SYNTHETIC APPROACHES TO THE *HUNTERIA* ALKALOIDS

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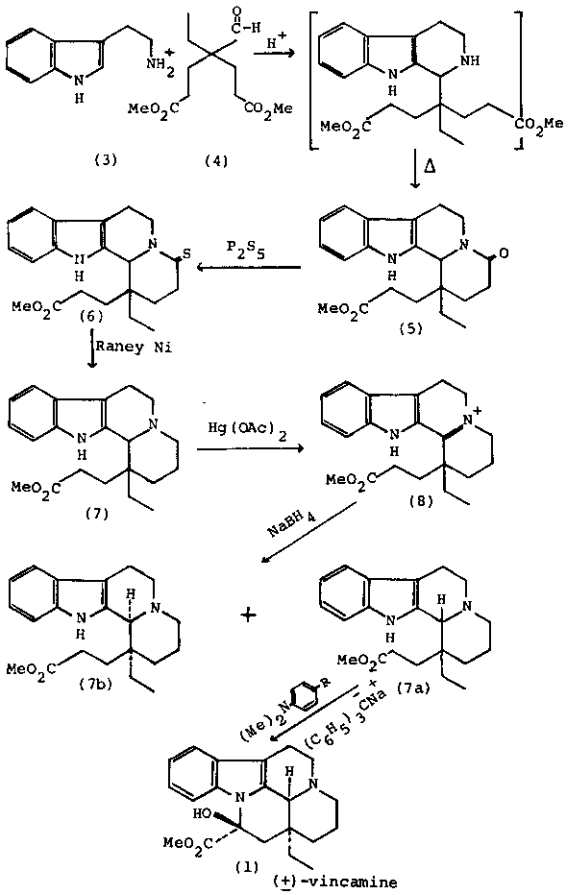
Abstract- Synthetic approaches to the *Hunteria* alkaloids are reviewed.

The *Hunteria* alkaloids are closely related to the *Aspidosperma* alkaloids bearing the same fundamental C_{10} non-tryptophan unit. Vincamine (1) and eburnamonine (2) are typical representatives and best known members of this class of alkaloids, exhibiting interesting physiological activity as cereberal vasodilators.[1] Synthetic studies towards these bases began as a part of structural elucidation studies of Bartlett and Taylor[2] and were continued by Kuehne,[3] Wenkert,[4] Harley-Mason[5] and Saxton.[6] A number of total syntheses have subsequently been reported, and interesting biomimetic transformations of the *Aspidosperma* alkaloidal system to vincamine have also been achieved.[7-9]

The first total synthesis of vincamine was reported in 1964 by Kuehne et al.[3] which involved the condensation of tryptamine (3) with 4-ethyl-4-formylpimelate (4). The latter was obtained by exhaustive alkylation of the pyrrolidine enamine of butyraldehyde with methyl acrylate followed by hydrolysis. The product (5) was converted to the epimeric mixture of thiolactams (6) which were desulphurized with Raney nickel to afford the corresponding amine (7). The latter was equilibrated through the immonium intermediate (8) to the two amino esters (7a) and (7b). Oxidation of (7a) followed by carefully controlled acid treatment furnished (±)-vincamine (1) in 30% yield (Scheme-1).

Harley-Mason and coworkers[5] have reported a similar approach to eburnamine (9) and vincaminol (10) (Scheme-2). Condensation of the aliphatic unit (11) with tryptamine afforded the amide (12). Subsequent elaboration of (12) gave (±)-eburnamine (9). Later it was found that the lactam (12) formed during the above synthesis was in fact an inhomogeneous mixture and on treatment with osmium tetroxide yielded a mixture of diols (13) which on oxidation and reduction/cyclisation afforded (±)-vincaminol (10) (Scheme-3).

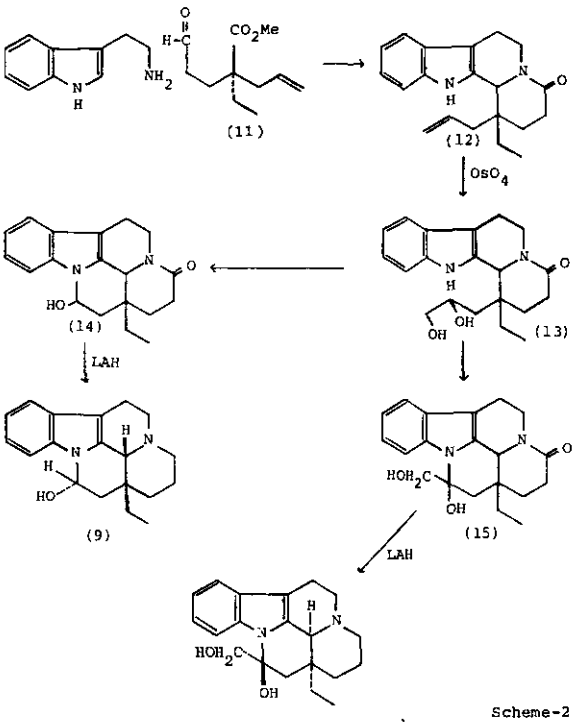
An interesting contribution to synthesis in this area includes the first synthesis of (±)-homoeburnamenine (26) and a total synthesis of vincamine by Gibson and Saxton.[6] The synthesis of (±)-homoeburnamenine (26) employs the ester diol (22) as the non-tryptophan unit. Condensation of (22) with tryptamine afforded the amide



