STUDIES TOWARDS THE SYNTHESIS OF *ASPIDOSPERMA* AND RELATED ALKALOIDS

A thesis submitted in fulfilment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

BY

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Particular thanks also go to my wife for her own priceless contribution.

ABSTRACT

In the introduction to this thesis syntheses of, and synthetic approaches to, the *Aspidosperma* and related alkaloids are discussed.

Initially investigations were carried out towards the heptacyclic alalakine (385) which led to a synthesis of the important hexacyclic intermediate (430) and to the precursor compound (438). Alongside this investigation 2 - cyano - N_a - methylaspidospermidine derivative (412) was produced.

A synthesis of strempeliopine (447) from the readily available model compound (267) is described. However, the yield obtained was not satisfactory and the alkaloid was not obtained analytically pure. The structures of three by - products: N_a - acetyl - 19 - carbethoxy - 19 - demethylaspidospermidine, the unusual N_a - ethyl - 19 - carbethoxy - 19 - demethylaspidospermidine, and 19 - carbethoxy - 19 - demethylaspidospermidine were determined.

An investigation towards the synthesis of cimicine derivative (467) led to the rhazinilam derivative (487). However, initial studies[137] indicated that the oxidation reaction is complex and dependent on the conditions of the reaction.

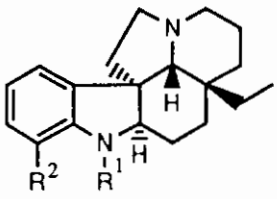
An important apovincamine derivative (504) has also been synthesised from the model compound (267). Reaction of the latter under oxidative conditions by means of m - chloroperbenzoic acid in dry benzene led to the vincamine derivative (503).

INTRODUCTION

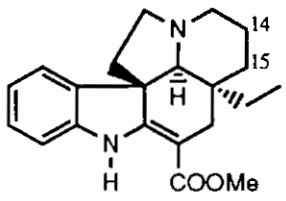
1.1 Occurrence and Isolation of *Aspidosperma* Alkaloids

The majority of naturally occurring indole alkaloids have been isolated from the three plant families, *Apocynaceae*, *Loganiaceae*, and *Rubiaceae*. The *Aspidosperma* alkaloids, which are the largest group of indole alkaloids with around 250 representatives, appear to occur in the *Plumerioideae*, one of the three subfamilies of the *Apocynaceae* family, which are found mainly in tropical areas, namely, South America, Africa, and Australasia, and they are most often creepers, bushes, or trees. The *Plumerioideae* are represented by seven tribes with 95 genera although A*spidosperma* alkaloids have only been isolated from 25 genera which belong to the four largest tribes, namely, the *Alstonieae*, *Carisseae*, *Tabernaemontaneae*, and the *Rauvolfieae*. Up to date more than 220 alkaloids have been isolated from the different parts of the plants, some of them with important pharmacological activity. The most notable of these therapeutic alkaloids are: vincamine (278), which has been shown to increase cerebral blood flow in both man and animal, vindorosine (7) and vindoline (8), which show antitumor activity, and the most valuable antileukemic drugs vinblastine (15) and vincristine (16).

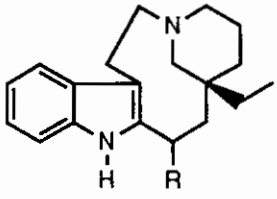
The two main skeletal types contained in the large number of natural systems can be exemplified by the quebrachamine (3) group, which consists of a total of 18 alkaloids and the aspidospermidine (1) group, with approximately 140 members. Some other complex *Aspidosperma* alkaloids with up to seven rings are shown in Scheme I.



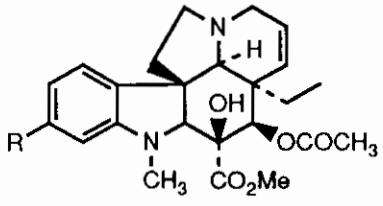
(1) R^1 = H, R^2 = H Aspidospermidine
(2) R^1 = Ac, R^2 = OMe Aspidospermine



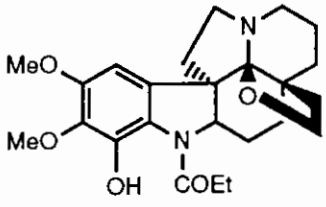
(5) (-) - Vincadifformine
(6) (-) - Tabersonine $\Delta^{14,15}$



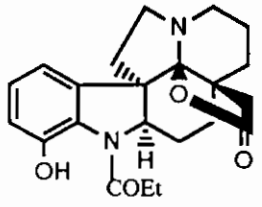
(3) R = H Quebrachamine
(4) R = CO_2Me Vincadine



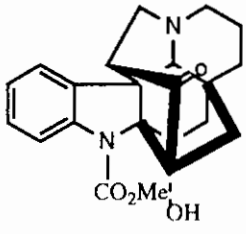
(7) R = H Vindorosine
(8) R = OMe Vindoline



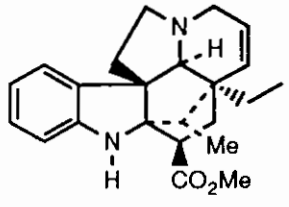
(9) Aspidoalbine



(10) Cimicine

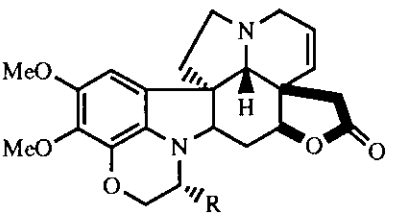


(11) Kopsine

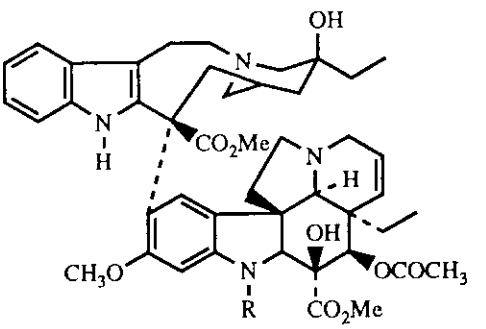


(12) Vindolinine

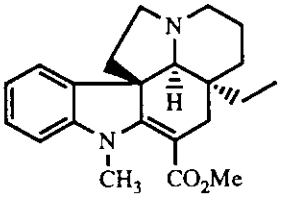
Scheme 1



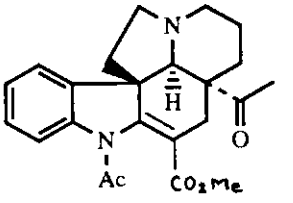
(**13**) R = Me Obscurinervidine
(**14**) R = Et Obscurinervine



(**15**) R = CH_3 Vinblastine
(**16**) R = CHO Vincristine



(**17**) minovine



(**18**) minovincine

Scheme 1

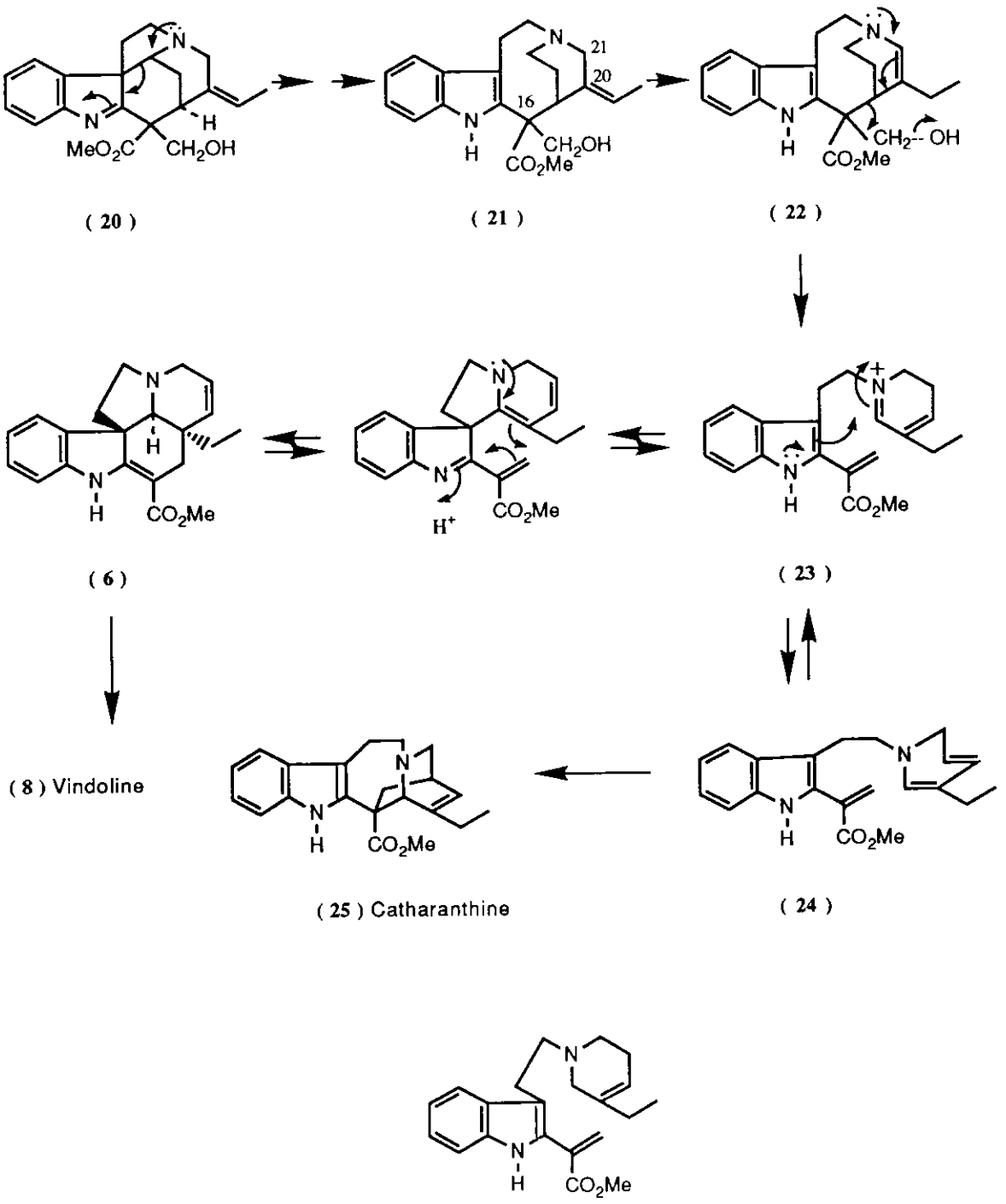
1.2 Synthetic routes to the vincadifformine - tabersonine group

During the past decade there has been an enormous effort by various groups to achieve syntheses of *Aspidosperma* alkaloids, partly due to the antitumor activity of a few of this alkaloid class and the central place they occupy in the biosynthesis of monoterpene alkaloids.

The first total synthesis of the *Aspidosperma* alkaloid, (±) aspidospermine (2), was reported by Stork and Dolfini in the early 1960 s utilizing the classical Fisher - indole synthesis[1]. Several reviews[2,3] concerning this group are available.

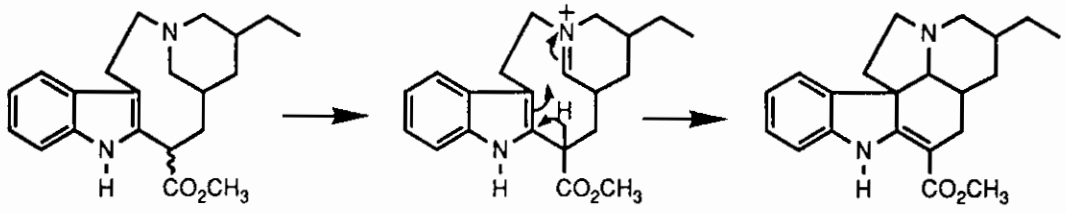
More attention has recently been focussed on the vincadifformine group, which currently numbers around 50 bases. Numerous publications of the isolation and structural elucidation of the parent alkaloid, (-) - vincadifformine (5), have appeared[4,5]. This alkaloid and the structurally related alkaloids such as tabersonine (6), minovine (17), minovincine (18), and vindolinine (12) have since been found to play a critical role in the biosynthesis of catharanthine (25) (*Iboga* type) and vindoline (8) (*Aspidosperma* type)[6a], as shown in Scheme 2. The validity of the biosynthetic intermediate (23) is supported by the isolation of a simple derivative of secodine (26) from plants and by the specific incorporation of labelled secodine (26) into vindoline (8)[6b].

Total syntheses of (+) - tabersonine (6) and (+) vincadifformine (5) have so far been accomplished by several groups independently. In 1964, Kutney and co-workers[7] reported the first elegant synthesis of a vincadifformine - type skeleton *via* a transannular cyclization reaction similar to that proposed in Wenkert's biosynthetic hypothesis[8] of *Aspidosperma* alkaloids. This observation was that the



Scheme 2

nine membered ring system of carbomethoxydihydrocleavamine (27) on reaction with mercuric acetate in acetic acid, undergoes a transannular cyclisation to give the pseudo - vincadifformine derivative (29).

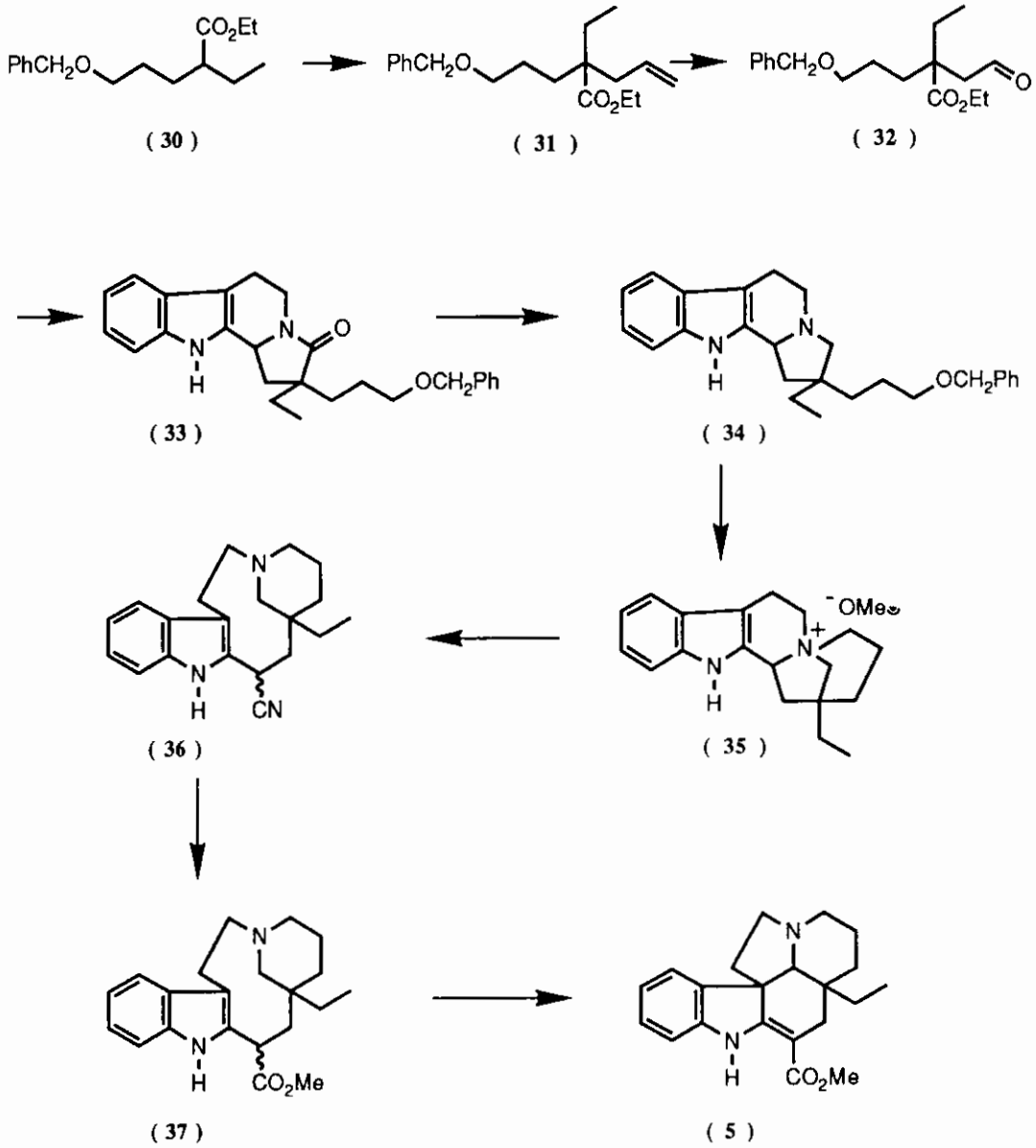


(27) (28) (29)

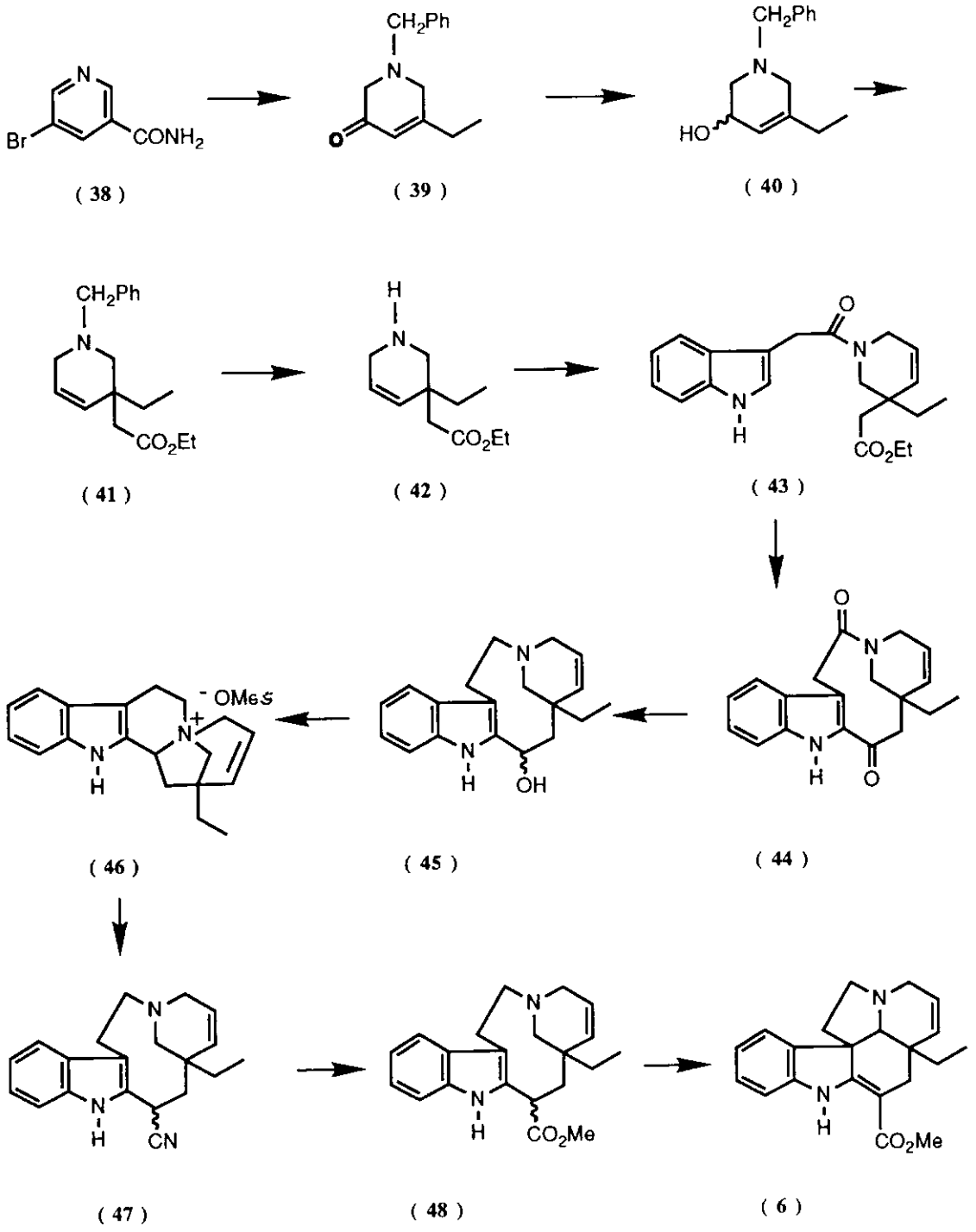
Vincadifformine (5) and minovine (17) were also obtained by means of the transannular cyclization approach with either mercuric acetate or oxygen in the presence of a catalyst (5% platinium on charcoal)[9]. It was obvious that the presence of the carbomethoxy function may alter the course of the cyclization reaction involving the iminium intermediate (28). There could be a preferential loss of the proton on carbon atom 16 which leads to the vincadifformine system in a completely stereoselective manner since the necessary " folding " of the nine - membered ring in the intermediates (28) , which provides the rigid cyclization products, must lead to stereoselectivity. This method provided a synthetic entry into the *Aspidosperma* vincadifformine group.

Subsequently Kutney[10,12] achieved the total syntheses of a series of monomeric alkaloids in the *Vinca* family such as (±) vincadifformine[11] (5) from a pentacyclic quaternary mesylate (35). Ethyl α - (γ - benzyloxypropyl) butyrate[10] (30) was converted to the allyl ester (31) by alkylation with allyl bromide and then oxidised with osmium tetroxide - sodium periodate to give the aldehyde (32) in 65% yield. Condensation with tryptamine yielded the cyclic lactam as a mixture of two

inseparable diastereoisomers (33), which were reduced with lithium aluminium hydride. Removal of the benzyl group provided an alcohol which upon treatment with methane sulphonyl chloride in triethylamine gave the quaternary mesylate (35). Nucleophilic displacement by cyanide ion in dimethylformamide resulted in generation of a nine - membered ring system possessing a nitrile group at C - 16 (36). Hydrolysis of the cyano compound and esterification of the resulting acid with ethereal diazomethane gave (37) which was transformed *via* an oxidative cyclization to give (±) vincadifformine (5) (Scheme 3).



Scheme 3



(38) (39) (40)

(41) (42) (43)

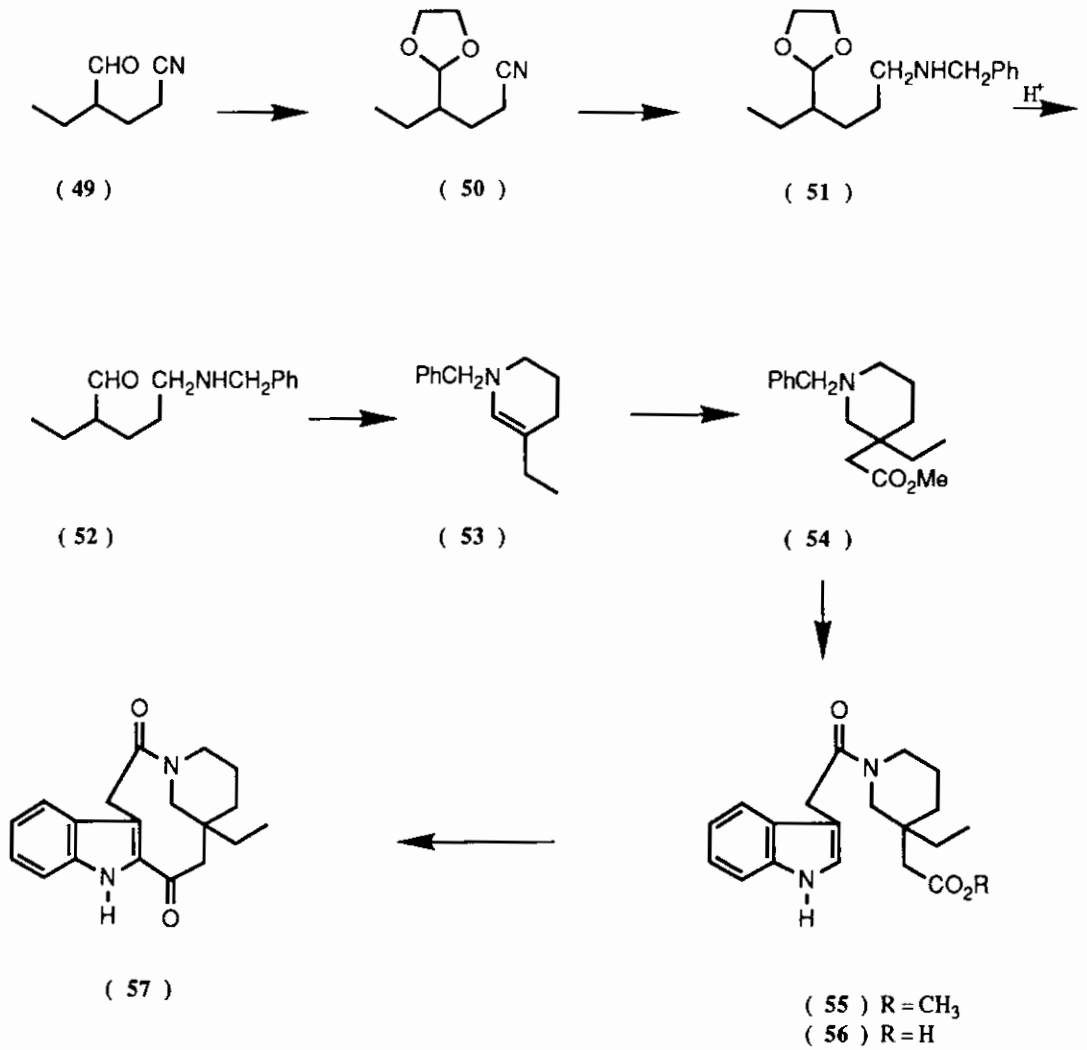
(44) (45) (46)

(47) (48) (6)

Scheme 4

Following this success Ziegler and Bennett[13, 14] also prepared (±) tabersonine (6) (Scheme 4) by an analogous route starting from an enone (39) previously prepared by Ziegler[15]. This enone was synthesized from 5 - bromonicotinamide (38) and reduced to an allylic alcohol (40) with lithium aluminium hydride. Claisen rearrangement of this alcohol on treatment with ethyl orthoacetate in the presence of pivalic acid as catalyst afforded the unsaturated ester (41). Removal of the benzyl group with ethyl chloroformate gave an amine (42) which was reacted with 3 - indoleacetyl chloride to yield the corresponding amide ester (43). Hydrolysis and condensation with polyphosphoric acid then gave the tetracyclic unsaturated keto-lactam (44). Reduction of this ketolactam with lithium aluminium hydride afforded a mixture of alcohols (45) which were converted to the quaternary mesylate (46). Reaction with cyanide followed by hydrolysis and esterification with diazomethane provided the quebrachamine type skeleton (48). Finally the reaction with mercuric acetate and the appropriate transannular cyclization process furnished the required (±) tabersonine (6).

In 1968 Ziegler and Zoretic[16] reported a synthesis of the intermediate (57) starting from α - (2 - cyanoethyl) - n - butyraldehyde (49). The latter was protected as its ethylene glycol acetal (50) and then reduced with lithium aluminium hydride to give the primary amine. Reductive benzylation gave (51). Hydrolysis with aqueous hydrochloric acid led to the formation of the cyclic enamine (53), alkylation of which with methyl bromoacetate in methanol, followed by debenzylation and reaction with 3 -indolyl acetyl chloride, gave the amide ester (55). Hydrolysis with dilute sodium hydroxide afforded the corresponding acid (56). Treatment with phosphoric acid then gave the desired ketolactam (57) (Scheme 5) in good yield. This lactam is a key intermediate in vincadifformine synthesis.



(49) (50) (51)

(52) (53) (54)

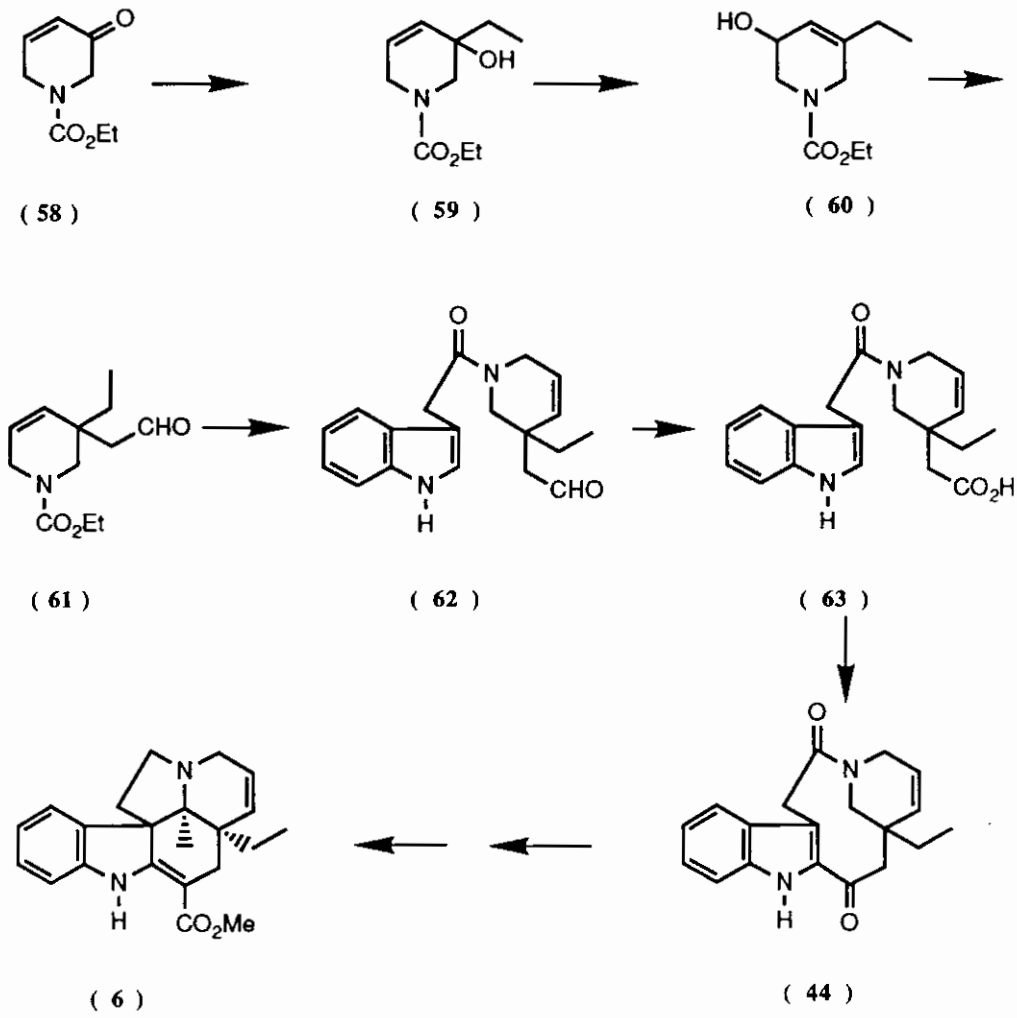
(57)

(55) R = CH_3
(56) R = H

Scheme 5

A further synthetic investigation had been undertaken by Hanaoka and co-workers[17] which made use of the 1, 6 - dihydro - 3 (2H) - pyridinone - 1 - carboxylate (58) as a common synthon to achieve the formal synthesis of (±) - tabersonine (Scheme 6). This pyridinone (58) was treated with ethyl magnesium bromide to give both the 1, 2 - adduct (59) and 1, 4 - adduct. However, reaction of the former (59) with 1% hydrochloric acid allowed an allylic rearrangement to produce the alcohol (60) in good yield. The Claisen rearrangement of (60) with ethyl

vinyl ether in the presence of mercuric acetate furnished the aldehyde (61) which was acetalated and later hydrolysed with potassium hydroxide to give the amine. Condensation with indole 3 - acetyl chloride followed by acid hydrolysis gave the aldehyde (62). Oxidation of (62) with silver (I) oxide to the carboxylic acid (63) and intramolecular cyclization using polyphosphoric acid produced the intermediate (44). Its conversion into tabersonine (6) proceeded as before see (Scheme 4).

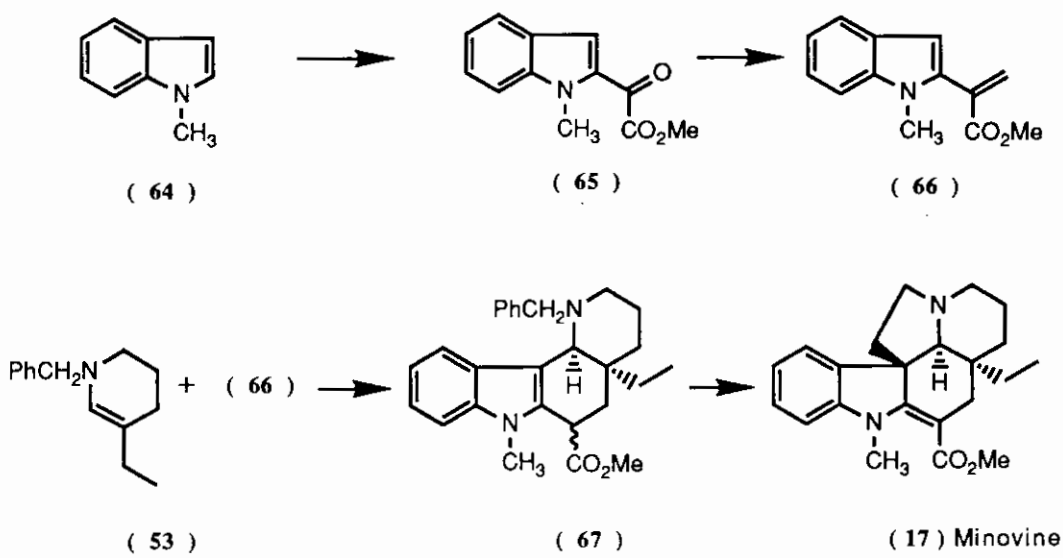


(58) (59) (60) (61) (62) (63) (44) (6)

Scheme 6

Ziegler[18] has also employed the enamine (53) in his synthesis of (±) minovine (17) (Scheme 7). Lithiation of N - methylindole followed by addition to an excess

of ethyl oxalate and a subsequent base hydrolysis with methanolic potassium hydroxide gave the N- methyl - α - indolylglyoxylic acid. Esterification of the acid using diazomethane furnished the methyl ester (65). A Wittig reaction using methylene triphenylphosphorane then produced the corresponding acrylic ester (66). Alkylation of the enamine (53) with the acrylic ester derivative (66) allowed the resultant iminium intermediate to undergo facile cyclisation at the β - position of the indole nucleus to give a mixture of two esters (67). Debenzylation and treatment with ethylene dibromide gave the required (±) minovine (17).



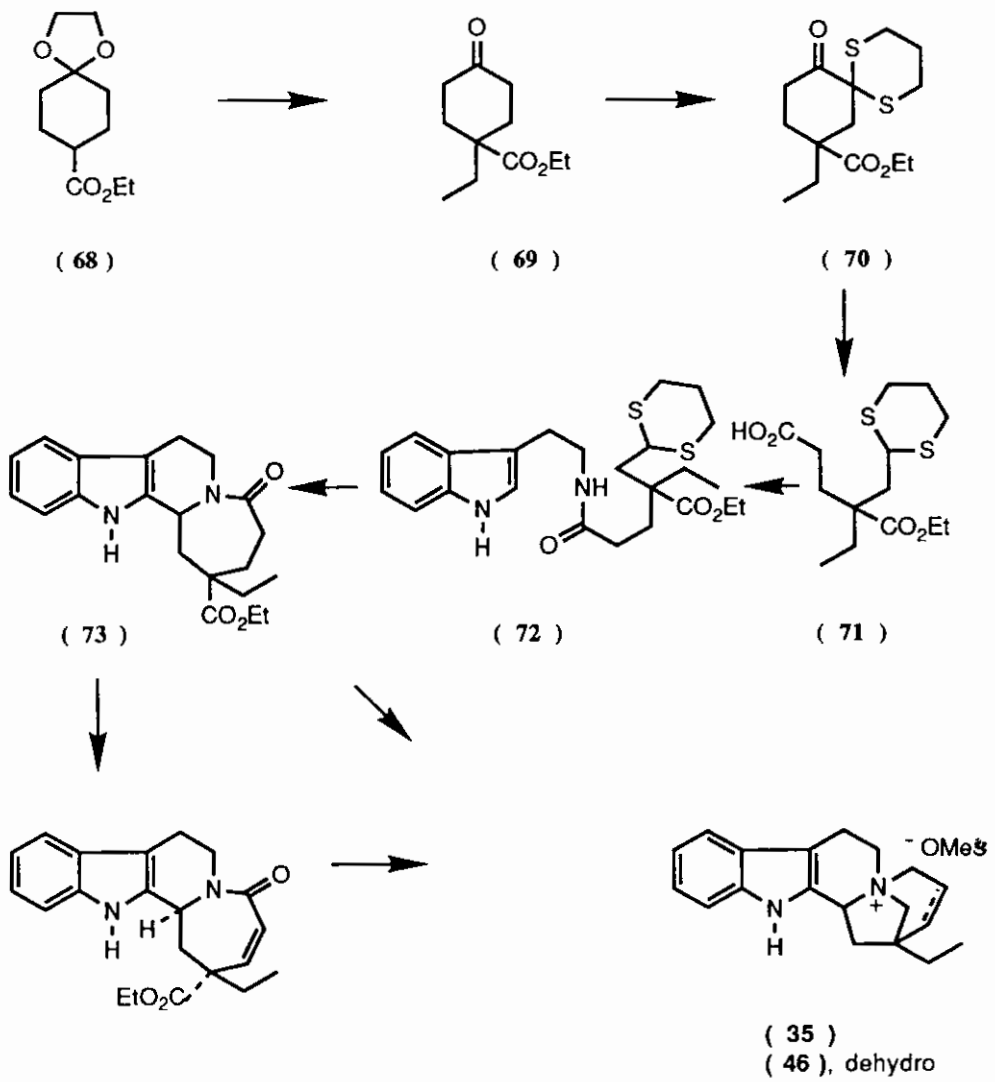
(64) (65) (66)

(53) (67) (17) Minovine

Scheme 7

Another synthesis of (±) tabersonine (6) has been reported by Takano[19] (Scheme 8). 4 - Ethoxycarbonylcyclohexanone ethylene ketal (68) was converted into ketoester (69) and then treated with propane - 1, 3 - dithiolditosylate to produce (70). Subsequent treatment with sodium hydride and condensation with tryptamine afforded the dithianyl amide (72). Hydrolysis of the latter led to the stereoisomeric tetracyclic lactams (73). This lactam could be converted either into the quaternary

salt (35) by reduction with lithium aluminium hydride and mesylation or into the salt (46) by introduction of the double bond *via* lithium diisopropylamide (LDA), diphenylsulphide, m - chloroperbenzoic acid and heating. The method which converts them to the corresponding tabersonine and vincadifformine has already been described (see Scheme 4).

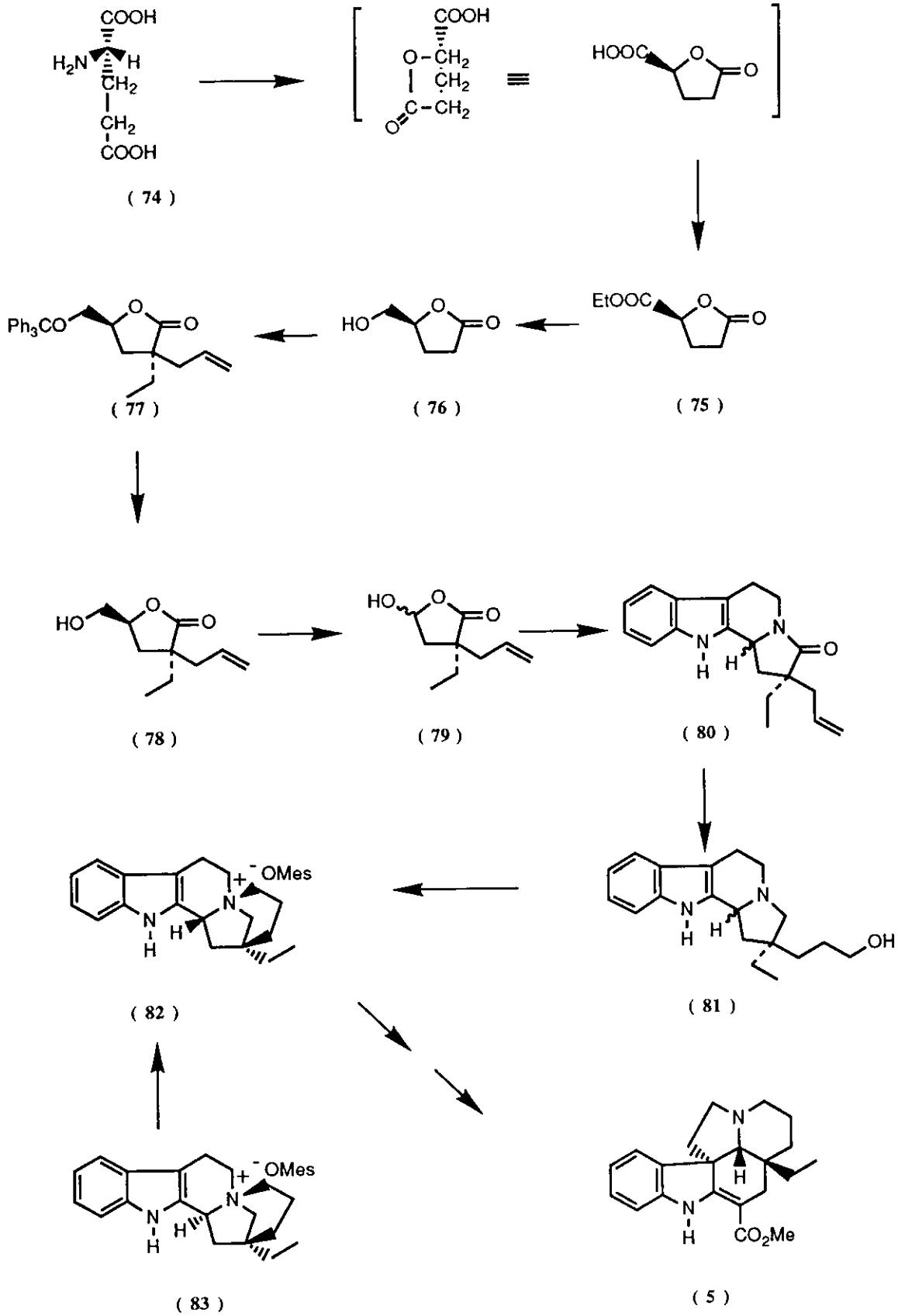


Scheme 8

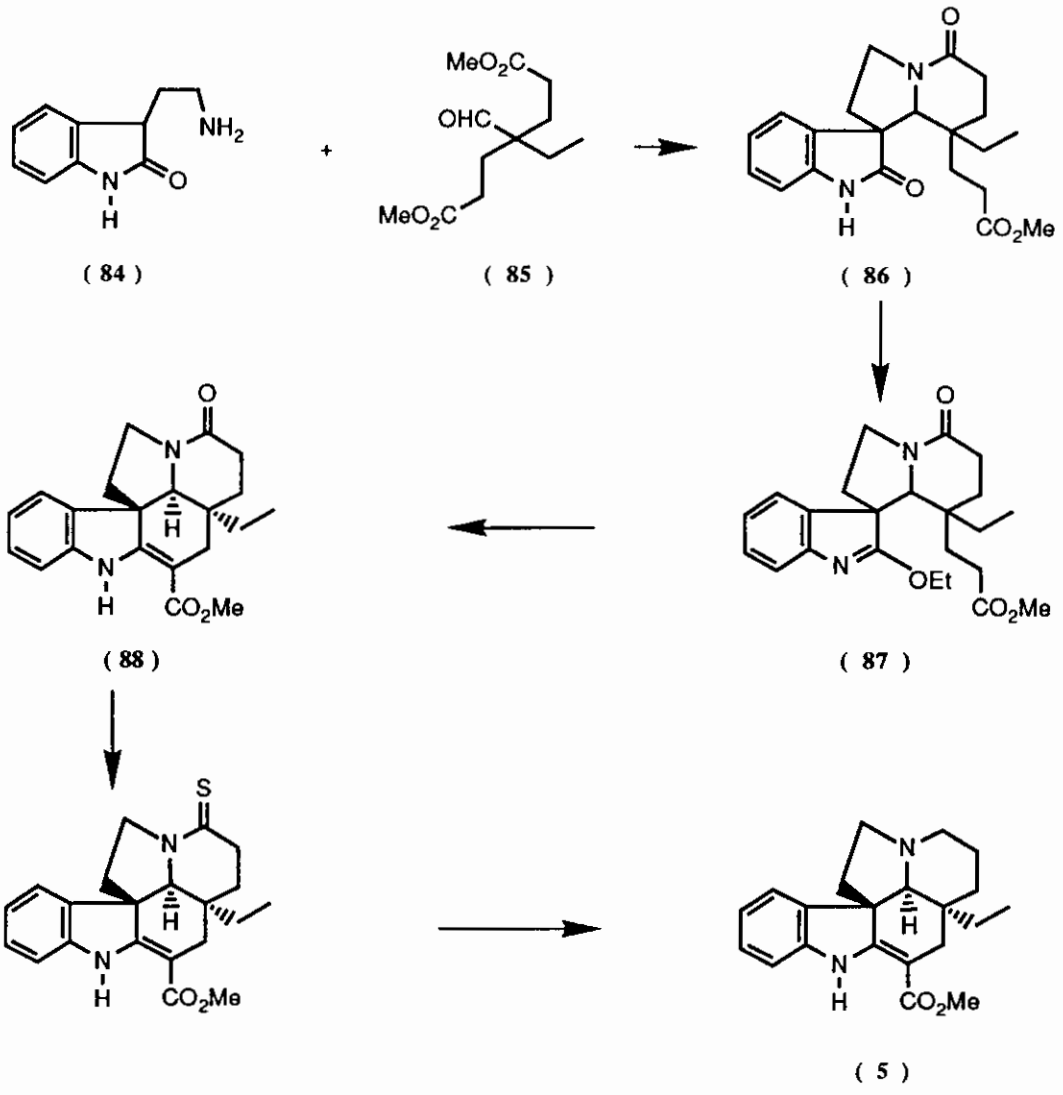
The first enantioselective synthesis of vincadifformine was reported by Takano and co - workers[20], using L- glutamic acid (74). This had previously been converted

to γ - hydroxymethyl - γ -butyrolactone (76) by the method of Yamada and co - workers[21]. Tritylation of the lactone - alcohol (76) with trityl chloride in pyridine afforded the lactone - ether, which on alkylation with allyl bromide in the presence of lithium diisopropylamide (LDA) and again with ethyl bromide led to lactone (77). Removal of the trityl group provided the alcohol (78) in moderate yield. Hydrolysis, followed by oxidation with sodium metaperiodate, then provided the hydroxylactone (79), which was condensed with tryptamine to give the lactam (80). Treatment of (80) with diborane - dimethyl sulphide complex, followed by oxidation with alkaline hydrogen peroxide, gave the primary alcohol, which was reduced with lithium aluminium hydride to give the amino alcohol as a mixture of epimers (81). Reaction with methanesulphonyl chloride gave the quaternary mesylate salts (82) and (83). Interestingly, the quaternary salt (83) which possessed the more unstable configuration was transformed into the more stable form (82) simply by heating in chloroform (Scheme 9).

Another access to vincadifformine (5) in 5 steps from 2 - hydroxytryptamine (84) was reported by Lévy and co - workers[22] (Scheme 10). Condensation of (84) with aldehyde diester (85) furnished the desired oxindole (86) which was then converted into the iminoether (87) in the presence of ethyl polyphosphate. Treatment of (87) with dimethylsulphoxide in the presence of dimsyl sodium produced 3 - oxovincadifformine (88). This was transformed into (±) vincadifformine by formation of the thiolactam with phosphorus pentasulphide and Raney nickel desulphurisation.



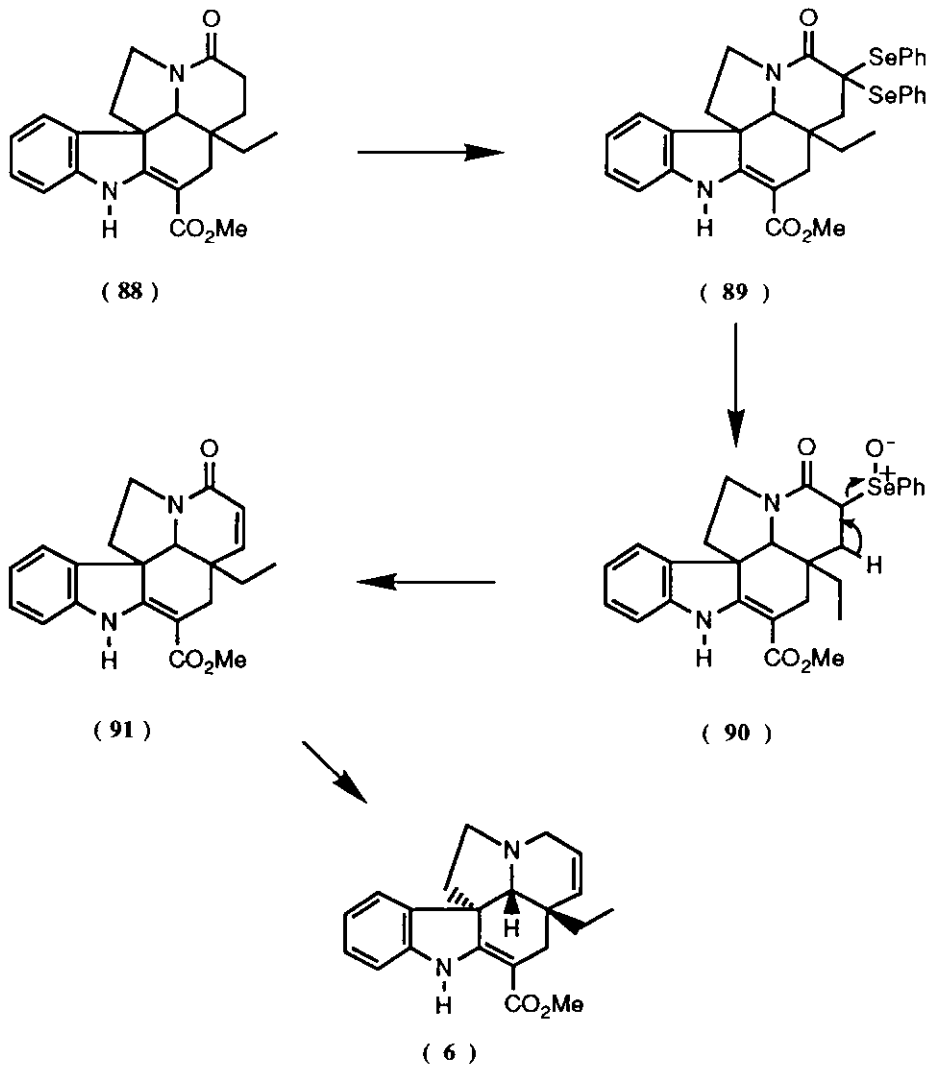
Scheme 9



(84) (85) (86) (87) (88) (5)

Scheme 10

The compound (88)[22-24] appeared to be a suitable key intermediate for the synthesis of (±) tabersonine[25] (6). The dianion of (88) obtained with lithium di - isopropylamide in tetrahydrofuran - hexamethylphosphoramide was treated with a large excess of phenylselenyl chloride to give the disubstituted derivative (89). Treatment with thiophenoxide ion and then oxidation with m - chloroperbenzoic acid gave the selenoxide (90), which immediately eliminated phenylselenenic acid to give 3 - oxotabersonine (91). Controlled reduction of the ketone function using lithium aluminium hydride gave (±) tabersonine (6) (Scheme 11).

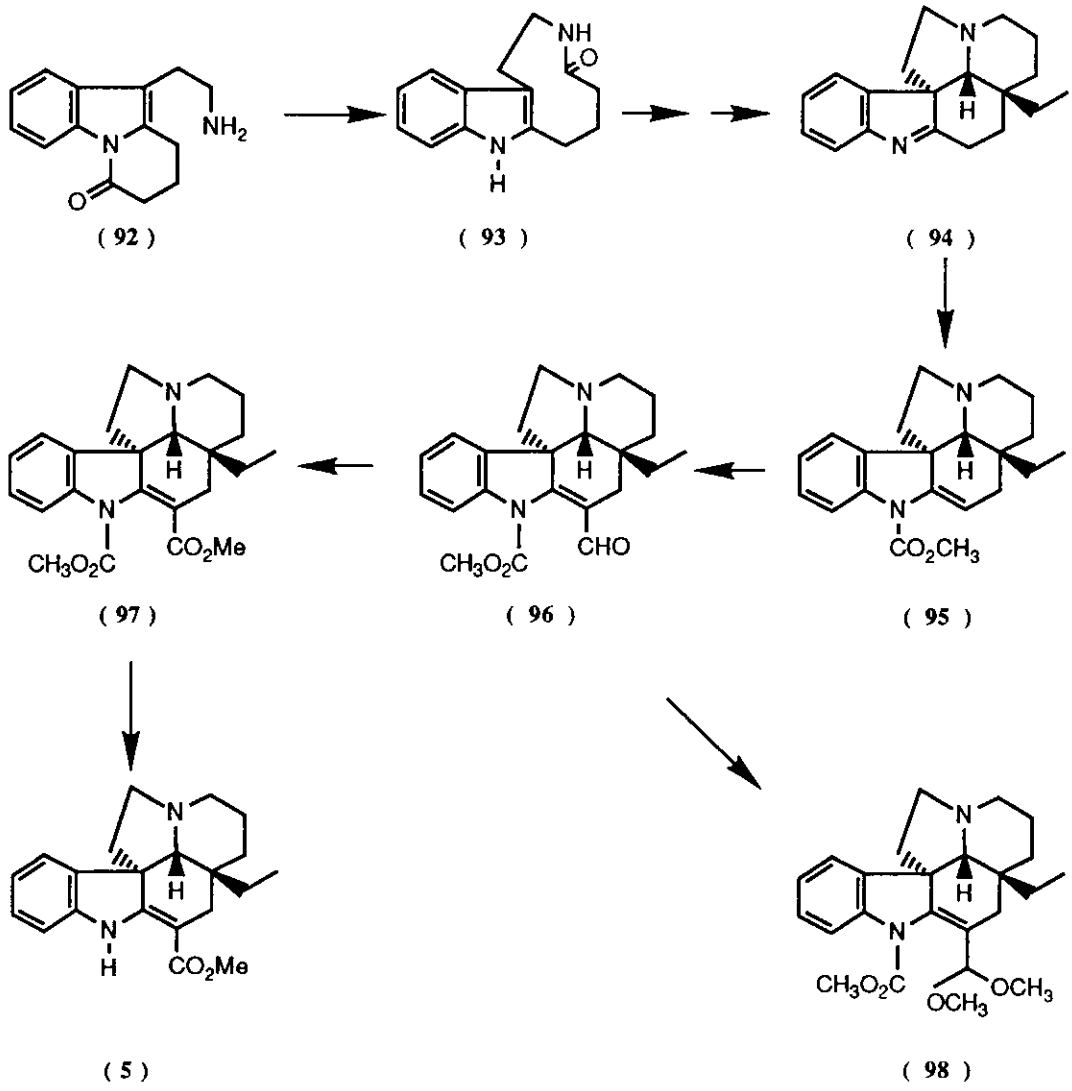


(88) (89) (90) (91) (6)

Scheme 11

Recently, (±) - vincadifformine (5) has been synthesised[26] from 1, 2 - dehydroaspidospermine (94), which was previously prepared by photoisomerisation of 1 - acylindole (92)[27]. The methoxycarbonyl group at C - 16 position in the *Aspidosperma* skeleton was introduced through Vilsmeier - Haack formylation. Thus the enamine (95) provided an important unsaturated aldehyde (96). The intermediate carbamate (95) was prepared from (94) using methyl chloroformate in the presence of triethylamine. Oxidation of (96) with sodium chlorite, then followed by esterification

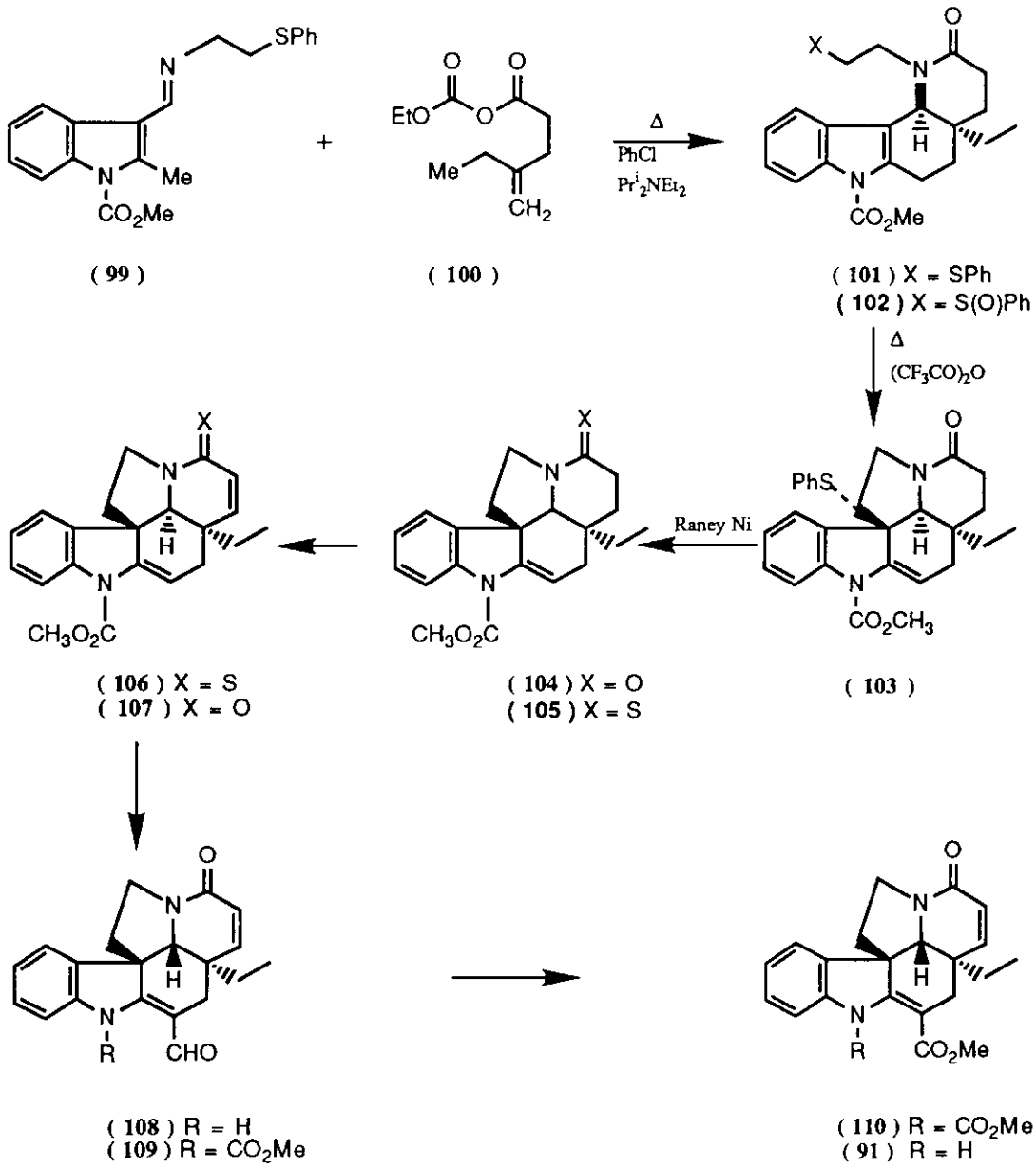
and acetalization gave 1 - methoxycarbonylvincadifformine (97) and dimethyl acetal (98). The latter was converted to (96) in quantitative yield. Hydrolysis of (97) with methanolic sodium methoxide gave the desired vincadifformine (5) (Scheme 12).



(92) (93) (94) (95) (96) (97) (5) (98)

Scheme 12

A total synthesis of (±) - 3 - oxotabersonine (91) was described by Magnus[28] (Scheme 13). Reaction of the imine (99)[28c] with the anhydride (100) in the presence of diisopropylethylamine resulted in formation of the cis tetracyclic adduct

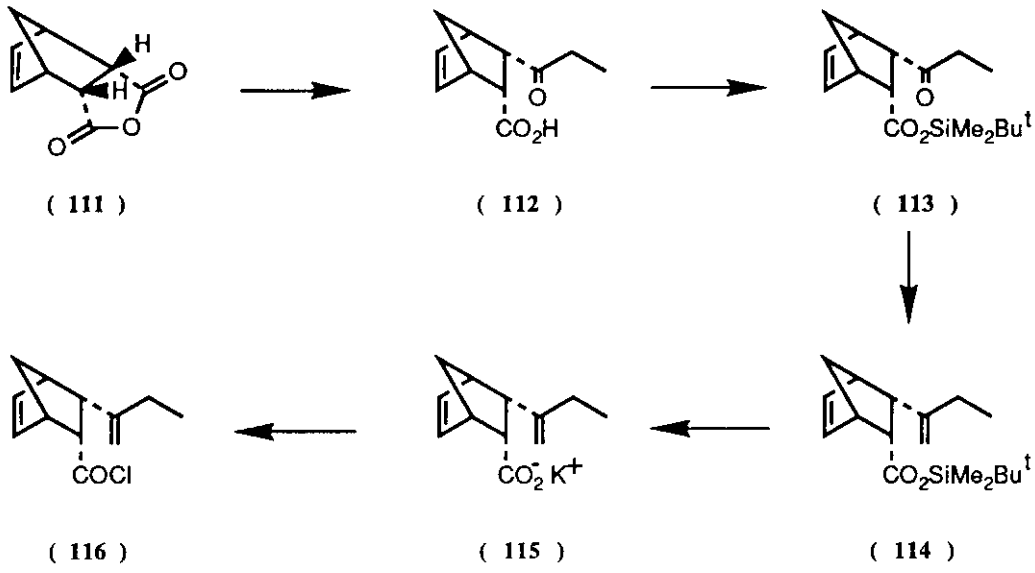

SPh
N
Me
N
CO2Me
(99)
+
O
O
EtO
O
Me
CH2
(100)
Δ
PhCl
Pr2iNEt2
X
O
N
H
N
CO2Me
(101) X = SPh
(102) X = S(O)Ph
Δ
(CF3CO)2O
PhS
Raney Ni
CO2CH3
(103)
(104) X = O
(105) X = S
CH3O2C
(106) X = S
(107) X = O
R
CHO
(108) R = H
(109) R = CO2Me
CO2Me
(110) R = CO2Me
(91) R = H

Scheme 13

(101) together with ethanol adduct. Oxidation of tetracyclic sulphide (101) with m - chloroperbenzoic acid followed by intramolecular Pummerer's rearrangement and cyclization afforded a pentacyclic lactam (103). Desulphurisation with Raney nickel in ethyl acetate gave the compound (104). Introduction of the 16 - methoxycarbonyl group proceeded by conversion of (104) into the thioamide (105) using Belleau's reagent in tetrahydrofuran and then treated with p - toluenesulphinyl chloride to give the α, β - unsaturated thioamide (106). Oxidation of (106) with m - chloroperbenzoic acid followed by the Vilsmeier's reagent ($POCl_3$ - dimethylformamide) gave the α, β - unsaturated aldehyde (108). Protection of the indole nitrogen with sodium hydride and methyl chloroformate, followed by oxidation and a subsequent esterification with diazomethane, gave the methyl ester (110), which was converted to (±) 3 - oxotabersonine (91) under mild basic hydrolysis.

More recently Magnus[28c] has synthesized (-) - 11 - methoxy - tabersonine (133) by a new strategy (Scheme 15). For this purpose 1 - carbomethoxy - 6 - methoxy - 3 - formyl - 2 - methylindole (122) was prepared from the commercially available 4 - methoxy - 2 - nitroaniline (117) which was converted first into the corresponding diazonium hydrosulphate (118). Meerwein arylation[29] gave (119). Reduction over Raney nickel afforded 6 - methoxy - 2 - methylindole (120) in good yield. Vilsmeier - Haack formylation of (120) using phosphorus oxychloride in dimethylformamide provided the expected 3 - formyl indole derivative (121) which on treatment with sodium hydride and methyl chloroformate in tetrahydrofuran gave the compound (122). This 3 - formylindole was converted into the derived imine (123) employing 2 - (phenylthio) ethylamine. Condensation of the imine (123) with the readily available bicyclo [2. 2. 1] hept - 5 - ene acid choride system (116), which was synthesized from (111), as outlined in Scheme 14 , gave the hexacylic adduct

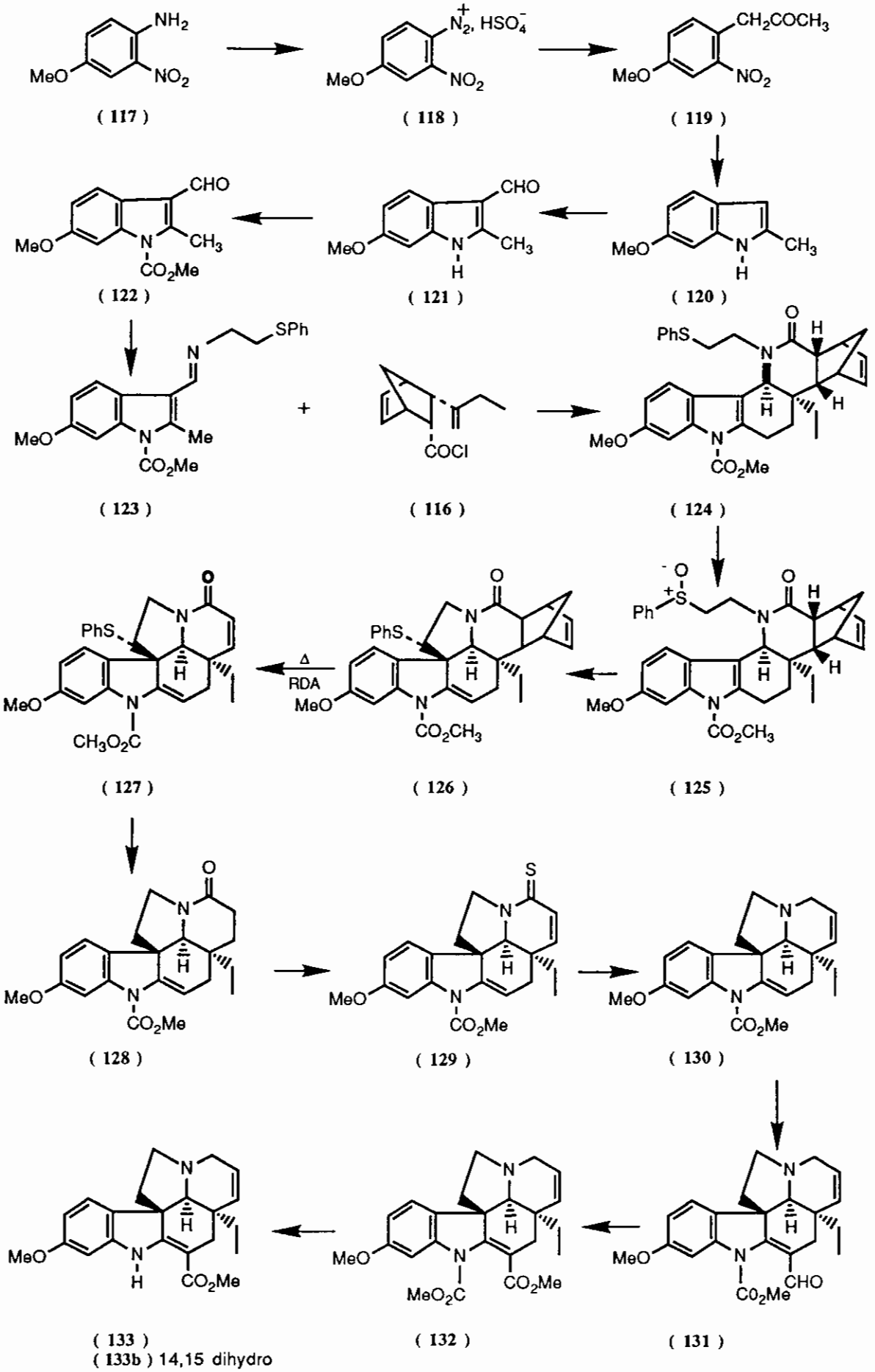
(124), which was converted by the Pummerer sequence and retro - Diels - Alder reaction into α, β - unsaturated amide (127). Desulphurization and reduction with activated Raney nickel in ethyl acetate gave (128). Reintroduction of the 14, 15 double bond using the thiolactam dehydrogenation procedure [30] furnished the α, β - unsaturated thioamide (129). Reduction of the thiocarbonyl group and formylation by Vilsmeier method gave (131), which on oxidation, methylation with diazomethane and finally deprotection gave (-) - 11 - methoxytabersonine (133). An identical sequence using the antipode of (116) gave (+) -11 -methoxytabersonine.



(111) (112) (113) (114) (115) (116)

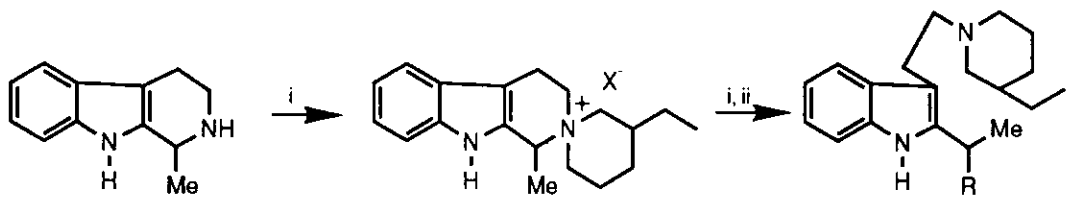
Scheme 14

As a result of the role played by the tetrahydrosecodine type (136) as intermediate in indole alkaloid biosynthesis of both *Iboga* - type alkaloids (i.e catharanthine (25)) and *Aspidosperma* - type alkaloids (i.e vindoline (8)), the first synthesis[31a] of a secodine derivative has been achieved *via* the condensation of 1 - methyl 1, 2, 3, 4 - tetrahydro - β - carboline (134) and 1,5 - diiodo - 2 - ethylpentane, which gave the spiroammonium salt (135). Treatment with potassium cyanide and


(117)
(118)
(119)
(120)
(121)
(122)
(123)
(116)
(124)
(125)
(126)
(127)
(128)
(129)
(130)
(131)
(132)
(133)
(133b) 14,15 dihydro
RDA

Scheme 15

esterification afforded the secodine ester (136), identical with natural tetrahydro - secodine [31b] (137).

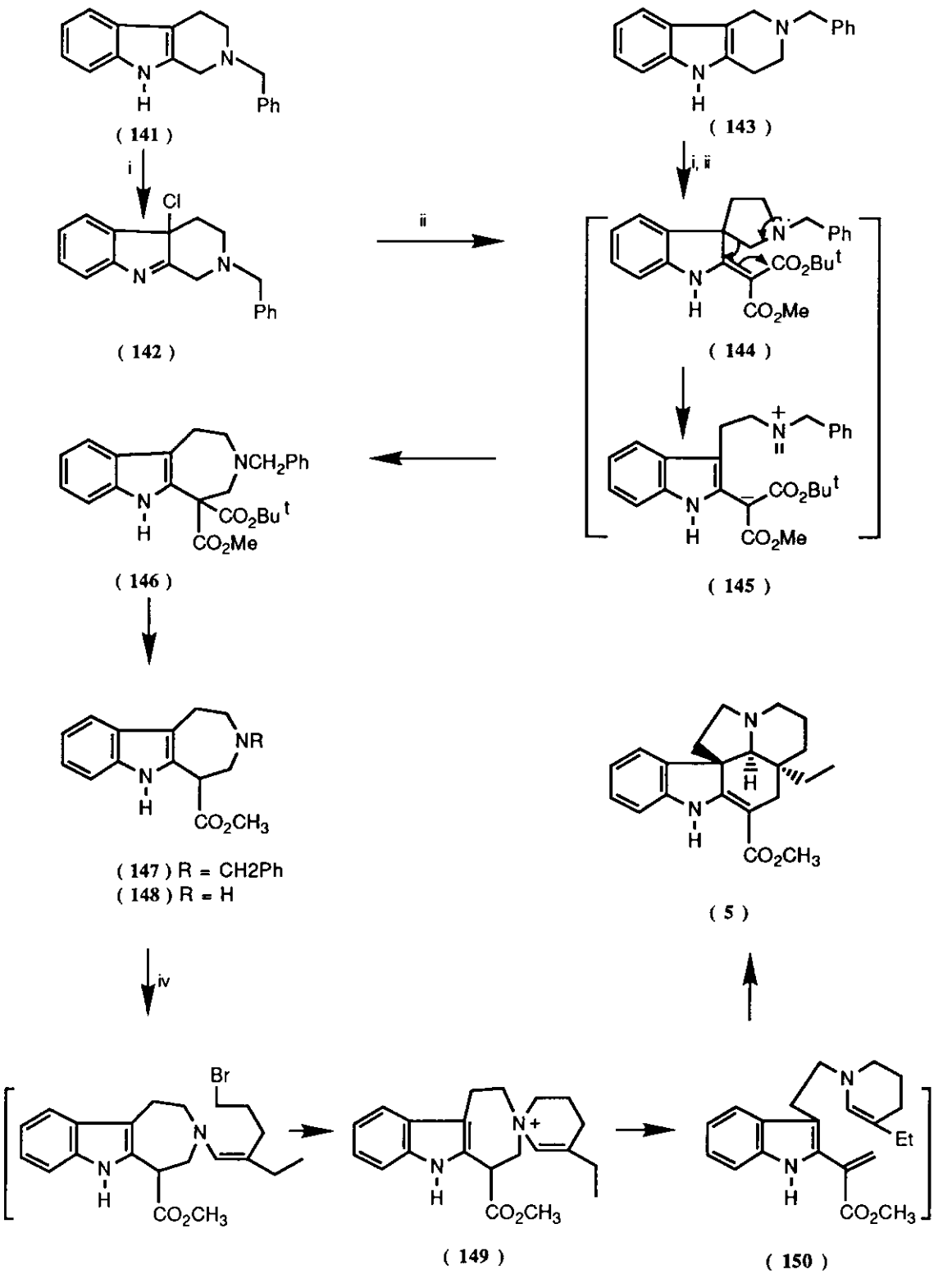


(134) (135) (136) R = COOEt
(137) R = H

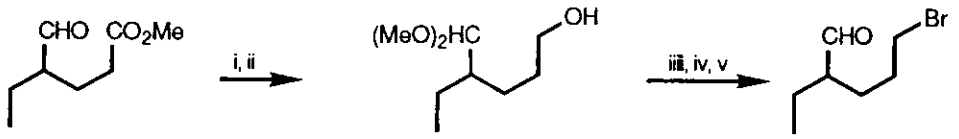
i, KCN, DMF, 100 °C; ii, CH_3OH, H^+

Scheme 16

Subsequently the first elegant biomimetic total synthesis of (+) vincadifformine (5) *via* a secodine intermediate (150) was reported by Kuehne and co - workers[31,32] (Scheme 17). The synthesis began with N_b - benzyltetrahydro - β - carboline (141), which was prepared in three steps from tryptamine hydrochloride[31]. Chlorination of (141) using t - butyl hypochlorite and triethylamine gave the chloroindolenine (142). Subsequent reaction with thallium t - butyl methyl malonate afforded the rearranged indoloazepine dicarboxylic ester (146). Evidence that the spiropyrrolidino derivative (144) was involved was obtained from an alternative preparation of (146) from the γ - carboline derivative[33] (143). It is clear that both conversions proceed *via* a common spirocyclic intermediate (144) and its rearranged zwitterionic immonium malonate (145). Hydrolysis and monodecarboxylation of the t - butyl ester of (146) and then catalytic debenzylation in acetic acid provided indoloazepine (148). The required bromoaldehyde (140) was prepared from methyl 4 - formylhexanoate[34] (138) by acetal formation, reduction to the alcohol and treatment with lithium bromide, as shown in Scheme 18 .


