TOTAL SYNTHESIS OF LYCOPODIUM ALKALOIDS

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Abstract-----This review described developments of total syntheses of seven Lycopodium alkaloids.

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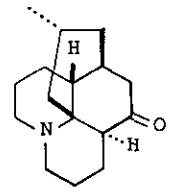
(I) Introduction

The history of the Lycopodium alkaloids was opened when Bödeker[1] reported the isolation of lycopodine (1) in 1881. Extensive investigation was commenced in the 1940's by the Canadian chemists and structural studies were continued throughout the 1950's. The structure establishment of the Lycopodium alkaloids was not, however, reported until the structure of annotinine (2) was elucidated by Wiesner et al.[2),3)] in 1957. In 1960, the structure of lycopodine (1)[4)] was elucidated and in rapid succession, thereafter, structures of annotine (3)[5)], cernuine (4)[6)], annopodine (5)[7)], lycopecurine (6)[8)], serratinine (7)[9)] and luciduline (8)[10)] possessing new skeletal structures were clarified and comprehensive reviews of the developments of this area are available.[11),12)] The Lycopodium alkaloids are divided into nine groups according to the carbon-nitrogen skeleton [(1) - (9)] as shown in Chart 1.

On the other hand, synthetic studies of the Lycopodium alkaloids began in 1964 and the earlier papers were concerned with the synthesis of degradation product of alkaloids and of synthetic intermediates.[14)] So far as we know, seven



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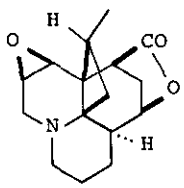

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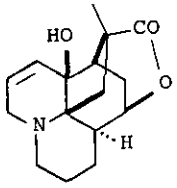

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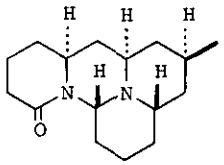

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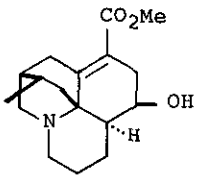

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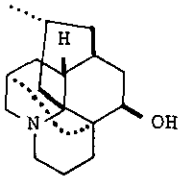

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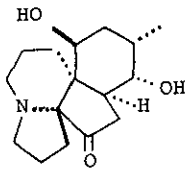

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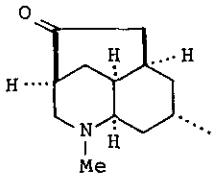

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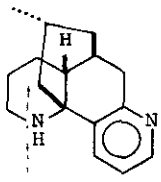

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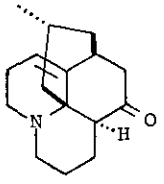

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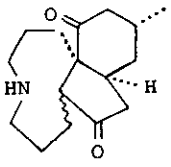

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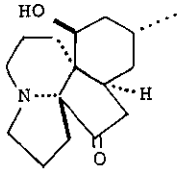


(12)

Chart 1

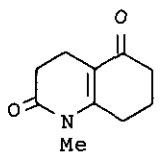
alkaloids, annotinine (2)[15], lycopodine (1)[16-18], anhydrolycodoline (10)[19], luciduline (8)[20-22], serratinine (7)[23], fawcettimine (11)[24] and 8-deoxy-serratinine (12)[24] have been now totally synthesized. It is the intention in this review to survey developments in total synthesis of these alkaloids.

(II) Synthesis of Annotinine (2)

Annotinine (2) is the only representative of this particular structure in which a cyclobutane ring and all the functional groups are situated on the perhydrojulolidine ring in cis relationship. Annotinine was the first Lycopodium alkaloid to yield to structural analysis and also the first alkaloid of the group to be prepared by total synthesis.[15] A key step in the total synthesis, the construction of a four-membered ring, was the photochemically-induced addition of allene to a vinylogous imide.[15] The addition of allene to the bicyclic vinylogous imide (13) as a model system was first examined to give a

1:1 mixture of (14) and (15) in 50 % yield.[25),26)] In contrast, the reaction of the tricyclic vinylogous imide (16) with allene gave a single adduct (17) in quantitative yield due to the steric hindrance arising from the C ring. Catalytic hydrogenation of (14) gave a mixture of (18) and (19), whereas reduction of its acetal derivative afforded solely the compound (20) in which the requisite orientation of the secondary methyl group was confirmed, the acetal group serving to hinder hydrogen attack from that side. This type of reaction was applied by Wiesner et al. to the synthesis of 12-epilycopodine (21) in which the reaction of (22) with allene gave (23) in 70 % yield.[27)]

The structure of (17) was inferred from the facts that (17) was transformed into (24) and that the most stable conformation (25) in the excited state may be responsible for this type of photochemical addition reaction.[15)] Catalytic hydrogenation of (17), after acetalization, led to the stereospecific production of the desired C-15 epimer (26) in 93 % yield. A sequence of reactions of (26), deacetalization, sodium borohydride reduction and mesylation, gave the mesylate (27) in 84 % yield. Treatment of (27) with various kinds of bases afforded a 1:1 mixture of (28) and (29) but the desired olefinic compound (28, R=H) was obtained using t-BuOK-DMSO in 83 % yield from (27). This was transformed, via the sequence, (28, R=~OAc)[SeO_2-AcOH], (28, R=~OH)[hydrolysis] and (30)[CrO_3/pyr.] in 30 % yield, into the enone-lactam (30) identical except for rotation with a sample of established stereochemistry prepared from annotinine (2). Hydrocyanation of (30) with KCN-NH_4Cl, followed by methanolysis afforded the keto-ester (31), identical with a sample derived from annotinine, in 38 % yield. Racemic acid (31, C-7~COOH) was resolved via the brucine salt to give, after esterification, the totally synthetic natural enantiomer (31). The lactone ring of annotinine was constructed as follows. Conversion of (31) to the enol-acetate (Ac_2O-p-TsOH) and reduction of this with sodium borohydride followed by hydrolysis gave a mixture of the carboxylic acids (32) and (33), in 64 % yield. This mixture was heated in benzene containing p-toluenesulfonic acid to give the lactone (34) in 38 % yield together with the starting material (33) which can be recycled via (31). Treatment of (34) with NBS in CCl_4 under visible radiation led, presumably by dibromination and dehydrobromination, to the unsaturated bromo compound (35) in 16 % yield, which was hydrated using aqueous hydrobromic acid to give a bromohydrin. Treatment of the bromohydrin



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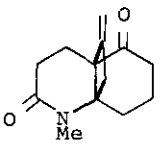

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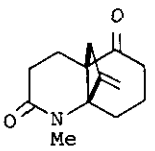

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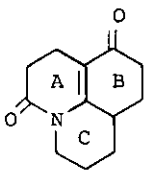

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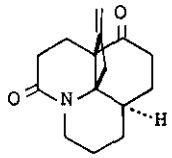

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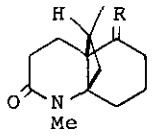
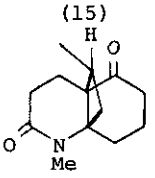


(18) R=O
(20) R=-O(CH$_2$)$_2$O-



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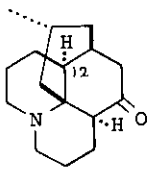

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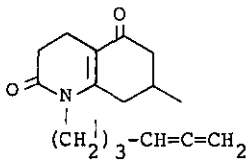

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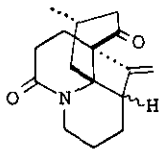

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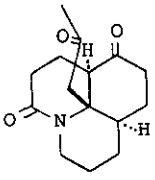

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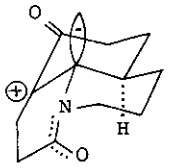

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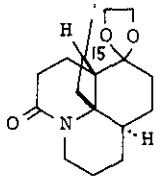

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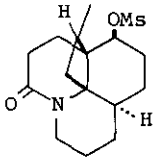

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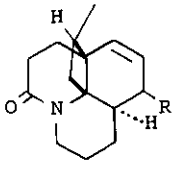