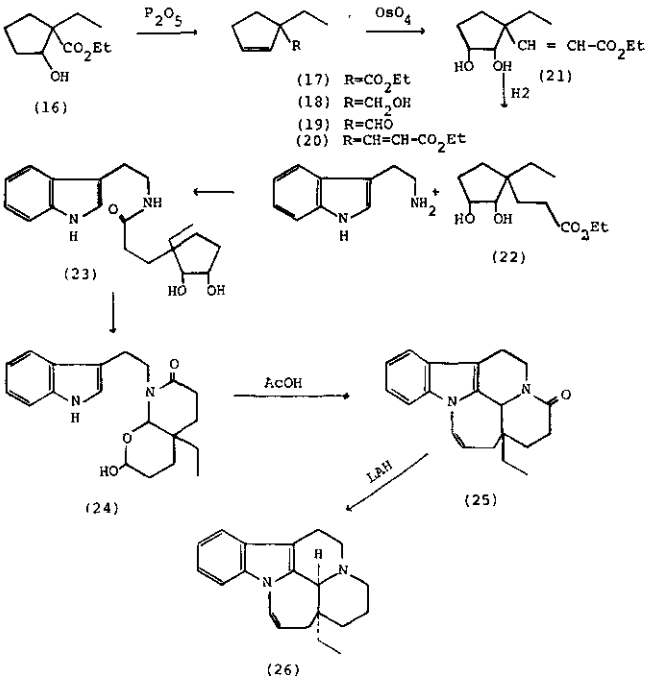
Scheme-1

(23) which on oxidation gave the carbinolamide lactol (24) as two separable isomers. Cyclisation and reduction afforded homoeburnamenine (26) (Scheme-3). Osmium tetroxide oxidation of (26) yielded the diol (27) in almost quantitative yields. Oxidation of the diol (27) to (28) was difficult as it was limited to the use of non-acidic conditions because of the high susceptibility of the system to acid-catalysed dehydration. However pyridine-sulphur trioxide complex in DMSO containing traces of water afforded the desired epimeric mixture of (28). Alkaline hydrolysis afforded the corresponding mixture of hydroxy acids (29) which were esterified by diazomethane to give the methyl ester (30). Oxidation of the hydroxy ester and subsequent cyclization in the presence of base afforded (±)-vincamine (1) (Scheme-4).

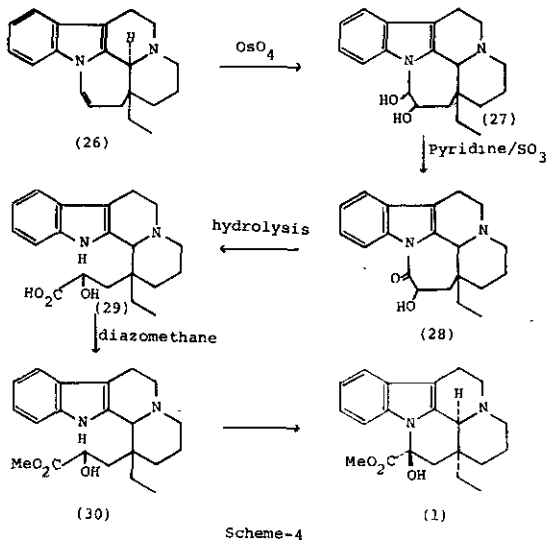
Bartlett and Taylor[2] have reported an efficient seven step synthesis of (±)-eburnamonine (2). The key step involved the condensation of β-ethylformyladipic acid (36) with tryptamine to give the (±)-eburnamonine lactam (37) which was reduced with lithium aluminium hydride to afford (±)-eburnamine (9). Oxidation of (9) afforded eburnamonine (2) (Scheme-5).