(141)
(142)
(143)
(144)
(145)
(146)
(147) R = CH2Ph
(148) R = H
(149)
(150)
(5)
i, Bu^t OCl, C6H6, NEt3; ii, TlCH(CO2Me), C6H6; iii, H2, Pd/C, AcOH;
iv, Br(CH2)3CHEtCHO, TsOH, MeOH, N2, 40 °C; v, NEt3, MeOH, 60 °C

Scheme 17

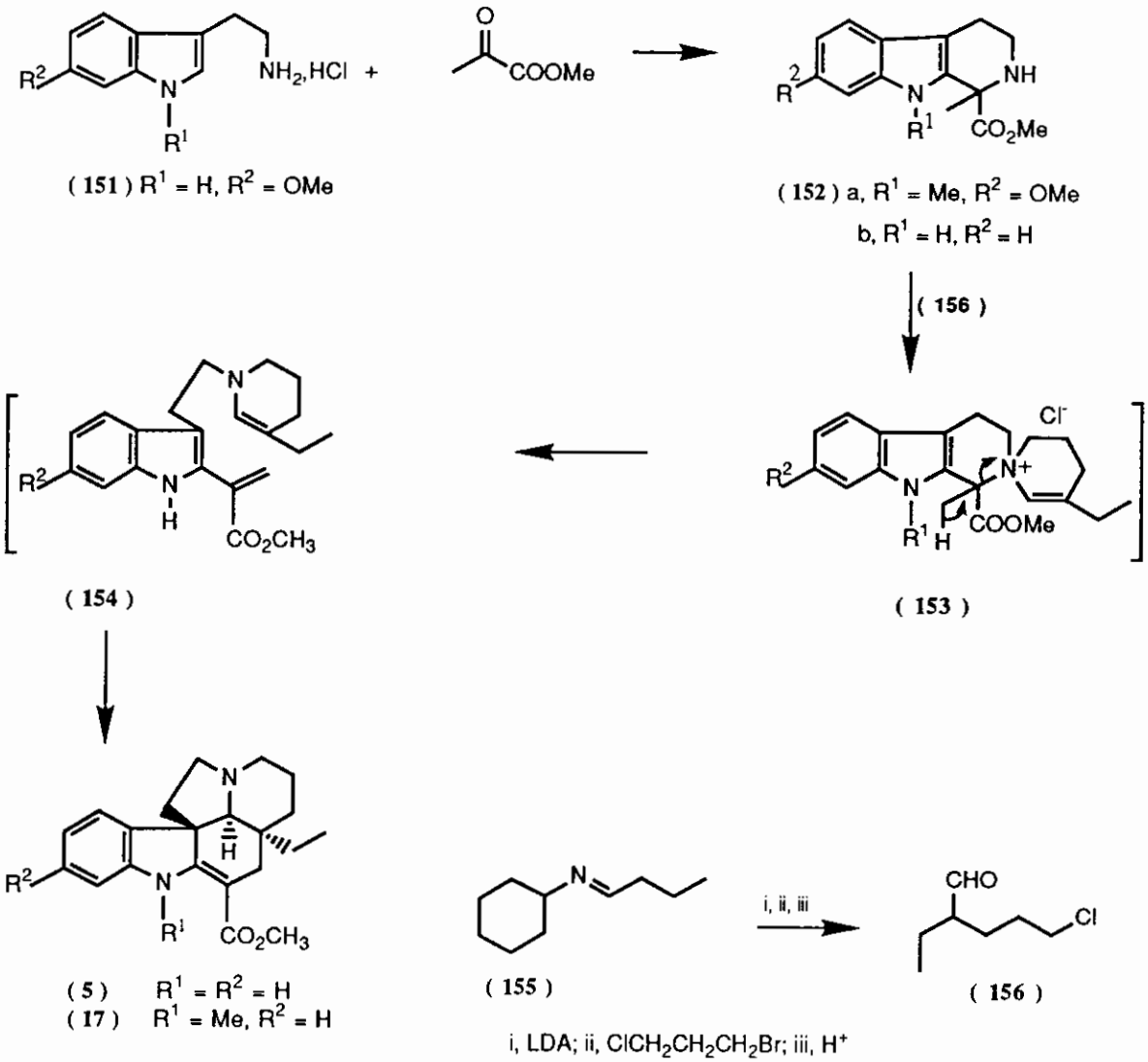


(138) (139) (140)

Scheme 18

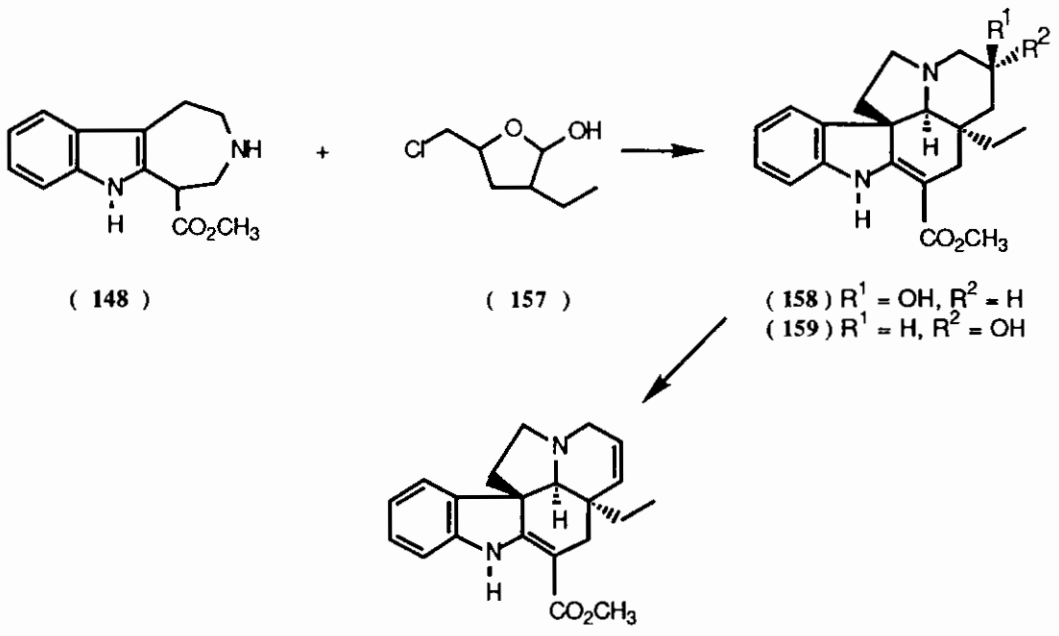
A much improved modification of this synthesis was subsequently reported[35], in which the important secodine precursor is a spirocylic tetrahydro - β - carbolinium salt (153). The required tetrahydro - β - carboline esters (152) are readily prepared by condensation of methyl pyruvate with the appropriate substituted tryptamine (151). Reaction of this tetrahydro -β - carboline with the chloroaldehyde (156) in toluene at a slightly elevated temperature followed by base - initiated fragmentation and recyclisation provided (±) vincadifformine (5) in good yield. This synthesis could be extended to other alkaloids such as : (±) ervinceine (391), (±) - minovine (17), and (±) N_a - methylervinceine (392) (Scheme 19).

Further extension[36] of this general route has involved the use of the chloro lactol (157) (Scheme 20) which was found to give 14 - hydroxyvincadifformine (158,159) and tabersonine (6). Condensation of the indoloazepine (148) with the lactol - chloride (157) in methanol gave the favoured 14 β - hydroxyvincadifformine (158) whereas in benzene the epimer, 14 α - hydroxyproduct (159), was primarily obtained. Dehydration of 14 β - hydroxyvincadifformine by treatment with triphenylphosphine and carbon tetrachloride in acetonitrile, with addition of triethylamine, gave (±) - tabersonine in good yield. This could also be obtained


NH2,HCl +
COOMe
NH
CO2Me
(151) R1 = H, R2 = OMe
(152) a, R1 = Me, R2 = OMe
b, R1 = H, R2 = H
(156)
Cl-
COOMe
(153)
CO2CH3
(154)
CO2CH3
(5) R1 = R2 = H
(17) R1 = Me, R2 = H
i, ii, iii
CHO
Cl
(155)
(156)
i, LDA; ii, ClCH2CH2CH2Br; iii, H+

Scheme 19

from the α - hydroxy epimer but only by thiocarbamate pyrolysis.



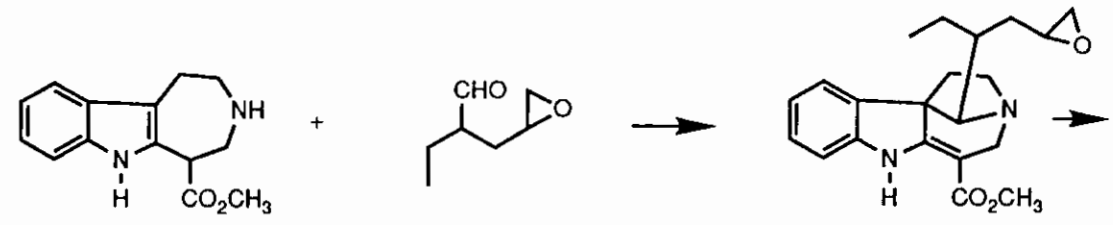
(148) (157) (158) R^1 = OH, R^2 = H
(159) R^1 = H, R^2 = OH

(6)

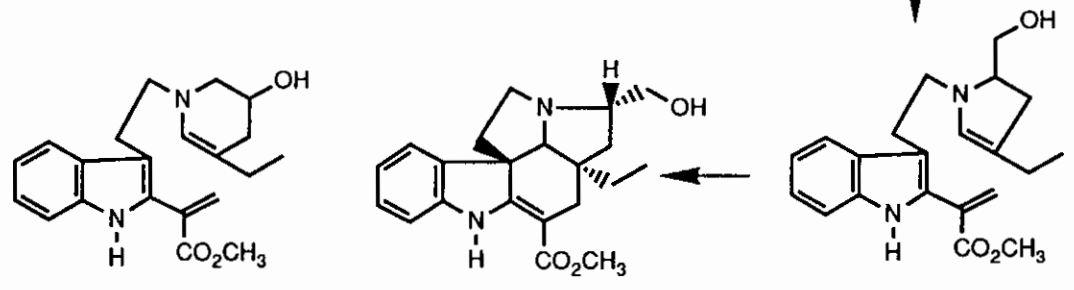
Scheme 20

The other alternative by which the C - 14 epimeric hydroxyvincadifformine has been synthesized[36] was by condensation of the indoloazepine (148) with the epoxy aldehyde (160) in methanol. The major product formed was a (hydroxymethyl) - D - norvincadifformine (166), together with the desired product (158) (Scheme 21).

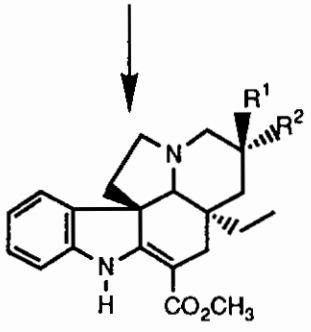
In their recent investigation on the reaction of indoloazepine (148) with simple aldehydes, Kuehne and co - workers[36, 24] isolated the two bridged indoloazepine epimers that result from reaction at N_b and the β position of the indole ring. An application of this concept was the synthesis of 3 - oxovincadifformine (171). The reaction of the indoloazepine (148) with methyl 4 - formylhexanoate (138) in



(148) (160) (161)

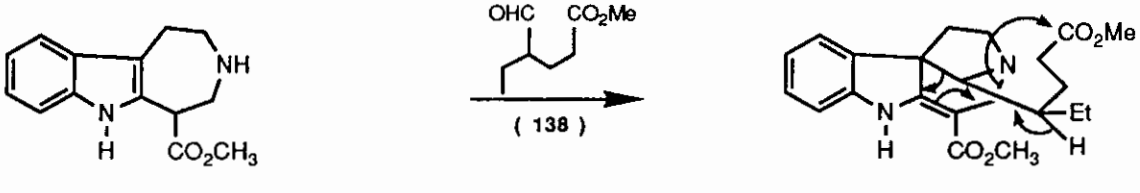


(162) (166) (163)

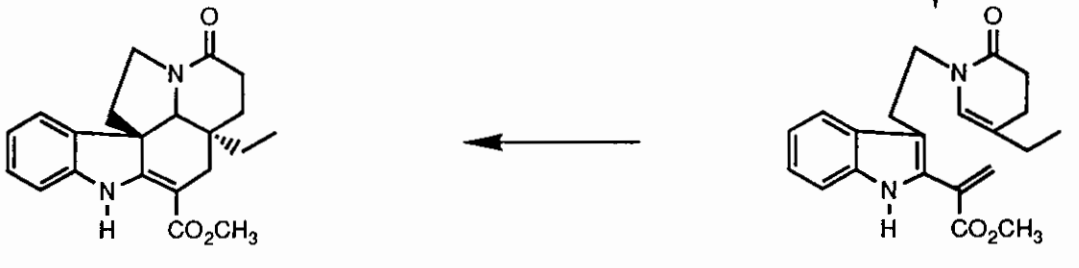


(158) R^1 = OH, R^2 = H
(159) R^1 = H, R^2 = OH

Scheme 21



(148) (138) (169)



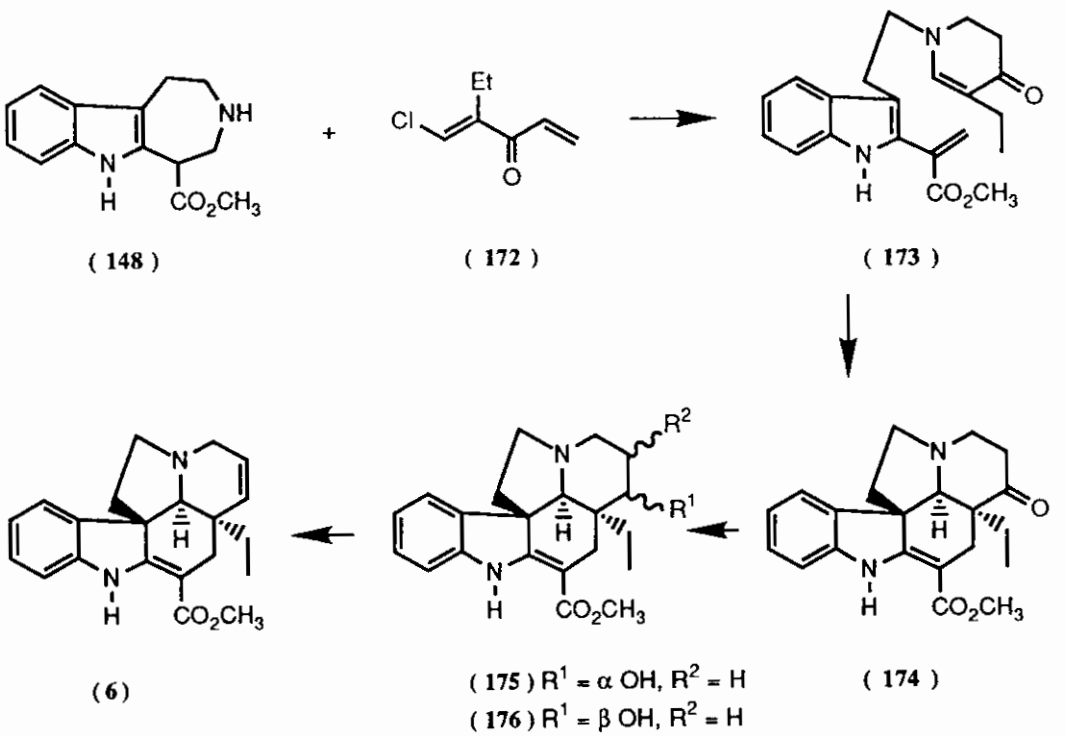
(171) (170)

Scheme 22

refluxing toluene produced a mixture of the epimeric bridged azepines which spontaneously fragmented and recyclised, to give (±) - 3 - oxovincadifformine (171) (Scheme 22).

A controlled, selective synthesis of tabersonine *via* 15 - oxo - $\Delta^{20(21)}$ - secodine (173) was achieved recently by thermolysis[37] (Scheme 23). The required 15 - oxosecodine (173) was obtained by condensation of the indoloazepine (148) with 1 - chloro - 2 - ethylpenta - 1,4 - diene - 3 - one (172)[38] in methanol. Reduction of 15 - oxovincadifformine (174) with sodium borohydride gave 15α - and 15β - hydroxyvincadifformine (175, 176) but with L - selectride (Aldrich) only the latter isomer was obtained (176), whereas the formation of the 15 - thioketal derivative of (174) with ethane dithiol followed by desulphurization provided (±) vincadifformine (5) with established D/E cis stereochemistry.

These biomimetic experiments suggest the two - step conversion of indoloazepine monoester (148) to the pentacyclic *Aspidosperma* nucleus occurs by the sequence of steps outlined for the formation of (±) - vincadifformine (5) in Scheme 24.

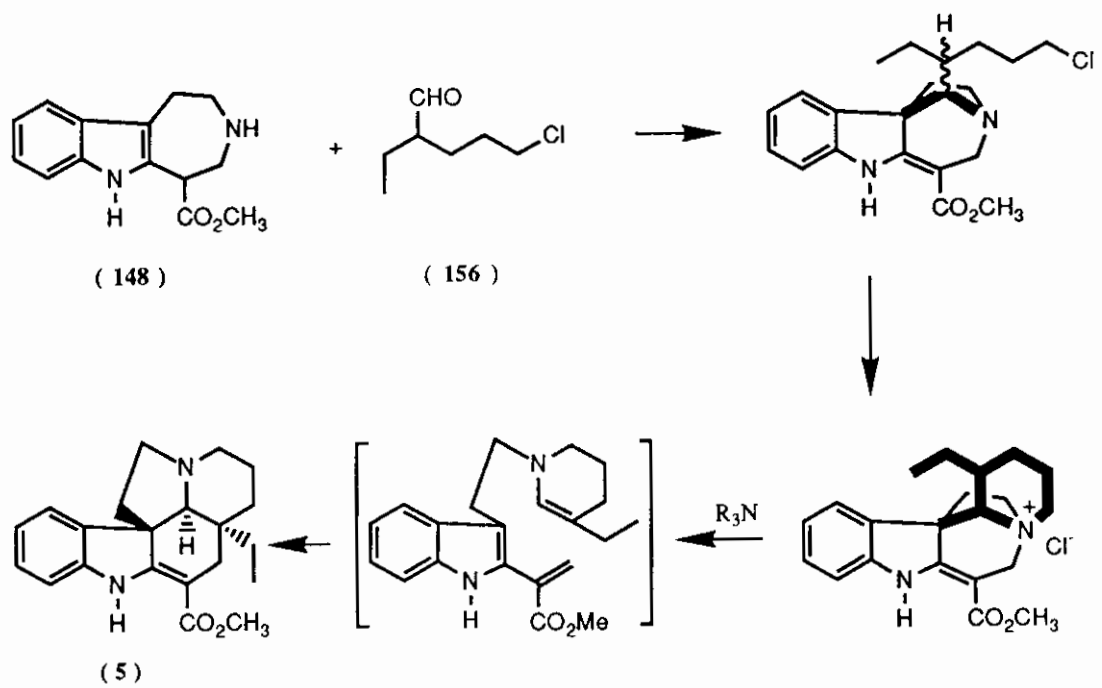


(148) (172) (173)

(6) (175) R^1 = α OH, R^2 = H (174)

(176) R^1 = β OH, R^2 = H

Scheme 23



(148) (156)

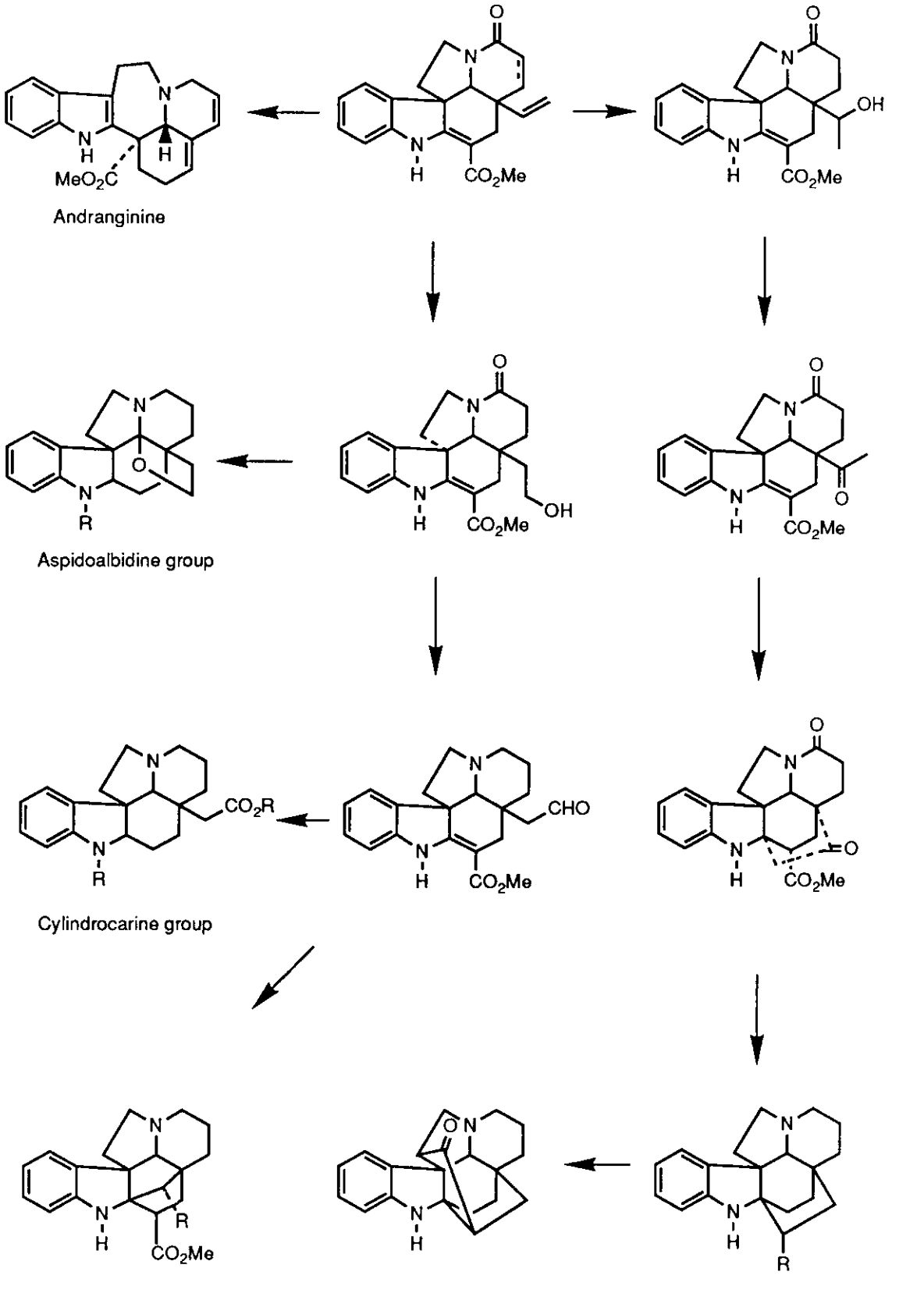
(5)

Scheme 24

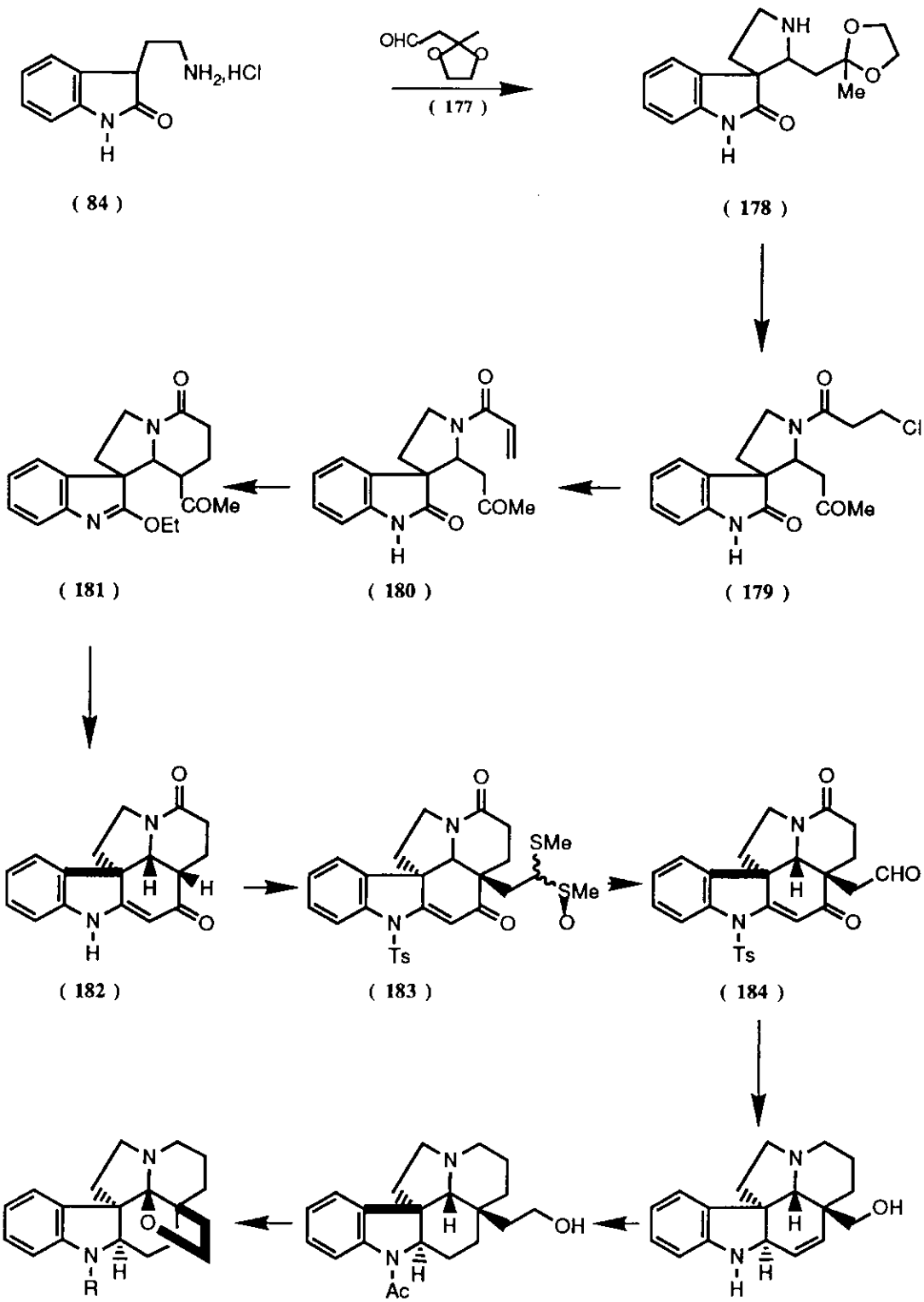
1.3 Recent synthetic routes to the C - 18 oxygenated *Aspidosperma* alkaloids

Among the numerous *Aspidosperma* alkaloids already reported there are several that contain a functionalised C - 18 atom. This functionality can provide a variety of alkaloid systems by modifying the side chain in a number of ways. (Scheme 25).

The first successful synthesis of an alkaloid of this group, by Ban and his collaborators[39,40], was that of N - acetylaspidoalbidine (187), in which the C - 18 carbon is attached *via* oxygen to C - 21 (Scheme 26). The required oxindole (178) was prepared by condensation of 2 - hydroxytryptamine hydrochloride (84) with 3 - oxobutanal ethylene ketal (177). The product was acetylated with β - chloropropionyl chloride and hydrolyzed with acid to give the diastereoisomeric products (179). Treatment of each isomer with base furnished the acryloyl derivatives (180) in very good yield. Cyclisation with the Meerwein reagent gave the tetracyclic imino ether (181), further cyclisation of which with sodium hydride in dimethylsulphoxide gave mainly the versatile intermediate ketoamide (182) with a very small amount of stereoisomer. The major product (182) was N - tosylated by reaction with tosyl chloride and then alkylated stereospecifically at C - 20 by Michael addition of ketene thioacetal monoxide to give the adduct (183) as two isomers at C - 18 which were converted into a single aldehyde (184). Reduction and detosylation with an excess of lithium aluminium hydride afforded an unsaturated amino alcohol (185), the acetylation of which with acetyl chloride followed by catalytic reduction yielded (±) - deoxylimapodine (186). The latter was then converted into N - acetylaspidoalbidine (187) by oxidation with mercuric acetate in acetic acid. Alternatively, (±) fendleridine (188) could be obtained from (185) by means of reduction and then oxidation with mercuric acetate. In a later investigation the

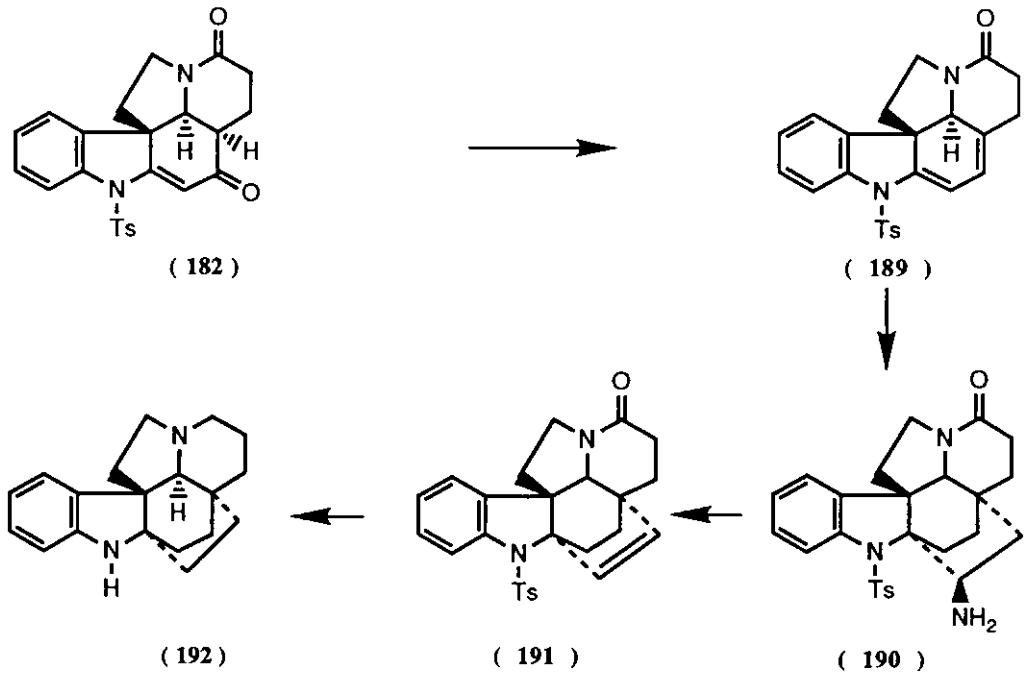

Andranginine
Aspidoalbidine group
Cylindrocarine group
R = Me Pseudokopsinine
R = CHO
Kopsanone
Aspidofractinine group
R = CO2R
R = H Aspidofractinine

Scheme 25


NH2,HCl
OHC
(177)
NH
O
Me
(84)
(178)
Cl
COMe
(179)
(180)
(181)
SMe
CHO
Ts
(182)
(183)
(184)
OH
Ac
R
(187) R = Ac
(188) R = H,
(186) Deoxylimapodine
(185)
(±)- aspidoalbidine

Scheme 26

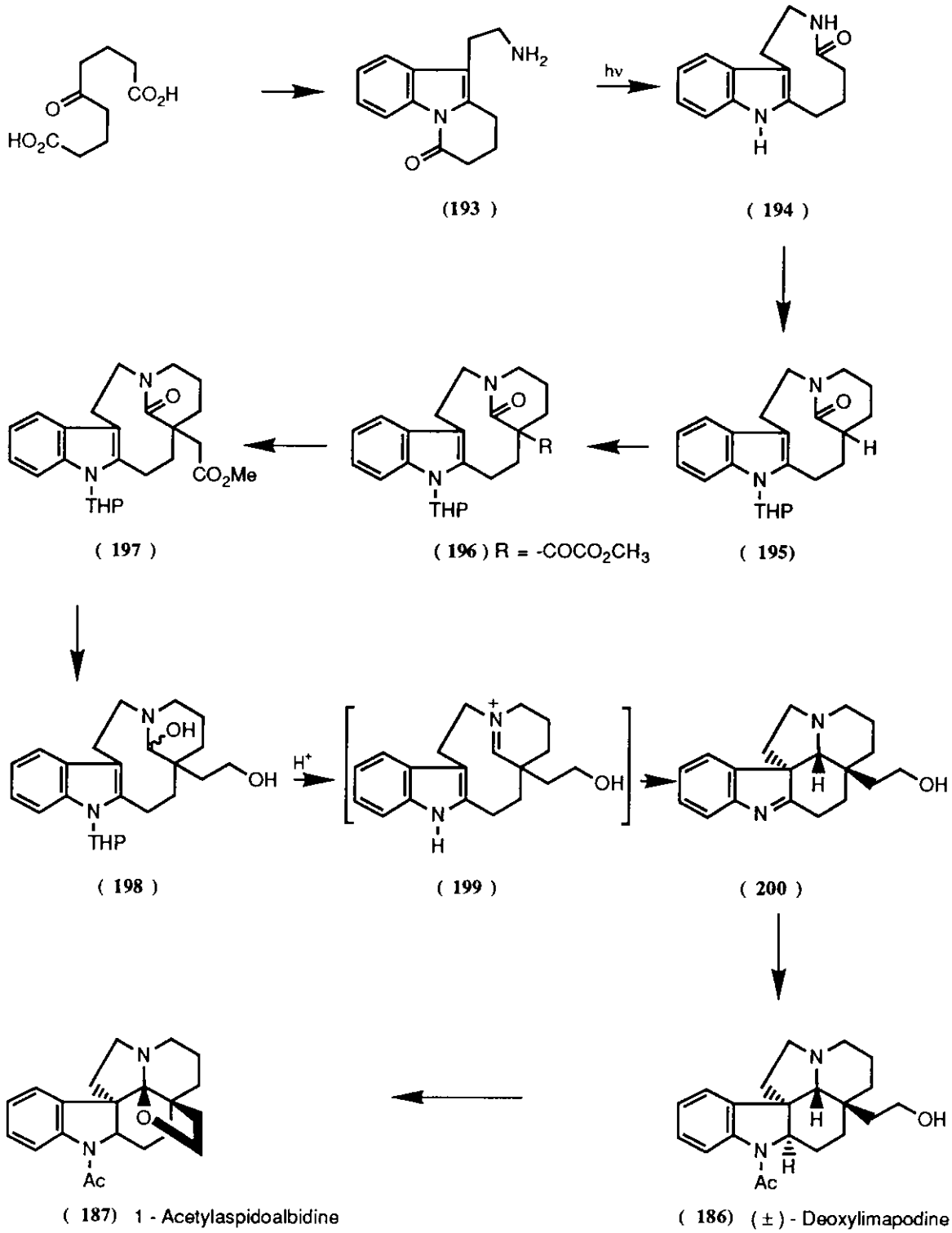
pentacyclic intermediate (182) was also utilised in a synthesis of the hexacyclic alkaloid, aspidofractinine[1] (192) (Scheme 27).



Scheme 27

More recently a second synthesis of N - acetylaspidoalbidine (187) has been reported by Ban et al[41]. This facile synthesis was accomplished from the previously prepared[42,43] tetracyclic lactam (195) , which is an important intermediate for the syntheses of oxygenated *Aspidosperma* alkaloids, by introduction of a C_2 unit at the

α - carbon atom of the lactam carbonyl group (Scheme 28). The quaternary anion derived from (195) was reacted with dimethyl oxalate to give the oxo - ester (196) in good yield, which by an appropriate reduction process, followed by esterification with diazomethane, afforded the keto - ester (197). Reduction with lithium aluminium hydride gave the carbinolamine derivative (198), which was subjected to acid - catalysed stereoselective transannular cyclisation to give an unstable indolenine (200). Reduction with lithium aluminium hydride and acetylation then gave

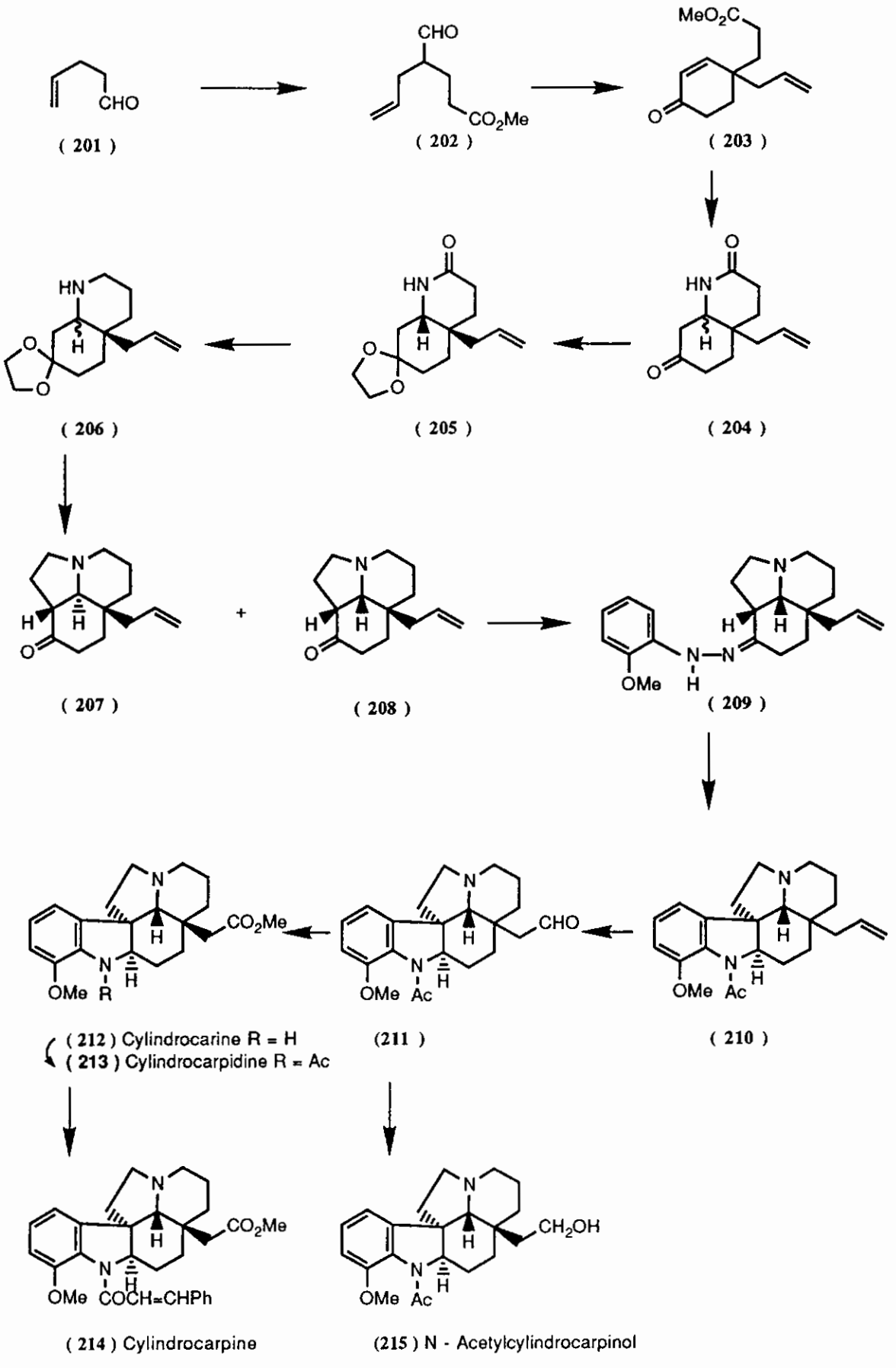

CO2H
O
HO2C
NH2
N
O
hv
NH
O
N
H
(193)
(194)
N
O
H
N
THP
(195)
N
O
R
N
THP
(196) R = -COCO2CH3
N
O
CO2Me
N
THP
(197)
N
OH
OH
N
THP
(198)
H+
[
N+
OH
N
H
]
(199)
N
H
OH
N
(200)
N
H
OH
N
H
Ac
(186) (±) - Deoxylimapodine
N
O
N
Ac
(187) 1 - Acetylaspidoalbidine

Scheme 28

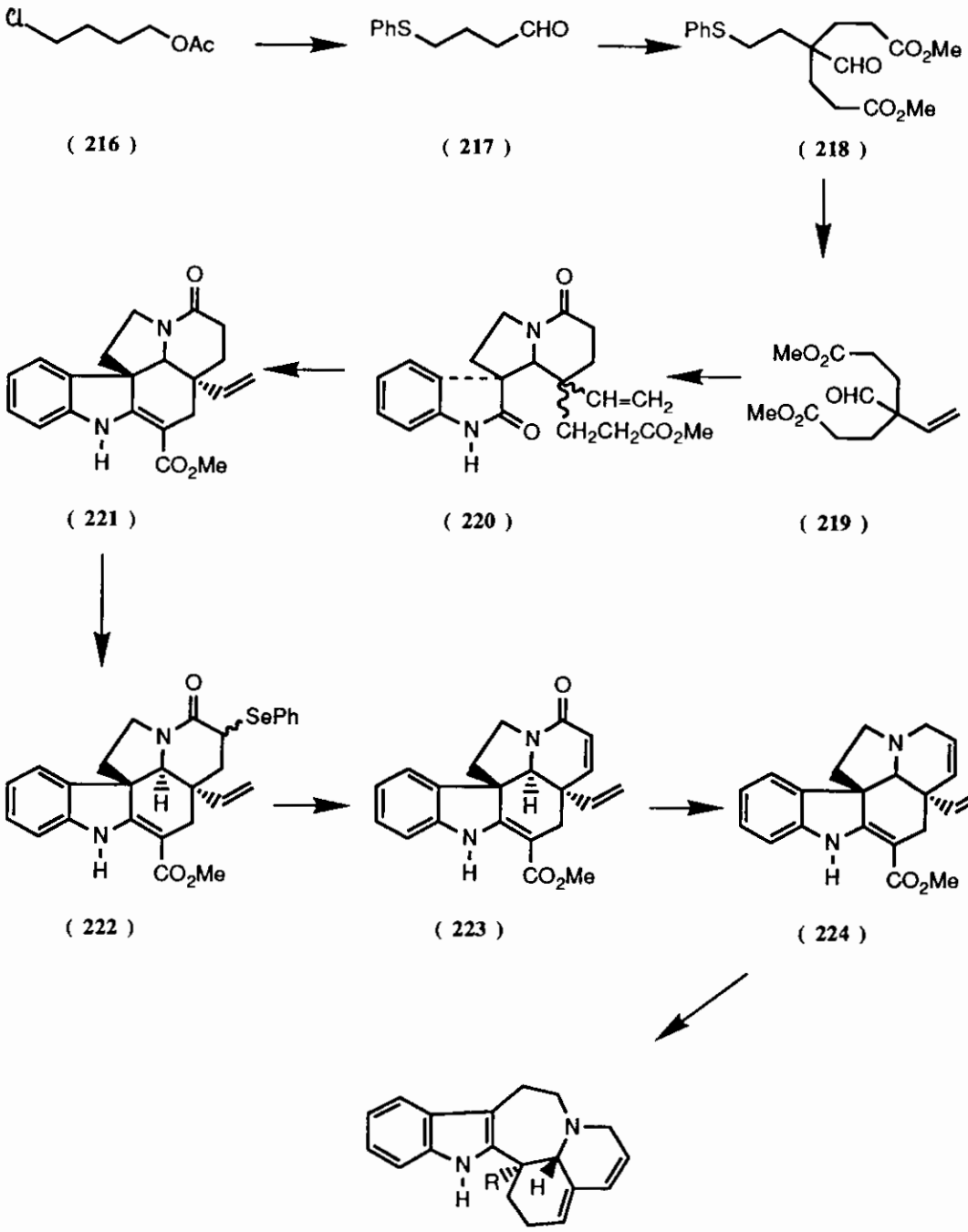
deoxylimapodine (186), which has previously been converted into N - acetylaspidoalbidine (187).

Lawton et al[44] have synthesized the cylindrocarpine group, in which C -20 carries a functionalised two - carbon unit (Scheme 29). For this purpose their investigation was directed towards the synthesis of the tricyclic ketone (208) bearing an allyl group attached to the future C - 20 atom, by a modification of Stork's original synthesis of aspidospermine[45] (2). Successive alkylation of the pyrrolidine enamine of pent - 4 - enal with methyl acrylate and methyl vinyl ketone gave, after hydrolysis and cyclisation, the desired cyclohexenone derivative (203) in a moderate yield. This ketone (203) was converted by reaction with ammonia into the bicyclic ketolactam (204). Conversion of (204) into the corresponding ethylene ketal (205) and reduction with lithium aluminium hydride then gave the isomeric aminoketals (206). Acylation of the secondary amine with chloroacetyl chloride followed by acid hydrolysis and then cyclisation by means of potassium t - butoxide afforded the tricyclic amidoketones which were converted *via* usual protection into the important amino - ketones (207, 208). Cyclisation of the derived o - methoxyphenylhydrazone (209) of the all - cis ketone (208) gave the pentacyclic *Aspidosperma* base (210) which was transformed into the N - acetylcylindrocarpinol (215) by oxidation with osmium tetroxide and sodium paraperiodate, followed by reduction. Several other naturally occurring compounds could be obtained by appropriate transformation of (210), namely, (±) - cylindrocarine (212), (±) - cylindrocarpine (214), and (±) - cylindrocarpidine (213) as outlined in Scheme 29.

The synthesis of 18, 19 - didehydrotabersonine (224), from which a variety of other alkaloids could be obtained by appropriate modification of the isolated double


CHO
(201)
CHO
CO2Me
(202)
MeO2C
O
(203)
HN
O
H
O
O
(204)
(205)
(206)
+
(207)
(208)
N–N
H
OMe
(209)
CO2Me
CHO
OMe R
OMe Ac
(212) Cylindrocarine R = H
(213) Cylindrocarpidine R = Ac
(211)
(210)
COCH=CHPh
CH2OH
(214) Cylindrocarpine
(215) N - Acetylcylindrocarpinol

Scheme 29



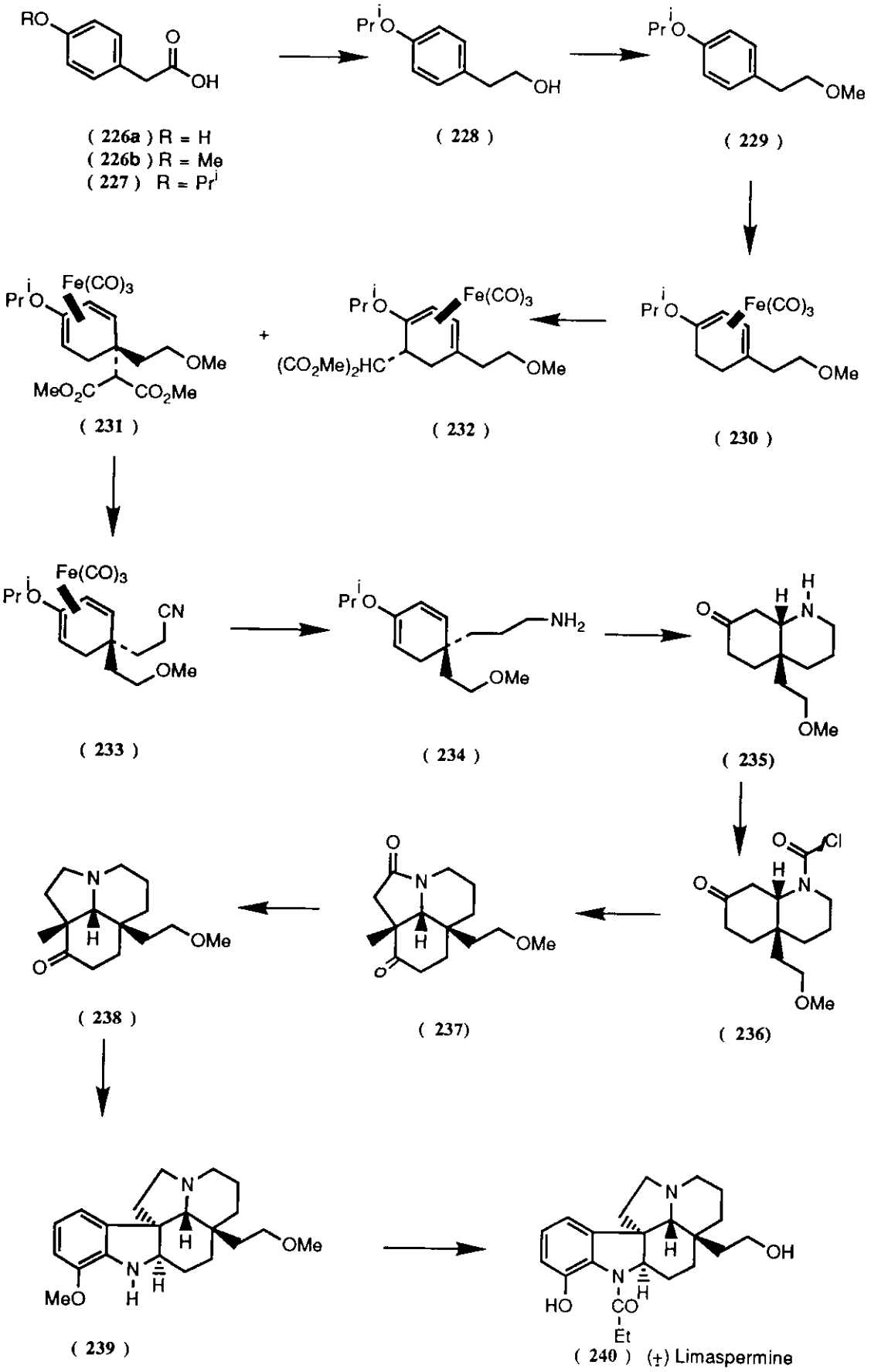
(216) (217) (218) (219) (220) (221) (222) (223) (224)

(225) Andranginine, R = CO_2Me

Scheme 30

bond, has also been reported[46,47] (Scheme30). Condensation of the aldehydoester (219) with 2 - hydroxy - tryptamine, followed by cyclisation, gave the tetracyclic lactam ester (220). Further cyclisation of the desired iminoether in dimsyl sodium gave the cis - fused pentacyclic lactam ester (221), which was treated with lithium di - isopropylamide and phenylselenyl chloride to give the monoselenylated lactam (222). Oxidation of (222) by means of meta-chloroperbenzoic acid followed by elimination gave 3 - oxo - 18, 19 - didehydrotabersonine. Controlled reduction by the Borch method[48] gave 18, 19 - didehydrotabersonine (224). This synthesis constitutes also a formal synthesis of andraginine (225), which can be obtained by thermal rearrangement of (224).

Pearson and Rees[49] achieved a total synthesis of (±) - limaspermine in 30 steps *via* a series of reactions starting from p-methoxyphenylacetic acid (226b). However, this route was extremely long and was by no means competitive with the conventional synthesis of (±) - N - acetylcylindrocarpinol (215) already described by Saxton et al[3]. Subsequently, Pearson[50] developed a more direct synthesis of chloroamide (236) which is outlined in Scheme 31. The required substituted aromatic starting material (227) was prepared from p-hydroxyphenylacetic acid (226a). Reduction of (227) with diborane gave the alcohol (228), which was converted into the methyl-ether (229) and then transformed into the iron complex (230) by a similar route to that reported previously[49]. The malonate compound (231) was obtained mainly, by reaction with dimethyl potassiomalonate, together with an undesired complex (232) as a mixture of (9 : 1). The required product (231) was transformed into the nitrile (233) by demethoxycarbonylation, reduction and then by cyanide displacement of a tosylate intermediate. Removal of the metal by the standard method (i.e anhydrous Me_3NO) in benzene, and reduction of the nitrile group with

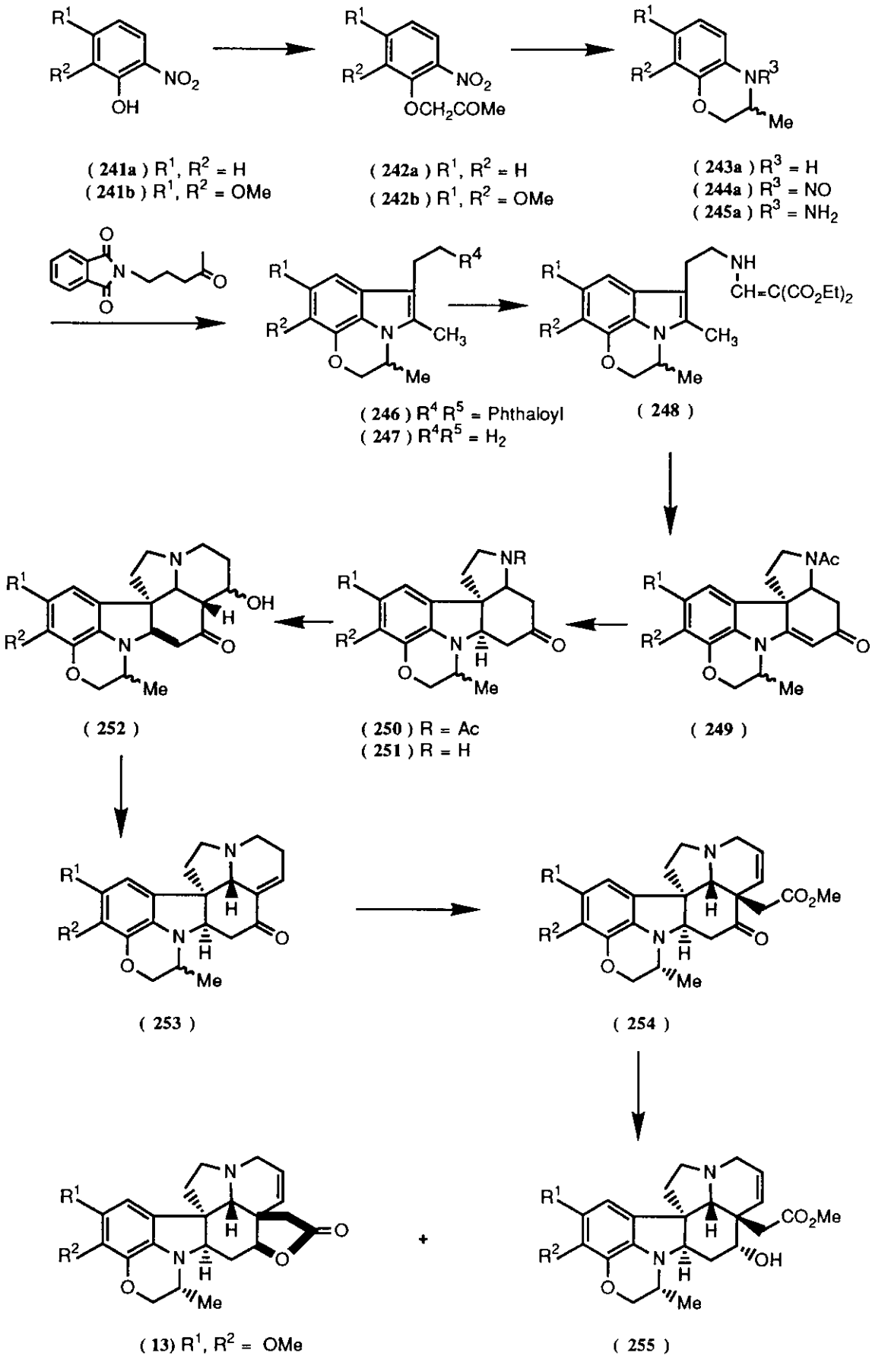

RO
O
OH
(226a) R = H
(226b) R = Me
(227) R = Pr^i
Pr^iO
OH
(228)
Pr^iO
OMe
(229)
Pr^iO
Fe(CO)3
OMe
(230)
Pr^iO
Fe(CO)3
(CO2Me)2HC
OMe
(232)
Pr^iO
Fe(CO)3
OMe
MeO2C
CO2Me
(231)
Pr^iO
Fe(CO)3
CN
OMe
(233)
Pr^iO
NH2
OMe
(234)
H
H
N
O
OMe
(235)
O
Cl
H
N
O
OMe
(236)
O
N
H
OMe
O
(237)
N
H
OMe
O
(238)
N
H
H
N
H
OMe
MeO
(239)
N
H
H
N
H
OH
HO
CO
Et
(240) (±) Limaspermine

Scheme 31

lithium aluminium hydride, gave the primary amine (234), which was hydrolysed with concomitant Michael cyclisation to give the derivative (235). This material was then converted into the amide (236). The transformation of (236) into (±) - O - methylcylindrocarpinol (215) was accomplished by the procedures used by Stork[51] and Saxton[44] in closely related systems. Finally the pentacyclic ether (239) was converted into the propionamide, followed by cleavage of both methyl ethers with trimethylsilyl iodide to give (±) limaspermine (240) in similar yield to that obtained in the first route.

Brennan et al[52] also succeeded in synthesising more complex functionalized aspidospermine derivatives. The first elegant synthesis of a heptacyclic alkaloid, exemplified by obscurinervidine (13), was achieved by a 13 - stage sequence which started from 2, 3 - dimethoxy - 6 - nitrophenol (241)[5,6] and proceeded *via* the pentacyclic vinylogous amide (249) (Scheme32).

The required potassium salt of (241) was reacted with chloroacetone to form the phenacetol (242), which on hydrogenation and concomitant cyclisation gave the dimethoxybenzoxazine (243). Reaction with nitrous acid followed by reduction with lithium aluminium hydride afforded the corresponding N - amino derivative (245). Reaction of 5 - phthalimido - 2 - pentanone[55] with the N - amino compound (245) in refluxing glacial acetic acid gave, *via* Fischer cyclisation, the phthalimido compound (246), which on hydrazinolysis gave the appropriate tryptamine derivative (247). Condensation of (247) with diethyl ethoxymethylenemalonate produced the vinylogous urethane (248) which was cyclised using the Takano procedure[56]. The produced racemates (249) were then reduced with lithium - t - butanol – liquid ammonia to give a mixture of racemates from which the desired stereoisomer (250) was isolated. Removal of the amide function by means of triethyloxonium tetrafluoroborate and aqueous sodium carbonate gave the amide (251), which was

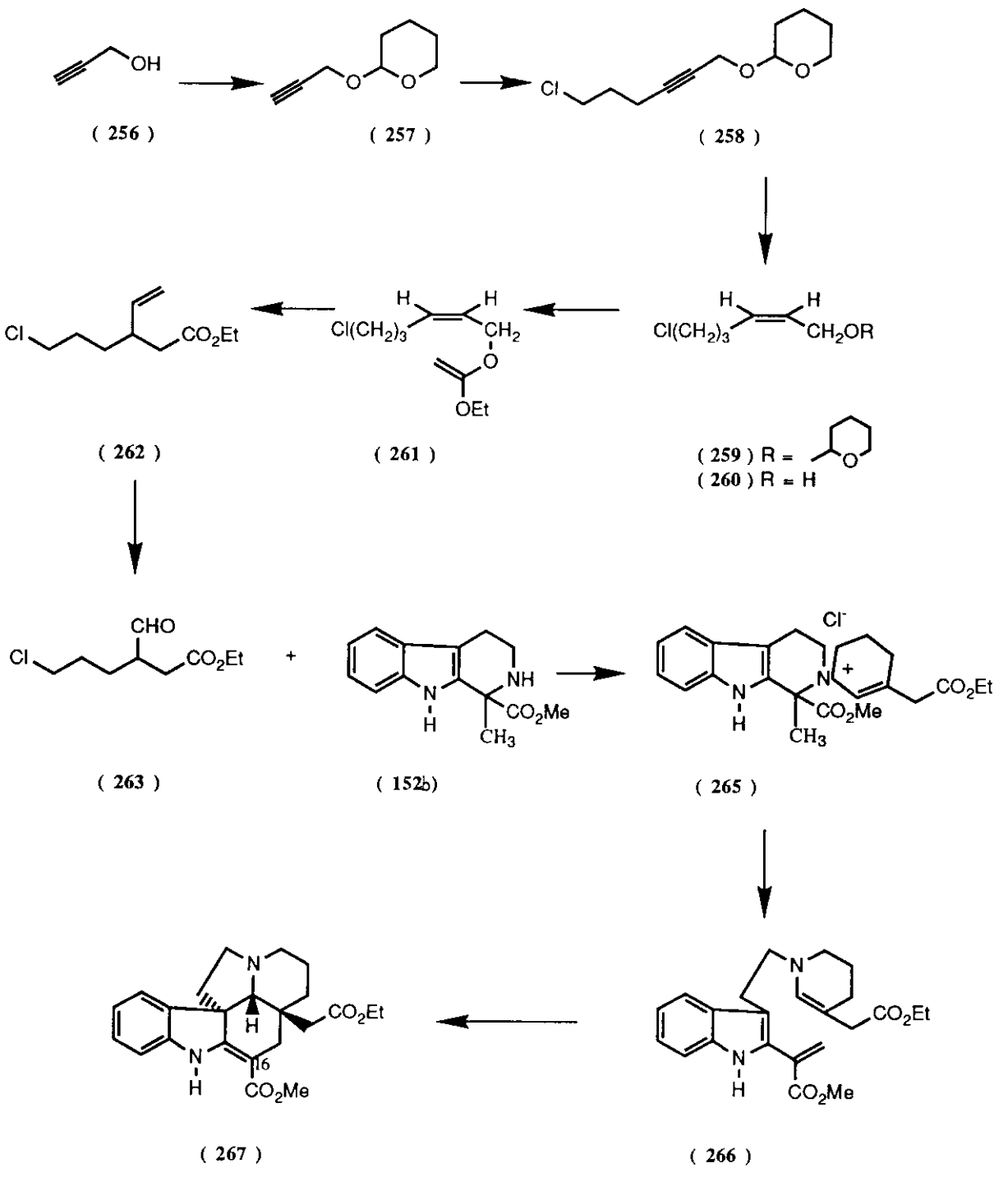

(241a) R1, R2 = H
(241b) R1, R2 = OMe
(242a) R1, R2 = H
(242b) R1, R2 = OMe
(243a) R3 = H
(244a) R3 = NO
(245a) R3 = NH2
(246) R4 R5 = Phthaloyl
(247) R4R5 = H2
(248)
(249)
(250) R = Ac
(251) R = H
(252)
(253)
(254)
(13) R1, R2 = OMe
(255)

Scheme 32

converted into the hexacyclic ketols (252) by Michael addition of acrolein in the presence of sodium methoxide. Subsequent dehydration with methane sulphonyl chloride in pyridine produced the enone (253). Alkylation of the enone (253) by methyl bromoacetate – potassium t - butoxide gave the keto-ester (254). Finally, reduction of this keto - ester (254) with sodium borohydride and lactonisation of the appropriate epimeric hydroxy - ester gave (±) - obscurinervidine (13) in moderate yield.

Another investigation by Saxton and co - worker[57] has resulted in the synthesis of anilinoacrylate diester (267), which is of potential use in the synthesis of several of the *Aspidosperma* alkaloids, as outlined in Scheme 33. This involves the use of the chloroaldehyde (263) which could be obtained from the propargyl alcohol (256). Previous work had shown that etherification of this alcohol with dihydropyran followed by alkylation with 1 - bromo - 3 - chloropropane using n - butyllithium as base gave the chloroalkyne (258) in good yield. Catalytic hydrogenation of the alkyne (258) over the Lindlar catalyst gave the cis - alkene (259) which was not isolated but directly converted to the chloroallyl alcohol (260) in presence of p - toluenesulphonic acid. Claisen rearrangement occurred when the unsaturated chloroalcohol (260) and triethyl orthoacetate were heated together in the presence of propionic acid as catalyst, to give the desired olefin (262). Finally, addition of ozone to the solution of (262) in methanol gave the chloroaldehydo - ester (263). Adaptation of the Kuehne type - synthesis to this novel chloroaldehyde (263) with the known tetrahydro - β - carboline ester (152b) in refluxing toluene, provided after 110 h the diester (267) in an optimum yield of 45%.

The transformation of (267) into a new synthesis of alkaloids of the cylindrocarine group as, for example : (±) - cylindrocarine (212), N -



(256) (257) (258)

(259) R =
(260) R = H

(262) (261)

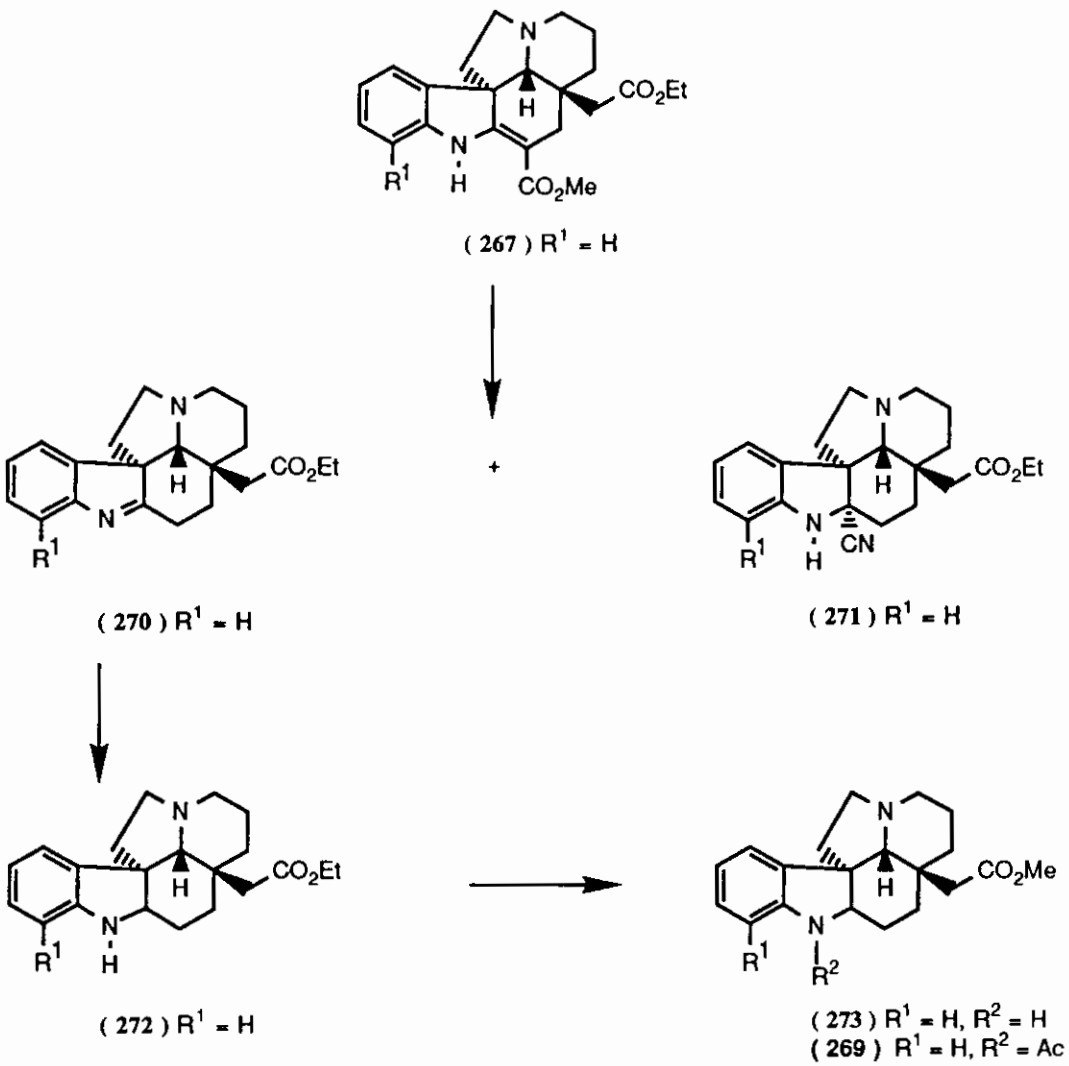
(263) (152b) (265)

(267) (266)

Scheme 33

formylcylindrocarine (268), and (±) - 12 - demethoxy - acetylcylindrocarine (269) was accomplished *via* a selective hydrolysis and decarboxylation of the ester group attached to C - 16 by means of an excess of sodium cyanide in hexamethylphosphoramide. This reaction produced two products which were shown to be the desired indolenine ester (270) and the aminonitrile (271). The former compound was then reduced with sodium borohydride to give 19 - ethoxycarbonyl - 19 - demethylaspidospermine (272), which was subsequently converted into (±) - 12 - demethoxy - N - acetylcylindrocarine (269) by transesterification with sodium methoxide in methanol followed by N - acylation of (273) (Scheme 34).

Choosing the appropriate 7 - methoxytryptamine, Saxton et al extended this synthesis to (±) cylindrocarine (212), cylindrocarpidine (213), cylindrocarpine (214), and Na - formylcylindrocarine (268) using the same method as before .



(**212**) R^1 = OMe, R^2 = H Cylindrocarine

(**213**) R^1 = OMe, R^2 = Ac Cylindrocarpidine

(**214**) R^1 = OMe, R^2 = COCH=CHPh Cylindrocarpine

(**268**) R^1 = OMe, R^2 = CHO N_a - Formylcylindrocarine

Scheme 34

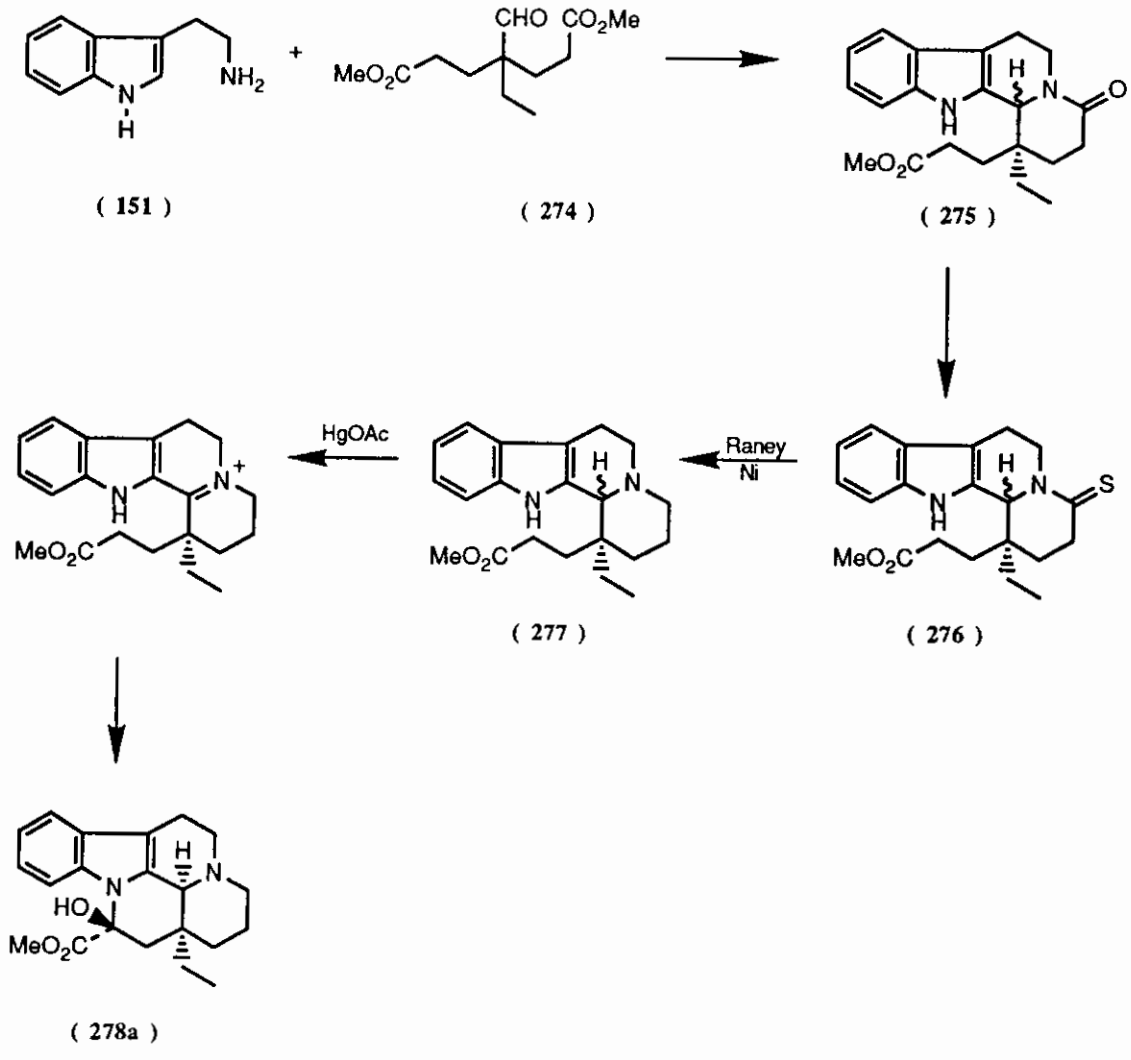
1. 4 Synthetic approaches to vincamine and related alkaloids

The discovery of the biological activity and therapeutic effect of vincamine (278a) as hypotensive and its use in the treatment of cerebral sclerosis, vascular, and metabolic diseases, has prompted intensive research activities for feasible total syntheses of this compound. Vincamine, the major alkaloid constituent of *Vinca minor* L. (*Apocynaceae*), was first isolated in 1953 by Schlittler[60]. It has been also found in *Vinca major*, *Vinca difformis*, and *Vinca erecta.*

Up to date a large number of syntheses of (278a) have been reported and most of the approaches have involved condensation of tryptamine with a suitably functionalised di or tri - carbonyl system followed by cyclisation.

The first total synthesis of (278a) was accomplished by Kuehne[61] (Scheme 35) starting from tryptamine (151) which was condensed with dimethyl 4 - ethyl - 4 - formylpimelate (274). The resultant product (275) was then converted into the thiolactam ester (276) by reaction of the epimeric lactam ester (275) with phosphorous pentasulphide. Removal of the thiolactam sulphur atom with Raney nickel gave the amino ester (277). Equilibration of the isomeric mixture through the immonium intermediate by means of mercuric acetate oxidation followed by reduction of the immonium salt with sodium borohydride afforded the desired isomer which was converted into (±) - vincamine (278a) by oxidation with p - nitrosodimethylaniline and excess of triphenylmethyl sodium, followed by acid hydrolysis. However this reaction gave a poor yield of vincamine (278a).

