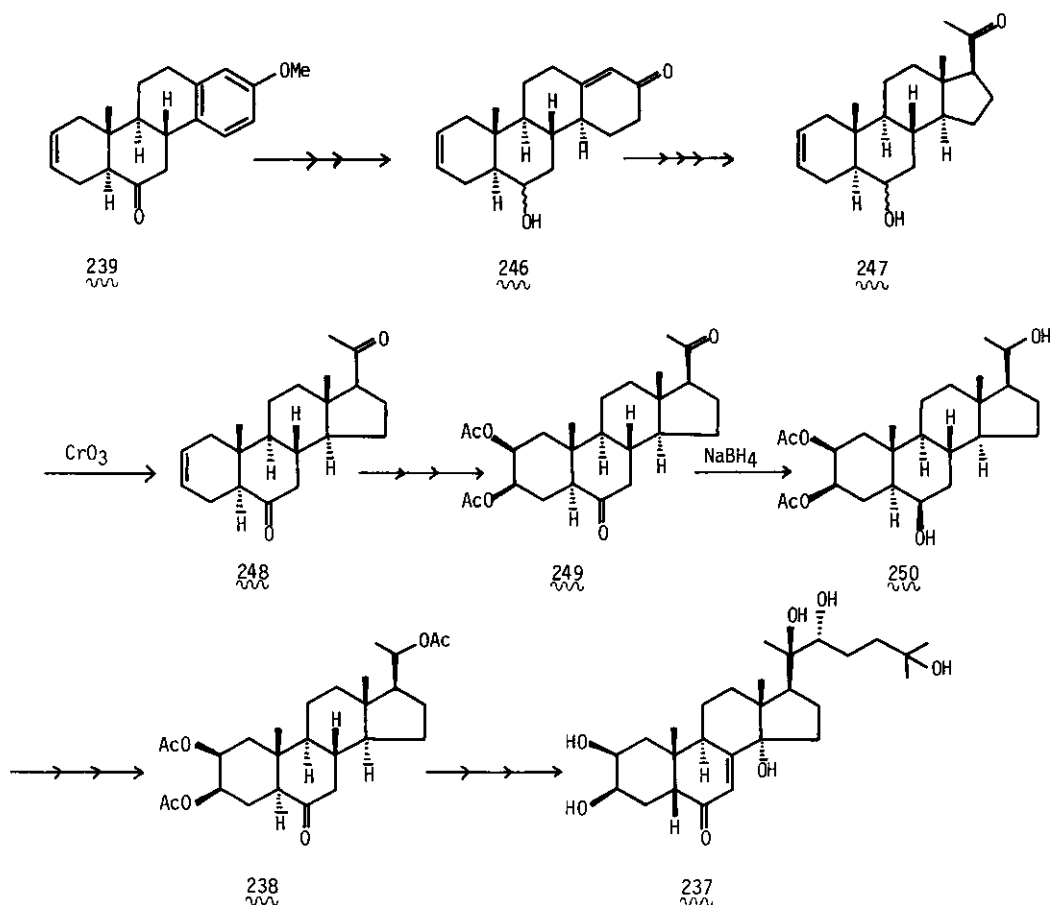
Michael addition of 1-cyano-4-methoxybenzocyclobutene to the nitroolefin (242) in the presence of sodium amide yielded the key intermediate (243), which on heating at 180° afforded the D-ring aromatic steroid (244) with cis-B, C ring juncture. The olefinic nitro compound (245), obtained from 244 by successive acid treatment, reduction and dehydration, was subjected to modified Neff reaction and subsequent reductive decyanation, followed by Jones' oxidation, and epimerisation at C<sub>5</sub>-position, to furnish the initial target molecule (239).

Chart 69



The olefinic enone (246), prepared by reduction of the above product with sodium borohydride followed by Birch reduction and acid treatment, was converted into the pregnane-type compound (247) by the same method as for the synthesis of 231. Oxidation with Jones' reagent gave the diketone (248). The diacetoxy compound (249), obtained from 248 by Prévost-Woodward reaction followed by acetylation, was reduced with sodium borohydride to afford the diol (250), which was finally converted into 238 by successive treatment with acetic anhydride in pyridine and Jones' reagent. Since compound 238 had already been transformed into  $\beta$ -ecdysone (237), this work constituted a formal total synthesis of  $\beta$ -ecdysone (237).