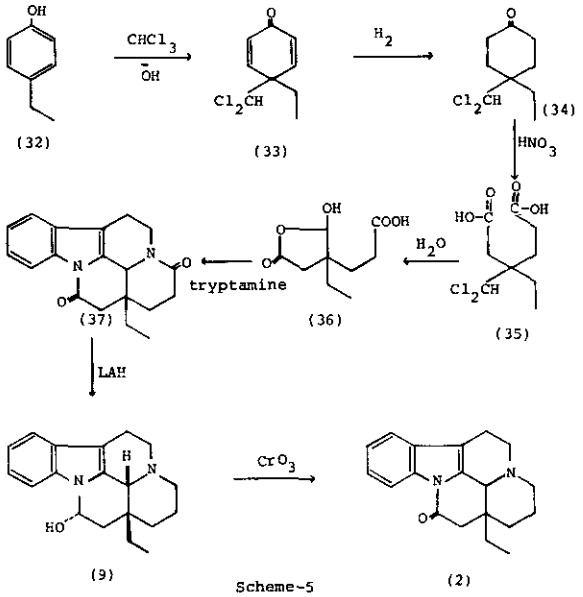
Scheme-2



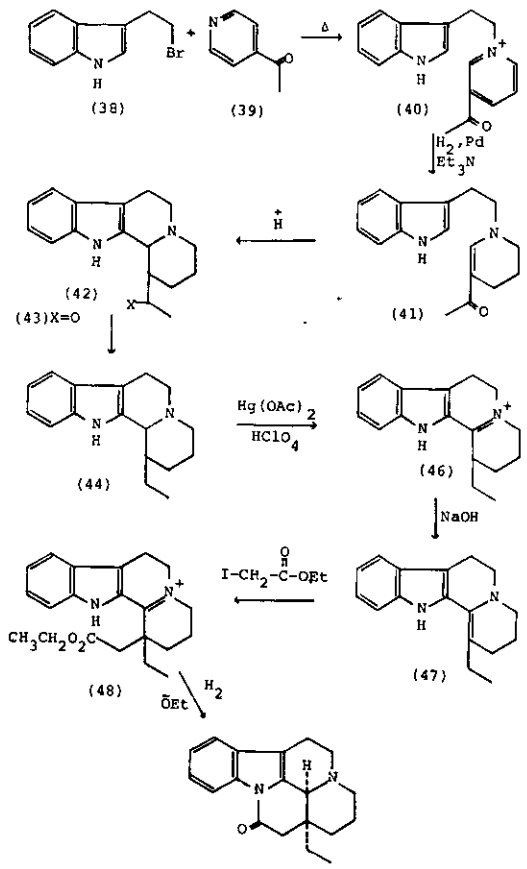
Scheme-3 Homoeburnamenine



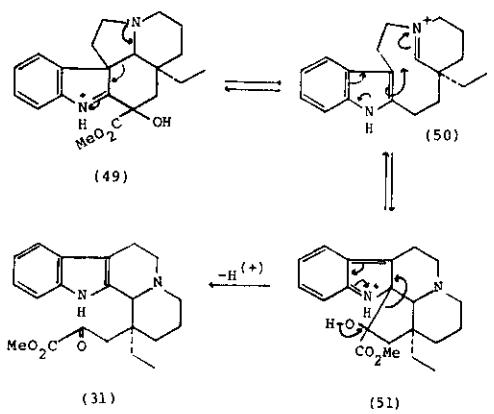
Scheme-4



Scheme-5



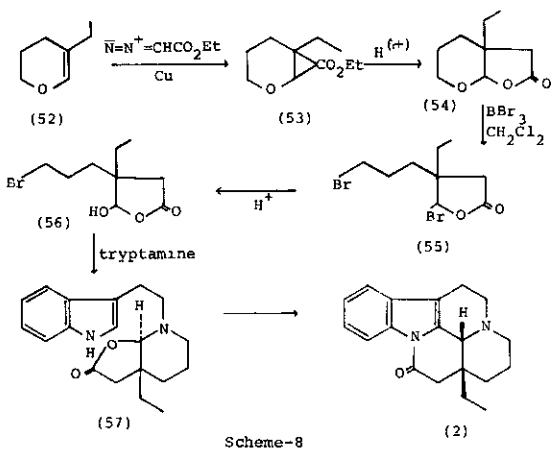
Scheme-6



Scheme-7

Wenkert and collaborators[4] in their general study on the use of piperidine intermediates in indole alkaloid synthesis, have published a different scheme for the synthesis of (±)-eburnamonine (2). The salt (40) prepared from β-acetylpyridine (39) and tryptophyl bromide (38) was hydrogenated to the tetrahydro derivative (41). Pictet-Spengler cyclization of (41) afforded (42) which on Wolff-Kishner reduction gave (44) which was oxidised with mercuric acetate to the ammonium salt (46). This underwent the expected base-catalyzed isomerization to the enamine (47), a key intermediate which has been used for transformation into the *Hunteria* alkaloids in several subsequent syntheses.[10,12] The enamine (47) can be alkylated to (48) which after reduction and treatment with base afforded (±)-eburnamonine (2) (Scheme-6). The vincamine system can be reasonably considered to give rise to eburnamonine (9) by oxidative transformation in the plants (Scheme-7).

An interesting synthesis of eburnamonine described by Wenkert[13] is based on an extension of the preparation of 1,4-diketones through a cyclopropanoid intermediate. Acid hydrolysis of the ester (53) prepared by a copper-assisted decomposition of ethyl diazoacetate in dihydropyran (52) yielded the lactone (54). Treatment of the latter with boron tribomide gave the dibromide (55) which on hydrolysis afforded a bromo-α-lactol (56). Condensation of (56) with the appropriate indolylethyl derivative led to the intermediate (57), thermolysis of which gave (±)-eburnamonine (2) (Scheme-8).

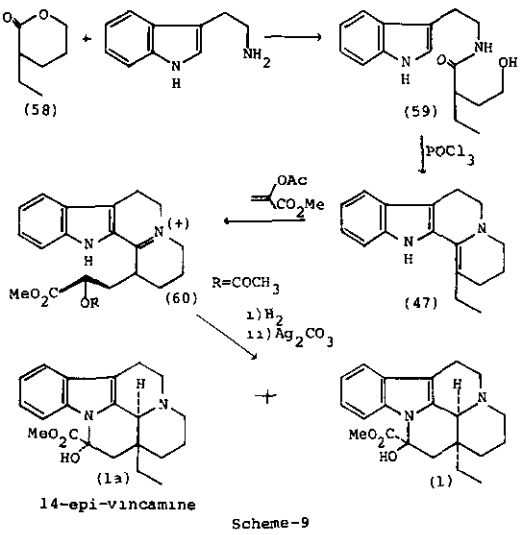


(52) (53) (54) (56) (55) (57) (2)

Scheme-8

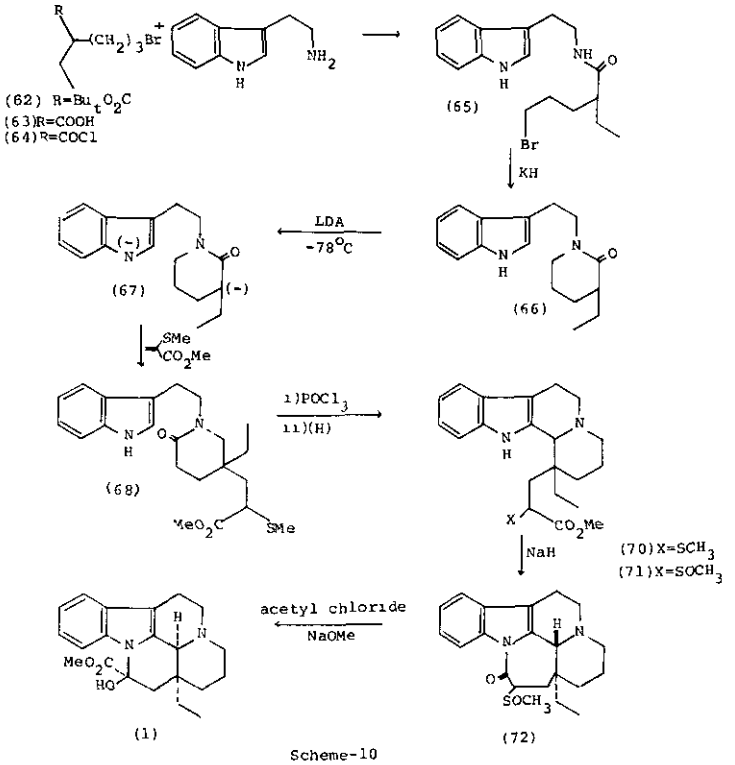
The first stereoselective total synthesis of (±)-vincamine (1) was accomplished by Szantay[10] et al. in 1973. The enamine (47) described earlier by Wenkert[4] was prepared by a potentially general method, and was employed as the starting material for the above synthesis. Alkylation of (47) with methyl α-acetoxyacrylate gave the adduct (60) in excellent yields. Reduction and subsequent oxidation with Ag_2CO_3/ celite gave a mixture of (±)-vincamine (1) and 14-epivincamine (1a) (Scheme-9).

