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TOTAL SYNTHESES OF NATURAL PRODUCTS BY THERMOLYSIS

Tetsuji Kametani

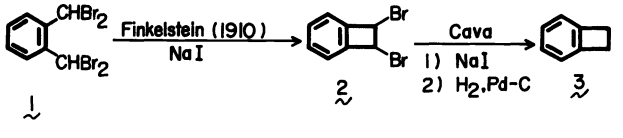
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Abstract — Total and formal total syntheses of protoberberine alkaloids, ochotensine type compounds, yohimbine, dihydrohibaene, hibaol, atisine and related compounds, alunusenone, friedelin, estrone and (+)-estradiol are described. In these synthetic works, the key step is electrocyclic reaction or inter- and intramolecular cycloaddition reaction of o-quinodimethanes generated in situ from benzocyclobutenes.

INTRODUCTION

The benzocyclobutenes (Ref. 1) have a long history in organic chemistry. The first synthesis of the benzocyclobutene ring system was reported by Finkelstein (Ref. 2) in 1910, who prepared 1,2-dibromobenzocyclobutene (2) by treatment of α,α',β,β'-tetrabromo-o-xylene (1) with sodium iodide. After long intermission of this chemistry, Professor Cava (Ref. 3), in 1956, synthesized the parent benzocyclobutene (3) by catalytic hydrogenation of the diiodide prepared from 2 as shown in the first Chart.

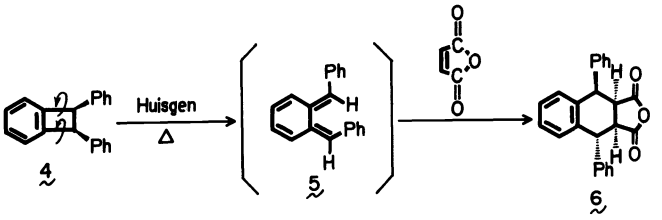
Chart 1



1 2 3

Soon thereafter, Jensen and Coleman (Ref. 4) carried out a thermolysis of 1,2-diphenylbenzocyclobutene (4) in the presence of maleic anhydride, and they obtained the tetralin derivative (6) and suggested the intermediate to be the o-quinodimethane (5). In 1964, Professor Huisgen (Ref. 5) proved that this type of reaction proceeded stereoselectively, and in 1970, Professor Woodward (Ref. 6) proposed that thermolytic ring-opening of benzocyclobutenes occurs in a conrotatory manner.

Chart 2

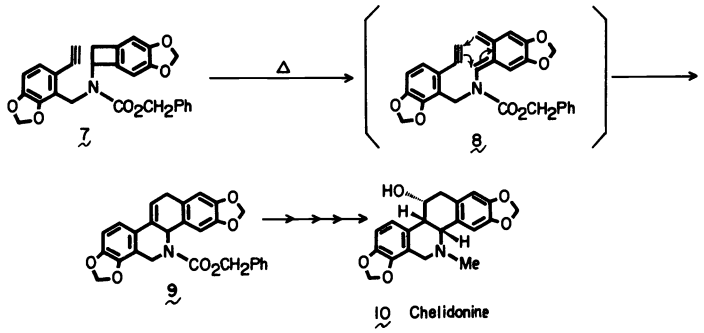


4 5 6

The first application of benzocyclobutene to synthesis of natural products was reported by Professor Oppolzer (Ref. 7) in 1971, who synthesized chelidonine (10), a kind of isoquinoline alkaloids, as shown in Chart 3. Key reaction in this synthesis was an intramolecular cycloaddition of the o-quinodimethane 8, derived from the benzocyclobutene (7) to form the benzophenanthridine system (9).

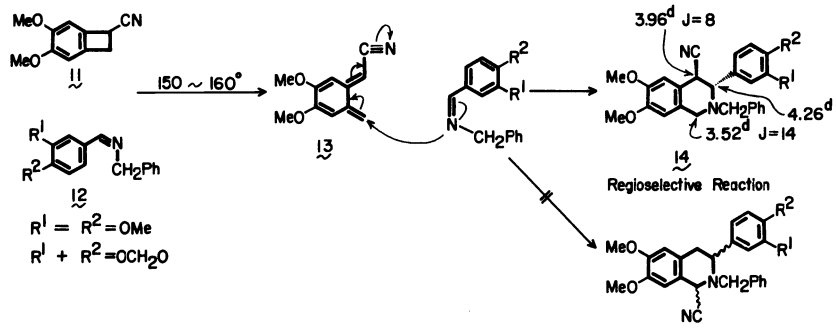
Based on the finding that o-quinodimethane, generated in situ by thermolysis of benzocyclobutenes, forms tetralin derivatives by an electrocyclic reaction or cycloaddition reaction, we investigated the possibility of converting benzocyclobutenes via ring-opened intermediates into natural products having a complicated ring system (Ref. 8). In this congress, I wish to talk on our recent works in this field.

Chart 3



Initially, we examined that thermolysis of benzocyclobutenes in the presence of imines as the dienophiles in order to develop a new method of isoquinoline synthesis (Ref. 9). Thus, reaction of 1-cyanobenzocyclobutene (11) with Schiff bases (12) was carried out at 150 - 160°C without solvent to give only the 3, 4-disubstituted 1,2,3,4-tetrahydroisoquinolines (14) whose structures were deduced from nmr spectral analysis. Although the stereochemistry of the C-3 and C-4 positions was unclear, we assumed that the trans-configuration was the preferred one since epimerisation at the C-4 position would give a more thermodynamically stable compounds. Since the 3,4-disubstituted isoquinoline was obtained as a single stereostructure, it may be concluded that the cycloaddition proceeded in both a regioselective and stereoselective manner. Therefore, we developed a new and simple synthesis of the isoquinoline ring in a regioselective and stereoselective manner and also found that the o-quinodimethane (13) reacted with an imine system.

Chart 4



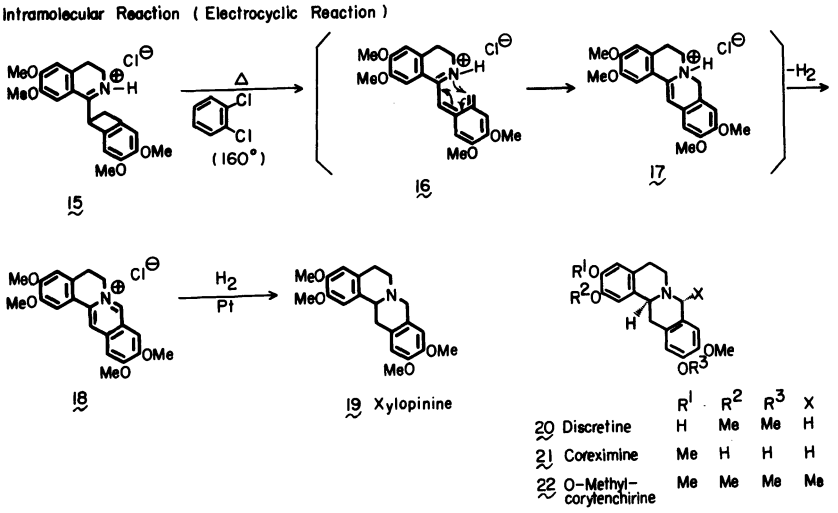
TOTAL SYNTHESIS OF ISOQUINOLINE AND INDOLE ALKALOIDS

Protoberberine alkaloids. As shown in the preceding Charts, since o-quinodimethanes could react intramolecularly (electrocyclic reaction) and intermolecularly (cycloaddition), we investigated protoberberine synthesis by both methods.

Thermolysis of the 1-benzocyclobutenyl-3,4-dihydroisoquinoline hydrochloride (15) at 160 - 180°C for 20 min gave the protoberberine (18) in 90 % yield. This probably involved an electrocyclic reaction of benzocyclobutene to form the o-quinodimethane (16) which underwent a second electrocyclic reaction with the 3,4-dihydroisoquinoline system to yield the 7,8-dihydroprotoberberine intermediate (17) which was then easily dehydrogenated in the air to give the protoberberine (18). Hydrogenation of the quaternary base thus afforded the alkaloid xylopinine (19) in quantitative yield (Ref. 10). In the same manner, discretine (20) (Ref. 11), coreximine (21) (Ref. 12) and O-methylcorytenchirine (22) (Ref. 13) have been synthesised from the appropriate benzocyclobutenes.

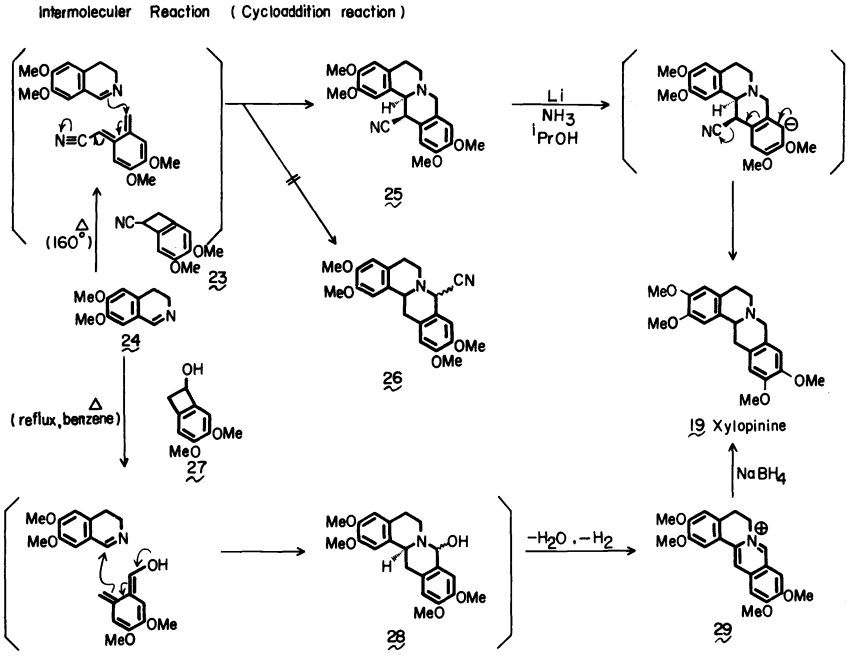
The second approach is an application of intermolecular cycloaddition of benzocyclobutenes to 3,4-dihydroisoquinolines. Thus, heating the 1-cyanobenzocyclobutene (23) with the 3,4-dihydroisoquinoline (24) at 150 - 160°C gave in good yield the 13-cyano-7,8,13,13a-tetrahydroprotoberberine (25) with regio- and stereoselectively but not the 8-cyano isomer (26) (Ref. 14). Decyanation

Chart 5



of the cyanoprotoberberine (25) by a Birch-type reduction with lithium in liquid ammonia in the presence of isopropyl alcohol afforded xylopinine (19) (Ref. 15). On the other hand, heating the benzocyclobutenol (27) with 3,4-dihydro-6,7-dimethoxyisoquinoline (24) in benzene at 80°C for 5 h gave the quaternary protoberberine (29) in 52 % yield via the transient 8-hydroxyprotoberberine (28). The former (29) was then converted into the protoberberine alkaloid xylopinine (19) in good yield by reaction with sodium borohydride (Ref. 16).
Thus, we found that the regioselectivity in cycloaddition of an o-quinodimethane depended upon an E-effect of the substituent on cyclobutene ring and also developed two new methods for protoberberine synthesis.