The second synthesis of vincamine (278a) was reported by Gibson and Saxton[62] using an extension of their previous method for the synthesis of eburnamine

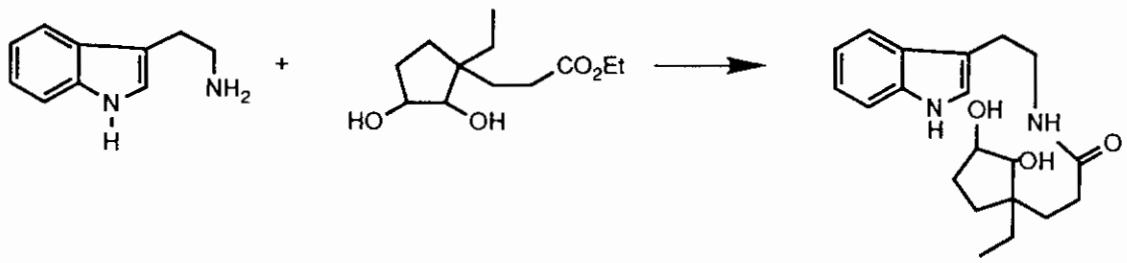


(151) (274) (275) (276) (277) (278a)

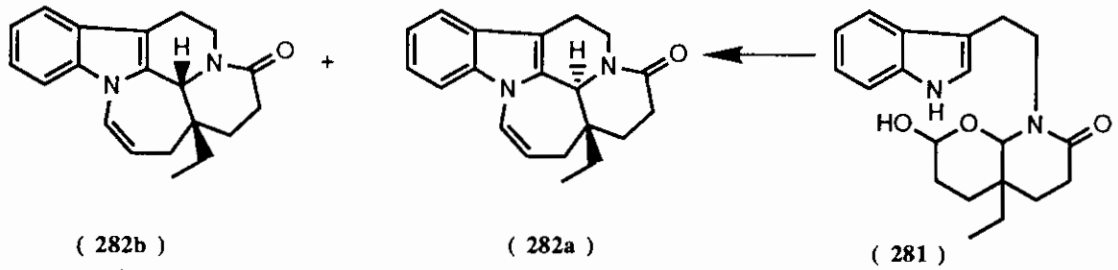
Scheme 35

(286) (Scheme 36). The starting ester diol (279) was condensed with tryptamine (151) to give the acyltryptamine derivative (280), which on periodate fission afforded the amide (281). Cyclisation with acetic acid then gave (282). Treatment of the desired isomer with osmium tetroxide and cleavage of the resulting diol (283) with lead acetate followed by removal of the N - formyl group gave (284). Reduction with lithium aluminium hydride provided (±) eburnamine (285) which is also of pharmacological importance. Homoeburnamenine[62] (286) obtained by reduction of (282b), was oxidised with osmium tetroxide to the dihydroxy compound (287). Oxidation of (287) by means of pyridine - sulphur trioxide complex in wet dimethylsulphoxide gave two diastereoisomeric lactams (288). Alkaline hydrolysis of the hydroxylactams (288) furnished the corresponding hydroxy - acids, which were esterified to the methyl ester (289) and then converted into (±) vincamine (278a) see (Scheme 37).

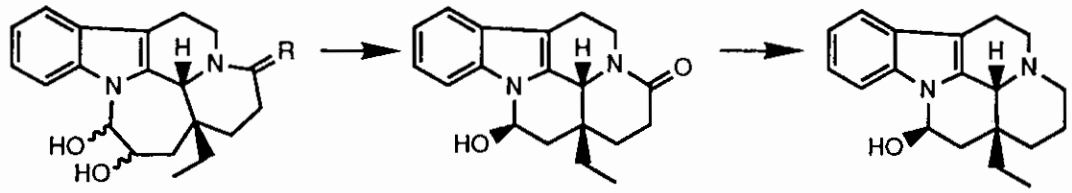
Le Men and co - workers[63] have investigated a variety of rearrangements under oxidizing or reducing conditions of the more easily accessible tabersonine (6). Some of these are of considerable significance; for example, the treatment of (6) with pulverized zinc and copper sulphate in glacial acetic acid gave two main products, the indole derivative (291) and the indoline, vincamsonine (292). According to Kuehne, the product (291) can be converted into vincamine (278a) (Scheme 38).



(151) (279) (280)

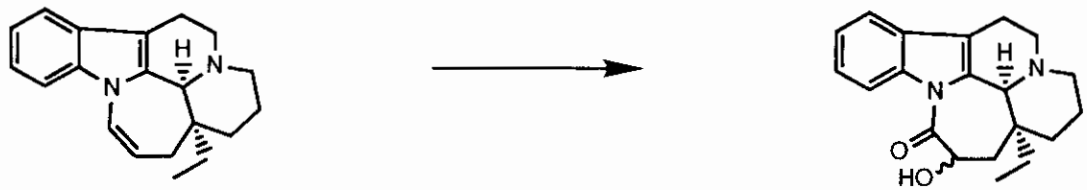


(282b) (282a) (281)



(283) R = O
(287) R = H_2 (284) (285)

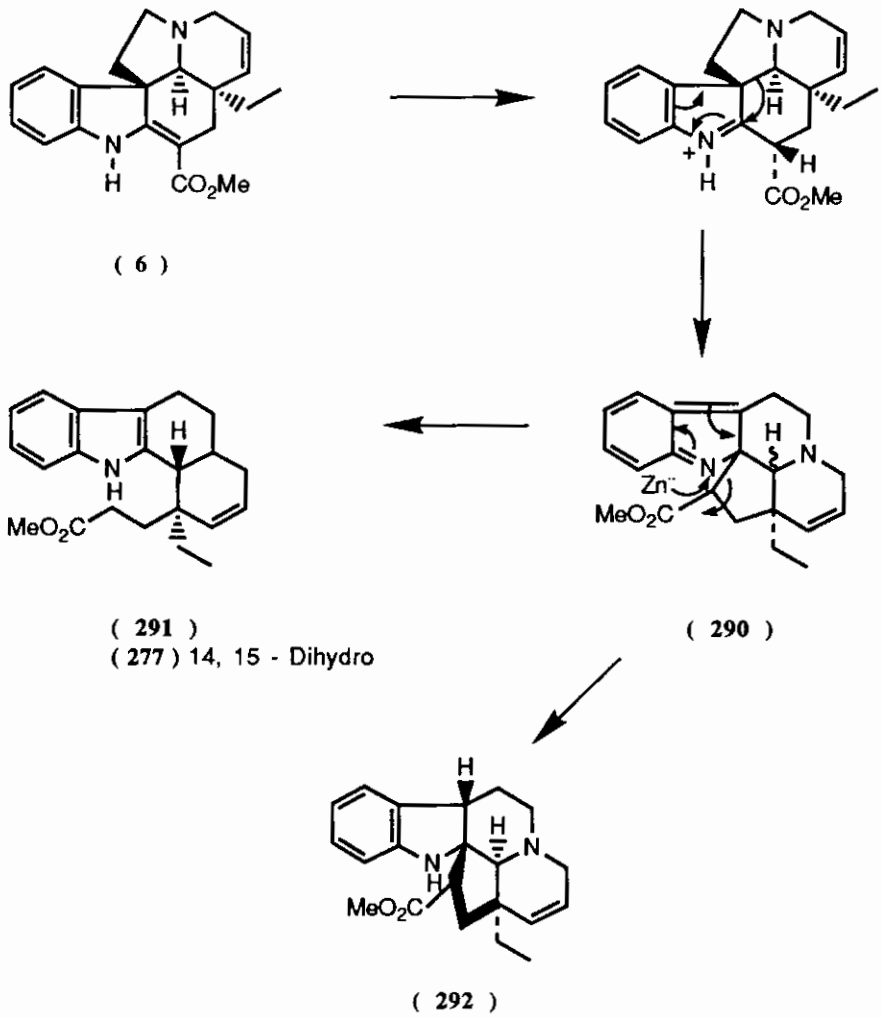
Scheme 36



(286) (288)

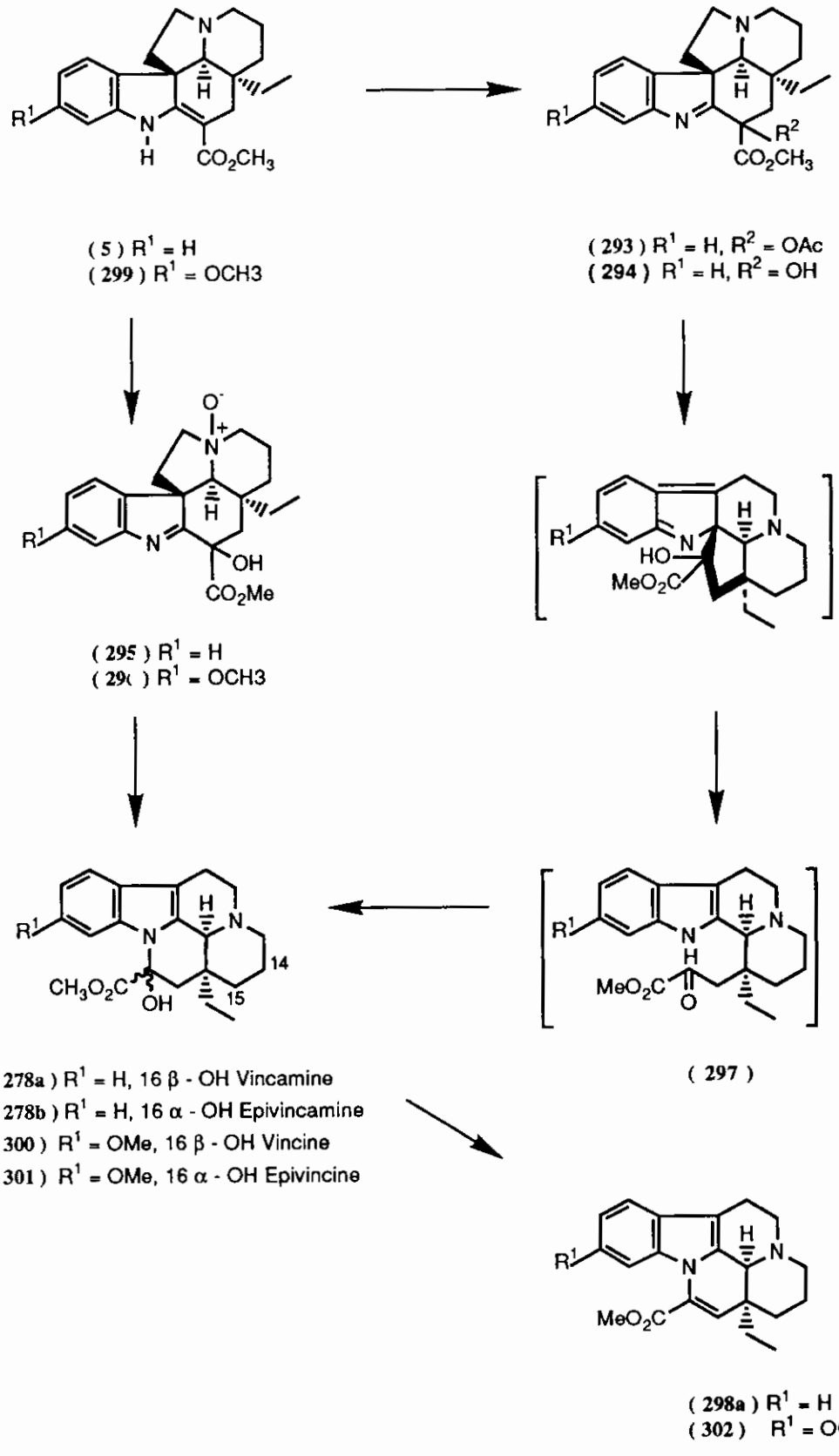
(278a) (289)

Scheme 37



Scheme 38

Lévy et al[64] have developed a new conversion of vincadifformine (5) which proceeds by two routes (Scheme 39) using a similar process, but a previous oxidation at C - 16 is needed before the rearrangement step. Thus, reaction of (-) - vincadifformine (5) with lead tetraacetate in benzene gave the acetoxyindolenine (293) which, on treatment with trifluoroacetic acid in chloroform followed by reaction with sodium acetate, is converted into a mixture of (+) - vincamine, (-) - 16 - epivincamine (278b), and (+) - apovincamine (298a). The same sequence of reactions was also applied to (-) - tabersonine (6), which gave a mixture of (+) - 14, 15 -

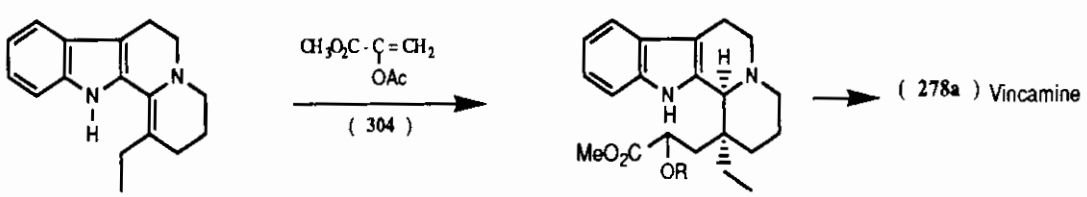

(5) R1 = H
(299) R1 = OCH3
(293) R1 = H, R2 = OAc
(294) R1 = H, R2 = OH
(295) R1 = H
(29( ) R1 = OCH3
(297)
(278a) R1 = H, 16 β - OH Vincamine
(278b) R1 = H, 16 α - OH Epivincamine
(300) R1 = OMe, 16 β - OH Vincine
(301) R1 = OMe, 16 α - OH Epivincine
(298a) R1 = H
(302) R1 = OCH3

Scheme 39

dehydrovincamine, (+) - 14, 15 - dehydro - 16 - epivincamine. 11 - Methoxyvincadifformine (299)[65] was also obtained from the appropriate tryptamine derivative.

The second route involved the same transformation and proceeded *via* 16 - hydroxyindolenine N_b - oxide (295), which was obtained by reaction of vincadifformine (5) with two equivalents of p - nitroperbenzoic acid. Treatment with triphenylphosphine in aqueous acetic acid gave the hydroxyindolenine (294) which subsequently underwent rearrangement to a mixture of vincamine (278a), 16 - epivincamine (278b), and apovincamine (298a).

A fully stereoselective synthesis of vincamine has been achieved by Szantay and co - workers[66] (Scheme 40) using the enamine (303), which was previously prepared by Wenkert[67]. This enamine was reacted with α - acetoxyacrylic acid methyl ester[68] (304) to give a product which was reduced catalytically. Only one stereoisomer (305) was obtained, and in good yield. Deacetylation of (305) and oxidation with Fetizon 's reagent [Ag_2CO_3 / Celite] in toluene furnished a mixture of vincamine and 16 - epivincamine. Epimerisation with sodium methoxide in methanol gave an almost quantitative yield of vincamine (278a)



(303)

(305) R = COCH3
(306) R = H

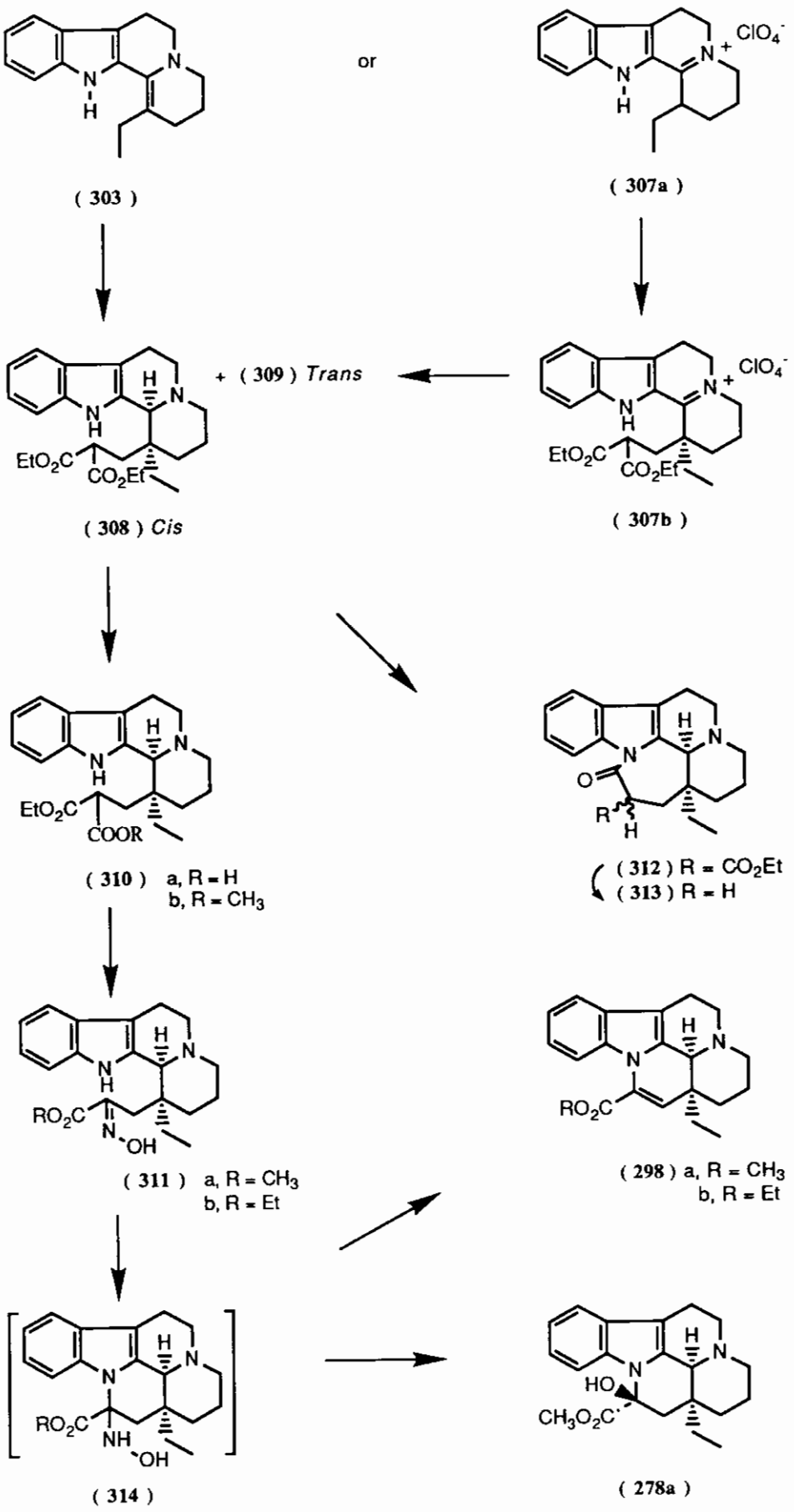
Scheme 40

Furthermore Szántay[69] elaborated a new synthesis from which (+) - apovincaminic acid esters (298a,b), (+) - vincamine (278a) and vincamone (315) can be prepared *via* a common intermediate (314) (Scheme 41).

The basic principle of this reaction was the alkylation in position 1 of the tetracyclic (303) or (307), by means of a bulky electrophilic olefin, to ensure the stereoselective hydrogenation of the molecule in the desired direction. Diethyl methylene malonate, with strong electrophilic character was required to facilitate the formation of the E - ring.

The enamine (303) was reacted with 4 equivalents of diethyl methylene malonate in dichloromethane, the product from which, after hydrogenation in the presence of palladium - carbon as catalyst, gave the cis - diester (308) and the trans diester (309), whereas the reaction of the iminium perchlorate (307a) in the presence of a very small amounts of $KOBu^t$, with 1.5 equiv. of diethyl methylene malonate, gave the adduct (307b) in very good yield. Catalytic hydrogenation of (307b) in the presence of 10% palladium - carbon in dimethylformamide gave with high stereoselectivity the cis - ester (308). The trans derivative (309) was obtained in a yield of only 3%. Base catalysed cyclisation of cis - ester (308) in benzene yielded lactam ester (312), from which lactam (313) can be prepared and converted to vincamine (278a) by known procedures[57].

Selective hydrolysis of (308) with ethanolic potassium hydroxide afforded the hemiester (310a), which was transformed into α - hydroxyiminoester (311b) on treatment with sodium nitrite in aqueous acetic acid. The ethyl ester (311b) can be converted into methyl ester (311a) by boiling in methanol in the presence of a catalytic amount of sodium methoxide. The oxime esters (-) (311 a,b) were converted into

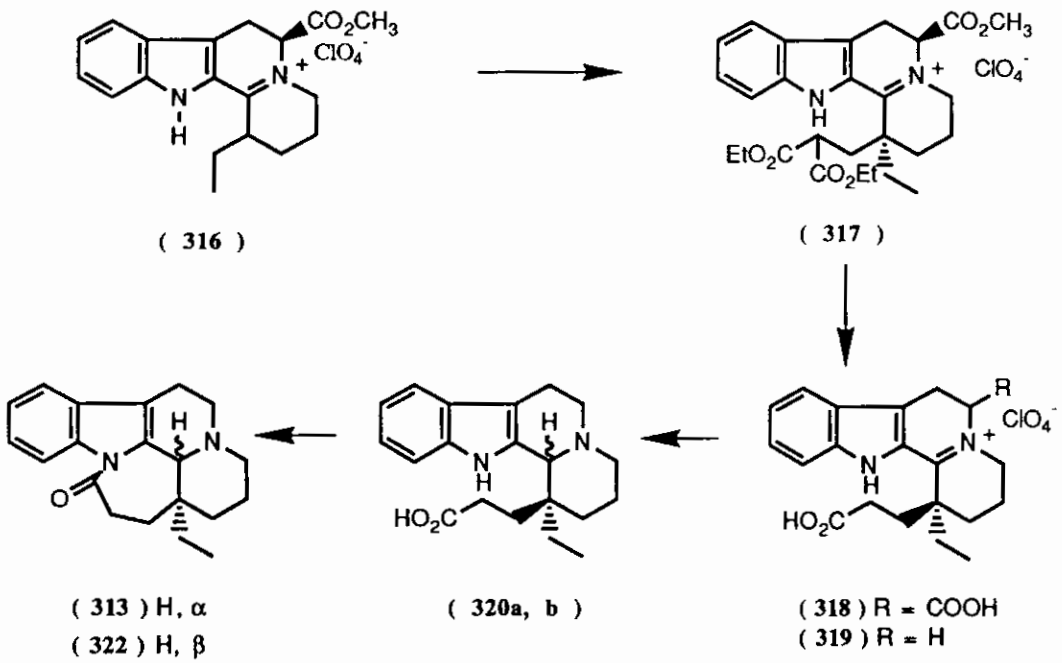

or
(303)
(307a)
+ (309) Trans
(308) Cis
(307b)
(310) a, R = H
b, R = CH3
(312) R = CO2Et
(313) R = H
(311) a, R = CH3
b, R = Et
(298) a, R = CH3
b, R = Et
(314)
(278a)

Scheme 41

the pharmaceutically important (+) - apovincaminic acid esters (298a,b) and (+) - vincamine by heating in methanol or ethanol containing concentrated sulphuric acid. However, the presence of sodium pyrosulphite increases significantly the proportion of (+) - vincamine (278a).

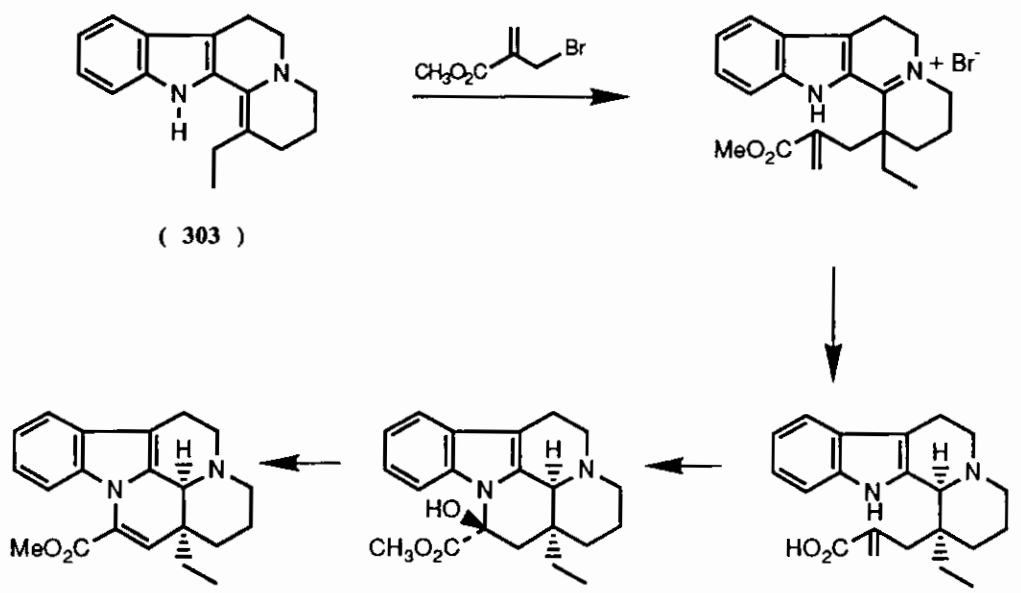
Similarly the intermediate lactam (313) for the preparation of (+) vincamine has been synthesised[70] starting from (-) - tryptophan. Alkylation of the iminium perchlorate (316) with diethyl methylene malonate in the presence of a catalytic amount of $KOBu^t$ gave the adduct (317). This was hydrolysed to give the salt (318), which was heated to 160 - 170 °C in decalin to produce the monocarboxylic acid (319). Catalytic hydrogenation of (319) in dimethylformamide and treatment of the epimeric acids (320a,b) by phosphoryl chloride furnished after intramolecular acylation the cis (313) and trans (322) lactams. The former compound can be converted by known procedures into (+) - vincamine and its derivatives (Scheme 42).

The enamine (303) has also been used by Husson and co - workers[71] in their synthesis of vincamine (278a) and apovincamine (298a) (Scheme 43). Alkylation of the enamine (303), previously prepared by Wenkert[67], with methyl α - bromomethyl - acrylate produced the iminium salt. Reduction with sodium borohydride and then oxidation gave the keto - ester which was converted spontaneously into vincamine (278a). Dehydration of the latter afforded apovincamine (298a).



(316) (317) (318) R = COOH (319) R = H (320a, b) (313) H, α (322) H, β

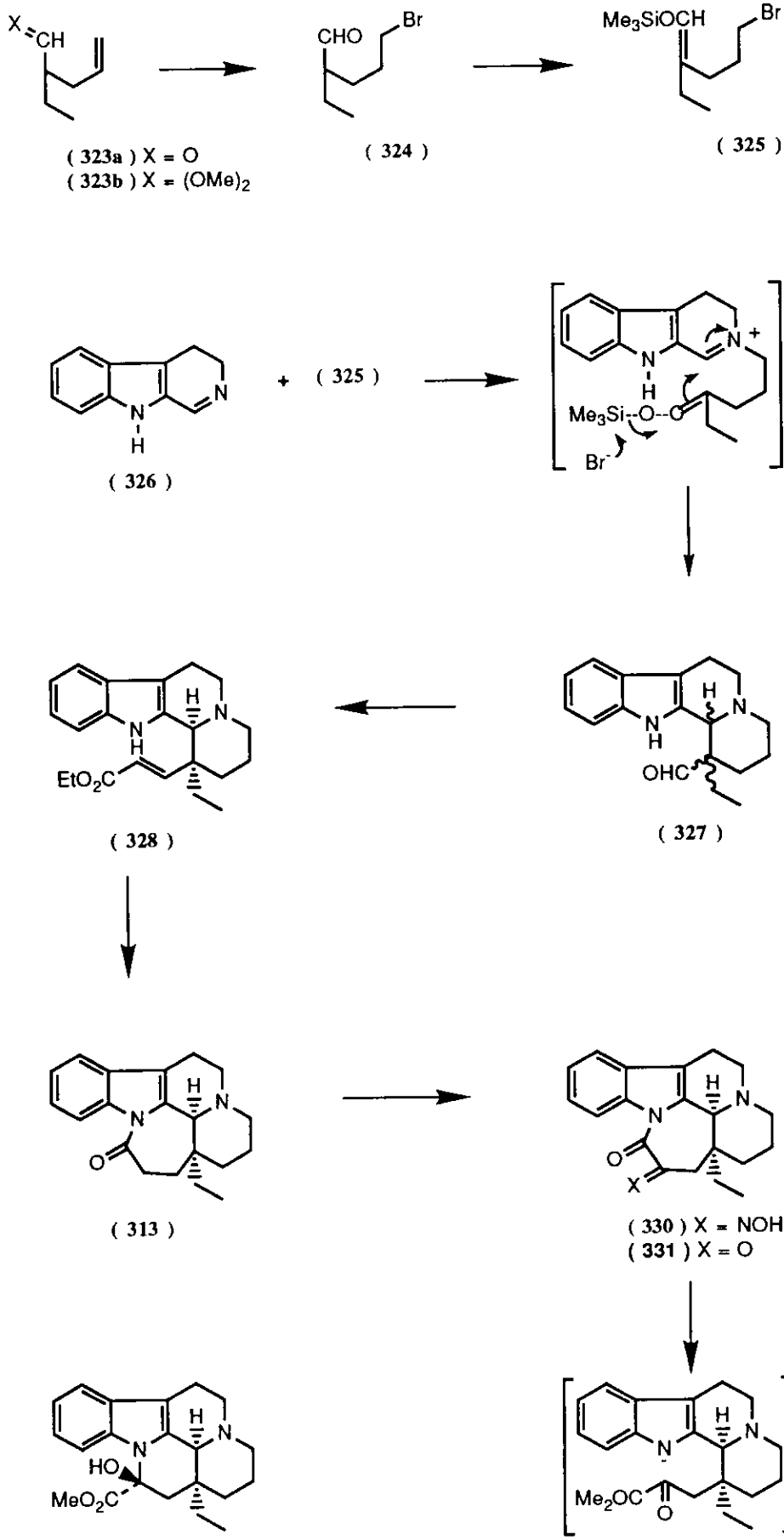
Scheme 42



(303) (298a) (278a)

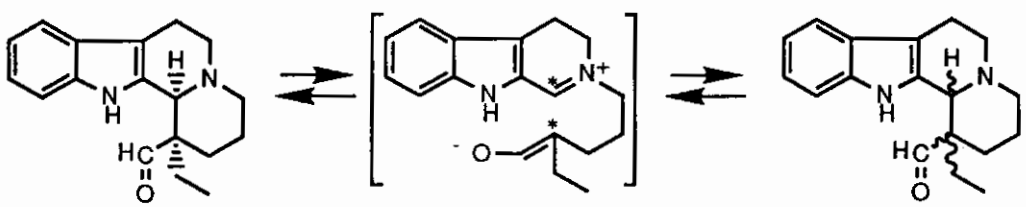
Scheme 43

Optically pure natural vincamine has been synthesized by Oppolzer[72] (Scheme 44) starting from the ethylpentanal (323) and proceeding *via* an aminoaldehyde (327) which was prepared by an ingenious new modification of the Mannich reaction.


X=CH
CHO
Br
Me3SiOCH
Br
(323a) X = O
(323b) X = (OMe)2
(324)
(325)
(326)
+ (325)
Me3Si
O
Br-
EtO2C
OHC
(328)
(327)
(313)
(330) X = NOH
(331) X = O
HO
MeO2C
Me2OC
(278a)

Scheme 44

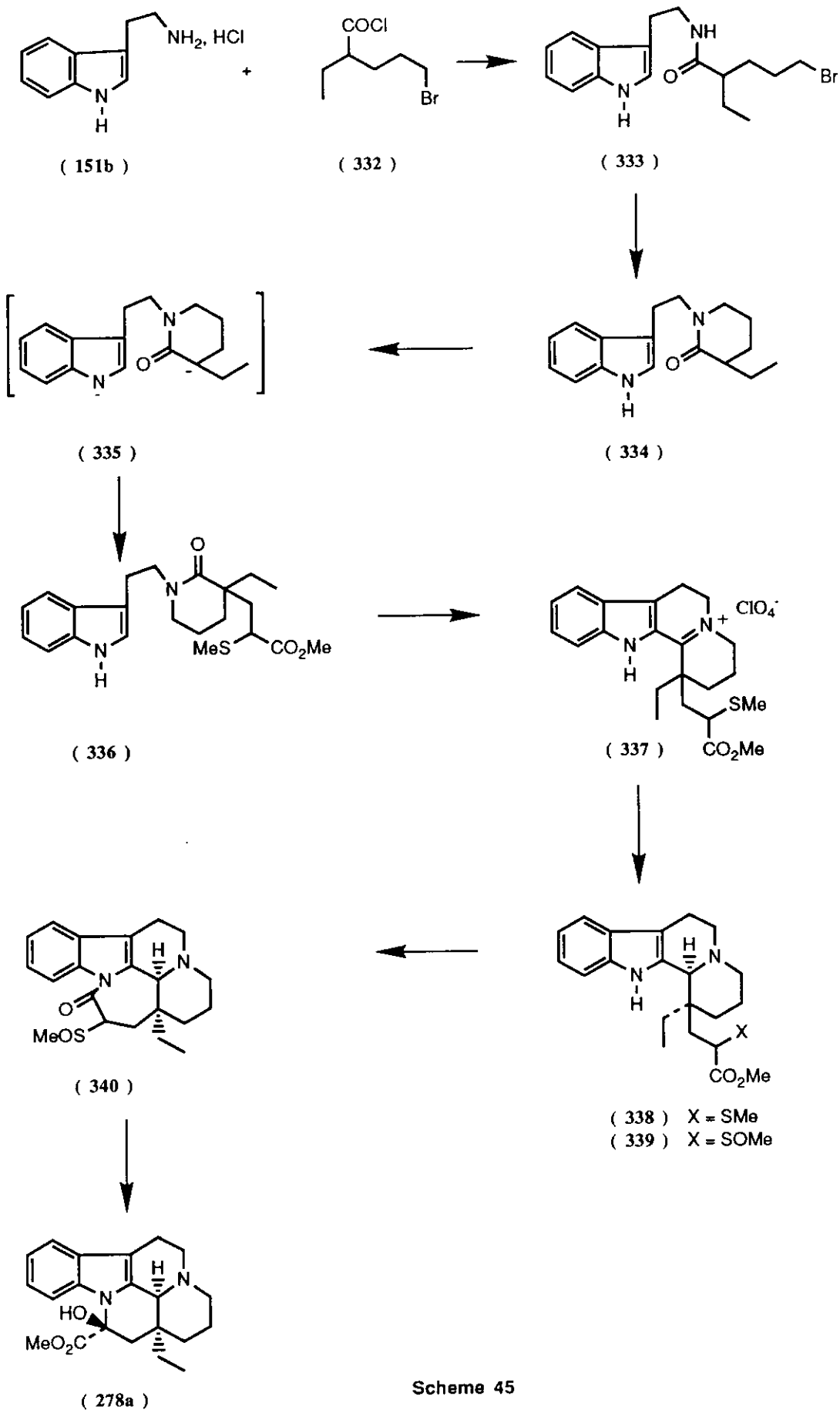
Protection of the carbonyl group, hydroboration of the olefinic bond in (323b), bromination of the intermediate organoborane and hydrolysis of the acetal furnished the bromoaldehyde (324). This was converted into the silyl enol ether using chlorotrimethylsilane in presence of ethyldiisopropylamine and then reacted with dihydro - β - carboline[73] (326) to give a mixture of the cis - trans isomers of the tetracyclic aldehyde (327) *via* the intermediate salt which underwent an intramolecular Mannich reaction involving cleavage of the Si - O bond and formation of the C - C bond. Separation of the cis racemate followed by resolution gives the desired stereoisomer. Re-equilibration of the unwanted cis enantiomer and the trans racemate gives more cis racemate, from which more of the desired enantiomer can be obtained



(327a) (327b)

by resolution. Conversion of (327a) into the lactam intermediate (313) was accomplished using the Horner reaction (triethyl phosphonoacetate / sodium hydride) in dimethylformamide followed by catalytic hydrogenation of (328). Treatment of the resulting saturated ester with sodium hexamethyldisilazane gave the required lactam (313). α - Nitrosation of (313) with amyl nitrite gave the oxime (330), which was cleaved to the α - ketolactam (331) with acidic formaldehyde. Finally methanolysis of the latter with sodium methoxide in methanol afforded natural vincamine (278a).

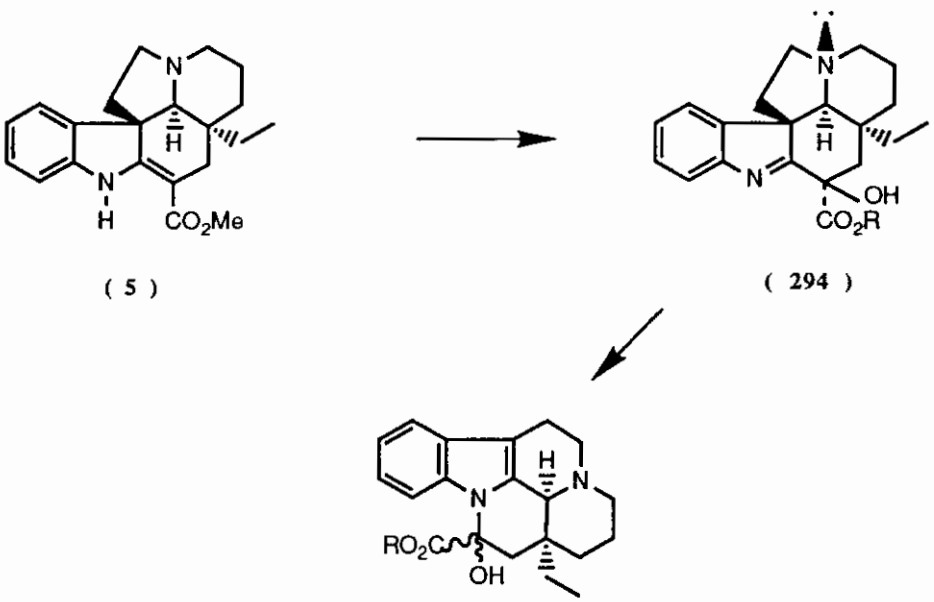
An interesting approach by Schlessinger[74] and co - workers (Scheme 45) involves the use of the tricyclic lactam (334), which was prepared from tryptamine


NH2, HCl
COCl
Br
NH
O
Br
N
H
(151b)
(332)
(333)
(334)
(335)
(336)
MeS
CO2Me
ClO4-
SMe
CO2Me
(337)
(338) X = SMe
(339) X = SOMe
MeOS
(340)
HO
MeO2C
(278a)

Scheme 45

hydrochloride and 5 - bromo - 2 - ethylvaleroyl chloride (332) *via* the amide (333). Cyclisation of (333) occurred rapidly when treated with potassium hydride in THF. The lactam (334) was then treated with 2 equiv. of lithium diisopropylamide to give the dianion (335). Reaction of (335) with 2 - methylthioacrylate gave the lactam (336) as an epimeric mixture, in almost quantitative yield. Cyclisation of the lactam (336) with phosphorus oxychloride gave the immonium perchlorate (337). Imine reduction of the salt (337) with lithium tri - tert - butoxyaluminium hydride led to the desired cis tetracyclic base (338). Oxidation of (338) with m - chloroperbenzoic acid gave the sulfoxide (339). Treatment with 2 equivalents of sodium hydride in THF produced the lactam sulfoxide (340). Reaction of (340) with acetyl chloride (2.2 equiv.) followed by treatement with sodium methoxide (7 equiv.) in methanol gave rise directly to vincamine (278a) (Scheme 45).

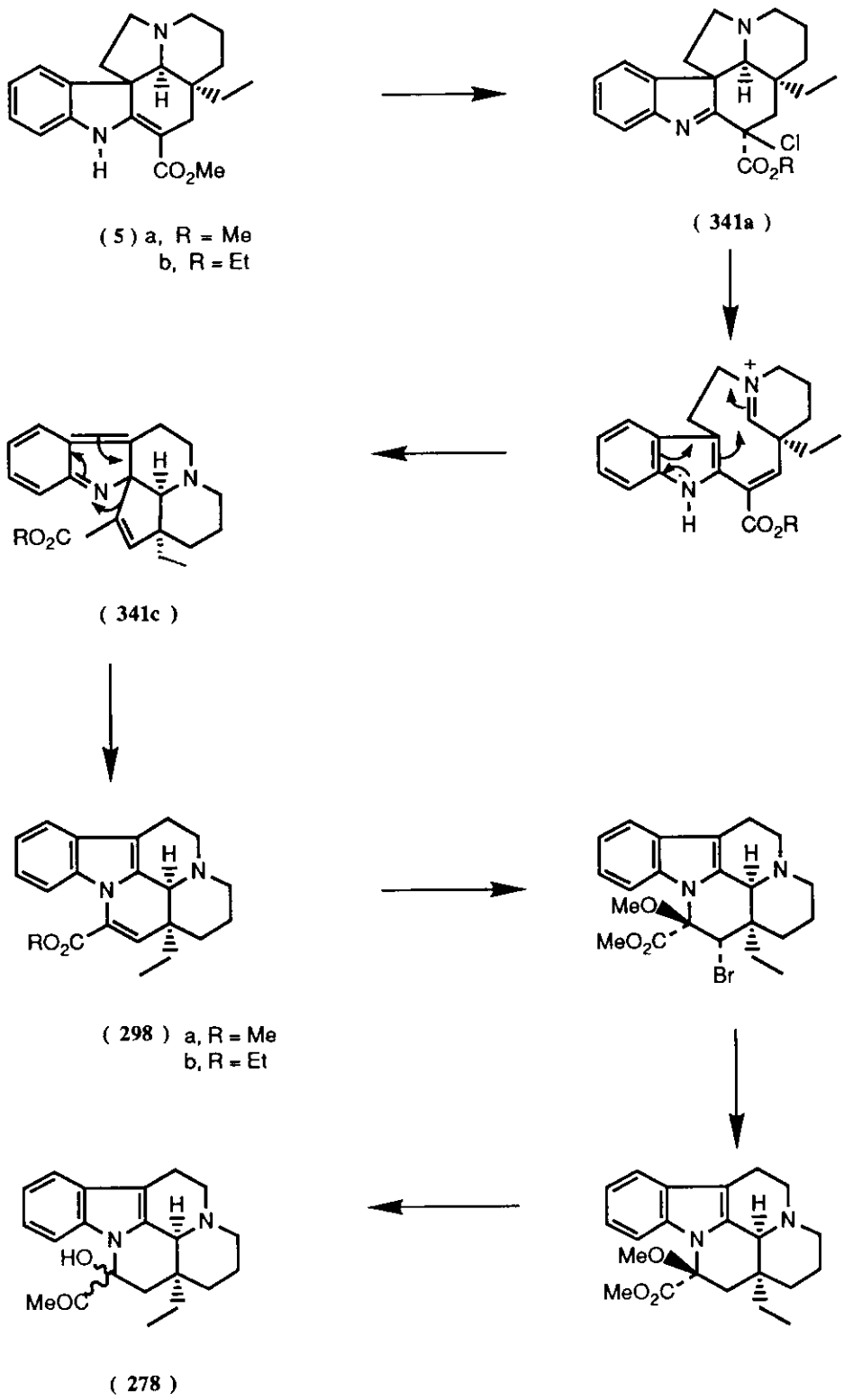
A more efficient ' one - pot ' method of converting vincadifformine (5) into vincamine (278a) by ozonization was developed recently by Palsimano et al[75]. This milder oxidative method, which avoids the formation of the N - oxide, involves ozonisation in 0.87 N H_2SO_4 - MeOH (3 : 1) at 60 °C and gives 74% yield of vincamine (278a) and 16 - epivincamine (278b). The key intermediate, 16 - hydroxy - 1, 2 - dehydrovincadifformine (294), can be isolated if the reaction is carried out at 20 °C (Scheme 46).



(5) (294) (278)

Scheme 46

It was also reported[76a,b] that apovincamine (298a) or vinpocetine (298b) is synthesized in a ' one - pot ' process from vincadifformine (5) *via* the 16 chloroindolenine (341a) by heating in trifluoroacetic or formic acid (Scheme 47). The chloroindolenine (341a) was obtained by reaction of (5) with N - chlorosuccinimide or calcium hypochlorite at room temperature. The conversion of the rearranged intermediate (341c) into the apovincamine skeleton is seen as a 1,5 - sigmatropic shift of C - 16 from carbon to nitrogen (Scheme 47). The partial synthesis of vincamine was then completed by an improved process for the overall hydration of apovincamine (298a). Bromination of (298a) in methanol gave a bromo - ether, which was hydrogenolysed to the **O** - methyl ether of vincaminic acid. Hydrolysis then gave a mixture of (+) - vincamine (278a) and 16 - epivincamine (278b).


N
H
N
H
CO2Me
(5) a, R = Me
b, R = Et
Cl
CO2R
(341a)
+
N
N
H
CO2R
H
N
N
RO2C
(341c)
H
N
N
RO2C
(298) a, R = Me
b, R = Et
MeO
MeO2C
Br
HO
MeOC
(278)

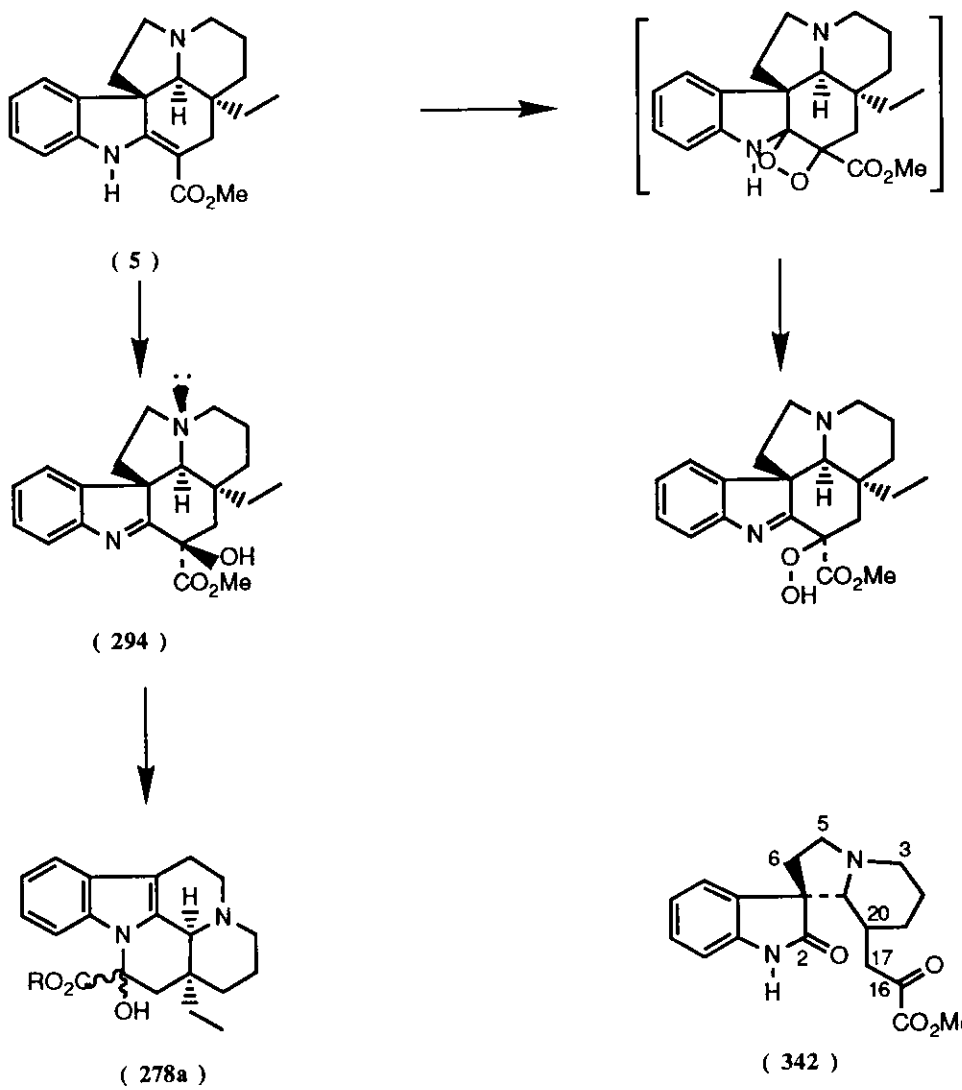
Scheme 47

More recently, Danieli et al[77]. performed a photo - oxygenation of (-) - vincadifformine in a methanolic solution with Rose Bengal in the presence of a reducing agent such as sodium thiosulphate, which gave 16 - hydroxyindolenine derivative (294). This was quantitatively converted into the (3 : 2) mixture of vincamine (278a) and its epimer 16 - epivincamine (278b) by simply heating in acetic acid (Scheme 48)

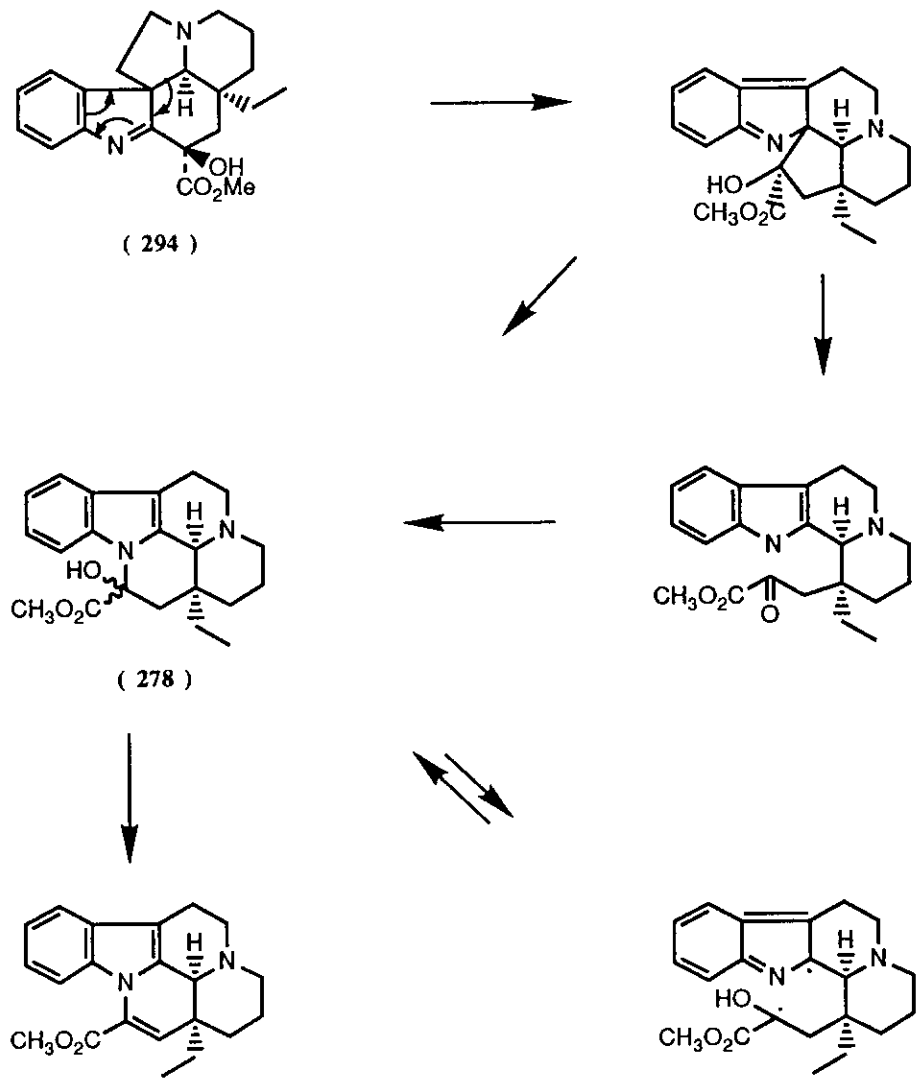
However, Lévy[78] reported that irradiation of a methanol solution of (5) in the presence of oxygen and the dyestuff Methylene Blue resulted in decomposition whereas vincadifformine hydrochloride, under the same condition, gave a mixture of vincamine and its 16 - epimer in 5.7%, the major product being the oxindole (342, 40%).

Subjected to thermolysis at 150 °C without solvent in evacuated sealed tubes[79], 16 - hydroxyindolenine (294) rearranged to vincamine (60%) and 16-epivincamine (278b). At higher temperature the two epimers gradually gave place to apovincamine (298a, 80%) as outlined in Scheme 49.

A new approach reported[80] by Rossey and Wenkert involves the use of enamine (303) as starting material for the synthesis of vincamine (278a) (Scheme 50) The required alkylation agent (343) previously prepared[81], was reacted with enamine (303) in presence of triethylamine to yield the salt (345). Reduction of (345) with zinc in acetic acid afforded mostly the (±) vincamine (278a), whereas with sodium borohydride (±) - 16 - epivincamine was obtained. Interaction of the hydrazone (346) obtained from the salt (344) with titanium chloride in hydrochloric acid solution gave a mixture of the desired (+) - vincamine and the corresponding 16 - amino derivative (347). The latter was transformed into vincamine by treatment with nitrous acid.



Scheme 48

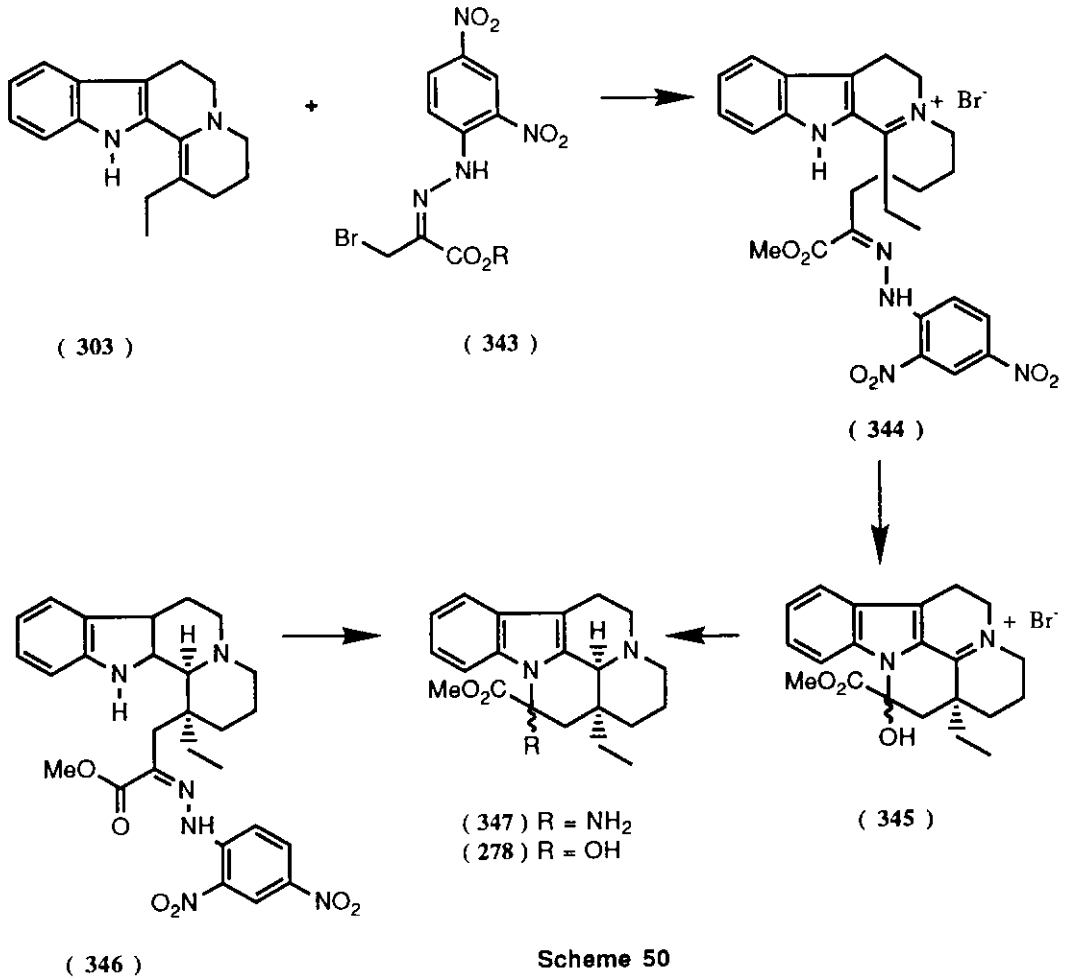


(294)

(278)

(298a)

Scheme 49

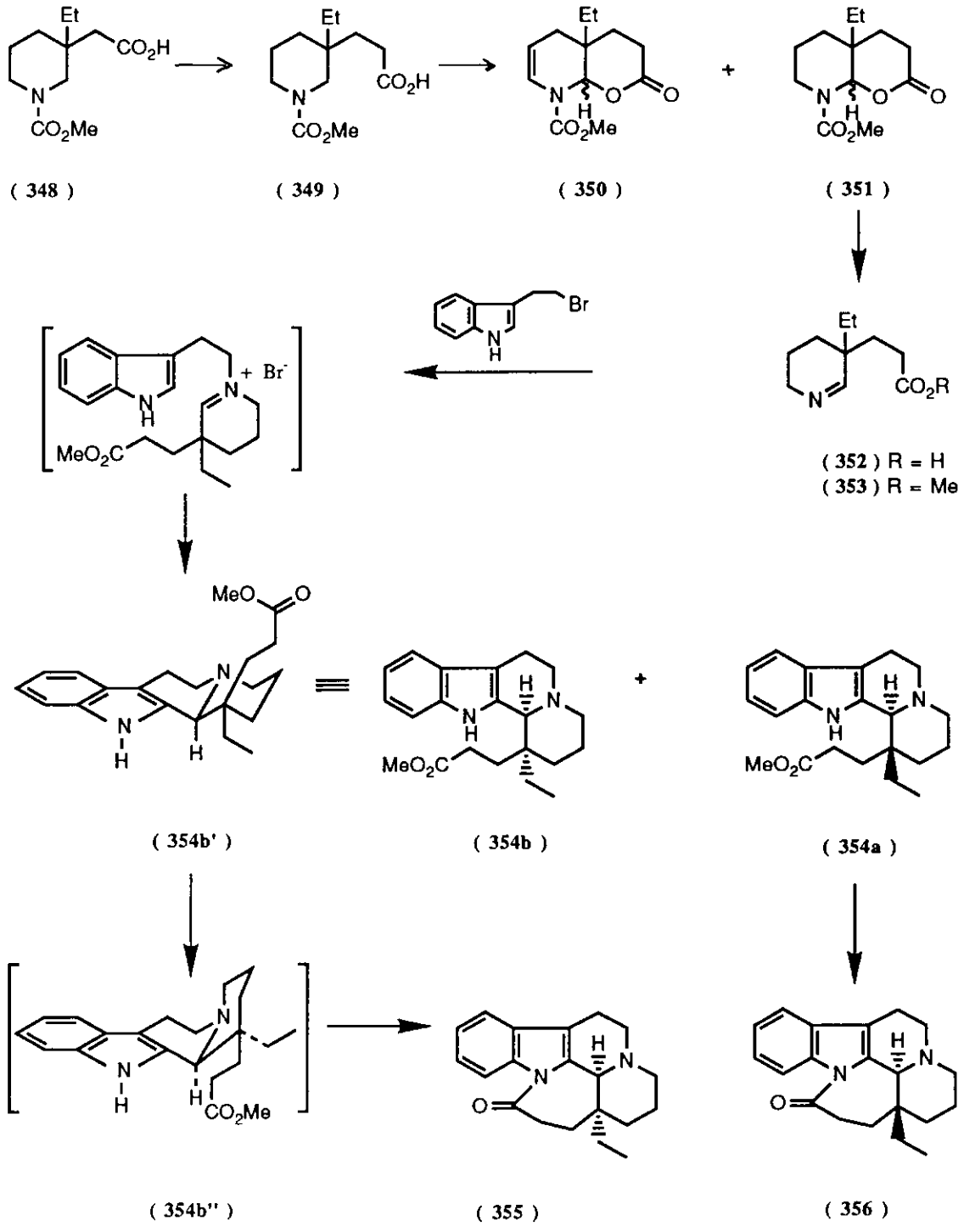

NO2
NO2
NH
N
Br
CO2R
+ Br-
MeO2C
O2N
NO2
MeO
O
OH
R
(303)
(343)
(344)
(345)
(346)
(347) R = NH2
(278) R = OH

Scheme 50

A different new route to the total synthesis of the alkaloid (278a) utilizing electrochemical oxidation was achieved by Ban and Irie[82] (Scheme 51). The compound (349), obtained previously from the acid (348) by Arndt - Eistert homologation, was oxidized by an electrochemical method and treated with formic acid to give the lactone (350). Catalytic hydrogenation of (350) in ethyl acetate afforded the lactone (351) in quantitative yield. Hydrolysis of (351) followed by esterification gave the methyl imino ester (353). Reaction of the intermediate (353) with tryptophyl bromide gave a mixture of isomers (354a,b). The isomer (354a) was readily cyclized to the product (356) whereas the epimeric ester (354b) did not cyclize under the same conditions. It could, however, be cyclized by the procedure of Oppolzer[72] to the product (355) *via* 354b" generated by ring inversion of the quinolizidine ring system from trans (354b') to cis (354b"). The lactam (355) can be converted into (+)vincamine (278a) following Oppolzer 's procedure[72].

In more recent work, an Indian group[83] explored a new route to the synthesis of Oppolzer 's aldehyde (327) in the synthesis of vincamine (278a), (see Scheme 52).

Condensation of aldehyde (357), available in 70% yield from diethyl α - ethylmalonate, with tryptamine (151) provided the secondary amine (358) in up to 75% yield. When heated, this compound was converted into lactam (359). Cyclisation of (359) with phosphorus oxychloride afforded iminium perchlorate (360), which was reduced with hydrogen in presence of palladium (Pd / C, Et_3N, methanol) to give exclusively the desired cis - isomer (361b). Sodium borohydride in methanol, however, gave a mixture of cis and trans - isomers (361a) and (361b) in the ratio of (1 : 4), but the yield of the required product (361b) could be optimized by conversion of the trans isomer into the cis - isomer by oxidation with mercuric acetate followed by reduction with either zinc / acetic acid or with catalytic



(348) (349) (350) (351)

(352) R = H
(353) R = Me

(354b') (354b) (354a)

(354b'') (355) (356)

Scheme 51

hydrogenation over Pd / C. This ester (361b) was reduced with lithium aluminium hydride and then oxidized using a modified Pfitzner - Moffat oxidation procedure[84] to give the aldehyde (327). The conversion of (327) into vincamine has already been reported by Oppolzer[72] (Scheme 52).

Finally, Lounasmaa and Jokela have repoted[85] a new ' one pot ' method from which the crucial vincamine intermediate (366) can be prepared (Scheme 53). Treatment of cyano compound[86] (363) with silver tetrafluoroborate in dichloromethane afforded the unstable BOC - protected enamine (364) which was reacted directly with methyl acrylate to give the intermediate salt (365). Acid cleavage permitted cyclisation, which led to the tetracyclic compounds (367) and (366). The conversion of (367) into (+) vincamine has been discussed earlier[61].

DISCUSSION

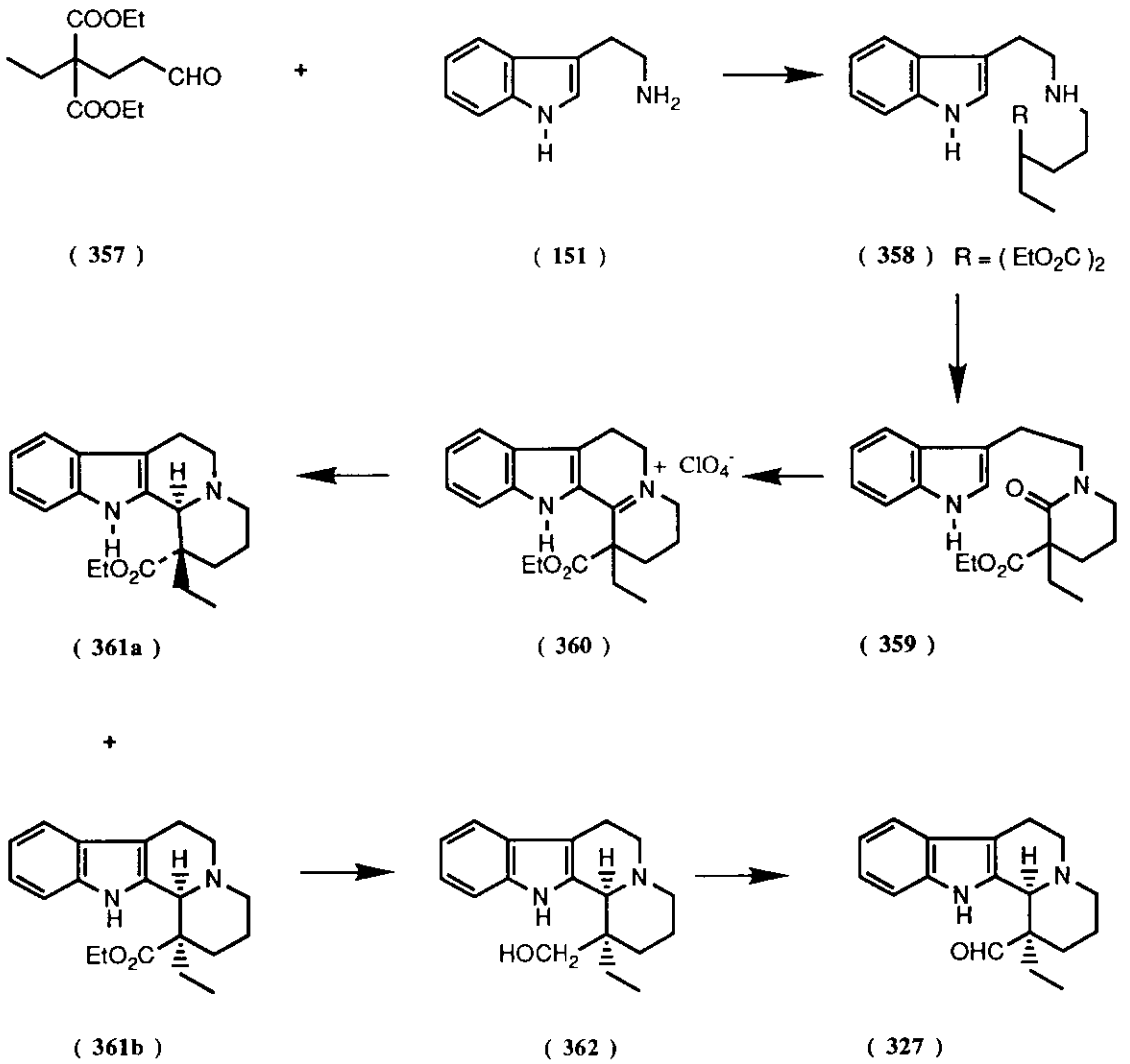
Introduction and summary

The major work described in this thesis is an attempt to synthesise alalakine (385) the heptacyclic alkaloid of the obscurinervine sub - group, which was first isolated from the seeds of *Aspidosperma album* R.Bent. (Apocynaceae), and characterised, by Potier et al[87]., who obtained a total of 25 alkaloids, of which fourteen were identified as known compounds. The name alalakine derives from ' alalaka ', the name given to the plant by the Wayapi tribe of French Guyana.

Like the two closely related alkaloids, 14, 15 - dihydro - obscurinervine (14) and obscurinervidine (13), from the bark of *Aspidosperma obscurinervium* Azembuja[88], alalakine contains, in addition to the aspidospermine ring system, a novel five - membered lactone ring attached to the aspidospermine skeleton. However, in alalakine this lactone ring is attached *via* C - 20 and C - 21, whereas in the obscurinervine group it is formed between position 20 and 17.

Two synthetic approaches to alalakine (385) were investigated. The first one involved the adaptation of the Kuehne reaction to the appropriate tetrahydro - β - carboline ester (378) with the known and readily synthesised chloroaldehyde (263) to give the diester (381), which can be selectively decarboxylated and then transformed into alalakine by reduction followed by an oxidative cyclisation (Scheme 54). The second approach is similar to that undertaken by Brennan[52] in his synthesis of obscurinervidine (13), from which it was hoped that by modifying the side chain, the five membered lactone ring at C - 20 and C - 21 could be obtained.

To this end, it was hoped that a synthesis of the less complex diethyl ester (267) from the readily available tryptamine hydrochloride (151, R^1,R^2 = H) would provide a model for an early investigation for the eventual synthesis of alalakine (385).



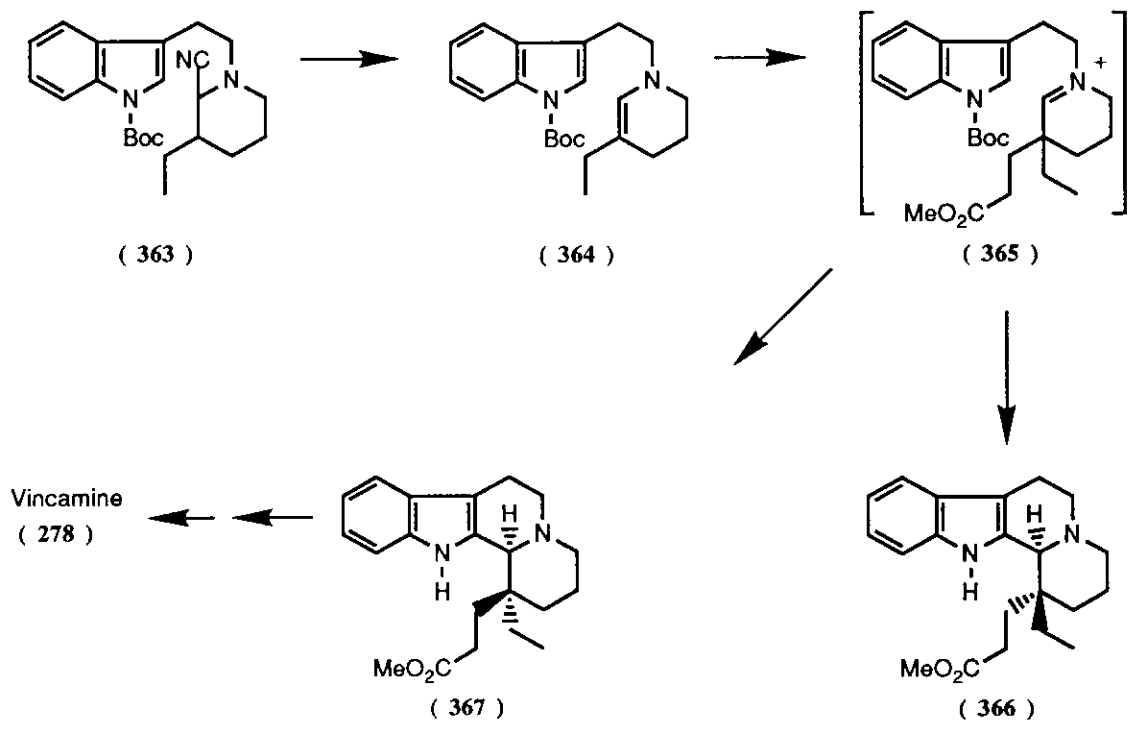
(357) (151) (358) R = (EtO_2C)$_2$

(359) (360) (361a)

+

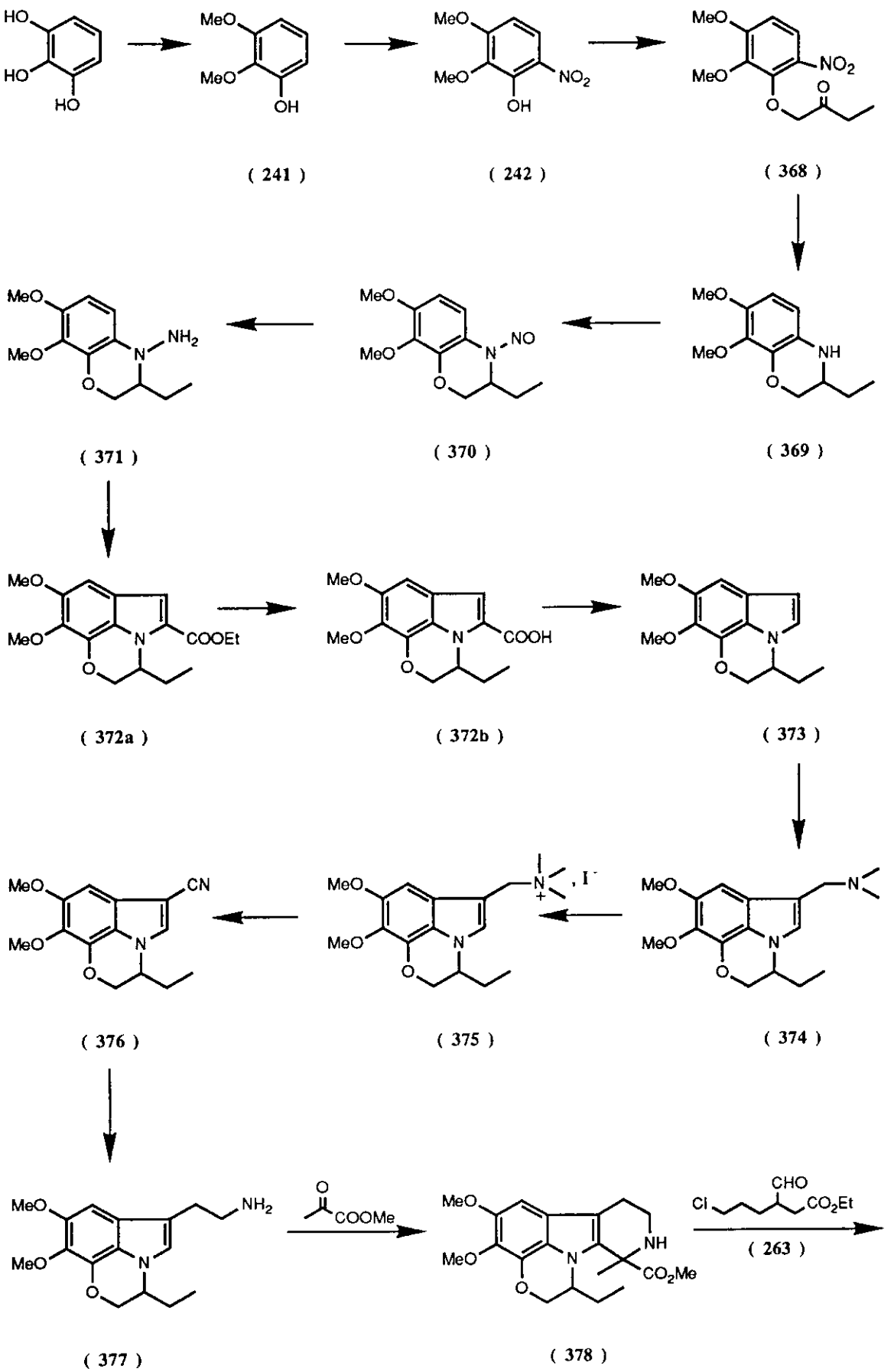
(361b) (362) (327)

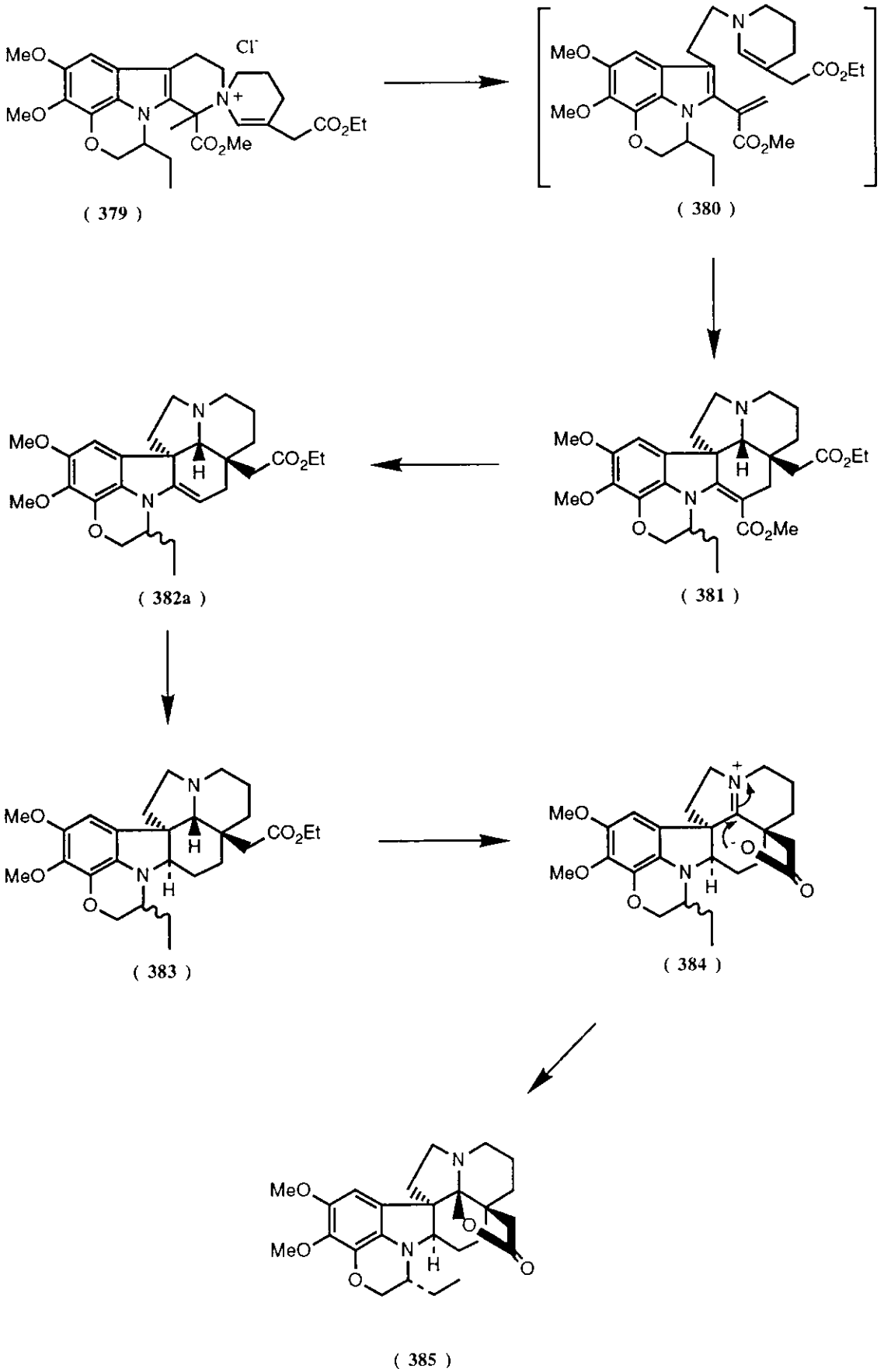
Scheme 52



(363) (364) (365) (367) (366)

Scheme 53


HO
HO
HO
MeO
MeO
OH
MeO
MeO
NO2
OH
MeO
MeO
NO2
O
O
(241)
(242)
(368)
MeO
MeO
NH
O
(369)
MeO
MeO
N
NO
O
(370)
MeO
MeO
N
NH2
O
(371)
MeO
MeO
N
COOEt
O
(372a)
MeO
MeO
N
COOH
O
(372b)
MeO
MeO
N
O
(373)
MeO
MeO
N
O
(374)
MeO
MeO
N
+
I-
O
(375)
MeO
MeO
N
CN
O
(376)
MeO
MeO
N
NH2
O
(377)
O
COOMe
MeO
MeO
N
NH
CO2Me
O
(378)
CHO
Cl
CO2Et
(263)



Scheme 54

Accordingly, attempts were made to synthesise 2 - cyano - 19 - carbethoxy - 19 - demethyl - N_a - methylvincadifformine (412). However, the lactonisation was not achieved because of lack of material.