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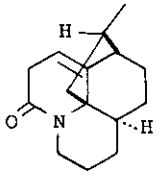

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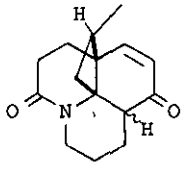

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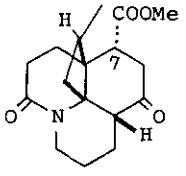

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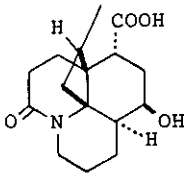

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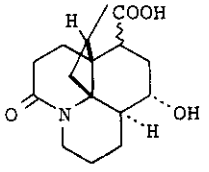

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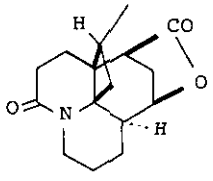

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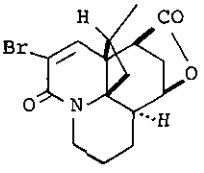

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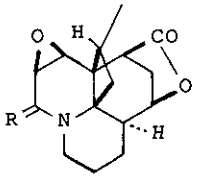


(36) R=O
(2) R=H$_2$

Chart 2

with aqueous bicarbonate yielded oxoannotinine (36) in 23 % yield. It had previously been shown that (36) underwent acid-catalyzed hydrogenolysis to afford annotinine (2) in presence of hydrogen and platinum.[28]

(III) Synthesis of Lycopodine and Related Alkaloids.

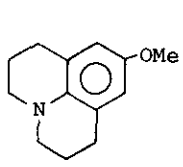
Members of this group[11),29)] have the carbon-nitrogen skeleton of lycopodine (1) whose structure was clarified by MacLean et al.[4] The difficulty encountered in the lycopodine synthesis was in establishing the cis (A-C) and the trans (B-C) ring junction and this stereochemical problem has been overcome in three syntheses of lycopodine itself.

(III-1) Synthesis of Lycopodine

(III-1-A) Synthesis by W. A. Ayer

Construction of hexahydrojulolidine skeleton possessing the natural cis-trans configuration was first examined.[30] The starting material was 9-methoxy-julolidine (37) which was reduced with Li-NH_3, followed by treatment with ethylene glycol-perchloric acid to give the immonium perchlorate (38). Addition of methallyl magnesium chloride to (38) occurred on the less hindered convex face to afford (39) in 50 % yield. The cis-cis configuration of the perhydro-julolidine skeleton was inferred from the facts that (39) showed the Bohlmann absorption band and that (39) reacted slowly with methyl iodide. The compound (39), therefore, should be transformed into the hexahydrojulolidine skeleton possessing the natural cis-trans configuration. The compound (39), after catalytic hydrogenation and deacetalization, was derived into the enone (40) by bromination and dehydrobromination. Either of two possible conformations (40a) and (40b) is assumed for the enone (40). The conformation (40b) was considered to be preferred on the basis of inspection of the molecular model, and the Bohlmann criteria may be used to distinguish between (40a:positive) and (40b: negative). Reduction of (40) with Li-NH_3 gave (41) which showed no Bohlmann absorption band.

In order to construct the bridged ring of lycopodine, the immonium salt (38) was allowed to react with 2-methyl-3-methoxypropyl magnesium chloride to give (42). Since the unnatural cis-cis configuration in (42) was suggested by the Bohlmann absorption band like those for (39), this configuration should be transformed into the natural cis-trans configuration. Thus, a sequence of reactions



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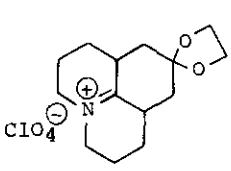

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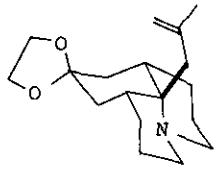

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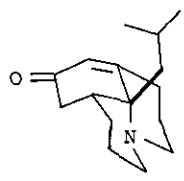

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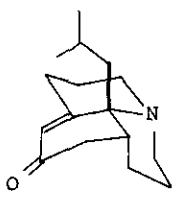

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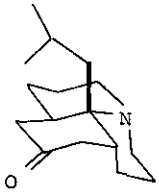

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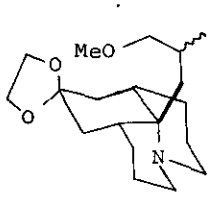

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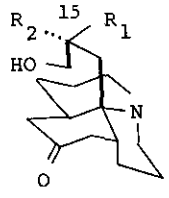
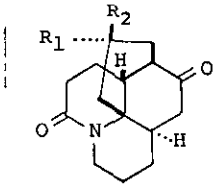


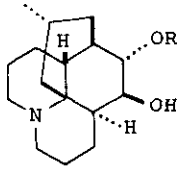
(43) R_1=Me, R_2=H

(44) R_1=H, R_2=Me



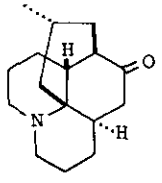
(45) R_1=Me, R_2=H

(46) R_1=H, R_2=Me



(47) R=H

(48) R=Ac



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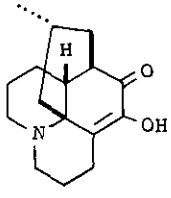

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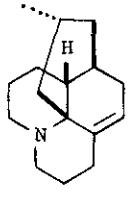

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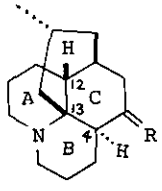


(1) R=O

(52) R=H_2

Chart 3

mentioned above via the unsaturated ketone was applied to (42) and subsequent treatment of the product with borontribromide gave a separable 2:3 mixture of diastereomeric alcohols (43) and (44), epimeric at C-15, in the total yield of 7.5 % from (42). Both alcohols were taken through to the tetracyclic system [(43) → (45) and (44) → (46)], but in this review, only the one with the configuration corresponding to that of C-15 of lycopodine will be considered.

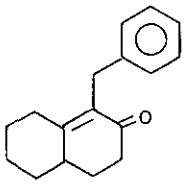
Compound (43) was acetylated and oxidized with potassium permanganate to the

lactam (to protect the nitrogen function for quaternalization). Hydrolysis of the acetate to the alcohol and treatment of the latter with methanesulfonyl chloride resulted in the formation of the mesylate. Treatment of the mesylate with potassium tert. butoxide in tert. butanol gave the racemic tetracyclic lactam (45) which was available from lycopodine in its optically active form by the following manner. Thus, the monoacetate (48) of the diol (47)[31),32)] derived from lycopodine (1) was successively treated with $SOCl_2$-pyridine, OH^-, MnO_2, and Li-NH_3 to give (49) in 60 % yield. Permanganate oxidation of (49) afforded (45) in 22 % yield. The optically active material was used as a natural relay to complete the synthesis. Hydride reduction of (45), followed by Jones' oxidation gave the ketone (49), which was oxidized with selenium dioxide to the diosphenol (50) in 26 % yield from (45). Heating of (50) with hydrazine in ethylene glycol gave lycopodine (1) (26 % yield)[16)] and lycopodane (52)(10 % yield) together with anhydrodihydrolycopodine (51)[33)](40 % yield).

(III-1-B) Synthesis by G. Stork

The second synthesis of lycopodine showed a different approach to the solution to the stereochemical problem at C-12. Stork et al. had revealed that treatment of (53) with polyphosphoric acid resulted in the formation of (55) via the intermediate (54). The key intermediate (57) of the synthesis was assumed to be obtained when this type of reaction is applied to (56) or its equivalent in which the methyl group and the benzyl group are in the trans relationship. Protonation of (56) may occur either on the same side as the methyl group to give the acylimmonium ion (58a) or on the opposite side to give the ion (58b). Intramolecular cyclization by the nucleophilic attack of the anisole ring to the acylimmonium ion is only possible in (58a), but in (58b) the cyclohexane ring would have to attain an energetically unfavourable boat conformation before cyclization could occur. Compound (56) for this cyclization reaction was synthesized in the following manner.

