ACADEMIC STUDIES BY PROFESSOR TETSUJI KAMETANI
Keiichiro Fukumoto, The Editor

Professor Kametani's research career as an organic chemist started in 1942 at Tokyo Imperial University* under the guidance of Professor Shigehiko Sugasawa and he published his first paper in J. Pharm. Soc. Japan [**65**, 572 (1945)]. This study aimed to synthesize an isoquinoline alkaloid, emetine, and greatly influenced his academic career. After he had completed his Ph. D. work, he moved to Osaka University and quickly established an international reputation of the studies of synthesis of heterocyclic compounds containing nitrogen atom(s), and had published 50 papers before being appointed to Tohoku University in 1959. From that time his works were rapidly extended and blossomed. He has published more than one thousand papers on natural product and heterocyclic chemistry. Professor Kametani obtained the Academic Prize of the Pharmaceutical Society of Japan in 1969 and he was conferred the Fujihara Prize for "Synthetic Studies on Physiologically Active Natural Products" in 1980. He also obtained the Medal of Honor with Purple Ribbon (Shiju Hosho) from Emperor in 1979 for "Synthesis of Natural Products and Development of New Medicines". Recently the third International Award of Heterocyclic Chemistry for "Total Syntheses of Heterocyclic Natural Products" was given to him in 1985.

In 1974, Professor Kametani developed an effective method of analysis for designing synthetic approaches, based on fragmentation processes in mass spectrometry, and named this "Retro Mass Spectral Synthesis". Using this method, he has synthesized many type of natural products in the last 20 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 Japan.

As it is impossible to list here all of his numerous publications, his main research work on the basis of the following classification was divided by the types of reactions developed by him.

1. Biomimetic-type Synthesis of Natural Products
2. Modified Pschorr Reaction
3. Photochemical Reaction
4. Benzyne Reaction
5. Natural Products Synthesis via Enamines
6. Natural Products Synthesis via Sulfeno-cycloamination
7. Retro Mass Spectral Synthesis
8. Thermolysis of Benzocyclobutenes
9. Chelation-controlled Stereoselective Carbon-Carbon Bond Formation
10. Natural Products Synthesis via Inter- and Intra-molecular Carbenoid Displacement Reaction
11. Natural Products Synthesis via Tandem Electrocyclic-[3,3] Sigmatropic Reaction.
12. Natural Products Synthesis via Double Michael Reaction
13. Medicinal Chemistry

* The name "Tokyo Imperial University" was changed to "University of Tokyo" after the second world war.

## 1. Biomimetic-type Synthesis of Natural Products

Some types of natural products, especially isoquinoline alkaloids such as morphine, are biosynthesized 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, and more recently by oxidation with singlet oxygen as follows.

1.1 Phenolic Oxidation

A. Chemical Oxidation: Morphine and related alkaloids can be biosynthesized via phenolic oxidation of reticuline (1) followed by some modification. Professor Kametani has mimicked this sequence and succeeded in the total synthesis of pallidine (3), a kind of morphinan alkaloids, from 1. A similar type of oxidative coupling was observed in Nature in the biogenesis of aporphine, proaporphine, cularine, homoaporphine, homoproaporphine and Amaryllidaceae alkaloids, and he has synthesized about 50 alkaloids along their biogenetic pathways by oxidation of the appropriate phenolic isoquinolines with potassium ferricyanide and ferric chloride.

B. Enzymic Oxidation: He investigated the oxidation of racemic and optically active reticuline (1) 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.

(Scheme 1)

$$(1) \qquad (2) \qquad (3)$$

$$(4) \qquad (5)$$
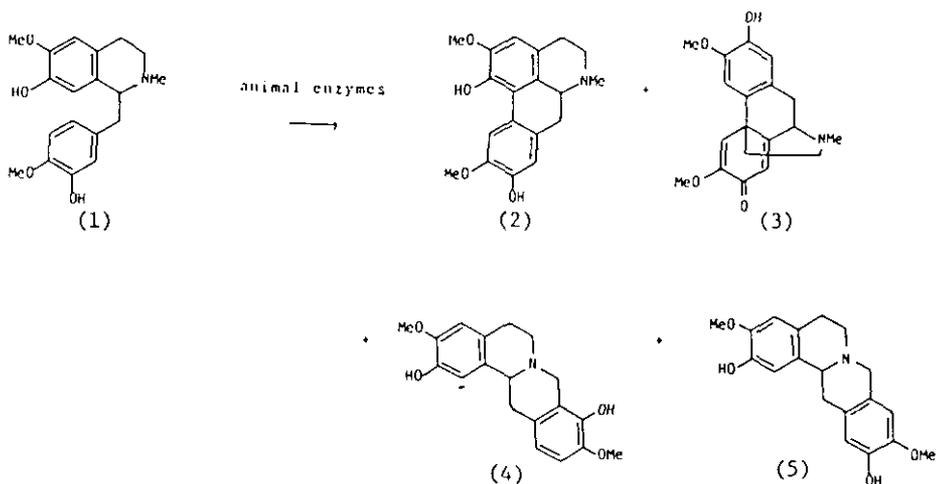
C. Enzymic Model: On the grounds that oxydases such as laccase and tyrosinase contain a copper ion, as the coenzyme, Professor Kametani assumed that a Cu_2Cl_2-O_2 system would show enzymic action. He investigated the oxidation of reticuline with this system in pyridine under mild conditions, and found the preferential formation of the ortho-ortho coupling product, which could not be obtained by other oxidizing agents. This work was further extended to the synthesis of aporphine and proto-berberine alkaloids from the N-oxide derivatives.

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 (7) is biosynthesized from deoxybrevian-amide E (6) by an oxidative coupling, and he has used singlet oxygen to realise this step in the laboratory. Thus (−)-deoxybrevianamide E (6), prepared from a gramine and a diketopiperazine, was treated with singlet oxygen to yield (−)-brevianamide E (7). This work also proved the structure of the alkaloid to be as represented by formula (7).

(Scheme 2)
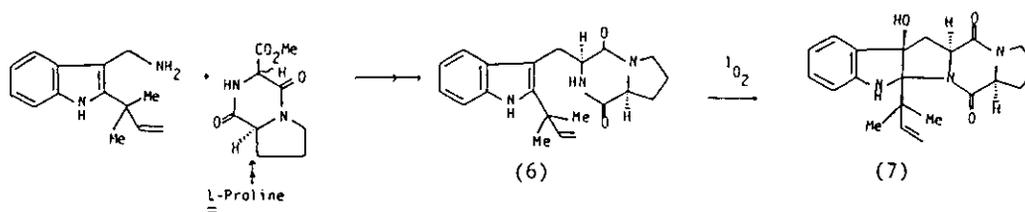
B. Total Synthesis of Camptothecin: Camptothecin (9), an anticaner alkaloid, is biosynthesized from an indole derivative, and the key step in this biogenesis is the transformation of the indole ring into a quinoline system. Professor Kametani has succeeded in this conversion by using singlet oxygen as shown in the following chart. This product was then converted into camptothecin (9).

(Scheme 3)
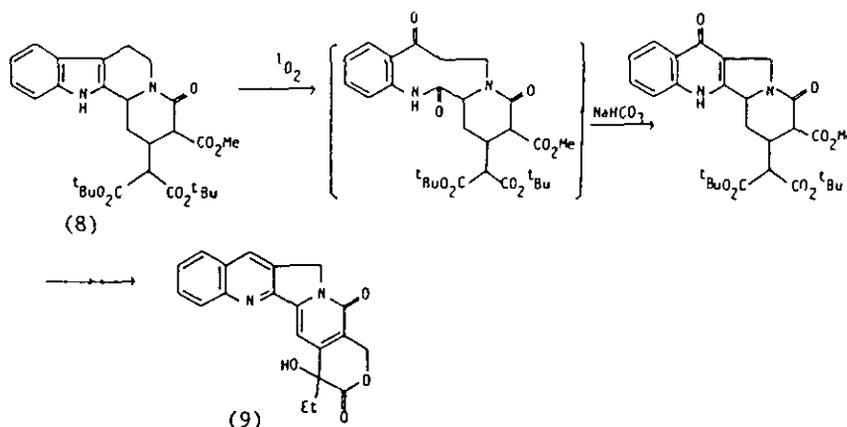
## 2. Modified Pschorr Reaction

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. 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 isoquinoline 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.