Hermann et al.[14] have reported a stereospecific total synthesis of vincamine, based on a high yield construction of the tricyclic lactam (66). The lactam was prepared from the lithium enolate of tert-butyl butyrate by alkylation with 1,3-dibromopropane which afforded the bromo-ester (62). Subsequent hydrolysis to the corresponding acid and its conversion to the acid chloride afforded (64). Condensation of the



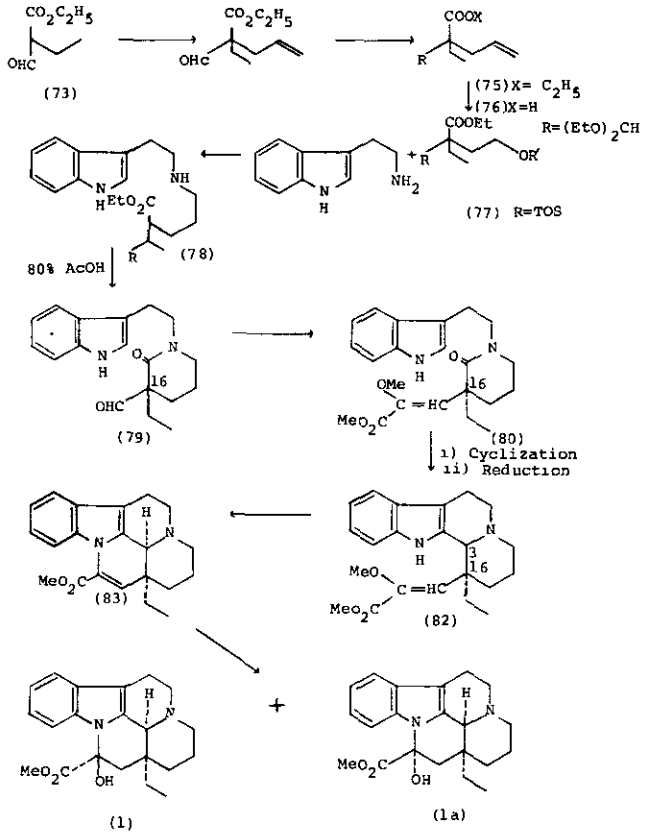
Scheme-9

latter with tryptamine gave the amide (65) which was then cyclized by potassium hydride to give the lactam (66). Reaction with lithium diisopropyl-amide produced the dianion (67) which upon treatment with methyl 2-thiomethylacrylate afforded the lactam ester (68). Cyclisation and stereospecific reduction of (68) gave the tetracyclic amine ester (70) in 98% yield. The fifth ring was introduced by oxidation of (70) to the sulfoxide (71) and its reaction with acetyl chloride (Scheme-10).



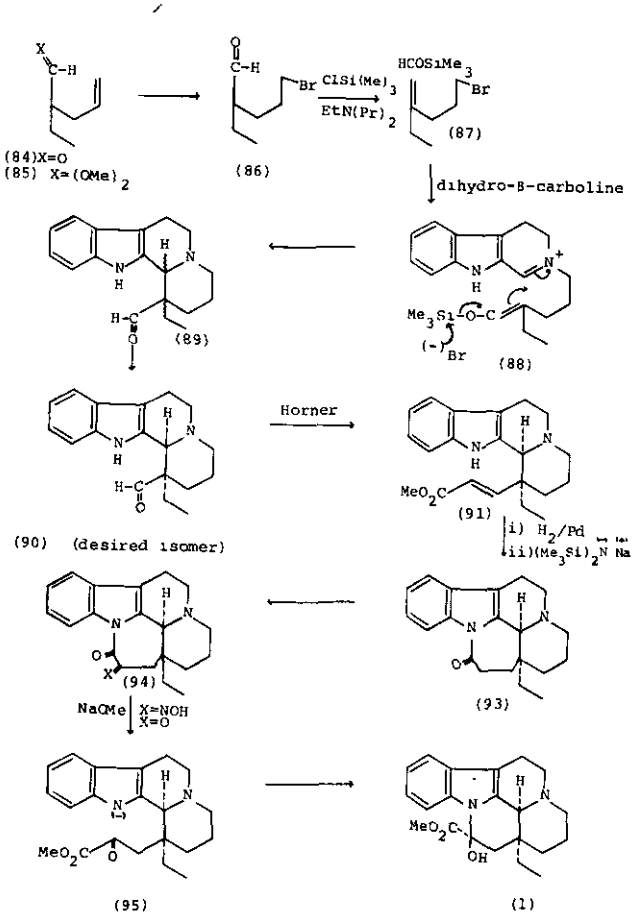
Scheme-10

Another total synthesis of optically pure vincamine involves the synthesis of a key intermediate (79) containing the quaternary center C-16 with the natural chirality. During the reduction of the immonium salt, center C-16 selectively induces the desired stereochemistry at center C-3 which at a later stage along with center C-16 controls the epimerizable center C-14 (Scheme-11).