Chart 70



Since Professor Kametani's first introduction of the intramolecular cycloaddition reaction of *o*-quinodimethanes for the synthesis of D-homoestrone, many papers, by several groups including his own, on the synthesis of various types of steroids, in which this reaction is the key step, have appeared in the literature. This shows that such reaction may be a general and highly flexible method for steroid synthesis.

#### 10 Total Synthesis of Indole Alkaloids

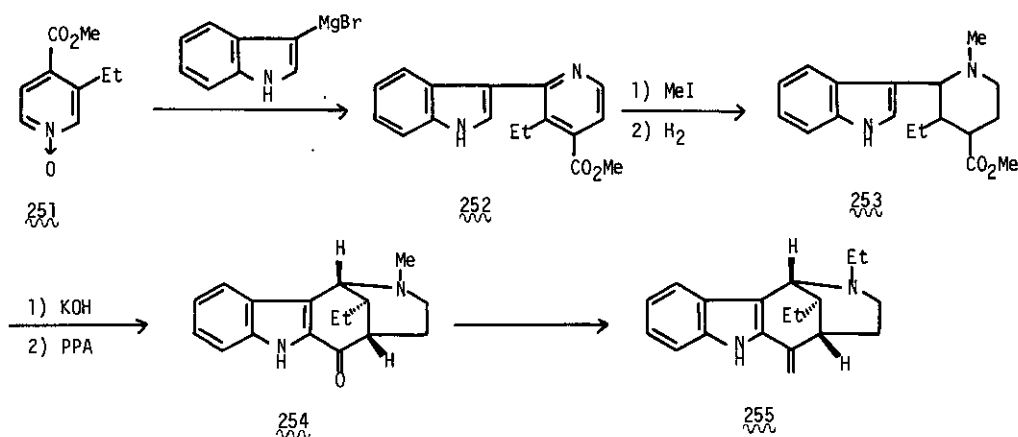
Although Professor Kametani's work on the total synthesis of natural products has mainly been concerned with isoquinoline alkaloids, he has also carried out the synthesis of indole alkaloids, some of which have been described in earlier sections (yohimbine, olivacine, harman, camptothecin, tubulosine). In this section, I will

mention his total syntheses of indole alkaloids other than those already described, which were carried out by step-by-step and biomimetic methods.

#### 10.1.1. Step-by-step Synthesis

The first indole alkaloids synthesised by Professor Kametani were dasycarpidone (254) and uleine (255), the key step in which involved condensation of indolylmagnesium bromide with methyl 3-ethylnicotinate 1-oxide (251) to afford the pyridylindole (252). Hydrogenation of the methiodide of 252 yielded the amino ester (253), saponification of which, followed by heating with polyphosphoric acid gave dasycarpidone (254) and its epimer. Since dasycarpidone (254) had already been converted into uleine (255), a formal total synthesis of uleine had also been accomplished.