(Scheme 4)

Kametani Cyclisation
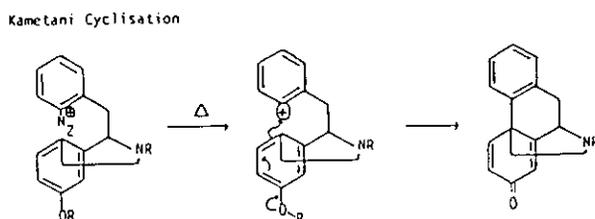
Based on this consideration, Professor Kametani has achieved a total synthesis of morphine (14), one of the most interesting and complicated isoquinoline alkaloids. Thus, the R-(−)-2'-aminobenzyl-isoquinoline (10) was diazotised and the resulting diazonium salt was decomposed thermally without a catalyst to give salutaridine (11), which on reduction with sodium borohydride followed by dehydration in the presence of hydrochloric acid furnished thebaine (12). Since thebaine (12) had previously been converted into morphine (14) via codeine (13), the total synthesis of morphine and related alkaloids was achieved.

(Scheme 5)
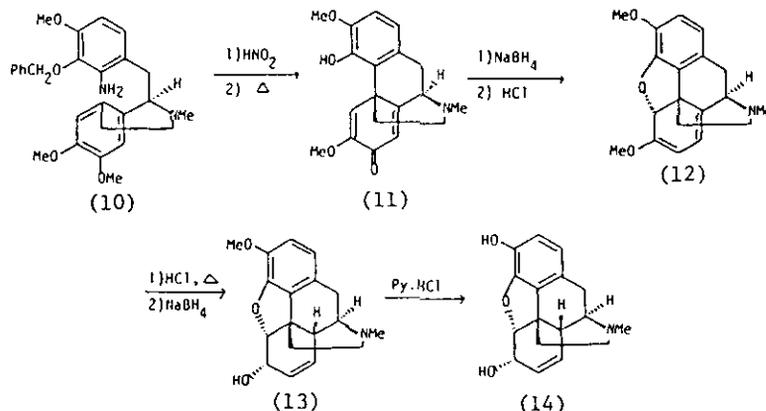
3. Photochemical Reaction

3.1 Photo-Pschorr 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. 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. He found in practice that irradiation of the diazonium salt (15) afforded androcymbine (16) after debenzylation and went on to synthesize many isoquinoline alkaloids using this photolysis.

(Scheme 6)
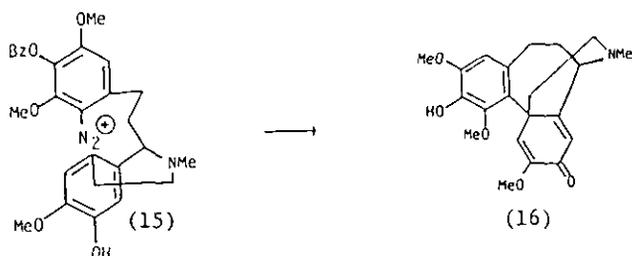


3.2 Photolytic Cyclodehydrohalogenation

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 benzylisoquinoline to also afford the dienone. Based on this consideration, Professor Kametani investigated utility of photolytic cyclodehydrohalogenation in the synthesis of dienone and aporphine alkaloids.

(Scheme 7)
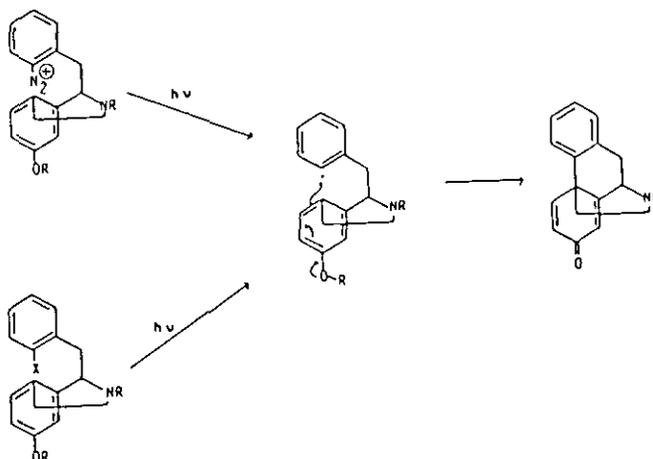
He firstly attempted a synthesis of aprophine and morphinandienone alkaloids; irradiation of 6'-bromoorientaline in the presence of sodium hydroxide afforded bracteoline and flavinantine. By this route he obtained many aporphine, morphinandienone, proaporphine, androcymbine, and Amaryllidaceae alkaloids. Among these studies, the synthesis of salutaridine (11) from 2'-bromoreticuline (17) provided a formal total synthesis of thebaine, codeine and morphine (14), because salutaridine (11) had already been converted into these alkaloids.

(Scheme 8)
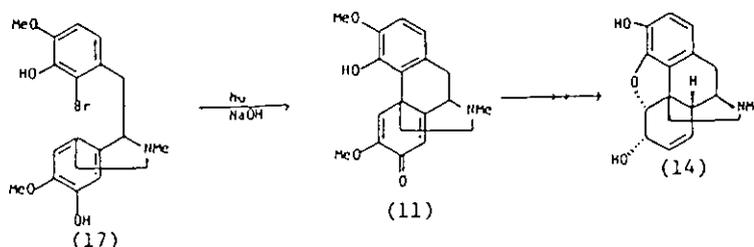
4. Benzyne Reaction

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. 2'-Bromoisoquinoline (18) was treated with sodium amide in liquid ammonia to give domesticine (19), amurine (20) and cryptowoline (21). 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.

(Scheme 9)
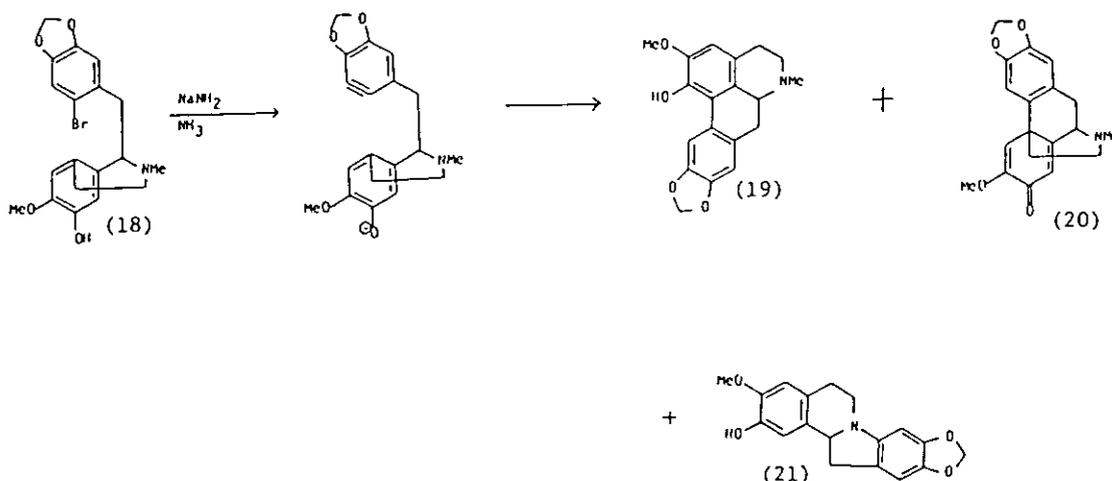
5. Natural Product Synthesis via Enamines

It is well known that the β-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-1-methyleneisoquinolines. He devised an enamine annelation whereby 3,4-dihydro-1-methylisoquinolines are converted to benzo-[a]quinolizines by Michael addition to α, β-unsaturated esters, and has synthesized emetine (26) by use of this reaction. Thus, reaction of the 3,4-dihydro-1-methylisoquinoline (22) with the ester (23) gave, in one step, the enamide (24) which was stereoselectively converted into the aldehyde (25). This was subjected to Pictet-Spengler reaction with homoveratrylamine to give emetine (26). I believe this to be the shortest route to emetine. In the same way, tubulosine, dihydrocorynantheol, corynantheine and ajmalicine were stereoselectively synthesized. The key intermediate (8) for total synthesis of camptothecin (9) was also prepared from 3,4-dihydro-β-carboline by enamine annelation.