Scheme-11

An alternative sequence has been reported by the same group for the enantioselective synthesis of (+)-vincamine (1).[16] The approach involves the preparation of the tetracyclic aldehyde by an intramolecular Mannich reaction of the silyl enol ethers which efficiently participate as enol equivalents in the reaction. This modification dramatically enhanced the yield of the tetracyclic aldehyde (89) to 74% as compared to the yield previously obtained (10%) by the classical method (direct condensation of aldehyde with tryptamine). This synthesis is also remarkable in that the cis-racemate of (89) could be separated and resolved to afford the wanted cis-enantiomer while the trans-racemate could be recycled by equilibration to give the desired cis-racemate by reversible Mannich fission. In this way virtually all the amino aldehyde (89) could be utilized (Scheme-12).

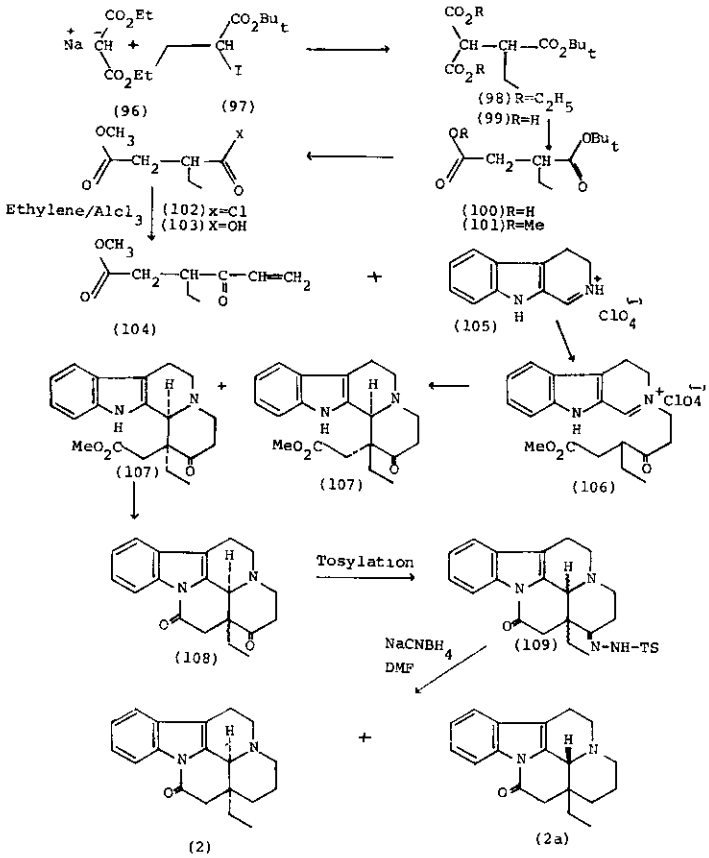


Scheme-12

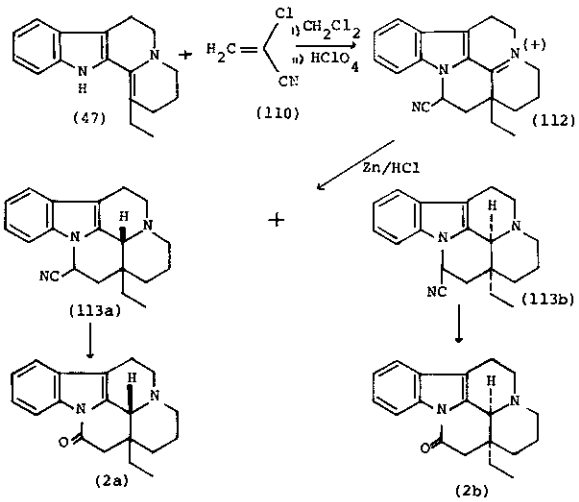
In their synthesis of eburnamonine Szantay and collaborators have utilized an annelation reaction between 3,4-dihydro-β-carboline (105) and an appropriate enone (104) for constructing the tetracyclic intermediate (107). Both epimers were obtained and separated and the synthesis carried out separately with each epimer (Scheme-13).[12]

Recent work in the eburnamine-vincamine area includes a new synthesis of eburnamine which involves a Micheal addition/cyclisation reaction of 2-chloroacrylonitrile with the enamine (47). Reduction of the product following oxygenation in the presence of a strong base gave eburnamonine (Scheme-14).[18]

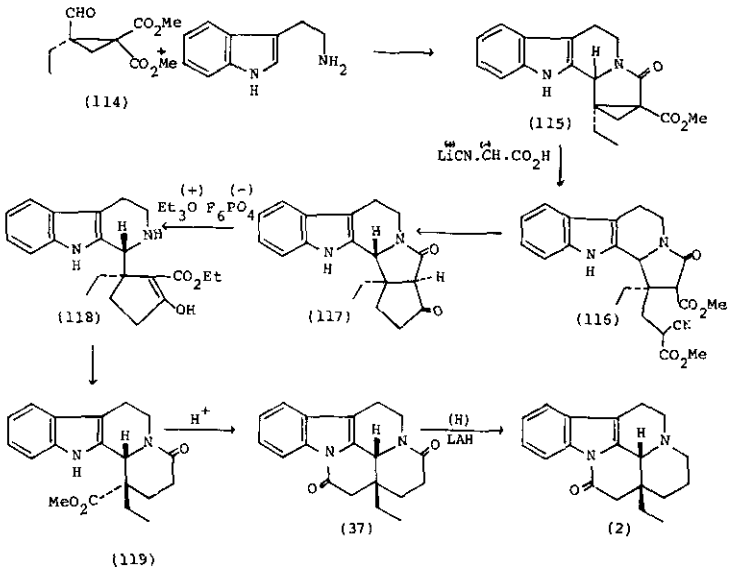
Winterfeldt's synthesis of eburnamonine follows quite different lines from the previous approaches and has been accomplished with a high degree of stereoselectivity. The synthesis involves the regioselective ring opening of the cyclopropane (114) of defined configuration. Condensation of tryptamine with (114) gave the pentacyclic lactam ester (115) in 85% yield which was then converted to (±)-eburnamonine (2) via the dilactam (37) after several steps (Scheme-15).[19]