Treatment of m-methoxybenzaldehyde with ethyl acrylate-triphenylphosphine, followed by heating with ethyl acetoacetate in ethanol in the presence of sodium ethoxide and subsequent alkaline hydrolysis gave (59) in 36 % yield. Lithium aluminum hydride reduction of ethyl enol ether of (59), followed by acid treatment afforded the cyclohexenone (60), which was allowed to react with methylmagnesium iodide-Cu_2Cl_2 gave (61) in 90 % yield. Aza-annulation of (61) with



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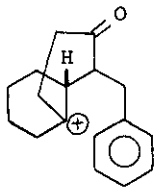

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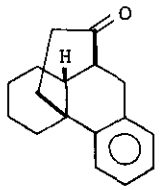

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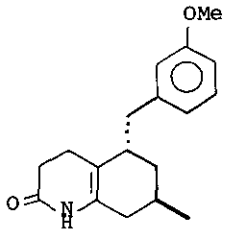

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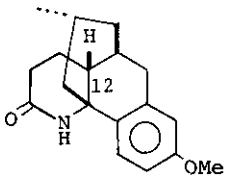

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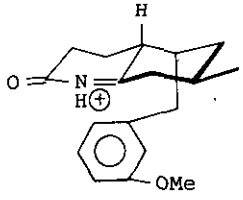

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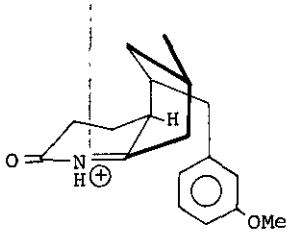

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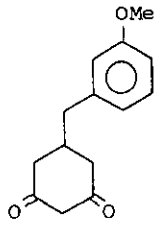

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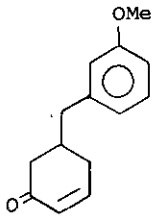

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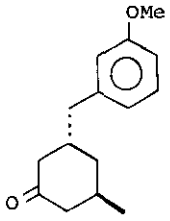

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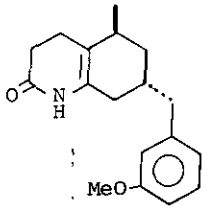

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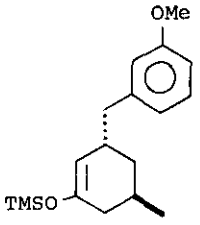

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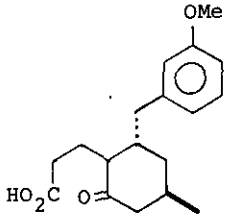

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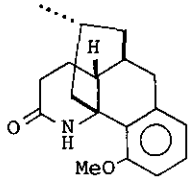

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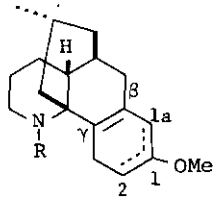

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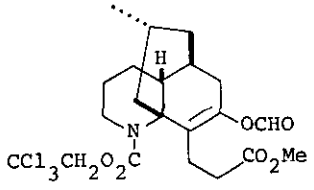

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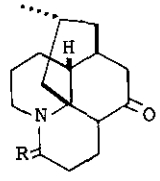


(1′) R=O

(1) R=H_2

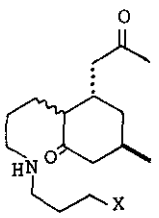
Chart 4

acrylamide-pyrrolidine gave the desired (56) in 20-25 % yield and the isomer (62). In order to obtain compound (56) regioselectively, an alternative route using the trapping method[34] was examined. Thus, copper-catalyzed 1,4-addition of m-methoxybenzylmagnesium bromide to 5-methyl-2-cyclohexenone and trapping the product with trimethylsilyl chloride gave (63). The lithium enolate of (63) was alkylated with allyl bromide and the product, after acetalization, was transformed into the acid (64) by hydroboration and Jones' oxidation. The methyl ester of (64) gave regioselectively (56) when heated with ammonia.

Treatment of (56) with 85 % phosphoric acid in formic acid at room temperature gave the desired 12β compound (57) in 55 % yield along with the ortho-substituted isomer (65) in 29 % yield. Lithium aluminum hydride reduction of the amide (57) followed by Birch reduction gave the dihydroanisole (66: R=H, $\Delta^{1,2}$; not $\Delta^{1,1a}$), which on hydrolysis gave the β,γ-unsaturated ketone. All attempts to isomerize the β,γ-unsaturated ketone to the α,β-unsaturated ketone were unsuccessful presumably because the non-bonded interaction developed in the α,β-unsaturated system. Treatment of the dihydroanisole (66: R=H, $\Delta^{1,2}$) with strong base, however, gave the isomeric dihydroanisole (66: R=H, $\Delta^{1,1a}$), which was acylated with trichloroethyl chlorocarbonate to give (66: R=$CO_2CH_2CCl_3$). Since ozone attacks only the less hindered $\Delta^{1,1a}$ double bond in (66: R=$CO_2CH_2CCl_3$), ozonization of (66: R=$CO_2CH_2CCl_3$) gave the aldehyde. Selenium dioxide-hydrogen peroxide oxidation (modified Baeyer-Villiger oxidation of the aldehyde group) gave the enol ester (67). Methanolysis of (67) followed by removal of the N-protective group (Zn-MeOH) and lactam formation of the product led to racemic lycopodine lactam (1'), which was reduced with lithium aluminum hydride followed by Jones' oxidation to give racemic lycopodine (1).[17]

(III-1-C) Synthesis by C. H. Heathcock

Since the ketone group and the tertiary amine group in the lycopodine molecule are located at positions in the 1,4-relationship, the authors anticipated that the intramolecular Mannich cyclization of (68) may be accessible for construction of the tricyclic compound (69). Two intermediates (70a) and (70b) may be present in equilibrium during cyclization, but the more facile cyclization may be possible only to compound (70a) with the configuration corresponding to that of C-12 of lycopodine by the analogy to Stork's lycopodine synthesis[17] (see III-1-B).



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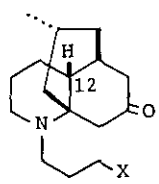

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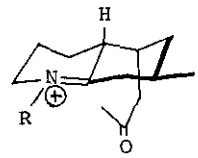
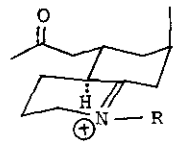


(70a)



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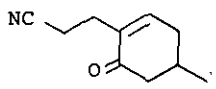

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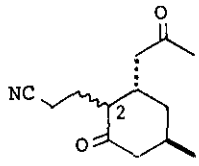

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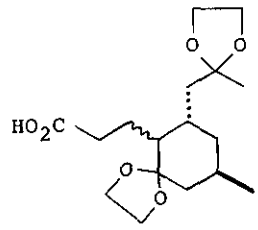

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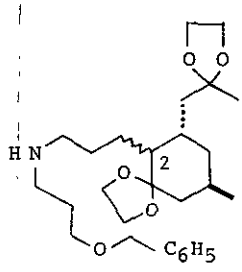

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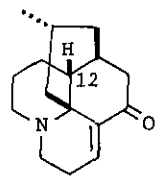

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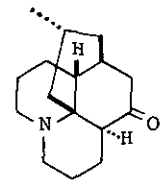


(1)

Chart 5

The cyano-enone (71) was derived into the cyano-dione (72) by stereoselective trans addition of lithium dimethallyl copper, followed by ozonolysis, (56 % yield) or by conjugate addition of the cuprate derived from the lithiated N,N-dimethylhydrazone of acetone, followed by aqueous hydrolysis (60 % yield). Both procedures gave the cyano-dione (72) as a mixture of epimers at C-2 in an equimolar ratio, but this mixture, without separation, was used for the subsequent stage. The cyano-dione (72) was converted via cyano-diacetal to the diacetal acid (73). Successive treatments of the acid with ethyl chloroformate and 3-benzyloxypropylamine afforded the secondary amide, which was reduced with lithium aluminum hydride to give the secondary amine (74) in 76 % yield from (72). Treatment of the amino diacetal (74) with 3.2M HCl results in slow intramolecular Mannich cyclization, affording a single tricyclic amino-ketone (69, X=O-Benz.) in 65 % yield. Although compound (74) was an equimolar mixture

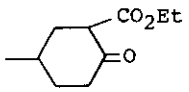
of C-2 epimers, none of the 12-epidiastereomer (lycopodine numbering) was found in the reaction product. Compound (69), after debenzylation, was subjected to Oppenauer oxidation, and subsequent intramolecular aldol cyclization of the product and dehydration gave racemic dehydrolycopodine (75) in 69 % yield. Finally, catalytic hydrogenation of (75) afforded racemic lycopodine (1) in 87 % yield.[18] The efficiency of this synthesis was demonstrated by the high overall yield [17.7 % from enone (71)].