(Scheme 10)
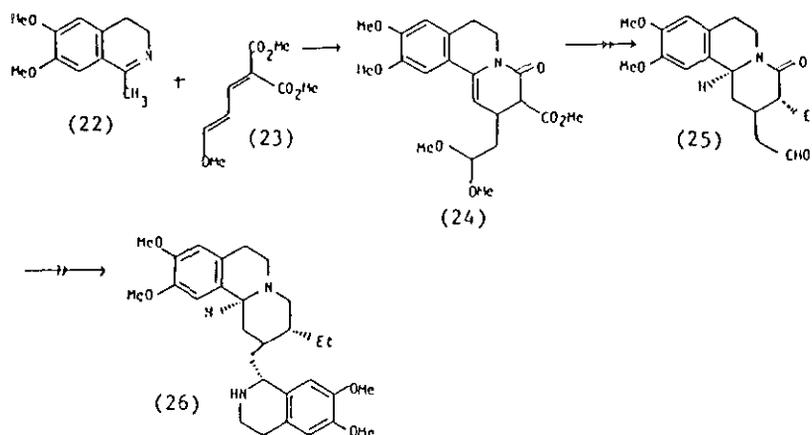
6. Natural Products Synthesis via Sulfeno-Cycloamination

A novel C-N bond formation was accomplished through addition of sulfenyl chlorides to amino- or amido-olefins followed by treatment of the adducts with bases. This method was applied to the syntheses of β-lactam antibiotics and pyrrolizidine alkaloids.

6.1 β-Lactam Antibiotics

α, β-Unsaturated amides (27) were reacted with benzenesulfenyl chloride to give the mixture of regioisomers of adducts which was treated with potassium hydride in the presence of phase transfer catalyst to afford β-lactams (28). Key synthetic intermediates of monobactams and nocardicin derivatives were prepared via this method. Thus, a stereoselective and efficient synthesis of β-lactams has been achieved.

(Scheme 11)
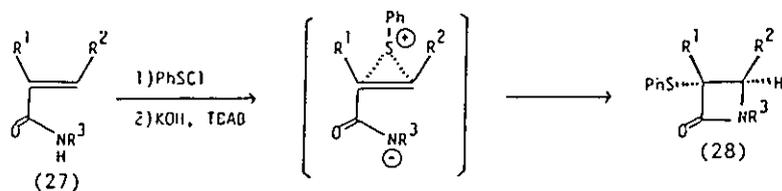
6.2 Pyrrolizidine Alkaloids

The amino-olefin (30) was prepared from 3-pyrrolidinone (29) through ragio- and stereoselective [3.3] sigmatropic rearrangement as a key step. This compound (30) was converted into (±)-retronecine (31) and turneforcidine (32) via the sulfeno-cycloamination. A highly effective synthesis of necine bases has been thus established.

(Scheme 12)
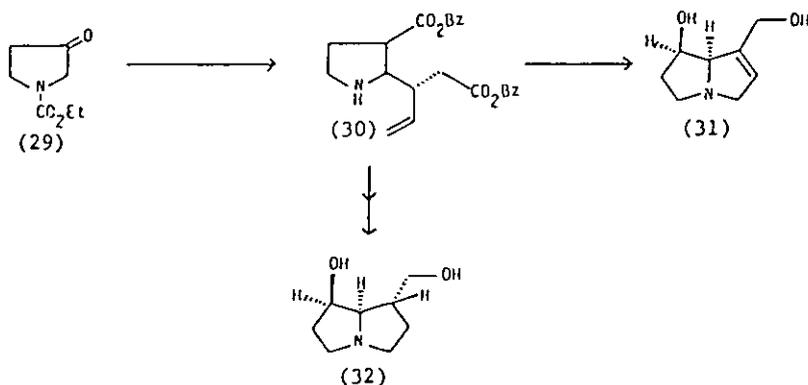
7.   Retro Mass Spectral Synthesis

In 1974, Professor Kametani proposed a new and effective synthetic design that he called "Retro Mass Spectral Synthesis". This analysis is based on fragmentation processes in mass spectrometry, and he has synthesized 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-methylisoquinoline (33), fragment ions (34 and 35) formed by loss of the C-1 substituent or C-1 hydrogen are observed, in addition to an M⁺-43 ion (36) derived by retro-Diels-Alder reaction of (33).

Reduction of 1-substituted 3,4-dihydroisoquinolines (34) is the most common method for the synthesis of 1-monosubstituted 1,2,3,4-tetrahydroisoquinoline derivatives (33). Another method is the alkylation of 1-unsubstituted 3,4-dihydroisoquinoline (35) 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 (34) from the molecular ion (33), and the alkylation method to a retrograde of the formation of ion (35) from (33) 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.

(Scheme 13)

→ mass spectral fragmentation process
→ chemical reaction
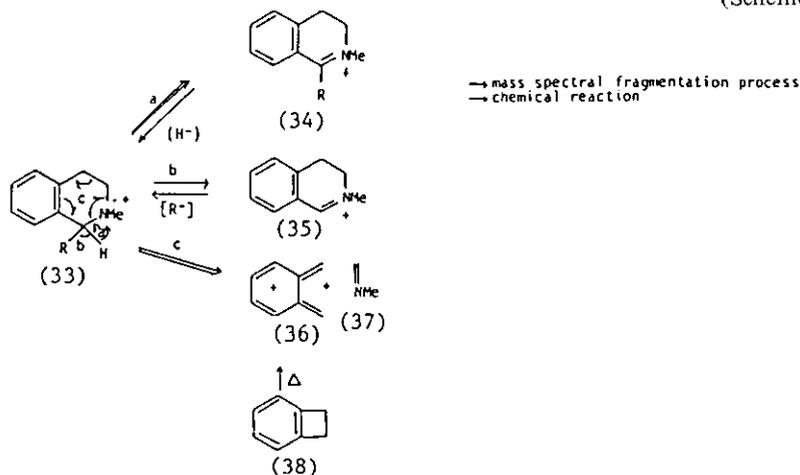
Professor Kametani therefore examined a synthesis of 1,2,3,4-tetrahydroisoquinoline from the compounds which correspond to the ion (36) and the fragment (37) formed by retro-Diels-Alder reaction of the molecular ion. He selected the benzocyclobutene (39) as the chemical equivalent of ion (36), because benzocyclobutene (38) readily produces o-quinodimethane (36) on heating. Reaction of (39)
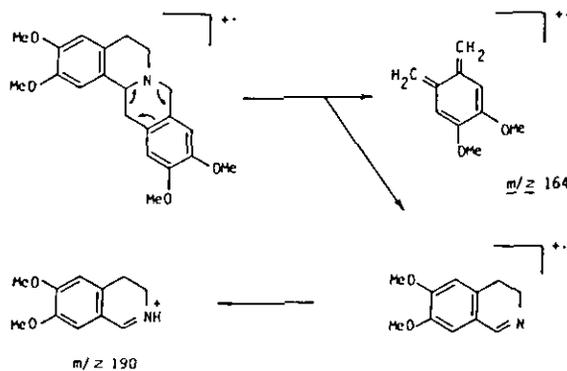
(Scheme 14)
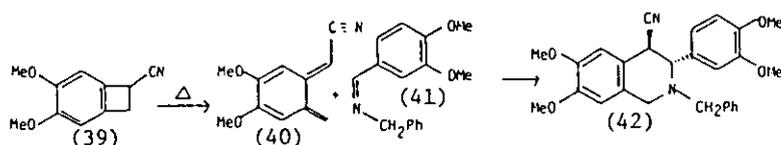
with the Schiff base (41), the synthon corresponding to ion (37), at 150 – 160°C, afforded the 1,2,3,4-tetrahydroisoquinoline (42) in both regio- and stereospecific manner by cycloaddition of the o-quinodimethane (40) to the Schiff base. Thus, he succeeded in developing a new synthesis of 1,2,3,4-tetrahydrosioquinolines by applying Retro Mass Spectral Synthetic Analysis.