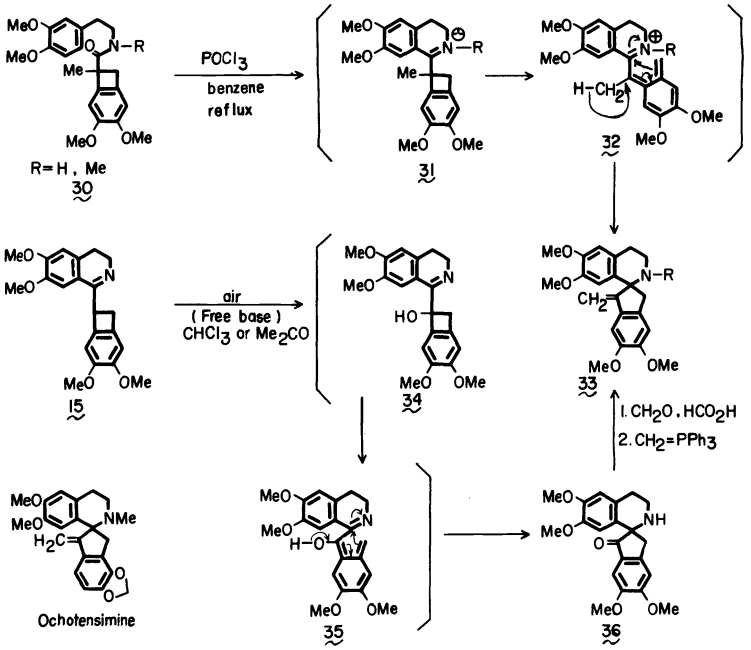
Chart 6



Spirobenzylisoquinolines. In connection with our protoberberine synthesis, a novel synthesis of the spirobenzylisoquinoline was achieved. It was surprising that Bischler-Napieralski reaction of the amide (30) with phosphoryl chloride in refluxing benzene for 22 h did not provide the expected 3,4-dihydroisoquinolinium salts (31). Instead, we obtained directly the spirobenzylisoquinolines (33). It is probable that the 3,4-dihydroisoquinolinium salts (31) were initially formed and then rearranged thermally via o-quinodimethanes (32) to yield

the ochotensine-type compounds (33). The different chemical behaviour of the amide must arise from hyperconjugation and the steric effect of the methyl group on cyclobutene ring (Refs. 17 & 18).
This finding would provide a more direct route for the synthesis of the ochotensine-type alkaloids although the stepwise procedure had already been reported and this transformation also represents a convenient entry into the synthesis of the spirobenzylisoquinoline alkaloids.
The hydrochlorides of the 1-benzocyclobutenyl-3,4-dihydroisoquinoline (15) are stable at room temperature but the free bases of these compounds are unstable in air. A chloroform or acetone solution of the free base on standing at room temperature for 2 or 3 days was transformed, in good yield, into the ketospirobenzylisoquinolines (36). The mechanism of this reaction could be explained by air oxidation of the benzocyclobutenes (15) to the benzocyclobutenols (34) followed by ring opening to o-quinodimethanes (35) and then cyclisation reaction as shown in Chart 7 (Refs. 19 & 20).

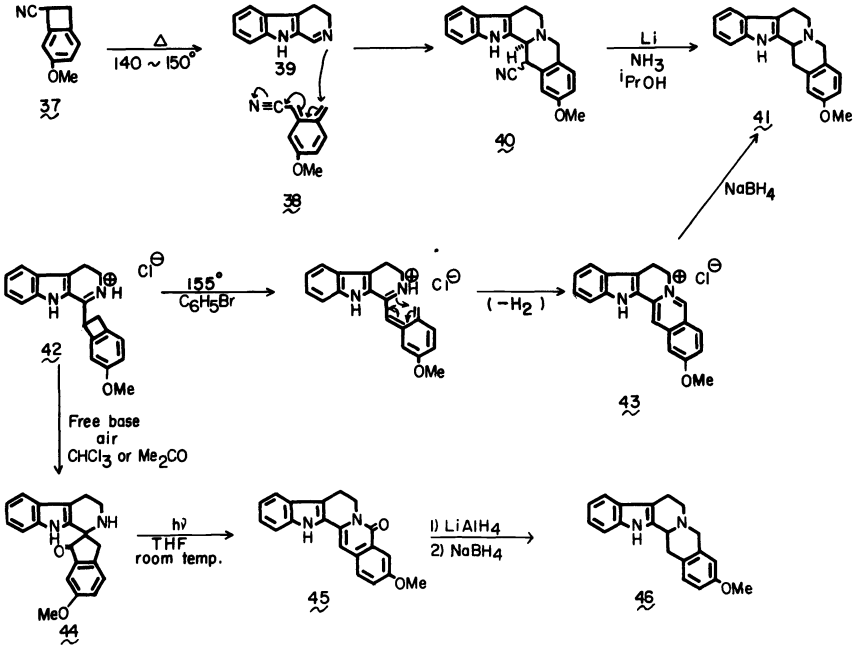
Chart 7



Total synthesis of yohimbine. The successful synthesis of a protoberberine-type compounds from benzocyclobutenes by an electrocyclic reaction and an intermolecular cycloaddition reaction suggested that the hexadehydroyohimbanes or yohimbones, possible intermediates to yohimbine, could be obtained by the same reaction of the appropriate o-quinodimethanes with 3,4-dihydro-β-carbolines. Based on this idea, we firstly investigated a yohimbone synthesis as follows.
An intermolecular cycloaddition of 1-cyanobenzocyclobutene (37) to 3,4-dihydro-β-carboline (39) was effected at 150 - 160°C without solvent over 2 h in a current of nitrogen to give regioselectively the 14-cyanohexadehydroyohimbane (40) in 85 % yield which was decyanated by treatment with metallic lithium and liquid ammonia in the presence of isopropyl alcohol to afford in 65 % yield the hexadehydroyohimbane (41). The regioselectivity of this reaction is rationalised by the electron-attracting power of the cyano group in quinodimethane system (38) (Ref. 15).
Moreover, thermolysis of 1-benzocyclobutenyl-3,4-dihydro-β-carboline hydrochloride (42) at 155°C in bromobenzene for 30 min in a current of nitrogen gave the expected decadehydroyohimbane (43) in 70 % yield which was reduced with sodium borohydride to give the hexadehydroyohimbane (41) (Ref. 21), identical with the product formed via an intermolecular cycloaddition reaction.
In addition, we synthesised another type of hexadehydroyohimbane (46) differing only in the position of the methoxyl substitutent by utilizing the difference in reactivity between the free base and the hydrochloride. Thus, the free base of the 1-benzocyclobutenyl-3,4-dihydro-β-carboline (42) rearranged on standing for 3 days in chloroform or acetone at room temperature to the ketospirobenzyl-β-carboline (44) followed by irradiation in dry tetrahydrofuran at room temperature for 3 h to give the lactam (45) which had already been con-

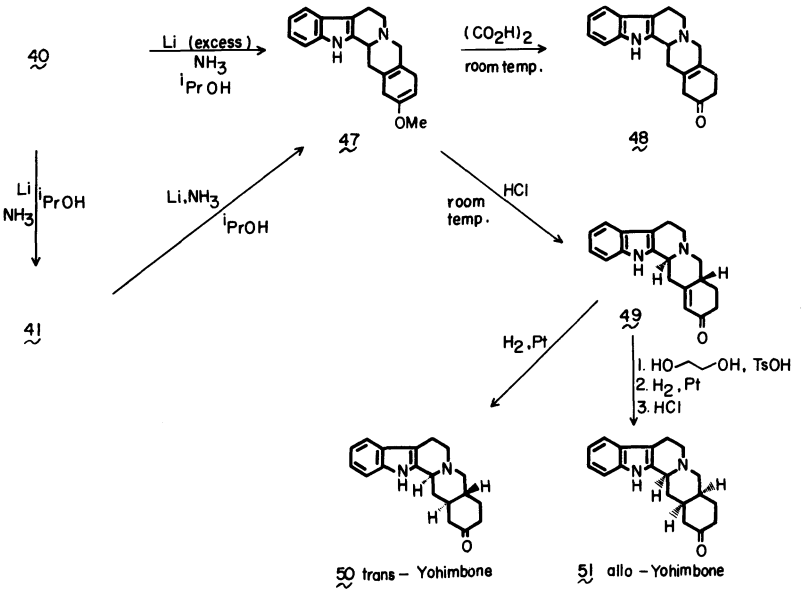
verted into 18-methoxyyohimbane (46) (Ref. 15).
It is interesting that the same starting material gives the two yohimbanes which are position isomers as shown in Chart 8.

Chart 8



Birch reduction of the hexadehydroyohimbane (41) with the lithium and liquid ammonia-isopropyl alcohol system gave the enol ether (47). The same enol ether was obtained by reduction of 14-cyanoyohimbane (40) with a large excess of lithium in liquid ammonia and isopropyl alcohol. Finally, treatment of the enol ether (47) with oxalic acid gave the β,γ-unsaturated dehydroyohimbone (48) in good yield while the reaction with hydrochloric acid by Swan's method afforded the dehydroyohimbones (49), which had already been correlated with trans- and allo-yohimbones (50 and 51).