(III-2) Synthesis of Anhydrolycodoline

Anhydrolycodoline (10) has been isolated from the natural source[35] and converted into lycopodine by catalytic hydrogenation.[36] The bicyclo[3.3.1]-nonane system found in rings B and D of lycopodine has been used for the synthesis of anhydrolycodoline (10) by Horii et al.

The reaction of the keto-ester (76) with acrolein in the presence of sodium ethoxide and subsequent treatment with dil. hydrochloric acid gave (77) in 58 % yield. Compound (77), a diastereomeric mixture at C-6, was converted into the mesylate, which was heated with γ-collidine to give a single product (78) in 53 % yield. The Michael addition occurred stereoselectively from the side opposite the methyl group, and this result was explicable by the following facts. The alkylation will occur preferentially through the pre-chair transition state of (79) at α-attack, leading to the product in which the methyl group is trans to the alkyl group. Furthermore, the epimer (80) having the unnatural configuration regarding the methyl group was synthesized through a different route.[37] The Curtius reaction ($ClCO_2Et$-NaN_3, $C_6H_5CH_2OH$) of (78), after hydrolysis, afforded the benzyl carbamate (81) in 47 % yield.[38]

On treatment of (81) with dimethyl sulfonium methylide, the oxirane (82) was stereoselectively obtained in 66 % yield. In this reaction, the ylide may attack the ketone group from the less hindered α-side of the ring bearing a double bond where the π-electron participation may be assumed in the transition state (83). For these reasons, the oxirane ring of (82) seemed to have the requisite stereostructure for the synthesis of lycodoline (84), which was the author's original synthetic target. Reaction of the oxirane (82) with ethyl ethoxymagnesium malonate and subsequent treatment with AcOH-HCl gave the amino-lactone (85) in 45 % yield, which was transformed into the tricyclic hydroxy-lactam (86) by treatment with a catalytic amount of Triton B in ethanol in 85 %



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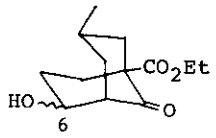

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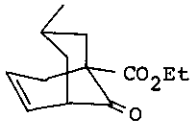

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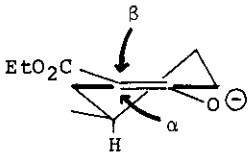

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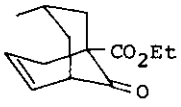

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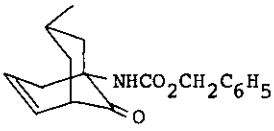

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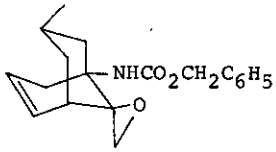

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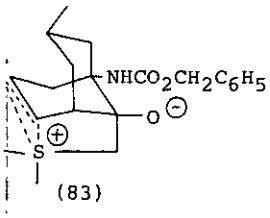

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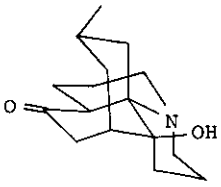

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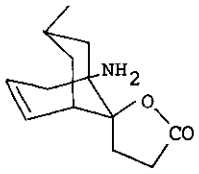

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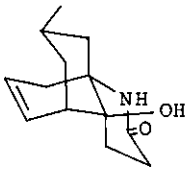

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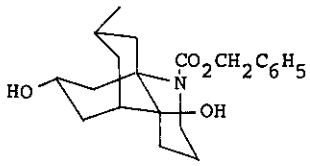

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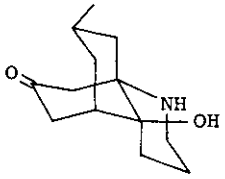

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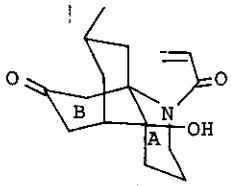

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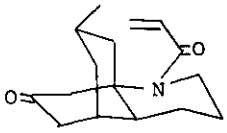

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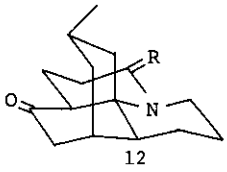
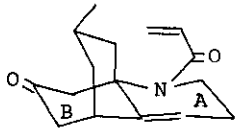


12

(21) R=H_2
(91) R=O



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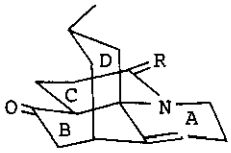


(10) R=H_2
(93) R=O

Chart 6

yield.[39] Successive treatments of (86) with $LiAlH_4$, $ClCO_2CH_2C_6H_5$ and B_2H_6-OH^--H_2O_2 gave stereo- and regioselectively the diol (87) in 41 % yield. Jones' oxidation of (87), followed by deprotection with H_2/10% Pd-C gave compound (88), which reacted with acrylyl chloride to give the amide (89) in 61 % yield. All attempts to cyclize compound (89) by intramolecular Michael addition using various bases were unfruitful owing to an unsatisfied stereoelectronic requirement. On the contrary of this result, it had been shown that (90) was converted into (91) by intramolecular Michael addition in the 12-epilycopodine (21) synthesis by Wiesner et al.[40] This fact suggests that this type of cyclization reaction seems to be sensitive to the conformation of rings A and B. Thus, the trans or the nearly trans ring junction seemed to be essential for the intramolecular cyclization reaction.[41),42] Then, compound (89) was converted into (92) by dehydrarion with c-H_2SO_4 and subsequent treatment of (92) with a catalytic amount of NaOEt-18-crown-6 afforded the desired tetracyclic compound (93) in 48 % yield from (88). Lithium aluminum hydride reduction of (93), followed by Jones' oxidation gave anhydrolycodoline (10) in 63 % yield.[19]

(IV) Synthesis of Luciduline

Luciduline has been shown by Ayer et al. to possess the structure (8)[10] in which the cis decahydroquinoline or the cis 2-decalone system having two hydrogen atoms at the ring junction is present.