The mass spectal fragmentation of protoberberine-type isoquinoline alkaloid is shown as follows.
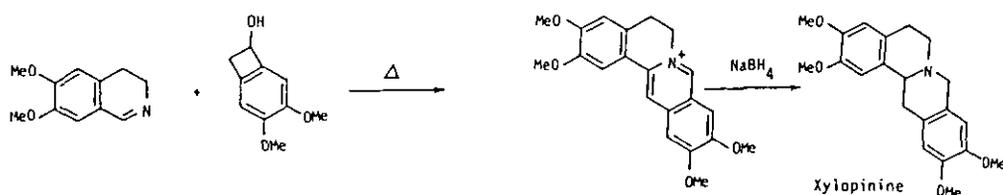
(Scheme 15)

Therefore Professor Kametani chose two synthons (equivalent to each mass fragment), one is dihydroisoquinoline (43) and the other benzocyclobutene (44) corresponding to the mass fragment of m/z 164.
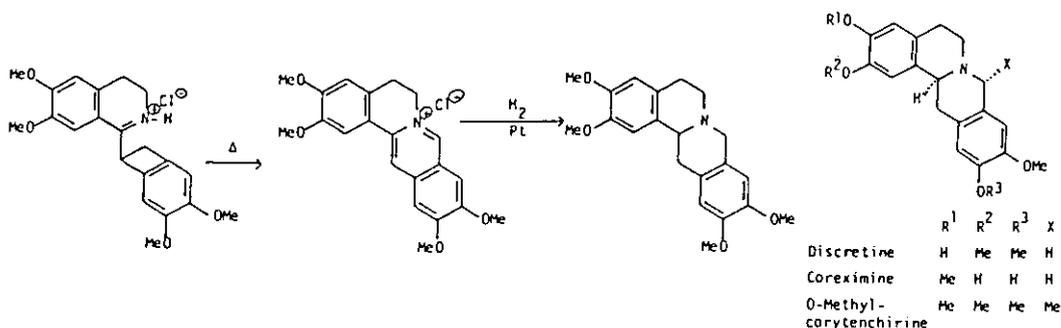
(Scheme 16)

(43)   (44)

Furthermore, in order to give a high regioselectivity of the cyclobutene synthon, some suitable substituent was introduced on the cyclobutene ring and it was also clarified that its selectivity was greatly affected by the E-effect of the introduced substituent on the cyclobutene ring. Xylopinine and berberine were synthesized by this method.
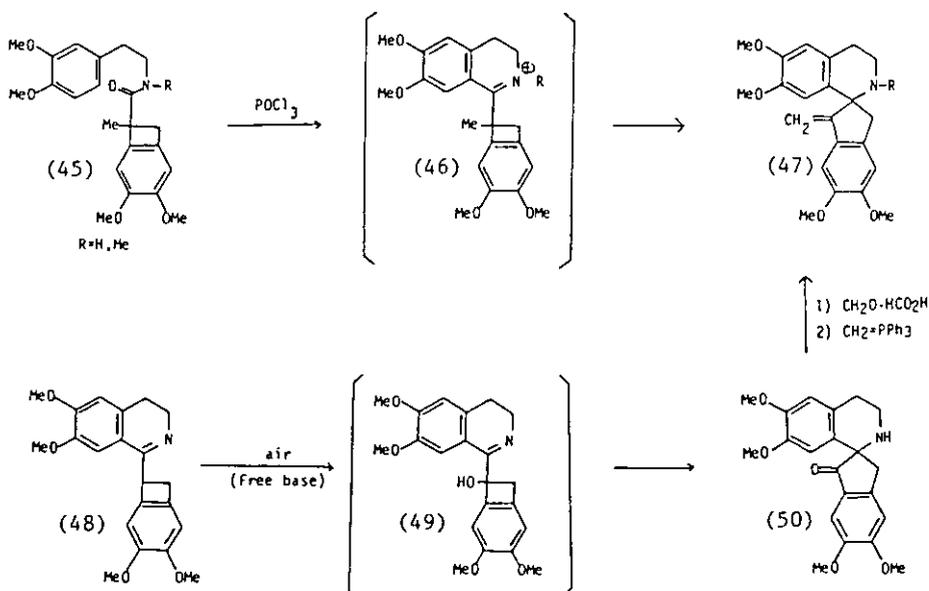
(Scheme 17)

— 10 —

By analogy, emetine, phthalideisoquinoline alkaloids, quinazolone alkaloids and yohimbine, as well as the indoloisoquinoline-type alkaloid, olivacine, and the fundamental skeleton of the very common antibiotics terramycin or adriamycin were also synthesized with very simple and effective procedures.

8. Thermolysis of Benzocyclobutenes

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.

(Scheme 18)

$\longrightarrow$ cycloaddition reaction
$\longrightarrow$ electrocyclic reaction
$\longrightarrow$ sigmatropic raction

8.1 Protoberberine Synthesis

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

(Scheme 19)

|	R^1	R^2	R^3	X
Discretine	H	Me	Me	H
Coreximine	Me	H	H	H
O-Methyl-corytenchirine	Me	Me	Me	Me

8.2 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 (45) with phosphoryl chloride in refluxing benzene did not provide the expected 3,4-dihydroisoquinolinium salt (46). Instead, he obtained the spirobenzylisoquinoline (47), 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 (48) is stable at room temperature, the free base is unstable in air. The free base (48) on standing in chloroform solution at room temperature was transformed into the ketospirobenzylisoquinoline (50) through the hydroxylated compound (49). He thus achieved a new synthesis of ochotensine-type compounds.

(Scheme 20)

Based on the above experiment, Professor Kametani accomplished a total synthesis of yohimbine (53) from the 1-spirobenzyl-β-carboline (51) via photo-rearranged product (52).

(Scheme 21)
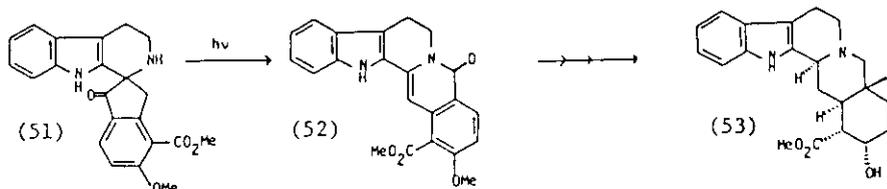
Professor Kametani further investigated the intramolecular cycloaddition reaction using benzo-cyclobutenes and succeeded in the synthesis of terpenes and steroids as follows.
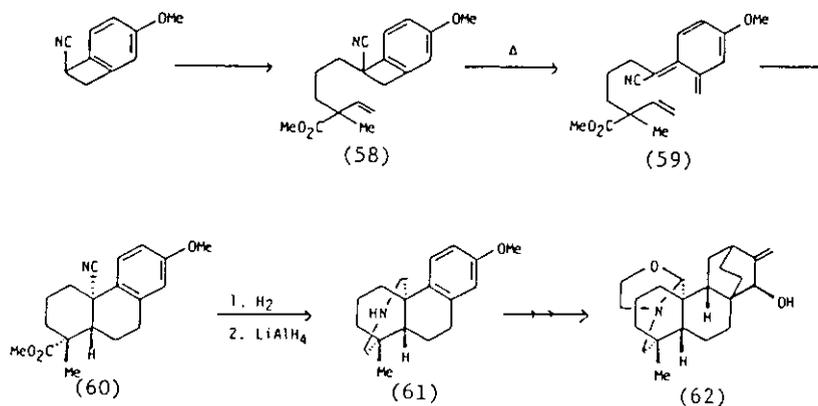
8.3 Diterpene Synthesis

A. Total Synthesis of Hibaol: Professor Kametani has developed a synthetic route to the hydro-phenanthrene ring, using intramolecular cycloaddition of an olefinic benzocyclobutene, and so he thought that it should be possible to synthesize, in one step, the hibaene ring system if a benzocyclo-butene substituted by a methylenecyclopentane unit is subjected to thermolysis. Based on this consideration, he investigated a total synthesis of dihydrohibaene and hibaol from 2-benzocyclobutenyl-ethylcyclopentanone. Heating the benzocyclobutane (54) in o-dichlorobenzene afforded the tetracyclic compound (56) in a regioselective and stereoselective manner via the o-quinodimethane (55). This was converted into hibaol (57) via several steps.

(Scheme 22)
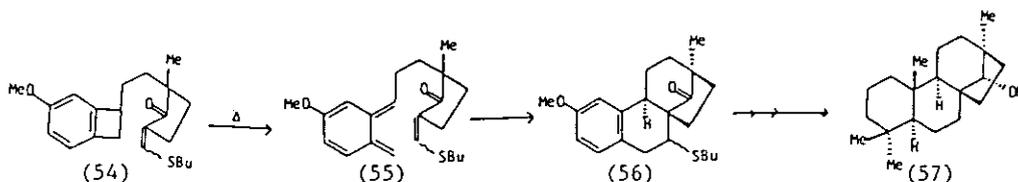
B. Diterpene Alkaloids: Professor Kametani attempted a simple synthesis of the key intermediate (61) for atisine (62) by intramolecular cycloaddition of o-quinodimethane. The olefin (58), was heated to give the tricyclic compound (60), in addition to its stereoisomer through the o-quinodimethane (59). Hydrogenation of the product (60) followed by lithium aluminium hydride reduction of the resulting lactam, afforded Nagata's intermediate (61). Thus, he achieved a simple and short synthesis of (61) by using the intramolecular cycloaddition reaction.