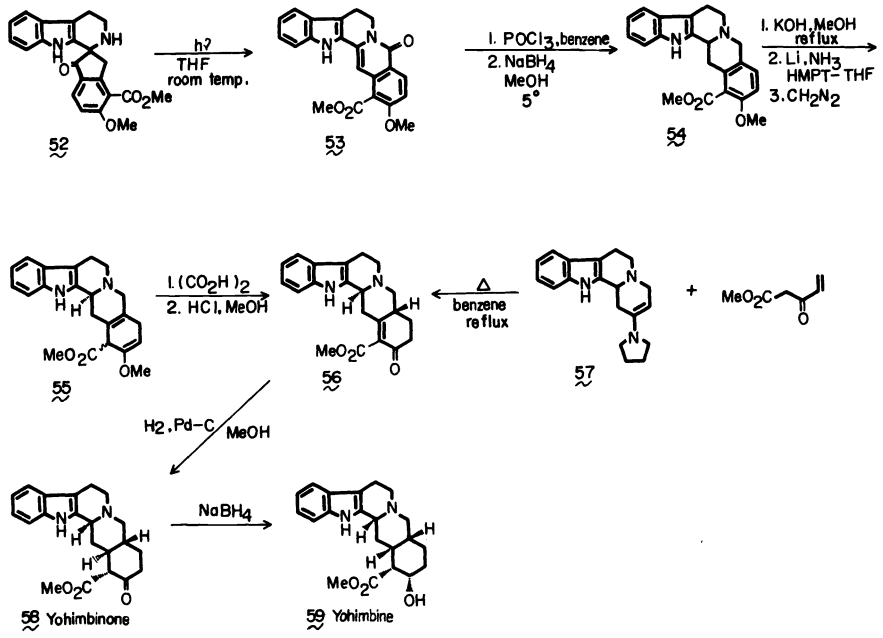
Chart 9



Our method would be specially useful for the synthesis of yohimbanes and yohimbones having an electron-withdrawing group on ring E since this type of compound could not be obtained by the usual Mannich reaction of 1-benzyl-1,2,

3,4-tetrahydro-β-carboline with formalin while in our synthesis the key starting materials have already a "berberine bridge carbon" in the molecule. Based on the above model experiments, we have accomplished a total synthesis of yohimbine (59) from the key intermediate 1-spirobenzyl-β-carboline (52) via hexadehydroyohimbine (54) as shown in the Chart 10. Photolysis of the spirobenzyl-β-carboline (52) with a Hanovia 450 W mercury lamp in tetrahydrofuran yielded the decadehydroyohimbane and the decadehydroyohimban-21-one (53). Reduction of both products with sodium borohydride gave O-methylhexadehydroyohimbine (54) (Ref. 22). Hydrolysis of this ester with aqueous methanolic potassium hydroxide followed by Birch reduction of the resulting carboxylic acid, afforded the enol ether which was esterified with diazomethane to give the O-methyltetradehydroyohimbine (55). Treatment of the latter first with oxalic acid and then with dilute hydrochloric acid afforded dehydroyohimbinone (56) which was catalytically hydrogenated with 30 % palladium on carbon to give (±)-yohimbinone (58), followed by sodium borohydride reduction to afford (±)-yohimbine (59) and β-yohimbine (Refs. 22 & 23). Moreover, dehydroyohimbinone (56) was also obtained by annelation of the enamine (57) with methyl vinyl ketone (Ref. 22). Thus, a total synthesis of (±)-yohimbine has been accomplished by a method developed in our laboratory.

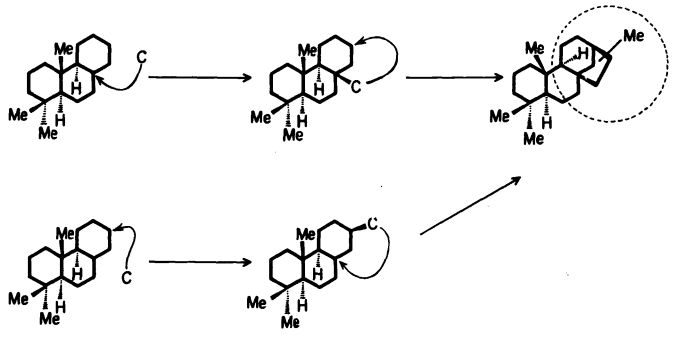
Chart 10



TERPENOIDS

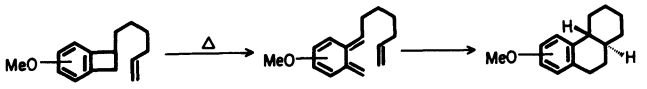
Diterpenes. a) Dihydrohibaene and hibaol. The bridged bicyclo[3.2.1]octane system is found in numerous tetracyclic diterpenoids and constitutes the C/D ring of these terpenoids (Ref. 24). Although many types of approaches to the

Chart 11



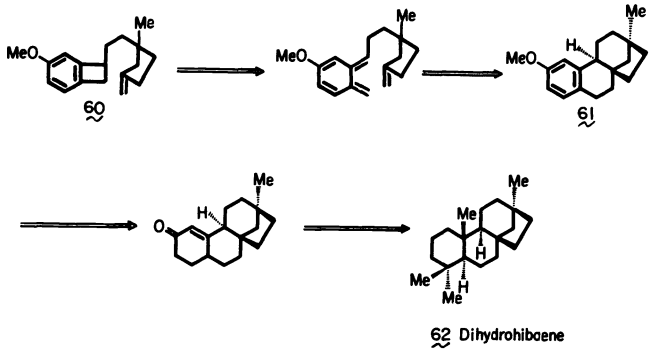
synthesis of kaurene, hibaene and related groups of tetracyclic diterpenoids have been reported, major obstacles in these syntheses are a construction of the bridged bicyclo[3.2.1]octane part and a control of the stereochemistry of the whole ring system having a correct array of methyl substituents. In order to build up bicyclo[3.2.1]octane system, perhydrophenanthrenes are usually used as starting materials shown in Chart 11 (Ref. 25).
Previously, we developed a new synthesis of hydrophenanthrenes by an intramolecular cycloaddition of an olefinic benzocyclobutenes as a general reaction of o-quinodimethanes as shown in Chart 12 (Ref. 26).

Chart 12



Therefore, it should be possible to synthesize, in one step, the hibaene ring system (61), if the benzocyclobutene (60) substituted by a methylenecyclopentane unit is subjected to thermolysis. Based on this consideration, we have planned synthesis of dihydrohibaene (62) and hibaol as shown in Chart 13.

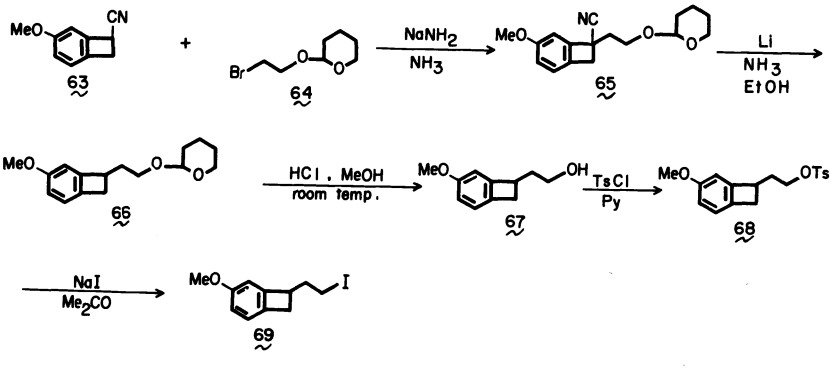
Chart 13



62 Dihydrohibaene

The benzocyclobutenylethyl group which forms ring A and a part of ring B and C was synthesised as shown in the following Chart 14. Condensation of the cyanobenzocyclobutene (63) with the bromide (64) in the presence of sodium amide in liquid ammonia gave the 1,1-disubstituted benzocyclobutene (65), which was treated with sodium in liquid ammonia to afford the decyanated compound (66). Cleavage of the tetrahydropyranyl group of the resulting compound (66) with hydrochloric acid in methanol, gave the alcohol (67). Treatment of the alcohol (67) with p-toluenesulphonyl chloride in pyridine at room temperature furnished the tosylate (68), which was converted into the iodide (69) by reaction with sodium iodide in boiling acetone.

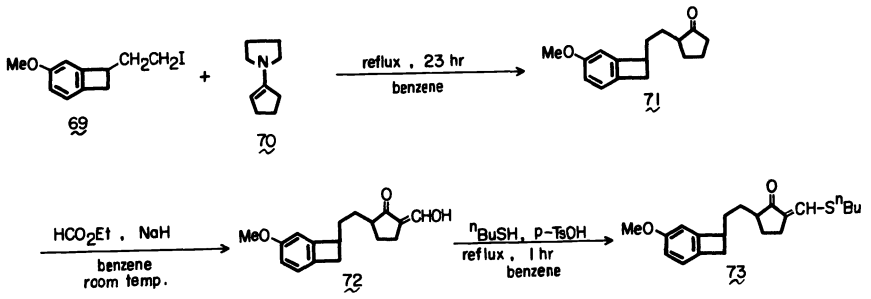
Chart 14



Condensation of this iodide (69) with the pyrrolidine enamine (70) of cyclopentanone in boiling benzene for 23 h gave the 2-benzocyclobutenylethylcyclopentanone (71) in 60 % yield. Prior to introducing the methyl group at the C_2-position of cyclopentanone ring, the C_5-position was blocked by a protecting group which would react as a dienophile in a later stage. Reaction of

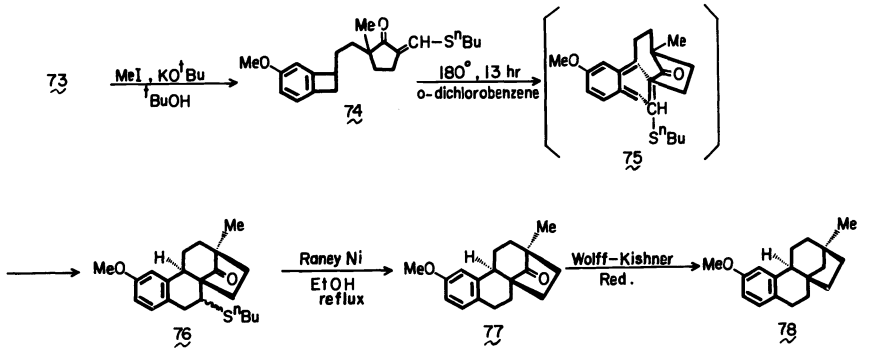
this product (71) with ethyl formate in the presence of sodium hydride in benzene with butyl mercaptan in the presence of p-toluenesulphonic acid afforded the sulphide (73) in 79 % yield.

Chart 15



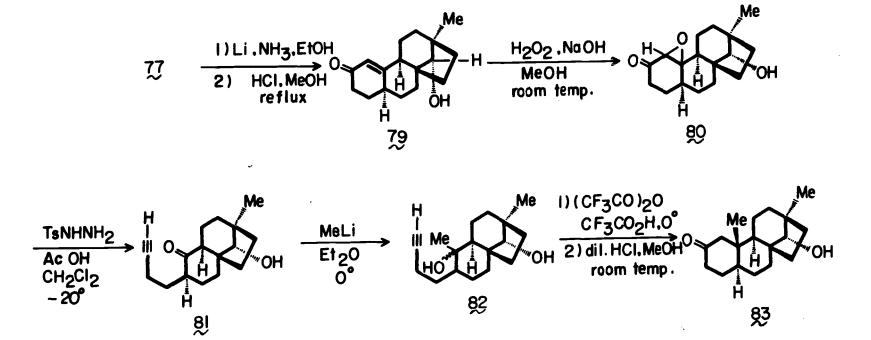
A methyl group was then introduced at the C_2-position of the cyclopentanone (73) by reaction with methyl iodide in tert-butanol in the presence of potassium intermediate (74). Heating this compound (74) in o-dichlorobenzene at 180°C for 13 h in a current of nitrogen afforded via the o-quinodimethane (75) in 65 % yield. Desulphurisation of this product with Raney nickel in ethanol gave, in 86.2 % yield, the potential intermediate (77) whose 13-methyl signal in nmr spectrum was observed in the normal position. This fact showed that the relative configuration of the 13-methyl and 9-hydrogen was probably cis. The stereochemistry of this product was thus considered to be cis although the alternative trans-structure cannot be ruled out in this stage (Ref. 27). The carbonyl group of this compound was converted into a methylene function by Wolff-Kishner reduction. Thus, we could establish a novel and short synthesis of the tetracyclic moiety which forms the framework in hibaene.