Alternatively, the pentacyclic diester (267) was also employed as an intermediate for the synthesis of 19 - carbethoxy - 19 - demethylvincamine (503) and the apovincamine derivative (504). (see Section 2.4.1).

The removal of the β - anilinoacrylate function in the diester (267) under mild basic hydrolysis produced the pentacyclic lactone (466), which was subjected to oxidation with m - chloroperbenzoic acid or mercuric acetate in order to generate an *Aspidosperma* skeleton such as the cimicine derivative (467); however, the reaction proceeded differently and gave 19 - carbethoxy - 19 - demethylrhazinilam (487).

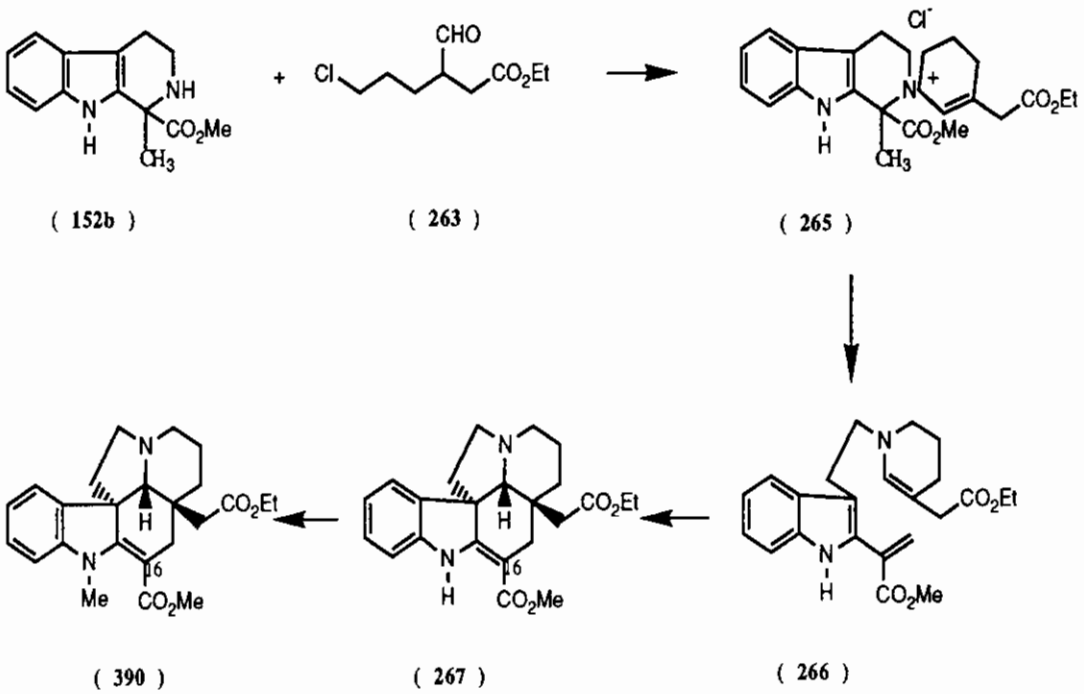
When the pentacyclic diester (267) was reacted with sodium cyanide in hexamethylphosphoramide (HMPA) at 90 °C, two products were obtained : the indolenine (270) and the α - nitrile (271), which was subsequently converted into the indolenine (270) with silver tetrafluoroborate. It was hoped that this indolenine would undergo a rearrangement over zinc / copper catalyst to give the amino - ester (456) which should spontaneously cyclise to form strempeliopine (447)[89]. However, with the zinc dust used (Aldrich), the major product obtained was the N - acetyl - 19 - carbethoxy - 19 - demethylaspidospermidine (462) together with 19 - carbethoxy - 19 - demethylaspidospermidine (463) and the N - ethyl derivative (461).

Finally, vincadifformine (5)[35], prepared from the readily available tryptamine hydrochloride, was converted into strictanine(507)[90], an alkaloid which was isolated

from the fruit of *Rhazya stricta*, a medicinal plant used in Pakistan for the treatment of various diseases.

2.1.1 Model study: Synthesis of N_a - methyl - 19 - carbethoxy - 19 - demethylvincadifformine (390).

The adaptation of Kuehne's elegant biomimetic synthesis to the tetrahydro - β - carboline ester (152b) with the known and readily synthesized chloroaldehydo - ester (263) produced the pentacyclic diester (267) *via* the secodine intermediate (266). Alkylation of the diester (267) with sodium hydride and methyl iodide in N, N - dimethylformamide gave a good yield of 19 - carbethoxy - 19 - demethyl - Na - methylvincadifformine (390) (Scheme 55).



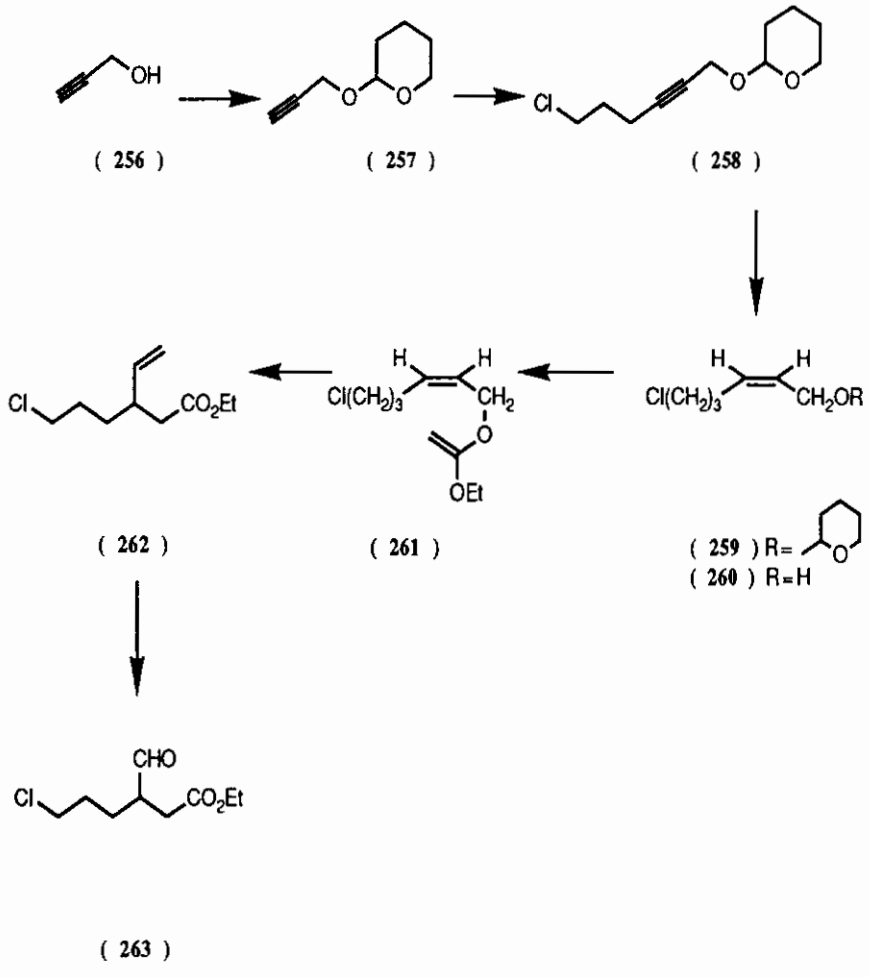
(152b) (263) (265)

(390) (267) (266)

Scheme 55

The required precursor, 1 - carbomethoxy - 1 - methyl - 1, 2, 3, 4 - tetrahydro - β - carboline (152b), for the above synthesis was readily prepared by condensation of tryptamine hydrochloride, derived from tryptophan,[91,92] with methyl pyruvate, which gave the α, α - substituted tetrahydro - β - carboline (152b) in 78.4% yield.

A method has been reported[57] which describes the preparation of ethyl 3 - formyl - 6 - chlorohexanoate (263) from the known 6 - chlorohex - 2 - yn - 1 - ol tetrahydropyranyl ether (258)[59,93]. Protection of the hydroxy - group of propargyl alcohol with dihydropyran, followed by alkylation with 1 - bromo - 3 - chloropropane using n-butyl lithium as base gave the chloroalkyne (258) in good yield. This substituted alkyne (258) was partially hydrogenated over the Lindlar catalyst to give the desired cis - alkene (259) which was not isolated, but instead hydrolysed to the parent unsaturated chloroalcohol (260) in the presence of p - toluenesulphonic acid. Claisen rearrangement occurred when this allyl alcohol (260) and triethyl orthoacetate in the presence of propionic acid as catalyst were heated overnight at 135 - 140 °C, and the product was the desired olefin (262). Ozonolysis in a stream of oxygen in methanol gave rise to the ozonide intermediate which was reduced with dimethyl sulphide to give the required unstable chloroaldehyde (263) in good yield (Scheme 56).



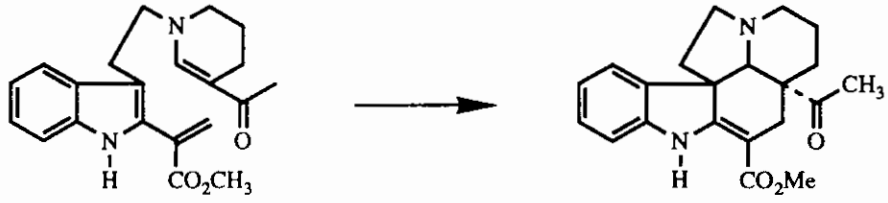
Scheme 56

Kuehne and co - worker, in many biomimetic preparations of *Aspidosperma* alkaloids, use either the indoloazepine (148) or a tetrahydro - β - carboline (152). Since the preparation of (152b) from the available tryptamine hydrochloride with methyl pyruvate is much easier than the preparation of the indoloazepine (148), the tetrahydro - β - carboline derivative (152b) was the preferred intermediate.

Acid - catalysed reaction of the chloroaldehydo - ester (263) with the tetrahydro - β - carboline (152b) in refluxing toluene, followed by treatment with DBU (1, 8 -

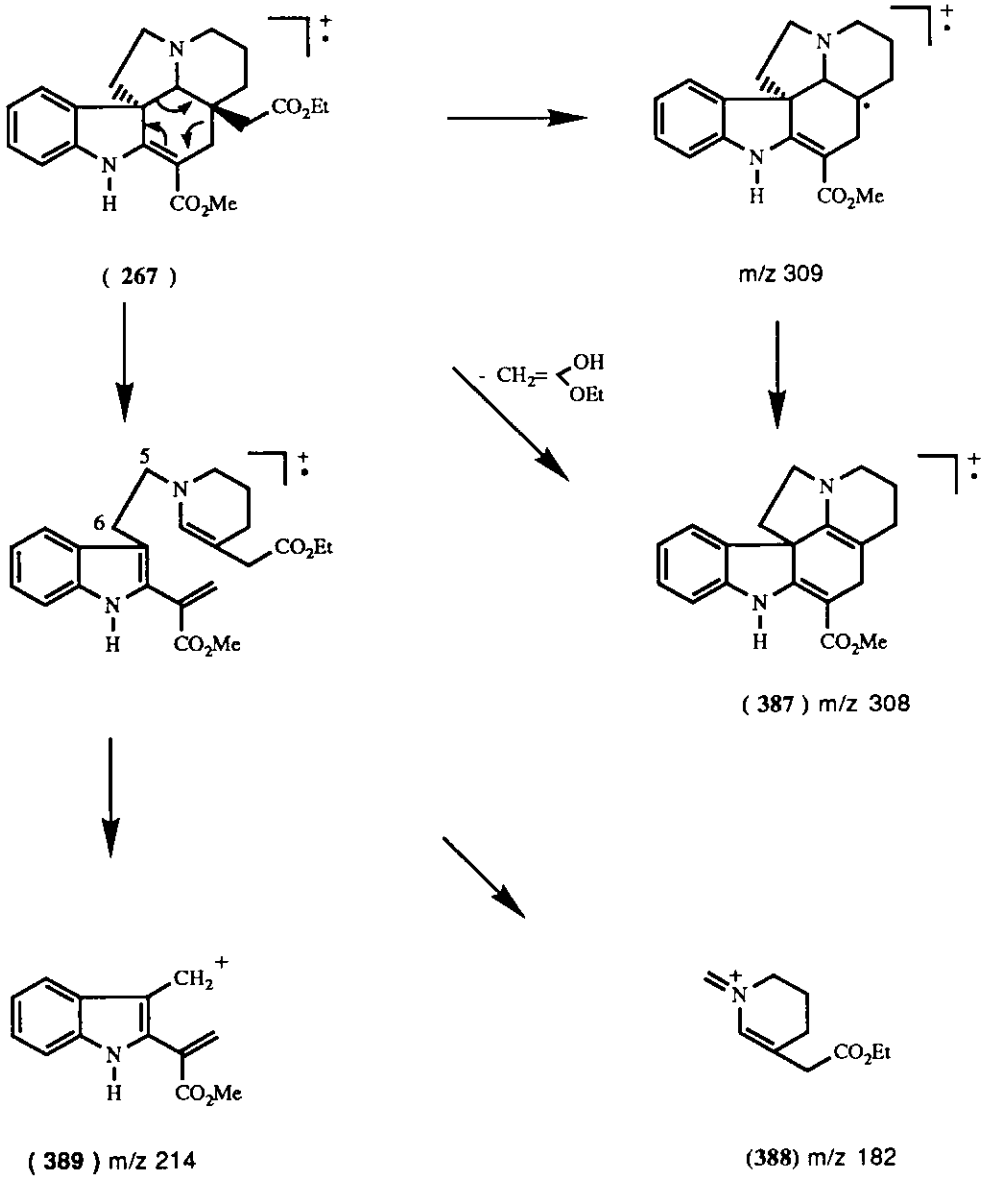
diazabicyclo - [5,4,0] undec - 7 - ene), provided after 128 h the pentacyclic β - anilinoacrylate compound (267) in an optimum yield of 40.5% (Scheme 55).

The mechanism of this reaction is supported by the previously cited isolation of the spiroenammonium salt (265), which underwent fragmentation to the secodine intermediate (266). Spontaneous biomimetic cyclisation of (266) then produces the pentacyclic β - anilinoacrylate compound (267). It should be stressed that, although this sequence is quite reasonable, the presumed secodine intermediate in this reaction has not been isolated or detected. However, Kuehne[94] has described the total synthesis of (±) - minovincine (18) from an isolated and thoroughly characterized 19 - oxosecodine intermediate (386).



(386) (18)

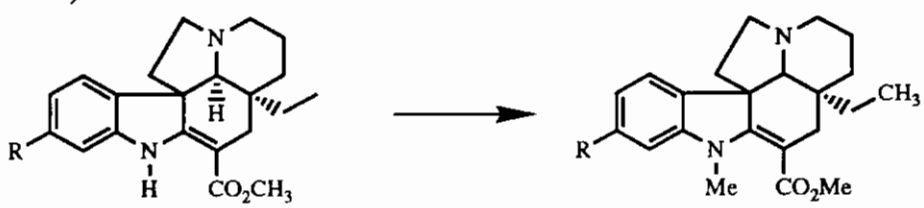
Compounds such as the diester (267), which have a β - anilinoacrylate group, have a very characteristic fragmentation pattern in the mass spectrometer (Scheme 57) The main fragmentation occurs by a type of retro - Diels - Alder fission of ring C. Further fragmentation by homolysis of its 5, 6 bond leads to the principal fragments (388) (m/z 182) and (389) (m/z 214). In the particular case of (267) the C - 20 substituent is lost from the molecular ion by a McLafferty rearrangement which gives rise to the radical cation (387) at (m/z 308). This diester also shows the typical anilinoacrylate u.v. absorption at λ_{max} 234, 296, and 324 nm and the infra-red absorption at 1605, 1675, and 1720 cm^{-1}.



Scheme 57

In order that the subsequent intermediate (390) could be used as an appropriate model in synthetic studies towards alalakine (385), the pentacyclic diester (267) was methylated according to the procedure of Kuehne for his synthesis of minovine[35] (17), using sodium hydride (50%) and methyl iodide in N, N - dimethylformamide at 20 °C, which gave a good yield of the N_a - methyl derivative (390). In contrast the alkylation of vincadifformine (5) in liquid ammonia[95] resulted in product mixtures containing variable amounts of starting material.

It was also reported[96] that the methylation of 11 - methoxyvincadifformine (391) with sodium hydride (99%) in dry tetrahydrofuran at ambient temperature gave a very moderate yield of the N_a - methyl - 11 - methoxyvincadifformine (392) (Scheme 58).

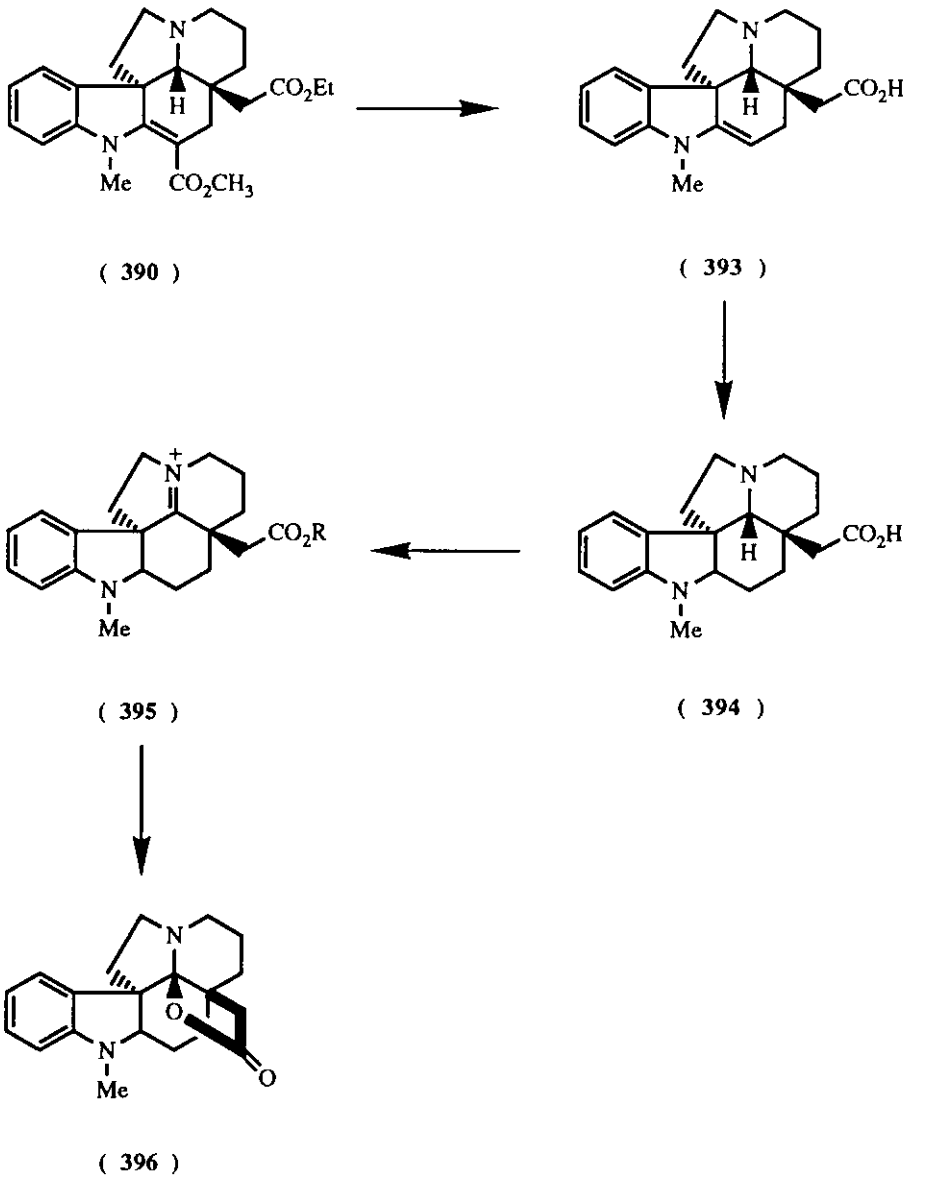


(5) R = H
(391)

(17) R = H
(392) R = OMe

Scheme 58

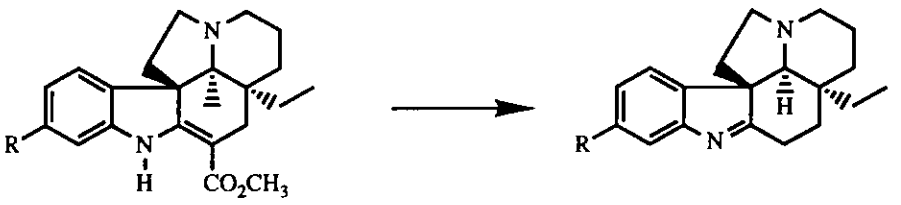
Subjecting the N_a - methyldiester (390) to hydrolysis conditions should produce the 2, 16 - dehydroaspidospermidine derivative (393), which could then be reduced to give the acid (394). Esterification and oxidation using mercuric acetate should produce the immonium salt (395) which might then undergo lactonisation to form the desired hexacyclic compound of the cimicine sub - group (396) (Scheme 59).



(390) (393) (394) (395) (396)

Scheme 59

Acid hydrolysis of the (-) - 11 - methoxyvincadifformine (391) with 5M hydrochloric acid on a water - bath followed by decarboxylation afforded a very good yield of amorphous (-) - 1, 2 - dehydro - 11 - methoxyaspidospermine[97] (399).



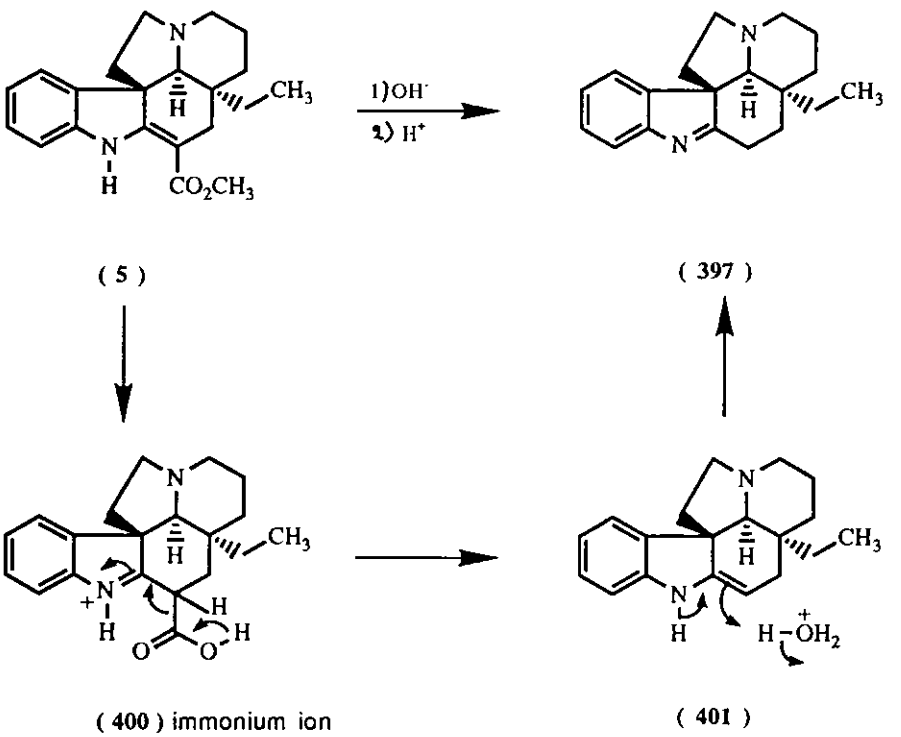
(5) R = H
(391) R = OMe

(397) R = H
(398) R = OMe
(399) R = H, $\Delta^{14,15}$

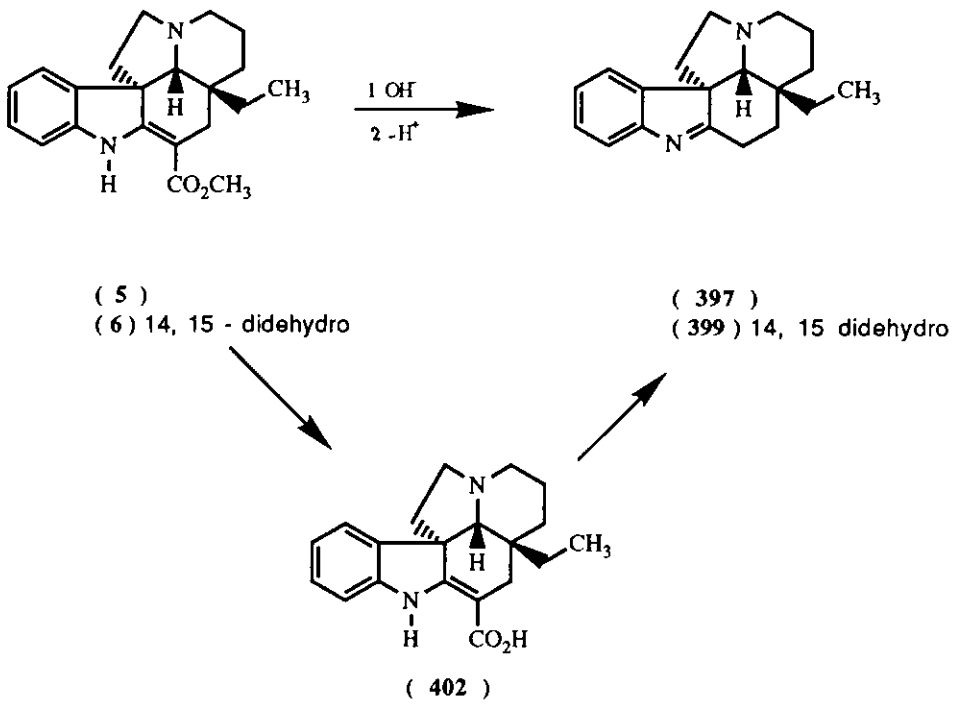
Similarly, vincadifformine under rather vigorous reaction conditions (i. e. 105 °C for 6 h) gave the indolenine[98a] (397).

Later Le Men[98b] found that vincadifformine (5) could be easily hydrolysed with 1.25M potassium hydroxide solution and then decarboxylated (1.25M HCl, Δ) to give dehydro - 1, 2 - aspidospermidine (397) *via* the enamine (401) (Scheme 60).

Similarly, Zsadon[99] and Otta reinvestigated the hydrolysis of vincadifformine (5) and tabersonine (6) and found that vigorous reaction conditions were not required; heating in 1M hydrochloric acid at reflux for 6 h was sufficient to effect hydrolysis and decarboxylation, giving excellent yields of the corresponding indolenines (397, 399). However, the hydrolysis of these alkaloids carried out under mild basic reaction conditions (i.e. 5% KOH in ethanol solution, at reflux for 1h) gave a 96% yield of vincadifformic acid (402), which was unstable in solution and underwent decarboxylation to give the indolenine (397) (Scheme 61).

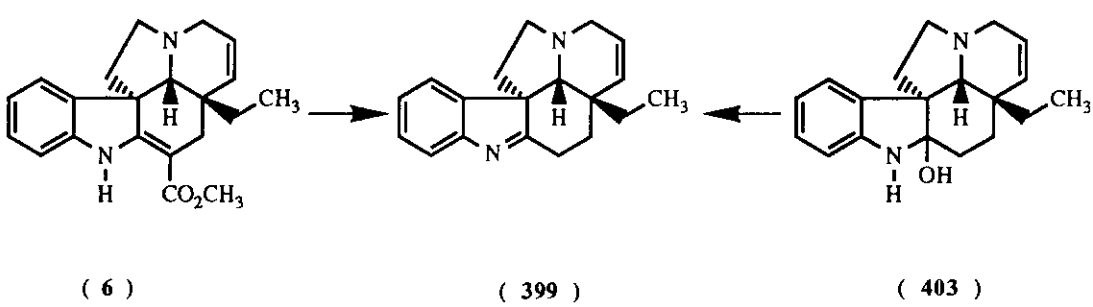


Scheme 60



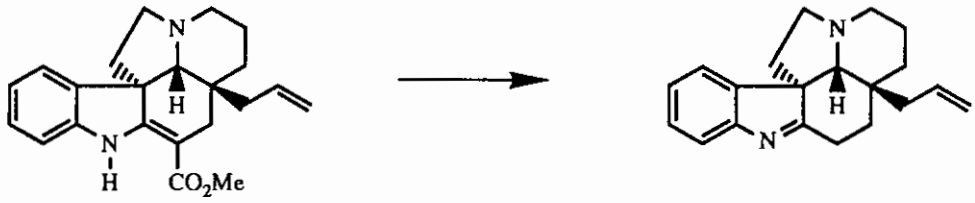
Scheme 61

Husson and co - workers[100] reported that the reaction of tabersonine (6) with 10M hydrochloric acid at reflux produced two products in a 1 : 2 ratio. The minor product was the expected indolenine (399); the major product was found to be the carbinolamine (403) which was converted back into (399) on treatment with p - toluenesulphonic acid in benzene.



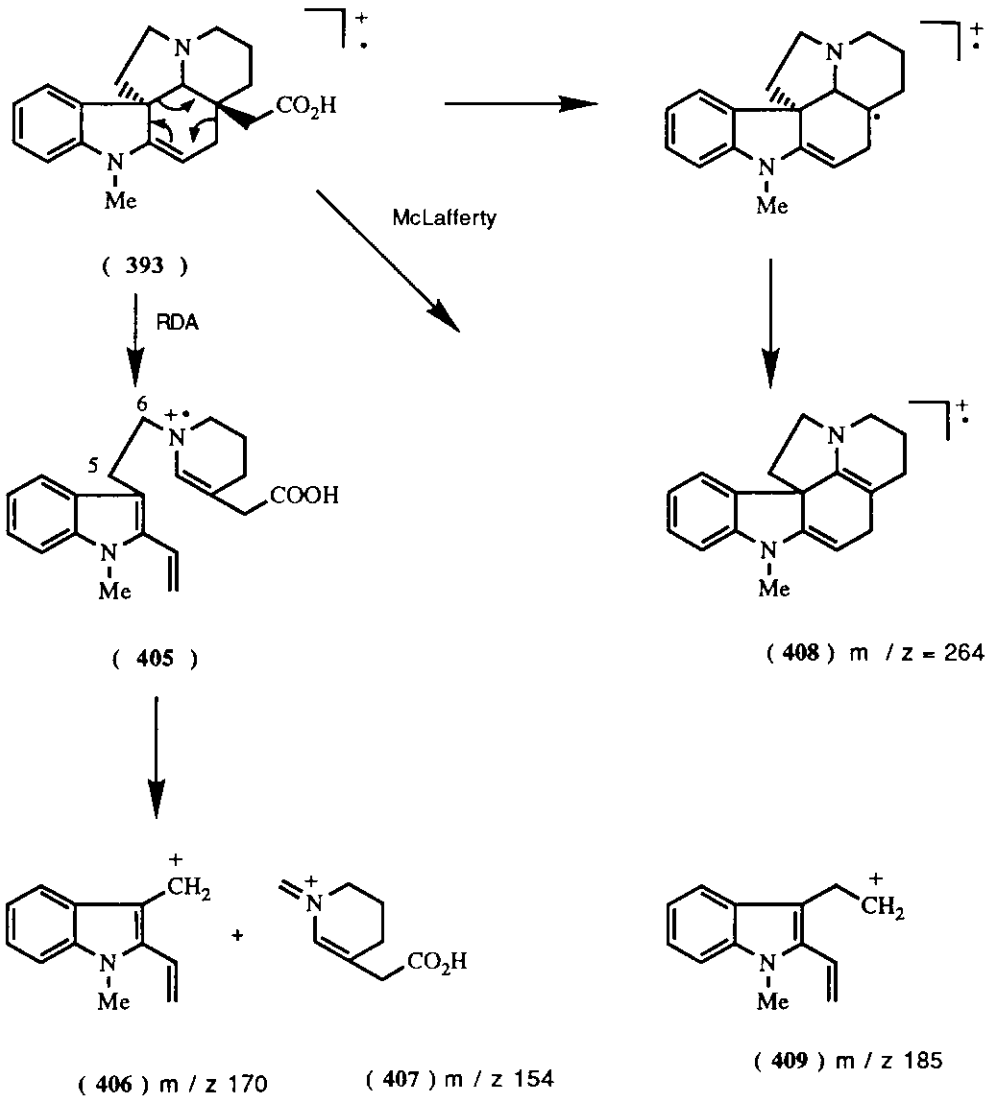
Scheme 62

It was also reported[101] by Hajicek and Trojanek that the transformation of 18 - methylenevincadifformine (180b) into the indolenine (404) could be achieved using p-toluenesulphonic acid.



(180b) 14, 15 dihydro (404)

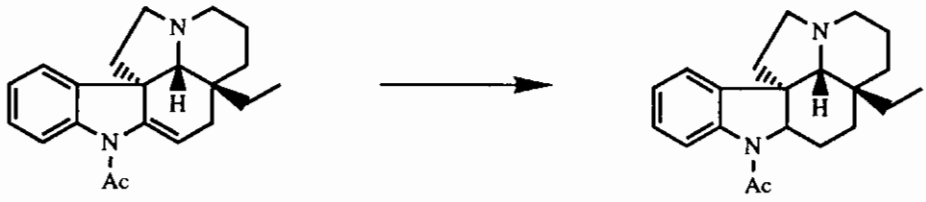
In our hands acidic hydrolysis of the N - methyl - diester (390) using 5M hydrochloric acid at steam bath for 5 h afforded after extraction with dichloromethane 19 - carboxy - 19 - demethyl - N - methyl - 2, 16 - dehydroaspidospermidine (393) which shows in the mass spectrum a molecular ion at m/z 324. A retro Diels - Alder fragmentation occurs in ring C to form the charged species (405), which then undergoes cleavage of the C, -5 , C - 6 bond to give ions (406) and (407) (less intense peak at m/z 154). Also the C - 20 substituent is lost from the molecular ion *via* a McLafferty rearrangement to give the ion (408) at m/z 264. Other characteristic peaks were seen at m/z 144 and m/z 130, which are due to fragments consisting of the indole system with one and two carbon atoms, respectively. In the i.r. spectum, absorptions are seen for the C - 18 carboxy group at 1720 cm^{-1}, and for the double bond at 1620cm^{-1}. The proton n.m.r. spectrum showed that no carbethoxy group was present.



Scheme 63

Hydrogenation of the carboxy alkaloid (393) in the presence of platinum (IV) oxide in methanol at room temperature and atmospheric pressure resulted in a low yield. The material was not fully characterised. However the molecular peak at m / z 326 was observed.

Ban and co - workers[102] had shown that catalytic hydrogenation of the N_a - acetyl - 2, 16 - dehydroaspidospermidine (410) with platin.um oxide gave only 35% of N - acetylaspidospermidine (411).



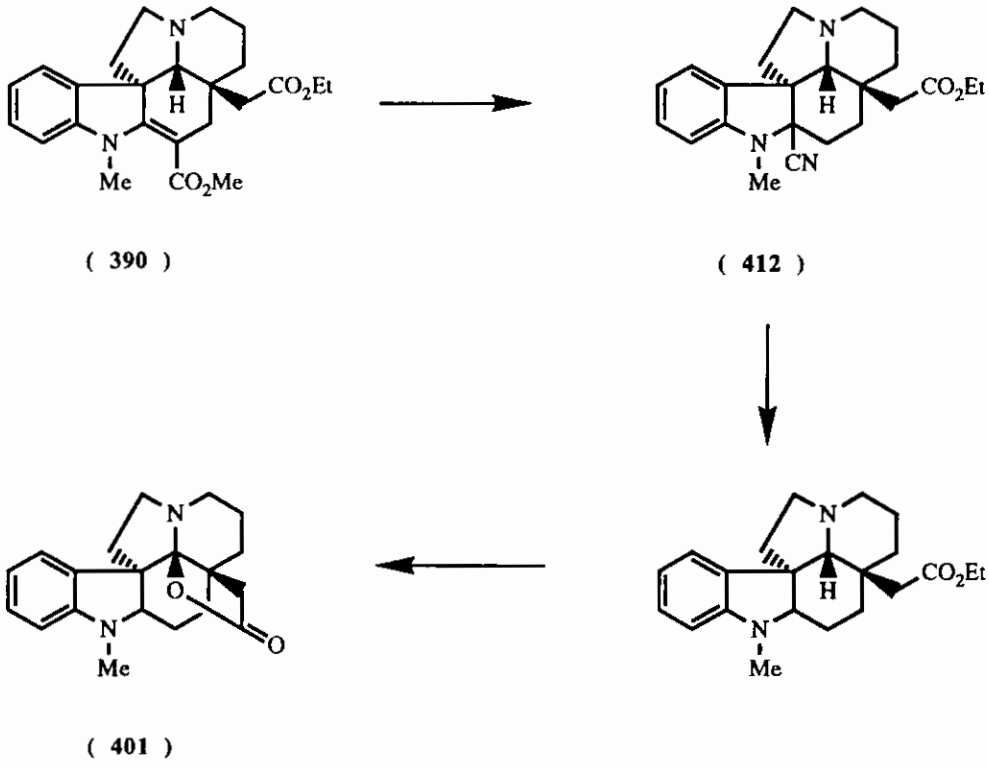
(410) (411)

As the reaction was not encouraging, Brennan 's method[57] was used. This method allowed the methyl ester group in the N - methyl diester (390) to be preferentially cleaved. Some preliminary investigations were carried out by Brennan on the diester (267), from which it appeared that sodium cyanide in hexamethylphosphoramide (HMPA) seemed to be the most promising reagent. There are several reports of the cyanide anion acting as a nucleophile in promoting S_N2 ester cleavages[103].

Therefore, the N_a - methyl pentacyclic diester (390) was reacted with sodium cyanide in hexamethylphosphoramide at 80 °C for 4.5 days under nitrogen. After chromatography on silica gel the desired product, 2 - cyano - 19 - carbethoxy - 19 - demethyl - N_a- methylaspidospermidine (412) was obtained in 41.7% yield (Scheme 64).

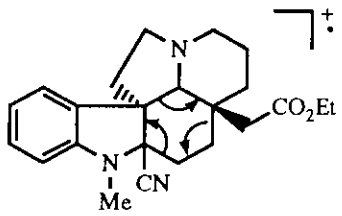
The u.v. spectrum of (412) showed maxima at λ_{max}(MeOH) 206, 248, and 294 nm which are almost identical with those given by the compound (271), i.e.

λ_{max} (EtOH) 204, 239, and 292 nm. In the i.r. spectrum of the cyano compound (412), the nitrile absorption was weak and seen at 2240 cm^{-1} and the C -18 carbonyl absorption was seen at 1720 cm^{-1}.

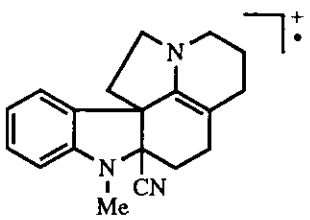


Scheme 64

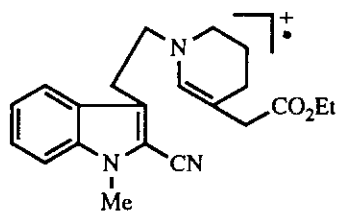
The molecular ion in the mass spectrum of (412) (Scheme 65) appeared at m/z 379 and confirmed the molecular formula $C_{23}H_{29}N_3O_2$. A comparison of the mass spectra of these two compounds (271) and (412) showed that the two were very similar excepting that some of the peaks in (412) differed from the corresponding peaks in (271) by 14 mass units owing to the N - methyl group. Its most intense peak at m/z 182 (415) resulted from a retro - Diels-Alder decomposition of ring C followed by homolysis of its C - 5, C - 6 bond. The C - 20 substituent is lost from the molecular ion via a McLafferty rearrangement to give the ion (416) at m/z 291,



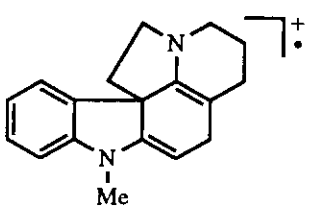
(**412**) m / z 379



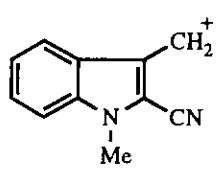
(**416**) m / z 291



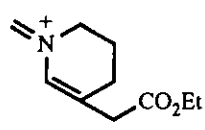
(**413**) m / z 351



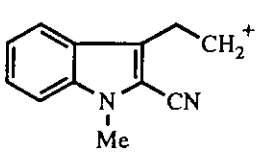
(**417**) m / z 264



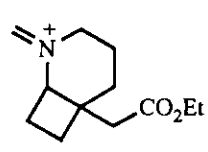
(**414**) m / z 169



(**388**) m / z = 182



(**418**) m / z 183



(**419**) m / z = 210

Scheme 65

which then expels HCN to give the ion (417). The ^{1}H n.m.r. spectrum of (412) revealed clearly certain structural features. The peak at 2.85 ppm corresponding to three protons could be assigned to the N - methyl group. The complex pattern at 7 ppm region corresponded to four aromatic protons. The quartet at 4.02 ppm corresponding to two protons and the triplet at 1.2 ppm corresponding to three protons confirmed the presence of the carbethoxy group.

Table 1 summarizes the ^{13}C n.m.r. chemical shifts for (267), (390), and (412). Twenty - three resonances could be seen for (412) with the nitrile carbon atom at 120.78 ppm and the N - Me carbon atom at 29.69 ppm.

However, at this stage the scarcity of the 2 - cyano - 19 - carbethoxy - 19 - demethyl - Na - methylaspidospermidine (412) meant that further investigations in this synthesis were not possible.

Table I: ^{13}C n.m.r. chemical shifts

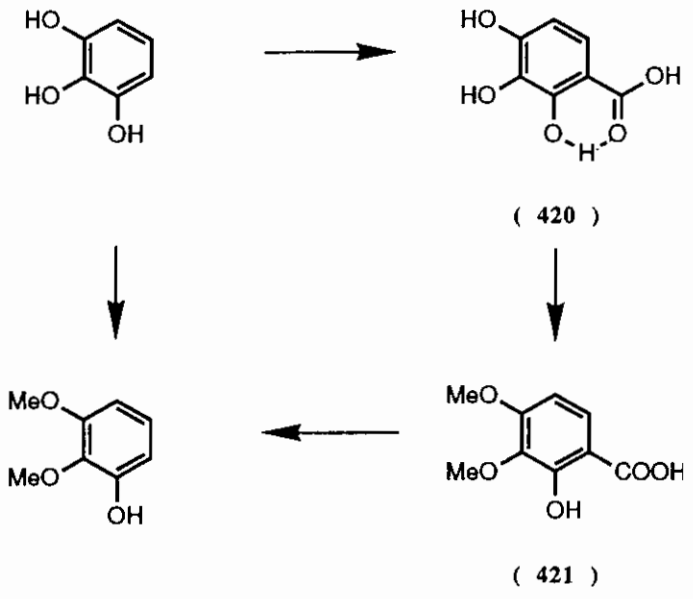
Carbone N°	diester (267)	N - methyl diester (390)	2 - cyano - N - methyl ester (412)
2	166.8	167.4	68.42
3	50.92	51.77	52.92
5	51.57	52.04	51.44
6	45.45	47.02	36.15
7	55.37	56.62	56.94
8	137.17	137.1	132.60
9	121.02	121.15	122.40
10	120.59	120.65	119.34
11	127.63	127.63	128.42
12	109.43	108.62	108.06
13	143.34	146.76	148.06
14	22.10	21.6	21.29
15	33.53	33.25	34.71
16	93.12	92.87	29.66
17	26.82	33	22.67
18	171.46	171.39	171.42
19	41.50	41.60	42.46
20	38.52	40.16	35.94
21	71.45	73.74	69.91
22	169.08	171	-------
$CO_2\underline{C}H_3$	50.92	50.87	-------
$CO_2\underline{C}H_2CH_3$	59.92	59.98	60.09
$CO_2CH_2\underline{C}H_3$	14.08	14.05	14.25
N - Me	-------	36.13	29.69
CN	-------	-------	120.78

2.1.2 Approach to the synthesis of alalakine: Biomimetic reaction

This approach had as its initial target the synthesis of the appropriately substituted tetrahydro - β - carboline derivative (378), which could be reacted with the readily synthesised aldehydo - ester (263) in a Kuehne - type cyclisation to give the hexacyclic diester (381) (Scheme 54). This ester possesses at C - 18 a carbethoxy group, which could eventually be transformed to give the corresponding lactone ring present in alalakine (385).

In order to have a convenient starting material for this investigation, the cheap and readily available pyrogallol was methylated according to the procedure of Bredereck[104], which is direct although the product purification is laborious. The desired 2, 3 - dimethoxyphenol (b.p. 129 - 134 °C / 15 mm Hg) was isolated in a moderate yield of 40% together with 2, 6 - dimethoxyphenol (b.p. 90 °C / 15 mm Hg), and pyrogallol 1 - methyl ether (b.p. 146 °C / 15 mm Hg) as by - products. However, pyrogallol trimethyl ether was eliminated at the first stage by ether extraction from the aqueous alkaline solution.

The second method[105] involves Kolbe's reaction on pyrogallol (i.e. K_2CO_3 / CO_2 / water / heat) which gives a low and variable yield of 2, 3, 4 - trihydroxybenzoic acid (420). The established strong hydrogen bonding which resulted between the carboxylic acid function and the ortho - hydroxy - group led to methylation of the hydroxy - groups at position 3 and 4 only. Distillation of the acid (421), under reduced pressure promoted decarboxylation to give 2, 3 - dimethoxyphenol in variable yield (Scheme 66).



(420)

(421)

Scheme 66

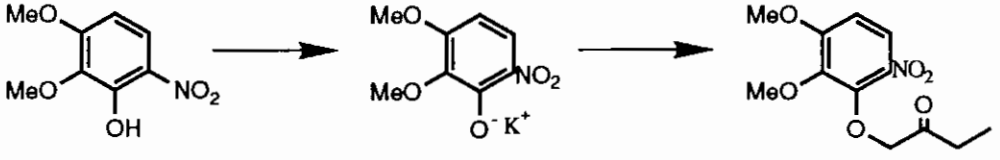
Nitration of 2, 3 - dimethoxyphenol at the 6 - position was carried out according to the method described by Smith and Baker[106]. However, using carefully controlled reaction conditions, the yield of the reaction was improved to an approximate 41% overall yield.

The potassium salt of (241b), obtained by reaction of 2, 3 - dimethoxy - 6 - nitrophenol with potassium hydroxide in methanol, was converted into the phenoxyketone (368) using 1 - bromo - 2 - butanone which could be obtained by two methods. The first of these was the reported procedure[107] which involves a reaction of dry methyl ethyl ketone with bromine. This reaction gave a mixture of two isomers from which 1 - bromo - 2 - butanone was separated by distillation using a spinning band fractionating column. This method gave mainly the undesired bromoethyl methyl ketone and a considerable decomposition of material, therefore another route was thought necessary for carrying out this preparation.

The second method involves the initial reaction of Matile and Montmollin[108]. Reaction of 1 - butene with hypobromous acid gave 1 - bromo - 2 - butanol as

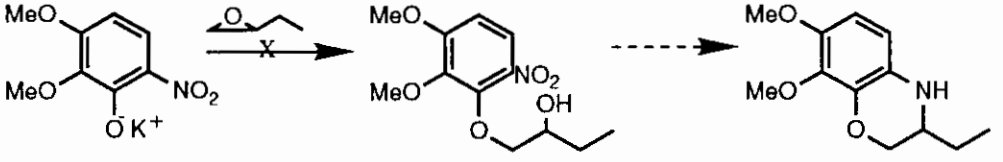
a colourless oil (b.p. 60 °C / 12 mm Hg). Oxidation of the secondary alcohol function with potassium dichromate[109] in dilute sulphuric acid gave a satisfactory yield of 1 - bromo - 2 - butanone (79%). These ketones do not normally undergo extensive further oxidation under the reaction condition.

Reaction of 1 - bromo - 2 - butanone in excess with the potassium salt of 2, 3 - dimethoxy - 6 - nitrophenol (241) in refluxing dry methyl ethyl ketone produced 1 - (2, 3 - dimethoxy - 6 - nitrophenoxy) - butan - 2 - one (368) in 71% yield, with a small recovery of 2, 3 - dimethoxy - 6 - nitrophenol (241). Alternative solvents (acetone or dioxane) were tried as were various reaction periods to improve the yield but these were not successful.



(241) (368)

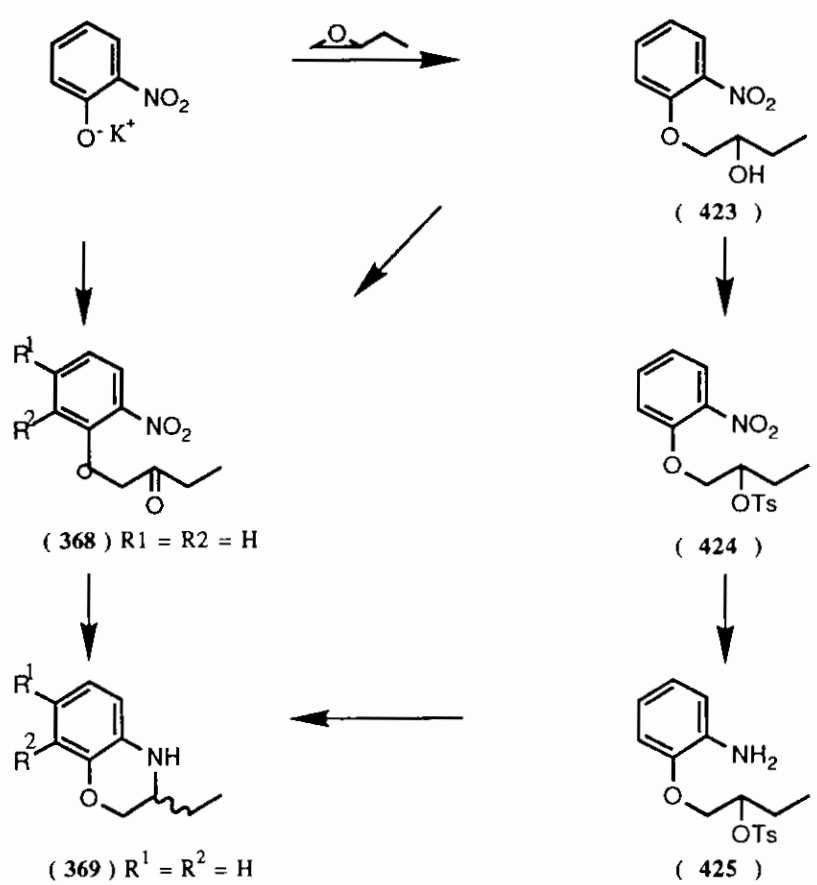
Meanwhile, attempts to prepare 7, 8 - dimethoxy - 3, 4 - dihydro - 2H - 1, 4 - benzoxazine (369) from condensation of the 2, 3 - dimethoxy - 6 - nitrophenoxy compound with butene oxide failed and all the starting material was recovered after several attempts at various temperatures and various reaction periods.



(369)

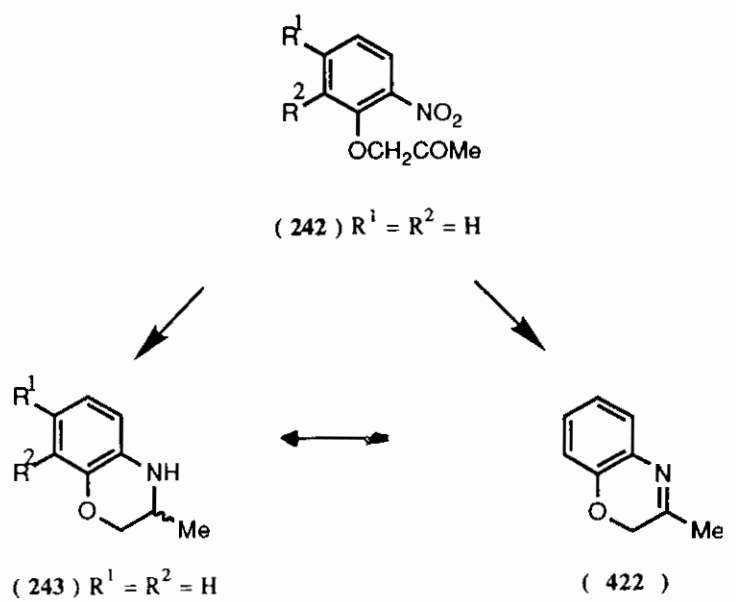
This contrasts with the report that phenoxides undergo nucleophilic attack on oxiranes at the less substituted carbon atom, and with Brennan's observation[110]

that reaction of potassium o - nitrophenoxide with butene oxide produced the unstable o - nitrophenoxy alcohol (423) in low yield (34%), together with much unreacted material. This compound (423) was then reacted with p - toluenesulphonyl chloride in pyridine to give a good yield of the corresponding tosylate (424). Catalytic hydrogenation over palladium on carbon catalyst (10 atm / 60 °C) of the nitro group in (424) gave the desired amino compound (425) in good yield. This was cyclised by heating in DMF to give 1, 4 - benzoxazine (369, $R^1 = R^2 = H$) in moderate yield. Alternatively the o - nitrophenoxy alcohol (423) was oxidised, using pyridinium chlorochromate, which gave the phenoxy ketone (368, $R^1 = R^2 = H$) in unoptimised yield of 33%; hydrogenation of (368, $R^1 = R^2 = H$) then gave (369, $R^1 = R^2 = H$) in 85% yield (Scheme 67).



Scheme 67

Reaction involving 1 - bromo - 2 - butanone or chloroacetone has been reported by Saxton and co - workers[110] in preliminary investigations towards the synthesis of model compounds lacking the two aromatic methoxy groups. In their work the nitrophenoxybutanone (242) was converted into the 1, 4 - benzoxazine system (243) by medium pressure (30 atm) hydrogenation over 10% palladium on carbon catalyst. An alternative method[111] involved reduction of the nitro - group in (242) using iron in hydrochloric acid; this gave the imine (422) which could then be reduced further to give the desired 1, 4 benzoxazine (243). Since in the first method both reduction steps were done simultaneously, it was the preferred procedure (Scheme 68).



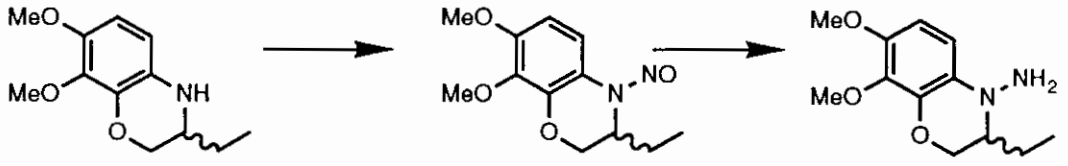
(242) $R^1 = R^2 = H$

(243) $R^1 = R^2 = H$ (422)

Scheme 68

When treated with sodium nitrite in diluted hydrochloric acid, the benzoxazine derivative (369) was converted into the N - nitroso derivative (370) in almost quantitative yield. Reduction of (370) with lithium aluminium hydride gave (371). As reported in the literature[113], reduction of the nitroso derivative (244) was more successful with lithium aluminium hydride in ether than with zinc and acetic acid[92],

which resulted in considerable N - N - bond cleavage producing a mixture of the required N - amino derivative (245) and the parent 1, 4 - benzoxazine compound (243).

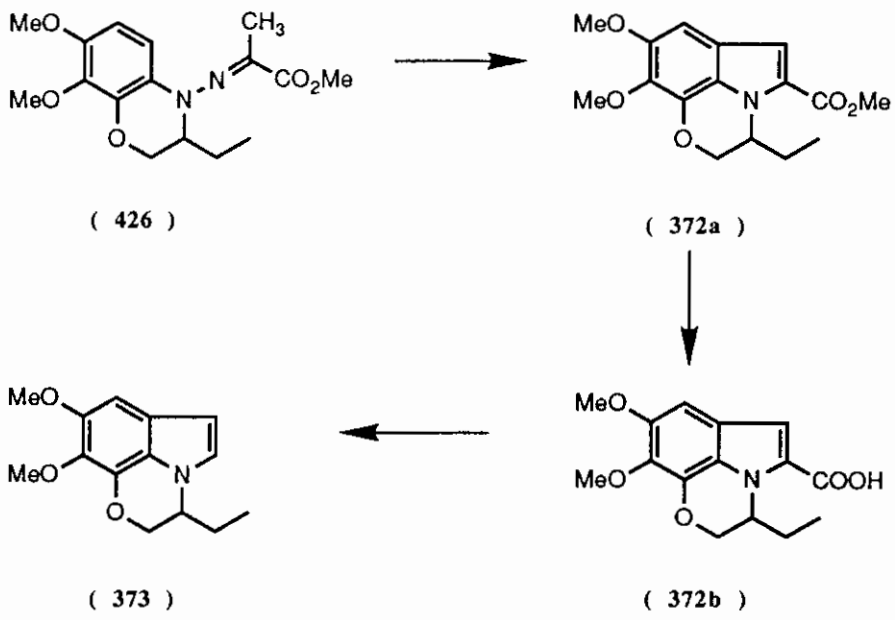


(369b) (370) (371)

Subsequently the N - amino benzoxazine (371) was cyclised to give the tricyclic pyrrolo [1, 2, 3 - de] benzoxazine ring system *via* the phenylhydrazone (426) using a Fisher - type cyclisation (Scheme 69). Synthetic investigations on the model series[110] showed that the most successful conversion of (245) (Scheme 32) into the corresponding tricyclic compound occurred when no additional acid catalyst was used. Similarly, it was found that simply heating the pyruvate derivative (426) under reduced pressure furnished the tricyclic ester (372a), in which the empirical formula, $C_{16}H_{19}NO_5$, indicated by elementary analysis, was confirmed by mass spectrometric determination. The n.m.r spectrum showed the typical signal of the carbomethoxy group as a 3H singlet at 3.94 ppm and the i.r. spectrum confirmed the presence of the carbonyl group at 1700 cm^{-1}.

Hydrolysis of the ester compound (372a) was achieved by refluxing in 2M sodium hydroxide solution to give an almost quantitative yield of the desired tricyclic acid (372b) as an amorphous solid. Removal of the carboxyl group by refluxing the compound in quinoline using 5% of the copper salt of the acid as catalyst[114] furnished a good yield of 8, 9 - dimethoxy - 3 - ethyl - 3, 4 - dihydropyrrolo [1, 2, 3 de] - 2H - 1, 4 - benzoxazine (373), which was purified by column chromatography

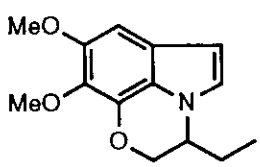
on Kieselgel G. The infrared spectrum of compound (373) shows no carbonyl absorption and in the n.m.r. the sharp singlet owing to the proton of the methoxy carbonyl group was absent.



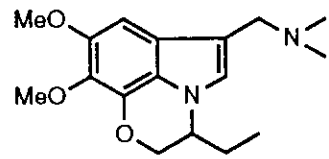
Scheme 69

Among the numerous syntheses of tryptamine derivatives from the indole ring system, the application of the Mannich reaction is particularly interesting (Scheme70). This method is based on the reaction of aqueous formaldehyde, dimethylamine and acetic acid with the indolic tricyclic compound (373) which afforded the gramine derivative (374) in very satisfactory yield. Its proton n.m.r. spectrum exhibited the presence of the N - dimethyl group as a singlet at 2.3 ppm and the methylene proton (2H, s, -CH_2N:) at 3.55 ppm.

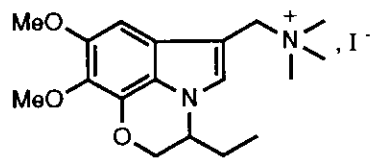
Reaction of (374) with methyl iodide gave the methiodide (375) which was subjected to attack by cyanide ion to give the required nitrile (376), together with a



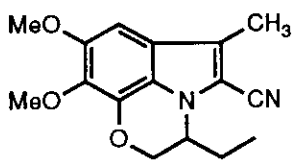
(373)



(374)

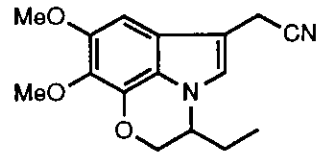


(375)

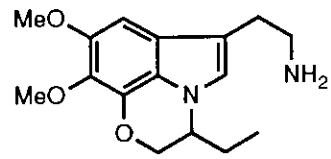


(427)

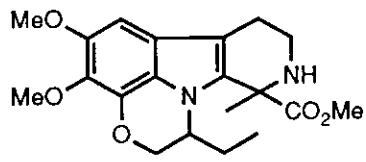
+



(376)



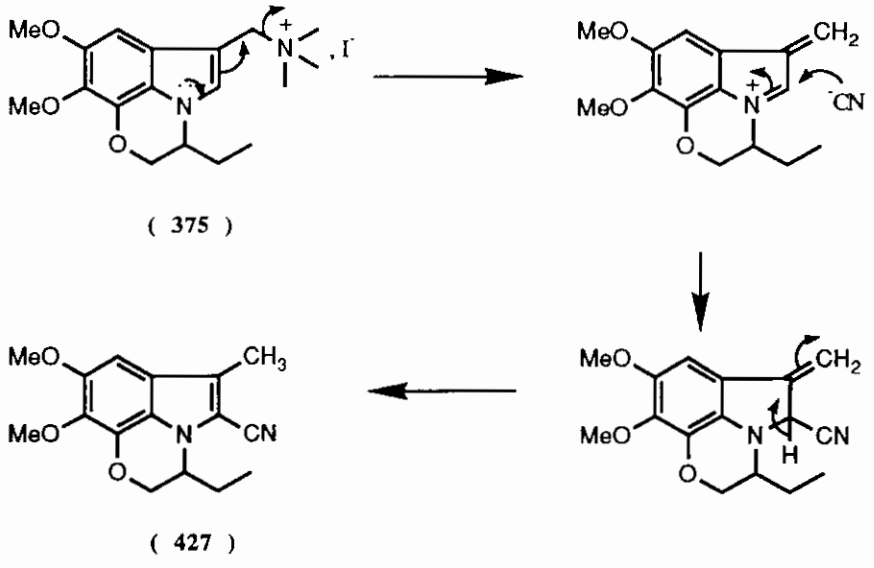
(377)



(378)

Scheme 70

small amount of an isomer (427). The formation of the isomer (427) could be explained by the following mechanism (Scheme 71):



(375)

(427)

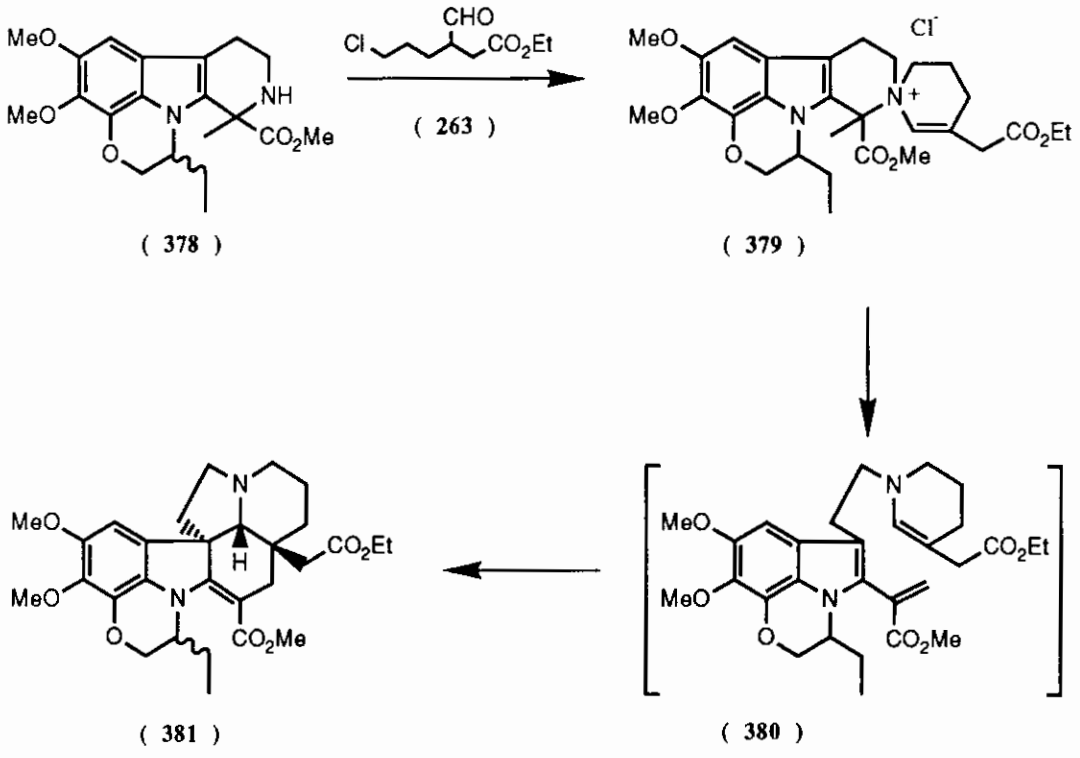
Scheme 71

Reduction of the nitrile compound (376) was carried out in two ways, either using sodium borohydride / cobalt chloride[115] or lithium aluminium hydride[116]. However, the latter reagent gave a mixture of products when the reaction was carried out on a large scale.

Reaction of the tryptamine derivative (377) with methyl pyruvate in refluxing methanol under nitrogen gave a good yield of the tetrahydro - β - carboline derivative (378) as an amorphous solid. The molecular ion at m/z 374 confirmed the molecular formula ($C_{20}H_{26}N_2O_5$, M = 374).

It was now planned to follow an analogous route to that used by Kuehne and co -workers[35] in their synthesis of (±) - ervinceine (11 - methoxyvincadifformine) (133b). The tetrahydro - β - carboline derivative (378) was reacted with the aldehyde

- ester (263) in refluxing toluene with added p - toluenesulphonic acid for 120 h. However, in contrast to Kuehne 's reaction, more time was required for the formation of (381). Diazabicycloundecene (DBU) was added after 110 h to aid the Hofmann elimination to form the secodine intermediate (380), which underwent biomimetic cyclisation to give the diester (381) as a mixture of two isomers (Scheme 72a).

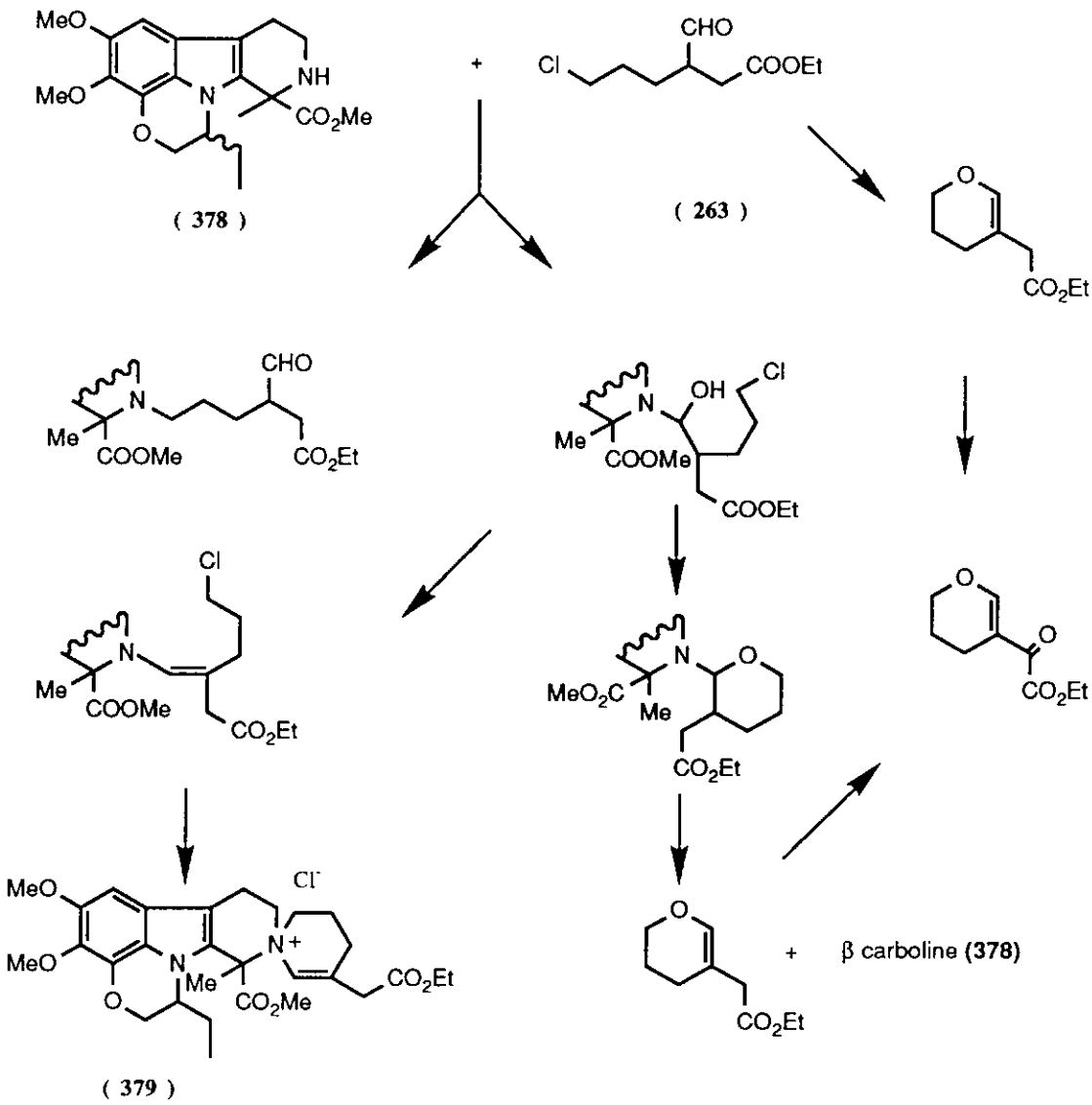


Scheme 72a

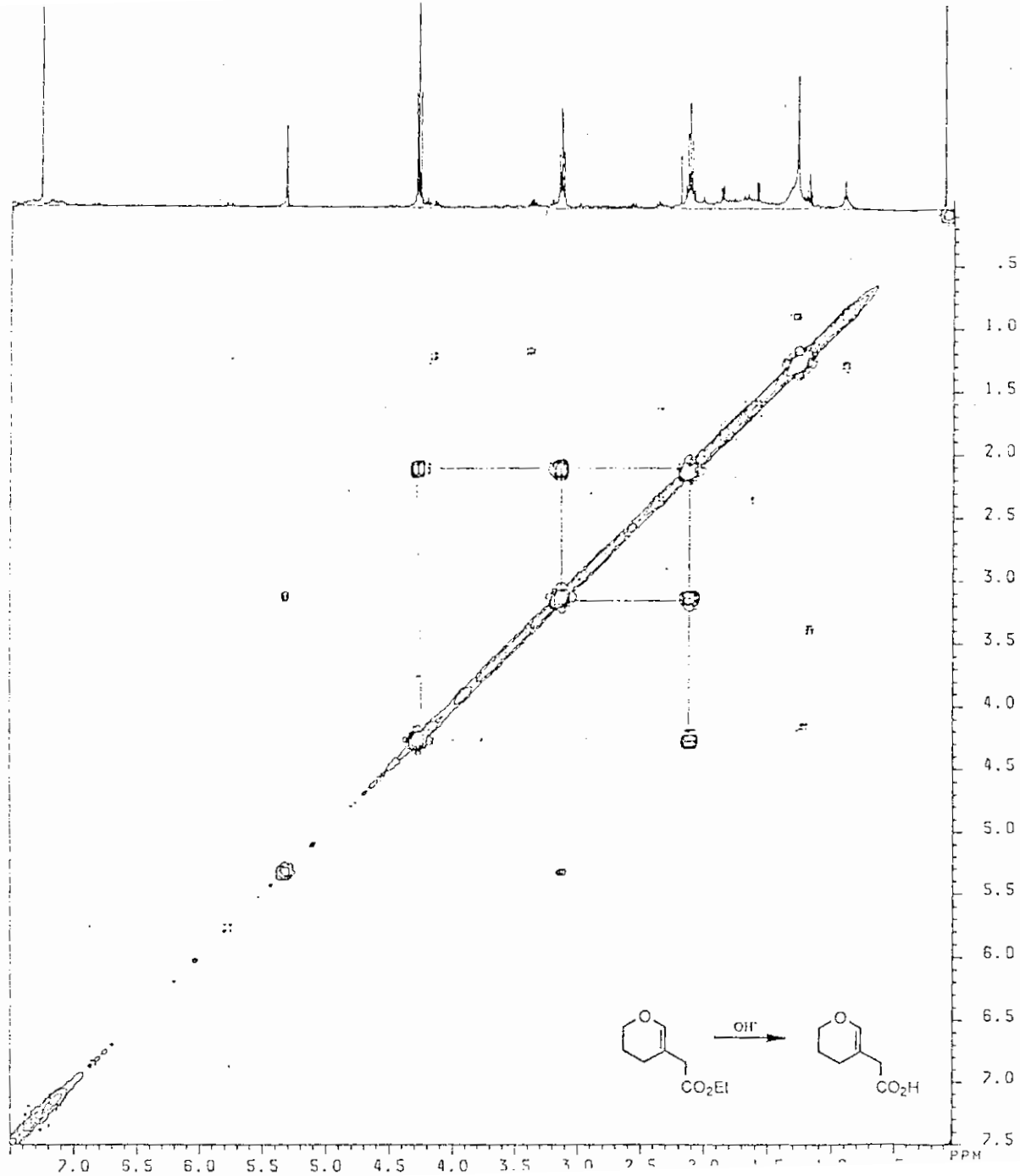
Its elementary analysis indicated the empirical formula $C_{29}H_{38}N_2O_7$ which was confirmed by high - resolution mass spectrometry (M^+ 526.267, calcd. 526.266). The u.v. spectrum in methanol gave maxima at 203, 210, 230, 302, and 344 nm, while the infra-red spectrum (ν_{max} 1720 and 1670 - 1570 cm^{-1}) indicated the presence of the conjugated β – anilinoacrylate ester function (ArN-C=C-CO_2Me).