(Scheme 23)

(58)   (59)

(60)   (61)   (62)

8.4 Triterpene Synthesis

The pentacyclic aromatic diethers (63 and 64), 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 (65) and friedelin (66) by Ireland.

Since Professor Kametani found that intramolecular cycloaddition of an o-quinodimethane in the synthesis of diterpenes could proceed stereoselectively, 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}(Me)-C_7 unit of the target molecule corresponds to isoprene, and the remainder to the bis-o-quinodimethane.

(Scheme 24)

(65)

(63) R^1=Me, R^2=C_2H_5
(64) R^1=C_2H_5, R^2=Me

(66)
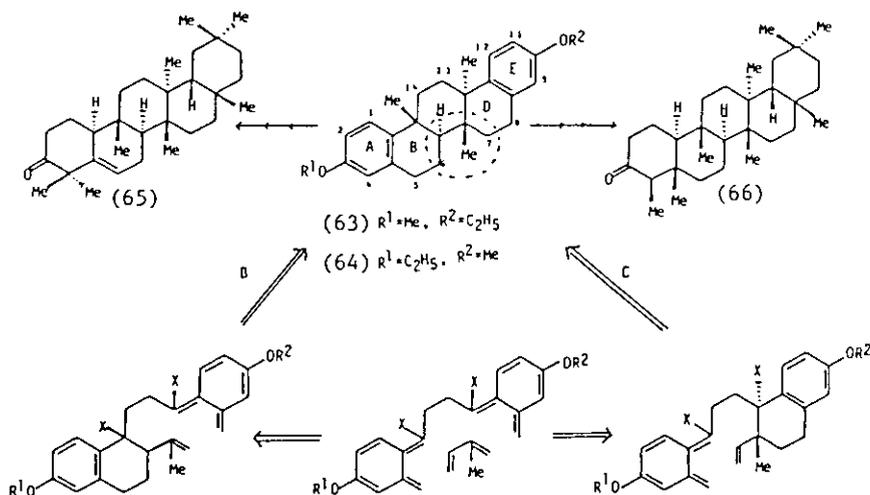
Heating (67, R^1 = Me) with isoprene gave, in good yield, a mixture of the tetralins (68 and 69) in the ratio of 1 : 1. Condensation of the former (68) with benzocyclobutenylethyl iodide (70, R^2 = Et), proceeded stereoselectively to give the key intermediate (71) with the 1-cyano and 2-vinyl groups in a cis relationship. Thermolysis of (71) provided the pentacyclic compound (72) stereoselectively, via o-quinodimethane. This product was reduced with DIBAL followed by Wolff-Kishner reduction to yield the expected 6a,12b,14aβ-trimethylated pentacyclic compound (63), identical to that obtained by Ireland.

By analogous reactions, using 1-cyano-4-ethoxybenzocyclobutene (67, R^1 = Et) and 1-cyano-1-(2-iodoethyl)-4-methoxybenzocyclobutene (70, R^2 = Me), the pentacyclic aromatic diether (64), which had been converted into friedelin by Ireland, was synthesized as shown in the following chart.

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.

(Scheme 25)
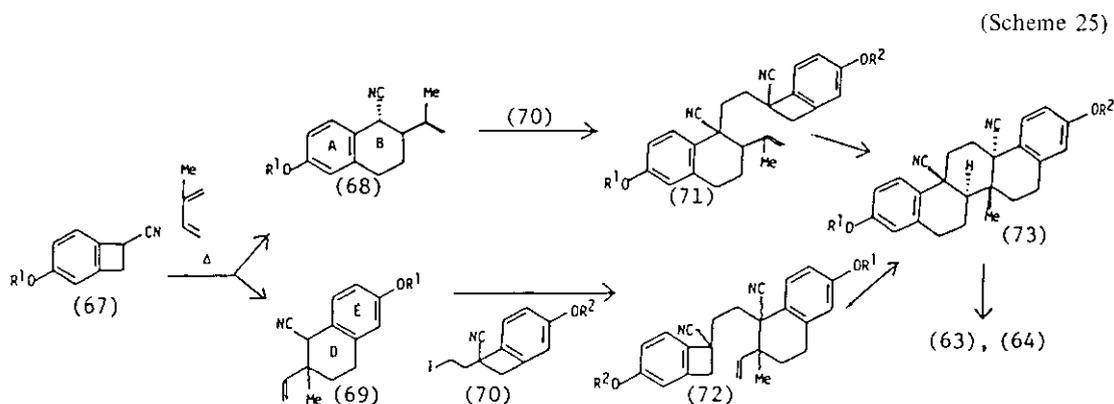
8.5 Steroid Synthesis

A. Estrone: With the above knowledge of benzocyclobutene thermolysis, Professor Kametani firstly designed a novel synthesis of D-homoestrone (77), which had been correlated to estrone (78), from the benzocyclobutene (74) via o-quinodimethane (75).

(Scheme 26)
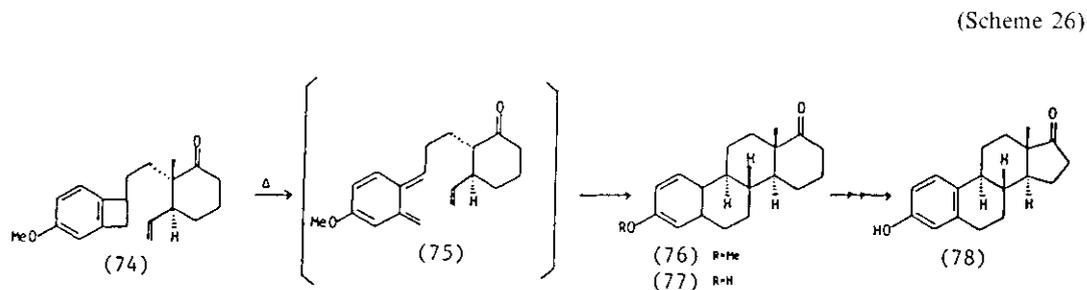
Thus, the olefinic benzocyclobutene (74) was smoothly and stereoselectively converted, in boiling o-dichlorobenzene for 4 h, to O-methyl-D-homoestrone (76) which was correlated to estrone (78). Based on the highly stereoselective cycloaddition reaction described above, thermolysis of the optically active olefinic benzocyclobutene was expected to give an optically active steroid by asymmetric induction. According to this assumption, optically active estradiol was also stereoselectively synthesized.

B. β-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 β-ecdysone (83). Michael addition of 1-cyano-4-methoxybenzocyclobutene to the nitroolefin (79) yielded the key intermediate (80), which on heating afforded the D-ring aromatic steroid (81) with cis-B, C, ring juncture. This was converted into the triacetate (82), through many steps. Since compound (82) had already been transformed into β-ecdysone (83), this work constituted a formal total synthesis of β-ecdysone (83).