Chart 16



With the tetracyclic compound (77) having an appropriate functional group in A ring for elaborations of substitution patterns of tetracyclic diterpenoids in hand, our attention was focused on the introduction of methyl groups at correct positions. For conversion of the A-ring aromatized tetracyclic com-

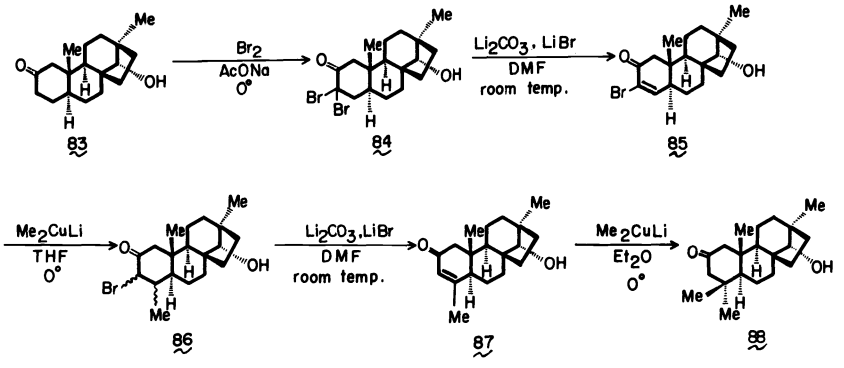
Chart 17



pound (77) into hibaol and dihydrohibaene, stereoselective introduction of methyl group at C_{4b}-position in the β-orientation was explored and the following reaction sequence was found to proceed in moderate yield in each step. Birch reduction of this compound (77) using sodium in liquid ammonia, followed by treatment with hydrochloric acid in methanol at room temperature afforded the enone (79) in 48.7 % yield, in which the carbonyl group on ring C was also reduced to the β-oriented hydroxyl group. The enone (79) was oxidized with hydrogen peroxide in the presence of sodium hydroxide at room temperature to give the epoxide (80) in 56.5 % yield, which was treated with p-toluenesulphonylhydrazine in acetic acid at -20°C to afford the acetylenic ketone (81) in 91.8 % yield.

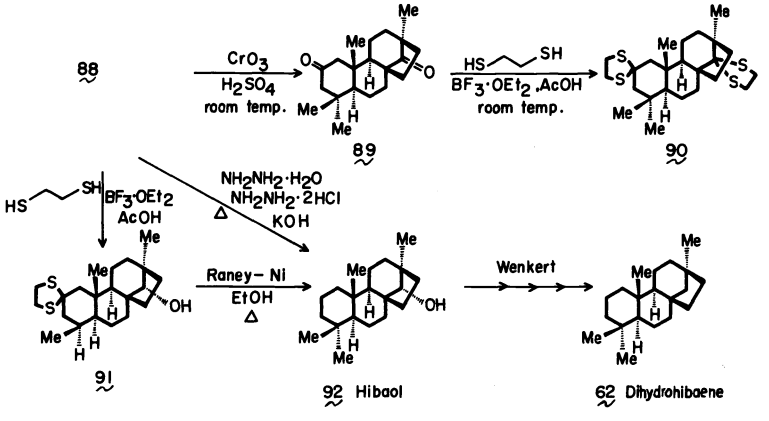
This ketone was reacted with methyllithium in ether at 0°C to give the acetylenic alcohol (82) in 81.8 % yield, which was successively treated with trifluoroacetic anhydride in trifluoroacetic acid at -18°C and then hydrochloric acid in methanol to give the cyclised compound (83) in 55.2 % yield. Bromination of the ketone (83) with bromine in the presence of sodium acetate in chloroform at 0°C afforded the dibromide (84) in 67.1 % yield, and then dehydrobromination was effected by treatment with lithium bromide and lithium carbonate in dimethylformamide at room temperature to give the α-bromoenone (85) in 74.5 % yield. 1,4-Addition of methyl group to the enone (85) by using lithium dimethyl cuprate in ether at 0°C gave the methylated ketone (86) in 90.9 % yield, which was dehydrobrominated again by using lithium bromide and lithium carbonate in dimethylformamide in 52.1 % yield to afford the second enone (87). Treatment of the second enone (87) with lithium dimethyl cuprate in ether at 0°C furnished the 4,4-dimethylated compound (88) in 68.1 % yield. Thus we could arrange all the expected substituents of hibaol and dihydrohibaene at correct positions under correct stereochemistry by using oxygen-functional group presented in A aromatic ring of the key compound (77).

Chart 18



Finally our attention was turned into the removal of oxygen function to get dihydrohibaene (62) directly. Jones oxidation of this compound (88) afforded the diketone (89) in 50.3 % yield, which was converted into the dithioketal (90) in 77.2 % yield by reaction with ethanedithiol in the presence of boron trifluoride etherate in acetic acid at room temperature. Desulphurisation of

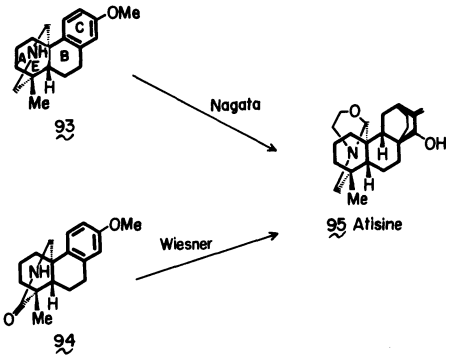
Chart 19



the thioketal (90) was investigated under various conditions, but resulted in undesired reactions to give unidentified products, but not the expected dihydrohibaene (62). Then, reaction of (88) with ethanedithiol in the presence of boron trifluoride etherate in acetic acid afforded the thioketal (91) in 30.5 % yield, which was treated with Raney nickel in boiling ethanol to furnish hibaol (92) in 76.4 % yield. Hibaol (92) was also obtained by treatment of (88) with hydrazine hydrate and hydrazine dihydrochloride in triethylene glycol and then potassium hydroxide at 205 - 215°C in 16.6 % yield.
The synthetic hibaol (92) was identical with authentic sample in its nmr spectral comparison. Since hibaol (92) was correlated to dihydrohibaene (62) by Wenkert, this work constitutes a formal total synthesis of dihydrohibaene (62) (Ref. 28).

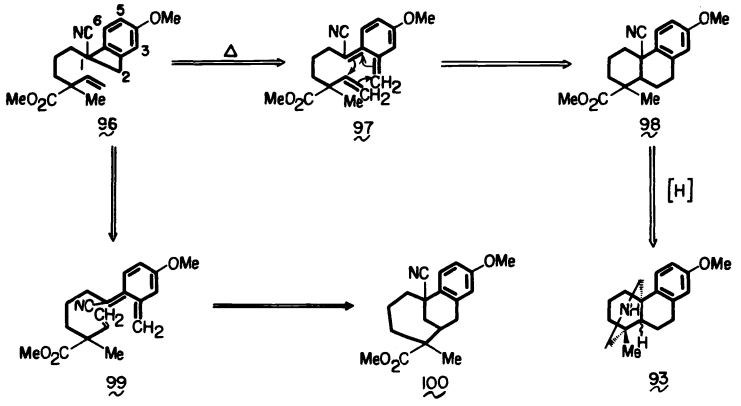
b) Diterpene alkaloids. Nagata (Ref. 29) had achieved the total synthesis of the diterpene alkaloids, atisine (95), veatchine and garryine during 1964 - 1967. In these syntheses the key and common intermediate was 16,17-imino-13-methoxy-5β,10α-podocarpane-8,11,13-triene (93). Wiesner (Ref. 30) also succeeded in a synthesis of atisine (95) from the 15-carbonylpodocarpane derivative (94).

Chart 20



Our synthesis was based on the idea that a hydrophenanthrene derivative (98) which has two functional groups would be most effective for construction of the 16,17-imino-bridge (E-ring) or Nagata's intermediate (93) and that such an intermediate could be prepared in one step by an intramolecular cycloaddition reaction of an o-quinodimethane derivative (97). The benzocyclobutene (96) was chosen as a suitable starting material because it forms an o-quinodimethane (97) on heating and also has cyano and carbomethoxyl groups which are necessary for building up the ring E, although there are two different routes for the intramolecular cycloaddition reaction of the o-quinodimethane as shown in Chart 21. One is the formation of the expected hydrophenanthrene (98) and the other generates the bicyclo[4.3.2]decane (100) through (99).
The starting key compound, 1-substituted 1-cyanobenzocyclobutene (96) was prepared by condensation of the 1-cyanobenzocyclobutene with olefinic ester.

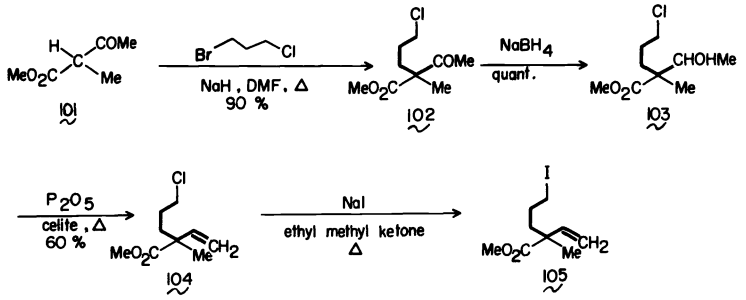
Chart 21



The olefinic ester (105), which is an element for building up A ring, was synthesised from methyl methylacetoacetate (101). Alkylation of methylacetoace-

tate (101) with 1-bromo-3-chloropropane in the presence of sodium hydride gave the chloropropyl derivative (102), which was reduced with sodium borohydride to afford the alcohol (103). Dehydration of this alcohol with phosphorous pentoxide, and then treatment of the resulting olefin (104) with sodium iodide in ethyl methyl ketone provided the iodide (105).