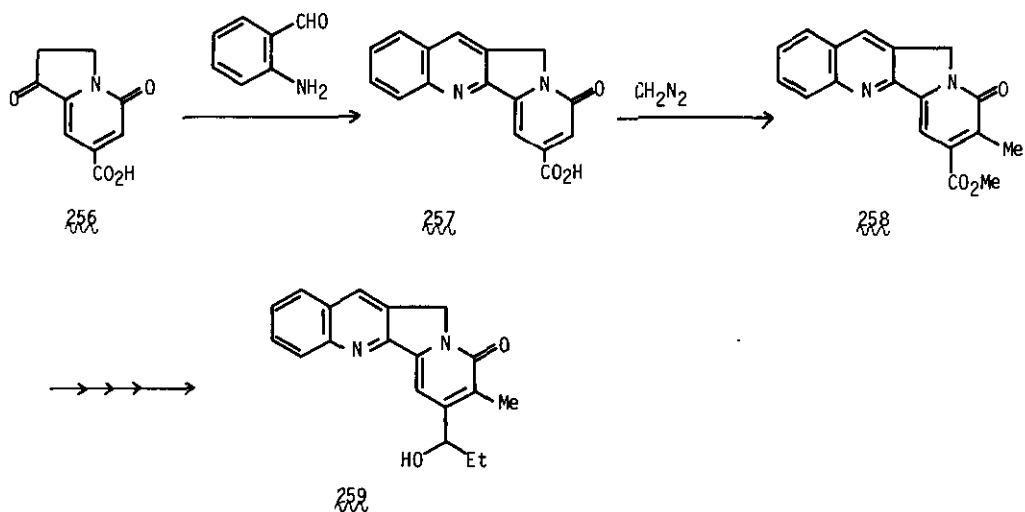
Chart 71



In 1975, Professor Kametani found the new reaction whereby treatment of 4-carboxy-2-methyl-2-pyridones with diazoalkane gave the 3-alkylated products. He attempted a total synthesis of mappicine (259), which belongs to the indole alkaloid group biogenetically, using this new reaction as the key step.

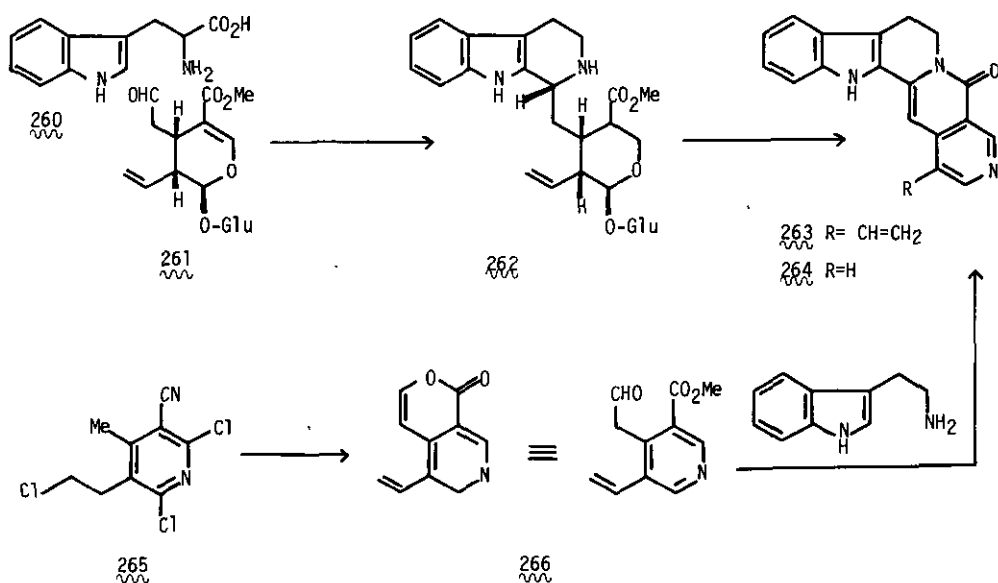
Thus, Friedländer reaction of the pyrrolidone (256) with *o*-aminobenzaldehyde gave the quinoline (257) which was subjected to the new reaction with diazomethane to afford the methylated compound (258). This product was transformed into mappicine (259) by conversion of the methoxycarbonyl group into an  $\alpha$ -hydroxypropyl residue by the usual method. He thus achieved a total synthesis of mappicine by using a new reaction which he had developed himself.

Chart 72



Recently, Professor Kametani has been investigating a synthesis of reserpine using a Diels-Alder reaction of furans as the key step.

Chart 73



### 10.2 Biogenetic-type Synthesis

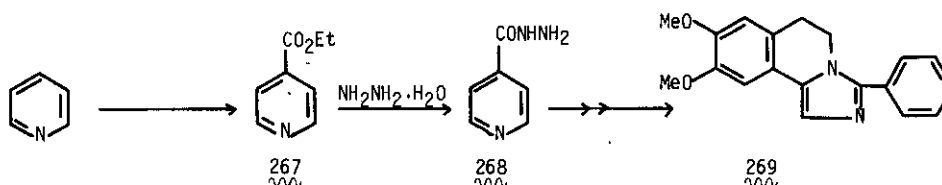
Angustine (263) is biosynthesised from tryptophan (260) and secologanin (261) (or its biogenetic equivalent) via vincoside (262). Professor Kametani assumed that dehydrogentianine (266) would be a more effective equivalent than secologanin in a biogenetic-type synthesis, because angustine has a nitrogen atom in ring E. He firstly synthesised dehydrogentianine (266) from the pyridine trichloride (265) in three steps, and then subjected 266 to condensation with tryptamine in the presence of acetic acid to afford angustine (263). By a similar method, nauclefine (264) was also obtained from tryptamine.