(IV-A) Synthesis by D. A. Evans

A key step in the synthesis was the construction of the cis decalin ring system through the oxy-Cope rearrangement. A bicyclo[2.2.2]oct-5-en-2-one derivative reacted with methallylmagnesium bromide gave (95), which on oxy-Cope rearrangement followed by acetalization afforded (96) in greater than 65 % yield as an equilibrium mixture of methyl epimers (α-Me:β-Me=6:4). The desired α-methyl epimer of (96) was derived to its tosylhydrazone, which was transformed into a single acetal olefin by treatment with 2 eq. of methyllithium. The crude olefin was stereoselectively oxidized to the epoxide (97) with m-chloroperbenzoic acid in 80 % yield. Cleavage of the epoxide ring of (97) with sodium thiophenoxide proceeded regioselectively to (98a), which was cleanly desulfurized to the acetal-alcohol (98b) with Raney nickel. The entire sequence (97)-(98b)

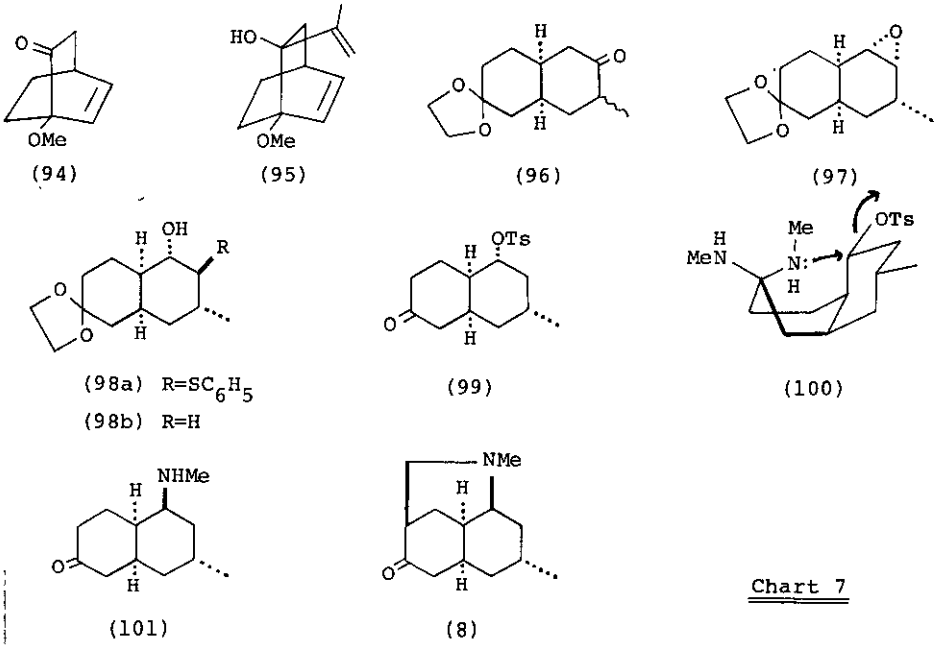


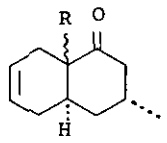
Chart 7

was carried out in 70 % yield. Treatment of (98b) with p-toluenesulfonyl chloride followed by acid hydrolysis afforded (99) in 89 % yield. When (99) was treated with excess monomethylamine in benzene in a sealed tube, the desired keto-amine (101) was obtained in 94 % yield via (100). The final step was accomplished by heating (101) with paraformaldehyde to afford luciduline (8).[20]

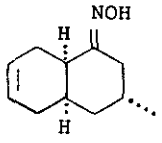
(IV-B) Synthesis by W. Oppolzer

The authors applied the unexplored thermal reaction of an transient N-alkenylnitrone (105), being equivalent to an intermediate of the Mannich reaction, to a simple total synthesis of racemic luciduline (8).[21]

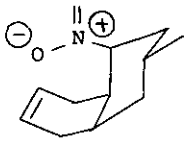
The first step of synthesis was the reaction of butadiene with 5-methyl-cyclohexenone which gave a mixture of the cis (102) and the trans isomer (103) in a 3:2 ratio.[43] It was noticed that the cis-isomer (102) reacted faster with hydroxylamine than its trans-isomer (103). Consequently, oximation of the mixture was carried out with a stoichiometric amount corresponding to the cis-isomer of hydroxylamine hydrochloride and the pure desired cis oxime (104) was readily obtained by recrystallizations of the reaction product in 40 % yield. Reduction of (104) with sodium cyanoborohydride afforded a stereochemically single hydroxylamine, which on heating with paraformaldehyde gave regioselectively the bridged isoxazolidine (106) via the transient nitrone (105). Methylation of



(102) R=α-H
(103) R=β-H



(104)



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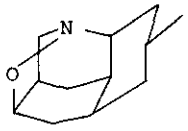

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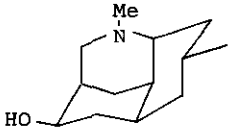


(107)

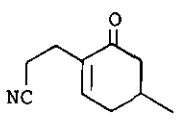
Chart 8

(106) with methyl fluorosulfonate followed by reduction of the resulting salt with lithium aluminum hydride gave the alcohol-amine (107) in 97 % yield. Finally, Jones' oxidation of (107) furnished racemic luciduline (8) in 98 % yield.

(IV-C) Synthesis by D. B. MacLean

This synthetic approach is not biomimetic but leads to an intermediate (110 type amino acid) that may be involved in the biosynthesis of luciduline and other alkaloids.

The synthesis was started from (71) which was used by Heathcock et al. in their synthesis of lycopodine.[18] Treatment of (71) with methanolic alkali gave a 5:1 mixture of bicyclic cis lactam (108) and trans lactam (109) in 43 % total yield. The mixture of (108) and (109) in a 7:3 ratio reacted with lithium



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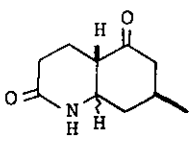
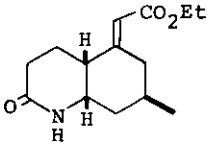


(108) β-H
(109) α-H



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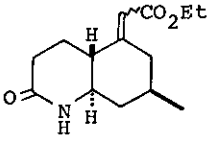

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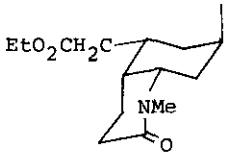

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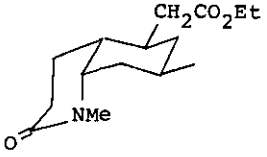

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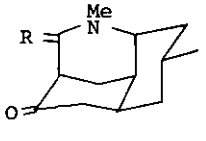


(8) R=H_2
(114) R=O

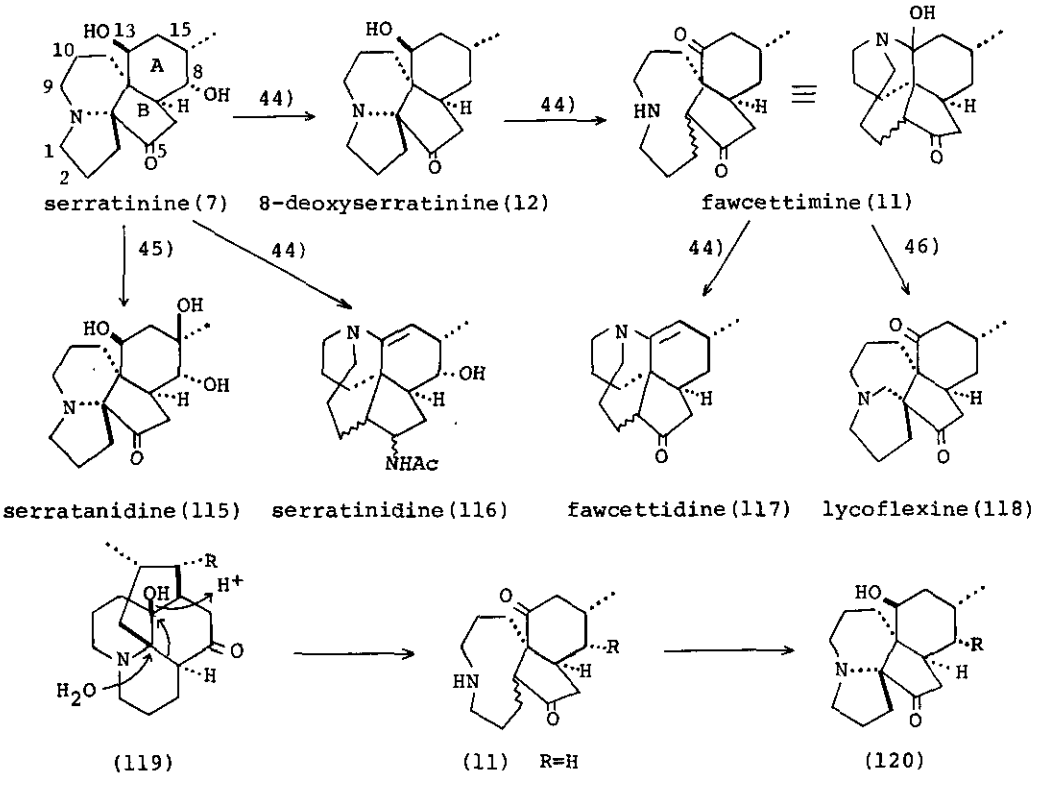
Chart 9

isopropylcyclohexylamide (LiICA) and ethyl trimethylsilylacetate to give the desired (110) and (111) in 18 % and 24 % yields, respectively. N-Methylation of (110) with LiICA and dimethyl sulfate, followed by catalytic hydrogenation over Adams' catalyst afforded quantitatively (112) and (113) in a 1:1 ratio. Cyclization of (112) with LiICA gave luciduline lactam (114) in 90 % yield, which was successively treated with lithium aluminum hydride and Jones' reagent to furnish luciduline (8) in 50 % yield.[22]