Scheme-13

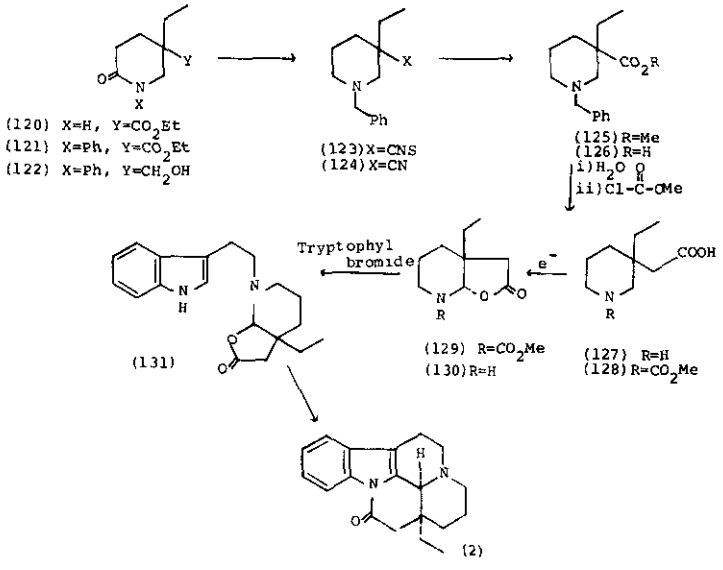


Scheme-14



Scheme-15

A considerable amount of new synthetic work reported in this area during recent years includes a new total synthesis of (±)-eburnamonine (2)[20] and a formal synthesis of vincamine (1).[21] The basic strategy of the scheme lies in the anodic oxidation of the desired carbamates (128) and (134) to the five- and six-membered lactones which were further utilized for the synthesis of eburnamonine (2) and vincamine (1). The amino lactone (130) was condensed with tryptophyl bromide to afford the tryptophyl amino lactone (131). The latter when refluxed in acetic acid afforded (±)-eburnamonine (2) in 60% yield (Scheme-16).



Scheme-16

The six-membered amino lactone (134) which was previously employed for the synthesis of (±)-vincamine by Oppolzer[16] has been used for the formal synthesis of (±)-vincamine (1). The intermediate (134) was converted to vincamine by an already established method (Scheme-17).

An entirely new approach for the enantioselective preparation of the key compound (145) for the synthesis of (-)-eburnamonine (2) was reported recently by Takano[22] which would promise an entry to (-)-eburnamonine (Scheme-18).

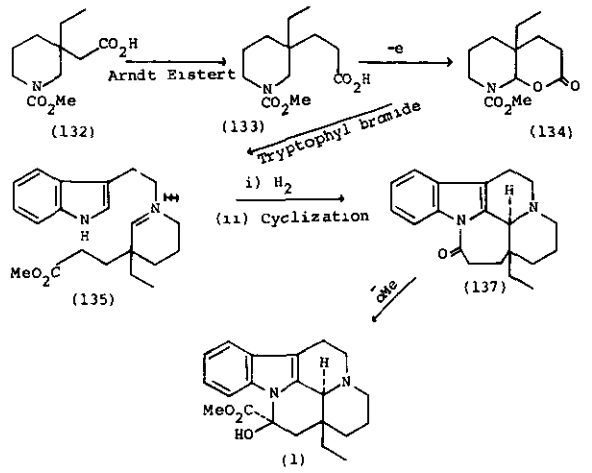
An elegant synthesis[23] of vincamine (1) makes use of the enamine (17) as the starting material. The critical step of the synthesis involves the introduction of a side chain by the alkylation of the enamine (17) with methyl bromopyruvate-2,4-dinitrophenyl hydrazone (168) to give the salt (165). Subsequent reduction of (165) gave the amine (166), hydrolysis of which did not prove to be feasible. Hydrolysis of the salt (165) prior to reduction however proceeded smoothly which was rationalised in terms of participation of iminium salt in the reaction. Reduction of the hydrolysed product (167) with sodium borohydride gave epivincamine (1a) (Scheme-19).

Completely different approaches to the partial synthesis of (±)-vincamine (1) have embodied biomimetic rearrangement reactions. Le Men and Levy were able to emulate the biogenetic route to vincamine from (-)-vincadifformine (146) by its oxidation to the 3-hydroxyindolenine (148), conversion to the N-oxide (149) followed by reaction with PPh_3 and acid-catalysed skeletal rearrangement (Scheme-20). Oxidative rearrangement of vincadifformine (146) to vincamine (1) can be affected directly in approximately 30% yield by the use of oxygen in the presence of metal salts and hydrochloric acid. This method avoids the undesired oxidation of N_b, and the necessity to remove the N_b-oxide function so produced by means of triphenylphosphine which was a feature of the earlier procedure.

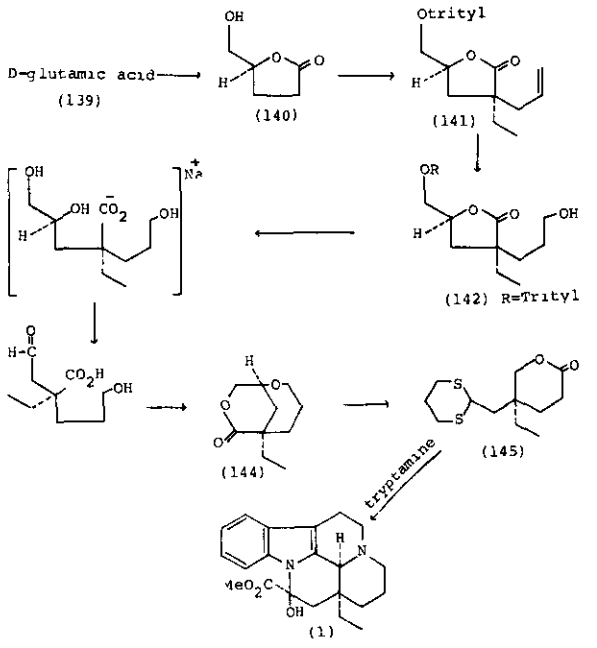
More recently Danieli and coworkers have employed the oxidant ozone for the functionalisation at C-3 of vincadifformine (146).[9] The 3-hydroxyvincadifformine (148) then undergoes a rearrangement to vincamine (1) (Scheme-21).