### 11 Medicinal Chemistry

One of the main work of Professor Kametani has been the development of new pharmacologically active heterocyclic compounds and the establishment of new routes for the industrial preparation of medicines. These studies started early in his academic life and many effective compounds have been synthesised. In this section I will describe his development of, and his modified synthesis of, medicines and pharmaceutically active compounds.

His first contribution to medicinal chemistry was in a preparation of isonicotinic acid hydrazide (INAH) (268) which was a famous antibacterial medicine against Tubercle bacilli. In 1951, he synthesised this compound (268), from pyridine through isonicotinate (267), as an important intermediate for the preparation of 9,10-dimethoxy-3-isonicotinyl-5,6-dihydrobezoglyoxalocoline (269). He did pharmaceutical tests on 268, but not on 267, and found the former to have emetic activity. After this study, INAH (268) was found to show very strong antibacterial activity, and was used as an effective drug against tuberculosis in the USA. He then tested his synthetic compound (267) and found this to inhibit the growth of bacilli at 10,000,000 dilution against human and bovine types.

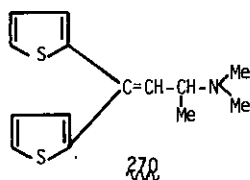
Chart 74





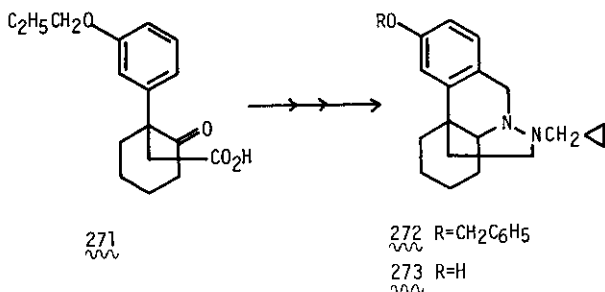
During his stay in Osaka University, Professor Kametani developed a new industrial preparation of 3-dimethylamino-1,1-di(2'-thienyl)-but-1-ene (270), an analgesic, and this compound was used in medicine for a short time. Moreover, he prepared many compounds showing antispasmodic and anticancer activities at this time.

Chart 75



After moving to Tohoku University, his interests in the development of pharmaceutically active compounds turned to analgesics with a polycyclic ring system related

Chart 76

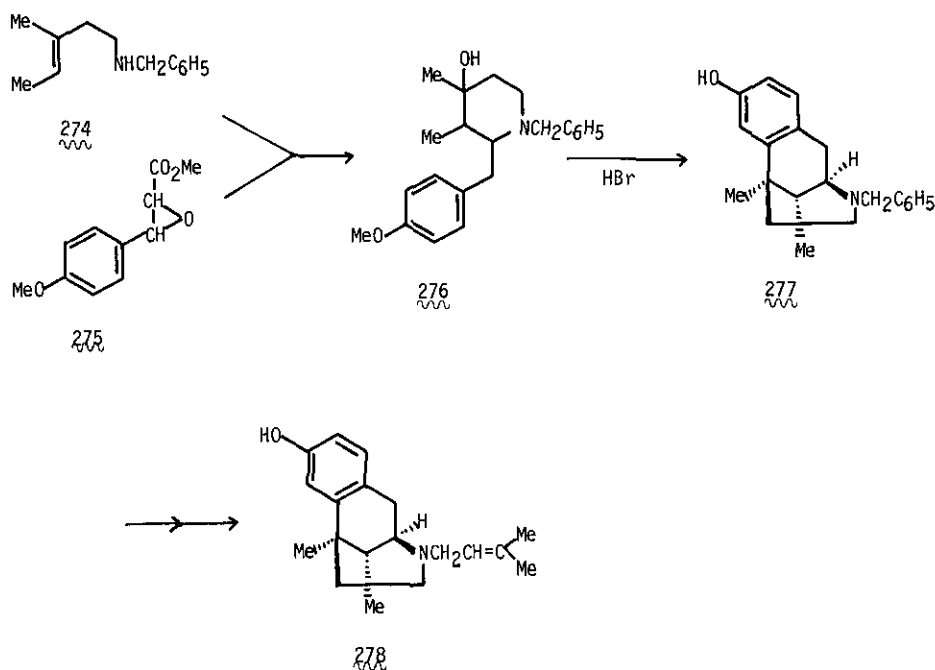


to morphine [Heterocycles, 2, 79,347 (1974)].