(Scheme 27)

(79)   (80)   (81)

(82)   (83)

(84) X=α-OH
(85) X=β-OH
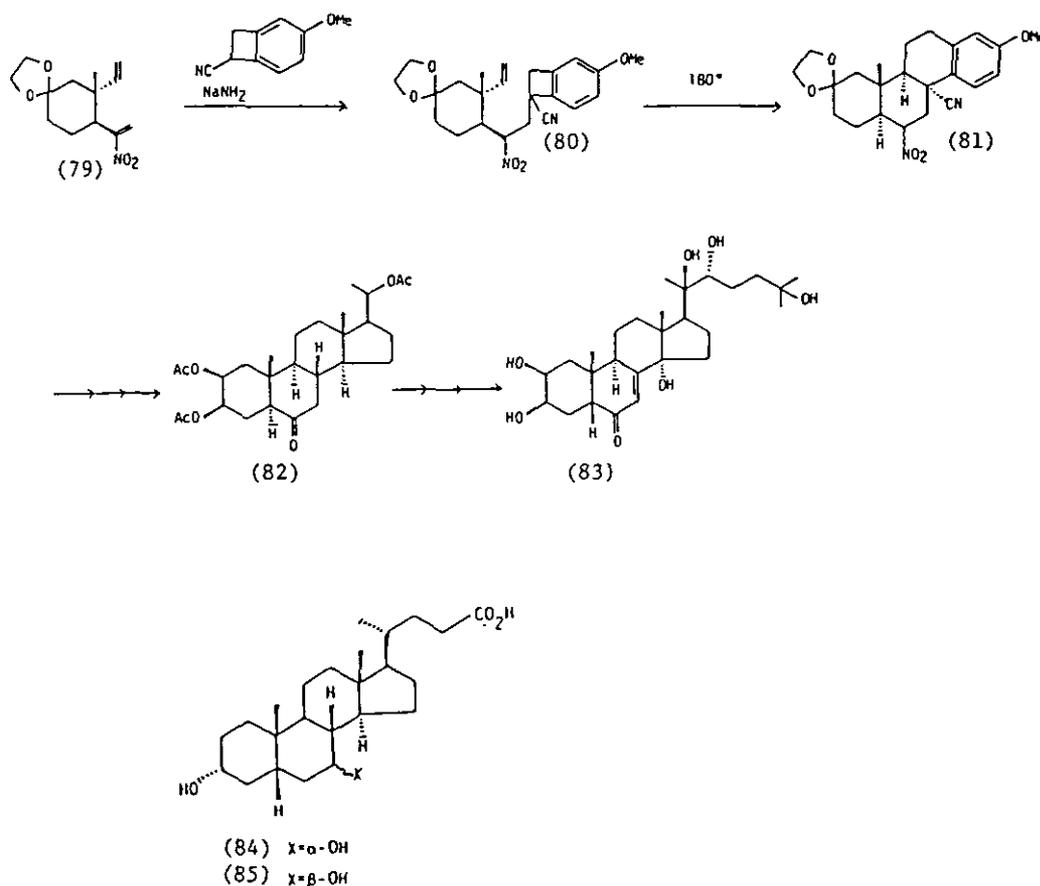
In the similar way, (+)-chenodeoxycholic acid (84) and ursodeoxycholic acid (85) were totally synthesized. Since Professor Kametani's first introduction of the intramolecular cycloaddition reaction of o-quinodimethanes for the synthesis of D-homoestrone, many papers, by several groups including his own, 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.

8.6 Vitamin D₃

The extraordinary accelerating effects of arylsulfinyl, arylsulfonyl, and diphenylphosphinoyl carbanion substituents for cyclobutene ring-opening reaction of bicyclo[4.2.0]oct-1(6)-ene derivatives were found by Professor Kametani. The dienes so generated by this method were applied for the synthesis of vitamin D_3 (90). Namely the diphenylphosphinoylcyclobutene (87) was prepared from the benzocyclobutene derivative (86) and subjected to the ring-opening reaction followed by condensation with Grundmann's ketone under the same reaction conditions. The triene formed was then transformed into vitamin D_3 via sulfur dioxide adduct. Recently Professor Kametani has developed a new alternative route to active vitamin D_3 via cyclovitamin D_3 derivatives. These methods are very effective for the synthesis of the important vitamins.

(Scheme 28)
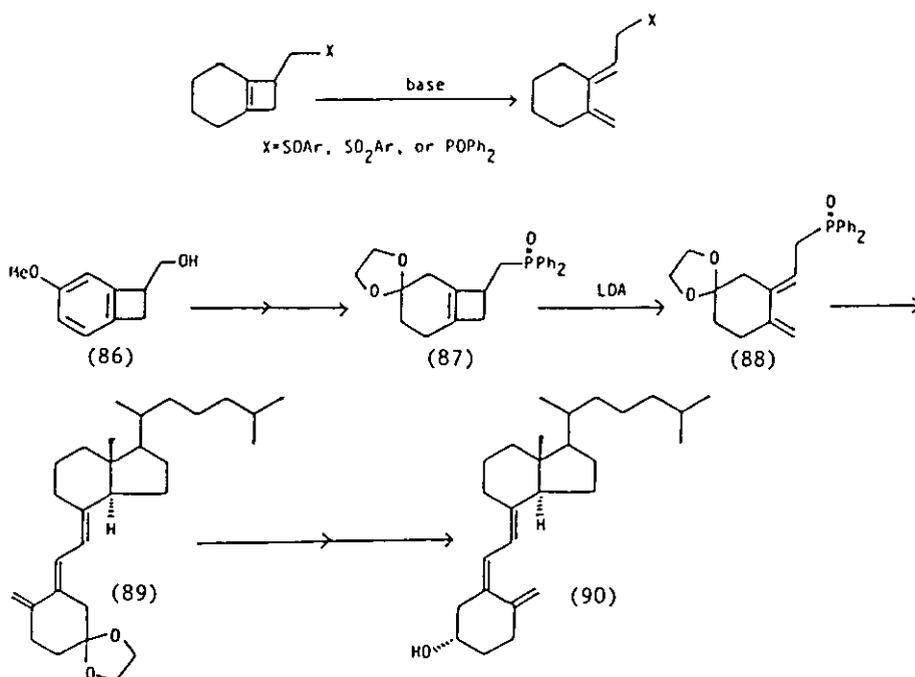
9. Chelation-controlled Stereoselective Carbon-Carbon Bond Formation

Stereoselective construction of steroidal side chains has been important subject, because physiological activity of steroids has been reflected in the stereochemistry of the side chain.

Professor Kametani has found that chelation-controlled carbon-carbon bond formation reaction was effective to construct steroidal side chain of physiologically active steroids. He applied his methodology to the synthesis of brassinolide, a plant growth promoting steroid.

The addition reaction of the dianion of 3-isopropyltetronic acid to the 20-oxo steroid afforded the chelation-controlled adduct, whose syn-dehydration reaction brought about the formation of the (Z)-5-ylidenetetronate (93). The stereoselective reduction of the (Z)-5-ylidenetetronate over 5% rhodium-alumina afforded the saturated lactone (94) as the sole product bearing 22R, 23R, and 24S-configuration. This lactone was further converted into brassinolide (95) by several steps.
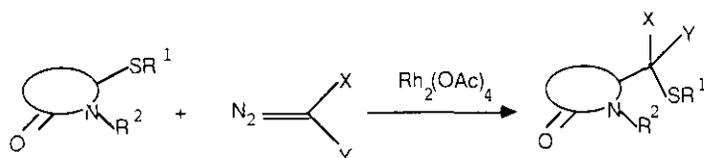
(Scheme 29)
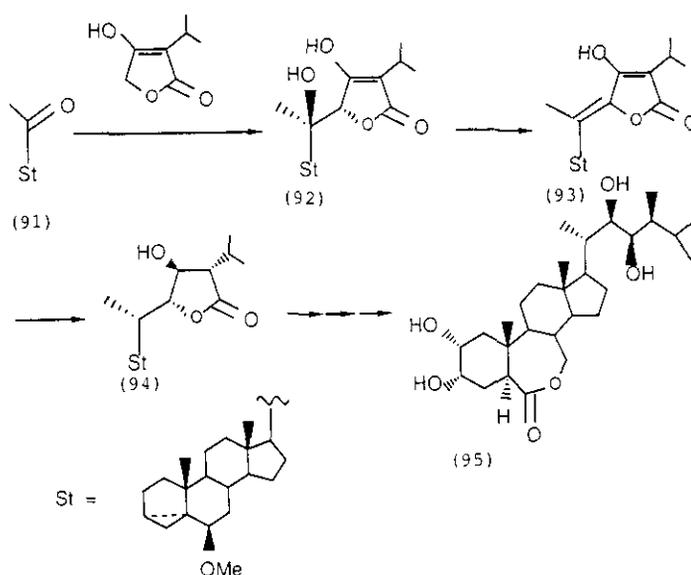
## 10. Natural Products Synthesis via Inter- and Intramolecular Carbenoid Desplacement Reaction

Professor Kametani has accomplished a development of a novel carbon-carbon bond formation reaction by employing an intramolecular and an intermolecular carbenoid displacement reactions. He found that the reaction of lactams bearing alkyl- or arylthio group at the α-position to nitrogen with carbenoid afforded the carbon-displaced products in moderate yields.
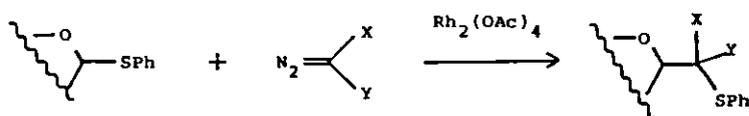
(Scheme 30)

This synthetic strategy was successfully applied to the synthesis of pyrrolizidine alkaloids such as supinidine (96), trachelanthamidine (97), and isoretronecanol (98).