A simple approach to potential intermediate (150) was reported recently by the Pakistani group.[24] The intermediate which contains four of the requisite five rings and two of the three chiral centers can be transformed to vincamine and eburnamonine by one of the several methods. The synthesis consists of constructing an appropriate aliphatic unit making use of the Stork's enamine alkylation procedure which is condensed with tryptamine to afford the lactam. Reduction and subsequent transformations lead to vincamine and eburnamonine (Scheme-22).

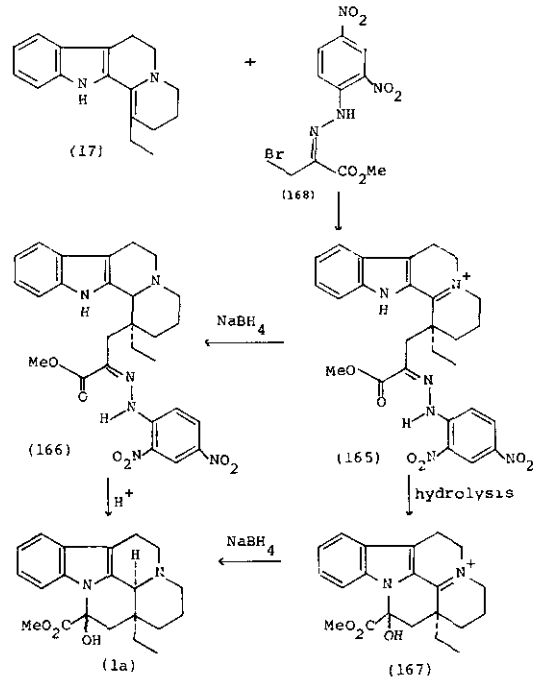
Because of their remarkable pharmacological activities, there has been growing interest in structure modification studies on these pentacyclic indole molecules. Thus Ono[25] has reported new synthetic analogs (151) of vincamine (1) and eburnamonine (2) in which the oxygen atom was transpositioned from 14-position of the corresponding natural alkaloid into the neighbouring position. Using the same analog (151) as an intermediate a novel synthesis of apovincaminate (152) was thus accomplished (Scheme-23).