The proton n.m.r. spectrum shows the presence of two epimers at C'- 3. For example, the aromatic proton was observed as two singlets at δ 6.44 and 6.42 ppm ; two double doublets corresponding to the methylene of a cyclic ether linkage -O-C$\underline{H}_2$-CH: were seen at 4.85 - 4.54 and 4.3 - 4.2 (H_2 - 4'). The methylene of the carbethoxy group was seen as two quartets at δ 4 ppm, two methoxyl groups appeared as four singlets (at δ 3.9 - 3.89 and 3.83 - 3.86), and the carbomethoxy group as two singlets at δ 3.7 and 3.68 ppm. The triplet owing to the CH_3 group of the ethoxycarbonyl group appeared at δ 1.15 and 1.12 ppm, whereas the methyl proton of C' - 1 gave triplets at 1.0 and 0.9 ppm. This was confirmed by ^{13}C which showed 2 x 29 absorptions (see table II).

Reaction of the tetrahydro - β - carboline (378) with the chloroaldehyde (263) also introduced an alternative reaction in competition with enamine formation to give the 3, 4 - dihydro - 2H - 5 - ~~ethoxycarbonylmethylpyran~~ ethoxalylpyran (Scheme 72b). Its n.m.r. spectrum exhibits a signal at 5.28 ppm as triplet (J: 0.5 Hz) corresponding to the vinyl proton and a triplet at 4.25 ppm (J: 6.5 Hz) corresponding to two protons of (C - 2). A quartet was also seen at 4.2 ppm (J: 7.2 Hz; COOC$\underline{H}_2CH_3$), which disappeared after hydrolysis with potassium hydroxide. The methylene protons of C - 4 appeared as a double triplet (J: 6.5 and 2 Hz) at 3.12 ppm and the methylene protons of C - 3 as quintet at 2.1 ppm. A triplet (J: 7.2 Hz) was seen at 1.2 ppm and corresponds to the carbethoxy group ($COOCH_2CH_3$). The molecular ion was observed at m/z 170 (15%).


MeO
MeO
NH
N
O
CO2Me
(378)
+
CHO
Cl
COOEt
(263)
O
CO2Et
CHO
N
Me
COOMe
CO2Et
OH
Cl
COOEt
Cl
MeO2C
Me
O
O
CO2Et
Cl-
N+
CO2Et
(379)
+ β carboline (378)

Scheme 72b



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SI2	1024
SI1	512
SW2	2994.012
SW1	1497.006
NDO	1

WDW2	S
WDW1	S
SSB2	0
SSB1	0
MC2	M
PLIM ROW:	
F1	7.500P
F2	.032P
AND COLUMN:	
F1	7.500P
F2	.032P

D1	1.0000000
P1	13.0
DO	.0000030
P2	13.0
RD	0.0
PW	0.0
DE	208.8
NS	16
DS	2
NE	128
IN	.0003340

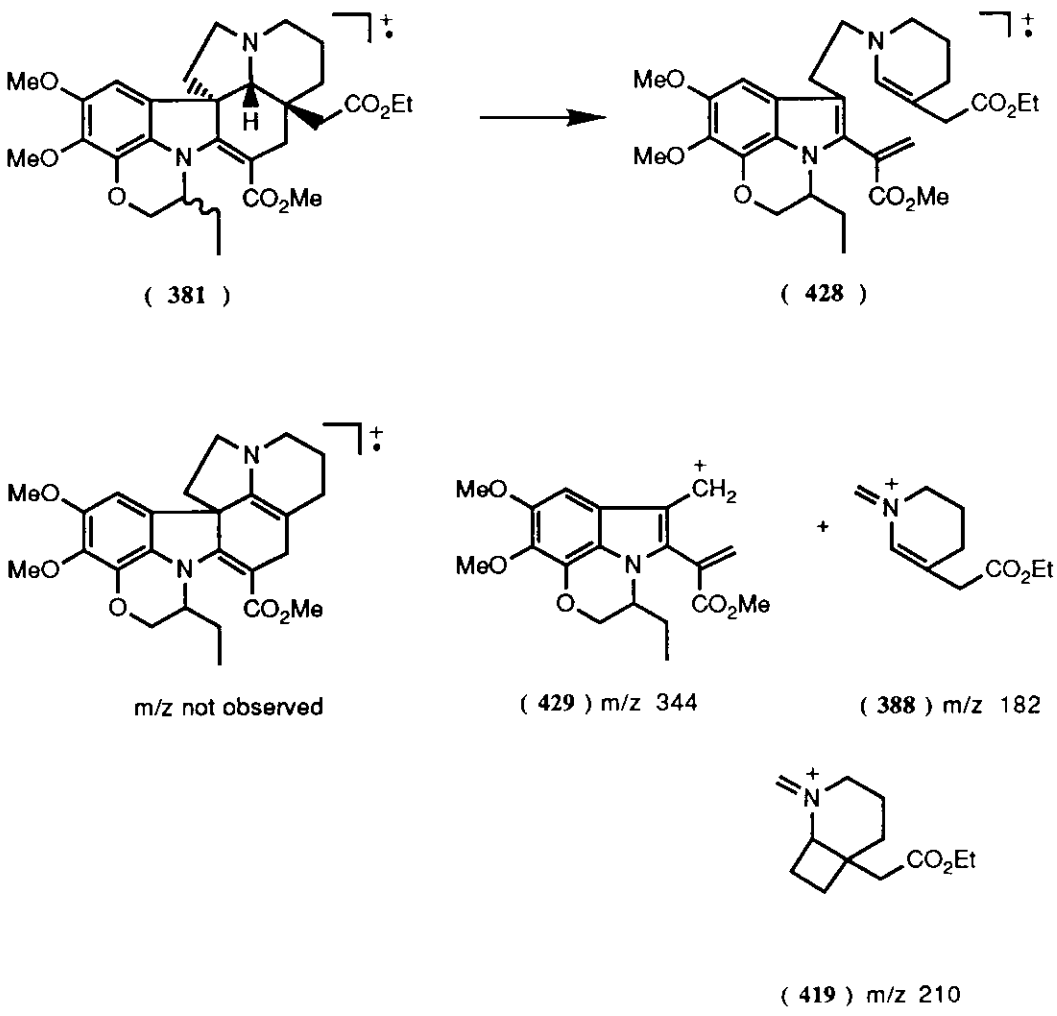
16K

Table II: ^{13}C n.m.r. data obtained on obscurinervidine (13), pentacyclic diester (267), (381) and (381') the diastereoisomers of the alalakine skeleton.

Carbone N°	(13)	diester (267)	(381) and	(381')
2	69.7	166.8	162.76	161.97
3	54.3*	5O.9	53.36	51.61
5	52.2*	51.6	51.0	50.95
6	39.3	45.4	49.78	46.85
7	55.2	55.4	58.92	57.84
8	129.4	137.2	131.0	129.87
9	100.8	121.0	99.6	98.66
10	130.5	120.6	125	124.74
11	147.8	127.6	148.18	147.52
12	137.3	109.4	136	136.1
13	135.6	143.3	135.81	134.9
14	133.8*	22.1*	21.74*	16.63*
15	122.9*	33.5*	33.3*	33.15*
16	23.8	93.1	93.84	93.01
17	81.3	26.8	24.87	22.06
18	176.0	171.5	171.53	171.26
19	38.7	41.5	37.53	37.25
20	40.7	38.5	46.53	41.24
21	65.0	71.4	73.24	71.30
22	------	169.1	167.48	166.48
1' - CH_3	10.5	-------	10.4	9.52
2' - CH_2	abs	-------	29.92	29.59
3' - CH	44.5	-------	61.22	61.09
4' - CH_2	71.9	-------	67.92	66.30
$CO_2\underline{C}H_3$	-------	50.9	50.83	50.29
$CO_2\underline{C}H_2CH_3$	-------	59.9	59.85	59.81
$CO_2CH_2\underline{C}H_3$	-------	14.1	14	13.98
OMe	57.75	-------	56.02	53.68
OMe	61	-------	57.39	57.15

* Asterisk indicates some ambiguity regarding the assignment.

The mass spectrum of the diester (381) (Scheme 73) is simpler with the only significant peaks arising from the retro Diels - Alder decomposition of ring C to form the charged species (428) which undergoes homolysis of its C - 5, C - 6 bond to give the principal fragment (388) at m/z 182 (100%). The molecular ion is observed at m/z 526.



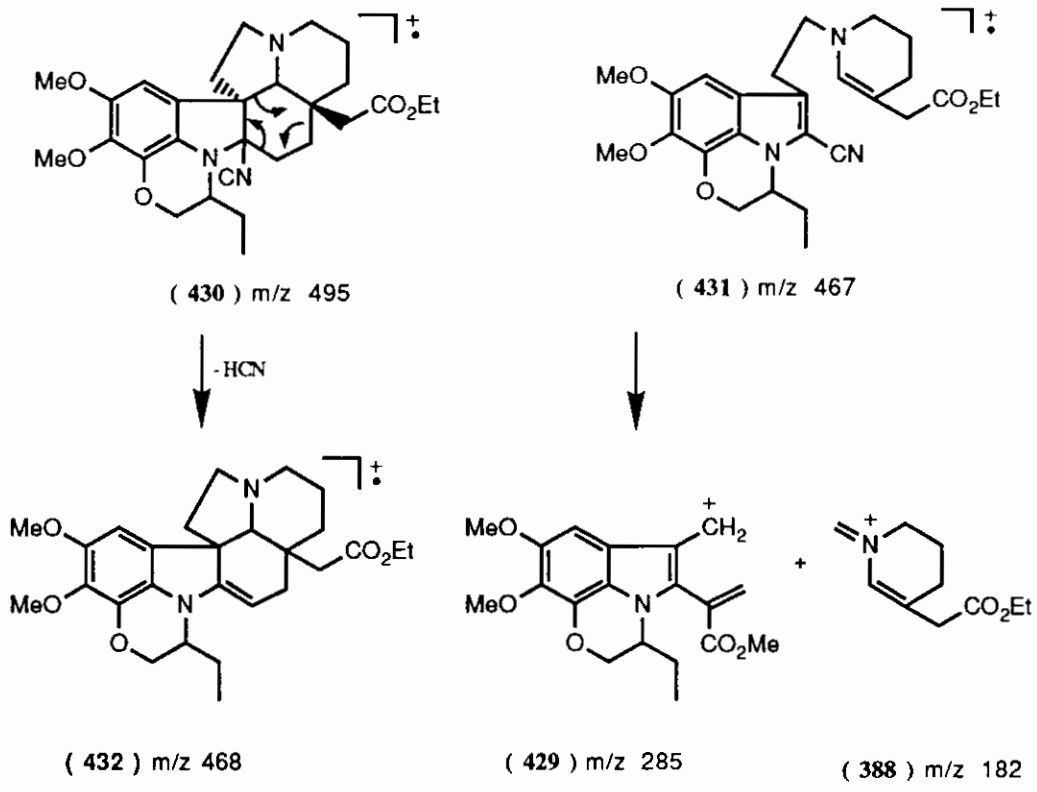
Scheme 73

Brennan 's procedure [57] was usually used to convert the hexacyclic diester (381) into the α - nitrile compound (430) using sodium cyanide in hexamethylphosphoramide (HMPA). This reagent was known to allow the methyl ester group in the diester (267) to be preferentially cleaved, as outlined in Scheme 34.

The hexacyclic diester (381) was reacted with sodium cyanide in hexamethylphosphoramide at 82 °C for 102 hours under nitrogen. After purification by column chromatography, the product, obtained in 57% yield, was found to be a mixture of diastereoisomers of the desired cyano - hexacyclic ester (430). For example, the i.r. gave two distinct absorptions at 2240 cm^{-1} (weak) and at 1725 cm^{-1}, which correspond to the nitrile function and the carbethoxy group respectively. The u.v. spectrum gave maxima at 218, 250, and 300 nm.

The mass spectrum (Scheme 74) was in agreement with the proposed structure (430), being very similar to that of (271) apart from an additional 130 mass unit owing to the benzoxazine ring and two methoxy groups, showing the typical aspidospermine type fragmentation pathways; the molecular weight, 495, is consistent with the formula $C_{28}H_{37}N_3O_5$.

The n.m.r. spectrum confirmed the presence of two diastereoisomers at C' - 3 in a ratio of (3, 1). Partial separation by column chromatography gave one stereoisomer which showed in the n.m.r. spectrum that the aromatic proton absorbs as a singlet at 6.35 ppm and the grouping $-OCH_2-CH-N$: appears as a multiplet at 4.3 ppm. The carbethoxy group was observed as a quartet at 4.05 ppm and a triplet at 1.15 ppm. Two methoxy groups were observed at 3.8 and 3.82 ppm.

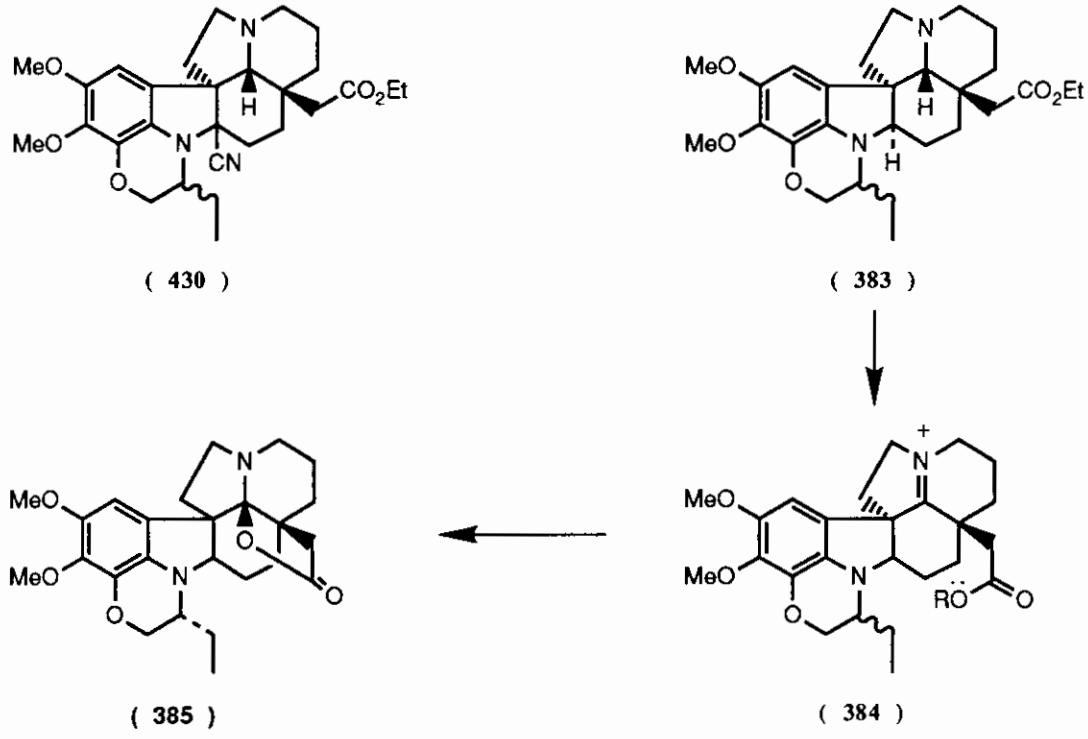


Scheme 74

Finally, the synthesis of alalakine could in principle be completed by reductive decyanation with either sodium borohydride[117] in methanol / pyridine solution as in the conversion of the α - aminonitrile (434) into (435) (Scheme 75), or by conversion to the methylene - indoline derivative (382a) (Scheme 54, p.40) by means of silver tetrafluoroborate, followed by reduction of the double bond. Both methods should give the indoline (383). Oxidation of the N_b, C - 21 bond in (383) (Scheme 76) using mercuric acetate should then furnish the immonium salt (384), which should then undergo a transannular cyclisation reaction to give alalakine (385).

(434) (435)

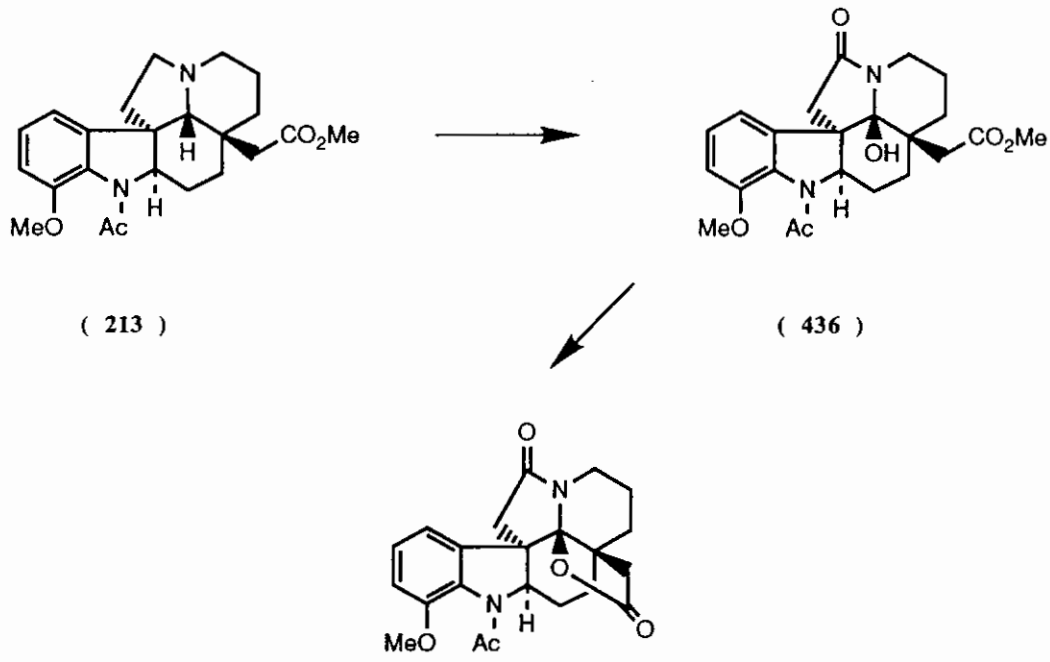
Scheme 75



(430) (383) (384) (385)

Scheme 76

Djerassi[118] reported that the oxidation of N - acetylcylindrocarine (213) with m - chloroperbenzoic acid gave the 5 - oxo - 21 - hydroxy derivative (436) which on treatment with acetic anhydride in pyridine gave N_a - deformyl - N_a - acetyl - 5 - oxodichotamine (437) (Scheme 77).



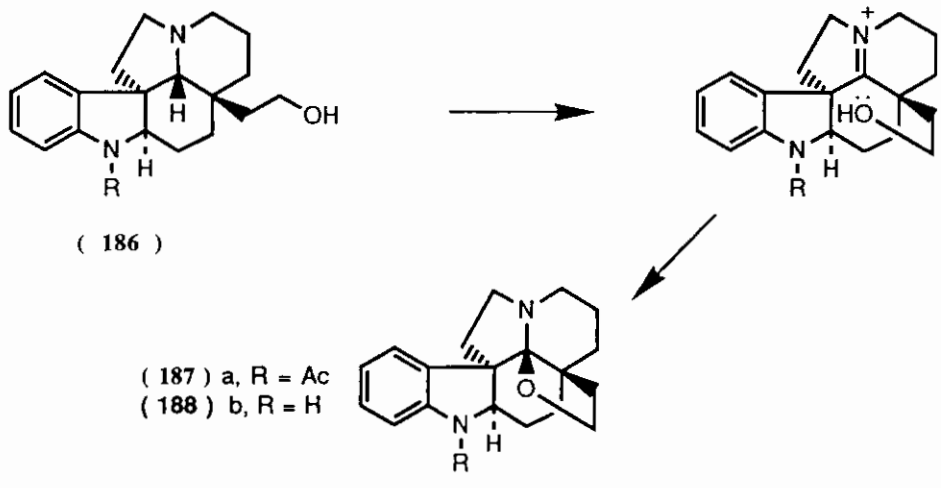
(213)

(436)

(437)

Scheme 77

Also, Ban and co - workers[119] have achieved a synthesis of (±) - N_a - acetylaspidoalbidine (187) and (±) - fendleridine (188) by heating the alcohols (186 a, b) with excess mercuric acetate in 5% aqueous acetic acid (Scheme 78).

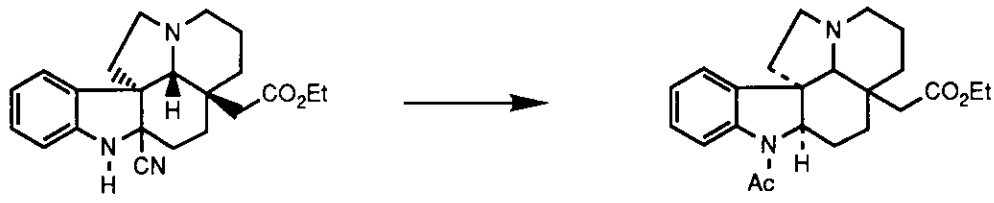


(186)

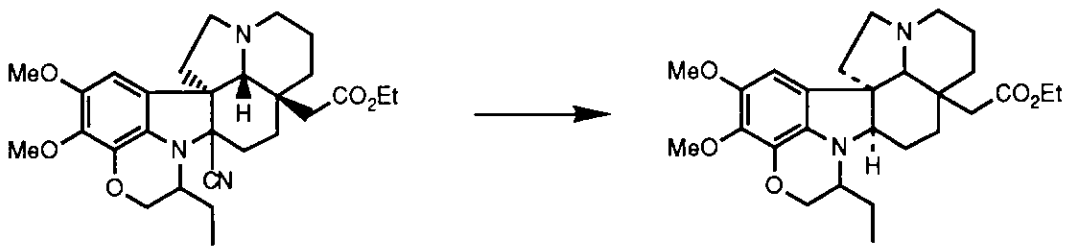
(187) a, R = Ac
(188) b, R = H

Scheme 78

However, zinc dust in acetic acid in presence of cupric sulphate pentahydrate under a nitrogen atmosphere has been tried on the model compound (271) which gives an optimum yield of 44% of N_a - acetyl - 19 - carbethoxy - 19 - demethylaspidospermidine (462) (Scheme 79). This could be applied to the conversion of (430). Unfortunately this investigation was not further carried out because of lack of material.



(271) (462)

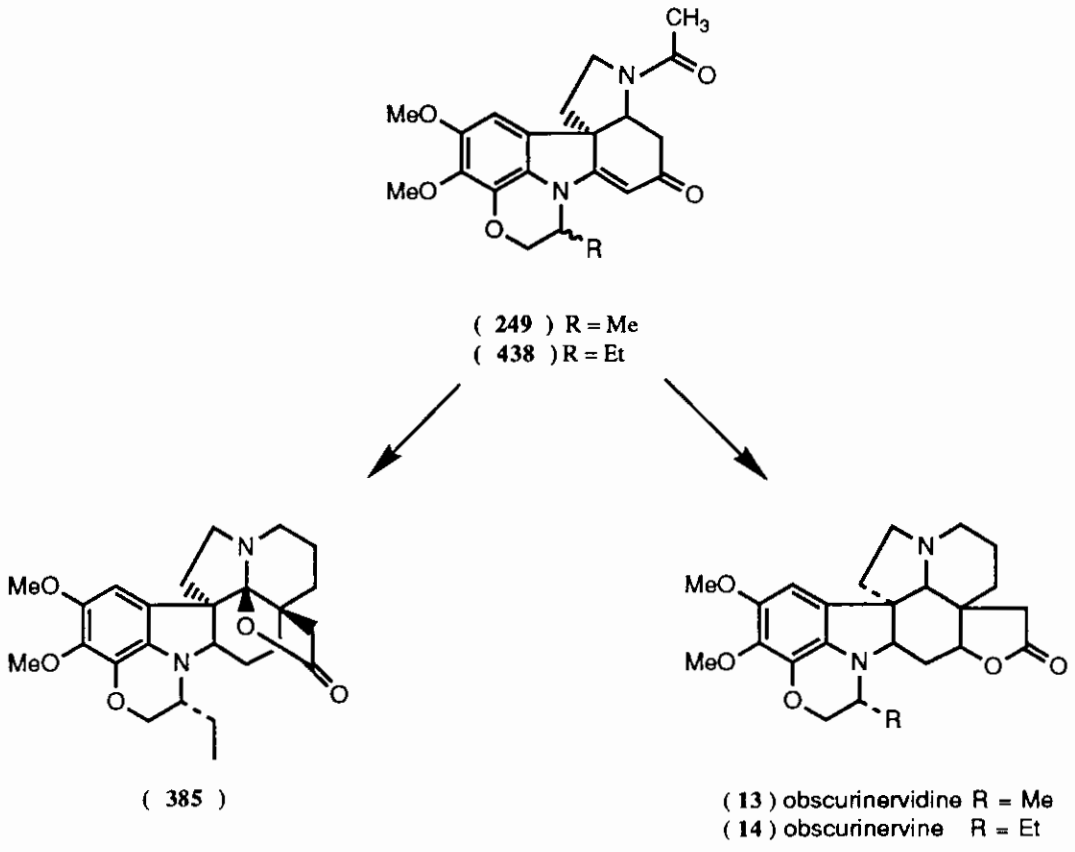


(430) (383)

Scheme 79

2.1.3 Synthesis of the key pentacyclic vinylogous amide (438)

The alternative approach to alalakine (385) and obscurinervine (14) using as starting material the readily synthesized N - aminobenzoxazine (371) led to a synthesis of the pentacyclic vinylogous amide (438), which may be considered to be the precursor for the synthesis of both (385) and (14).

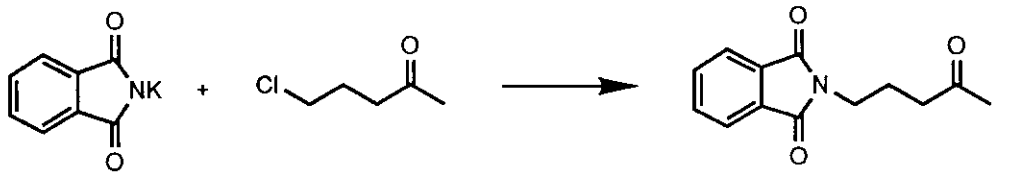


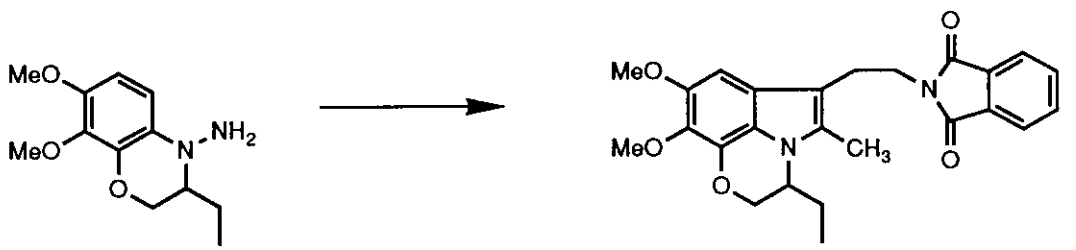
As mentioned earlier Saxton et al[52] synthesized the alkaloid obscurinervidine (13) via the methyl analogue (249). The planned synthetic Scheme is outlined in Scheme 32.

Reaction of the N - amino derivative (371) with 5 - phthalimido - 2 - pentanone, previously prepared[120] from 5 - chloro - 2 - pentanone and potassium phthalimide,

furnished the phthalimido tryptamine derivative (439) in 75% yield. Hydrazinolysis of (439) by means of hydrazine hydrate in ethanol gave the desired tryptamine (440).

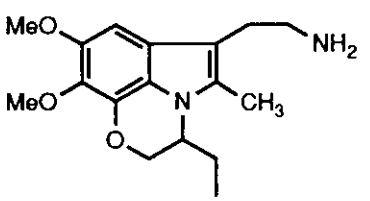
This compound displayed absorption owing to the primary amino group at ν_{max} 3350 cm^{-1}, and u.v. maxima at 220, 276 nm. The n.m.r. spectrum exhibits a signal at 6.55 ppm corresponding to one aromatic hydrogen, a multiplet at 4.3 ppm corresponds to three protons of a cyclic ether linkage (-O-CH_2-CH-), and two methoxyl groups as two singlets at 3.97 and 3.87 ppm. The methylene protons of the aminoethyl group were seen as multiplet at 2.9 ppm and those of 5 - methyl group appeared as singlet at 2.3 ppm. The methylene protons of C' - 2 appeared as multiplet at 1.7 ppm and the methyl group C'- 1 as triplet at 1 ppm. The amino group protons were seen at 1.3 ppm as multiplet. The molecular ion was observed at m / z 304 (15.6%) (Scheme 80).





(371)

(439)

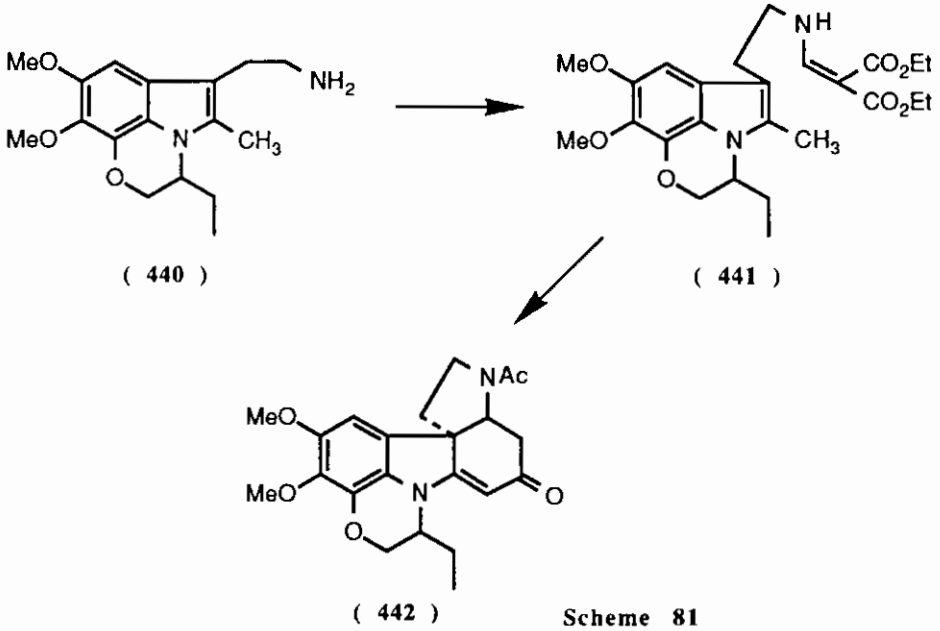


(440)

Scheme 80

Reaction of the amino compound (440) with diethyl ethoxymethylenemalonate in refluxing ethanol gave the vinylogous urethane (441) in very good yield. High - resolution mass spectrometry (M^+, 474.235) confirmed the formula $C_{25}H_{34}N_2O_7$. Two absorptions at 226 and 274 nm were observed in the u.v. spectrum, while in the i.r. region absorptions were observed at 3360 cm^{-1} (NH), 1710, 1680 (diester), 1640 and 1603 cm^{-1}.

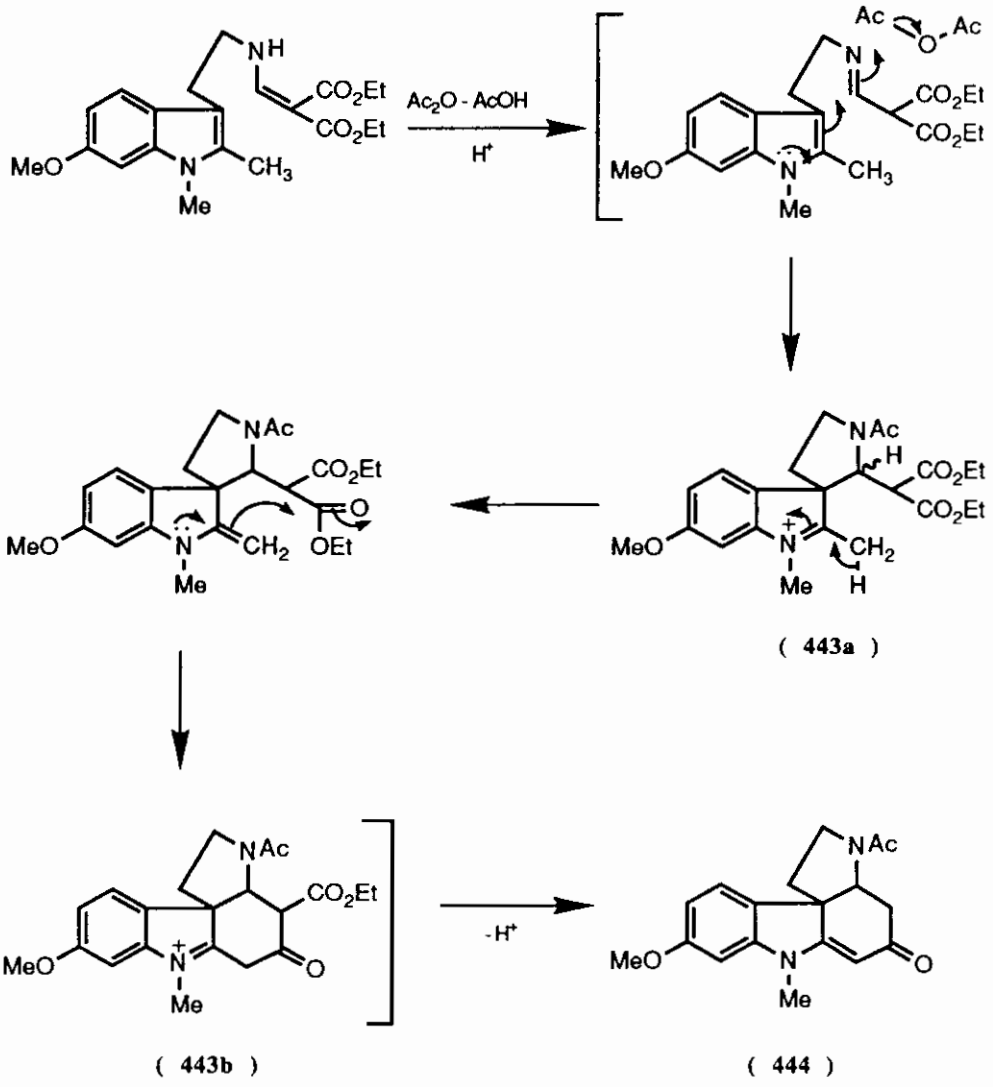
Takano cyclisation[121] of (441) by heating with a mixture of acetic anhydride and acetic acid (3: 2, v / v) at reflux temperature for 4 days gave a very complex mixture of products which was separated by extensive chromatography to give the pentacyclic vinylogous amide (442) in moderate yield as a mixture of epimers. The products from this cyclisation would be expected to have the more stable cis C/E ring junction, as has earlier been observed in analogous cyclisations[121]. The presence of the vinylogous amide function in (442) was confirmed by the long wavelength absorption observed in the u.v. spectrum at λ_{max} 218.5, 245.5, 297, 353 nm. The molecular ion was observed at m/z 398 (Scheme 81).



(440) (441) (442)

Scheme 81

Takano *et al*[121]. have proposed the following mechanism for the formation of the tetracyclic vinylogous amide (444), presumably *via* the Fischer base (443a) followed by an intramolecular nucleophilic cyclisation to give (443b) which then loses an ethoxy carbonyl unit (Scheme 82).



Scheme 82

The very complex mixture obtained on this reaction and the laborious separation of the desired product made this approach less advantageous. However, if the yield of (438) can be increased then this synthetic route to alalakine (385) would be an alternative method.

2.2 Approaches to the synthesis of strempeliopine (447)

Strempeliopine (447), which is the parent base of the schizozygane alkaloids (e.g. schizozygine (449), schizogaline (450), schizogamine (451), isoschizogaline (452) and isochizogamine (453)[122] (Scheme 83), has recently been isolated by Hájiček and Trojánek[123a] from the Cuban species *Strempeliopsis strempelioides K. Schum.* (*Apocynaceae*). Soon after its isolation, the same authors[123b] reported the total synthesis of racemic strempeliopine (447), which is based on the reductive rearrangement of indolenine (445) under the effect of zinc in hot acetic acid in the presence of cupric sulphate. This gave the 1 - demethylvallesamidine derivative (446) and 18 - methylenequebrachamine (448) (Scheme 84). Formylation of (446) with a mixture of formic acid and acetic anhydride gave the formylindole. Separation from (448) followed by oxidative ozonolysis, and removal of the N - formyl group, then gave (±) - strempeliopine (447).

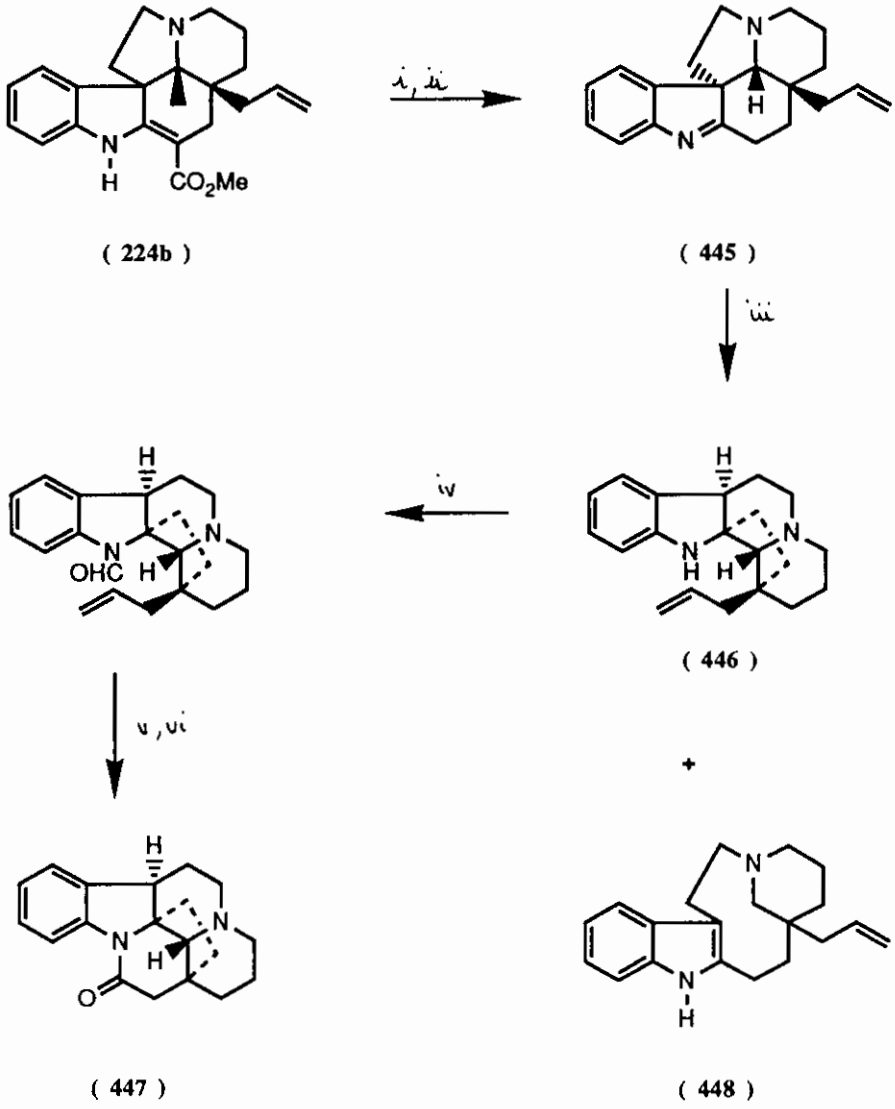
Later[123c], the absolute configuration of natural (-) - base (447) was determined by its stereospecific synthesis from (+) - 18 - methylenevincadifformine (224b).

In 1971 Lévy *et al*[124, 125] reported a reductive rearrangement of 1, 2 - dehydroaspidospermidine (397) under the same conditions which gave 1 - demethylvallesamidine (454) in addition to unrearranged aspidospermidine (1), and quebrachamine (3) (Scheme 85).

(449)

	R	7H
(450)	H	β
(451)	MeO	β
(452)	H	α
(453)	MeO	α

Scheme 83



(224b)

(445)

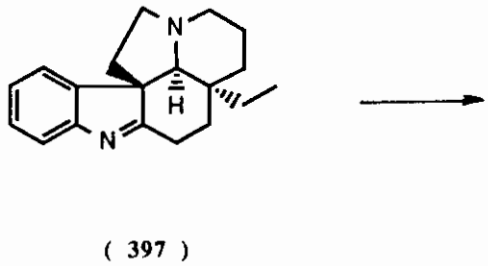
(446)

(447)

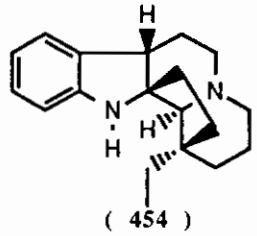
(448)

Reagents: i, OH^-, H_2O; ii, C_6H_6, Δ; iii, Zn, $CuSO_4$, $5H_2O$, AcOH, 103 °C; iv, HCO_2H, Ac_20; v, O_3, HCl, MeOH; vi, H_2O_2.

Scheme 84

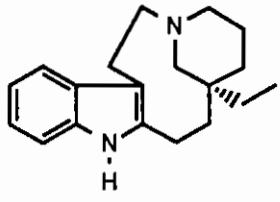


(397)



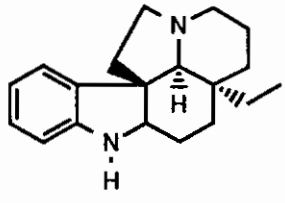
(454)

+



(3) (-) Quebrachamine

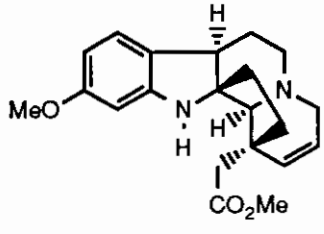
+



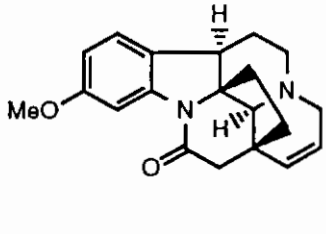
(1) - (-) aspidospermidine

Scheme 85

Accordingly, an intermediate with appropriate substitution on the C - 18 atom in the indolenine should undergo a similar rearrangement leading to the closure of the lactam ring (455) to form the schizozygane skeleton. As an example of this transformation, the alkaloid schizophylline (455) was converted into isoschizogaline (452) on chromatography on alumina (Scheme 86).



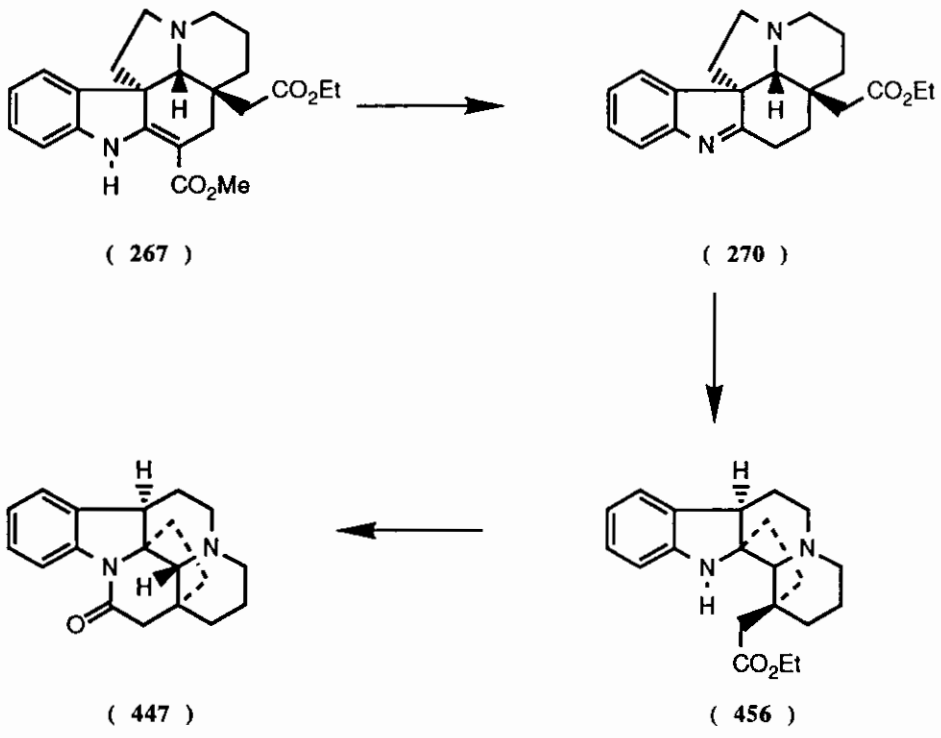
(455)



(452)

Scheme 86

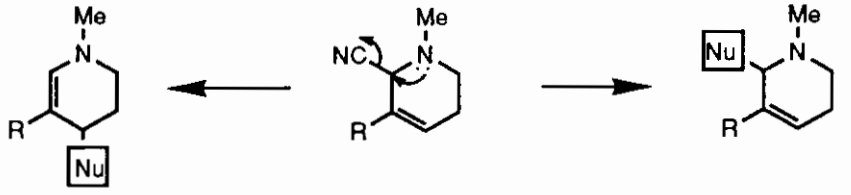
Therefore the pentacyclic diester (267) could be converted in the same manner to give the corresponding aminoester (456) which should spontaneously cyclise to form the desired (±) strempeliopine (447) (Scheme 87).



Scheme 87

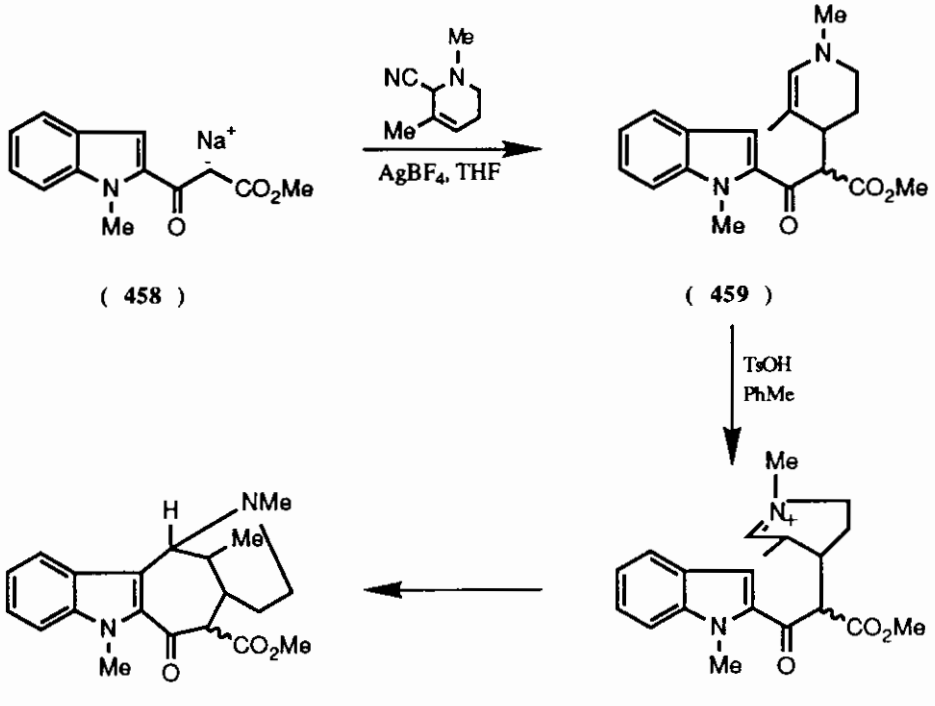
In addition, an investigation was carried out towards the possibility of increasing the yield of the required indolenine (270).

Recently, Husson and co - workers[126, 127] investigated the synthetic potential of 2 - cyano Δ^3 - piperidines of type (457) and their ability to act as potential and masked dihydropyridinium salts. These compounds seem to react with high regioselectivity with nucleophiles at C - 4 (457a) or C - 2 (457b) depending on the nature of the nucleophile (Scheme 88).



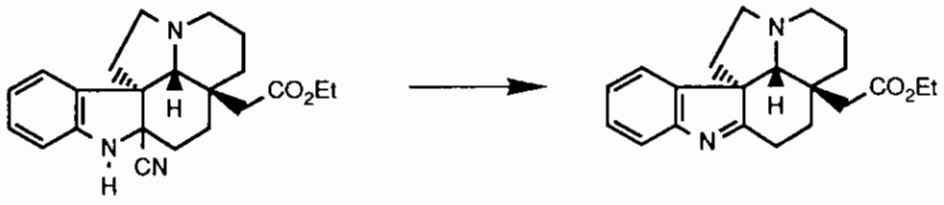
Scheme 88

For example, addition of the sodium salt (458) to (457, R = Me) in the presence of silver tetrafluoroborate led to the formation, in 91% yield, of the enamine (459) as an approximately (1: 1) mixture of isomers (Scheme 89).



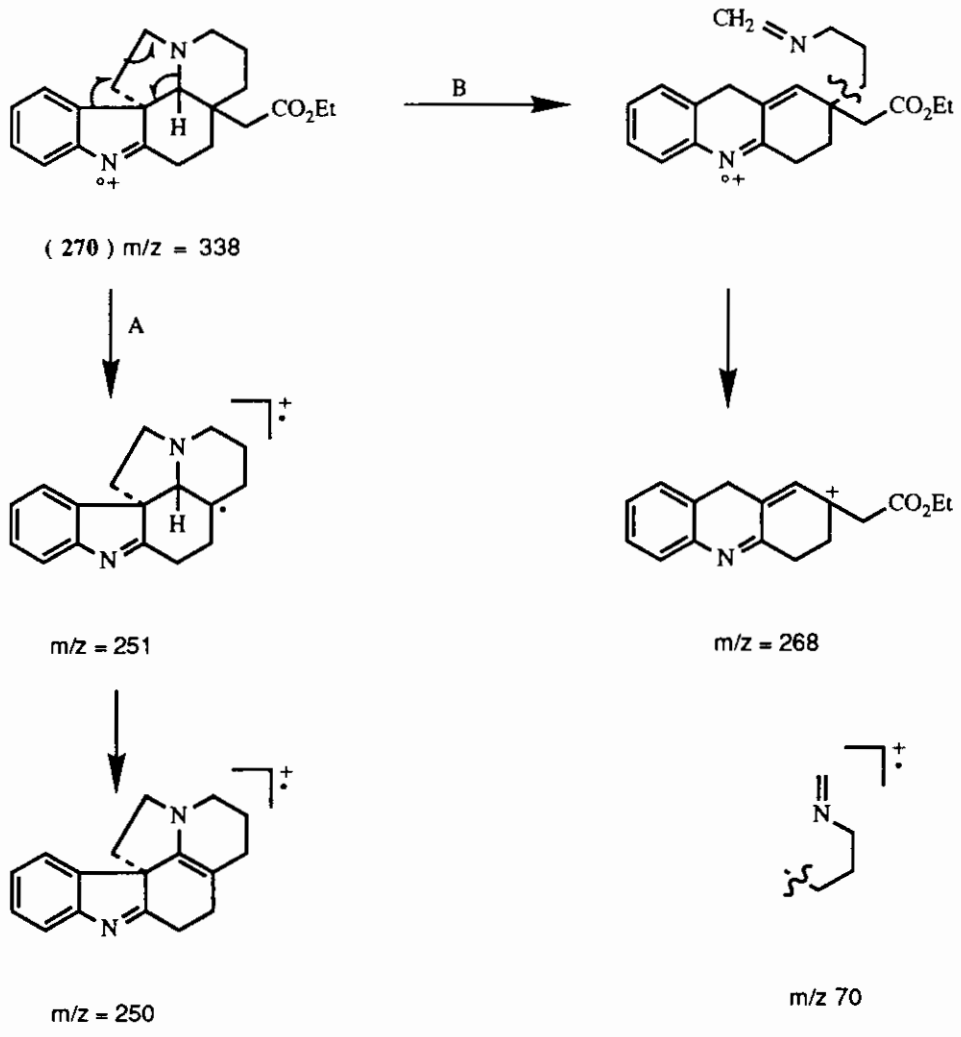
Scheme 89

Therefore, the application of this reaction to the α - nitrile (271) under similar conditions offered an attractive possibility for its conversion into the indolenine (270)



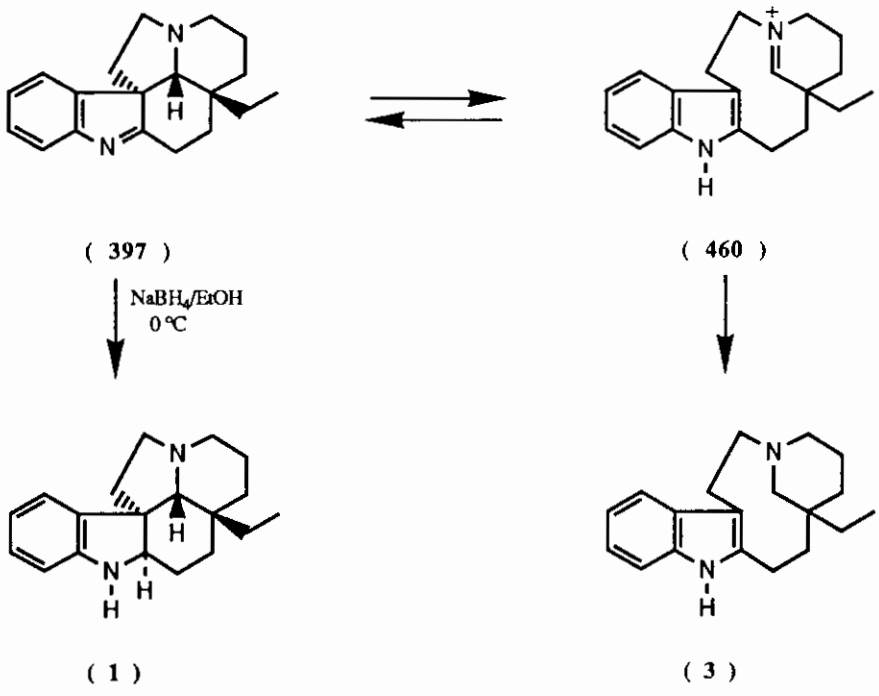
(271) (270)

The aminonitrile (271) in anhydrous tetrahydrofuran was reacted with silver tetrafluoroborate under nitrogen and stirred for 4 hours, then diluted with aqueous ammonia and extracted with dichloromethane; this gave a brown oil which was purified by column chromatography (33.7% yield) and was found to be the desired indolenine (270). The empirical formula, $C_{21}H_{26}N_2O_2$ (M = 338), was confirmed by elementary analysis and by mass spectrometry, which exhibited a strong molecular ion peak at m/e 338 (100%). The ultraviolet absorption spectrum (λ_{max} 220, 225, 259 nm) is similar to that previously obtained by Brennan[57], while the infrared band at 1720 cm^{-1} showed the existence of the carbethoxy group. This was also confirmed by the n.m.r. spectrum, in which the signals for the four aromatic protons (7 - 7.6 ppm), two protons (q, 3.95 ppm) and three protons of the carbethoxy group at 1.1 ppm were observed. The mass fragmentation pattern of the pentacyclic indolenine (270) is completely changed owing to the presence of the 1, 2 - double bond. Thus on electron impact the M^+ ion (270) is presumably seen to fragment by two pathways (Scheme 90). In pathway A the C - 20 substituent is lost from the molecular ion *via* a McLafferty rearrangement to give the ion at m/z 250. In pathway B, the only characteristic fragment observed is at m/z 268.



Scheme 90

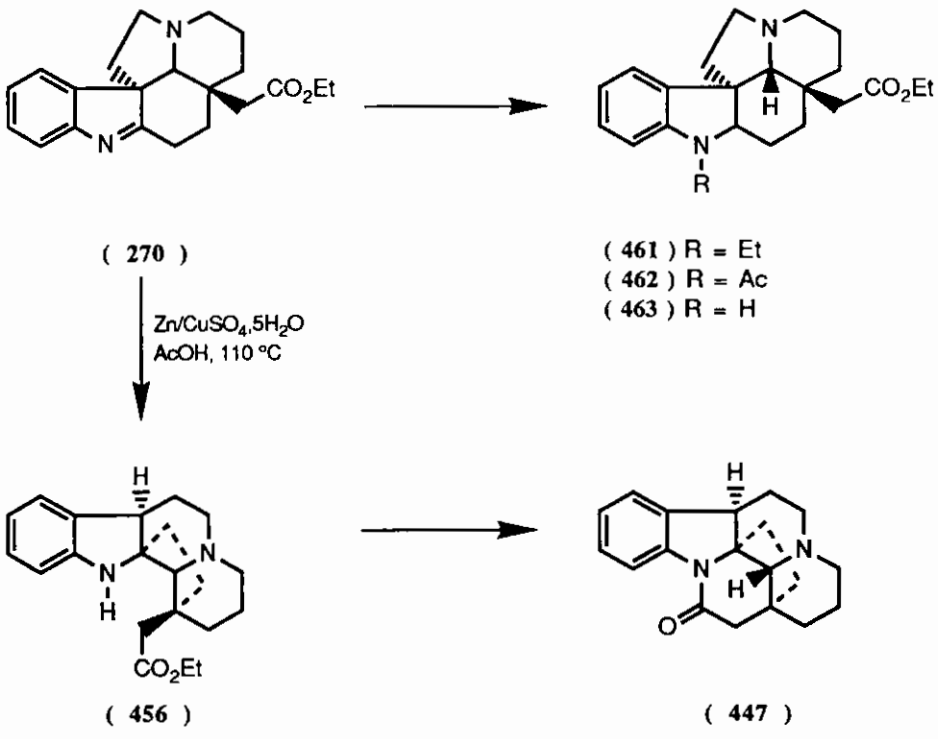
This indolenine was for the first time fully characterised in spite of its instability, because of the high reactivity of the imine bond. Indolenines such as (397) are known to be in equilibrium with the immonium salt (460) via a reverse Mannich reaction. This proof came from its reactivity with sodium borohydride in ethanol which led to two products[128]. At 0 °C the reaction produces aspidospermidine (1) exclusively, whereas at elevated temperatures quebrachamine (3) is obtained.



Scheme 91

Therefore, to minimise the loss of indolenine (270), the diester (267) was first reacted with either DMPU (dimethyltetrahydropyrimidinone urea) or HMPA (hexamethylphosphoramide) in the presence of sodium cyanide at 75 °C. However, the latter reagent is known to be carcinogenic even on a small scale, but more reactive than the former. Reaction with DMPU was very slow and most of the starting material was recovered after 6 days at 75 - 80 °C, whereas with HMPA no starting material was detected after 4 1/2 days. Secondly, because of the instability of the indolenine and the opportunity to transform the α - nitrile compound (271) into the corresponding indolenine (270) under the effect of silver tetrafluoroborate ($AgBF_4$), the residue was immediately reacted with zinc dust (type Aldrich) in hot acetic acid in the presence of cupric sulphate pentahydrate and heated to 105 °C. After the usual work up and after two column chromatographies on alumina and Kieselgel, four

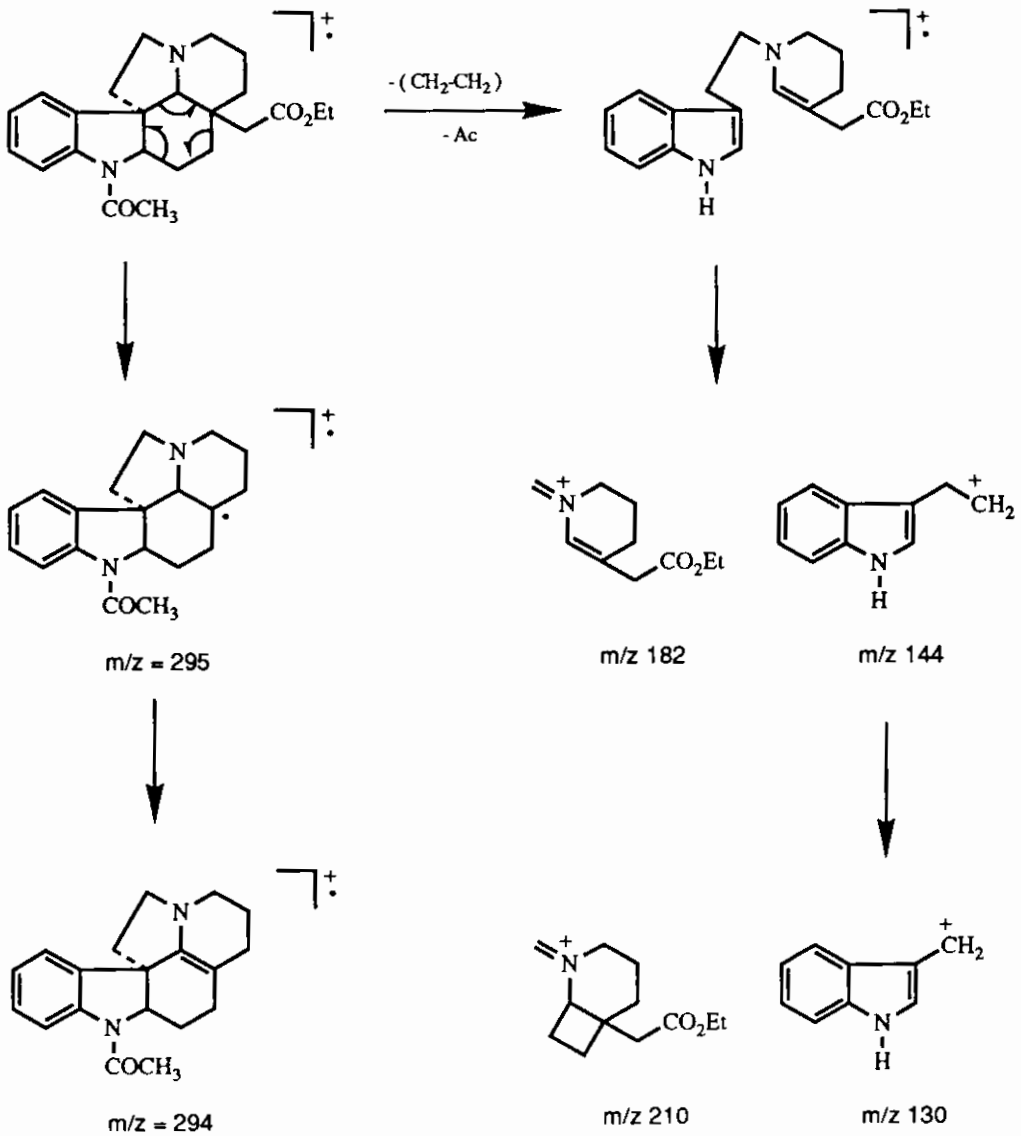
products were isolated and identified (yield is based on vincadifformine (Scheme 92a)



Scheme 92a

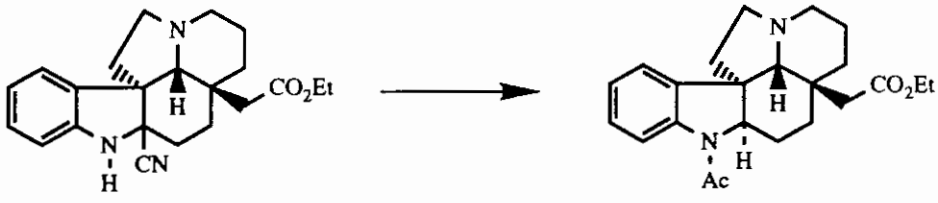
The main product, obtained in 18% yield, was found to be the N_a - acetyl derivative (462). Its ultraviolet absorption spectrum is very similar to that of (±) - 12 - demethoxy - N - acetylcylindrocarine (269)[52] and the infrared spectrum clearly shows the presence of the carbethoxy and the acetyl groupings at 1720 and 1640 cm^{-1} respectively. Further evidence was provided by elementary analysis, the mass spectrum (found M^+, m/z 382.2262) and the proton n.m.r. spectrum which gave a singlet at 2.26 ppm corresponding to three protons of N - acetyl group. The chemical shift of the C - 12 proton was observed at 8.15 ppm and the C - 2 hydrogen at 4.05 ppm. The ^{13}C n. m. r. spectrum displayed twenty - three resonances with the N - acetyl carbonyl atom being observed at 168.38 ppm. The most important evidence came from mass spectrometry which shows a typical aspidospermidine - type

fragmentation pattern (Scheme 93). The base peak was found at m/z 182, arising from fission of the 5 - 6 bond; other major peaks are those due to the indole fragment (m/z 144) and (m/z 130). The loss of the C - 20 substituent from the molecular ion by a McLafferty rearrangement was observed at m/z 294.



Scheme 93

To confirm the result obtained earlier, the α - aminonitrile (271) was subjected to reaction with zinc dust in hot acetic acid in the presence of cupric sulphate to give the 19 - carbethoxy - 19 - demethyl - N - acetylaspidospermidine (462) in 53% yield.



(271) (462)

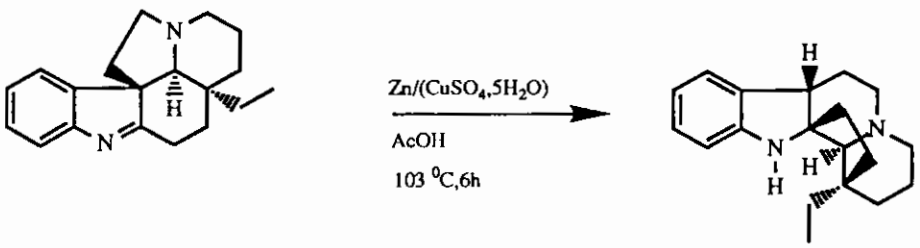
The second product, which is less polar, was the unusual N_a - ethyl - 19 - carbethoxy - 19 - demethylaspidospermidine (461) . However, no alkaloid has been found in nature to have the N - ethyl function. The elementary analysis and the accurate mass obtained by high resolution mass spectrometry confirmed the empirical formula $C_{23}H_{32}N_2O_2$. However, the low resolution spectrum exhibited the molecular ion at m/z 368 and many other identical peaks as for the N - acetyl compound (462). The n.m.r. showed that no C - 12 proton shift is observed in the region of 8 ppm, indicating the absence of an N_a - acetyl group.

The third fraction contained some strempeliopine (447); however its purification proved to be difficult because of the very close Rf value with the N_a - ethyl compound (461). The product was separated by careful chromatography (preparative t l c) but still mixed with (461). The accurate mass, obtained by high resolution mass spectrometry, confirmed the molecular formula, $C_{19}H_{22}N_2O$ (M^+ m/z = 294.17311). The lactam function gave rise to a carbonyl absorption at ν_{max} 1660 cm^{-1}. The most intense peak, which corresponds also to the molecular ion, was

observed at m/z 294 (88.5%). The mass spectral peaks differ markedly in intensity from those reported by Trojanek[123b]. In the n.m.r. spectrum the chemical shift of the C - 12 proton is observed at $\delta = 8$ ppm, whereas in the N_a - acetyl compoud (462) this one is shifted to 8.15 ppm (see Table).

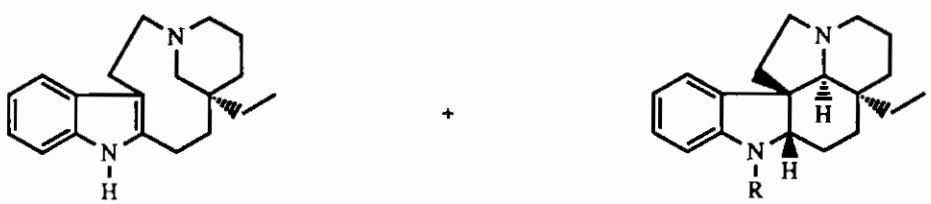
Finally, the fourth fraction was 19 - carbethoxy - 19 - demethylaspidospermidine (463) (11%) which was obtained as a colourless oil. Elementary analysis confirmed the empirical formula, $C_{21}H_{28}N_2O_2$. In the n.m.r. spectrum, the signals of the aromatic protons appeared at 7.1 - 6.6 ppm and those corresponding to the carbethoxy group at 4 ppm and 1.2 ppm respectively. The absorption at ν 3380 cm^{-1} indicated the presence of an N - H function. The structure elucidation of this compound is given by the mass spectrum (Scheme 94) which exibits a molecular ion at m/z 340. A retro Diels - Alder fragmentation occurs in ring C to form the charged species a, which then undergoes cleavage of the C - 5, C -6 bond. The C - 20 substituent (CH_2CO_2Et) was lost by a McLafferty rearrangement.

However, the course of the reaction depends markedly on the exact quality of the zinc used as Trojanek observed[123b] (Scheme 92b). Unfortunately, I have no means of knowing exactly what type of zinc Trojanek used.



(397) (454)

+



(3) (1) a, R=H
b, R=COCH3

Yields of the products of the rearrangement of (±)-1,2-dehydroaspidospermidine

Experiment	454	1a	3	1b
A	3%	2%	4%	44%
B	36%	2%	2%	7%

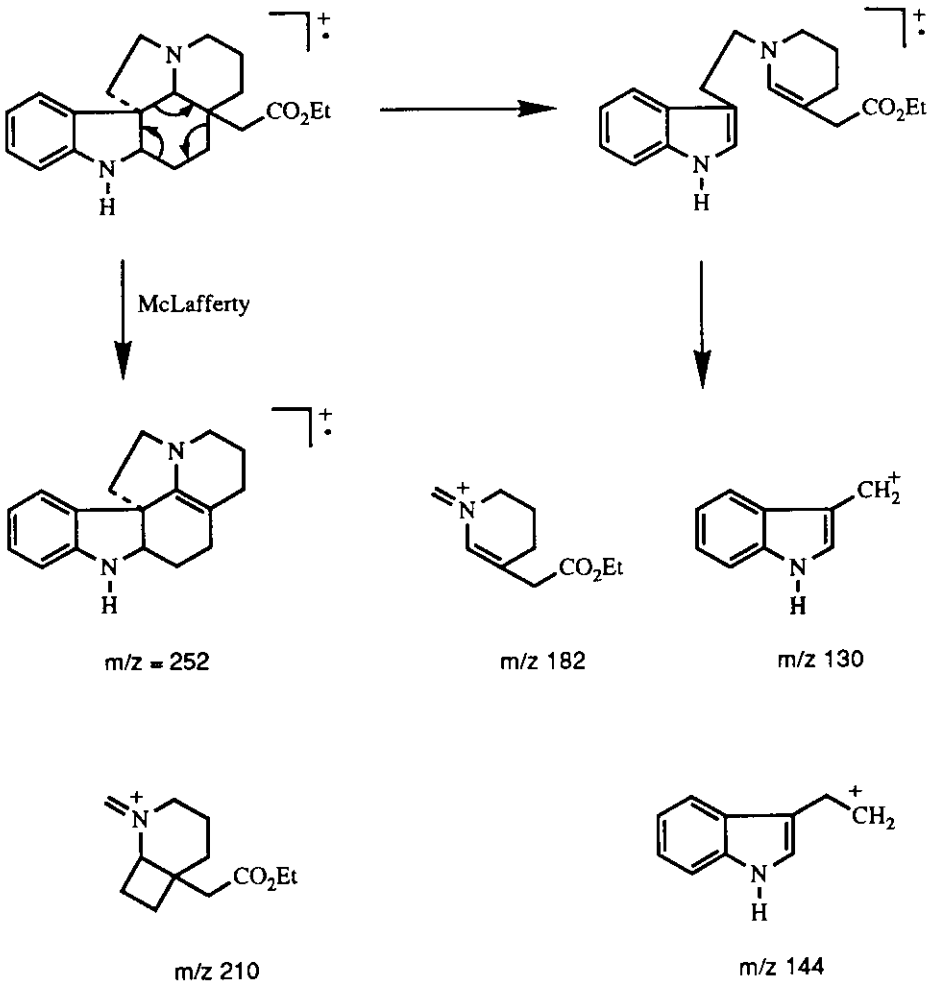
In both case the origin of the zinc was unknown.No differences were found either in their morphology (oval to spherical particles) or other properties compared (trace elements etc.), except for the particle size.