Firstly, Professor Kametani investigated the synthesis and the analgesic activity of a range of azamorphinans which were anticipated to show activity from drug design considerations. He found that the 17-cyclopropylmethyl-9-azamorphinan (273) had analgesic activity twice as strong as that of pentazocine, and also showed an antagonist effect to morphine. The synthesis of this compound (273) was carried out as shown in the following chart. Thus, 2-(3-benzyloxyphenyl)-2-carboxymethyl-cyclohexanone (271) was treated successively with cyclopropylmethylhydrazine, lithium aluminium hydride, and formalin, to give the 9-azamorphinan (272), which was hydrolysed with hydrochloric acid to afford 273.

At the same time as the above study, Professor Kametani attempted an alternative and industrial synthesis of pentazocine (278), which in those days was called "a dream analgesic", because addiction to this material was very weak in comparison to morphine. He developed many routes to pentazocine, the simplest of which involved Grewe-type cyclisation as the key reaction. Thus, Pictet-Spengler reaction of the amine (274) with the glyoxalate (275) gave the 2-benzylpiperidin-4-ol (276), which was subjected to Grewe cyclisation using hydrobromic acid to

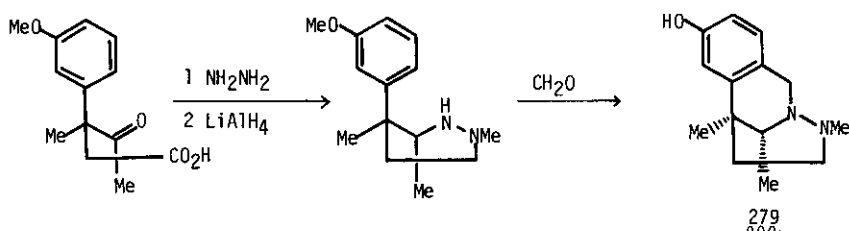
Chart 77



produce the benzomorphan (277). Quaternisation of this product with 3,3-dimethylallyl bromide, followed by debenzylation with sodium thiophenolate, a new reaction developed by Professor Kametani, afforded pentazocine (278). Furthermore, he determined the stereochemistry of pentazocine to be as shown in 278 by physico-chemical methods.

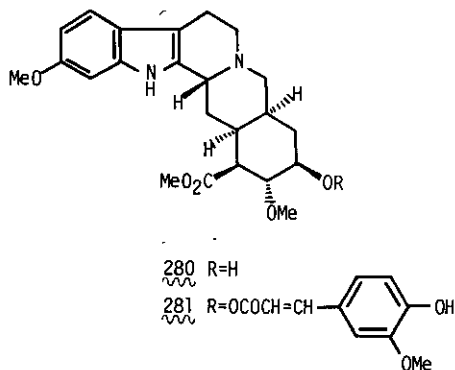
After accomplishment of pentazocine synthesis, Professor Kametani investigated the synthesis of azabenzomorphan which have structures overlapping those of benzomorphan and azamorphinans, and he synthesised twelve different azabenzomorphan. Among these, 8-hydroxy-2,3-benzomorphan (279), which corresponds to a 1-aza-analog of pentazocine, showed the same analgesic activity as pentazocine (278). The synthetic sequence to 279 was analogous to that to azamorphan, as shown in the following chart.