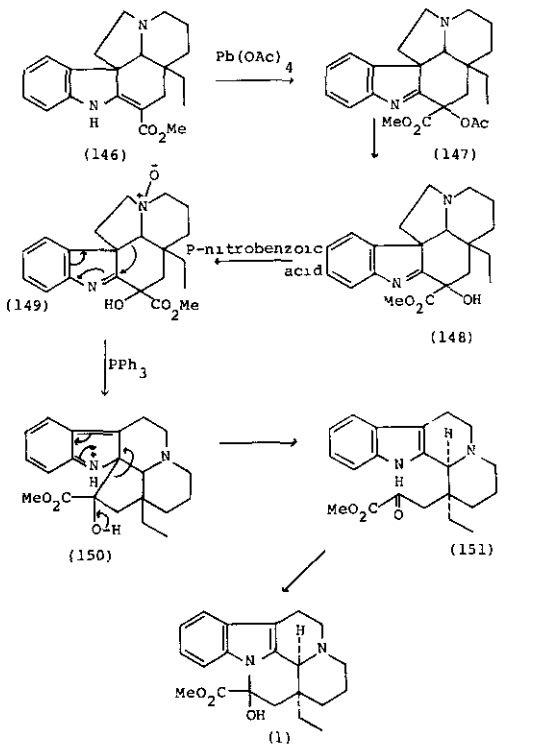
Scheme-17



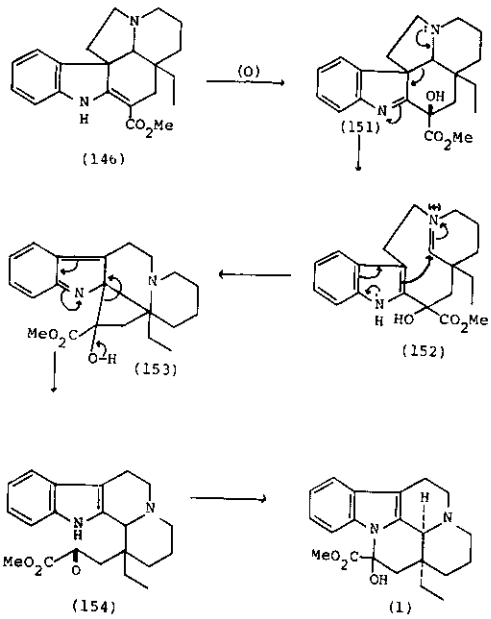
Scheme-18



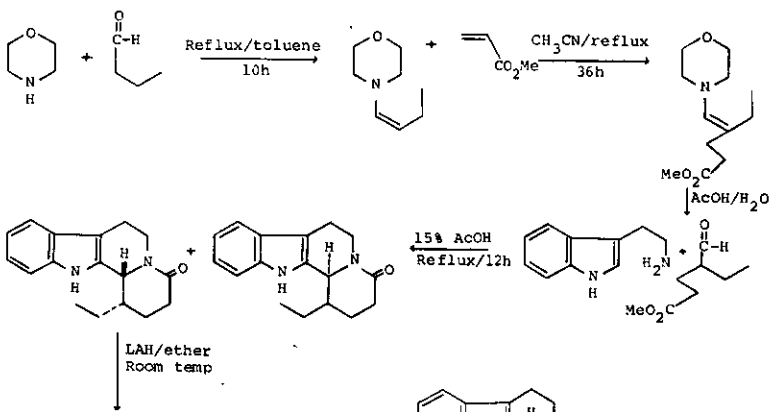
Scheme-19

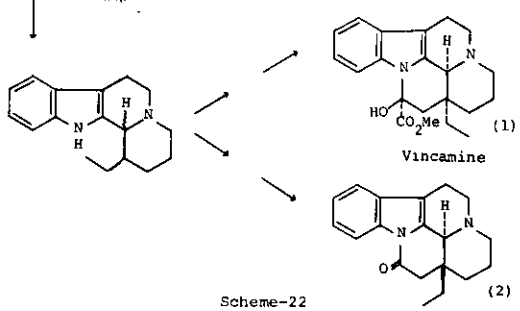


Scheme-20

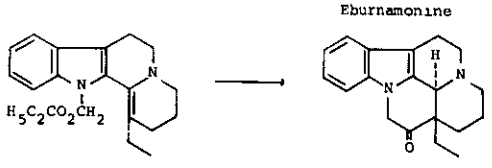


Scheme-21



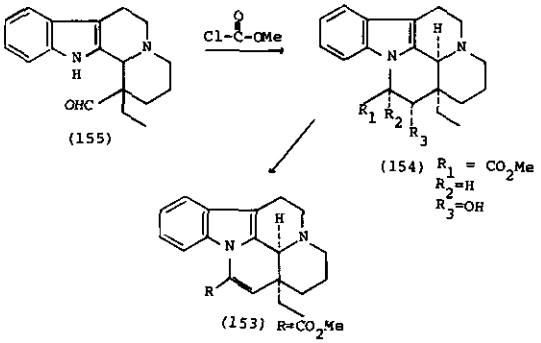


Scheme-22



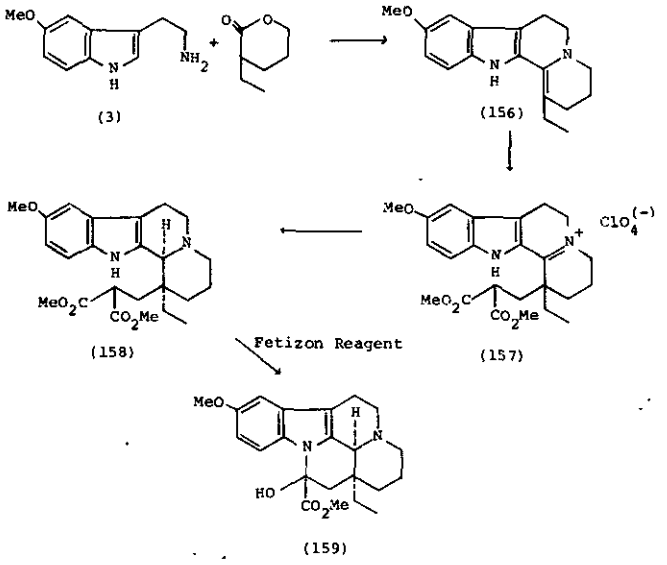
Scheme-23

A new approach to apovincamine (153) which by-passes the intermediacy of vincamine (1) has been reported by Danieli.[26] Apovincamine (153) was synthesised by the dehydration of β-hydroxyester (154) obtained by alkylation of the aldehyde (155) with methyl chloroacetate (Scheme-24).



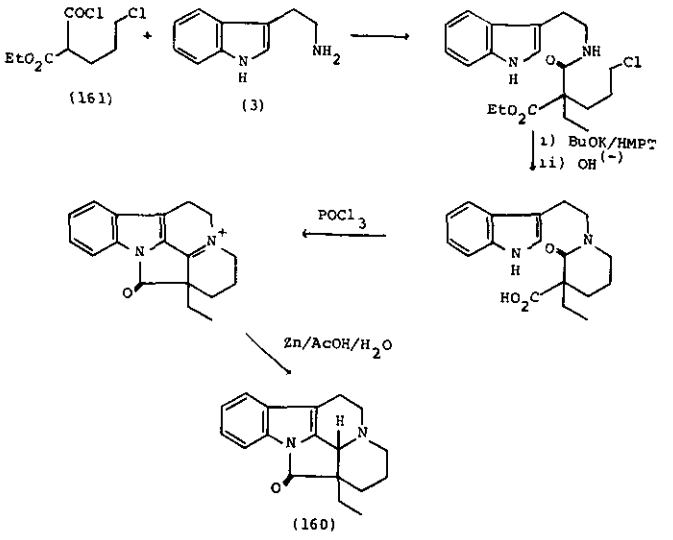
Scheme-24

The methoxy analogue of vincamine (1) which possesses interesting pharmacological properties[27] and showed close similarity to the biologically active serotonin has been synthesised by Kalaus.[28] The methoxy analogue (156) of the enamine (47) was employed as the starting material for the synthesis. The enamine (156) on reaction with methyl α-acetoxyacrylate and subsequent reduction gave (158). Deacetylation of (158) followed by oxidation gave isovincine (159) (Scheme-25).



Scheme-25

Recently a French group has reported the synthesis of norvincamone (160) by a route involving the reaction of tryptamine with a suitable aliphatic moiety (161)[29] (Scheme-26).



Scheme-26

The synthetic approaches to the *Hunteria* alkaloids described above reflect the importance of these pharmacologically active bases which have greatly interested organic chemists during recent years. The numerous international patents of various derivatives of vincamine which continue to appear in the literature bear testimony to the fact that these substances will remain a target for synthetic organic chemists for quite some time.

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