- In zinc A the size of the majority of the particle was up to 5-7μm,
- In zinc B up to 17 μm.

Scheme 92b

Strempeliopine (447)		Literature[123b] data for (447)
accurate mass	Found: M^+, m/z 294.17311 requires M^+, m/z 294.17320	----
microanalysis	----	----
i.r. ν_{max} ($CHCl_3$)	*2920, *2860,2800, 2740, *1720, 1660,1598, 1485, 1460, 1400, 1370, 1040 cm^{-1}	2805, 2765, 1643, 1597, 1475, 1460, 1395, 1370 cm^{-1}
u.v. λ_{max} (MeOH)	210, *230, 255 (sh), 280, 290 nm	291, 281, 255 nm
^1H n.m.r. δ ($CDCl_3$)	8.0 (1H, brd, J: 8 Hz; 12 - H)	8.05 (1H, bd, J: 8, 1.1 Hz; 12 - H)
	7.3 - 7.0 (3H, m, Ar - H)	7.23 (1H, bt, J: 8, 7.4, 1 Hz; 11 - H)
		7.17 (1H, bd, J: 7.4, 1 Hz; 9 - H)
	*4.1 (2H, q, J: 7.5 Hz; $CO_2C\underline{H}_2CH_3$)	7.06 (1H, dt, J: 7.4 Hz; 10 - H)
	3.2 (1H, t, J: 7 Hz, 7 - H)	3.25 (1H, bt, J: 7.2 Hz; 7 - H)
	3.0 (1H, m, 5 - H)	2.97 (1H, ddd, J: 11.3, 8, 5.3 Hz; 5 - H)
	2.8 (1H, m, 3 - H)	2.86 (1H, bdt, J: 11.2, 3.2 Hz; 3 - H)
	2.55 (1H, d, 19 - H)	2.63 (1H, d, J: 18.2 Hz; 19 - H)
	2.38 (1H, dd, 19 - H')	2.46 (1H, dd, J: 18.2, 2.4 Hz; 19 - H)
	2.21 (1H, dt, 3 - H')	2.23 (1H, dt, J: 11.2, 6Hz; 3 - H')
	2.08 (1H, dq, 6 - H)	2.09 (1H, dq, J: 14.1, 6.2 Hz; 6 - H)
	2.04 (1H, ddd, 5 - H')	2.04 (1H, ddd, 11.2 Hz, 5 - H')
	2.0 (1H, s, 21 - H)	2.03 (1H, s, 21 - H)
	1.9 (1H, m, 6 - H')	1.96 (1H, m, 6 - H').
	*1.2 (3H, t, 7.5 Hz; $CO_2CH_2C\underline{H}_3$)	
mass m/z (%)	*368 (12), 295 (28.9, [M + 1]), 294 (M^+, 76.2), 293 (3.5), 266 (1.4), 265 (1.9), 251 (5.2), 249 (1.6), 238 (0.3), 237 (2.3), 160 (3.9), 144 (10.4), 143 (5.7), 130 (7.3).	295 (22, [M + 1]), 294 (100, M^+), 293 (93), 266 (28), 265 (20), 251 (15), 249 (7), 238 (17), 237 (17), 160 (7), 147 (10), 144 (9), 143 (9), 130 (16).

* This sample contained some N_a - ethyl - 19 - carbethoxy - 19 - demethylaspidospermidine (461).



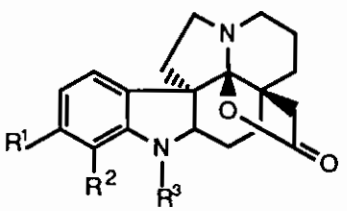
Scheme 94

Table III: ^{13}C n.m.r. chemical shifts obtained on N_a - acetyl - 19 - carbethoxy - 19 - demethyl aspidospermidine (462), 19 - carbethoxy - 19 - demethyl-aspidospermidine (463), and 12 - demethoxy - N - acetyl cylindrocarine (269)

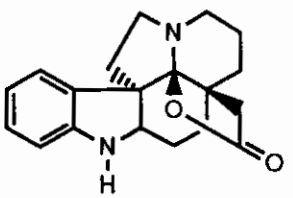
Carbone N°	(462)	(463)	(269)
2	67.56	64.79	67.61
3	52.8	53.56	53.04
5	52.23	52.5	52.22
6	39.22	38.08	39.33
7	53.33	53.52	53.52
8	137.34	134.30	137.44
9	124.33	122.76	124.33
10	122.23	119.13	122.32
11	127.8	127.53	127.96
12	118.35	110.58	118.59
13	140.8	149.63	141.12
14	34.54	21.56	21.61
15	34.54	34.89	34.83
16	25.80	28.12	29.74
17	24.35	24.32	24.59
18	171.4	171.79	171.84
19	42.47	42.47	42.36
20	35.84	36.13	36.03
21	69.15	69.83	69.85
$\underline{C}OCH_3$	168.38	-------	168.26
$CO\underline{C}H_3$	23.22	-------	23.19
$CO_2\underline{C}H_2CH_3$	60.52	59.86	--------
$CO_2CH_2\underline{C}H_3$	14.25	14.25	--------
OMe	-------	-------	51.03

2.3 Approach to the synthesis of the cimicine derivative (467).

Investigations were also carried out towards the conversion of the diester (267) into the selected cimicine - type compound (467). This group is represented by cimicine (10) and its 11 - methoxy derivative, cimicidine (464), isolated from *Haplophyton cimicidum*[129], and dichotamine (465), isolated from *Vallesia dichotama* Ruiz et Pav[130].

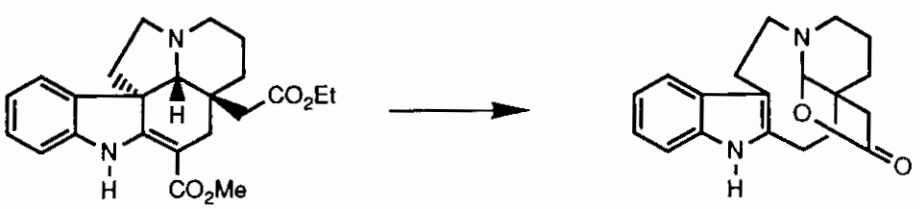


	R^1	R^2	R^3
(10) cimicine	H	OH	CO_2Et
(464) cimicidine	MeO	OH	CO_2Et
(465) dichotamine	H	MeO	CHO



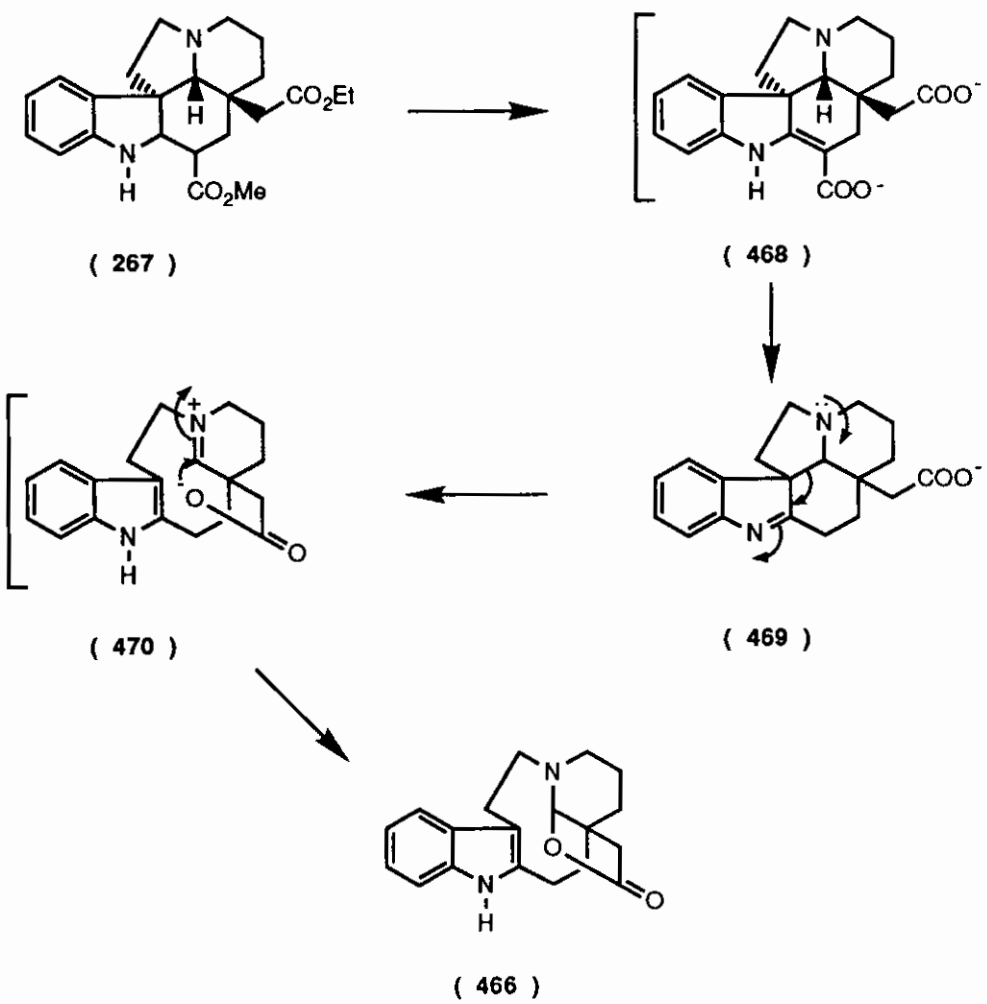
(467)

Brennan[57,131] has investigated the removal of the β - anilinoacrylate group of the diester (267) and found that mild basic hydrolysis procedure produced the pentacyclic lactone (466), simply by refluxing the diester in an excess of 5% potassium hydroxide in ethanol solution for 6 h.



(267) (466)

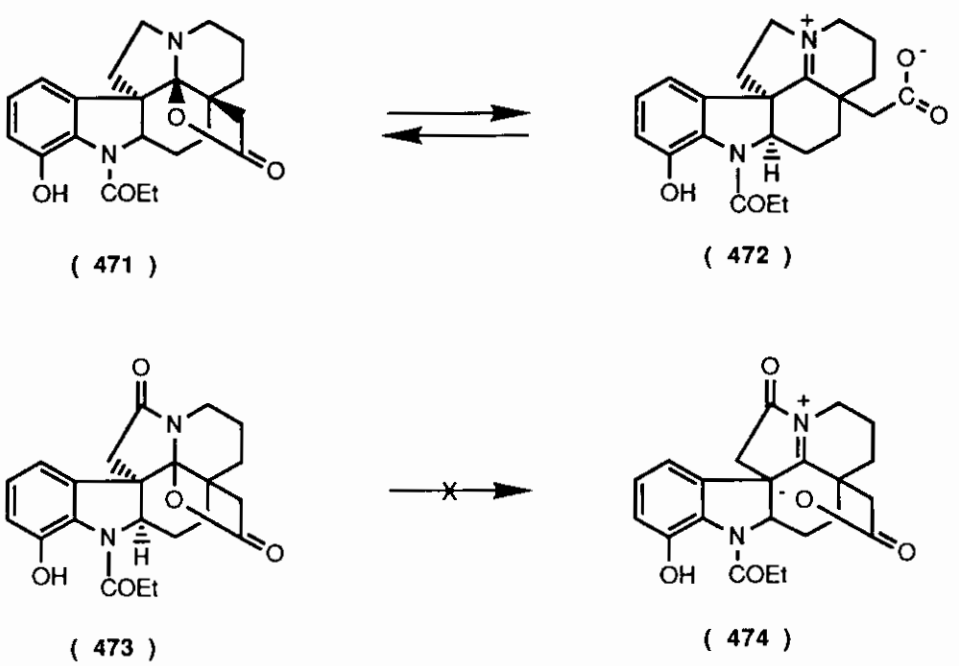
In our hands this reaction gave 38% yield of the lactone (466). Brennan[57] observed that the pentacyclic lactone (466) could have been formed from the indolenine (469) by a reverse Mannich fission of the 7, 21 bond in the indolenine (469), followed by reaction of the C - 18 carboxylate anion at C - 21 (Scheme 95).



Scheme 95

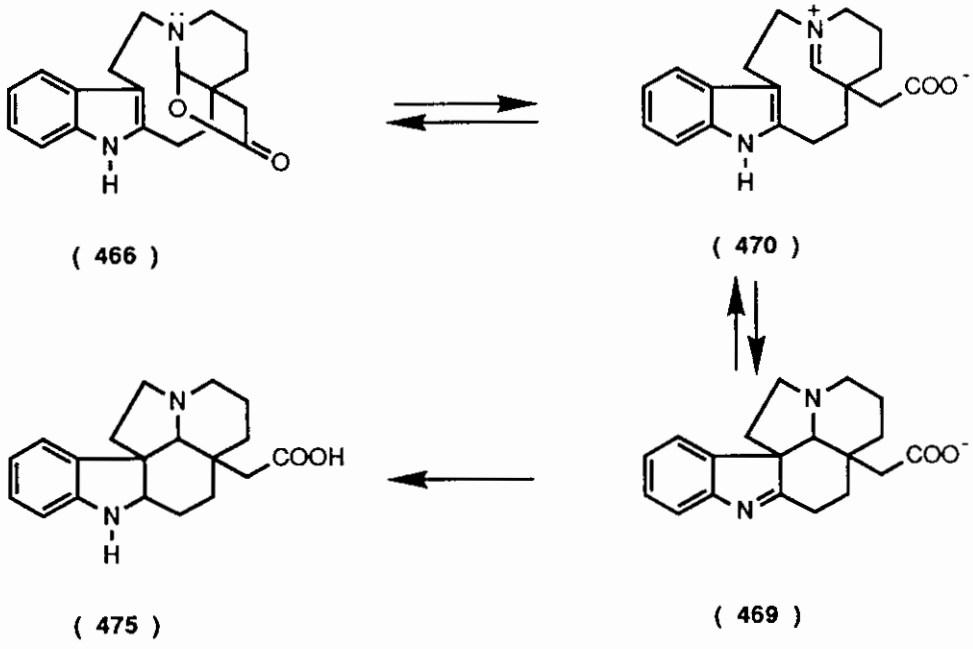
The spectroscopic data obtained on this material were found to be identical to those reported by Brennan[57]. Thus the n.m.r. spectrum showed signals at 8.2 and 5.1 ppm assignable to N - H and 21 - H protons respectively. Also, this spectrum

showed that both ester groups had been hydrolysed. The molecular ion was observed at m/z 310. Comparison of this pentacyclic - lactone (466) with cimicine (10) showed that both compounds produce a similar absorption in the i.r. spectrum at 1745 cm^{-1}, whereas the carbonyl stretching absorption of γ - lactones is normally observed at 1760 - 1780 cm^{-1}. However, Cava *et al.*[132] explained that the dramatic difference between the lactone carbonyl absorptions of cimicine (10) and the prepared 5 - oxocimicine (1800 cm^{-1}) is due to a major contribution from the zwitterionic, ring open dipolar canonical form (472), which lowers the wavelength of the carbonyl absorption. In contrast the 5 - oxocimicine (473) would not show resonance of this type, since in the dipolar form (474) the positively charged nitrogen is also part of a lactam function. This dipolar form (474) would therefore make little or no contribution to the overall structure (Scheme 96).

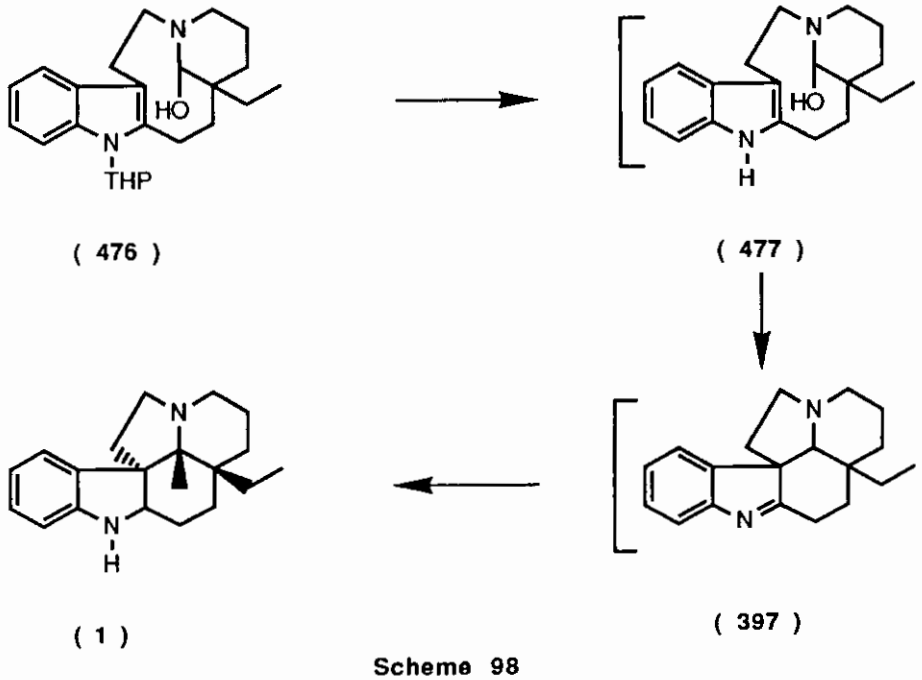


Scheme 96

Brennan's attempts to convert this carbinolamine lactone (466) into the indoline acid (475) (Scheme 97) using zinc metal in either hydrochloric acid - ethanol (pH = 4) or in acetic acid were unsuccessful, although Ban and co - workers[133] had shown that removal of the tetrahydropyranyl protecting group in (476) by the action of dilute acid afforded (397), which could then be reduced to aspidospermidine (1) (Scheme 98).

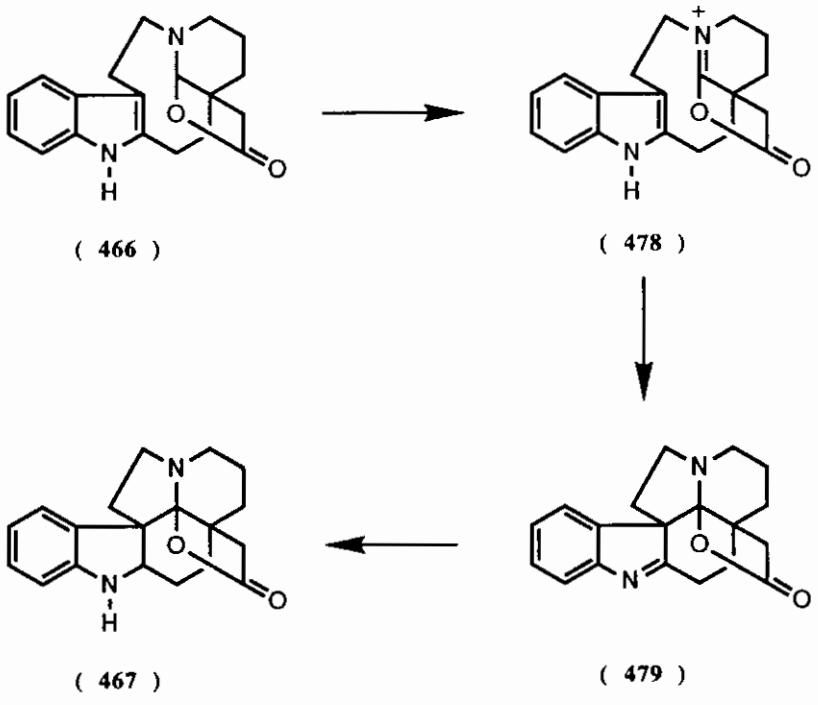


Scheme 97



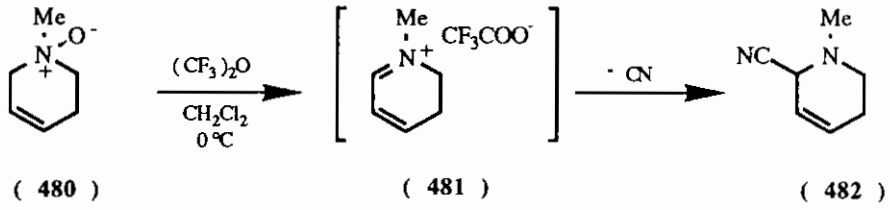
Scheme 98

It was therefore intended to reinvestigate the conversion of (466) into the iminium salt (478), which might then proceed *via* a transannular cyclisation to generate the indolenine (479). This compound (479) could then be reduced with the acid - stable, sodium cyanoborohydride, to give the cimicine type compound (467) (Scheme 99).



Scheme 99

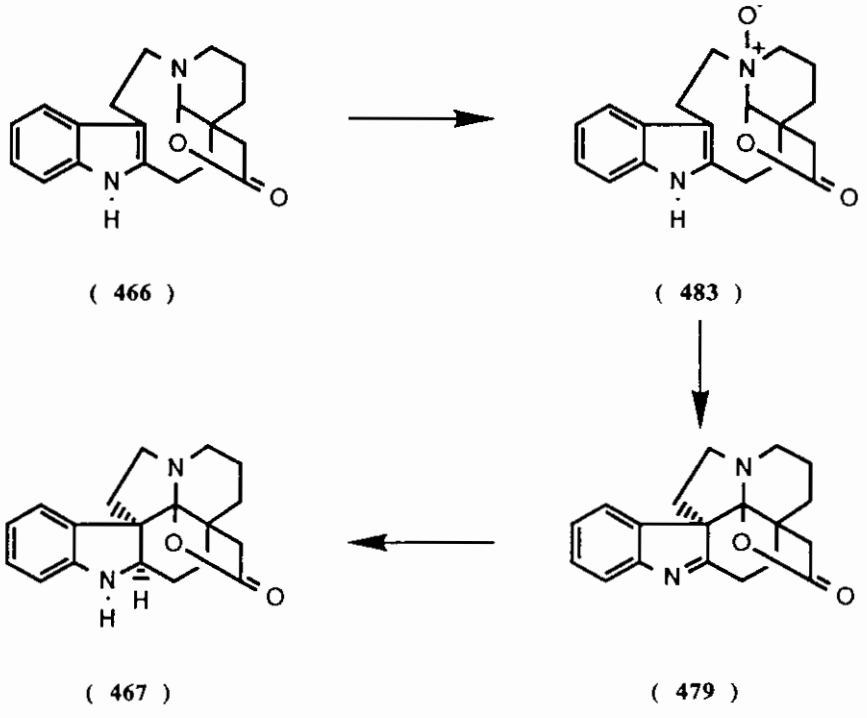
In 1980, Husson and co - workers[134] synthesized 5, 6 - dihydropyridinium salt (481) from the reaction of tetrahydropyridine N - oxide (480) with trifluoroacetic anhydride, which gave the nucleophilic addition product (482) with cyanide ion (Scheme 100).



(480) (481) (482)

Scheme 100

By analogy with their experiment it appeared to us that the reaction of the lactone (466) with peracid would give the N - oxide (483) which could be converted into (467) (Scheme 101). Therefore, the pentacyclic lactone (466) was reacted with m - chloroperbenzoic acid in anhydrous benzene at room temperture for 24 h . The residue was taken up in deuteriochloroform and cooled to 0 °C and then treated with trifluoroacetic anhydride. The resulting unstable indolenine was not fully characterised but immediately taken up in methanol and reduced with sodium cyanoborohydride under a nitrogen atmosphere. However, only a very polar unidentified compound was recovered from this reaction.



(466) (483)

(467) (479)

Scheme 101

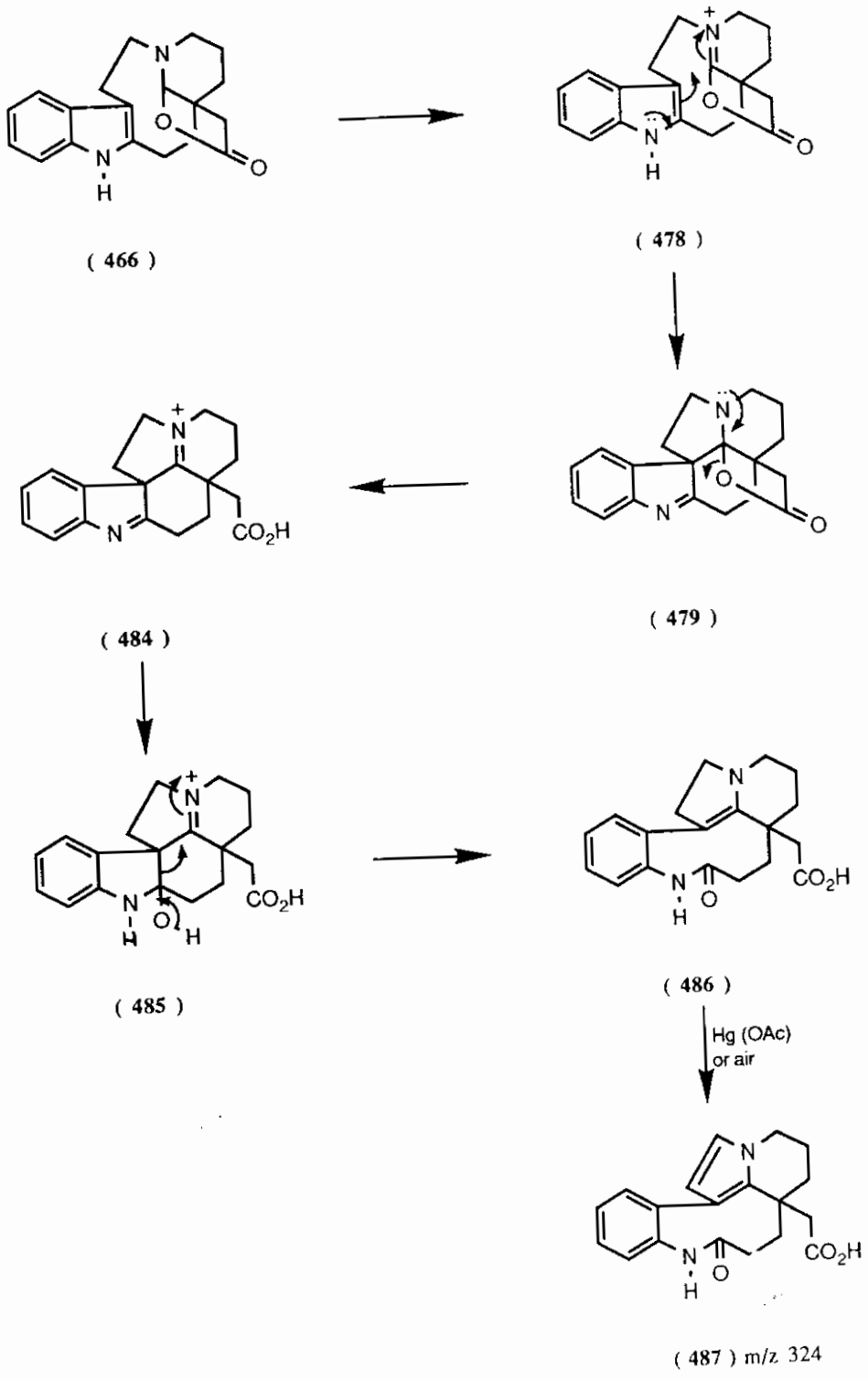
The second attempt involved the oxidation of the C - 21, N_b bond of the lactone (466) with mercuric acetate in acetic acid. This kind of reaction has been already reported in the introduction (Section 1.2)

The lactone (466) and mercuric acetate in acetic acid were stirred together at room temperature for 24 h and then refluxed under a nitrogen atmosphere for 6 h. The reaction of the resulting mixture with sodium cyanoborohydride produced the unexpected rhazinilam derivative (487), rather than the cimicine derivative (467) (Scheme 102).

The accurate mass obtained by high resolution mass spectrometry indicated the formula $C_{19}H_{20}N_2O_3$ (molecular ion at m/z 324) with a peak at m/z 265 confirming the loss of CH_2CO_2H group from the molecular ion. The proton n.m.r. spectrum of (487) exhibited an AB system corresponding to the two pyrrolic hydrogens at 6.25 and 5.6 ppm, a singlet resonance was also observed at 7.9 ppm (NH), and a multiplet owing to the aromatic protons at 7.45 - 7 ppm.

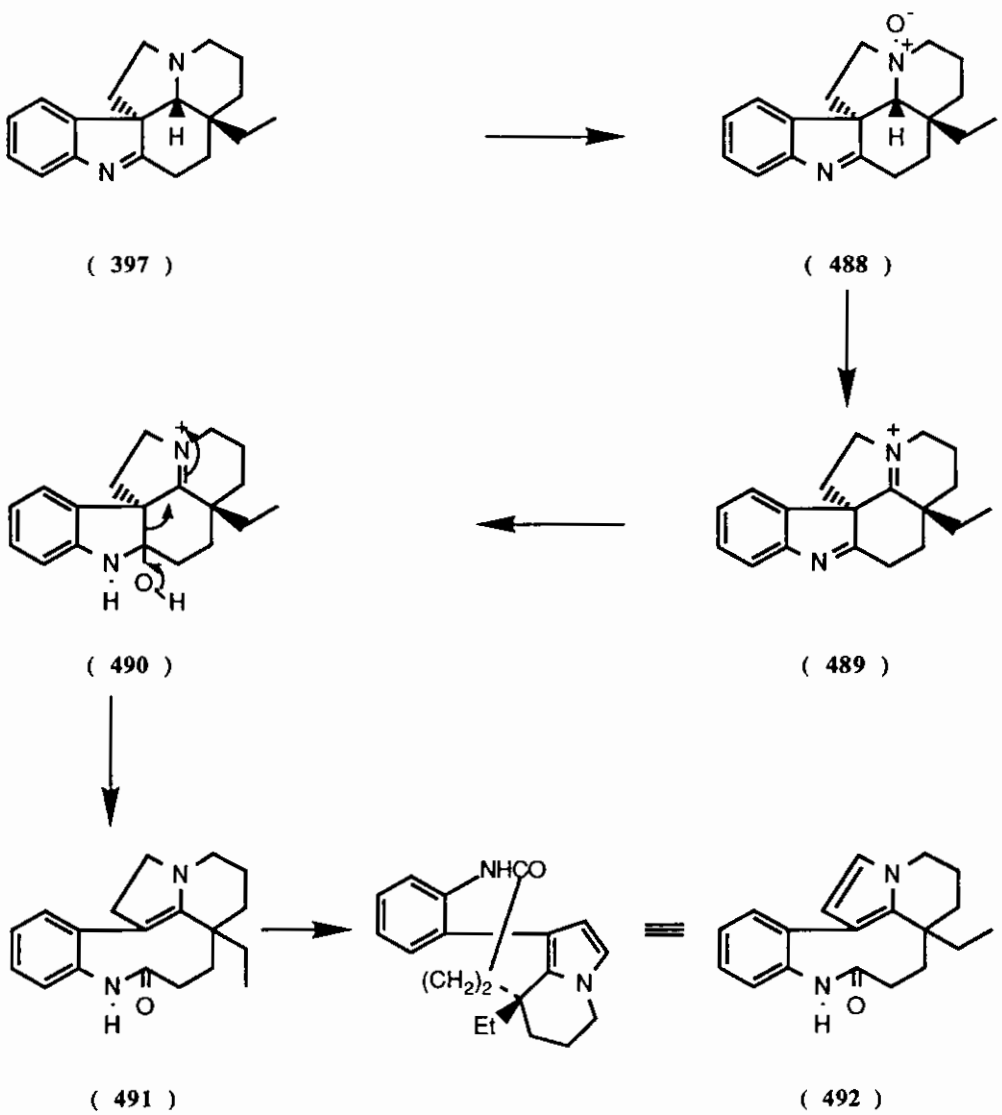
The alkaloid artefact (-) - rhazinilam[135a] (492) has been isolated by several authors from a number of different plant species; for example, *Rhazya stricta* Decaisne and *Melodinus australis*[135b].

A partial synthesis of rhazinilam (492) was reported by Smith and co - workers[136], starting from (+) - 1, 2 - dehydroaspidospermidine (397). The latter was oxidised with m - chloroperbenzoic acid, and then treated with aqueous iron (II) sulfate. Grob fragmentation of the intermediate (490), generated from the N_b - oxide (488) by a Polonovski reaction and hydration of the indolenine, gave (491) which



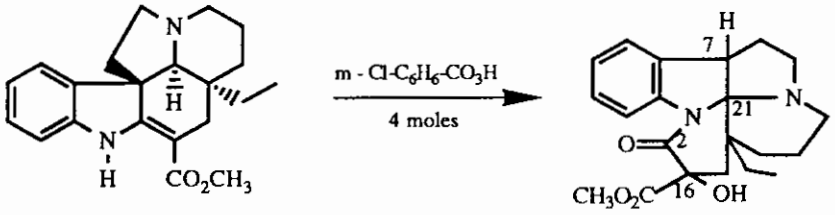
Scheme 102

was then dehydrogenated to give (-) - rhazinilam (492) in about 30% yield (Scheme 103).



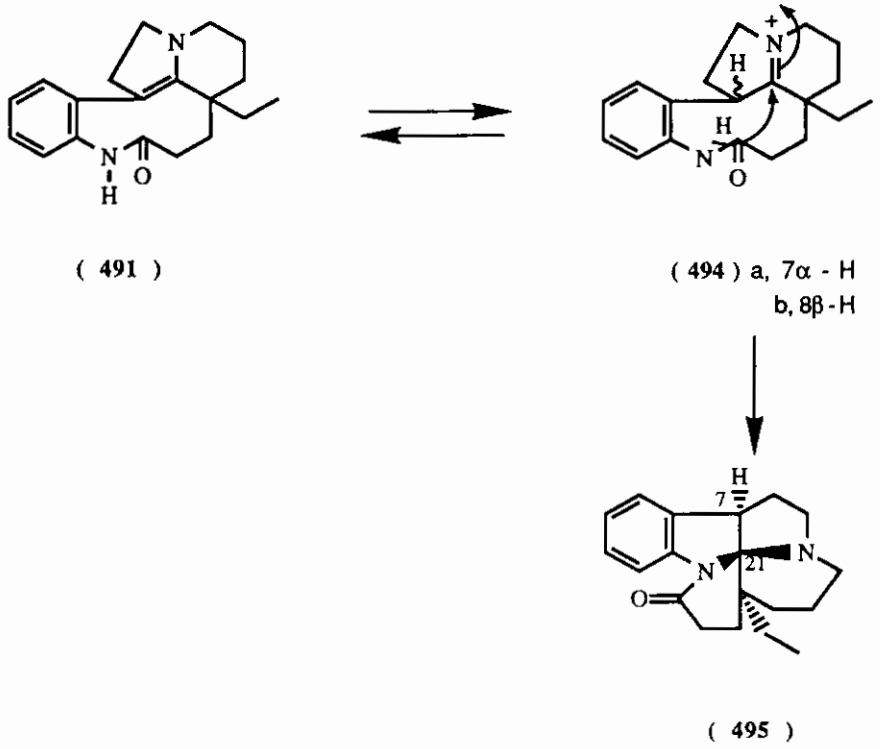
Scheme 103

Initial studies indicated[137] that the oxidation reaction is complex and depend on the conditions of the reaction; for example, treatment of vincadifformine (5) with an excess of m - chloroperbenzoic acid in refluxing benzene produced the lactam (493).



(5) (493)

Contemporaneously Le Men and Lévy[138] suggested that the intermediate (491) can yield an immonium ion by protonation at C - 7, which can then cyclise to form a pentacyclic lactam (495). However, only one of the C -7 epimers can cyclise to give the product (495) whose structure is given in Scheme 104a.



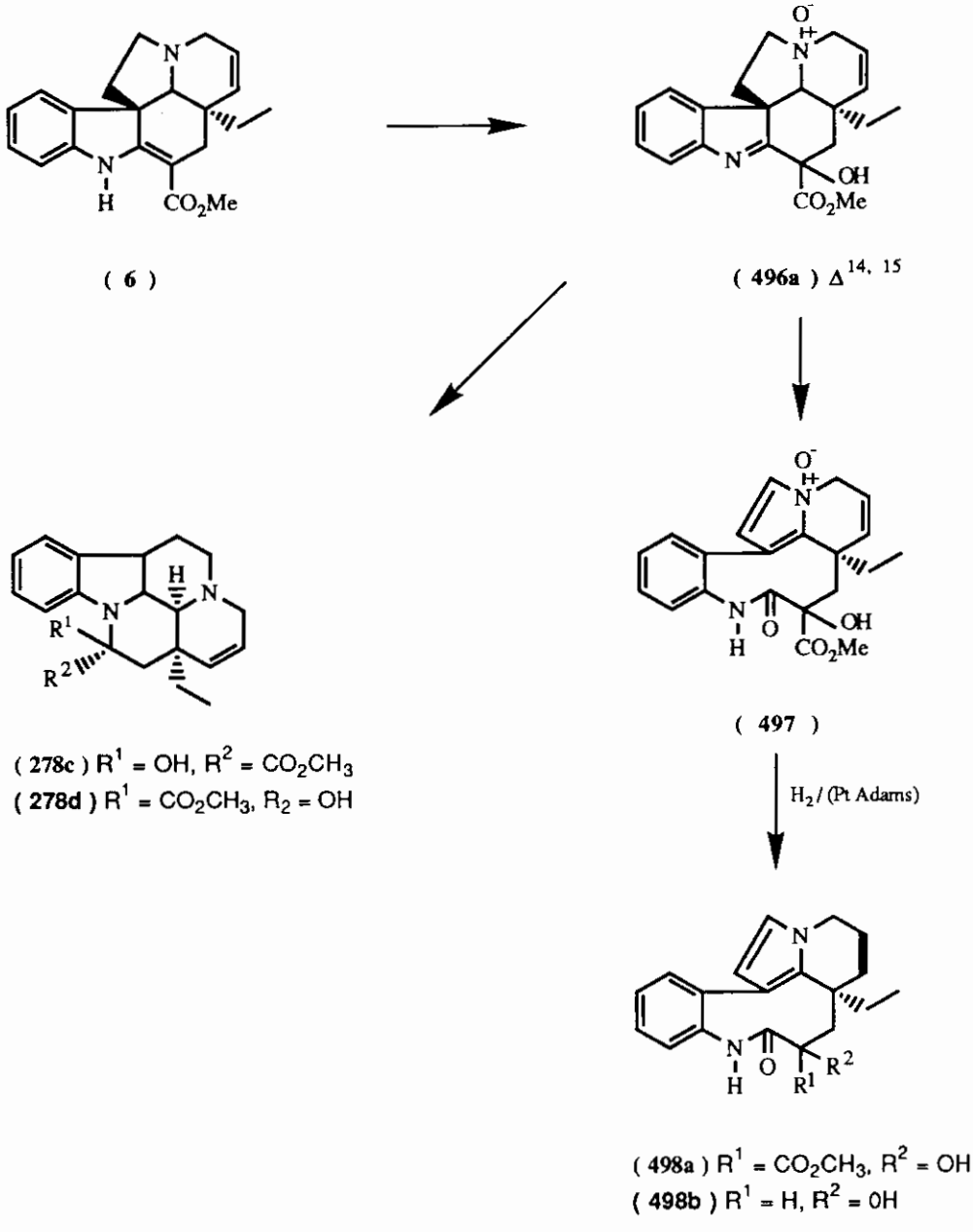
(491) (494) a, 7α - H
b, 8β - H

(495)

Scheme 104a

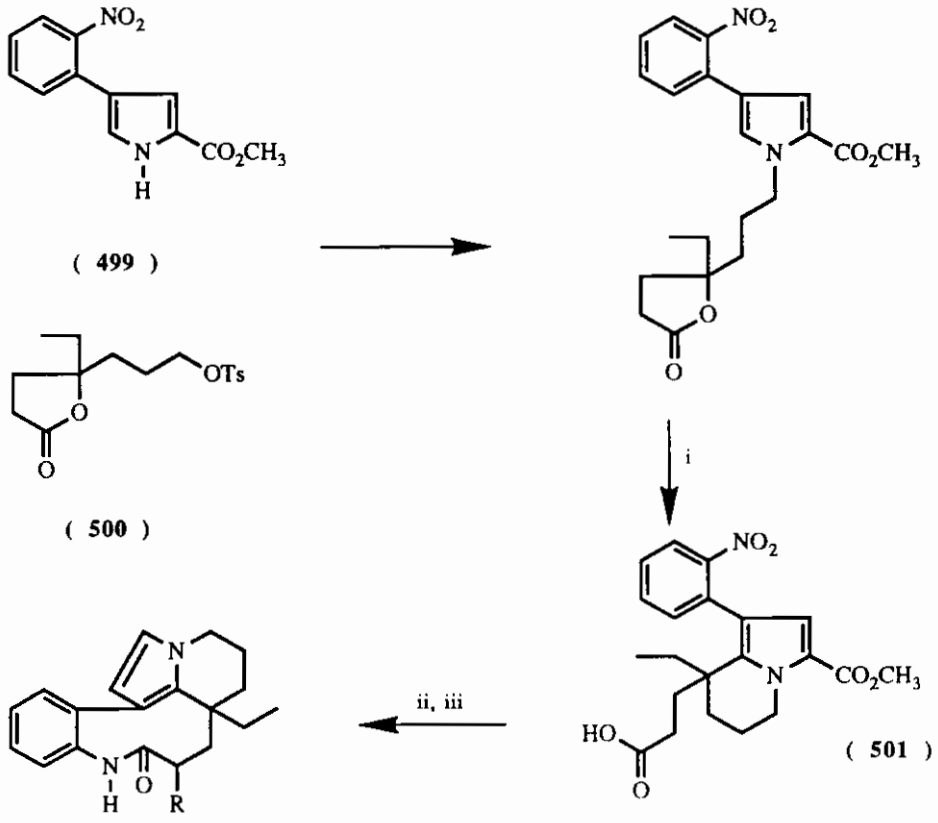
Similarly, Lévy and co - workers [139] during their transformation of tabersonine (6) into (+) - 14, 15 - dehydrovincamine (278c) and (+) - 14, 15 - dehydro, 16 - epivincamine (278d) (see section 1. 4) under oxidizing conditions (i.e. m -

chloroperbenzoic acid in benzene), followed by reaction with aqueous acetic acid and triphenylphosphine, isolated a new compound which was assigned the structure (498a) (Scheme 104b). Catalytic reduction (Pt) of the intermediate (497) led to (498a). Hydrolysis and decarboxylation of the ester (498a) gave 16 - hydroxyrhazinilam (498b).



Scheme 104b

Smith and co - worker[136a] have also achieved a total synthesis of rhazinilam. The key steps were the N - alkylation of 2 - methoxycarbonyl - 4 - (2' - nitrophenyl) pyrrole (499) with 4 - ethyl - 4 - hydroxy - 7 - tosyloxyheptanoic acid γ - lactone (500)[130], which on cyclisation gave the indolizine derivative (501). Reduction of the nitro group in (501) and lactonization with dicyclohexylcarbodiimide in tetrahydrofuran gave (±) - 5 - methoxycarbonylrhazinilam (502). Hydrolysis and decarboxylation then gave (±) - rhazinilam (492) in good yield (Scheme 105).

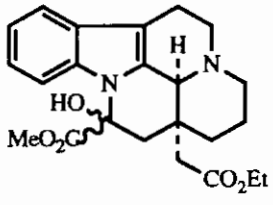


i, $AlCl_3$, CH_3NO_2; ii, PtO_2 / H_2 / EtOAc; iii, DCHCD / THF

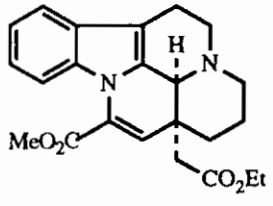
Scheme 105

2.4 Approach to the synthesis of vincamine derivatives.

In view of the therapeutic importance[141] of vincamine (278a), the major alkaloidal constituent of *Vinca minor* L. (*Apocynaceae*) and the fact that this alkaloid has been successfully obtained from vincadifformine in recent years by several authors (section 1.4) we took the opportunity to convert the novel alkaloid 19 - carbethoxy - 19 - demethylvincadifformine (267) into the analogous vincamine (503) and apovincamine derivatives (504).



(503)



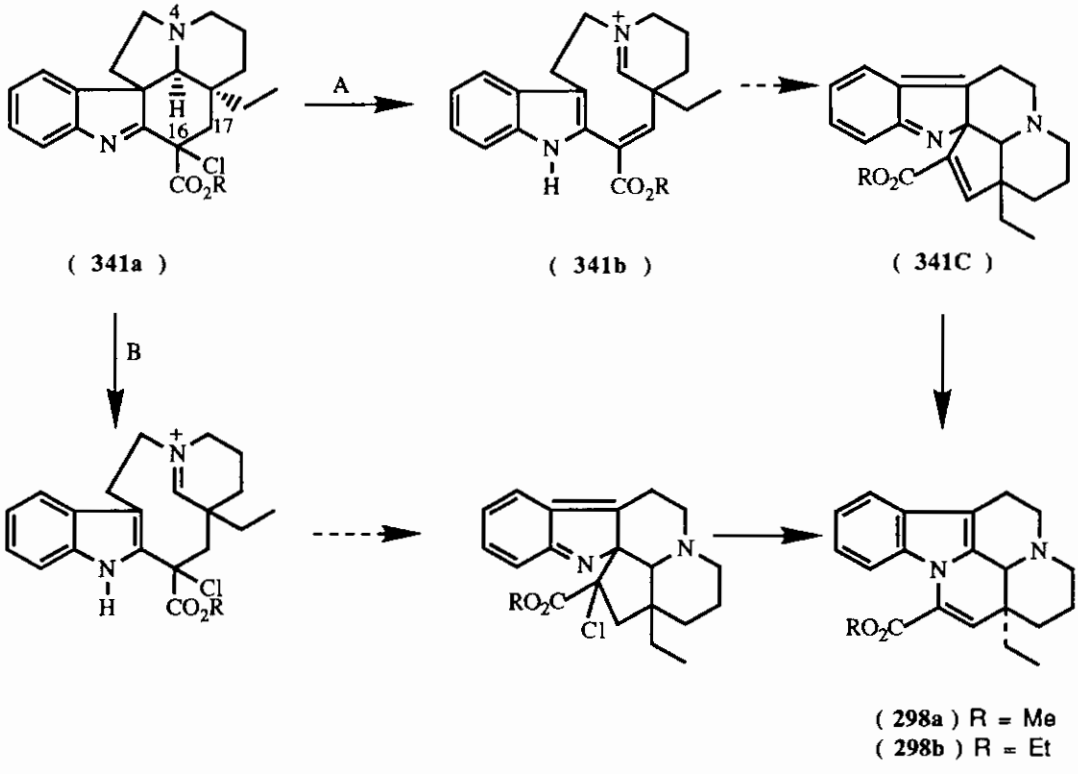
(504)

First of all, the synthesis of 19 - carbethoxyapovincamine (504) was achieved in one - pot process from the pentacyclic ester (267), *via* the chloroindolenine (341a).

Reaction of 19 - carbethoxy - 19 - demethylvincadifformine (267) with N - chlorosuccinimide in dry trifluoroacetic acid at room temperature for 4 h gave the corresponding chloroindolenine intermediate. This compound, when refluxed in trifluoroacetic acid without isolating it, gave the analogous apovincaminate ester (504) in about 56% yield. Alternatively[142], the chloroindolenine could also be obtained by means of t - butylhypochlorite in dichloromethane.

Because no intermediates were isolated in this transposition, two mechanisms have been proposed[76] (Scheme 106). In the first route (A), the chlorine is eliminated in the first step whereas in the second route (B), this is conserved until the end of the

reaction. However, in both cases, the last step is most likely to undergo a [1, 5] sigmatropic shift to form the desired apovincamine (298a)



Scheme 106

The empirical formula, $C_{23}H_{26}N_2O_4$, of (504) indicated by microanalysis was also confirmed by the mass spectrum, which exhibited a molecular ion at m/z 354.

The u.v. spectrum showed it to be an indole derivative with λ_{max} at 226, 272, 313 nm. Further structural information was obtained from the infrared spectrum in chloroform, e.g., the band at 3350 cm^{-1} characteristic for an NH - grouping was absent, a band at 1720 cm^{-1} (COOEt) as well as the appearance of two new bands 1638, 1618 cm^{-1} (COOMe) suggested extended conjugation in (504). The proton n.m.r. spectrum showed a singlet at 6.46 ppm attributed to the olefinic proton (H -

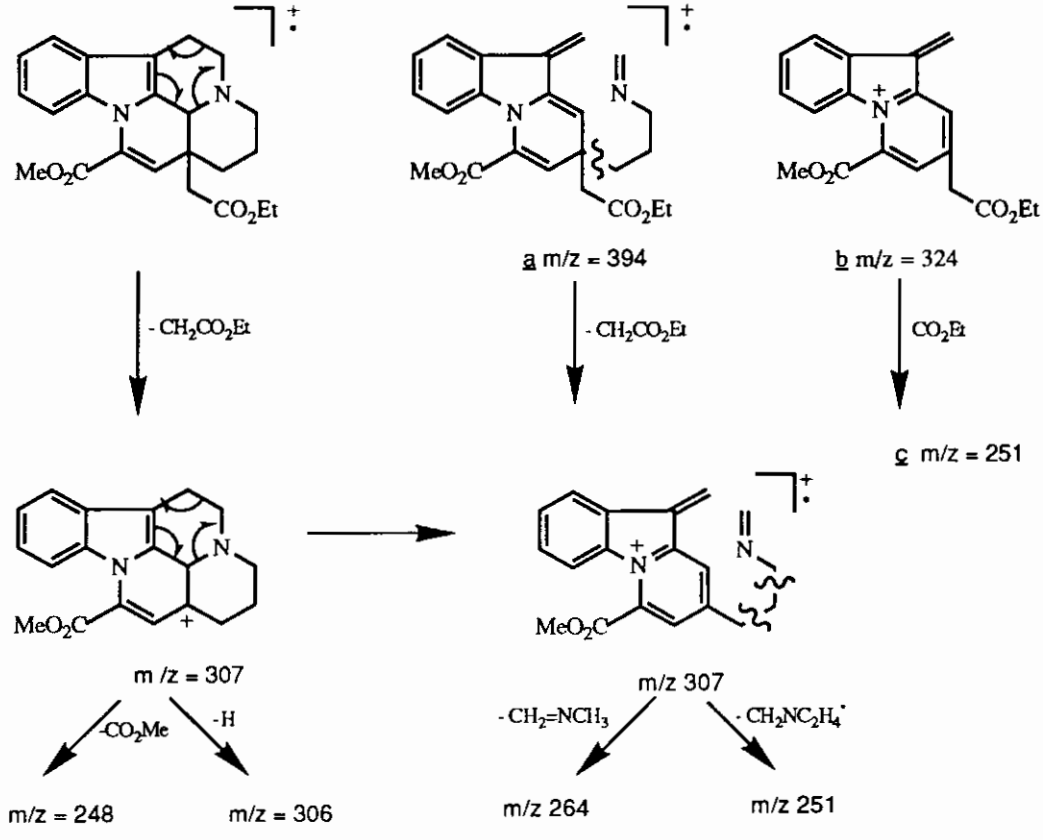
17), a signal owing to the proton H - 21 at 4.29 ppm, the protons of $COOCH_3$ are shown at 3.94 ppm as a singlet, and the methylene protons of C - 19 at 2.17 (s) ppm. The CH_2 of the ester group is observed as a quartet at 4.17 ppm, the methyl group as a triplet at 1.28 ppm and the aromatic protons between 7.25 and 7.1 ppm as multiplets in accord with Csaba Szántay's product (298b) which has valuable therapeutic properties[143]. The ^{13}C n.m.r. spectrum displayed twenty - three resonances which are given in Table IV.

Furthermore, it has been noted that the apovincamine derivative (504) exhibits a fragmentation behavior which is in satisfactory agreement with those of eburnamenine (286) and apovincamine (298a) when allowance is made for the appropriate mass unit increments in (504). The only significant primary decomposition is apparently the retro Diels - Alder fission of the β - carboline ring (ring C), which leads to species a in which the highly activated 16 - 17 bond can break by homolysis to the aromatic fragment b [M - 70]. This ion b, in turn, can lose a COOEt radical to give species c (Scheme 107)

The results obtained are very similar to those reported in the literature. However, Trojánek[144] *et al.* have reported that vincamine (278a) on being heated to 220 °C or by reaction with acetic anhydride lost one molecule of water forming apovincamine (298a). This compound (298a)[145] can also be produced in good yield by heating vincamine in dry methanol saturated with gaseous hydrogen chloride.

(278a) (298a)

In view of the reported pharmacological properties of apovincamine (298a) and (+) - apovincaminic acid ethyl ester (298b) (cavinton or vinpocetine DCI) as cerebral antianoxic, we hope that the new alkaloid (504) will have a significant therapeutical value.



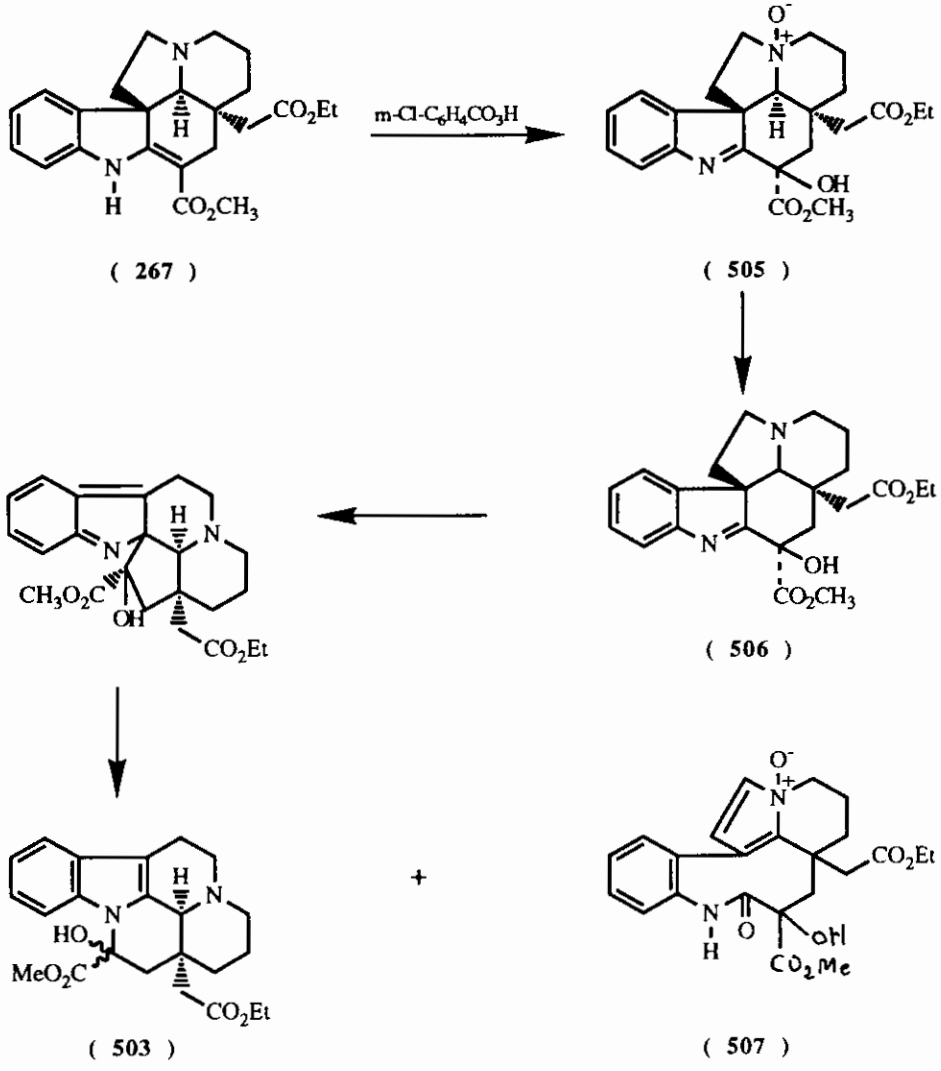
Scheme 107

Table IV: ^{13}C n.m.r. data of 19 - carbethoxyapovincamine (504), (+) - apovincaminic acid ethyl ester (cavinton) (298b), and vincamine (278a).

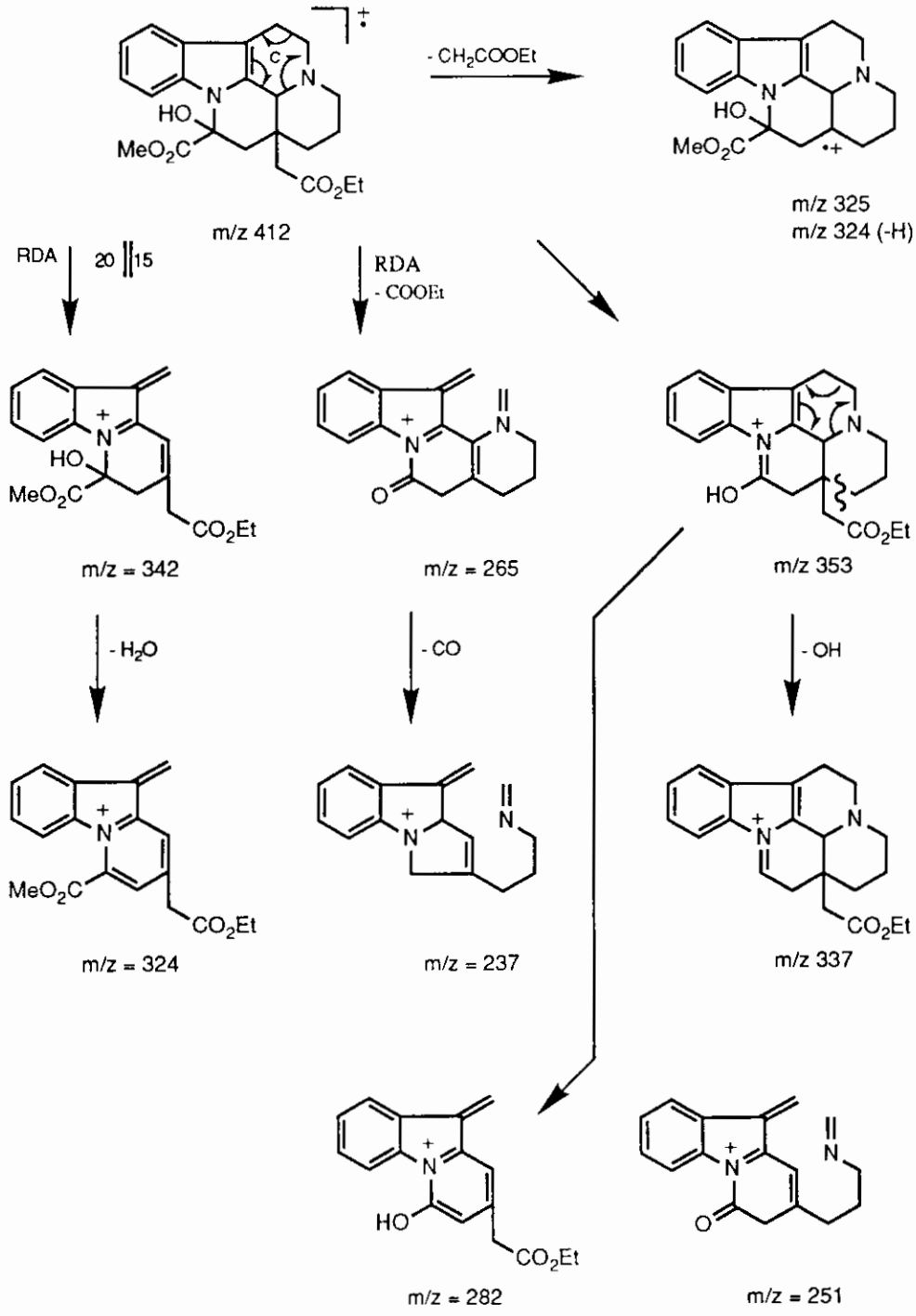
Carbone N°	apovincamine deriv. (504)	Cavinton (298b)	vincamine (278a)
2	130.33	130.93	131.4
3	44.7	44.81	44.5
5	51.40	51.37	50.9
6	16.35	16.28	16.9
7	108.97	108.51	105.9
8	128.96	128.93	128.9
9	118.26	118.05	118.4
10	120.32	120.03	121.5
11	122.07	121.62	120.1
12	112.52	112.42	110.2
13	134.12	133.89	134.1
14	20.42	20.28	20.8
15	36.8	27.20	25.2
16	127.66	128.32	81.9
17	126.86	127.84	44.5
18	171.36	8.68	7.6
19	29.31	28.6	28.8
20	39.52	37.57	35.1
21	56.32	55.58	59.1
22	163.64	163.34	174.4
$CO_2\underline{C}H_3$	52.47	--------	54.1
$CO_2\underline{C}H_2CH_3$	60.44	61.64	------
$CO_2CH_2\underline{C}H_3$	14.24	14.12	------

The ^{13}C spectrum of cavinton has not been reported in literature (sample received from C. Szántay).

Meanwhile, the reaction of the diester (267) under oxidative conditions[65b] by means of m - chloroperbenzoic acid (2.2 equiv.) in dry benzene involves an early key intermediate (505) which was hydrogenated at room temperature and pressure using 5% palladium on barium sulphate. Treatment of (505) with a mixture of (2: 3) (v / v) acetic acid and water produced after 12 h stirring a very polar mixture. Nevertheless, four products were detected by t l c and were found to be the rhazinilam derivative (507), in which the empirical formula $C_{23}H_{26}N_2O_7$ gave a molecular ion at m/z 442, the N_b - oxide - hydroxyindolenine (505) ($C_{23}H_{28}N_2O_6$, m/z 428), and the desired vincamine derivative (503) with some trace of recovered material (Scheme 108).



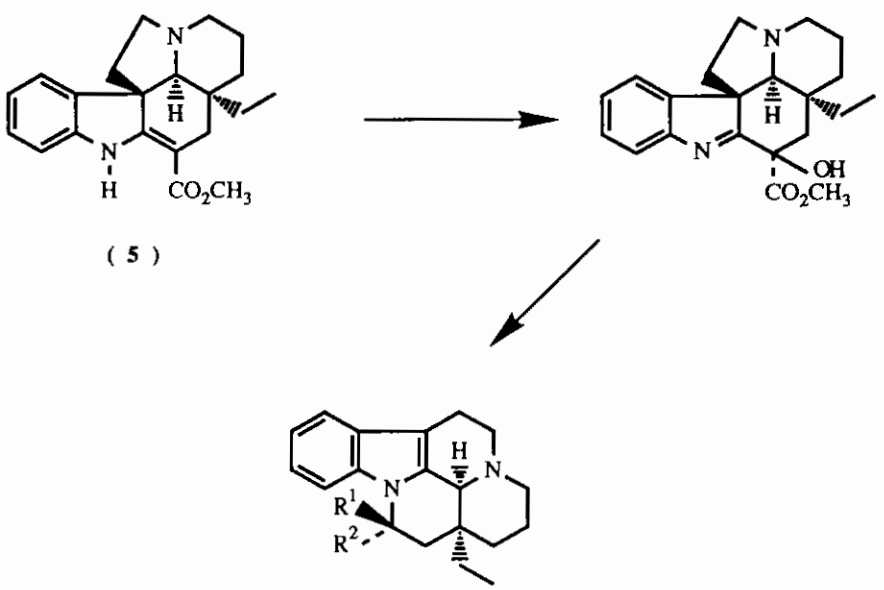
Scheme 108


- CH2COOEt
m/z 412
m/z 325
m/z 324 (-H)
RDA
20 ‖15
RDA
- COOEt
m/z = 342
m/z = 265
m/z 353
- H2O
- CO
- OH
m/z = 324
m/z = 237
m/z 337
m/z = 282
m/z = 251

Scheme 109

The structure of the vincamine derivative (503) was fully confirmed by mass spectrometry. The spectrum showed the well established[146] fragmentation pattern of the eburnamine (286) and vincamine (278a) skeleton (Scheme 109). The molecular ion corresponding to the formula, $C_{23}H_{28}N_2O_5$, was found at m/z 412.

Recently, Danieli has reported briefly that when vincadifformine (5) is treated under mild oxidative conditions, which avoid the formation of the N_b - oxide (i.e. bubbling a stream of ozone into a 5% w/v solution of vincadifformine (5) in 0.87 N - H_2SO_4 - MeOH (3 : 1) at 60 °C) the product obtained was a (7 : 3) mixture of vincamine and its 16 - epimer (Scheme 110).



(**278a**) R^1 = OH, R_2 = CO_2Me
(**278b**) R^1 = CO_2Me, R_2 = OH

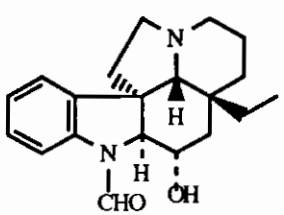
Scheme 110

In our hands, this ' one - pot ' method of converting the pentacyclic diester (267) into the vincamine analogue (504) resulted in a very polar material which was

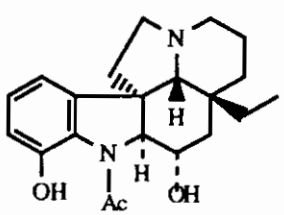
difficult to extract over a range of pH values (basic, neutral). The solvent polarity is crucial to the success of the reaction. Changing the solvent to the ethyl acetate, for example, may give the desired product. Unfortunately, the lack of material (267) did not allow this rearrangement to be investigated further.

2.5 Approaches to the synthesis of strictanine (507)

Strictanine (507) was recently isolated by Atta - Ur - Rahman and Sohail Malik[90] from the fruit of *Rhazya stricta* Decsne which is an indigenous medicinal plant widely distributed through Western Asia and abundantly found in Pakistan[147,149]. This medicinal plant has long been used for the treatment of various diseases; for example, the anticancer activity of some of the indole alkaloids of the plant has been reported[148,149]. However, the structure of (507) was proposed on the basis of nuclear magnetic resonance spectrometry.



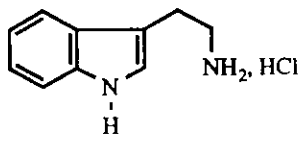
(507)



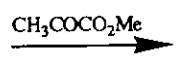
(508)

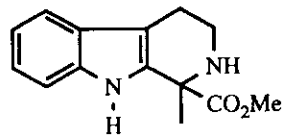
We report here the first total synthesis of this compound (507) starting from (±)-vincadifformine (5) which was previously prepared from tryptamine hydrochloride (Scheme 111). This Scheme could also be extended to a synthesis of spegazzinine (508)[150] by choosing the appropriate 7 - hydroxy - tryptamine.

Kuehne[32,33,35] and his co - workers have elegantly synthesized vincadifformine (5) through a secodine intermediate (150) in only three steps with 60% overall yield from the readily available tryptamine hydrochloride (151a). Condensation of (151a) with methyl pyruvate in dry methanol gave the α - carbomethoxy - α - methyltetrahydro - β - carboline ester (152b), which on reaction with the appropriate chloroaldehyde (156) in toluene produced the spiroenammonium

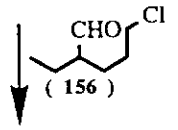


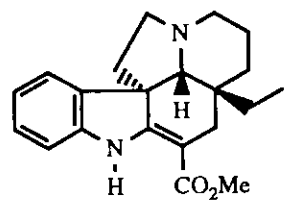
(151a)



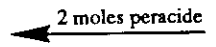


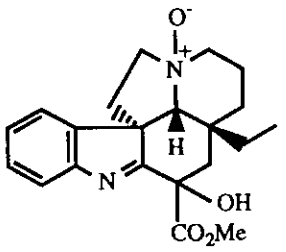
(152b)



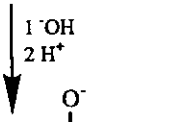


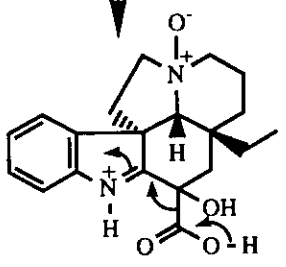
(5)



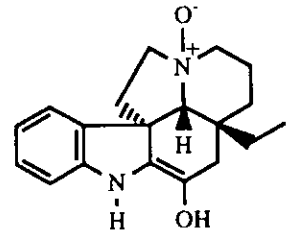


(496b)

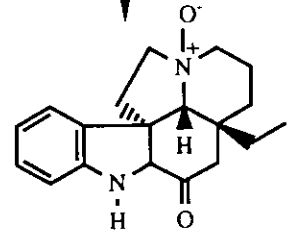




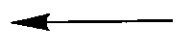
(509)

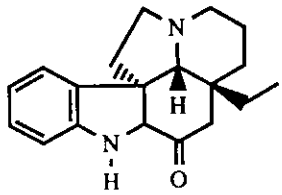


(510)

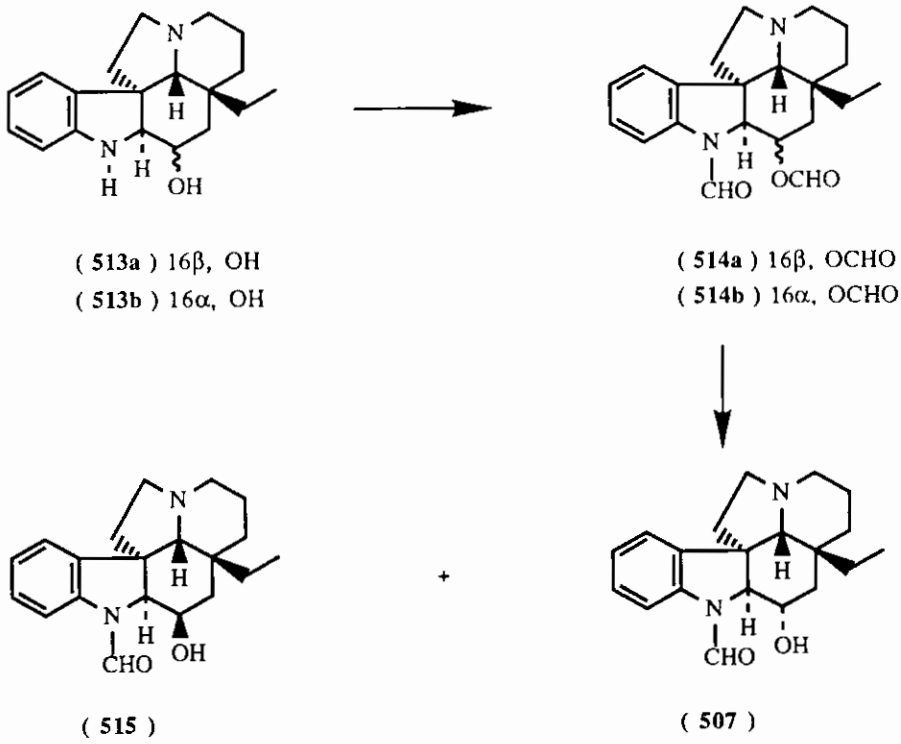


(511)





(512)



(**513a**) 16β, OH
(**513b**) 16α, OH

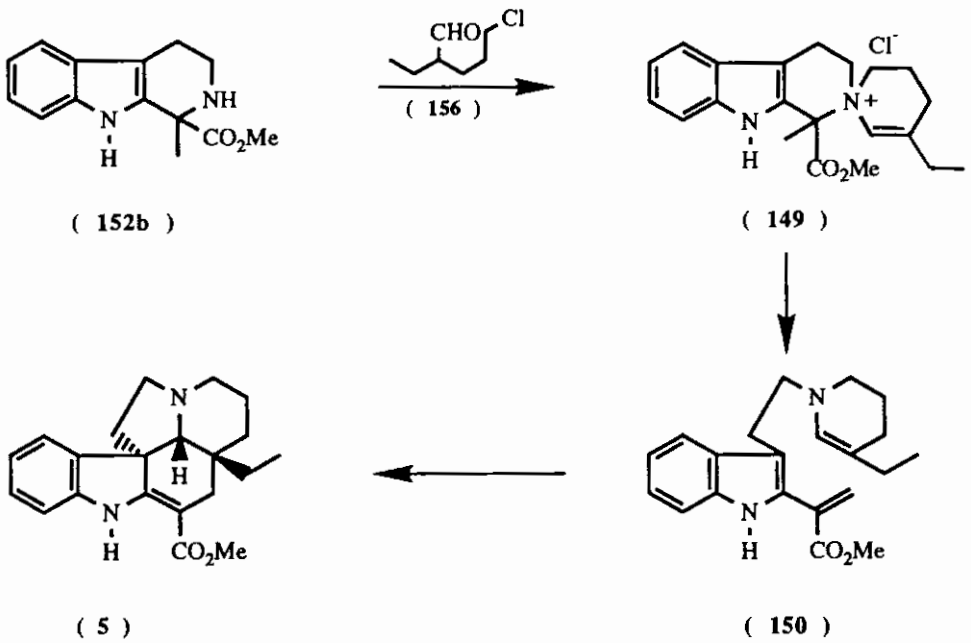
(**514a**) 16β, OCHO
(**514b**) 16α, OCHO

(**515**)

(**507**)

Scheme 111

intermediate (149), generated by enamine formation and intramolecular quaternization. It was reported that this intermediate undergoes fragmentation to produce the transient secodine intermediate (150), which undergoes spontaneous biomimetic cyclisation to give vincadifformine (5) (Scheme 112).

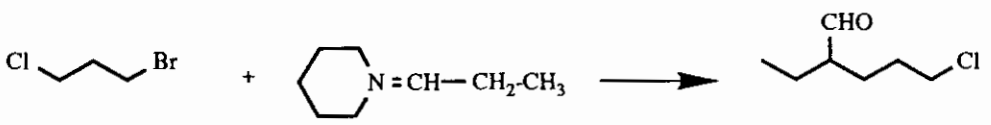


Scheme 112

Although the preparation of the required 5 - chloro - 2 - ethylpentanal (156) used in this synthesis was not described by Kuehne[33], it could be obtained most directly by alkylation of the lithium salt of an imine derivative of butyraldehyde (155) with 1 - bromo - 3 - chloropropane. Thus, condensation of cyclohexylamine and butyraldehyde gave the corresponding aldimine in 68% yield as a colourless oil.

Such aldimines[151] are conveniently metallated at the position α to the functional group, by using a very powerful base, i.e. activated lithium diethylamide generated in situ from lithium and a secondary amine in benzene/hexamethylphosphoramide. The anion obtained is alkylated with 1 - bromo - 3 - chloropropane to give, after aqueous

acid hydrolysis, the desired chloroaldehyde (156) in about 80% yield as a colourless oil (b.p. 100 °C/0.5 mm Hg). The i.r. spectrum showed two distinct absorptions at ν_{max} 1720 cm^{-1} and 650 cm^{-1} corresponding to the aldehydic group and the C - Cl bond respectively, while the n.m.r. spectrum showed that the formyl group resonated as a doublet at 9.5 ppm.