(V) Synthesis of Serratinine and Related Alkaloids

Serratinine has been shown by Inubushi et al. to possess the structure (7)[9] and correlated chemically to several alkaloids as shown in Chart 10. The possible biogenetic relationship between members of the serratinine group and those of the lycopodine group has been pointed out and fawcettimine (11) has been presumed to be the biogenetic precursor of members of the serratinine group.[9]

Chart 10

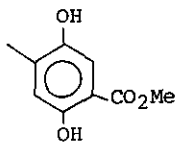


(V-1) Synthesis of Serratinine

Total synthesis of serratinine has been accomplished and in this synthesis, compound (135) was selected as the first objective of the synthesis since this has the cis hydrindene skeleton found in rings A and B of serratinine and steric control is predictable in the reactions utilized for achieving the construction of nitrogen-containing rings.

Successive treatments of (121) with NaH-$ClCH_2OMe$, $LiAlH_4$ and Collins' reagent gave (122), which was reacted with $NaNH_2$-$(EtO)_2POCH_2CO_2Et$ to furnish the unsaturated ester (123) in 86 % yield from (121). Compound (123), after deprotection with HCl, was oxidized with $FeCl_3$ to give the benzoquinone (124). The Diels-Alder reaction of (124) with butadiene gave the adduct (125) in 39 % yield from (123). Reduction of (125) with Zn-AcOH followed by sodium borohydride reduction afforded the diol (126), in which the secondary methyl group and its adjacent hydroxy group have the unnatural configurations, respectively, in 40 % yield. This stereochemical problem will be solved at the last stage of this synthesis [see the triketone (141)]. Compound (126), after acetylation, was oxidized with OsO_4-$NaClO_4$ to give the glycol (127) and the ketol (128) in 35 % and 11 % yields, respectively. Hydrogenation of (127) over Adams' catalyst gave quantitatively the saturated diol (129), which was also obtained from the ketol (128) by catalytic hydrogenation followed by sodium borohydride reduction. Periodate oxidation of (129) furnished the dialdehyde (130). Treatments of (130) with Al_2O_3 or a catalytic amount of piperidine acetate in benzene (the Woodward's method[47]) gave the α,β-unsaturated aldehyde (131) generated by the cyclization in the undesired direction. The formation of compound (131) may be explicable by assuming that the cyclization proceeds via pathways such as (132) or (133). The authors predicted that if the immonium salt (134), generated from the less hindered aldehyde group and the amine, undergoes in situ ring closure, the desired α,β-unsaturated aldehyde (135) may be obtained. Then, the dialdehyde (130) was treated with excess pyrrolidine acetate in methanol to give (131) and (135) in a 1:8 ratio and 70 % total yield.[48]

Compound (135) reacted with NaH-$(EtO)_2POCH_2\dot{C}N$ and subsequent hydrogenation of the product using the Wilkinson reagent furnished the nitrile (136) in 50 % yield. Selective reduction of the cyano group of (136) with $NaBH_4$-$CoCl_2$[49] afforded the primary amine, which without purification was allowed to react with NCS and Cu_2Cl_2 to give two kinds of aziridine, (137) and (138), stereoisomeric



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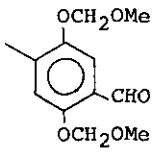

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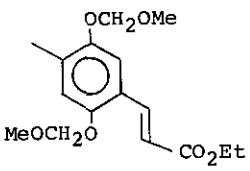

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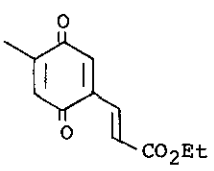

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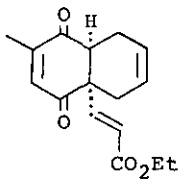

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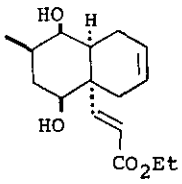

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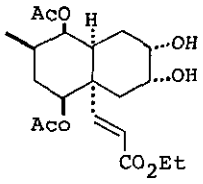

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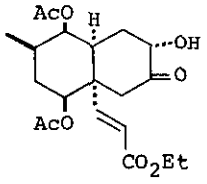

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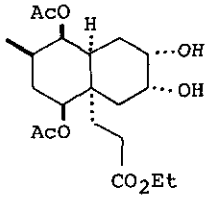

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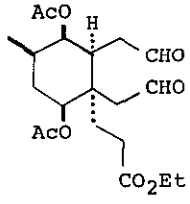

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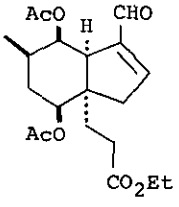

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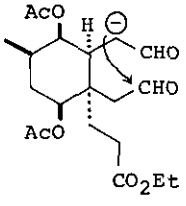

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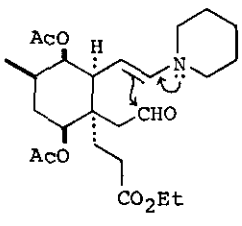

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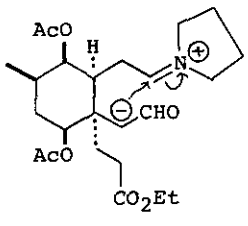

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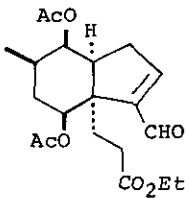

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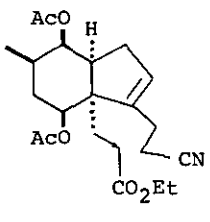

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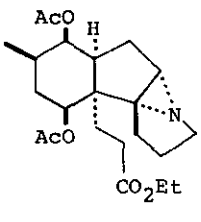

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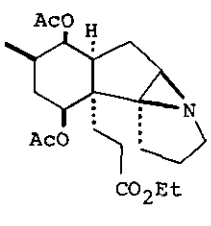
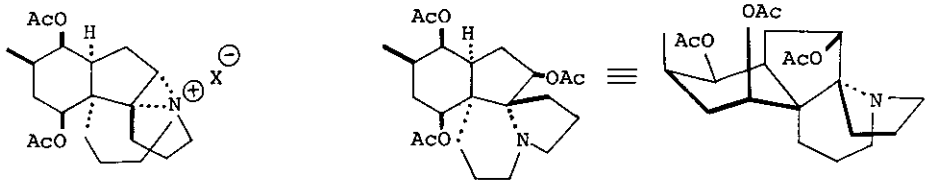
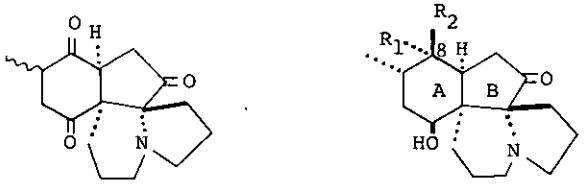


(138)

Chart 11



(139) (140)