Chart 78



Apart from this development of pharmaceutically active compounds by synthetic study,

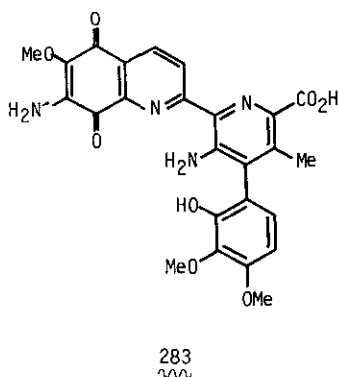
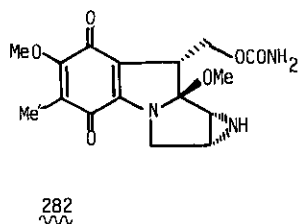
Chart 79



Professor Kametani has investigated the development of new medicines by structural modification of compounds already used clinically. As a result of this work, he found a new antihypertensive agent which will be used for medicinal purposes in 1981. Methyl reserpate (280) was esterified with acid chlorides, derived from several alkoxyated cinnamic acids, to give rescinnamine-like derivatives, among which the compound 281 showed effective activity in decreasing systemic blood pressure.

In addition to these studies, Professor Kametani attempted the total synthesis of antibiotics with complicated heterocyclic systems, e.g. camptothecin, mitomycin (282) and streptonigrin (283), and succeeded in a synthesis of camptothecin along the biogenetic pathway as already described.

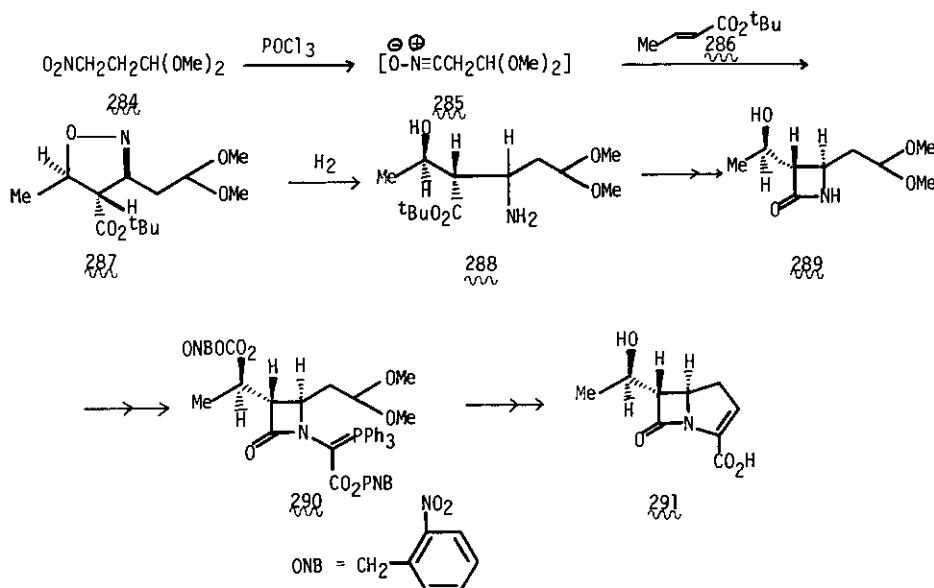
Chart 80



Recently, Professor Kametani focussed his interest in medicinal chemistry on an effective synthesis of carbapenem-type antibiotics, for example thienamycin (294), isolated from Streptomyces cattleya, which has a wide range of antibacterial spectra. He has developed new and stereoselective synthetic routes to thienamycin and related antibiotics using a new reaction found by him. Firstly, he synthesised des-cysteaminylthienamycin (291), which showed almost the same antibacterial activity as thienamycin, via the isoxazoline (287) prepared by 1,3-dipolar cycloaddition. The reaction of crotonate (286) with the nitrile oxide (285), derived from the nitroacetal (284), gave the isoxazoline (287) as the cycloaddition product, which was reduced to the amino alcohol (288). After protection of the hydroxyl group with a silyl residue, this compound was cyclised with methylmagnesium bromide to stereoselectively give the  $\beta$ -lactam (289), having the same stereochemistry as

thienamycin. The hydroxyl group of the  $\beta$ -lactam (289) was then protected with *o*-nitrobenzyl group and this product was converted into descysteaminylthienamycin (291) by an intramolecular Wittig reaction of the phosphorane (290) followed by removal of the protecting group.