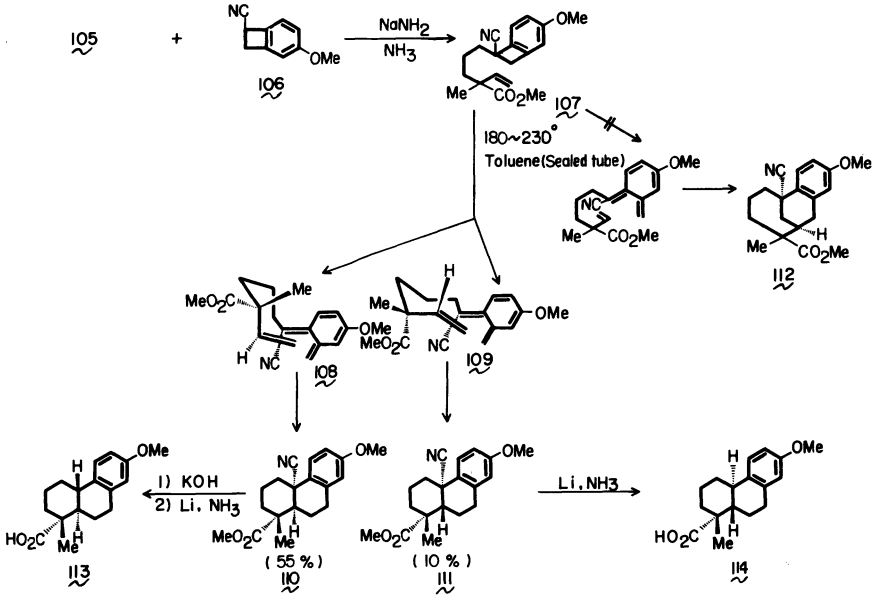
Chart 22



The iodide (105) was condensed with 1-cyano-4-methoxybenzocyclobutene (106) in the presence of sodium amide in liquid ammonia to give in 75 % yield the 1-cyano-1-(4-vinylpentyl)benzocyclobutene (107). Heating the benzocyclobutene (107) in dry toluene in a sealed tube at 180 - 230°C afforded 4aα-cyano-7-methoxy-1α-methoxycarbonyl-1β-methyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (110) in 55 % yield and the 10aβ-isomer (111) in 10 % yield in a regiospecific and stereospecific manner. In this stage, the stereochemistry could not be determined but was evidenced by hydrogenation of these products over Raney nickel in ethanol under 115 atm of hydrogen at 80°C to the lactams in quantitative yield as mentioned later. This fact revealed the relative configuration between cyano and ester groups to be cis and also ruled out another possible structure (112) in the thermolysis of the benzocyclobutene derivative since the bicyclo[4.3.1]decane could not form a lactam from a stereochemical point of view. The AB ring juncture and also relative configuration between methyl group and angular hydrogen of both products were determined by their conversion into known compounds (113 and 114).

The stereocontrolled rearrangement of the benzocyclobutene into the hydrophenanthrene can be explained as follows. On thermolysis of the benzocyclobutene (107), which might be an epimeric mixture, the o-quinodimethanes (108 and 109) are formed by an electrocyclic reaction of the cyanocyclobutene ring where one (109) has a steric repulsion between the cyano and methoxycarbonyl groups while the other (108) has no repulsion. Therefore, it is the latter epimer (108) that gave the major product (110) with the cis-AB ring junction while the former (109) gave the minor product (111).

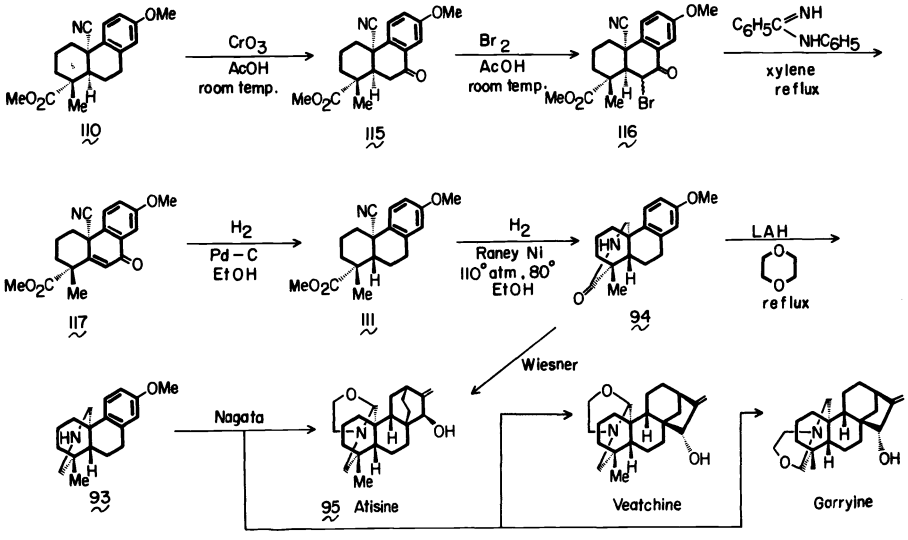
Chart 23



In order to obtain the trans-fused octalin (111) belonging to the natural series, thermolysis of the benzocyclobutene (107) was carried out by refluxing in triglyme in the presence of 10 % palladium on carbon for 6 h, however the cis-fused octalin (110) was obtained. Further the direct epimerisation of the cis-product (110) into the trans-fused octalin (111) by Pelletier's method was examined but once again the starting octalin was recovered. Therefore, the indirect conversion of the cis-fused octalin (110) into the trans isomer (111) was investigated as follows.

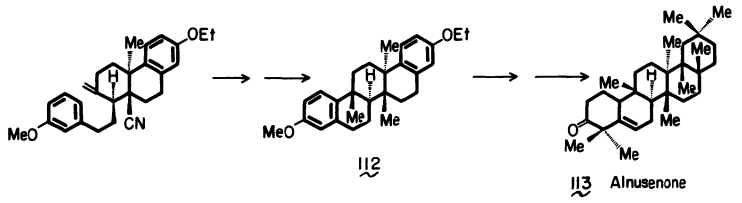
Oxidation of the cis-fused octalin (110) with chromium trioxide in acetic acid for 16 h at room temperature and then at 60°C for 1 h gave, in 45 - 50 % yield, the ketone (115), which was treated with bromine in acetic acid at room temperature to produce the α-bromoketone (116) in 98 % yield. Dehydrobromination of this compound was achieved by treatment with N-phenylbenzamidine in boiling xylene for 3 h to give, in 90 - 95 % yield, the α,β-unsaturated ketone (117) which was subjected to catalytic hydrogenation on 10 % palladium on carbon in ethanol to afford the expected 4aα-cyano-1,2,3,4,4a,9,10,10aβ-octahydro-7-methoxy-1α-methoxycarbonyl-1β-methylphenanthrene (111). High-pressure reduction of this cyano ester under 115 atm of hydrogen on Raney nickel in ethanol at 80°C gave the lactam (94) in 80 % yield, which was converted into atisine (95) by Wiesner (Ref. 30). Treatment of the lactam (94) with lithium aluminium hydride in boiling dioxane for 7 h afforded 16,17-imino-13-methoxy-5β,10α-podocarpane-8,11,13-triene (93) characterised as its hydrochloride which was identical with an authentic sample (Ref. 29). Since our product had been correlated to atisine (95), veatchine and garryine by Nagata, this work constituted a formal total synthesis of these alkaloids (Ref. 31).

Chart 24



Triterpenes. The pentacyclic aromatic diethers (112) having the 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 alunusenone (113) and friedelin by Ireland (Refs. 32 & 33). A crucial step in the synthesis of this pentacyclic diethers (112) is the introduction of methyl groups at angular positions with the required stereochemistry.

Chart 25

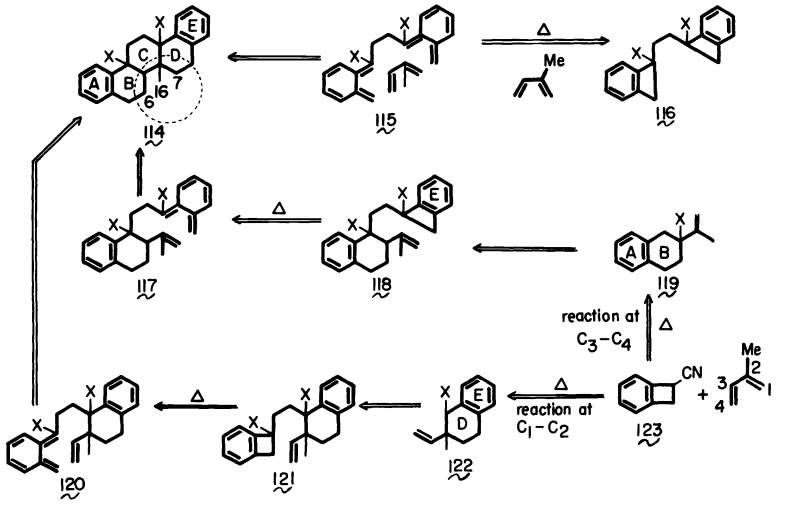


Since we found that intramolecular cycloaddition of an o-quinodimethane in the synthesis of diterpenes could proceed stereoselectively as described before, we

investigated a novel synthesis of triterpenoids by this methods. In this connection, a simple and stereoselective synthesis of the key intermediates for triterpenoid synthesis is discussed.

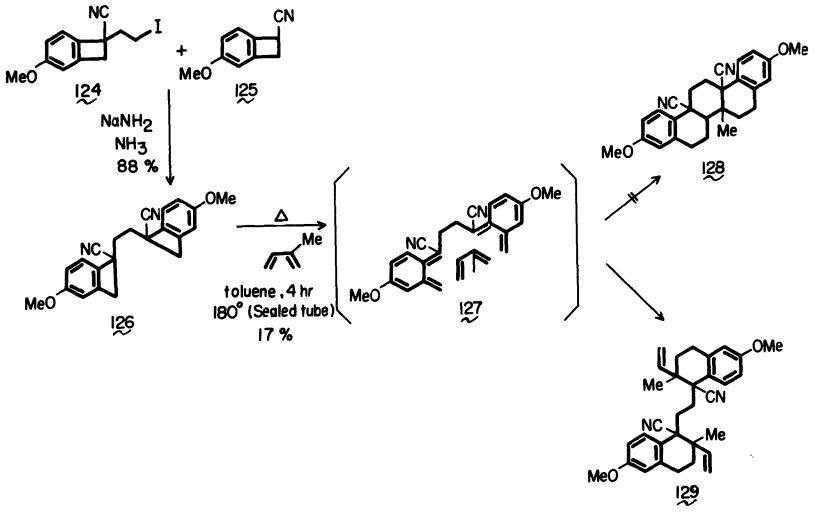
Our plan was designed on the fact that the portion surrounded by a dotted line in the pentacyclic compounds (114) corresponds to an isoprene unit. The first idea is that the pentacyclic ring system (114), which is a basic framework of the key compounds in the total synthesis of alnusenone and friedelin by Ireland, would be formed in one step by an intermolecular double cycloaddition of the bis-o-quinodimethane (115), generated from the bisbenzocyclobutene (116), with isoprene. The second approach involves the intramolecular cycloaddition of the o-quinodimethanes (117 and 120), having an olefinic group at an appropriate position, derived from the benzocyclobutenes (118 and 121). Both benzocyclobutenes (118 and 121) could be synthesised from common starting material (123) through the tetralin 119 and 123 as shown in Chart 26. In these trials, we used the 1-substituted 1-cyanobenzocyclobutenes because 1-substituted 1-methylbenzocyclobutenes are transformed into the o-methylstyrene derivatives by [1, 5]sigmatropic hydrogen migration in o-quinodimethane generated in situ (Ref. 26). Keeping this mind, we examined a simple and stereoselective synthesis of the diaromatic pentacyclic compounds from benzocyclobutenes having the appropriate substituent that could be converted into methyl group after a cycloaddition reaction.