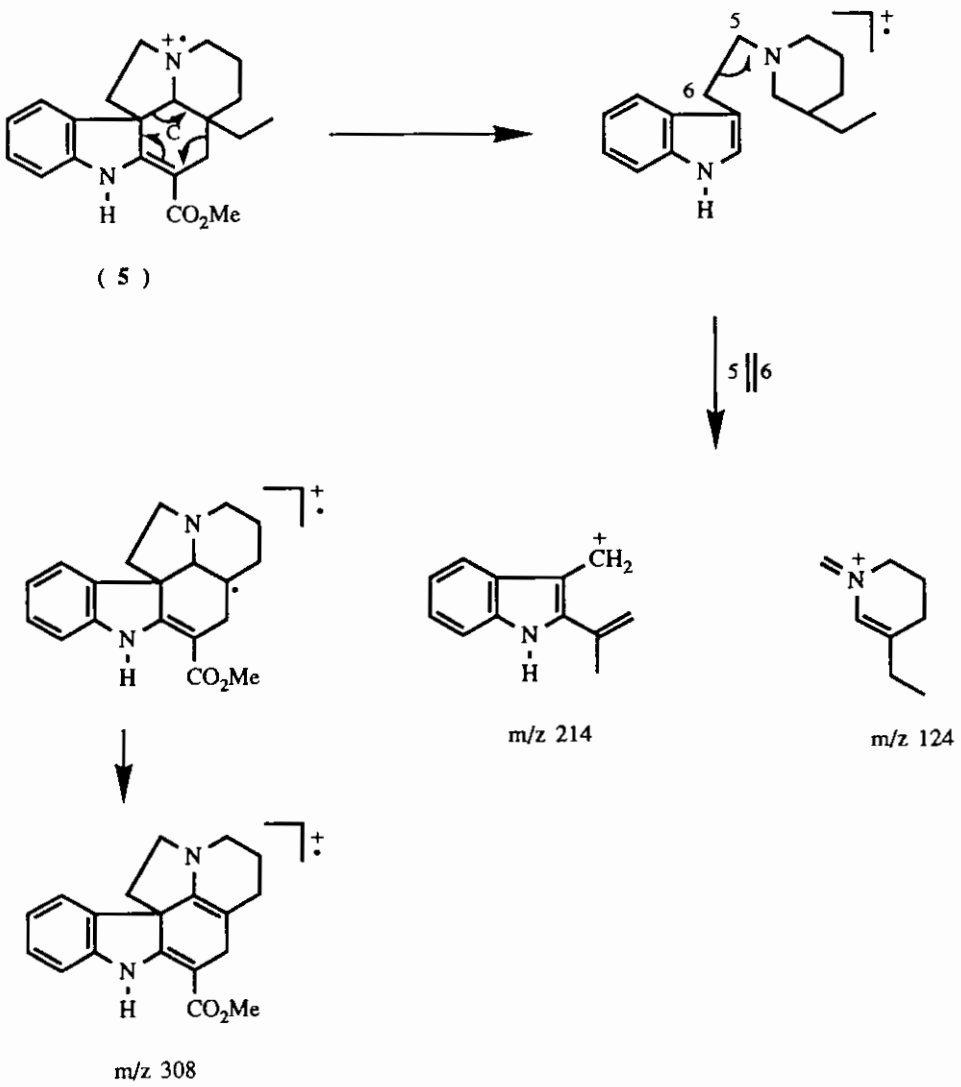
(155) (156)

The aldimine (155) was obtained by condensation of cyclohexylamine and butyraldehyde according to the general procedure used by Thiollais[152].

Reaction of the α - carbomethoxy - α - methyltetrahydro - β - carboline (152b), prepared already from the condensation of tryptamine hydrochloride and methyl pyruvate in dry methanol, with the readily available chloroaldehyde (156) in refluxing toluene under nitrogen with a Dean Stark water separator proceeded smoothly and was judged to be complete after 120 h. Diazobicycloundecene (DBU) was added to the reaction mixture after 100 h in order to help the Hofmann fragmentation to form the secodine intermediate (150). Separation by careful chromatography gave the desired vincadifformine as a colourless crystalline solid, m.p. 125 °C, in 81% yield.

The u.v. spectrum showed maxima at 222, 296, 324 nm, identical with those reported for natural vincadifformine[153]. The microanalysis gave the required formula, $C_{21}H_{26}N_2O_2$, which was confirmed by mass spectrometry. The molecular ion was found at m/z 338 and the major fragment at m/z 124. The

fragmentation occurred by a type of retro Diels - Alder decomposition of ring C followed by homolysis of its C - 5, C - 6 bond as for the aspidospermine - type skeleton (Scheme 113).

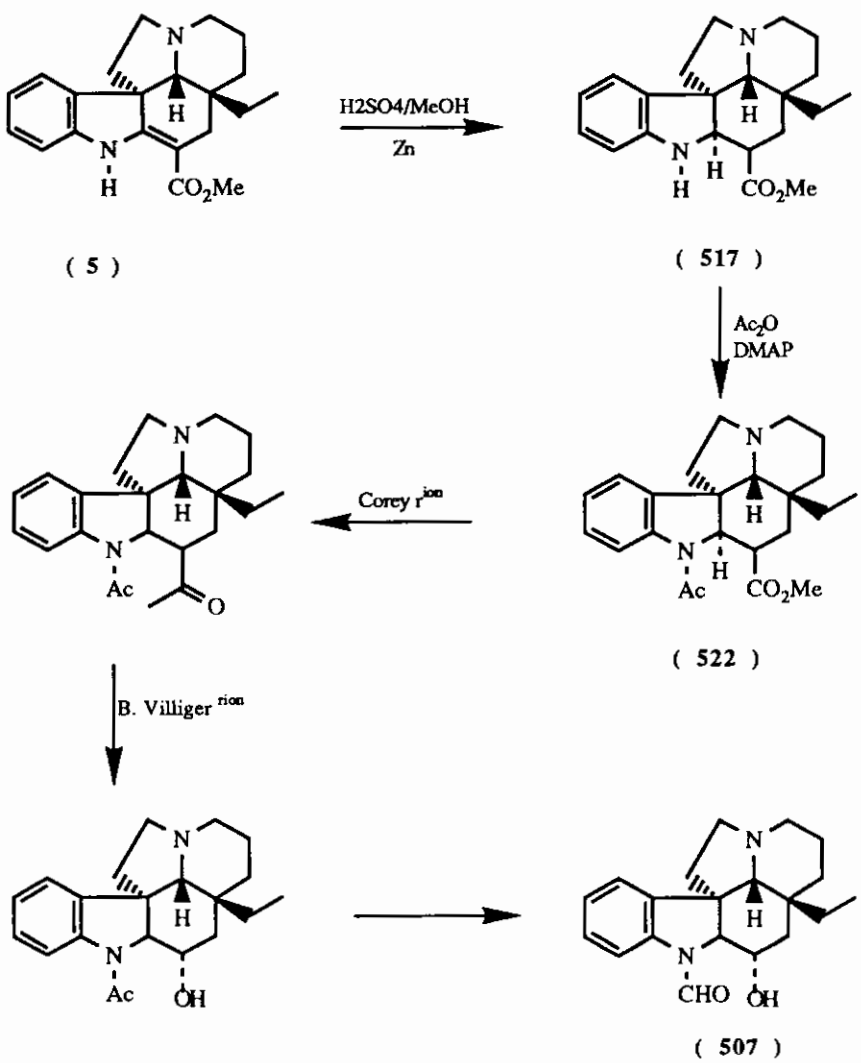


Scheme 113

In the proton n.m.r., the most characteristic signals were a methoxy group at 3.75 ppm, four aromatic protons at 7.2 - 6.5 ppm, an NH proton at 8.9 ppm and a

triplet at 0.6 ppm, corresponding to the protons of the C - 18 atom. The ^{13}C n.m.r. gave 21 absorptions and are listed in Table V.

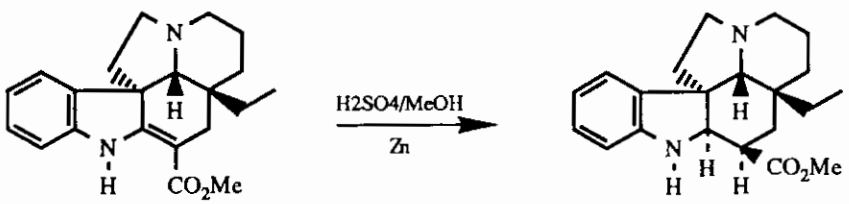
Two methods were investigated concurrently towards the synthesis of the Aspidosperma alkaloid strictanine (507) (N_a - Formyl - 16α - hydroxyaspidospermidine). It was hoped that the use of the readily available (±) - vincadifformine in the planned synthetic scheme 114 would allow this synthesis to be completed.



(5) (517) (522) (507)

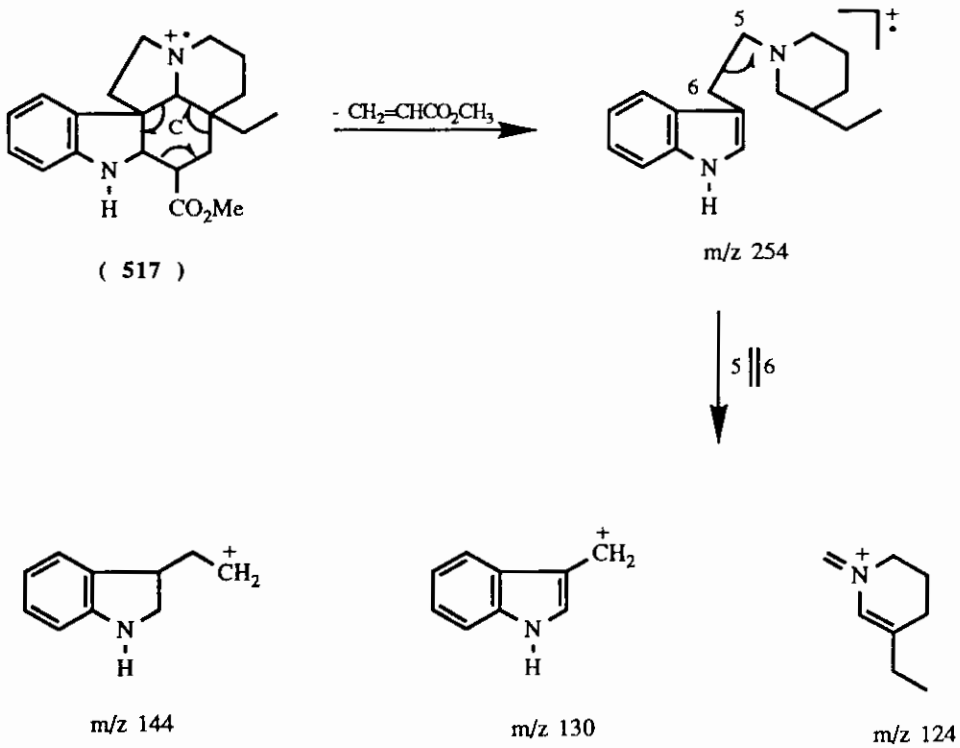
Scheme 114

First, reduction of (±) - vincadifformine (5) with zinc and 10% absolute methanolic sulphuric acid under reflux for 30 minutes produced racemic dihydrovincadifformine (517) as a colourless oil in 92% yield. However, none of the other stereoisomer was detected.



(5) (517)

The u.v. spectrum showed absorption at λ_{max} 207, 244, 298 nm, typical of dihydroindole derivatives, and the mass spectrum indicated a molecular weight of 340 in agreement with an empirical formula, $C_{21}H_{28}N_2O_2$. The most abundant fragment ion in the mass spectrum of dihydrovincadifformine was found at m/z 124 as well as the expected peak at m/z 254 owing to the loss of methyl acrylate (Scheme 115).



(517)

m/z 254

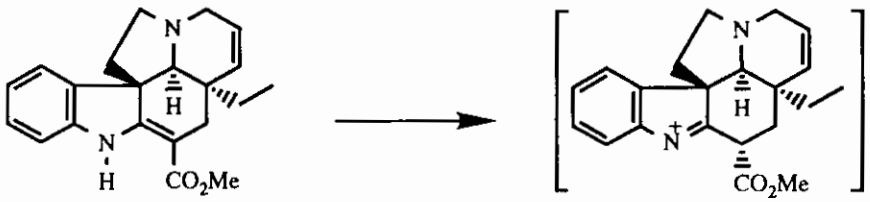
m/z 144

m/z 130

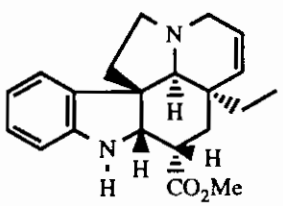
m/z 124

Scheme 115

In the n.m.r. spectrum, the signals of H -2 and H - 16 in (517) appeared at 3.97 (d, J = 2Hz) and 3.92 ppm (m), respectively. The stereochemistry of the carbomethoxy group was determined by the smaller coupling constant of H - 2. This suggest a cis configuration of proton at C -2 and C - 16. On the other hand, the stereochemistry at the chiral position of the carbomethoxy group was determined by analogy with the assigned structure of 2βH, 16βH - dihydrotabersonine (519), obtained by Le Men and co - workers[63] from the reduction of the indoleninium ion (518) by zinc - sulphuric acid (Scheme 116).



(6) (518)



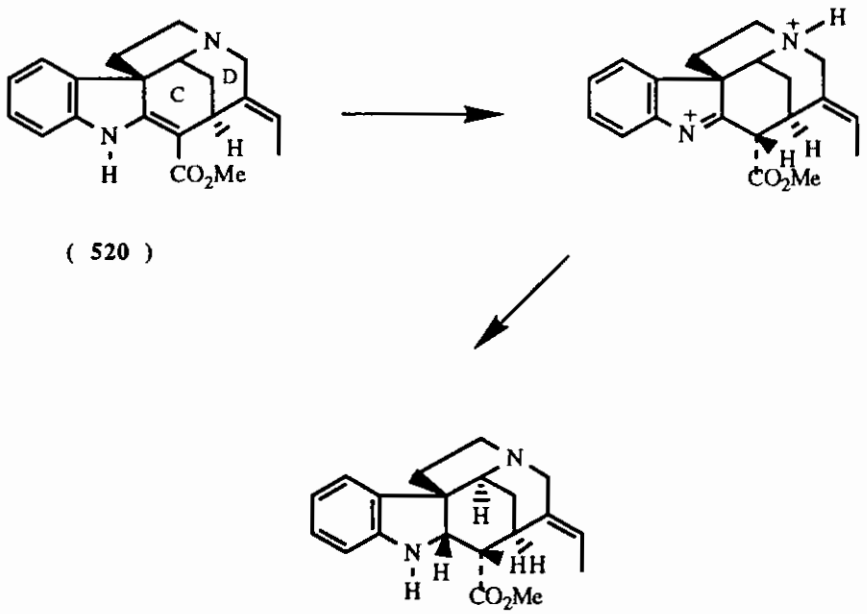
(519)
(517) 14, 15 - dihydro

Scheme 116

Alternatively, reduction of (-) - vincadifformine with zinc in acetic acid gave also the 2βH, 16βH dihydroderivative (517) in low yield.

Akuammicine (520)[154] was also quantitatively reduced by zinc and methanolic sulphuric acid to afford the dihydro derivative (521), in which the akuammicine ultraviolet absorption, with λ_{max} at 329 nm has been replaced by absorption characteristic of an indoline base. Protonation at the β - face allowed the methoxycarbonyl group to take up the thermodynamically more stable equatorial configuration, ring C being in the boat conformation. Reduction again at the β - face of C - 2 gave (521) in which the B/C ring junction is the more stable cis - form and rings C and D have chair conformations. This forces the methoxy carbonyl group

into an axial orientation (Scheme 117).

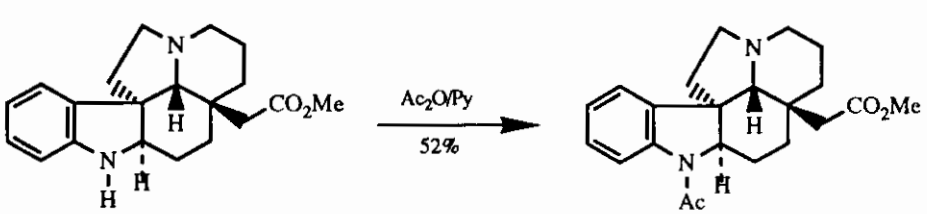


(520)

(521)

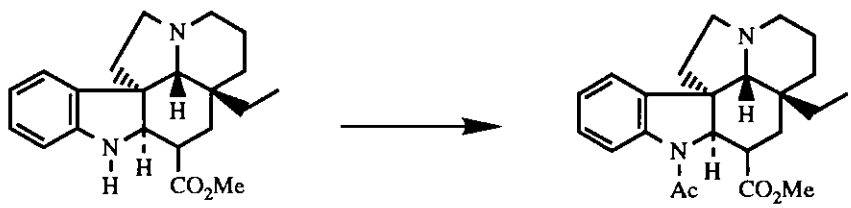
Scheme 117

Reaction now of the 2, 16 - dihydrovincadifformine (517) with acetic anhydride in dry pyridine at 40 °C resulted in high recovery of starting material. However, this was not the case in the acylation of 19 - methoxycarbonyl - 19 - demethylaspidospermidine (272) achieved by Saxton and co - worker[57].



(272) (269)

However, treatment of (517) with acetic anhydride in the presence of N, N - dimethylaminopyridine (DMAP) at room temperature afforded after 12 h stirring the desired compound (522) (25%) together with an unknown compound in the ratio (1: 2), respectively.



(517) (522)

The less polar product (m.p. 172 - 173 °C), obtained in 49% yield, was not fully identified (fig.1 - 4). Its empirical formula $C_{25}H_{32}N_2O_4$ indicated by microanalysis was also confirmed by the mass spectrum which exhibited a molecular ion at m/z 424 (37.7%). The u.v. spectrum gave absorption at λ_{max} 206, 246, 276, 288 nm. In the infrared spectrum the bands at 3350 cm^{-1}, 1720 characteristic for an NH grouping and a carbethoxy group, respectively are absent. However, two new bands appeared at 2780 and 1690 cm^{-1}. The proton n.m.r. showed a doublet (J: 7.5 Hz) at 8.16 ppm which could be attributed to the C -12 proton, a multiplet owing to two aromatic protons at 7.26 ppm and a triplet at 7.1 ppm (J: 7 Hz, 9 - H), a broad singlet corresponding to one hydrogen was seen at 4.5 ppm, the protons of the carbomethoxy group are shown at 3.75 ppm as an intense peak, and a triplet at 0.35 ppm corresponding to the C - 18 methyl group. The ^{13}C spectrum showed 25 absorptions in which three absorptions at 72.87, 60.30, and 14.4 ppm are still not attributed (Table V).

Compound (522) exhibited the characteristic absorptions of a methoxycarbonyl group (ν_{max} 1720 cm^{-1}) and an acetyl group at (1630 cm^{-1}) in its i.r. spectrum. The u.v. spectrum showed maxima at 208, 250, 280, 288, and 302 (sh). The mass spectrum exhibited a molecular ion at m/z 382 and a fragmentation peak due to the

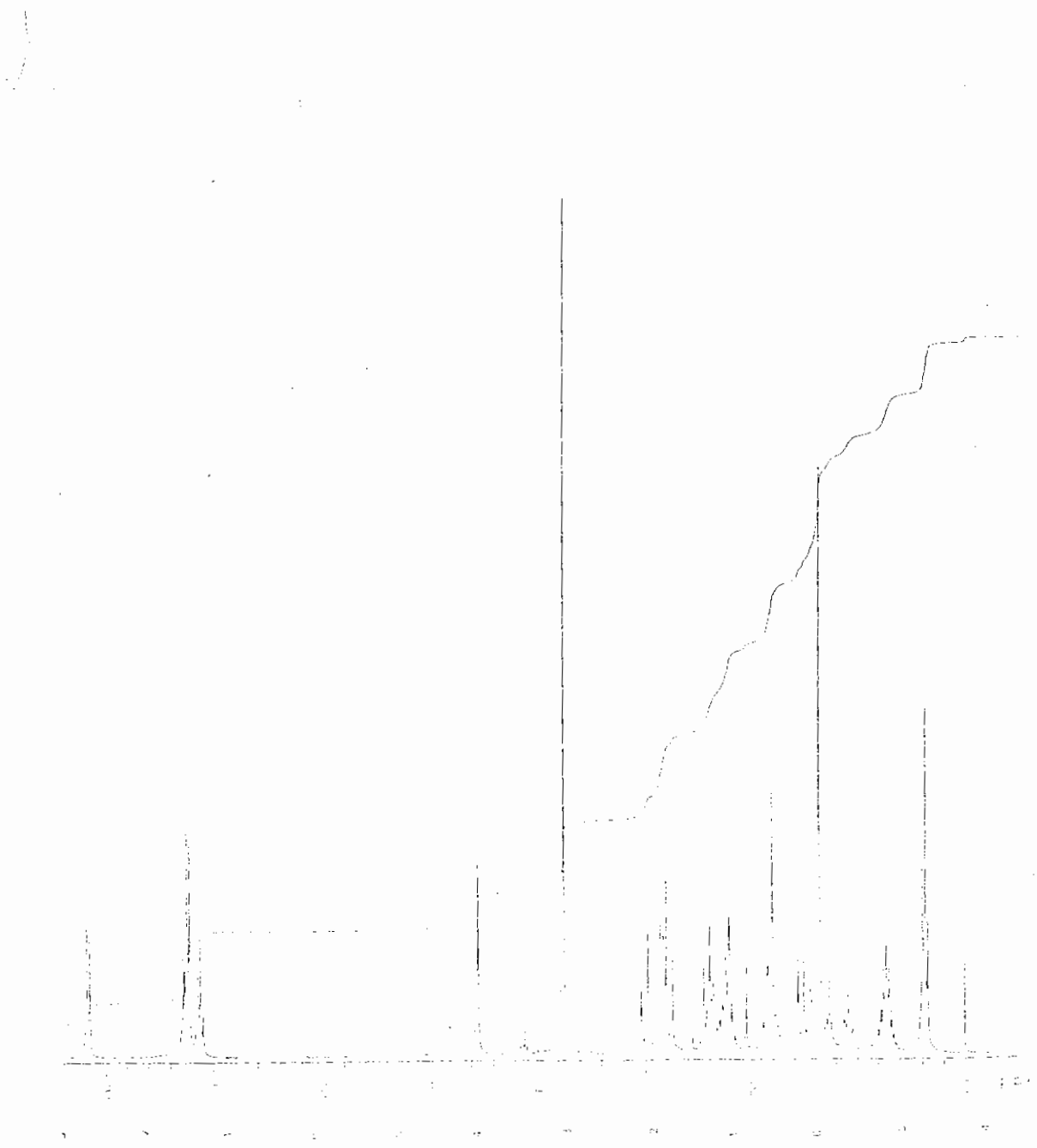
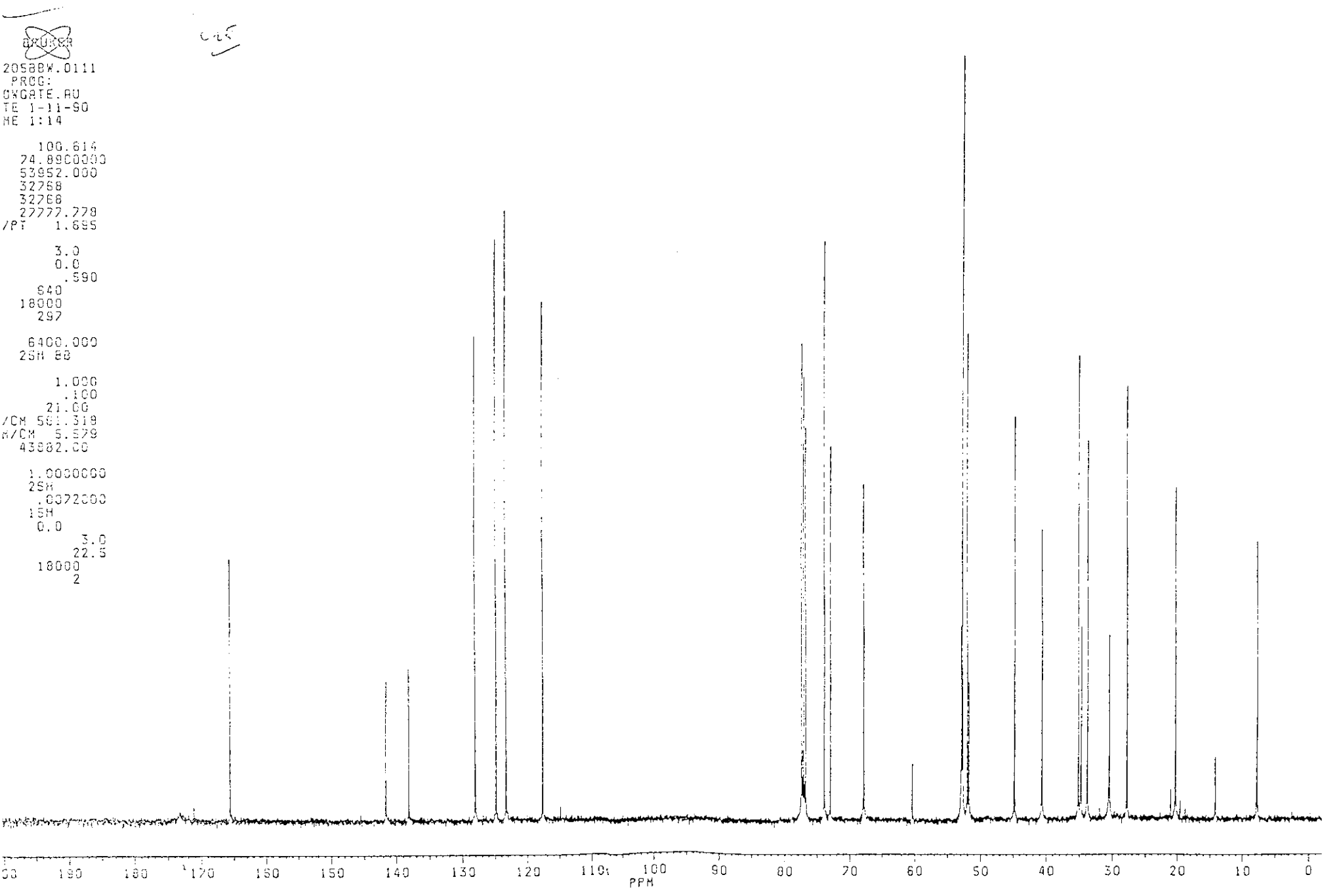


Fig. 1


BRUKER
205BBW.0111
PROG:
GWGATE.AU
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ME 1:14
100.614
24.8900000
53952.000
32768
32768
27777.778
/PT 1.685
3.0
0.0
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640
18000
297
6400.000
2SH 88
1.000
.100
21.00
/CM 581.319
M/CM 5.579
43882.00
1.0000000
2SH
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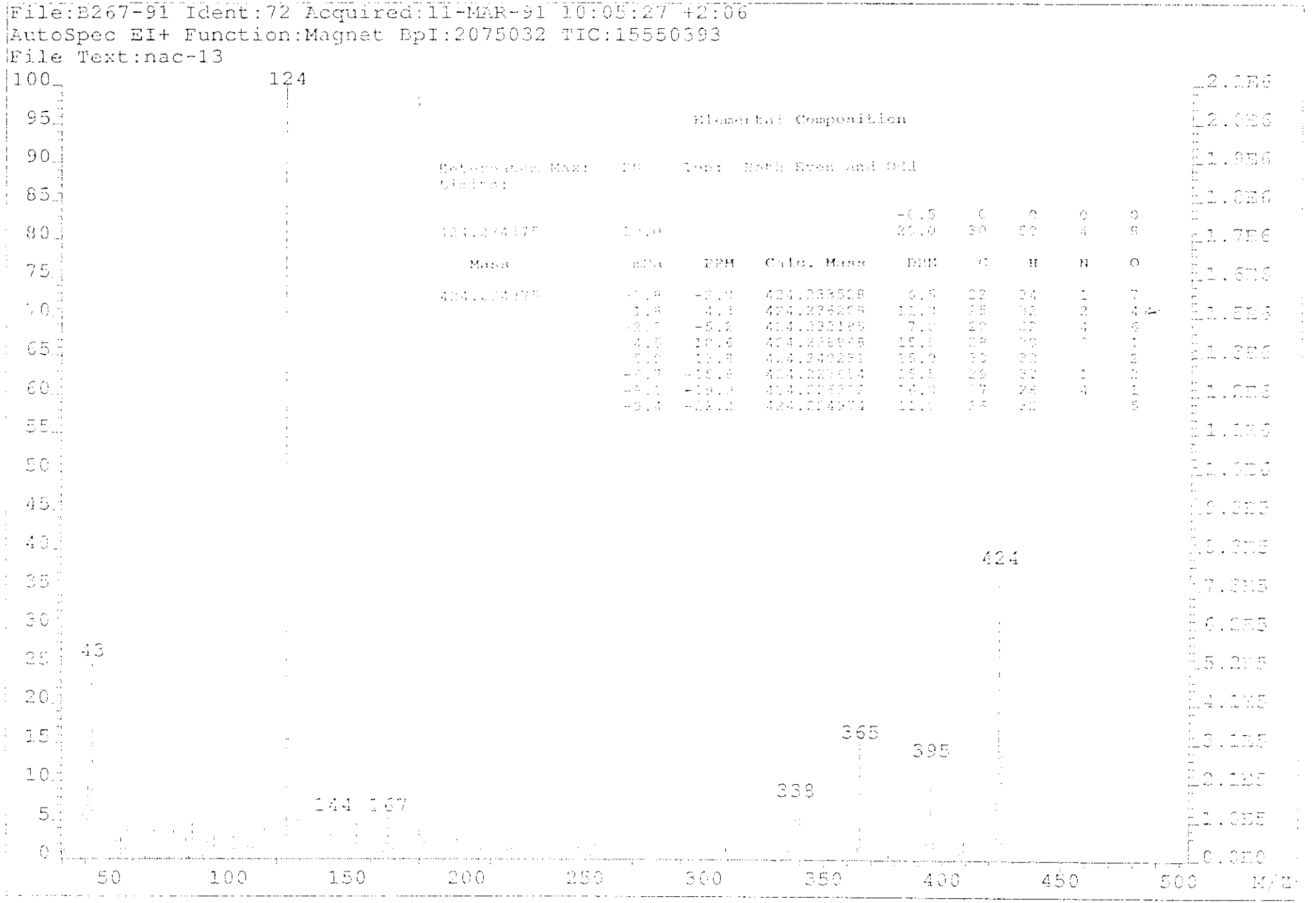
1SH
0.0
3.0
22.5
18000
2
PPM

Fig. 2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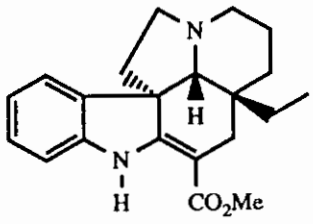
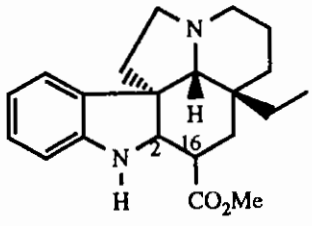
AutoSpec EI+ Function:Magnet BpI:2075032 TIC:15550393
File Text:nac-13
Elemental Composition
124
424
43
365
395
338
144
167
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
50
100
150
200
250
300
350
400
450
500
M/Z

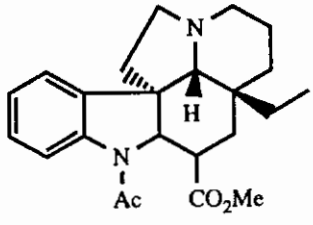
Fig. 4



(5)



(517)



(522)

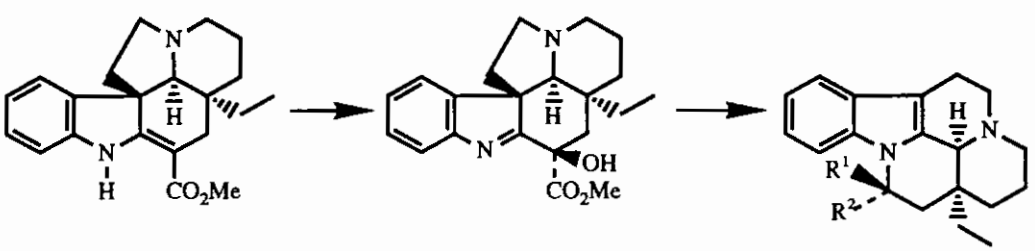
Table V: ^{13}C n.m.r. chemical shifts obtained on (±) - vincadifformine (5), 2, 16 - dihydrovincadifformine (517), N_a - acetyl - 2, 16 - dihydrovincadifformine (522), and by - product of (522).

Carbone N°	(5)	(517)	(522)	by - product
2	167.61	67.33	67.12	67.75
3	51.69	52.47	52.42	52.6
5	50.56	52.4	52.11	52.83
6	45.1	43.22	41.3	40.58
7	55.42	53.47	51.77	51.65
8	137.77	135	141	138.09
9	120.99	123.21	124.3	124.7
10	120.43	118.21	122.57	123.22
11	127.36	127	127.51	127.9
12	109.23	108.89	116.18	117.57
13	143.17	150	142.59	141.54
14	22.02	22.10	21.38	20.23
15	32.08	33.75	34.22	34.6
16	92.52	39.14	39.64	44.73
17	25.57	33.93	34.00	33.7
18	7.09	7.74	7.28	7.66
19	29.31	28.36	30.3	30.4
20	38.08	36.33	34	35.09
21	72.5	75.32	72.4	73.8
22	169.05	176.6	176.2	not recorded
$CO_2\underline{C}H_3$	50.9	51.5	51.6	51.9
$\underline{C}OCH_3$	------	------	165.8	165.4
$CO\underline{C}H_3$	------	------	22.08	27.69

* Three absorptions at 72.87, 60.3, and 14.4 ppm corresponding to the by - product are still not attributed.

The alternative route by which the strictanine compound (507) might eventually be synthesised is outlined in Scheme (111).

The existing literature[64,65] method for the conversion of the readily available (±) - vincadifformine into the key intermediate 16 - hydroxyindolenine (294) showed that the latter compound is particularly unstable and rearranges to give a mixture of vincamine (298a) and 16 - epivincamine (298b); for example, reaction of vincadifformine with ozone under acid catalysis is reported to produce the 1, 2 - dehydro - 16 - hydroxyvincadifformine (294), which undergoes a rearrangement to give vincamine (298a) and its 16 - epivincamine (298b).

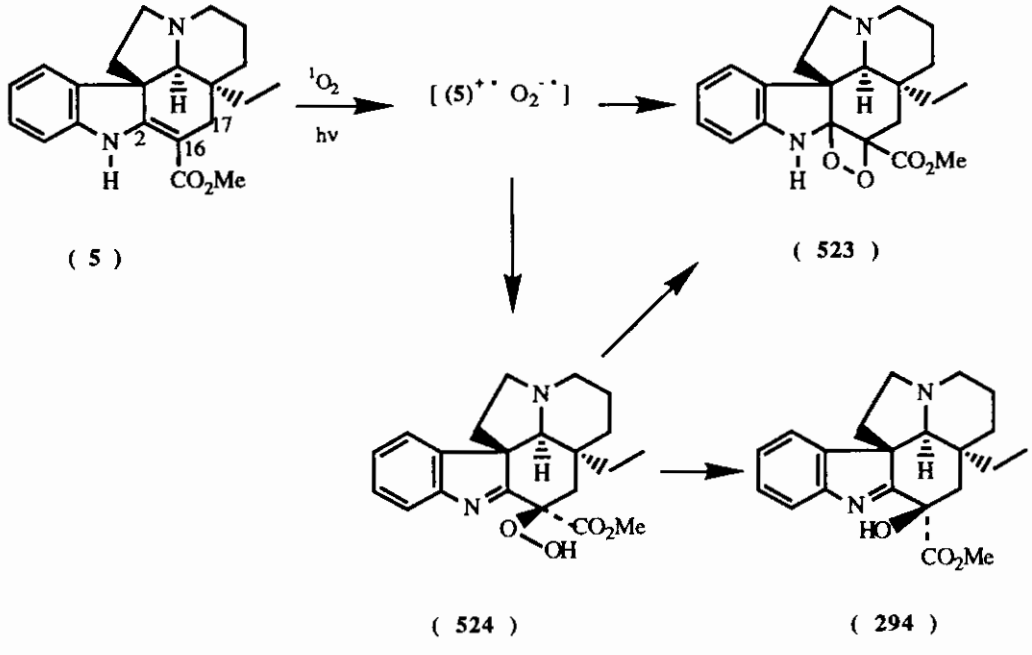


(5) (294) (298a) R^1 = OH, R^2 = CO_2Me
(298b) R^1 = CO_2Me, R^2 = OH

This transformation could also be realised by dye - sensitized photo - oxygenation of (-) - vincadifformine[77] in the presence of Rose Bengal and sodium thiosulphate as reducing agent to give 16 - hydroxyindolenine (294), vincamine, and 16 - epivincamine.

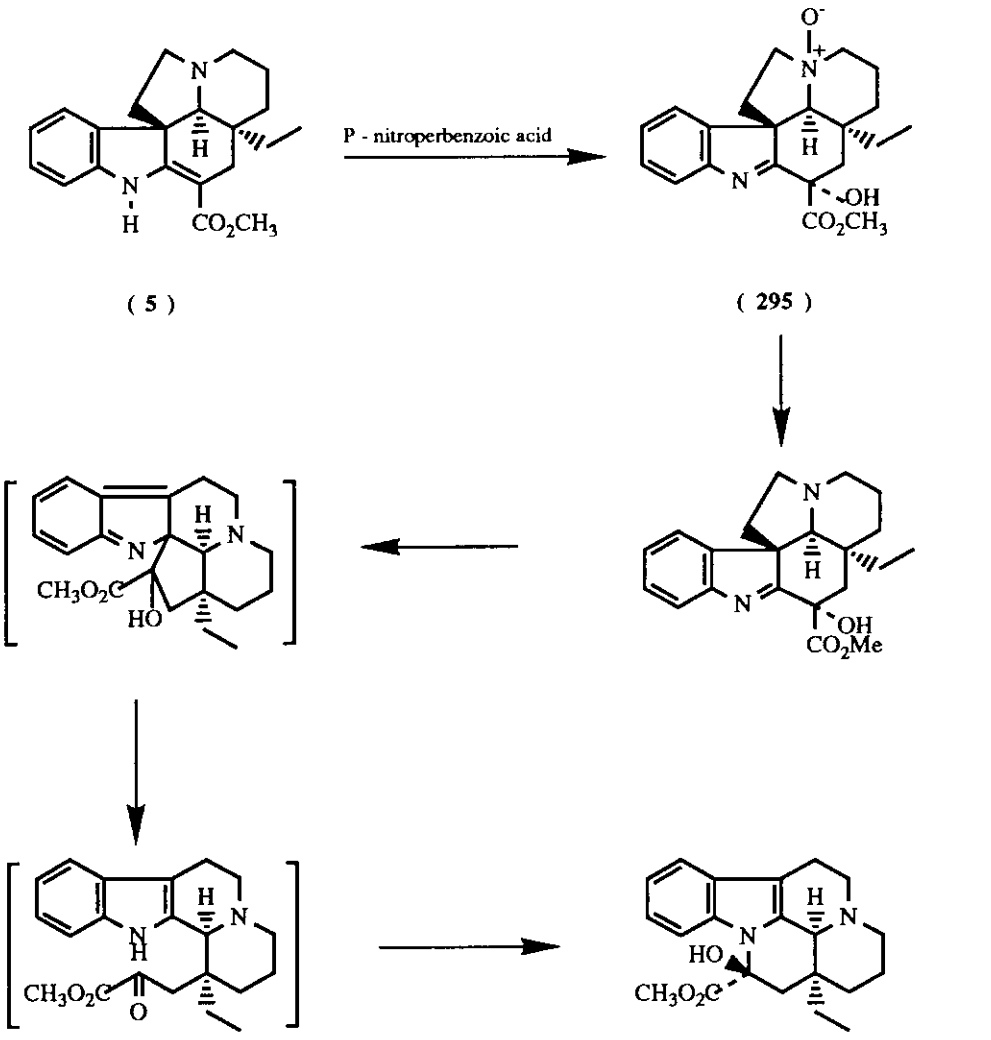
However, when (±) - vincadifformine (5) was irradiated in a methanolic solution of Rose Bengal for 1 h between 20 - 30 °C using two 150 w tungsten lamps in the presence of oxygen only 30% yield of the desired compound (294) was obtained. The other product was mainly recovered starting material. The lower yield

is undoubtedly due to the use of different size of lamp. Such photoxidations of enamines through singlet oxygen might proceed by electron transfer from the donor vincadifformine (5) to $^1O_2$ to give a radical cation - superoxide anion pair $[(5)^{+\bullet}O_2^{-\bullet}]$ or charge - transfer (C T) complex. Recombination of the ion pair might give the dioxetan (523) followed by retrocycloaddition to the hydroperoxide (524). Reduction either photochemically or by intramolecular interactions gives the corresponding hydroxy compound (294) (Scheme 118).



Scheme 118

Le Men and co - workers[64] also achieved this conversion *in vitro* through a multi - step procedure involving the prior oxidation with peroxy - acids to the 16 - hydroxy - 1, 2 - dehydrovincadifformine N_b - oxide (295) in which the N_b centre was blocked to avoid the spontaneous rearrangement to vincamine (298a) (Scheme 119).



(5)

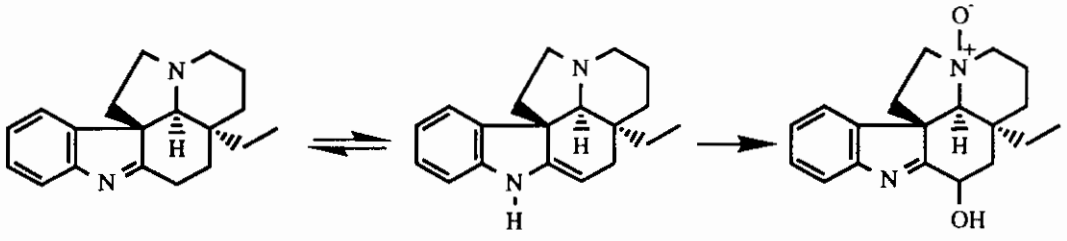
(295)

(**278a**) 16β - OH, vincamine

(**278b**) 16α - OH, 16 - epivincamine

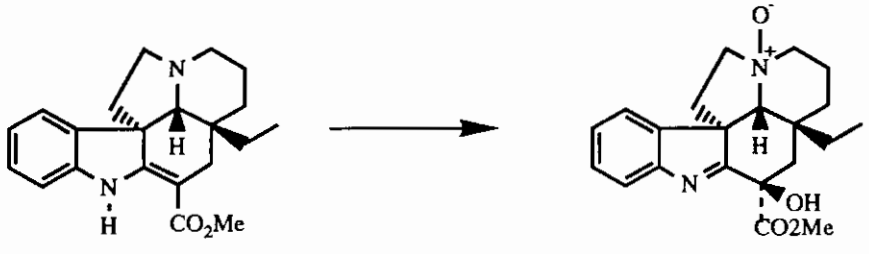
Scheme 119

It was then found that oxidation of 1, 2 - dehydroaspidospermidine (525) with p - nitroperbenzoic acid occurred on the tautomeric form to give the 16 - hydroxyindolenine N_b - oxide (526).

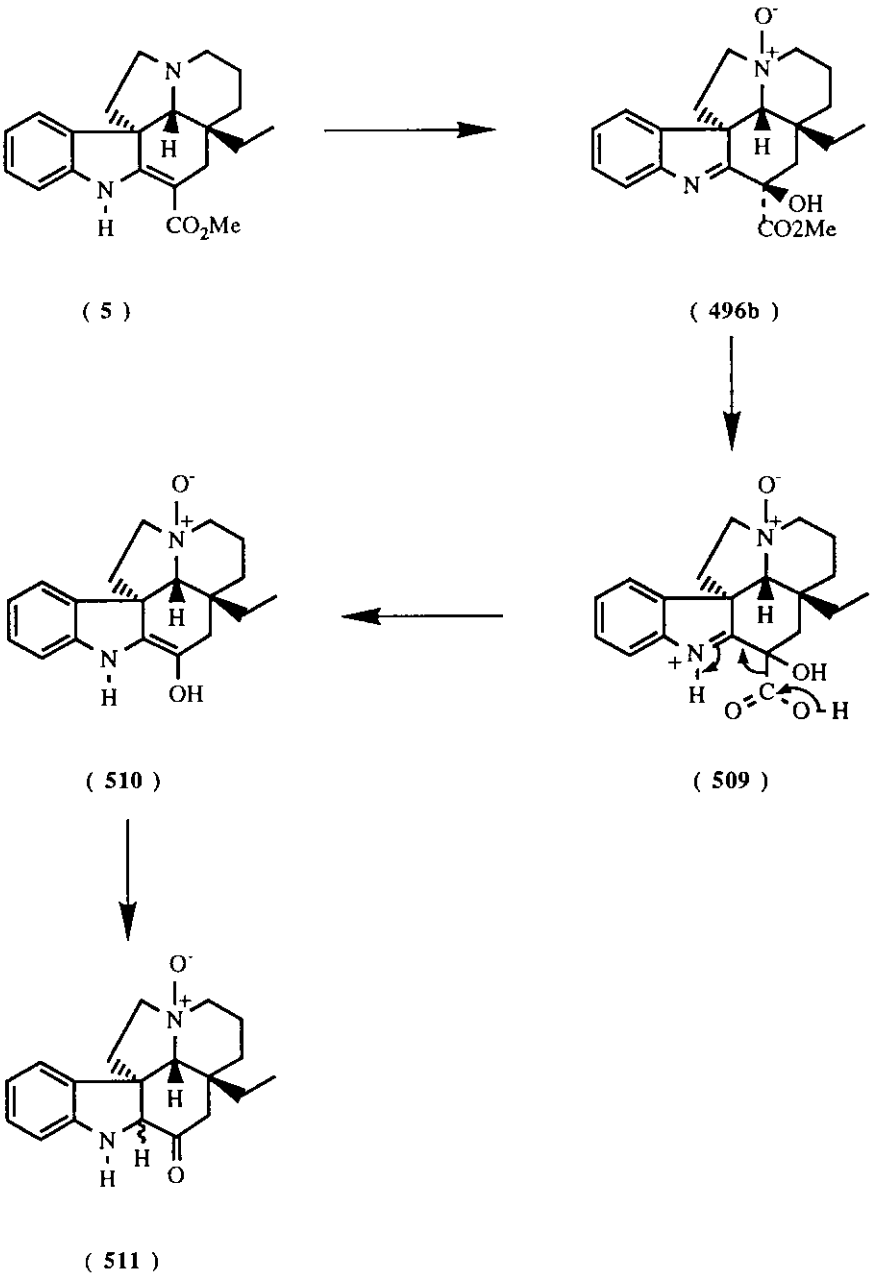


(525) (526)

Consequently, the 16 - hydroxyindolenine N_b - oxide (496b) was converted into 16 - oxoaspidospermidine N_b - oxide (511) according to Le Men's procedure[155]. Reaction of vincadifformine with m - chloroperbenzoic acid in dry benzene gave after evaporation of the solvent a variable yield of 16 - hydroxyindolenine N_b - oxide derivative (496b). However, an essentially quantitative yield of (496b) was obtained when vincadifformine was treated with 3 equivalents of m - chloroperbenzoic acid in the dark for 36 h under a nitrogen atmosphere. The solvent was removed under reduced pressure ($t_{bath} < 40$ °C).



(5) (496b)



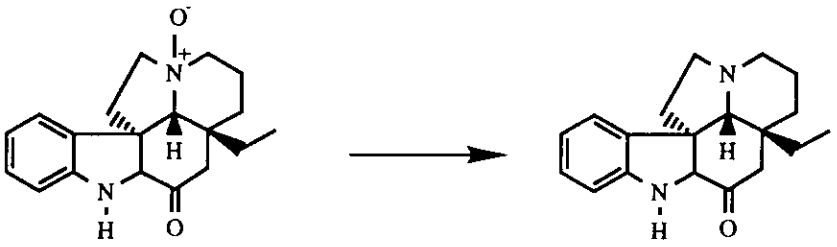
Scheme 120

The molecular ion was observed at m/z 370 in agreement with the empirical formula, $C_{21}H_{26}N_2O_4$, which was also supported by microanalysis. The u.v. spectrum in methanol gave maxima at 223, 270 nm and the i.r. spectrum indicated a non - conjugated ester (1738 cm^{-1}) (contrast the absorption in the starting material at ν_{max} 1670 and 1610 cm^{-1}), and a hydroxy group at 3450 cm^{-1}. The proton n.m.r. spectrum showed a multiplet at 8 ppm (OH), a doublet owing to the C - 9 proton at 7.6 ppm, a multiplet at 7.5 - 7.1 (3 Ar - H), the methoxy carbonyl methyl group at 3.95 ppm, and the methyl group (C - 18) as a triplet at 0.5 ppm.

Subsequently, hydrolysis with 1.25M sodium hydroxide solution, followed by decarboxylation under acidic conditions (pH = 1) at 100 °C for 20 min, produced the desired product (511) as a yellow amorphous solid in 98% yield (Scheme 120).

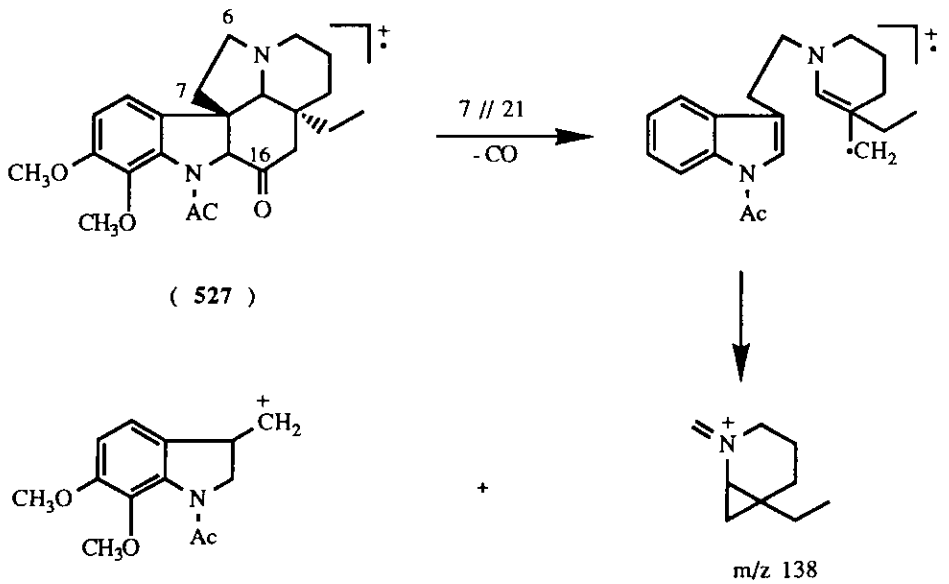
The presence of the carbonyl function in (511) was confirmed by the long wavelength absorption observed in the u.v. spectrum (λ_{max} 218, 243 (sh), 300 nm) typical of an indolinic compound and by the absorption in the i.r. spectrum at 1720 cm^{-1} (CO). The molecular ion in the mass spectrum was observed at m/z 312 and was consistent with the molecular formula $C_{19}H_{24}N_2O_2$.

Attempts to reduce the N - oxide group with palladium - hydrogen gave a low yield (32%) of (512), whereas Adams' catalyst (PtO_2) and hydrogen at atmospheric pressure afforded a good yield (80%).



(511) (512)

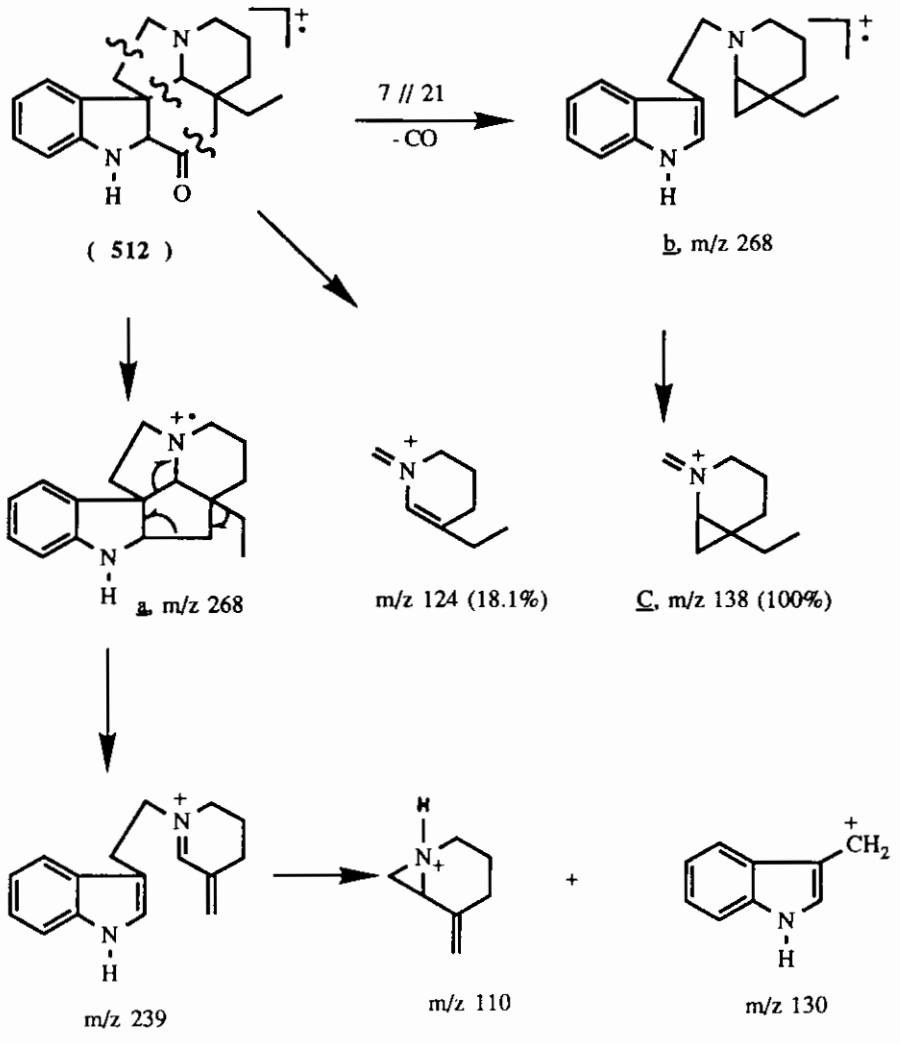
The u.v. spectrum of (512) showed absorption at λ_{max} 210, 240, 292 nm, indicative of the nature of the chromophore. The i. r. spectrum showed the presence of a carbonyl group (ν_{max} 1720 cm^{-1}), and the n.m.r. spectrum exhibited signals at δ: 7.22 - 6.8 ppm as a multiplet corresponding to 4 aromatic protons, a singlet at 4.9 ppm which exchanges with D_2O (NH), and a triplet at 0.7 ppm (3H, C - 18). The molecular ion in the mass spectrum appeared at m/z 296, as expected for $C_{19}H_{24}N_2O$. However, the major fragment was not at m/z 124 as for vincadifformine and its derivatives. Instead, the molecule exhibits a M - 28 peak at m/z 268 and shows its most intense peak at m/z = 138, which is also observed in the 16-dehydrospegazzinidine dimethyl ether (527)[150] fragmentation pattern (Scheme 121).



(527) m/z 138

Scheme 121

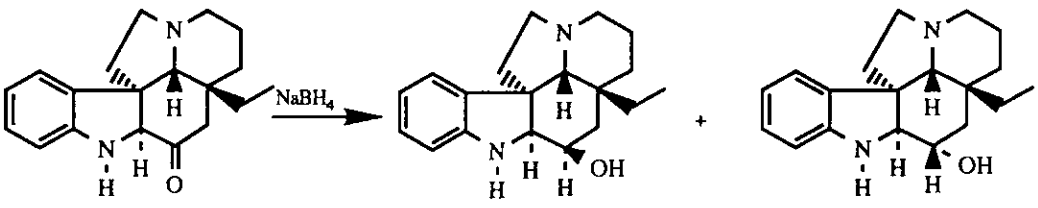
Consequently, the retro Diels - Alder fragmentation is less important in compounds such as (512) with a carbonyl group at C - 16 which thus alters the typical aspidospermine mass spectral fragmentation. The molecular ion decomposes by expulsion of carbon monoxide to give b (m/z = 268). Subsequent fission of the C - 5, C - 6 bond therefore produces not the anticipated ion at m/z 124, but rather the ion c (m/z 138, 100%) as major fragment (Scheme 122).



Scheme 122

16 - Oxoaspidospermidine (512), when subjected to reduction with sodium borohydride in ethanol, followed by heating, gave a mixture of C - 16 epimers,

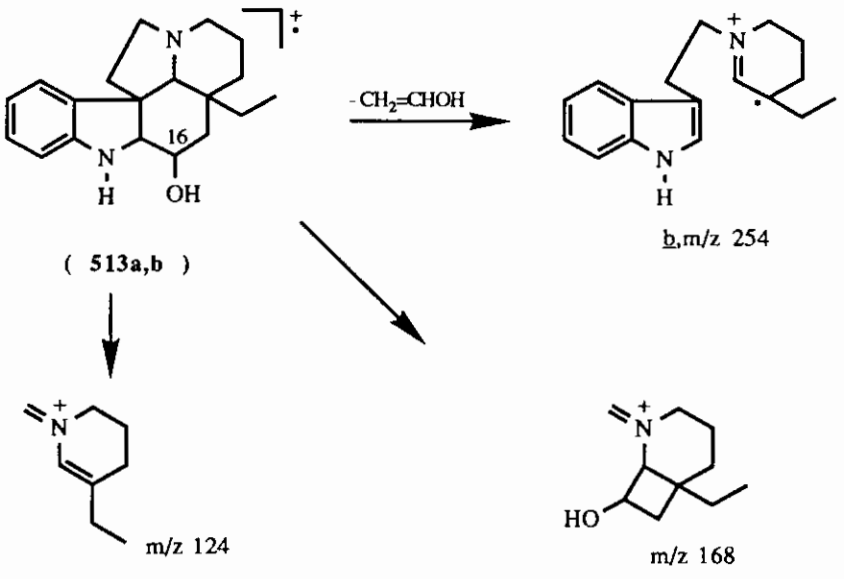
which were separated by column chromatography on Kieselgel G using chloroform - methanol (9: 1) as eluent (Scheme 123).



(512) (513a) (513b)

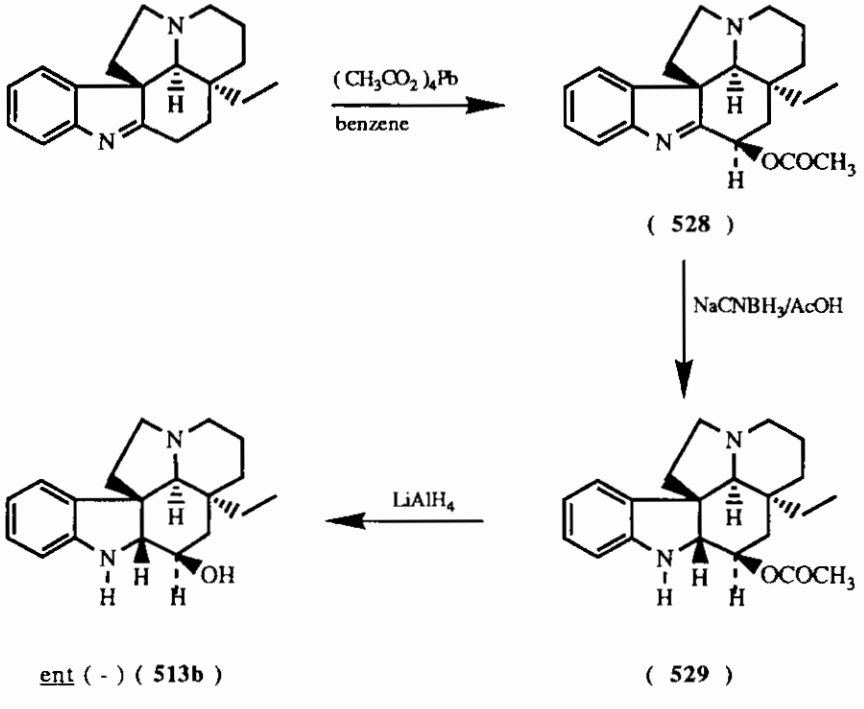
Scheme 123

The major product (less polar), 16α - H, 16β - OH aspidospermidine (513a) (72.5%), obtained as colourless plates m.p. 55 °C, exhibited absorptions in its u.v. spectrum at λ_{max} 212, 244, 300 nm . The mass spectrum gave the molecular ion peak at m/z 298 (5.7%) in agreement with an empirical formula, $C_{19}H_{26}N_2O$ which was also confirmed by microanalysis, and the base peak was observed at m/z 124 (100%). The ion b (Scheme 124) is observed at m/z 254 (8.7%). The i.r. spectrum exhibited absorption at 3420 cm^{-1} (OH) and 1600 cm^{-1} (NH indolic). The exact nature of this substituent was deduced from the n.m.r. which exhibited signals clearly indicating that the coupling constant (J = 4 Hz) of H - 2 (d, 3.77 ppm) and H - 16 (m, 4.85 ppm) is compatible with a *cis* configuration (2α - H, 16α - H) Irradiation of 16 - H gave C - 2 as a singlet at 3.75 ppm. Therefore the configuration of the hydroxyl group is β. The ^{13}C spectrum showed nineteen resonances with the C - 16 atom giving rise to the resonance at δ 67.65 ppm.



Scheme 124

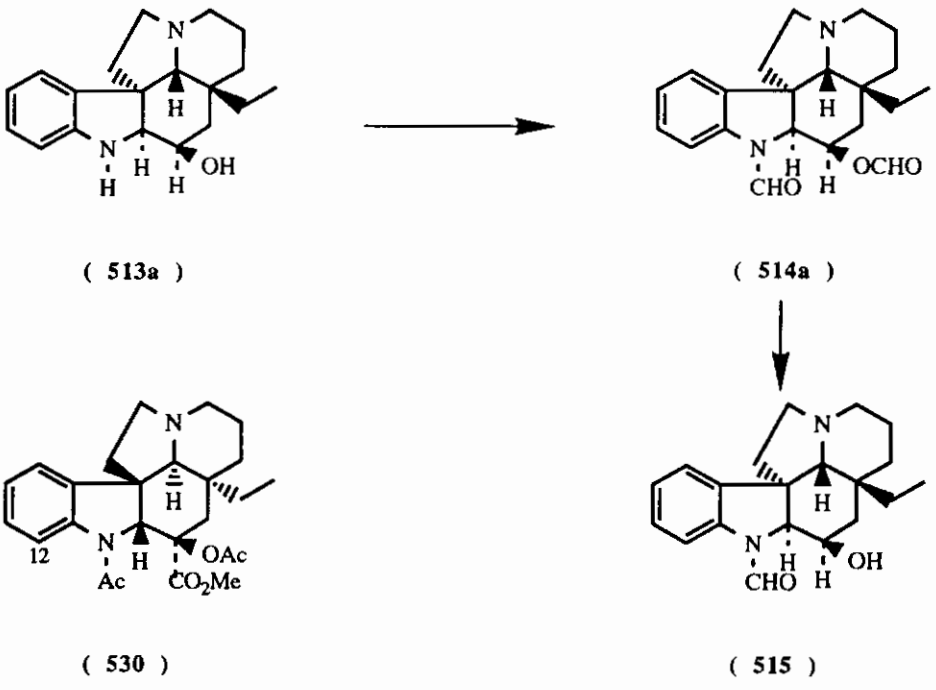
The more polar product (12.5%) was found to be epimeric at C - 16 and was compared with that also obtained by le Men *et al* [155]from the reduction of 16 - acetoxyaspidospermidine (529) with lithium aluminium hydride, a product of known absolute configuration (Scheme 125).



Scheme 125

The infrared spectrum showed absorption at 3400 cm^{-1} (OH) and the mass spectrum indicated a molecular weight of 298 in agreement with the empirical formula, $C_{19}H_{26}N_2O$. The most abundant ion fragment in the mass spectrum of (513b) was found at m/z 124. The fragmentation pattern is given in Scheme 124. The ion b is formed by the loss of CH_2=CHOH group.

Reaction of 16 β - hydroxyaspidospermidine (513a) with formic acid and acetic anhydride afforded the N, O - diformyl derivative (514a) (90% yield) as colourless plates, m.p. 70 - 72 °C (Scheme 126). The infrared spectrum indicated the presence of two characteristic absorptions at ν 1720 (OCHO) and 1670 cm^{-1} (NCHO), with no free NH group, and the u.v. spectrum showed absorption at λ_{max} 210, 250, 282, and 290 nm. Its molecular formula according to analysis is $C_{21}H_{26}N_2O_3$ which was also proven by mass spectrometry with a molecular ion peak at m/z 354. The major peak was observed at m/z 124 (100%). In the n.m.r. spectrum, the two singlets which correspond to the two formyl functions (OCHO) and (NCHO) were observed at 8.9 and 8.6 ppm respectively. The peak at 7.9 ppm (dd, J: 9.3 and 18 Hz) was attributed to the C - 12 hydrogen, the same as that in the N, O - diacetate (530)[77] at 7.9 ppm (dd, J: 8 and 1Hz, 12 - H) except for the coupling constants, which are different. The H - 16 and H - 2 protons were shifted downfield to 5.75 ppm (m) and 4.6 (d), respectively. In the ^{13}C n.m.r. spectrum twenty one resonances was observed. The data are reported in Table VI for comparison.



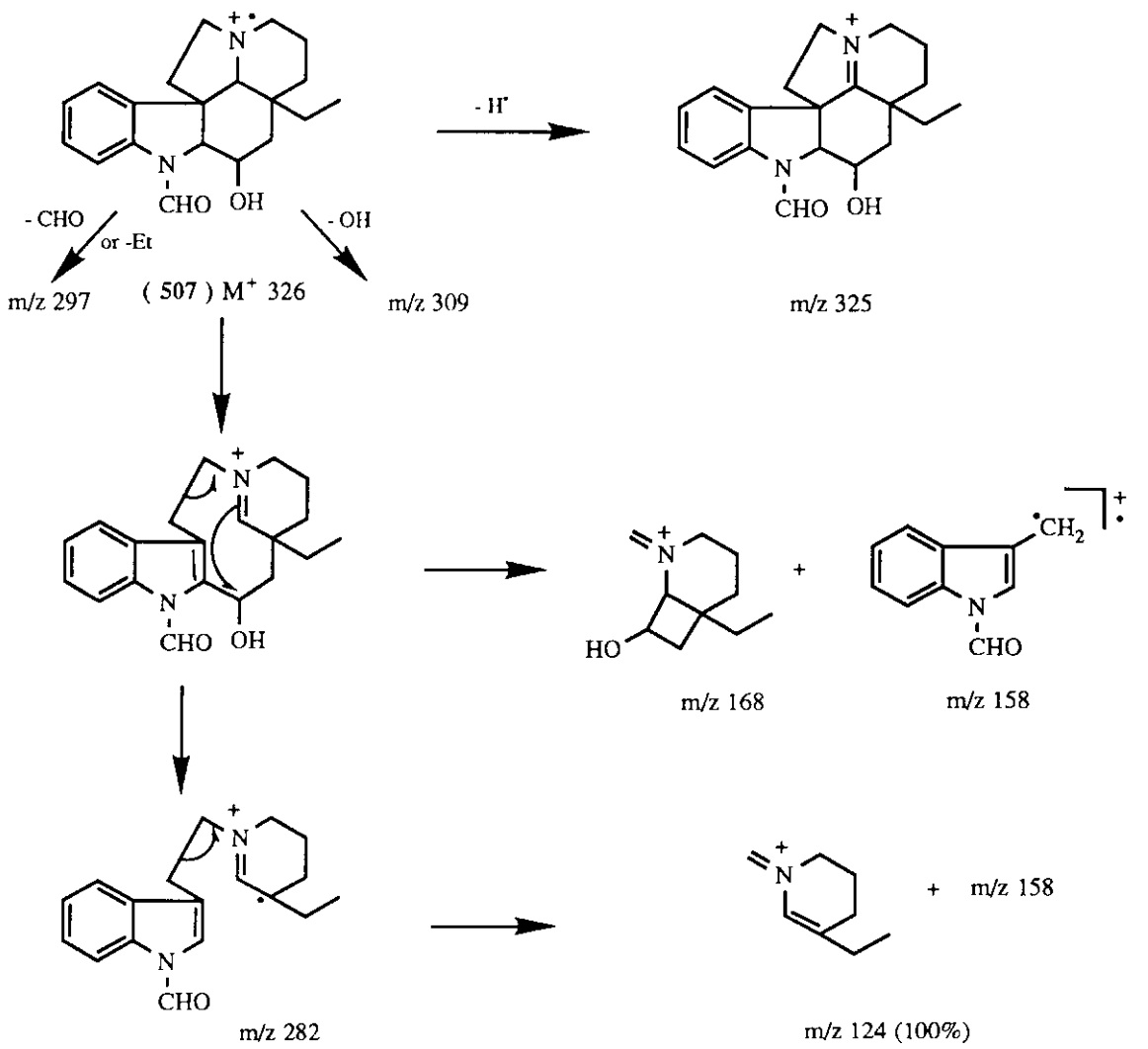
(513a) (514a)

(530) (515)

Scheme 126

Sodium carbonate solution was added to a solution of the diformyl compound (514a) in methanol. The resulting mixture was stirred for 15 minutes. After work - up, the reaction produced the desired product, N_a - formyl 16β - hydroxyaspidospermidine (515) in 98% yield (m.p. 66 - 68 °C).

The spectroscopic data suggested that the correct relative stereochemistry had been obtained. In the i.r. spectrum a broad absorption was seen at 3400 cm^{-1} (OH) and a strong absorption at 1680 cm^{-1} which was assigned to the N_a - formyl group. The u.v. spectrum in methanol is found to be essentially identical to that reported by Atta - Ur - Rahman[147] for the alkaloid strictanine. The mass spectrum shows the anticipated fragmentation pattern (Scheme 127).

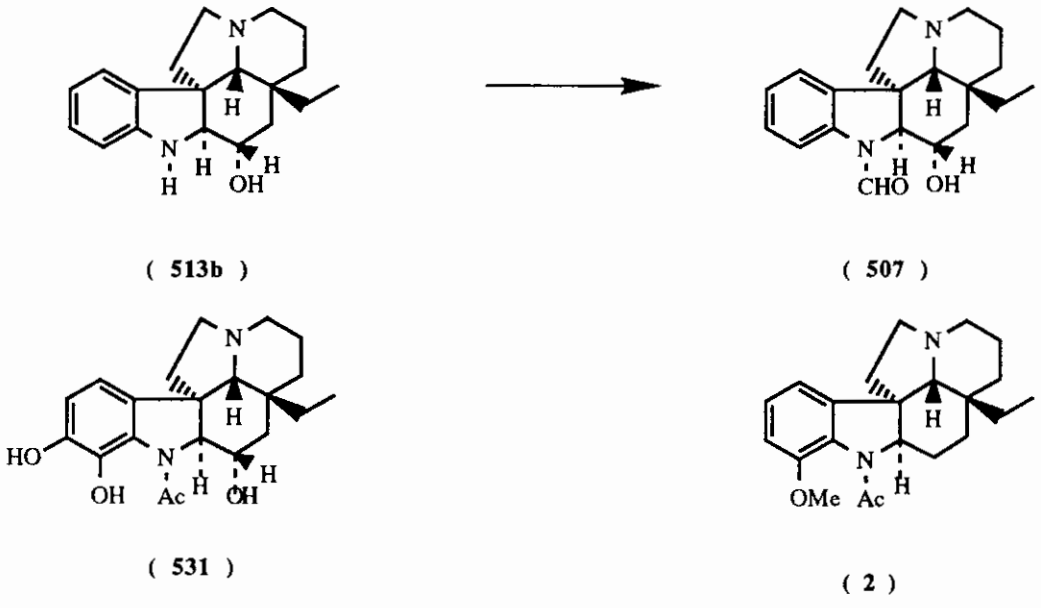

- H·
- CHO
or -Et
- OH
m/z 297
(507) M+ 326
m/z 309
m/z 325
m/z 168
m/z 158
m/z 282
m/z 124 (100%)
+ m/z 158

Scheme 127

The molecular ion at m/z 326 is in agreement with the molecular formula, $C_{20}H_{26}N_2O_2$, which was also confirmed by microanalysis. In the proton n.m.r. spectrum the N - formyl proton (NCHO) was seen as two singlets (intensity 7: 1) at 9 and 8.72 ppm respectively. Saturation of one peak showed that the other has gone. This is due probably to the effect of restricted rotation of the formyl group. The H - 12 proton was observed as a doublet at 8.03 ppm, the aromatic protons at 7.2 - 7 ppm and the H - 2 proton was seen as a doublet at 4.15 ppm with a coupling constant J = 4.6 Hz which suggests a cis relationship between the protons at positions 2 and 16. A broad singlet at 5 ppm was attributed to the H - 16 proton and a triplet at 0.55 ppm corresponded to the methyl protons of C -18. In the ^{13}C spectrum, 20 resonances were recorded. These are given in Table VI.

The more polar alcohol (513b) was reacted with formic acid and acetic anhydride at 0 °C for 18 h as for the less polar one (513a). However, the produced N, O - diformyl compound (514b) was not isolated but directly converted into the corresponding N_a - formyl - 16 - hydroxyaspidospermidine (507). This gave a clear, yellow oil in 77% yield, which was purified by preparative chromatography (Kieselgel G) using dichloromethane - methanol 5%. The spectroscopic data (u.v. and mass) obtained on this material were found to be essentially identical to those reported by Atta - Ur - Rahman and S. Malik[90] as well as to those of the less polar compound (515). However, the n.m.r. showed that the N_a - formyl proton resonated again as two singlets, at 9 and 8.6 ppm, whereas Atta - Ur - Rahman reported only one signal for the NCHO group at 8.58 ppm as one singlet. The C -2 proton exhibited a signal as a doublet at 4.37ppm ($J_{2,16}$ = 7.5 Hz), against 4.05 ppm (Atta - Ur - Rahman) showing trans diaxial coupling with C - 16 hydrogen ($J_{2,16}$ = 7.03 Hz).

The published data are incomplete, and Atta - Ur - Rahman has been unable to furnish any more information, particularly the ^{13}C spectrum. In fact his conclusion was suggested by comparing with the n.m.r. spectrum of spegazzinidine (531) which showed a coupling constant of 8 Hz involving the axial protons at C - 2 and C -16 and therefore an equatorial C - 16 hydroxy group. The stereochemistry of the proton at C - 2 in (507) was related chemically to (-) aspidospermine (2) (Scheme 128).



Scheme 128

Le Men reported[155] that the configuration of *ent* (-) - 16 - oxoaspidospermidine (512) is 2β - H according to the curve given by circular dichroism and also by correlation with products containing the vincadifformine skeleton (Scheme 129). The coupling constant of the proton at C -2 in the structure *ent* (513a) is compatible with 2β - H configuration (J = 4 Hz) as it is for all the structures (533), (529), *ent* (513b), and (534) which have the configuration 2β-H.