(141) (7) R_1=OH, R_2=H

(142) R_1=H, R_2=OH

Chart 12

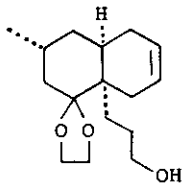
with respect to the aziridine ring, in 20 % and 3 % yields, respectively. The stereostructure of the main product (137) was presumed to have the desired α-configuration since the double bond seemed to be attacked preferentially from the convex face. Selective reduction of an ethoxycarbonyl group of (137) with lithium borohydride gave the primary alcohol in 74 % yield. Treatment of the primary alcohol with p-toluenesulfonyl chloride-pyridine furnished the aziridinium salt (139), which was allowed to react with potassium acetate to give the triacetate (140) possessing the serratinine ring system in 24 % yield from (137). Alkaline hydrolysis of (140) followed by Jones' oxidation gave the triketone (141) identical, except for rotation, with a sample derived from natural serratinine, this fact indicating that the secondary methyl group epimerized predominantly to the natural configuration. Finally, reduction of (141) with sodium borohydride gave serratinine (7) and 8-episerratinine (142) in 18 % and 25 % yields, respectively.[23]

(V-2) Synthesis of Fawcettimine and 8-Deoxyserratinine

Stereoselective synthesis of fawcettimine and 8-deoxyserratinine has been completed. As is distinct from serratinine, there is no oxygen function at C-8 in these alkaloids. Such structural feature requires that an intermediate with the natural configuration with respect to the secondary methyl group must be stereoselectively synthesized at the stage as early as possible in the sequence.

For this reason, the first subgoal of this synthesis was compound (143).

It had been shown that addition of butadiene in the Diels-Alder reaction of 2,5-dialkylcyclohexenone in the presence of Lewis acid took place stereoselectively from the side opposite the 5-alkyl group.[43),50)] By taking advantage of this type of Diels-Alder reaction, compound (143) was supposed to be stereoselectively obtainable. The dienophile (145) was synthesized as follows.[51)] Lithium aluminum hydride reduction of the vinylogous ester (144) and subsequent Claisen rearrangement of the product caused by heating in toluene, followed by heating with p-toluenesulfonic acid gave regioselectively the enone (145) in 62 % yield. The Diels-Alder reaction of (145) with butadiene in the presence of $BF_3 \cdot Et_2O$ proceeded stereoselectively to give the adduct (146) in 29 % yield (53 % yield based on the consumed starting material). Treatment of (146) with disiamylborane-OH^--H_2O_2, after acetalization, afforded compound (143), the first subgoal of the synthesis, in 51 % yield. Successive treatments of compound (143) with benzyl chloride, OsO_4-N-methylmorpholine-N-oxide and HIO_4 afforded the dialdehyde (147) in 76 % yield. Intramolecular aldol cyclization of (147) by the Corey's method[52)], followed by treatment with the Wadsworth-Emmons reagent gave (148) and (149) in 19:1 ratio and 76 % total yield. The method utilized in the serratinine synthesis (excess pyrrolidine acetate in MeOH) followed by treatment with the Wadsworth-Emmons reagent gave an equimolar mixture of (148) and (149). Since the cyclization reaction proceeded in the undesired direction under these conditions, a detailed investigation of this reaction was made. A variety of reaction conditions employing various solvents, bases and acids were explored. Finally, it was found that the condition using morpholine-camphoric acid in Et_2O-HMPA served the present purpose. Reaction of (147) under this reaction condition, followed by treatment with the Wadsworth-Emmons reagent afforded compound (148) and the desired compound (149) in 1.5 % and 37.5 % yields, respectively.[53)] Selective reduction of the side chain with tris(triphenylphosphine)chlororhodium and subsequent treatments with $LiAlH_4$ and $N_3CO_2Bu^t$ gave the carbamate (150) in 72 % yield. Compound (150) was successively treated with Na-liq. NH_3, Jones' reagent, N-hydroxysuccinimide-DCC (formation of the activated ester), CF_3CO_2H, $(n\text{-}Bu)_3N$ in CH_3CN (high dilution method) gave the nine membered lactam (151) in 41 % yield. Acetalization of (151) and reduction of the thiolactam derived from (151) were unsuccessful. Then, compound (151) was reduced with sodium borohydride to give epimeric alcohols



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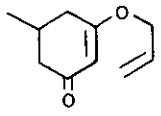

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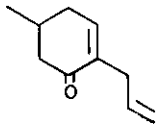

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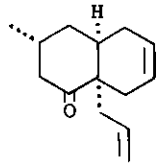

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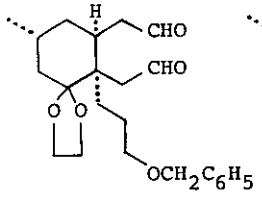

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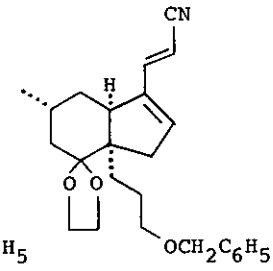

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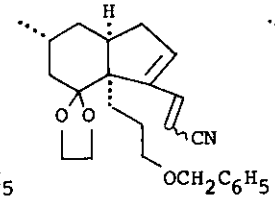

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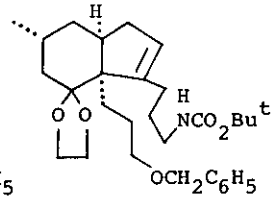

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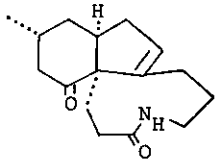

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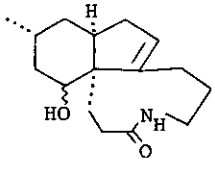
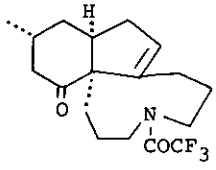
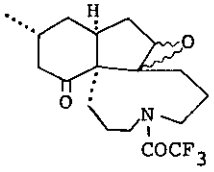


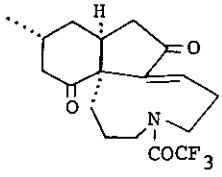
(152) β-OH
(153) α-OH



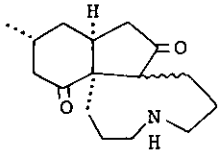
(154)



(155) α-epoxide
(156) β-epoxide



(157)



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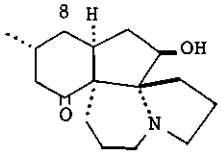
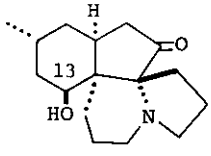


(158)



(12)

Chart 13

(152) and (153) in 66 % and 31 % yields, respectively. Each epimeric alcohol was subjected to the same series of reactions as follows. Reduction with lithium aluminum hydride and subsequent treatment of the product with trifluoroacetic anhydride-pyridine afforded the N,O-bistrifluoroacetyl derivative. Selective hydrolysis of the O-trifluoroacetate group, followed by Jones' oxidation gave the same ketone (154) in 61 % yield from (152) and in 56 % yield from (153). Oxidation of (154) with m-chloroperbenzoic acid afforded epimeric epoxides (155) and (156) in 58 % and 40 % yields, respectively. Since the reagent seems to attack the double bond of (154) preferentially from the convex face, the stereostructure of the main product was assigned to (155) and that of the minor product to (156).

Treatment of the epoxide (155) with $BF_3 \cdot Et_2O$, followed by Jones' oxidation afforded the enone (157), which underwent successively catalytic hydrogenation and hydrolysis with 1N-KOH to give fawcettimine (11) in 61 % yield, a sample of which was identical with an authentic sample of natural fawcettimine except for rotation.