Chart 26



Our first approach was a one-step construction of the diaromatic pentacyclic compounds (128) by an intermolecular double cycloaddition of the bis-o-quinodimethanes (127), derived from the 1,2-di(benzocyclobutenyl)ethanes (126), with

Chart 27



isoprene. The preparation of the requisite bisbenzocyclobutene (126) was achieved by a reaction of the iodoethylbenzocyclobutene (124) with the cyanobenzocyclobutene (125) in the presence of base.

For conversion of the 1,2-di(benzocyclobutenyl)ethane (126) into the corresponding pentacyclic compounds (128), which constitute the framework of the key intermediates in the total synthesis of alnusenone (113) and friedelin by Ireland, the bisbenzocyclobutene (126) was heated with an excess of isoprene in a sealed tube at 180°C for 4 h. However, the product was not the expected compound (128) which was formed by an intermolecular double cycloaddition of the bis-o-quinodimethane (127) to an equimolar amount of isoprene, but the bistetralin derivative (129) formed by a cycloaddition of 2 moles of isoprene with each part of the bis-o-quinodimethane (Ref. 34).

As attempts to convert the bisbenzocyclobutene (126) into the corresponding pentacyclic compounds (128) under several conditions failed, our attention is turned to the second approach which synthesises pentacyclic compounds in a stepwise manner by an application of the intramolecular cycloaddition of the o-quinodimethanes derived from the benzocyclobutenes.

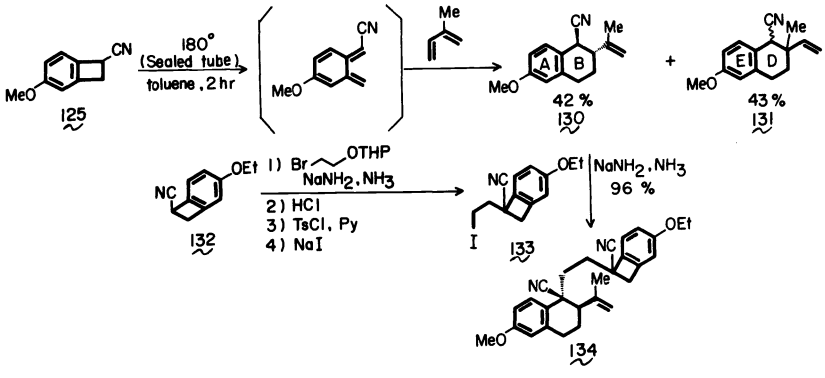
a) Stepwise and stereoselective synthesis (Ref. 34). The second idea is that the cycloaddition of benzocyclobutenes to isoprene forms tetralin derivatives corresponding to A and B rings and then introduction of benzocyclobutene residue constructing C,D, and E rings, followed by an intramolecular cycloaddition of benzocyclobutene to the olefinic system derived from the isoprene unit, would give the pentacyclic compounds (see, Chart 26).

Condensation of 2-(2-bromoethoxy)tetrahydropyran with the cyanobenzocyclobutene (132) afforded the 1-cyano-1-tetrahydropyranyloxyethylbenzocyclobutene, which was converted into the 1-cyanobenzocyclobutenylethyl iodide (133) through the alcohol and the tosylate by the same method mentioned before. The iodide (133) forms the unit which is necessary for making C, D, and E rings in the pentacyclic compound.

On the other hand, the A and B ring system in the pentacyclic compound was synthesised from 1-cyano-4-methoxybenzocyclobutene (125) as follows. Thus, heating the benzocyclobutene (125) with an excess of isoprene in a sealed tube at 180°C for 2 h gave 1-cyano-2-isopropenyl-6-methoxytetralin (130) in 42 % yield, in addition to a diastereoisomeric mixture of 1-cyano-6-methoxy-2-methyl-2-vinyltetralin (131) in 43 % yield by an intermolecular cycloaddition of the quinodimethane with each olefinic system in isoprene. Both products could be separated by silica gel column chromatography.

Condensation of the 1-cyano-2-isopropenyltetralin (130) with the iodide (133) was carried out in liquid ammonia in the presence of the freshly prepared sodium amide to furnish the key starting material (134) in 96 % yield. In this stage, an alkylation of the tetralin derivative (130) with the iodide (133) is expected to proceed from the less hindered side at the C_1 position to form the product (134) in which the relative configuration between the 1-cyano and 2-isopropenyl group could be cis to each other.

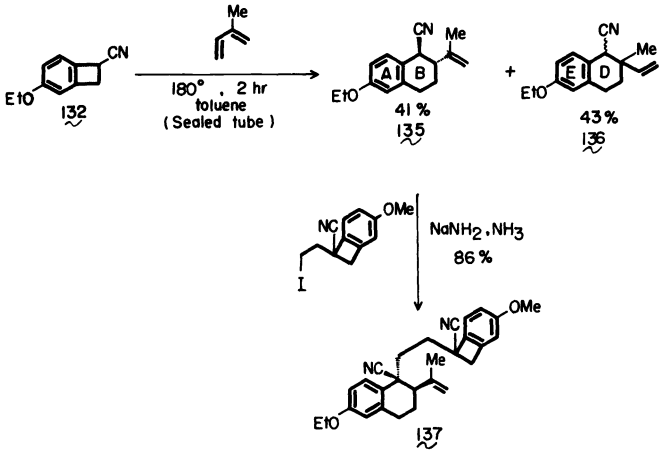
Chart 28



Similarly, the reaction of 1-cyano-4-ethoxybenzocyclobutene (132) with isoprene afforded a mixture of the 1-cyano-2-isopropenyltetralin (135) in 41 % yield an a diastereoisomeric mixture of the 1-cyano-2-methyl-2-vinyltetralin (136) in 4 % yield. The second key starting compound (137) for the pentacyclic product i friedelin synthesis could be also prepared by the reaction of the tetralin derivative (135) with the iodide (124) in 86 % yield by the same way.

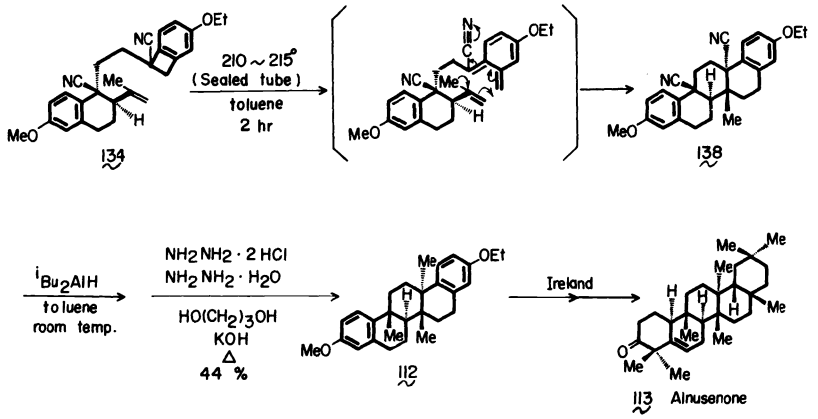
Heating the benzocyclobutene (134) in dry toluene in a sealed tube at 210 - 215°C for 2 h provided stereoselectively, in 58 % yield, the pentacyclic dinitrile (138) whose structure was easily determined by nmr spectral analysis,

Chart 29



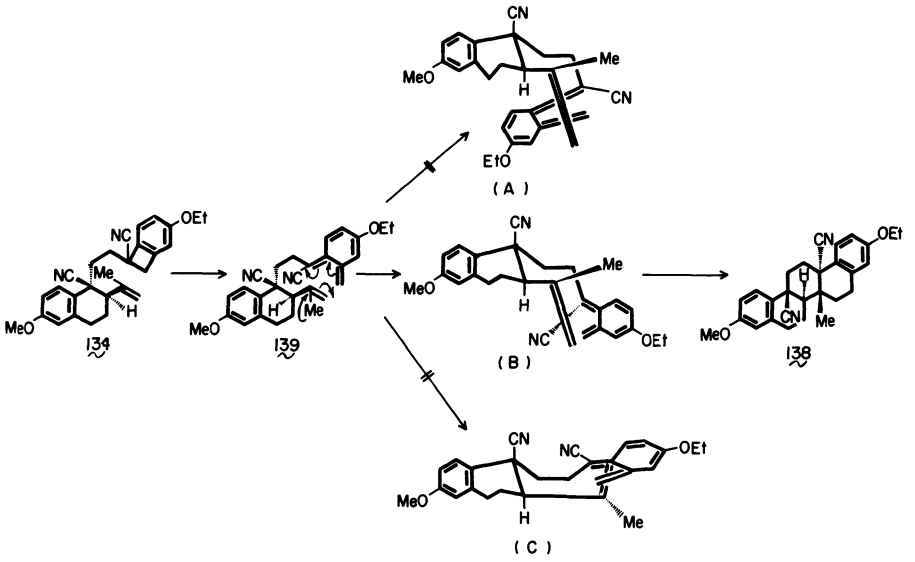
which showed a C-methyl resonance at δ 0.88 as a singlet but lacked olefinic protons and methylene protons on cyclobutene ring. This product (138) was reduced with diisobutylaluminium hydride in benzene at room temperature for 12 h to give the diimine in 90 % yield whose Wolff-Kishner reduction with hydrazine hydrate and hydrazine dihydrochloride in triethylene glycol in the presence of potassium hydroxide at 160 - 165°C by Nagata's method gave the 6bβ,12bα,14aβ-trimethylated pentacyclic derivative (112) (Ref. 34), whose ir and nmr spectra and melting point were identical with those of the authentic sample provided by Ireland (Ref. 32). This product (112) has been converted to a pentacyclic triterpenoid, alnusenone (113), by Ireland (Ref. 32).