(Scheme 31)
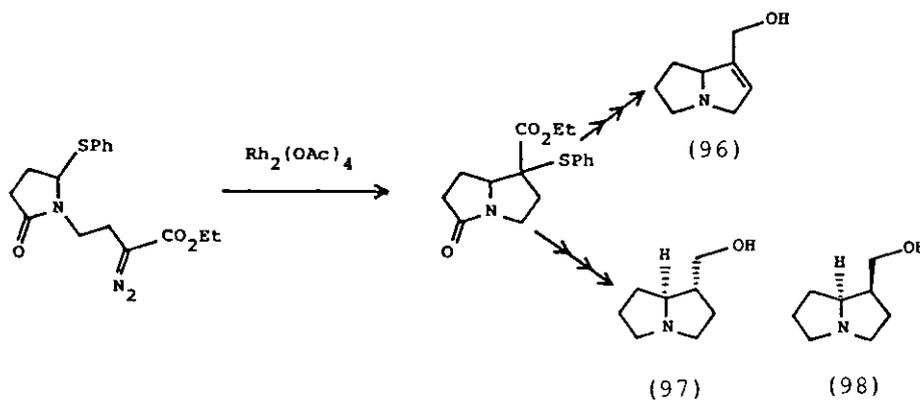
Moreover, the treatment of 1-phenylthiotetrahydrofuran and 1-phenylthiotetrahydropyran with diazo-compounds also brought about the carbon introducing reaction to give the carbon-displaced products, and this procedure was utilized in the C-glycosilation reaction of furanose and pyranose derivatives.

(Scheme 32)

Professor Kametani applied this reaction to the synthesis of anti-bacterial and anti-viral C-nucleoside, (+)-showdomycin (99).

(Scheme 33)

(99)
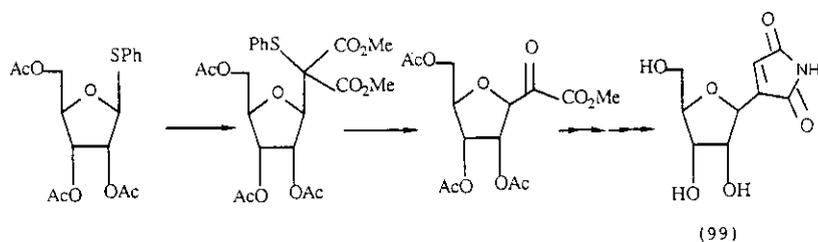
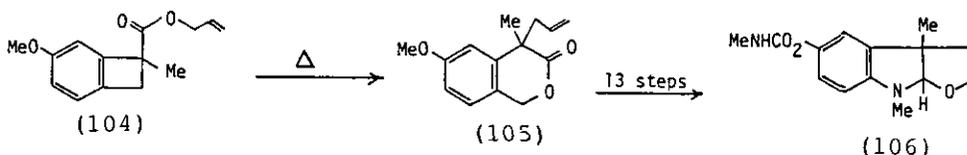## 11. Natural Products Synthesis via Tandem Electrocyclic-[3,3] Sigmatropic Reaction

Professor Kametani developed a novel and practically useful tandem electrocyclic-[3,3] sigmatropic reaction of benzocyclobutene derivatives. The thermolysis of 1-alkyl-1-carballyloxybenzocyclobutenes (100), readily derivable from 1-cyanobenzocyclobutene, gave 4-alkyl-4-allylisochroman-3-ones (101) via a tandem electrocyclic-[3,3] sigmatropic reaction in an excellent yield. On the other hand, 1-alkyl-1-carbobenzyloxybenzocyclobutenes (102) afforded 4-alkyl-4-benzylisochroman-3-ones (103) via a tandem electrocyclic-[1,3] sigmatropic reaction.

(Scheme 34)

(100)   (101)

(102)   (103)
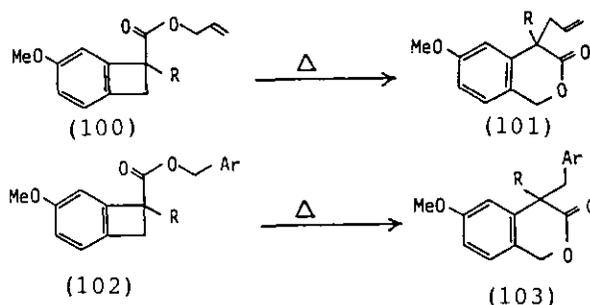
He successfully applied this methodology to a total synthesis of (+)-physovenine (106), a minor alkaloid of Calabar bean. 4-Allyl-6-methoxy-4-methylisochroman-3-one (105), obtained quantitatively from the thermolysis of 5-methoxy-1-methylbenzocyclobutene (104) was converted to physovenine in a 13-step sequence in 20% overall yield. The procedure might be applicable for synthesizing other alkaloids of Calabar bean.

(Scheme 35)

(104)   (105)   (106)

12. Natural Products Synthesis via Double Michael Reaction

Using new synthetic strategy, intramolecular double Michael reaction, a synthetic approach to aconitine alkaloids, a formal total synthesis of (+)-atisirene and syntheses of indolizidine and quinolizidine alkaloids were performed by Professor Kametani.

12.1 Synthetic Approach to Aconitine Alkaloids: Stereoselective Construction of CDE Ring System

4-Formyl-4-methyl-1-pentene (107) was transformed into the α, β-unsaturated enone ester (108), which was treated with lithium hexamethyldisilazide to give the bicyclo[5.2.2.0]undecane (109). After conversion of the ethoxycarbonyl group into the methoxymethyloxymethyl group and introduction of the epoxide, acidic treatment formed the alcohol having furan ring, whose solvolysis afforded the CDE part (110) of lycoctonine skeleton.

(Scheme 36)

(107)   (108)   (109)   (110)
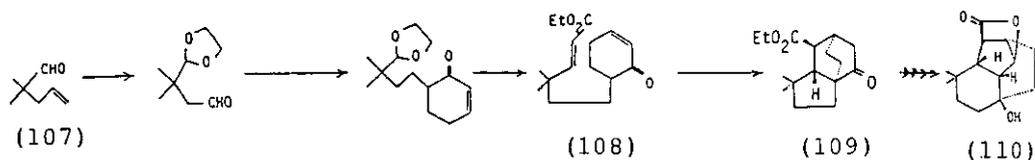
12.2   Formal Total Synthesis of (+)-Atisirene

The trans-decaline (112) derived from (+)-Wieland-Miescher ketone (111) was converted into the α, β-unsaturated enone ester (113), whose intramolecular double Michael reaction using lithium hexamethyldisilazide furnished quantitatively 11-methoxycarbonyl-15-noratisiran-15-one (114). The tetracyclic product was transformed into 15-norisoatisirene (115), which had been correlated to (+)-atisirene (116).

(Scheme 37)

(111)   (112)   (113)   (114)

(115)   (116)
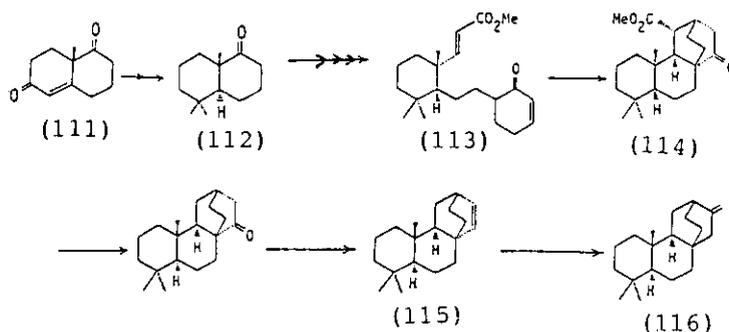
12.3   Total Syntheses of Quinolizidine and Indolizidine Alkaloids

Novel syntheses of quinolizidines and indolizidines from α, β-unsaturated enamide esters by heating with TMSCl, Et₃N and ZnCl₂ at 180°C or by treatment with TBSOTf and Et₃N at ambient temperature were exploited. Application of these methodologies led to facile total syntheses of (±)-epilupinine (117) and (±)-tylophorine (118).