On the other hand, treatment of the epoxide (156) with 1N-KOH caused removal of the N-protective group and successive ring closure in one operation to yield the alcohol (158), which was oxidized with Jones' reagent to give the diketone (12: C=O in place of C-13-OH). Finally, reduction of the diketone with sodium borohydride afforded 8-deoxyserratinine (12) identical, except for rotation, with an authentic sample in 55 % yield.[24)]

(VI) References

1. K. Bödeker, Liebig Ann., 1881, 208, 363.
2. K. Wiesner, Z. Valenta, W. A. Ayer, L. R. Fowler, and J. E. Francis, Tetrahedron, 1958, 4, 87.
3. M. Przybylska, and L. Marion, Can. J. Chem., 1957, 35, 1075.
4. W. A. Harrison, M. Curcumelli-Rodostamo, D. F. Carson, L. R. C. Barclay and D. B. MacLean, Can. J. Chem., 1961, 39, 2086.
5 W. A. Szarek, K. A. H. Adams, M. Curcumelli-Rodostamo, and D. B. MacLean, Can. J. Chem., 1964, 42, 2584.
6. W. A. Ayer, J. K. Jenkins, S. Valverde-Lopez, and R. H. Burnell, Can. J. Chem., 1967, 45, 433 ; W. A. Ayer, J. K. Jenkins, K. Piers, and S. Valverde-Lopez, ibid., 1967, 45, 445.
7. W. A. Ayer, G. G. Iverach, J. K. Jenkins, and N. Masaki, Tetrahedron

Letters, 1968, 4597.

8. W. A. Ayer, and N. Masaki, Can. J. Chem., 1971, 49, 524.
9. Y. Inubushi, H. Ishii, B. Yasui, M. Hashimoto, and T. Harayama, Chem. Pharm. Bull., 1968, 16, 82 ; Idem, ibid., 1968, 16, 92 ; Y. Inubushi, H. Ishii, B. Yasui, and T. Harayama, ibid., 1968, 16, 101 ; K. Nishio, T. Fujiwara, K. Tomita, H. Ishii, Y. Inubushi, and T. Harayama, Tetrahedron Letters, 1969, 861.
10. W. A. Ayer, N. Masaki, and D. S. Nkunika, Can. J. Chem., 1968, 46, 3631.
11. D. B. MacLean, "The Alkaloids" ed. by R. H. F. Manske, Academic Press, New York, 1973, Vol. XIV, pp 347.
12. W. A. Ayer, "M. T. P. International Review of Science, Alkaloids, Organic Chemistry Series One" ed. by K. Wiesner, Butterworth Publishers, 1973, Vol. 9, pp 15.
13. F. A. L. Anet, and C. R. Eves, Can. J. Chem., 1958, 36, 902 ; W. A. Ayer, and G. G. Iverach, ibid., 1960, 38, 1823. See the formula (9) in Chart 1.
14. T. Harayama, J. Synthetic Organic Chemistry, Japan, 1977, 35, 253.
15. K. Wiesner, L. Poon, I. Jirkovský, and M. Fishman, Can. J. Chem., 1969, 47, 433.
16. W. A. Ayer, W. R. Bowman, T. C. Joseph, and P. Smith, J. Amer. Chem. Soc., 1968, 90, 1648.
17. G. Stork, R. A. Kretchmer, and R. H. Schlessinger, J. Amer. Chem. Soc., 1968, 90, 1647 ; G. Stork, "I. U. P. A. C. Fifth International Symposium on the Chemistry of Natural Products, Special Lectures Abstract Papers" 1968, pp 383.
18. C. H. Heathcock, E. Kleinman, and E. S. Binkley, J. Amer. Chem. Soc., 1978, 100, 8036 ; Idem, "Stereoselective Synthesis of Natural Products" Exlerpta Medica, Amsterdam-Oxford, 1979, pp 71.
19. S. Kim, Y. Bando, N. Takahashi, and Z. Horii, Chem. Pharm. Bull., 1978, 26, 3150.
20. W. L. Scott, and D. A. Evans, J. Amer. Chem. Soc., 1972, 94, 4779.
21. W. Oppolzer, and M. Petrzilka, J. Amer. Chem. Soc., 1976, 98, 6722.
22. J. Szychowski, and D. B. MacLean, Can. J. Chem., 1979, 57, 1631.
23. T. Harayama, M. Ohtani M. Oki, and Y. Inubushi, Chem. Pharm. Bull., 1975, 23, 1511.
24. T. Harayama, M. Takatani, and Y. Inubushi, Tetrahedron Letters, 1979, 4307 ;

Idem, Chem. Pharm. Bull., in Press.

25. E. H. W. Böhme, Z. Valenta, and K. Wiesner, Tetrahedron Letters, 1965, 2441.
26. K. Wiesner, I. Jirkovsky, M. Fishman, and C. A. L. Williams, Tetrahedron Letters, 1967, 1523.
27. K. Wiesner, V. Musil, and K. J. Wiesner, Tetrahedron Letters, 1968, 5643.
28. E. E. Betts, and D. B. MacLean. Can. J. Chem., 1957, 35, 211.
29. D. B. MacLean, "The Alkaloids", ed. by R. H. F. Manske, Academic Press, New York, 1968, Vol. X, pp 305.
30. W. A. Ayer, W. R. Bowman, G. A. Cooke, and A. C. Soper, Tetrahedron Letters, 1966, 2021.
31. W. A. Ayer, and D. A. Law, Can. J. Chem., 1962, 40, 2088.
32. W. A. Ayer, J. A. Berezowsky, and D. A. Law, Can. J. Chem., 1963, 41, 649.
33. B. Douglas, D. G. Lewis, and L. Marion, Can. J. Chem., 1953, 31, 272.
34. G. Stork, and P. F. Hudrlik, J. Amer. Chem. Soc., 1968, 90, 4462, 4464.
35. W. A. Ayer, B. Altenkirk, S. Valverde-Lopez, B. Douglas, R. F. Raffauf, and J. A. Weisbach, Can. J. Chem., 1968, 46, 15.
36. W. A. Ayer, and G. G. Iverach, Can. J. Chem., 1964, 42, 2514.
37. Z. Horii, T. Imanishi, S. Kim, and I. Ninomiya, Chem. Pharm. Bull., 1968, 16, 1918.
38. Z. Horii, S. Kim, T. Imanishi, and I. Ninomiya, Chem. Pharm. Bull., 1968, 16, 2107.
39. Z. Horii, S. Kim., T. Imanishi, and T. Momose, Chem. Pharm. Bull., 1970, 18, 2235.
40. H. Dugas, M. E. Hazenberg, Z. Valenta, and K. Wiesner, Tetrahedron Letters, 1967, 4931.
41. T. Momose, S. Uchida, T. Imanishi, S. Kim, N. Takahashi, and Z. Horii, Heterocycles, 1977, 6, 1105.
42. T. Momose, Uchida, and T. Imanishi, Chem, Pharm. Bull., 1978, 26, 972.
43. T. Harayama, H. Cho, M. Ohtani, and Y. Inubushi, Chem. Pharm. Bull., 1974, 22, 2784.
44. H. Ishii, B. Yasui, R. Nishino, T. Harayama, and Y. Inubushi, Chem. Pharm. Bull., 1970, 18, 1880.
45. Y. Inubushi, T. Harayama, M. Akatsu, H. Ishii, and Y. Nakahara, Chem. Pharm. Bull., 1968, 16, 2463.
46. W. A. Ayer, Y. Fukazawa, P. P. Singer, and B. Altenkirk, Tetrahedron Letters,

1973, 5045.

47. R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. H. McLamore, J. Amer. Chem. Soc., 1952, 74, 4223.

48. T. Harayama, M. Ohtani, M. Oki, and Y. Inubushi, Chem. Pharm. Bull., 1973, 21, 1061.

49. T. Satoh, S. Suzuki, Y. Suzuki, Y. Miyaji, and Z. Imai, Tetrahedron Letters, 1969, 4555.

50, T. Harayama, H. Cho, and Y. Inubushi, Chem. Pharm. Bull., 1977, 25, 2273.

51. T. Harayama, M. Takatani, and Y. Inubushi, Chem. Pharm. Bull., 1979, 27, 726.

52. E. J. Corey, R. L. Danheiser, S. Chandrasekaran. P. Siret, G. E. Keck, and J. -L. Gras, J. Amer. Chem. Soc., 1978, 100, 8031.

53. T. Harayama, M. Takatani, and Y. Inubushi, Chem. Pharm. Bull., 1980, 28, 1276.

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