Chart 30



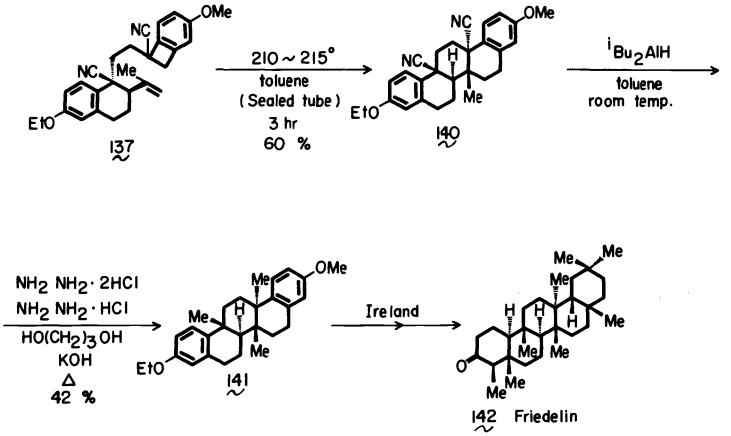
Regioselectivity in this cycloaddition would be due to an electron-attracting effect by the cyano group on o-quinodimethane (139) and an electron-providing power of the methyl function in the olefin system as shown in the intermediate. The stereoselective formation of the pentacyclic compound (138) in the thermolysis of the benzocyclobutene can be explained as shown in Chart 31. Conrotatory ring opening of the cyclobutene unit in 134 would form the sterically fovoured o-quinodimethane (139). Synchronous intramolecular cycloaddition of 139 would most favourably proceed through the "exo chair" conformation B to give 138 with the required stereochemical arrangement, rather than through the less stable "endo chair" form A having a steric repulsion between tetralin and o-quinodimethane ring or "boat" form C which would produce the trans-anti-cis-BCD and trans-syn-trans-BCD ring stereoisomers of our product (138).

Chart 31



Similarly, thermolysis of the benzocyclobutene (137) in a sealed tube at 210 - 215°C for 3 h gave, in 60 % yield, the pentacyclic compound (140). This product was reduced with diisobutylaluminium hydride in benzene, followed by Wolff-Kishner reduction of the resulting diimine to afford, in 42 % yield, the pentacyclic trimethyl compound (141) (Ref. 34), which has also been converted into friedelin (142) by Ireland (Ref. 33).
Thus, we could obtain the key compounds which have been converted to triterpenoid, alnusenone and friedelin by Ireland, in a convenient and stereoselective way, and this reaction provides an effective method for a general synthesis of the pentacyclic diaromatic diethers which would play an important role as a potential intermediate for pentacyclic triterpenoid synthesis.

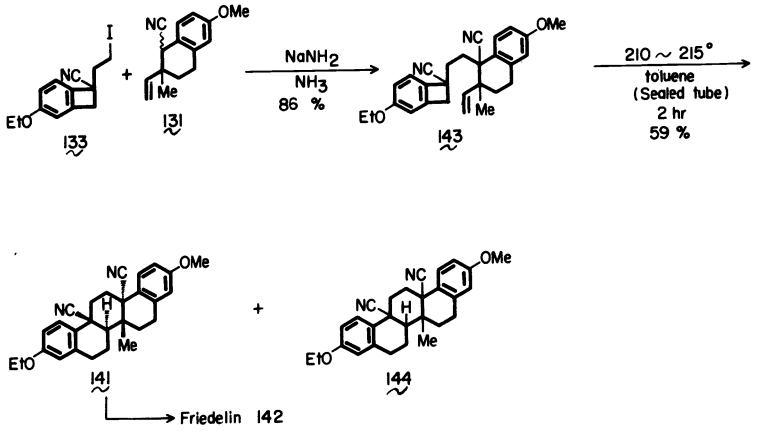
Chart 32



b) Non-stereoselective synthesis of pentacyclic compounds (Ref. 34). The third approach is a use of the by-products (131 and 136) in the synthesis of the tetralin (130 and 135) from the benzocyclobutenes (125 and 132) because these compounds (131 and 136) correspond to C, D and E ring in pentacyclic compounds. In this approach, the benzocyclobutenyl iodide (133), which has been applied as a precursor for E and D ring formation, is used as a starting material for the A and B ring formation.
Alkylation of a diastereoisomeric mixture of the 1-cyano-2-methyl-2-vinyltetralin (131), which could not be separated, with the iodide (133) in the presence of sodium amide as usual gave, in 86 % yield, the 1,1,2,2-tetrasubstituted tetralin (143) as a stereoisomeric mixture. The compound was subjected to a thermolysis in a sealed tube at 210 - 215°C for 2 h to afford, in 59 % yield,

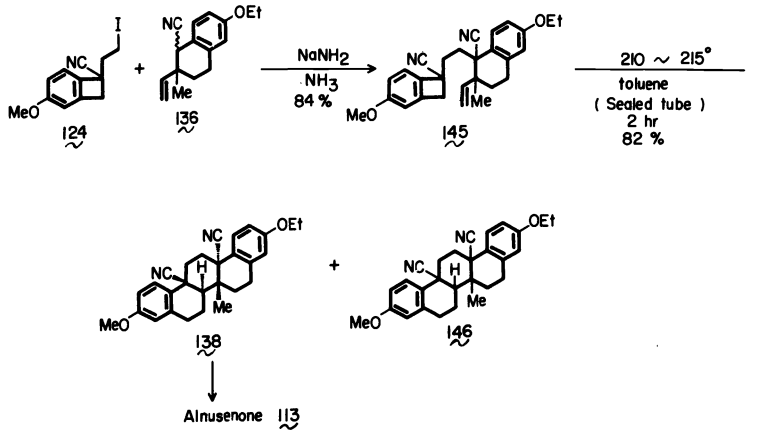
a mixture of the pentacyclic compound (141) and its stereoisomer (144), which was separated in a ratio of 1 : 2 by high-pressure liquid chromatography. The latter fraction on this chromatography gave the expected product (141), which was identical with the authentic sample, described above, in melting point and spectral comparisons. The stereochemistry of 144 was assigned tentatively as C_{6b}-methyl isomer since an intramolecular cycloaddition proceeds stereoselectively as described above.
This product (141) has been converted into the pentacyclic trimethyl derivative, thus the third method affording a simple but non-stereoselective synthesis of pentacyclic compounds related to triterpenoids (Ref. 34).

Chart 33



Similarly, the pentacyclic dinitrile (138) was obtained from the benzocyclobutene (124) and the tetralin (136) via thermolysis of the condensation product (145). In this case the stereoisomer (146) was also formed in thermolysis. The pentacyclic cyanide (138) was converted into alnusenone (113) as mentioned above (Ref. 34).

Chart 34



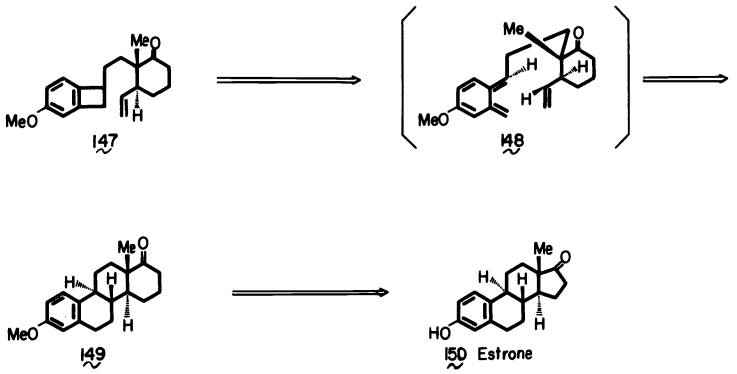
STEROIDS

Total synthesis of estrone (Ref. 37). The synthesis of estrone has held a special fascination for organic chemists and many types of approaches have been reported toward this natural sex hormone (Ref. 35). In the last decade, interest has focused on developing asymmetric syntheses of estrone and related compounds (Ref. 36).

In connection with our interest in the synthetic development of cycloaddition reaction starting from o-quinodimethanes based on benzocyclobutenes, we investigated a new synthesis of estrone (150) through D-homo-O-methylestrone (149) via the intramolecular cycloaddition reaction. The following discussion is a synthesis of D-homoestrone which constitutes a formal total synthesis of estrone by our methods.

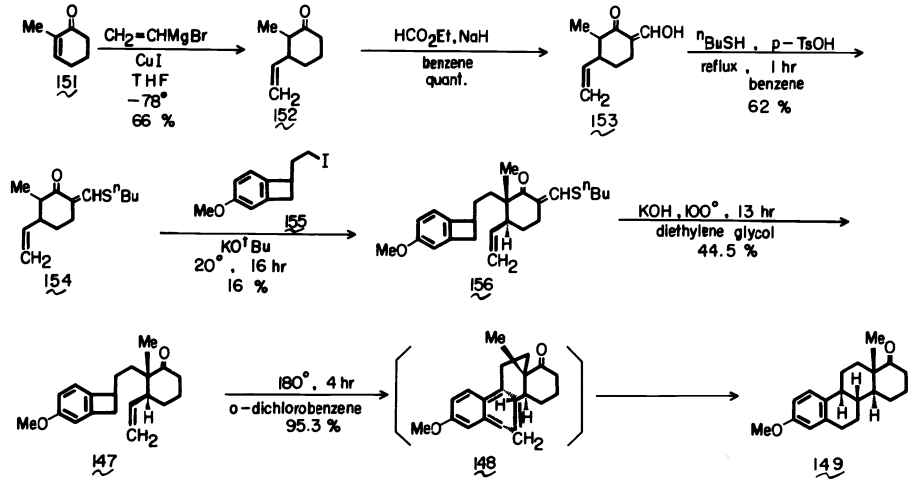
Our synthetic plan as shown in Chart 35 is that benzocyclobutene (147) readily undergoes thermal rearrangement to o-quinodimethane (148), which can further participate in intramolecular cycloaddition to give the D-homo-O-methylestrone (149). This compound (3) had already been correlated to estrone (150).