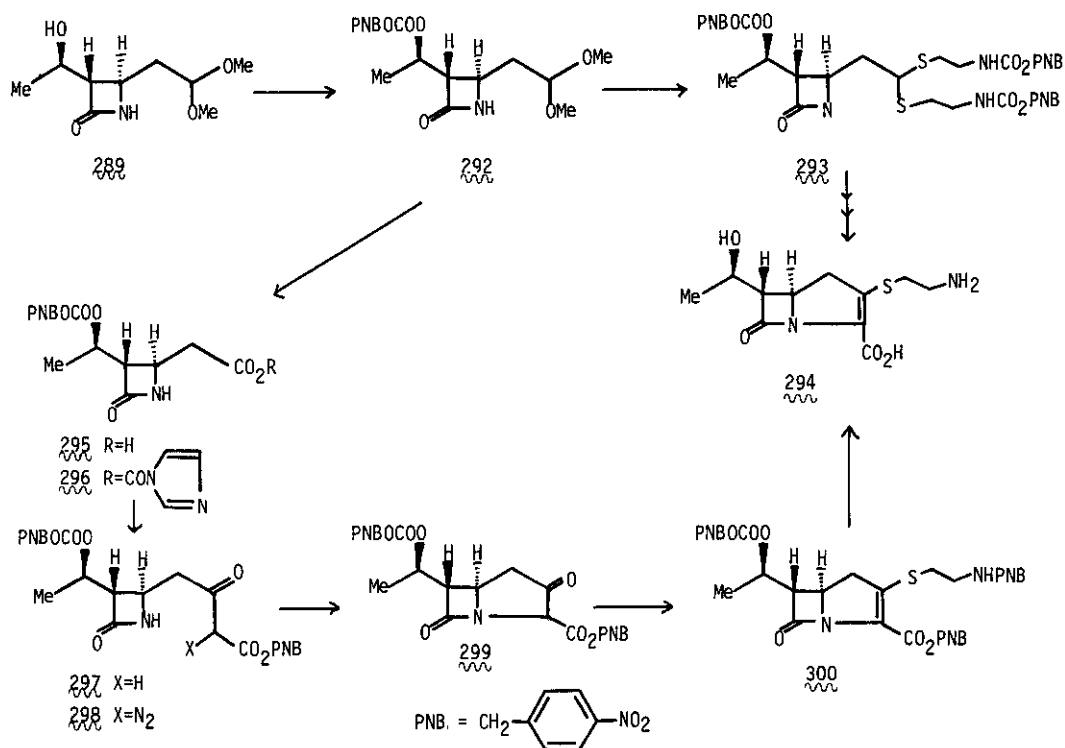
Chart 81



After accomplishment of the total synthesis of descysteaminylthienamycin (291), he attempted a synthesis of thienamycin (294) from the intermediate (289) in the aforementioned preparation of 291 as follows. The *p*-nitrobenzyl carbonate (292) of 289 was treated with *N*-*p*-nitrobenzyloxycarbonylcysteamine in the presence of acid to give, in one step, the thioacetal (293), which had already been converted into thienamycin (294) by the Merck group.

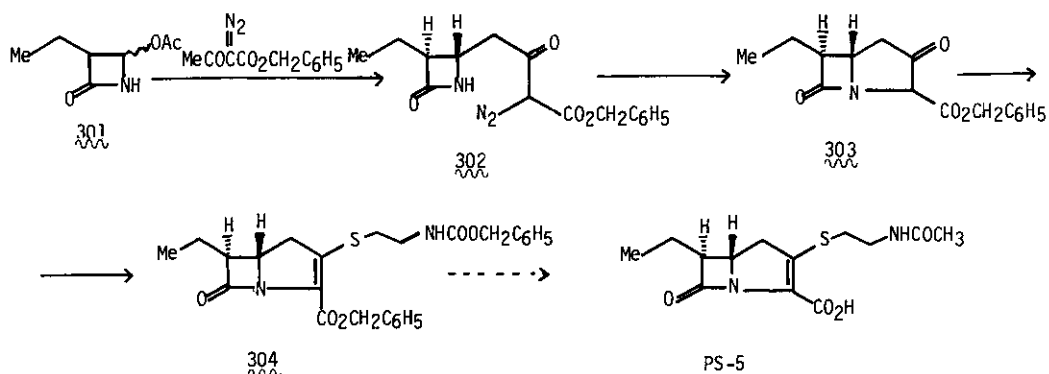
Moreover, Professor Kametani achieved a second synthesis of thienamycin from 292 by a different route from that described above. Thus, after conversion of 292 into the carboxylic acid (295), the latter was transformed into the  $\beta$ -keto ester (297) via the imidazoline (296). This product was subjected to a diazo exchange reaction with tosyl azide and the product (298) was converted into the carbapenam (299) by a carbene insertion method, and this was then converted into the PNB-protected thienamycin (300). As this compound had already been transformed into thienamycin (294), this work constituted a total synthesis of thienamycin.