(Scheme 38)

(117)

(118)
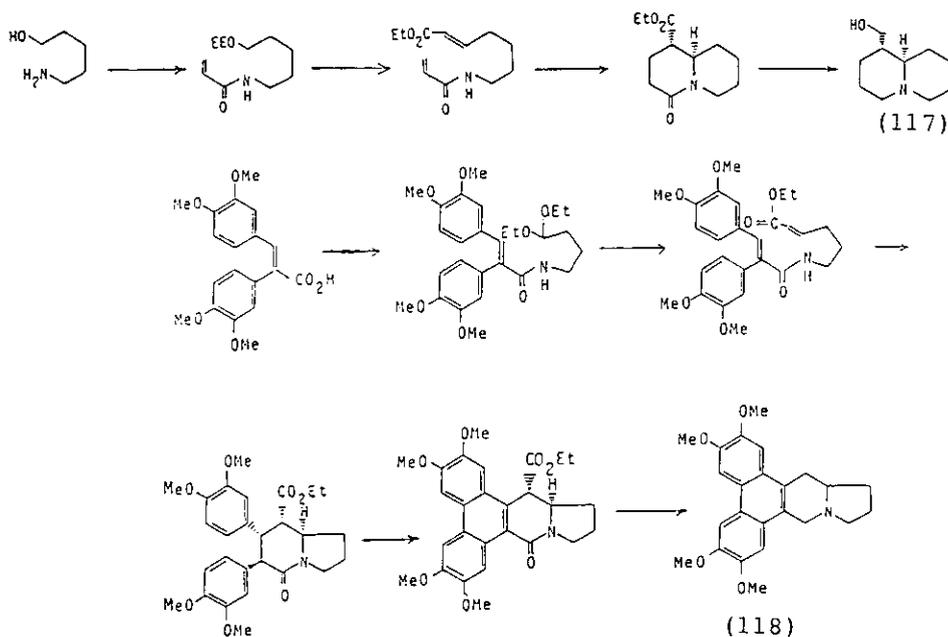
12.4 Total Synthesis of (±)-Pentalenic Acid and (±)-Pentalenene

The cyclopentenone (119) was converted into the bis-enone (120), which was subjected to the annulation carried out under the same conditions as above. Major isomer (121) of tricyclo[7.3.0.0.^{1,5}]-dodecanediones was contracted to the tricyclo[6.3.0.0.^{4,8}]undecane (122) via Wolff rearrangement. The ester (122) was transformed into (±)-pentalenic acid (123) and (±)-pentalenene (124).

(Scheme 39)

(119)   (120)   (121)   (122)

(123) R^1=CO$_2$H, R^2=OH

(124) R^1=Me, R^2=H
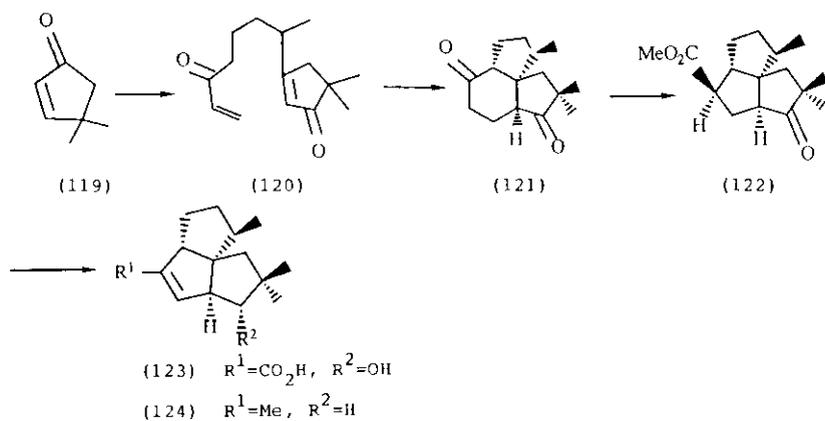
13. Medicinal Chemistry

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 synthesized. In this section only the synthesis of pentazocine and carbapenem antibiotics was described.

13.1 Pentazocine

Professor Kametani attempted an alternative and industrial synthesis of pentazocine (129), 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 (125) with the glyoxalate (126) gave the 2-benzylpiperidin-4-ol (127), which was subjected to Grewe cyclisation using hydrobromic acid to produce the benzomorphan (128). Quaternisation of this product with 3,3-dimethylallyl bromide, followed by dezenzylation with sodium thiophenolate, a new reaction developed by Professor Kametani, afforded pentazocine (129).
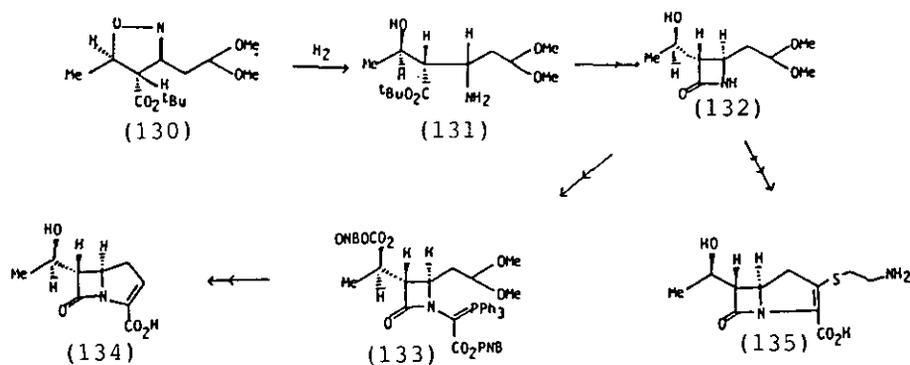
(Scheme 40)
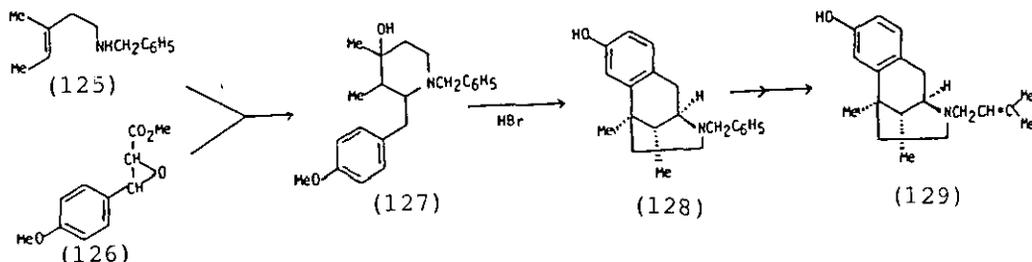
13.2 Carbapenem Antibiotics

Professor Kametani has developed new and stereoselective synthetic routes to thienamycin and related antibiotics using a new reaction found by him. Firstly, he synthesized descysteaminylthienamycin (134), which showed almost the same antibacterial activity as thienamycin, via the isoxazoline (130) prepared by 1,3-dipolar cycloaddition. The isoxazoline (130) was stereoselectively converted into the β-lactam (132), having the same stereochemistry as thienamycin. The hydroxyl group of the β-lactam (132) was then protected with o-nitrobenzyl group and this product was converted into descysteaminyl-thienamycin (134) by an intramolecular Wittig reaction of the phosphorane (133) followed by removal of the protecting group.

He also succeeded in the synthesis of thienamycin (135) from the above intermediate (132) by the application of the established method. Furthermore the alternative route to thienamycin was devised through the asymmetric 1,3-dipolar cycloaddition of the chiral nitrone derivative, and this strategy led to the enantioselective total synthesis of thienamycin.

(Scheme 41)

(130)   (131)   (132)

(134)   (133)   (135)

In addition to this work, Professor Kametani has developed a new and general alkylation reaction for the C_4-position of β-lactams, and using it has achieved the synthesis of PS-5 (136) and related antibiotics.

(Scheme 42)

(136)
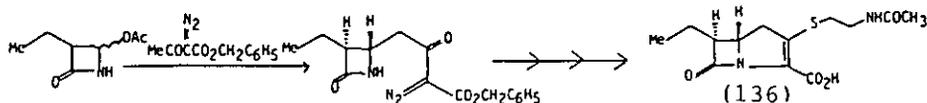
In conclusion, Professor Kametani accomplished the total syntheses of various type of natural products and also studied the synthesis of heterocyclic compounds by new reactions. In the above both cases he had used novel reactions and its application led to the synthesis of objective heterocyclic compounds and natural products. More recently he has published nearly 1200 papers regarding "Studies on the Syntheses of Heterocyclic Compounds and Natural Products".