Chart 35



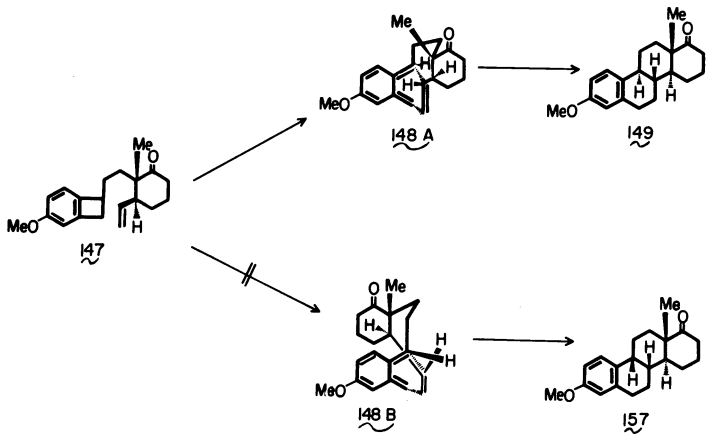
The key compound (147) was prepared from 2-methylcyclohexanone (151) and the 1-iodoethylbenzocyclobutene (155). Thus, 1,4-addition of vinylmagnesium bromide to 2-methylcyclohexenone (151) in the presence of cuprous iodide gave the 3-vinylcyclohexanone (152), which was converted into the corresponding 6-butylthiomethylene derivative (154), via the 6-hydroxymethylene compound (153) as usual. Condensation of the 1-iodoethylbenzocyclobutene (155) with the cyclohexanone (154) in the presence of potassium tert-butoxide afforded stereoselectively the 2,2-disubstituted cyclohexanone (156) by an attack of the iodide (155) on the less hindered side of cyclohexanone ring. Removal of the protecting group in this product (156)by potassium hydroxide in diethylene glycol at 100°C gave the key intermediate (147) having a correct stereochemistry in a relative configuration between C_2-methyl and C_3-hydrogen on the cyclohexanone ring. Thermolysis of this benzocyclobutene (147) proceeded smoothly in boiling o-dichlorobenzene for 4 h to afford D-homo-O-methylestrone

Chart 36



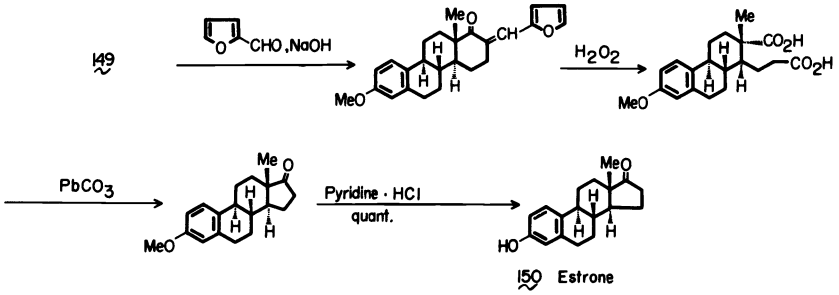
(149) is 95 % yield in regio- and stereoselectively.
The stereocontrolled formation of D-homo-O-methylestrone (149) can be explained as follows. The four-membered ring in benzocyclobutene (147) opens to form preferentially the sterically favoured (E)-oriented o-quinodimethane (148), whose synchronous cycloaddition reaction with vinyl group proceeds regio-specifically through the more stable exo transition state 148A rather than endo state 148B which has steric repulsion between the aromatic and cyclohexanone system, thus, leading to the D-homo-O-methylestrone (149) but not the stereo-isomer (157).

Chart 37



Since D-homo-O-methylestrone (149) has been transformed into estrone (150) (Refs. 38 & 39), a synthesis of D-homo-O-methylestrone constitutes a total synthesis of estrone.

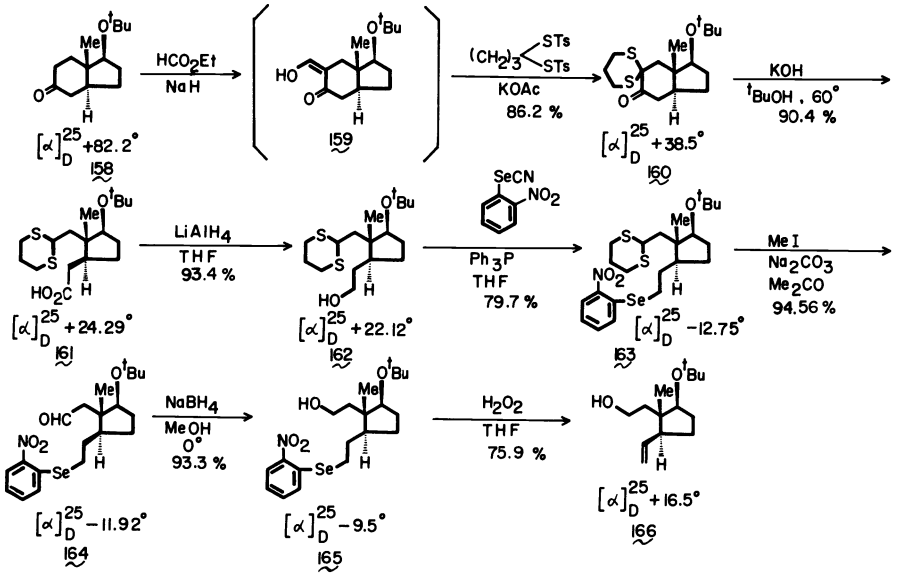
Chart 38



Asymmetric synthesis of estradiol (Ref. 40). Heating the racemic form of the olefinic benzocyclobutene (147) gave stereoselectively D-homo-O-methylestrone (149) in 95 % yield by an intramolecular cycloaddition through o-quinodimethane (148) as shown in Chart 37 and the stereoselectivity is controlled by a stereo-chemistry of substituents on cyclohexane ring. If we would use an optically active starting material whose array on cyclopentane ring is the same with that of natural estradiol, the absolute configuration of our product should be identical with that of natural one by the asymmetric induction under influence with the chiral centres already present in cyclopentane ring. As a continuation of our work aimed a total synthesis of natural products by a cycloaddition of o-quinodimethane, we have investigated a total synthesis of the optically active steroidal hormone.

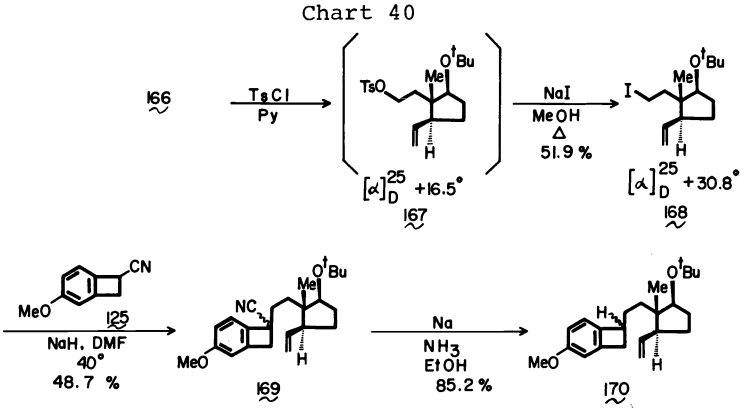
Treatment of the optically active indanone (158) with ethyl formate in the presence of sodium hydride gave the 2-formyl ketone (159), which without purification was converted into the ketone thioketal (160) in 86.2 % yield by the reaction with propane-1,3-dithiol di-p-toluenesulphonate and potassium acetate as usual. Hydrolysis of this product was carried out with potassium hydroxide in tert-butanol at 60°C, affording the carboxylic acid (161), in 90.4 % yield, which was reduced with lithium aluminium hydride in tetrahydrofuran at room temperature to furnish the alcohol (162) in 93.4 % yield. Treatment of this alcohol with o-nitrophenylselenyl cyanide and tri-n-butylphosphine in tetrahydrofuran at room temperature gave, in 79.7 % yield, the selenide (163) which was converted into the aldehyde (164) by hydrolysis with methyl iodide in the presence of sodium carbonate in aqueous acetone in 94.56 % yield. Sodium borohydride reduction of aldehyde (164) in methanol at 0°C afforded the alcohol (165) in 93.3 % yield, whose oxidative deselenation was carried out with 30 % hydrogen peroxide in tetrahydrofuran at room temperature for 3 h to form the olefinic alcohol (166) in 75.9 % yield.

Chart 39



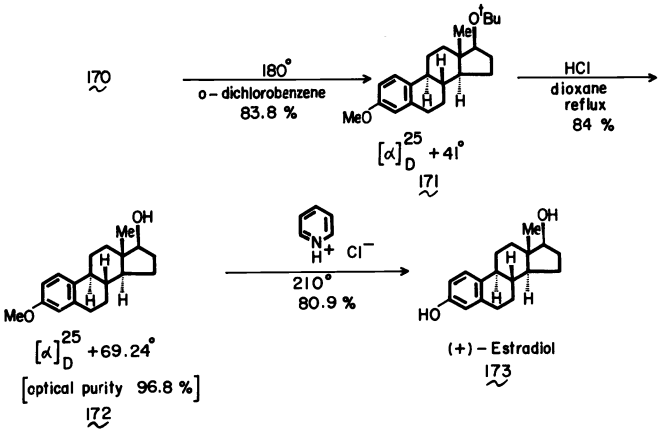
Tosylation of this alcohol (166) with p-toluenesulphonyl chloride and pyridine, followed by a treatment of the product (167) with sodium iodide in boiling acetone gave 1β-tert-butoxy-3β-ethenyl-2α-(2-iodoethyl)-2β-methylcyclopentane (168) in 51.9 % yield. Condensation of 1-cyano-4-methoxybenzocyclobutene (125) with the iodide (168) in the presence of sodium hydride in dimethylformamide at 40°C for 45 min furnished 1,1-disubstituted benzocyclobutene (169) in 48.7 % yield which was treated with sodium in liquid ammonia in the presence of ethanol to afford the decyanation product, 1-cyclopentylethylbenzocyclobutene (170) in 85.2 % yield.

Chart 40



Heating the benzocyclobutene (170) in o-dichlorobenzene at 180°C for 3 h in a current of nitrogen gave, in 83.8 % yield, 17-O-tert-butyl-3-methylestradiol (171). Previously we discussed that an intramolecular cycloaddition of the benzocyclobutenes carrying on C-1 a chain of six atoms with a terminal olefinic system proceed stereo- and regioselectively to form 1,3,5(10)-tridehydroestrane system having trans-anti-trans BCD ring via o-quinodimethane under the steric influence of chiral centres by the configuration of substituent already present in the bridge. Since we used the optically active starting material (170) whose array on cyclopentane ring is the same with that of natural estradiol, the absolute configuration of our product (171) should be identical with that of natural one. This was proved by the conversion of our product (171) into 3-O-methylestradiol (172) and (+)-O-estradiol (173) as follows. Thus, treatment of (171) with 5 N hydrochloric acid in dioxane under reflux for 7 h afforded 3-O-methylestradiol (172) in 84 % yield, which is identical with the authentic sample, prepared from natural estradiol by the known method, in all aspects except the value of optical reaction ($[\alpha]_D$ + 69.24°). This indicated optical purity of our product to be 96.8 %, i.e., l : d = 98.4 : 1.6. Finally demethylation of 3-O-methylestradiol (172) with pyridine hydrochloride at 210°C for 0.5 h gave, in 80.9 % yield, estradiol (173) not differentiated from natural estradiol in ir (KBr) and nmr spectra. Thus, we have accomplished an asymmetric total synthesis of estradiol (Ref. 40).
Our synthetic method described above provides a general route for an asymmetric synthesis of a wide range of steroidal substances.

Chart 41



CONCLUSION

Finally, I would like to say that the synthetic organic chemistry will live forever supported by the splendid development of physicochemical tool and by the appearance of new reagents and the discovery of new reactions. Although a computer system for the synthesis of complex molecules is under examination, we believe that the systematic methodology for the synthesis of organic compounds, such as thermolysis based on the retro-Mass Spectral Synthesis will always be necessary. Synthetic studies must continue so that new and more efficient drugs become available for medical use.

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