Chart 82



In addition to this work, Professor Kametani has developed a new and general alkylation reaction for the C<sub>4</sub>-position of  $\beta$ -lactams, and using it has achieved the synthesis of derivatives of a carbapenem antibiotic isolated from *Streptomyces* species by the Sanraku Ocean group. Thus, 4-acetoxy-3-ethylazetidin-2-one (**301**) was treated with benzyl  $\alpha$ -diazoacetoacetate in the presence of base to give the trans-3-alkylated product (**302**) stereoselectively, which was converted into the PS-5 derivative (**304**), via the carbapenam (**303**) in the same manner as in the case of the synthesis of thienamycin from the diazo compound (**298**).

Chart 83



These methods described above, provide simple and effective routes to carbapenem-type antibiotics, and will be used as general methods for the construction of carbapenem and carbapenam systems.

As can be seen from the above summary, Professor Kametani has contributed much to, and stimulated a lot of interest in, the progress of organic chemistry in Japan as well as in the world. In addition to his distinguished academic contributions, he has nurtured more than two hundred organic and pharmaceutical chemists, who are now working in the first line of each field. He holds a big party with them once or twice a year, which we call "Kame No Xo Kai" (Party of Kametani's Family) in Japanese. Everyone belonging to "Kametani's family" makes an effort to be present at these parties in order to meet again and discuss chemistry with Professor Kametani.

Apart from his work as a great Professor in Tohoku University, he was elected a Member of the Science Council of Japan in 1978, and has played an important role in the progress of Japanese Science and in the interchange of scholarships between Japan and foreign countries. He has also contributed much to the management and development of the Pharmaceutical Society of Japan, as a Vice-President in 1979. Moreover, he is a leading figure in several symposiums and congresses in Japan, such as the Symposium on the Chemistry of Natural Products and the Congress of Heterocyclic Chemistry, and he spares no effort in training young chemists who will play important roles therein in the future.

Professor Kametani's academic contributions are also well known abroad. He has spoken many times, as a plenary or invited lecturer, in international symposiums and congresses, and has also taught organic chemistry at many foreign universities as a

visiting lecturer. As I'm sure all chemists know, HETEROCYCLES was founded by Professor Kametani and he is now energetically working for the promotion of this journal as its Editor. Moreover he has acted as an editor of "Journal of Heterocyclic Chemistry" and "Bio-organic Chemistry" since their first publications. He was Chairman of the organising committee for "The Third International Congress of Heterocyclic Chemistry" held in Sendai in 1971, and the contributions he made to this congress are beyond description as all participants will testify.

Another important contribution made to Japanese chemistry by Professor Kametani is in the important role he has played, and is still playing, as an international bridge between Japan and abroad. He has invited many organic chemists to Japan and Sendai, and other foreign chemists who come to Japan, like to meet Professor Kametani. He is well liked and admired by many domestic and foreign chemists, this fact attesting not only to his fame as a chemist, but also to his warm personality and great humanity. By these qualities he has made Tohoku University famous to chemists around the world.

Professor Kametani appears to be an open-hearted man, but he is a steady chemist who thinks highly of human relationships("wa" in Japanese) in the laboratory, and holds to the beautiful traditions of Japanese chemistry. He occasionally plays golf and sometimes goes to see Kabuki (traditional Japanese drama) with Mrs. Kametani.

In closing, as a representative of his students, I offer my cordial thanks to Professor Kametani on the occasion of his retirement for his guidance to us over many years, and wish Professor and Mrs. Kametani a long continuation of healthy life. After retirement from Tohoku University he will continue his research work in Tokyo. I hope that his work will continue to flourish and that he will contribute further to the advancement of organic chemistry. I also beg his continuing guidance and encouragement of us for our future work in chemistry.

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