Table VI: ^{13}C n.m.r. data for 16β - hydroxyaspidospermidine (513a), Na - formyl - 16β - formyloxy - aspidospermidine (514a), strictanine (507), and its 16 - epimer (515).

Carbone N°	(513a)	(514a)	(515)	(507)
2	71.01	70.14	71.84	71.39
3	53.15	53.32	52.9	53.4
5	52.49	51.89	52.47	52.64
6	43	44.11	41.26	42.23
7	54.1	66.4	65.23	64
8	136.01	138.46	138	138.6
9	123	123.17	124.15	123.52
10	118.4	116.15	116	116(w)
11	127.61	124.79	125.11	125.43
12	109.26	109.05	109.66	110.54
13	150.35	140.97	142.23	142
14	22.10	21.57	21.86	21.38
15	34.7	32.76	33.62	32.78
16	67.65	127.81	128.02	127.86
17	35.97	34.84	35.46	31.30
18	7.75	7.12	7.58	6.8
19	34.23	32.15	34.35	34.31
20	36.11	35.04	35.79	36.74
21	74.49	71.05	74.09	73.85
NCHO	-------	160.18	159.82	160.2
OCHO	-------	160.05	--------	-------

EXPERIMENTAL SECTION

EXPERIMENTAL

Melting points are uncorrected and were determined on a Kofler hot - stage apparatus.

Infra - red spectra were obtained on either a Perkin - Elmer 1420 or 1310 spectrophotometer using chloroform as solvent unless otherwise stated. Solution spectra were recorded in NaCl cells of 0.5 mml path lengh. Signals are denoted as : w, weak signal, m, medium intensity, and s, strong intensity.

Ultra - violet absorption spectra were obtained on a Unicam PU 8800 spectrometer and refer to solutions in ethanol or methanol.

Proton nuclear magnetic resonance spectra were recorded on either a Jeol FX90Q Fourier transformer instrument at 90 MHz, a QE 300 Automated NMR at 300 MHz, or a Bruker A.M.400 spectrometer at 400 MHz. All nmr spectra were recorded in deuteriochloroform ($CDCl_3$), and chemical shifts are expressed in p.p.m. (δ) downfield from internal tetramethylsilane ($SiMe_4$) unless otherwise stated. The following abbreviation were used: s, singlet, d, doublet, t, triplet, q, quartet, and br, for a broadened signal.

^{13}C n.m.r spectra were obtained at 100 MHz from a Bruker A.M.400 pulsed Fourier - transformer.

Mass spectra (low resolution) were measured on a Kratos MS25 instrument and accurate mass on a AEI. MS950 spectrometer.

Chromatography refers to chromatography on Kieselgel G 60 (Merck 7731). All the eluents used are GPR solvents.

Preparative layer chromatography was conducted on pre - coated 2 mml (Merck 5717) silica plates G 60 F_{254}.

Thin layer chromatography (t.l.c) was performed on commercially available 0.25 mm thick layers of silica gel G 60 F_{254} (Merck 5714) glass plates. The plates were visualised by fluorescence under uv light at 254 nm, then by iodine. Ceric ammonium nitrate solution in 2M sulphuric acid was also used in some cases.

All solvents were purifued by standard procedures before use. Anhydrous THF was freshly distilled from sodium - benzophenone ketyl under nitrogen. Dry ether was prepared from the stabilized GPR grade solvent by refluxing over and subsequent distillation from sodium wire. Methanol and ethanol were distilled from magnesium methoxide.

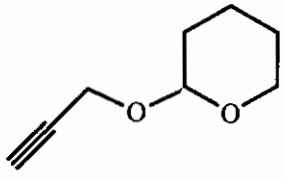
Photo - irradiation was performed by means of an OSRAM concentra (2 x 150W) at 20 °C (water cooling) with oxygen gas bubbled through the solution.

All reactions were conducted under a dry oxygen - free nitrogen atmosphere unless otherwise specified.

2.1 APPROACHES TO THE SYNTHESIS OF ALALAKINE

2.1.1Model study: Synthesis of N_a - methyl - 19 - carbethoxy - 19 - demethylvincadifformine (390)

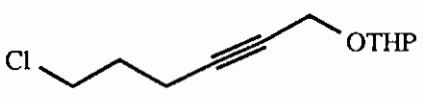
Propargyl tetrahydropyranyl ether (257)



This was carried out according to the method of Montijn and co - workers[58].

To a solution of 2, 3 - dihydropyran (101.4 g, 1.2 mol) and p-toluenesulphonic acid (10 mg) freshly distilled propargyl alcohol (56 g, 1 mol) was added dropwise, with stirring, at such a rate that the temperature of the reaction mixture did not exceed 65 °C. Stirring was continued for 10 minutes after the addition, then 5% aqueous potassium hydroxide solution (25 ml) was added with vigorous stirring, and the aqueous layer was extracted once with ether (30 ml). The organic layer was separated, dried with anhydrous potassium carbonate, and concentrated under reduced pressure. The residue was distilled to give propargyl tetrahydropyranyl ether (257) (126 g, 90%) as a colourless liquid, b. p. 94 - 98 °C / 20 mm Hg (lit.,[58] 71 - 74 °C / 12 mm Hg); ν_{max} (neat) 3280 (H-C≡), 2920 - 2840, 2110 (-C≡C-), 1440, 1380, 1350,1260, 1200, and 900 cm^{-1}; δ_H ($CDCl_3$, 90 MHz) 4.85 (1H, br s), 4.25 (2H, d, J: 2 Hz), 3.9 (2H, m), 3.6 (2H, m), 2.5 (1H, m), and 1.5 - 1.8 (6H, m).

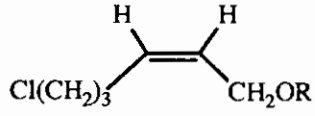
6 - Chlorohex - 2 - yn - 1 - ol tetrahydropyanyl ether (258)



This was prepared according to the procedure of J. P. Brennan[57].

1.6 M n-Butyl - lithium in hexane solution (56.6 ml, 90 mmol) was added by syringe to a stirred solution of propargyl tetrahydropyranyl ether (12.5, 90 mmol) in tetrahydrofuran (100 ml), cooled to - 5 °C. The resulting mixture was stirred for 1 h at - 5 °C and then transferred by syringe to a solution of 1 - bromo - 3 - chloropropane (15.7 g, 0.1 mol) in tetrahydrofuran (15 ml), cooled to - 40 ° C. The reaction mixture was stirred at - 40 °C for a further 1 h and then heated to reflux for 20 h. The solution was evaporated under reduced pressure, then taken up in ether, washed with water, brine, and dried over magnesium sulphate.The solvent was removed, and the residue distilled, which gave 6 - chlorohex - 2 - yn - 1 - ol tetrahydropyranyl ether (258) (15.55 g, 79.43%) as a colourless oil, b. p. 140 °C / 0.4 mm Hg (lit.,[57] 110 - 115 °C / 0.3 mm Hg); ν_{max} ($CHCl_3$) 3000 - 2840, 2220 (-C=C-), and 1140 cm^{-1}; δ_H ($CDCl_3$, 90 MHz) 4.8 (1H, br t), 4.24 (2H, m, $-CH_2-$), 3.7 (2H, m, $-CH_2-$), 3.64 (2H, t, J: 6Hz , $-CH_2Cl$), 2.42 (2H, m, $-CH_2-$), 1.96 (2H, m, $-CH_2-$) and 1.16 (6H, m).

6 - Chlorohex - 2 - en - 1 - ol (260)



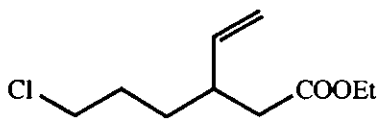
R = THP

R = H

A solution of 6 - chlorohex - 2 - yn - 1 - ol tetrahydropyranyl ether (258)(5.91 g, 27 mmol) in methanol (150 ml) was hydrogenated at room tempertaure and pressure using 5% palladium on calcium carbonate (100 mg) as catalyst. After absorption of one molar equivalent of hydrogen, the catalyst was removed by filtration through a pad of Celite. p - Toluenesulphonic acid (250 mg) was added to the filtrate and the solution was heated at reflux for 2 h. Removal of the solvent under reduced pressure gave a pale yellow oily residue which was purified by chromatography on Kieselgel G (70 g), using petroleum ether (b. p. 40 - 60 °C) -

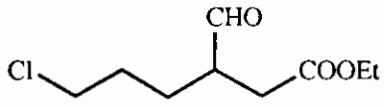
ether (20%) as eluent. 6 - Chlorohex 2 - en - 1 - ol (3.30 g, 90%) was obtained as a colourless oil (lit.,[57] b. p. 70 - 72 °C / 0.3 mm Hg); ν_{max} (neat) 3400 (OH), 3010 - 2810, 1660 (double bond), 1445, 1025, 975, 725, and 650 cm^{-1}; δ_H ($CDCl_3$, 90 MHz) 5.6 (2H, m), 4.22 (2H, d, J: 6 Hz), 3.54 (2H, t, J: 6 Hz, $-CH_2Cl$), 3.1 (1H, s, exchanges with D_2O, OH), 2.25 (2H, q, J: 6 Hz), 1.85 (2H, m).

Ethyl 3 - vinyl - 6 - chlorohexanoate (262)



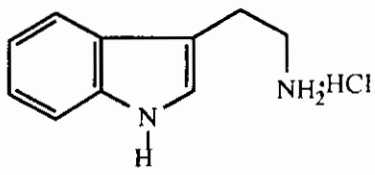
A stirred mixture of 6 - chlorohex - 2 - en - 1- ol (260) (5 g, 36.7 mmol), triethyl orthoacetate (42.2 g, 0.26 mol), and propionic acid (0.165 g, 2.25 mmol) was heated at 130 °C for 3 h. The ethanol produced during the reaction was distilled from the reaction mixture and the excess of triethyl orthoacetate removed under reduced pressure. The residue was stirred at 145 °C for 14 h. Distillation of the crude oil under reduced pressure gave ethyl 3 - vinyl - 6 - chlorohexanoate (4.67 g, 61% yield) as a colourless oil, b. p. 70 °C / 0.3 mm Hg (lit.,[57] b. p. 95 - 100 / 0.5 mm Hg) (Found: C, 58.4; H, 8.1; Cl, 17.1. $C_{10}H_{17}O_2Cl$ requires C, 58.7; H, 8.31; Cl, 17.1); ν_{max} (neat) 3080, 3000 - 2850, 1900 (w), 1737 (s), 1640 (w), 1448, 1370, 1030 - 1070, 920, and 650 cm^{-1}; δ_H ($CDCl_3$, 90 MHz) 5.10 (1H, m), 5.0 (1H, m), 4.96 (1H, m), 4.12 (2H, q, J: 7 Hz, $-CO_2C\underline{H}_2CH_3$), 3.50 (2H, t, J: 6 Hz, $-CH_2Cl$), 2.35 (3H, m), 1.7 (4H, m), and 1.24 (3H, t, J: 7 Hz, $-CO_2CH_2C\underline{H}_3$).

Ethyl 3 - formyl - 6 - chlorohexanoate (263)



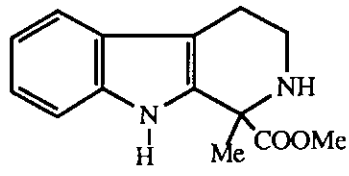
A stream of ozone in oxygen was bubbled through a stirred solution of ethyl - 3 - vinyl - 6 - chlorohexanoate (21.39 g, 0.1 mol) in methanol (650 ml), cooled to - 30 °C, during 3 h while cooling the solution to - 60 °C. The addition of ozone was stopped when a slight blue colour was obtained, after which the solution was flushed with nitrogen gas. Dimethyl sulphide (35.5 ml) was added to the solution, which was then allowed to warm to -10 °C and kept there for 1 h, then at 0 °C for a further 1 h. Stirring was continued for 2 h at room temperture, then the solution was concentrated under reduced pressure at ordinary temperture to give an oily residue, which was taken up in light petroleum (b. p. 40 - 60 °C) (400 ml), washed with water (4 x 180 ml), and then dried over anhydrous magnesium sulphate. Removal of the solvent under reduced pressure gave a colourless, oily residue which was purified by chromatography on silica gel G (200 g) with hexane - ethyl acetate (7 : 3) as eluent, to give ethyl 3 - formyl - 6 - chlorohexanoate (263) (78.36 - 81% yield) as a colourless oil (lit.,[57] unstable to distillation); ν_{max} (neat) 3000 - 2800, 2715, 1740, 1730, 1450, 1370, 1180, 1030, and 650 cm^{-1}. δ_H ($CDCl_3$, 90 MHz) 9.7 (1H, d, J: 0.3 Hz), 4.2 (2H, q, J: 7.2 Hz, $-CO_2C\underline{H}_2CH_3$), 3.5 (2H, m, $-CH_2Cl$), 2.7 (3H, m), 1.8 (4H, m), 1.25 (3H, t, J: 7.2 Hz, $-CO_2CH_2C\underline{H}_3$); m/z (%) 206 (M^+, 4), 205 (3.5), 204 (10), 179 (22.6), 177 (71), 141 (100) 115 (11.8), 99 (47.2), and 71 (67.1).

Tryptamine hydrochloride (151)



A stirred suspension of tryptophan (20 g, 98 mmol) in dry diphenyl ether (500 ml) was heated under reflux using a heating mantle for 45 minutes, then allowed to cool, in a nitrogen atmosphere, to room temperature. Ether (500 ml) was added and the mixture extracted with 2M hydrochloric acid (2 x 500 ml). The aqueous layer was first washed twice with ether (250 ml), then basified to litmus by the addition of 6M sodium hydroxide solution, and finally extracted with ether (3 x 400 ml). The combined organic extracts were dried ($MgSO_4$) and dry hydrogen chloride gas passed through the solution. Tryptamine hydrochloride was collected at the pump and recrystallised from methanol / ether, giving white needles (12.24 g, 64%), m. p. 252 - 254 °C (lit.,[92] 250 - 252 °C); ν_{max} (nujol) 3250, 1490 (w), 1450, 1370, 1230, 1090, 1005, 810, and 740 cm^{-1}; δ_H (DMSO, 90 MHz) 11.18 (1H, br s, $-NH_2$), 8.85 (1H, br s, -NH), 7.8, 7 (5H, m), 3.1 (4H, m).

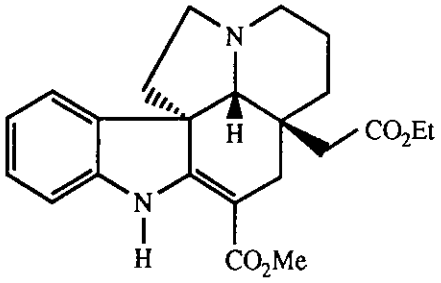
1 - Carbomethoxy - 1 - methyl - 1, 2, 3, 4 - tetrahydro - β - carboline (152b)



A mixture of tryptamine hydrochloride (8 g, 40 ml) and methyl pyruvate (4 ml, 44 mmol) in dry methanol (160 ml) was refluxed under nitrogen for 21 hours. The solution was then concentrated under reduced pressure at room temperature. The residue was dissolved in hot water (80 ml) and filtered, and ammonium hydroxide solution (6 ml) was added. The resulting solid was recrystallized from ethanol : water (3 : 5), which gave the title compound (152b) (7.4 g, 78.4%) as colourless prisms, m. p. 138 °C (lit.,[35] 136 - 138 °C); ν_{max} (nujol) 3380, 1720, 1600, 1450, 1370, 1230, and 1135 cm^{-1}; δ_H ($CDCl_3$, 90 MHz), 8.61 (1H, s, -NH-), 7.6, 7 (4H, m, Ar - H), 3.8 (3H, s, -OMe), 3.2 (2H, t, J: 7 Hz, $-CH_2-$), 2.75 ppm (2H, m, $-CH_2-$), 2.3 (1H, s, $-N_bH-$), and 1.7 ppm (3H, s, $-CH_3$); m / z (%) 244

(M^+, 4.3), 185 (100), 169 (9.1), 144 (6.3), 130 (1.6), 115 (5), 92 (9.5), 68 (4.9), 57 (2.8)

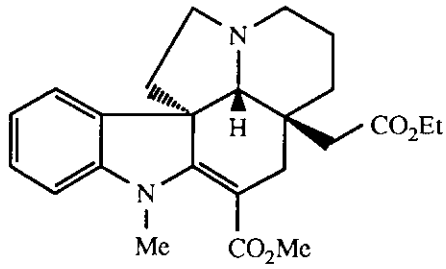
19 - Carbethoxy - 19 - demethylvincadifformine (267)



This was prepared using the procedure of J. P. Brennan[57].

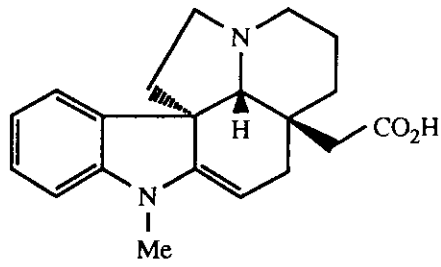
A mixture of 1 - carbomethoxy - 1 - methyl - 1, 2, 3, 4 - tetrahydro - β - carboline (152b) (1.5 g, 6.13 mmol), ethyl 3 - formyl - 6 - chlorohexanoate (263) (2 g, 9.76 mmol) and p - toluenesulphonic acid (32 mg) in toluene (65 ml) was refluxed under nitrogen for 110 h using a Dean - Stark trap to remove the water produced during the reaction. Further portions of chloroaldehyde (263) (2 x 0.62 g, 6 mmol) were added during the reaction to the hot solution. Diazabicycloundecene (DBU) (1.8 ml) was added after 114 h and heating continued for 14 h. The reaction mixture was allowed to cool to room temperature, then concentrated under reduced pressure after which the residue was purified by chromatography on a long column of Kieselgel G (80 g) using petroleum ether (b. p. 40 - 60 °C) - ether (40%) as eluent. This gave 19 - carbethoxy - 19 - demethylvincadifformine (267) (0.983 g, 40.45%), which was obtained from acetonitrile as colourless plates, m. p. 168 ° C (lit.,[57] 167 - 168 ° C); ν_{max} ($CHCl_3$) 3360 (NH), 1720 (-CO_2Et), 1675 (-CO_2Me), and 1605 cm^{-1}; λ_{max} (MeOH) 324, 296, and 224 nm; δ_H ($CDCl_3$, 90 MHz) 8.95 (1H, br s, -NH), 7.10 (2H, m, Ar - H), 6.8 (2H, m, Ar - H), 3.9 (2H, q, J: 7.2 Hz, -$CO_2\underline{CH_2}CH_3$), 3.71 (3H, s, -CO_2CH_3), 3.2 - 1.4 (15H, m), and 1.0 ppm (3H, t, J: 7.2 Hz); m / z (%) 396 (M^+, 7.3), 365 (0.7), 351 (1.4), 309 (1), 308 (0.9), 182 (100), 168 (3.7), 154 (6.3).

19 - Carbethoxy - 19 - demethyl - N_a - methylvincadifformine (390)

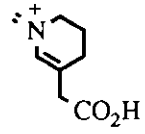


A solution of 19 - carbethoxy - 19 - demethylvincadifformine (267) (180 mg, 0.45 mmol) in dimethylformamide (4.5 ml) was added at ambient temperature to a mixture of 60% sodium hydride - mineral oil (45 mg, 0.9 mmol) in dimethylformamide (4.5 ml). After 20 min, methyl iodide (90 µl, 1.35 mmol) was added and the mixture stirred for 10 min. Water (22.5 ml) was added resulting in deposition of a gummy product. Decantation of the solvent, addition of ether, filtration of the ethereal solution and concentration under reduced pressure provided 19 - *carbethoxy* - 19 - *demethyl* - N_a - *methylvincadifformine* (390) (135 mg, 72.5%) as a colourless oil (Found: C, 70.1; H, 7.55; N, 7.0. $C_{24}H_{30}N_2O_4$ requires C, 70.25; H, 7.3; N, 6.8 %); ν_{max} ($CHCl_3$), 2940, 2880, 1730, 1680, 1620, 1475, and 1150 cm^{-1}; λ_{max} 206, 228 (sh), 300, 335, and λ_{min} 264; δ_H ($CDCl_3$, 300 MHz) 7.04 - 6.8 (4H, m, Ar - H), 4.1 (2H, q, J: 6.6 Hz, $-CO_2C\underline{H}_2CH_3$), 3.87 (3H, s, $-CO_2CH_3$), 3.25 (3H, s, :NCH3), 3.2 - 1.25 (18H, complex), and 1.17 ppm (3H, t, J: 6.6 Hz, $-CO_2CH_2C\underline{H}_3$); δ_C 171.39 (C - 18), 171 (C - 22), 177.4 (C - 2), 146.76 (C - 13), 137.1 (C - 8), 127.63 (C - 11), 121.15 (C - 9), 120.65 (C - 10), 108.62 (C - 12), 92.87 (C - 16), 73.74 (C - 21), 59.98 ($-CO_2\underline{C}H_2CH_3$), 56.62 (C - 7), 52.04 (C - 5), 51.77 (C - 3) 50.87 ($-CO_2\underline{C}H_3$), 47.02 (C - 6), 41.60 (C - 19), 40.16 (C - 20), 36.13 ($-NCH_3$), 33.25 (C - 15), 33 (C - 17), 21.6 (C - 14), and 14.05 ppm ($-CH_3$); m / z (%) 410 (M^+, 7.9), 365 (1.2), 351 (1), 182 (100), 168 (8.7), 144 (1.7) and 130 (1.3).

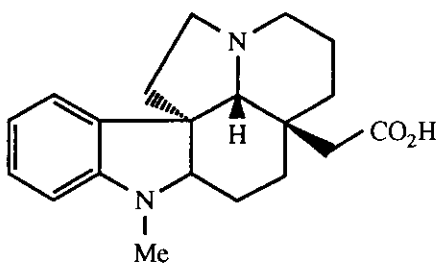
19 - Carboxy - 19 - demethyl - 2, 16 - dehydro - N_a - methylaspidospermidine (393)



A mixture of 19 - carbethoxy - 19 - demethyl - N_a - methylvinvincadifformine (390) (114 mg, 0.27 mmol) and 5M hydrochloric acid solution (10 ml) was heated on a steam bath fo 5 h, then cooled. The mixture was extracted with dichloromethane (4 x 30 ml). The combined organic fractions were washed with water (40 ml), and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by chromatography on Kieselgel G (15 g), using dichloromethane - methanol (2%) as eluent, which gave 19 - *carboxy* - 19 - *demethyl* - 2, 16 *dehydro* - N_a - *methylaspidospermidine* (393) (70 mg, 77.7%) as a yellow foam; ν_{max} ($CHCl_3$), 2960, 2875, 1720, 1620, 1480, and 1132 cm^{-1}, λ_{max} 206, 222 (sh), 250, and 280 nm; δ_H ($CDCl_3$, 300 MHz) carbonyl ester was absent, 3.44 ppm (3H, s, NCH_3); m / z (%) 324 (M^+, 6.7), 279 (9.1) [M^+- CO_2H], 264 (1.5) [M^+ - CH_3CO_2H], 185 (3.4), 170 (1.6), 168 (6.2), 154 (3.7) , 144 (2.5), 130 (2.5), 60 (6.4), 59 (7), and 43 (100). m/z 154

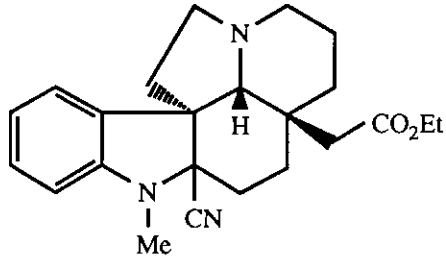


19 - Carboxy - 19 - demethyl - N_a - methylaspidospermidine (394)



A suspension of 19 - carboxy - 19 - demethyl - 2, 16 - dehydro - N_a - methylaspidospermidine (393) (70 mg, 0.21 mmol) and platinium (IV) oxide (PtO_2, 10 mg) in methanol (10 ml) was hydrogenated at room temperature and atmospheric pressure for 4 h. The catalyst was filtered and the solvent removed under reduced pressure and the residue was purified by chromatography on Kieselgel G (10 g), using dichloromethane - methanol (3%) as eluent, which gave 19 - *carboxy* - 19 - *demethyl* - N_a *methylaspidospermidine* (394) as oily product (10 mg, 14.5 %); ν_{max} ($CHCl_3$) 3450, 3035, 2960, 2880, 1720 cm^{-1}; λ_{max} (MeOH) 208, 246, 280 nm; m/z (%) 326 (M^+, 1.4), 324 (4), 281 (0.2), 279 (0.2), 168 (1.5), 154 (1.9), 144 (1.3), 138 (0.8), and 130 (2.6).

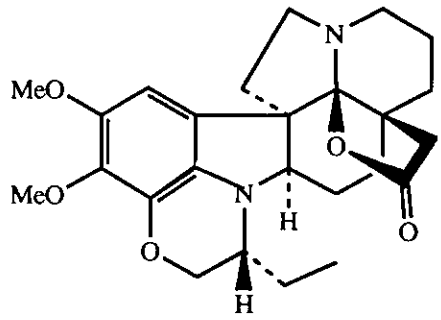
2 - Cyano - 19 - carbethoxy - 19 - demethyl - N_a - methylaspidospermidine (412)



To 19 - carbethoxy - 19 - demethyl - N_a - methylvincadifformine (390) (104 mg, 0.25 mmol) in dry hexamethylphosphoramide (HMPA; 13 ml) sodium cyanide (0.253 g , 5.16 mol) was added after which the mixture was stirred at 80 °C for 4.5 days, under nitrogen, then cooled. The mixture was diluted with water (12 ml) and extracted with ether (5 x 40 ml). The combined ethereal layers were washed with water (5 x 20 ml), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography on silica gel (15 g), using dichloromethane - methanol (1%) as eluent, provided 2 - *cyano* - 19 - *carbethoxy* - 19 - *demethyl* - N_a - *methylaspidospermidine* (412) (40 mg, 41.66%), which was recrystallised from methanol and obtained as colourless needles m. p. 143 - 145 °C (Found: C, 73.0; H, 8.0; N, 10.6; M^+, m/z 379.2260. $C_{23}H_{29}N_3O_2$ requires C, 72.8; H, 7.65; N,

11.0%; M^+, m/z 379.2259);ν_{max} ($CHCl_3$), 2940, 2860, 2815, 2740, 2240 (CN), 1720 (-CO_2Et), 1605, 1480, 1300, 1174 , and 1025 cm^{-1}; λ_{max} (MeOH) 206, 248, and 294 nm; δ_H ($CDCl_3$, 300 MHz) 7.12 - 6.45 (4H, m, Ar - H), 4.02 (2H, q, J: 7Hz, -$CO_2C\underline{H}_2CH_3$), 2.85 (3H, s, -NCH_3), 3.3 - 1.25 (17H, m), and 1.2 (3H, t, J: 7Hz, -$CO_2CH_2C\underline{H}_3$); δ_C171.42 (C - 18), 148.06 (C - 13), 132.60 (C - 8), 128.42 (C - 11), 122.40 (C - 9), 120.78 (CN), 119.34 (C - 10), 108.06 (C - 12), 69.91 (C - 21), 68. 42 (C - 2), 60.09 (-$CO_2\underline{C}H_2CH_3$), 56.94 (C - 7), 52.92 (C - 3), 51.44 (C - 5), 42.46 (C - 19), 36.15 (C - 6), 35.94 (C - 20), 34.71 (C - 15), 29.69 (NMe), 29.66 (C - 16), 22.67 (C - 17), 21.29 (C - 14), and 14.25 (-$CO_2CH_2CH_3$); m/z (%) 379 (M^+, 0.5), 352 (7.1) [M^+-HCN], 351 (10.3), 292 (0.4), 291 (8.3), 264 (2.4), 210 (1.2), 184 (5.6), 183 (14.4),182 (100), 181 (29), and 168 (3.7).

2.1.2 Approach to the synthesis of alalakine: biomimetic reaction



(385)

2, 3 - Dimethoxyphenol

To a vigorously stirred mixture of pyrogallol (38 g, 0.30 mol), water (34 ml) and carbon tetrachloride (70 ml) 5M sodium hydroxide (144 ml), and dimethyl sulphate (84 ml) were added dropwise separately and simultaneously, while maintaining the reaction mixture temperature around 40 °C. The mixture was then stirred for one hour, after which concentrated hydrochloric acid (10 ml) was added, and stirring was continued for a furthur 15min. The reaction mixture was then extracted with ether (4 x 100 ml) and the ether layer washed with 2M sodium hydroxide solution (5 x 100 ml). In this way the trimethoxy compound was removed by the ether. After acidification of the aqueous layer with concentrated hydrochloric acid, it was extracted with ether (5 x 150 ml).The combined ether layers were dried ($MgSO_4$), concentrated under reduced pressure, and distilled to give a mixture distilling at 120-127 °C / 10mm Hg. This oil was dissolved again in 2.5M sodium hydroxide solution (425 ml), when yellow crystals of 2,6 - dimethoxyphenol, m.p. 54 °C, were deposited. These were collected at the pump, and the filtrate was acidified with concentrated hydrochloric acid. The precipitated product was extracted with ether, dried ($MgSO_4$), and then distilled

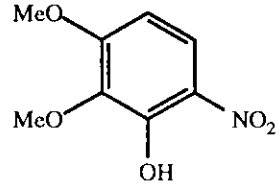
under reduced pressure to give three main fractions:

- The first fraction contained 2, 6 - dimethoxyphenol; b.p. 90 °C / 15 mm Hg, which gave colourless prisms, m.p. 54 °C (20.5 g, 44.2%); δ_H ($CDCl_3$, 90 MHz) 6.89 - 6.5 (3H, m, Ar-H), 5.53 (1H, s, OH, exchanges with D_2O), and 3.87 ppm (6H, 1s, 2 OMe).

- The second fraction contained the desired isomer, 2,3 - dimethoxyphenol (18.5 g, 40%) as a colourless oil, b.p. 129 - 134 °C / 15 mm Hg (Lit .,[104] 124-125 °C / 17 torr); δ_H ($CDCl_3$, 90 MHz) 7.05 - 6.39 (3H, m, Ar-H), 5.9 (1H, s, OH, exchanges with D_2O), and 3.8-3.7 ppm (6H, 2s, 2 OMe).

- The third fraction contained the pyrogallol 3 - methyl ether which was distilled at 146 °C / 15 mm Hg; δ_H ($CDCl_3$, 90MHz) 6.8 - 6.3 (3H, m, Ar-H), 5.3 - 5.4 (2H, 2s, 2 OH), and 3.8 ppm (3H, 1s, -OMe).

2.3 - Dimethoxy - 6 - nitrophenol (241)



Nitration of pyrogallol 1, 2 - dimethyl ether in a mixture of acetic acid and acetic anhydride was carried out according to the procedure of Baker and Smith. 2, 3 - Dimethoxy - 6 - nitrophenol (241b) (41.05 %) was recrystallised from a small

amount of methanol and obtained as yellow - green plates, m. p. 98 - 100 °C (lit.,[106] m. p. 102 - 103 °C). The maximum yield was obtained by keeping the temperature between 2 and 3 °C; δ_H ($CDCl_3$, 90 MHz) 10.79 (1H, s, OH), 7.9 (1H, d, J:10.8 Hz, H-5); 6.58 (1H, d, J:10.8 Hz, H - 4), 3.9 (3H, 1s, OMe), and 3.87 ppm (3H, 1s, OMe); m/z (%) 199 (M^+, 80.8), 182 (100), 156 (22.3) 139 (54.7), 123 (17.7), 109 (25.3), 96 (33.1), and 77 (9.2). Below 0 °C unreacted compound was recovered and above 5 °C 4, 6 - dinitropyrogallol 2, 3 - dimethyl ether, m. p. 76 °C was obtained, which was recrystallised from light petroleum ether (b. p. 60 - 80 °C); δ_H ($CDCl_3$, 90 MHz) 11.05 (1H, s, OH, exchanges with D_2O), 8.5 (1H, s, H - 5), 3.7 (3H, 1s, OMe), and 3.5 ppm (3H, 1s, OMe); m/z (%) 244 (M^+, 100), 227 (84.2), 197 (38.1), 181 (9.8), 167 (17.3), 151 (13.5), 110 (31.3) 94 (21.4), and 77 (22.6).

1 - Bromo - 2 - butanol.

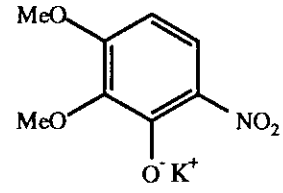
The preparation of the bromohydrin was carried out according to the method of Marcel de Montmollin. 1 - Bromo - 2 - butanol, b.p. 60 °C /12 mm Hg, was obtained in 50% yield based on consumed material. (Lit.,[108] b.p. 56 - 58 °C / 11 mm Hg).

1 -Bromo - 2 - butanone.

The oxidation of 1 - bromo - 2 - butanol with potassium dichromate in dilute sulphuric acid was carried out as for octan - 2 -one[108b]. This gave, as the only isolable product, the corresponding bromoketone in 79% yield. This was partially

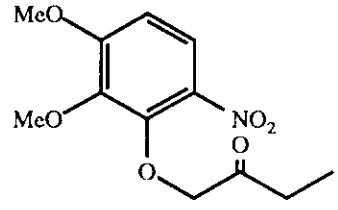
purified by flash chromatography, and used directly in the next step without furthur purification; δ_H ($CDCl_3$, 90 MHz) 3.88 (2H, 1s, - CH_2Br), 2.7 (2H, q, J: 6.4 Hz, - CH_2), 1.05 (3H, 1t, J:6.4 Hz, -CH_3); m/z (%) 152 (M^+, 3.3), 150 (3.3), 135 (29.5), 123 (9.9), 107 (4.4), 93 (5.6), 73 (4.2), and 57 (100).

Potassium salt of 2,3 - dimethoxy - 6 - nitrophenol



To a suspension of 2,3 - dimethoxy - 6 - nitrophenol (241) (30.7 g, 0.154 mol) in dry methanol (500 ml) potassium hydroxide pellets (8.6 g, 0.15 mol) were slowly added. The mixture was heated on a steam bath for 45 min, then cooled. Removal of the solvent under reduced pressure gave an orange solid, recrystallisation of which from acetone gave the potassium salt of 2, 3 - dimethoxy - 6 - nitrophenol (38.4, 94 %) as orange prisms, m.p. 294 - 296 °C (Lit.,[52] m.p. 294 - 296 °C)

1- (2, 3 - dimethoxy - 6 nitrophenoxy) - butan - 2 - one (368)



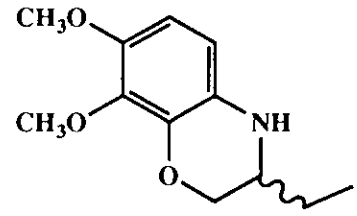
To a stirred suspension of the potassium salt of 2,3 - dimethoxy - 6-nitrophenol (241) (2.0 g , 8.4 mmol) in dry ethyl methyl ketone (20 ml) 1- bromo

- butan - 2 - one (3 g, 19.8 mmol) was added dropwise with stirring. The mixture was heated at reflux for 20 h in an atmosphere of nitrogen, then allowed to cool before being filtered. The solution was then filtered through a pad of Celite and the solvent removed under reduced pressure. The residue was purified by chromatography on Kieselgel G (60), using ether / petroleum ether (b.p. 60 - 80 °C) (20%) as eluent. Two fractions were obtained:

The first fraction contained 1 - (2, 3 - *dimethoxy* - 6 - *nitrophenoxy*) *butan* - 2 - *one* as a pale green oil (16 g , 71%) (Found: C, 53.5; H, 5.50; N, 5.15. $C_{12}H_{15}NO_6$ requires C, 53.50; H, 5.55; N, 5.2%); $\upsilon_{max.}$($CHCl_3$) 1726 , 1590, 1572, 1515, 1100, 1020, 905, 800, and 710 cm^{-1}; δ_H ($CDCl_3$, 90 MHz) 7.7 (1H, d, J: 9.5 Hz, 5 - H), 6.75 (1H, d, J: 9.5 Hz, 4 -H) 4.7 (2H, s, CH_2), 3.96 (3H, s, OMe), 3.87 (3H, s, OMe), 2.65 (2H, q, J: 7.2 Hz, CH_2), and 1.1 ppm (3H, t, J: 7.2 Hz, CH_3); m/z (%) 296 (M^+, 17.9), 196 (8.9), 183 (22.7), 166 (30.9), 139 (7.3), 109 (9.8), 96 (11.7), 80 (14.9), 69 (13), 57 (100), and 43 (11.7).

The second fraction was found to be unchanged 2, 3 - dimethoxy - 6 - nitrophenol, as verified by t.l.c., n.m.r. and i.r.

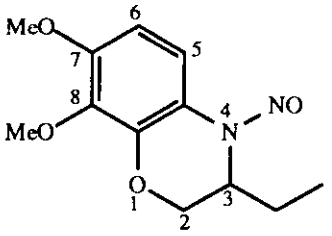
7, 8 - Dimethoxy - 3 - ethyl - 3, 4 - dihydro - 2H - 1, 4 - benzoxazine



(369)

A solution of 1 - (2,3 - dimethoxy - 6 - nitrophenoxy) - butan 2 - one (368) (2.57 g , 9.5 mmol) in absolute ethanol (40 ml) was hydrogenated at a pressure of 30 atmospheres and at 70 - 80 °C for 2 hours, using 5% palladium on carbon (0.24 g) as catalyst. The resulting mixture was allowed to cool and then filtered through a short pad of Celite. Removal of the solvent under reduced pressure gave a brown oil which was purified by chromatography on Kieselgel G (80g) using ether - petroleum ether (b.p. 40 - 60 °C) (30: 50) as eluent, which gave 7, 8 - *dimethoxy* - 3 - *ethyl* - 3, 4 - *dihydro* - 2H - 1, 4 - *benzoxazine* (369) as a clear oil (Found: C, 64.60; H,7.60; N, 6.30. $C_{12}H_{17}NO_3$ requires C, 64.90 ; H, 7.85; N, 6.5%); $\delta_{H.}$ ($CHCl_3$,400 MHz) 6.37 (1H, d, J: 8.5 Hz), 6.3 (1H, d, J: 8.5 Hz), 4.3 (2H, dd, J: 2.8, 10.5 Hz, CH_2), 3.86 (3H, s, OMe), 3.78 (3H, s, OMe), 3.24 (1H, br s, exchanges with D_2O) 3.25 (1H, m, 3 - H), 1.5 (2H, m, CH_2), and 1.02 (3H, t, J: 7.5 Hz, CH_3); $\lambda_{max.}$ (EtOH) 215, 245, and 300 nm; m/z (%) 223 (M^+, 100), 208 (61.7), 194 (52.3), 180 (51), 162 (19.1), 151 (74), 134 (98), 108 (6.6), 97 (7.1), 80 (13.6), 69 (11.6), and 53 (12.6).

N - Nitroso - 7, 8 - dimethoxy - 3 - ethyl - 3, 4 - dihydro - 2H - 1, 4 - benzoxazine (370)

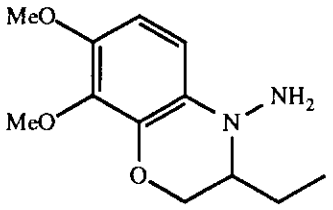


This was prepared according to the general procedure of J. W. Blowers[92].

To a solution of 7, 8 - dimethoxy - 3 - ethyl - 3,4 - dihydro - 2H - 1, 4 - benzoxazine (369) (26.31 g, 0.117 mol) in concentrated hydrochloric acid (27.36 ml) and crushed ice (40 g), sodium nitrite (8.63 g, 0.125 mol) in water (40.7 ml) was added dropwise at such a rate as to keep the temperature of the solution below 5 °C. After the addition was complete the reaction mixture was stirred for 1 h and then extracted with benzene (4 x 150 ml). The combined organic fractions were washed with water (100 ml), dried ($MgSO_4$), and then concentrated under reduced pressure. The residue was purified by chromatography on Kieselgel G (200 g) using benzene as eluent, which gave N *-nitroso* - 3 - *ethyl* -3, 4 - *dihydro* - 2H - 1, 4 - *benzoxazine* (370) (25.26 g, 87.5%) as a yellow oil (Found: C, 57.15; H, 6.35; N,11.1% .M^+, m/z 252.11061. $C_{12}H_{16}N_2O_4$ requires C, 57.0; H, 6.55; N,11.0%. M^+, m/z 252.110999); $\nu_{max.}$($CHCl_3$) 1605, 1500, 1450 (-N - NO), 1170, 810, 720 and 694 cm^{-1}; δ_H ($CDCl_3$, 400Mz) 7.3 (1H, d, J: 9.1 Hz, 5 - H), 6.65 (1H, d, J: 9.1 Hz, 6 - H), 5.1 (1H, m, 3 - H), 4.5 (1H, dd, J: 1.5, 12 Hz, 2 - H), 3.93 (1H, dd, J:2.8, 12 Hz, 2 - H), 3.95 (3H, s, OMe), 3.87 (3H, s, OMe), 1.55 (2H, m, - CH_2), 0.9 (3H, t, J: 7.5 Hz, CH_3); δ_C 146.02 (8), 138.3 (8a),138.13

(4a), 128.45 (7), 109.5 (6), 105.2 (5), 69.58 (C - 2) 60.87 (OMe) 56.66 (OMe) 50.9 (C - 3), 25.04 (-CH_2-), 9.87 (-CH_3); m/z (%) (M^+, no observed), 223 (100), 209 (7.9), 194 (53.7), 151 (11.5), 140 (27.2), 94 (10.8), 80 (24.7), 69 (46.5), and 53 (24.7).

N - Amino - 7, 8 - dimethoxy - 3 - ethyl - 3, 4 - dihydro - 2H - 1, 4 - benzoxazine (371)

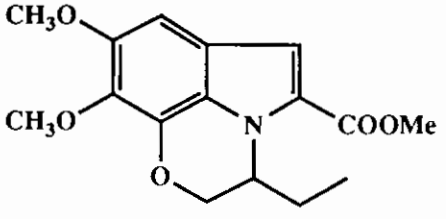


The N - nitroso compound (370) was reduced using lithium aluminium hydride by the procedure used by James P. Brennan[52b] in the preparation of the unmethoxylated analogue (245, 3 - Me).

To a solution of N - nitroso - 7, 8 - dimethoxy - 3 -ethyl - 3,4 - dihydro - 2H - 1, 4 - benzoxazine (20.93 g, 83 mmol) in dry ether (450 ml) and dry tetrahydrofuran (76 ml), cooled to 0 - 5 °C, a solution of lithium aluminium hydride (9.44 g, 0.24 mol) in dry ether (400 ml) was added dropwise, with stirring, at such a rate as to keep the reaction mixture temperature below 10 °C. After the addition was complete the solution was stirred at 5 - 10 °C for a further 2 h after which 30% sodium hydroxide solution (96 ml) was added dropwise. The aqueous phase was extracted with ether (3 x 100 ml) and then the combined ethereal layers were washed with water (200 ml), and then dried ($MgSO_4$). Concentration under reduced pressure then gave a brown oil which was purified by chromatography on Kieselgel G (200 g) using benzene / ether 10% as eluent; this gave N - *amino* - 7, 8-

dimethoxy - 3 - *ethyl* - 3, 4 - *dihydro* - 2H - 1, 4 - *benzoxazine* (371) (18.39 g, 93%) as a colourless oil (Found: C, 60.5; H, 7.55; N, 11.75. $C_{12}H_{18}N_2O_3$ requires C, 60.2; H, 7.7; N, 11.5%); ν_{max} ($CHCl_3$) 3435, 1607, 1500, 1100, 1050, 885, and 694 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 6.75 (1H, d, J: 9Hz), 6.4 (1H, d, J: 9Hz) 4.3 (1H, dd, J: 2.5, 11.5 Hz, 2 - H), 4.2 (1H, dd, J: 6, 11.5 Hz, 2 - H), 3.85 (3H, s, OMe), 3.8 (3H, s, OMe), 3.5 (2H, br s, exchanges with D_2O), 3.3 (1H, m, 3 - H), 1.85 (2H, m, $-CH_2$), and 0.96 (3H, t, 7 Hz, $-CH_3$); m / z (%) 238 (M^+, 100) 223 (88), 209 (65.4), 194 (39.5), 165 (28), 136 (27), 80 (30.7), 69 (38.1), and 53 (19.3).

5 - Carbomethoxy - 8, 9 - dimethoxy - 3 - ethyl - 3, 4 - dihydropyrrolo [1, 2, 3 - de] - 2H - 1, 4 - benzoxazine (372a)



N - Amino - 7, 8 - dimethoxy - 3 - ethyl - 3, 4 - dihydro - 2H - 1,4 - benzoxazine (371) (10.35 g, 0.043 mol) was dissolved in ethanol (186 ml) and methyl pyruvate (4.74 g, 0.046 mol) was added. The mixture was stirred for 1 h and then concentrated under reduced pressure. The residue was then slowly heated to 130 °C under reduced pressure (15 mm Hg) for 1 h. The crude product was purified by chromatography on Kieselgel G (180 g) using benzene / ether (10%) as eluent. This afforded 5 - *carbomethoxy* - 8, 9 - *dimethoxy* - 3 - *ethyl* - 3 -, 4 - *dihydropyrrolo* [1, 2, 3 - de] - 2H - 1, 4 -*benzoxazine* (372a) (7.5 g, 56%) as a

clear brown oil (Found M^+, m/z 305.1262. $C_{16}H_{19}NO_5$ requires M^+, m/z 305.1263); ν_{max} ($CHCl_3$) 1700, 1592, 1530, 1490, 1230, 1110, 1020, 981,840, 810, and 700 cm^{-1}; δ_H ($CDCl_3$, 90 MHz) 7.1 (1H, s, H - 7), 6.64 (1H, s, H - 6) 5.05 (1H, m, 3 - H), 4.3 (2H, m, $-OCH_2$), 3.94 (3H, s, $-CO_2CH_3$) 3.9 (3H, s, OMe), 3.85 (3H, s, OMe), 1.4 (2H, m, CH_2), and 0.94 (3H, t, J: 7.2 Hz, CH_3); m /z (%) 305 (M^+,100), 276 (14), 223 (34.7), 194 (19.6) 160 (3.4), 133 (11.7), and 77 (16.2).

8, 9 - Dimethoxy - 3 - ethyl - 3, 4 - dihydropyrrolo [1, 2, 3 - de] - 2H - 1, 4 - benzoxazine - 5 - carboxylic acid (372b)

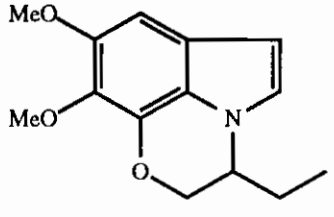
A mixture of 5 - carbomethoxy - 8, 9 - dimethoxy - 3 - ethyl - 3, 4 - dihydropyrrolo [1, 2, 3 - de] - 2H - 1, 4 - benzoxazine (372a) (7.5 g, 24 mmol) and 2M sodium hydroxide solution (71.5 ml) was heated at reflux for 2.5 hours. The solution was cooled to 0 °C and then concentrated hydrochloric acid was added until the mixture was acidic to litmus. The precipitate was collected by filtration and then recrystallised from benzene / ether, which gave 8, 9 - *dimethoxy* - 3 - *ethyl* - 3, 4 - *dihydropyrrolo* [1, 2, 3 -de] - 2H - 1, 4 - *benzoxazine* - 5 - *carboxylic acid* (372b) (6.73 g, 94.1%) as an amorphous solid, m. p. 165 - 167 °C (Found: C, 62.0; H, 5.95; N, 4.55%. M^+, m/z 291.11002. $C_{15}H_{17}NO_5$ requires C, 61.85; H, 5.85; N, 4.80%. M^+, m/z 291.11066); ν_{max} ($CHCl_3$) 2390, 1690, 1580, 1520, 1492, 1116, 920, and 650 cm^{-1}; δ_H ($CDCl_3$, 90 MHz) 9.0 (1H, br s, -OH), 7.27 (1H, s, H - 7), 6.68 (1H, s, H - 6), 5.1 (1H, m, 3 - H), 4.65 (1H, dd, J: 1.2, 12 Hz, - OCH_2-), 4.25 (1H, dd, J: 2.4, 12Hz, $-OCH_2$), 3.96 (3H, s, -OMe), 3.85

(3H, s, -OMe), 1.8 - 1.55 (2H, m, $-CH_2-$), and 1 (3H, t, J: 7.2 Hz, $-CH_3$); m/z (%) 291 (M^+, 100), 276 (58.1), 262 (16.5), 204 (21.8), 160 (17), 104 (10.3), 77 (21.9), 55 (52.6), and 44 (25.2).

Copper salt of 8, 9 - dimethoxy - 3 - ethyl - 3, 4 - dihydropyrrolo[1, 2, 3 - de] - 2H - 1, 4 - benzoxazine - 5 - carboxylic acid (372b)

The resulting precipitate from a mixture of 8, 9 - dimethoxy - 3 - ethyl - 3, 4 - dihydropyrrolo [1, 2, 3 - de] - 2H - 1, 4 - benzoxazine - 5 - carboxylic acid (372b) (0.5 g , 1.71 mmol), sodium carbonate (89 mg, 0.85 mmol), cupric sulphate pentahydrate (0.212 g, 0.85 mmol), and water (25 ml) was filtered off, washed with water, and then dried in a vacuum desiccator over calcium chloride to give *the copper salt of* (372b) as an amorphous green solid (0.498 g, 54%).

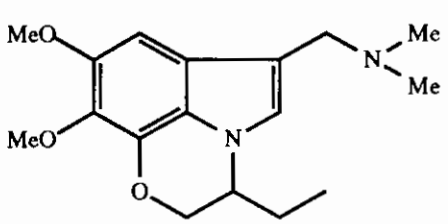
8, 9 - Dimethoxy - 3 - ethyl - 3, 4 - dihydropyrrolo [1, 2, 3 - de] - 2H - 1, 4 - benzoxazine (373)



8, 9 - Dimethoxy - 3 - ethyl - 3, 4 - dihydropyrrolo [1, 2, 3 - de] - 2H - 1, 4 - bezoxazine - 5 - carboxylic acid (372b) (1 g, 3.4 mmol) and its copper salt (74 mg) were added to freshly distilled quinoline (31.5 ml). The resulting mixture was heated at reflux for 5 hours, then cooled to room temperature. The mixture was diluted with ether (30 ml) , and washed with dilute hydrochloric acid solution (4 x

30 ml), water (30 ml), dilute sodium carbonate solution (2 x 30 ml), and water (30 ml) again. The ethereal layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by chromatography on Kieselgel G (40 g) using benzene / ether (10%) as eluent, which gave 8, 9 - *dimethoxy* - 3 - *ethyl* - 3, 4 - *dihydropyrrolo*[1, 2, 3 - de] - 2H - 1, 4 - *benzoxazine* (373) (0.79 g, 94%) as a clear oil (found: C, 67.7; H, 7.1; N, 5.6%; M^+, m/z 247.12081. $C_{14}H_{17}NO_3$ requires C, 68.0; H, 6.9; N, 5.65%; M^+, m/z, 247.120835); ν_{max} ($CHCl_3$) 1631, 1580, 1265, 1160, and 808 cm^{-1}; δ_H ($CDCl_3$, 90 MHz) 7.1 (1H, d, J: 2.57 Hz), 6.7 (1H, s, 7 - H), 6.3 (1H, d, J: 2.57 Hz), 4.4 - 4.1 (3H, m, -OC<u>H</u>$_2$C<u>H</u>-), 3.95 (3H, s, OMe), 3.85 (3H, s, OMe), 2.1 - 1.3 (2H, m, -C<u>H</u>$_2$CH$_3$), and 1.0 ppm (3H, t, J: 7.2 Hz, CH_3); m/z (%) 247 (M^+, 79.4), 232 (100), 218 (7.4), 160 (10.4) 133 (16.8), 104 (10.2), 77 (44.8), and 55 (21.1%).

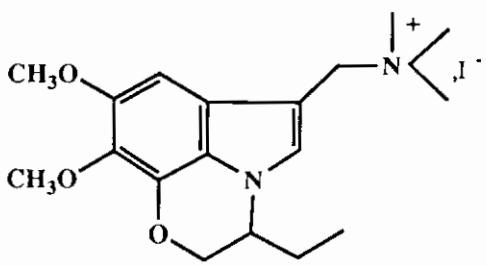
8, 9 - Dimethoxy 6 - dimethylaminomethyl - 3 - ethyl - 3, 4 - dihydropyrrolo [1, 2, 3 - de] - 2H - 1, 4 - benzoxazine (374)



A mixture of 40% aqueous dimethylamine solution (0.84 g, 5.05 mmol) and glacial acetic acid (0.84 g) was cooled in an ice - bath; when the temperature had fallen to 5 °C, 8, 9 - dimethoxy - 3, 4 - dihydropyrrolo [1, 2, 3 - de] - 2H - 1, 4 - benzoxazine (373) (1.207 g, 4.8 mmol) in 40% aqueous formaldehyde (26 mg, 80

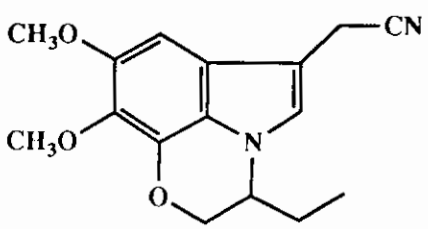
mmol) was added. The mixture was stirred at room temperature overnight after which the reaction mixture was made alkaline to litmus by the addition of dilute potassium hydroxide solution. The aqueous phase was extracted with chloroform (2 x 50 ml) and the combined extracts were dried ($MgSO_4$), concentrated under reduced pressure, and the residue chromatographed on Kieselgel G (40 g) using benzene / ether (15%) as eluent, which gave 8, 9 - *dimethoxy* - 6 - *dimethylaminomethyl* - 3 - *ethyl* - 3, 4 - *dihydropyrrolo* [1, 2, 3 - de] - 2H - 1, 4 - *benzoxazine* (374) (1.4 g, 94.5% yield) as a yellow oil (Found: C, 67.30; H, 7.75; N, 8.55. $C_{17}H_{24}N_2O_3$ requires C, 67.10; H, 7.8; N, 9.0%); ν_{max} ($CHCl_3$) 1640, 1595, 1250, 1040, 1020, and 820 cm^{-1}; δ_H ($CDCl_3$, 90MHz) 7.05 (1H, s, 7 - H), 6.7 (1H, s, 5 - H), 4.5 - 4.05 (3H, m, - $OC\underline{H}_2C\underline{H}$-), 3.9 (3H, s, -OMe), 3.85 (3H, s, -OMe), 3.55 (2H, s, -CH_2-N:), 2.3 (6H, s, -$N(CH_3)_2$), 1.85 (2H, m, -$C\underline{H}_2CH_3$), and 1.0 ppm (3H, t, J: 7.2 Hz, CH_3); m/z 304 (M^+, 25.5), 260 (100%), 232 (5), 161 (5.5), 69 (10.9), and 44 (1).

8, 9 - Dimethoxy - 6 - dimethylaminomethyl -3 - ethyl - 3, 4 - dihydropyrrolo[1, 2, 3 -de] - 2H - 1, 4 - benzoxazine methiodide (375)



8, 9 - Dimethoxy - 6 - dimethylaminomethyl - 3 - ethyl - 3, 4 -dihydropyrrolo [1, 2, 3 - de] - 2H - 1, 4 - benzoxazine (374) (2.5 g, 8.2 mmol) was added to iodomethane (21 ml, 0.336 mol) with rapid stirring. The resulting solution was stirred at room temperature and left overnight, during which period most of the product crystallised. Crystallization was completed by cooling, and the solid was collected, washed twice with ice-cold ether, and dried. The methiodide product was obtained as colourless prisms (3.5 g, 96%), m.p. 210 °C (dec) (Found: C, 48.30; H, 6.05; N, 6.00. $C_{18}H_{27}N_2O_3I$ requires C,48.40; H, 6.05; N, 6.25%); ν_{max} ($CHCl_3$) 1588, 1525 1460, 740, 725 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 7.6 (1H, s,), 6.9 (1H, s), 4.69 (2H, s, $-CH_2N$), 4.45 - 4.35 (3H, m, - OCH_2CH-), 3.9 (3H, s, OMe), 3.8(3H, s, OMe), 3.15 (9H, s, $-NMe_3$), 2 - 1.8 (2H, m, $-CH_2$), and 1.1 (3H, t, J: 7 Hz, CH_3); m / z (%) (M^+ not observed), 261 (5.4), 232 (5.7), 128 (38.4), 58 (100).

6 - Cyanomethyl - 8, 9 - dimethoxy - 3 - ethyl - 3, 4 - dihydropyrrolo [1, 2, 3 - de] - 2H - 1, 4 - benzoxazine (376)



To a solution of potassium cyanide (0.175 g, 2.7 mmol) in water (5 ml) was added 8, 9 - dimethoxy - 6 - dimethylaminomethyl - 3 - ethyl - 3 -, 4 - dihydropyrrolo [1, 2, 3 - de] - 2H - 1, 4 - benzoxazine methiodide (375) (0.2 g, 0.9 mmol), and

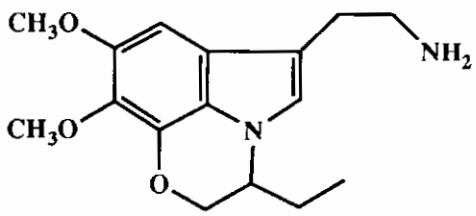
the mixture was boiled under reflux for two and one half hours, during which period an oil separated from the aqueous solution. This oil was extracted with chloroform (3 x 30 ml) and the combined organic extracts were washed with water, dried (Na_2SO_4), and then concentrated under reduced pressure. The crude product was purified by chromatography on Kieselgel G (80 g) using benzene / ether 10% as eluent, which gave two main fractions.

The first fraction was identified as 5 - *Cyano* - 8, 9 - *dimethoxy* - 3 - *ethyl* - 6 - *methyl* - 3, 4 - *dihydropyrrolo* [1, 2, 3 - de] - 2H - 1, 4 - *benzoxazine* (427) (0.180 g, 14% yield) (Found: C, 67.0; H; 6.6, N, 9.5. $C_{16}H_{18}N_2O_3$ requires C, 67.1; H, 6.3; N, 9.8%); ν_{max} ($CHCl_3$) 2215, 1620, 1550, 1265, 1135, and 740 cm^{-1}; δ_H ($CDCl_3$, 90 MHz) 6.6 (1H, s, 7 - H), 4.6 - 4.2 (3H, m, $-CH_2-CH$), 3.9 (3H, s, -OMe), 3.8 (3H, s, OMe), 2.4 (3H, s, 6 -Me), 1.95 - 1.8 (2H, m, $-CH_2-$), and 1 ppm (3H, t, J: 7.2 Hz, $-CH_3$); m / z (%) 286 (M^+, 100), 271 (62.6), 256 (11.9), 212 (7.5), 171 (1.7), 143 (1), 105 (1.5), 77 (0.6).

The second fraction contained 8, 9 - *dimethoxy* - 3 - *ethyl* - 3,4 - *dihydropyrrolo* [1, 2, 3 - de] - 2H - 1, 4 - *benzoxazine* - 6 -*acetonitrile* (376) (0.85g, 70% yield) as a clear oil (Found: C, 67.05; H, 6.20; N, 9.6 %. M^+, m/z 286.13091. $C_{16}H_{18}N_2O_3$ requires C, 67.1; H, 6.3; N, 9.8 %. M^+, m / z 286.131734); ν_{max} ($CHCl_3$) 2230, 1600, 1510, 1480, 1260, 1040 (-C-O-C-); δ_H ($CDCl_3$, 90 MHz) 7.1 (1H, s, 5 - H), 4.4 - 4.1 (3H, m, $-OCH_2CHN-$), 3.95 (3H, s, - OMe), 3.87 (3H, s, OMe), 3.7 (2H, s, $-CH_2CN$), 1.9 - 1.7 (2H, m,

-CH_2-), and 1ppm (3H, t, J: 7 Hz); m/z (%) 286 (M^+, 97.6), 271 (100), 216 (14.2), 166 (13), 143 (1.1), 105 (53.2), 83 (19.6), 69 (30.7).

8, 9 - Dimethoxy - 3 - ethyl - 6 - (2 - aminoethyl) - 3, 4 - dihydropyrrolo [1, 2, 3 - de] - 2H - 1, 4 - benzoxazine (377)



Method A

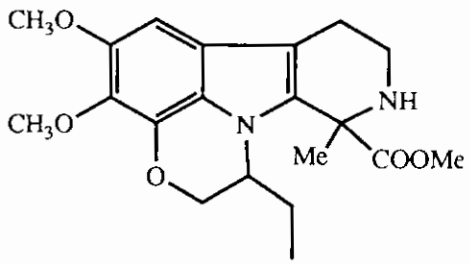
To a cooled solution of 6 - cyanomethyl - 8, 9 - dimethoxy - 3 - ethyl - 3, 4 - dihydropyrrolo [1, 2, 3 - de] - 2H - 1, 4 - benzoxazine (376) (2.3 g, 8.04 mmol) in dry tetrahydrofuran (20ml) a suspension of lithium aluminium hydride (1 g, 26.35 mmol) in dry ether (30 ml) was added dropwise, over a period of 25 minutes. The mixture was stirred overnight at ambient temperature and then diluted with water (20 ml) and 6M sulphuric acid solution (30 ml). The aqueous phase was extracted with ether (3 x 60 ml), after which the pH of the solution was adjusted to 10 by the addition of 2M potassium hydroxide solution. The solution was then extracted with ethyl acetate (4 x 100 ml). The organic layer was washed with brine (50 ml), dried ($MgSO_4$), and then concentrated. The oily residue was chromatographed on a column of alumina [elution with dichloromethane - ether (7 : 1)]. 8, 9 - *Dimethoxy* - 3 - *ethyl* - 6 - (2 - *aminoethyl*) - 3, 4 - *dihydropyrrolo* [1, 2, 3 - de] - 2H - 1, 4 - *benzoxazine* (377) (1.56 g, 77 %) was obtained as a yellow oil (Found: M^+, m/z 290.16276. $C_{16}H_{22}N_2O_3$ requires M^+, m/z

290.163032); ν_{max} ($CHCl_3$) 3400, 3050 - 2800, 1680, 1590, 1500, and 900 cm^{-1}; δ_H ($CDCl_3$, 90 MHz) 6.9 (1H, s, H - 7), 6.65 (1H, s, H - 5), 4.45 - 4 (3H, m, $-CH_2CHN-$), 3.95 - 3.85 (6H, s, OMe), 3.2, 2.8 (4H, m), 1.6 (2H, br s, exchangees with D_2O, NH_2), 1.8 (2H, m, $-CH_2$), and 1 ppm (3H, t, J: 7.1 Hz, $-CH_3$); m/z (%) 290 (M^+, 30), 260 (100), 232 (3.2), 187 (3.2), 161 (121), 119 (34), and 55 (12.6).

Method B

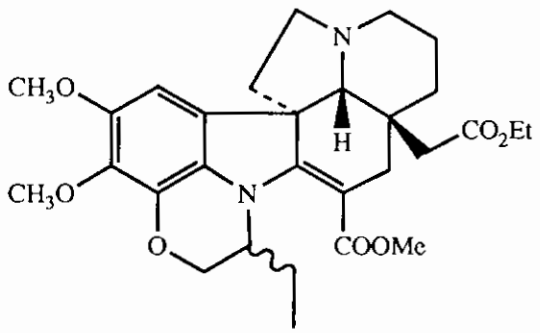
To a solution of 6 - cyanomethyl - 8, 9 - dimethoxy - 3 - ethyl - 3, 4 - dihydropyrrolo [1, 2, 3 - de] - 2H - 1, 4 - benzoxazine (376) (100mg, 0.3 mmol) and cobaltous chloride hexahydrate (142 mg, 0.6 mmol) in 99% methanol (4 ml) was added sodium borohydride (0.114 mg, 3 mmol) in portions with stirring at ambient temperature. After the addition was complete, stirring was continued for one hour. 3M Hydrochloric acid (1.2 ml) was then added and stirring continued until all the black precipitate had dissolved. After removal of the methanol under reduced pressure and unreacted starting material by extraction with ether, the aqueous layer was made alkaline with concentrated ammonia solution. Extraction with chloroform (3 x 20 ml), followed by drying (anhydrous $MgSO_4$) and evaporation to dryness, gave the desired product (377) (77 mg, 76.6%) as a brown oil, identical (ir, n.m.r., mass) with that prepared above.

1 - Carbomethoxy - 6, 7 - dimethoxy - 3' - ethyl - 1 - methyl - 1, 2, 3, 4 - tetrahydropyrido [3, 4 - b] - 3, 4 - dihydropyrrolo [1, 2, 3 - de] - 2H - 1, 4 - benzoxazine (378)



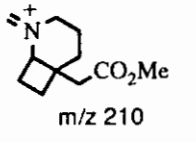
A solution of 8, 9 - dimethoxy - 3 - ethyl - 6 - (2 - aminoethyl) - 3, 4 - dihydropyrrolo [1, 2, 3 - de] - 2H - 1, 4 - benzoxazine (3.61 g, 12.4 mmol) and methyl pyruvate (1.83 g, 17.9 mmol) in dry methanol (100ml) was refluxed under nitrogen for 22 hours. The cooled solution was concentrated under reduced pressure, and the residue was partitioned between saturated aqueous sodium carbonate solution (200 ml) and dichloromethane (400 ml). The aqueous phase was extracted twice with ether (2 x 400 ml), washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on a silicagel column (80 g). Elution with dichloromethane - ether (7 : 1) yielded an amorphous solid (3.9 g, 86%), m.p. 75 - 78 °C (Found C, 63.85; H, 6.6; N, 6.95%; M^+, m/z 374.18304 $C_{20}H_{26}N_2O_5$ requires C, 64.1; H, 6.95; N, 7.4%; M^+, m/z 374.184159); ν_{max} ($CHCl_3$) 3510 (-NH), 1720 (-COOMe), 1600 (indole double bond); δ_H ($CDCl_3$, 90 MHz) 6.6 (1H, s, 5 - H), 4.7 - 4.1 (3H, m, $-OCH_2CH-$), 3.95 (3H, s, $-OCH_3$), 3.85 (3H, s, $-OCH_3$), 3.73 (3H, s, $-CO_2Me$), 3.3 (2H, m, $-CH_2-$), 2.8 (2H, m, $-CH_2-$), 2.2 (1H, s, -NH-), 1.2 (3H, s, $-CH_3$), 1.7 (2H, m, $-\underline{CH_2}CH_3$), and 1ppm (3H, t, J: 7 Hz, $-CH_3$); m/z (%) 374 (M^+, 9.9), 315 (100), 201 (8.5), 169 (4.8), 145 (4.5), 94 (28.8), and 69 (30.6).

Hexacyclic diester (381)

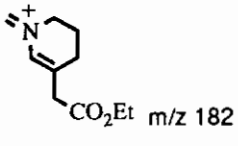


A solution of the tetrahydro - β - carboline derivative (378) (1.51 g, 4 mmol), ethyl 3 formyl - 6 - chlorohexanoate (263) (1.1 g, 4.8 mmol), and p - toluenesulphonic acid (20.8 mg) in toluene (100ml) was refluxed under nitrogen with a Dean - Stark separator for 110 h. Further portions of chloroaldehyde (263) (2 x 0.5 g, 2.4 mmol) were added during the reaction (after 70 and 90 h) to the mixture. To the hot solution, diazabicycloundecene (DBU) (1.5 ml) was then added and heating continued for further 10 h. Removal of the solvent under reduced pressure gave a brown oil wich was chromatographed on a long column of Kieselgel G (80 g) using dichloromethane - ether (7: 1) as eluent, which gave *the title compound* (381) (0.73 g, 34.5 %) as a pale yellow oil. Trituration with a small amount of ether gave an amorphous mixture of diastereoisomers, m.p. 130 - 138 °C (Found: C, 65.85; H, 7.25; N, 5.05%. M^+, m/z 526.267869. $C_{29}H_{38}N_2O_7$ requires C, 66.10; H, 7.2; N, 5.3%; M^+, m/z 526.266); ν_{max} ($CHCl_3$) 2940, 2920 - 2860, 2740, 1720 ($-CO_2Et$), 1670 ($-CO_2Me$), 1570, 1480, 1460, 1430, 1355, 1260, 1180, 1120, 1050, and 650 cm^{-1}; λ_{max} (MeOH) 203, 210, 230, 302, 344 nm; λ_{min} 274, 316 nm; δ_H ($CDCl_3$, 400MHz) 6.44, 6.42 (1H, 2s, 9 - H),

4.85, 4.54 (1H, dd, J: 2, 12 Hz), 4.3, 4.2 (1H, dd, J: 2, 12 Hz, H - 4'), 4 (2H, 2q, J: 7Hz, -$CO_2C\underline{H}_2CH_3$), 3.9, 3.89 (3H, 2s, -OMe), 3.83, 3.86 (3H, 2s, -OMe), 3.7, 3.68 (3H, 2s, -CO_2Me), 3.2 - 1.2 9 (17H, m), 1.15, 1.12 (3H, 2t, J: 7Hz, $CO_2CH_2C\underline{H}_3$), and 1.0, 0.9 (3H, 2t, J: 7.5 Hz, 1' - Me); δ_C ($CDCl_3$) 171.5, 171.25 (C - 18), 167.48, 166.48 (C -22), 162.76, 161.97 (C - 2), 148.18, 147.52 (C - 11), 136.92, 136.12 (C - 12), 135.81, 134.96 (C - 13), 131.00, 129.87 (C - 8), 125.64, 124.74 (C - 10), 99.60, 98.66 (C - 9), 93.84, 93.01 (C - 16), 73.24, 71.3 (C - 21), 67.92, 66.3 (C - 4'), 61.22, 61, 09 (C - 3'), 59.85, 59.81 (-$\underline{C}H_2$ ester), 58.92, 57.84 (C - 7), 57.39, 57.15 (-OMe), 56.02, 53.68 (-OMe), 51.61, 51.00 (C - 3), 50.9, 50.83 (-CO_2CH_3), 50.29, 49.78 (C - 5), 46.85, 46.53 (C - 6), 41.24 (C - 20), 37.53, 37.25 (C - 19), 33.3, 33.15 (C - 15), 29.92, 29.59 (C- 17), 24.87, 22.06 (C - 14), 21.74, 16.63 (C - 2'), 14.06, 13.98 (-CH_3 ester), and 10.14, 9.52 (C - 1'); m/z (%) 526 (M^+, 17.4), 344 (7.9), 260 (0.4), 210 (0.4), 182 (100).

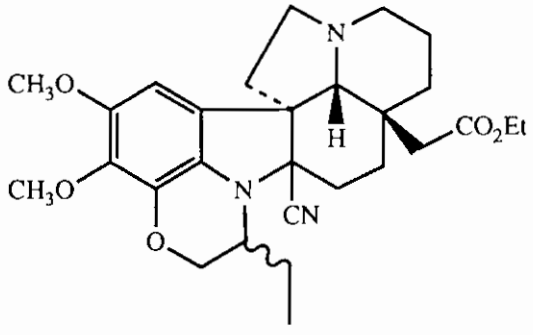


m/z 210



m/z 182

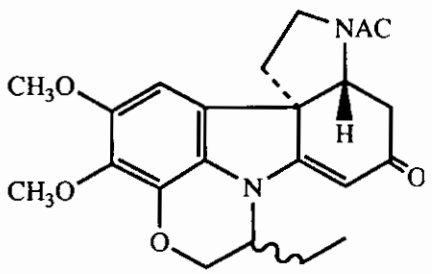
2 - Cyano - hexacyclic ester (430)



To the hexacyclic diester (381) (108 mg, 0.2 mmol) in dry hexamethylphosphoramide (HMPA , 10 ml), sodium cyanide (0.2 g, 4.08 mmol) was added, after which the reaction mixture was stirred at 82 °C for 102 h under nitrogen, then cooled. The mixture was diluted with water (20 ml) and extracted with ether (5 x 50 ml). The combined extracts were washed with water (5 x 20 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on Kieselgel G (25 g) using petroleum ether (40 - 60 °C) - ether (40%) as eluent, which gave 2 - *cyano* - *hexacyclic ester* (430) (58 mg, 57.4%) as a colourless needles m. p. 143 - 145 °C (Found: M^+, m / z 495.2727 $C_{28}H_{37}N_3O_5$ requires M^+, m / z 495.2733); ν_{max} ($CHCl_3$) 2960, 2880, 2240 (CN), 1725, 1490, 1470, 1125, and 1087 cm^{-1}; λ_{max} (MeOH) 218, 250, 300 nm, λ_{min} 278 nm; δ_H ($CDCl_3$, 300 MHz) 6.35, 6.3 (1H, 2s, 9 - H), 4.4, 4.3 (3H, m, OCH_2-CH), 4.1 (2H, 2q, J: 7.2 Hz, $CO_2C\underline{H}_2CH_3$), 3.9, 3.89 (3H, 2s, -OMe), 3.82, 3.8 (2H, s, -OMe), 3.3 - 1.2 (19H, m), 1.15, 1.2 (3H, 2t, J: 7.2Hz , $-CO_2CH_2C\underline{H}_3$), and 0.9, 0.8 (3H, 2t, J: Hz, 1'-Me); m / z (%) 495 (M^+, 3.9), 469 (6.9) [-CN], 468 (21.3) [-HCN], 423 (1.7) [- EtO], 286

(9.7), 234 (1.8), 183 (11.6), and 182 (100).

2.1.3 Synthesis of the key pentacyclic vinylogous amide (442)

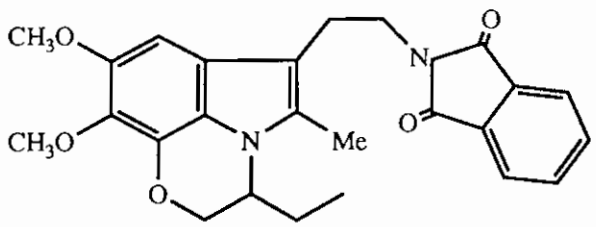


This was carried out according to the general procedure[52] used to prepare the methyl analogue (249).

5 - Phthalimido - 2 - pentanone

The condensation of potassium phthalimide with 5 - chloro - 2 - pentanone in dimethylformamide was carried out according to the procedure of Stetzinger and co - workers[120], which gave 5 - phthalimido - 2 - pentanone in (44.5 % yield), m.p. 74 - 75 °C (lit.,[120] 75 - 77 °C); δ_H ($CDCl_3$, 90 MHz) 7.9, 7.65 (4H, m, Ar - H), 3.7 2H, t, J: 7 Hz, -CH_2-), 2.5 (2H, t, J: 7 Hz, -CH_2-), 2.15 (3H, s, -CH_3), and 1.95 (2H, m, -CH_2-).

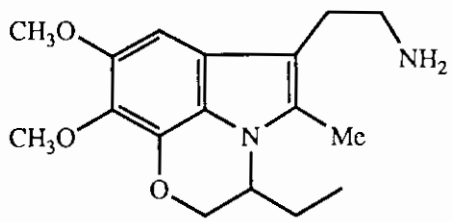
8, 9 - Dimethoxy - 3 - ethyl - 5 - methyl - 6 - (2 - phthalimidoethyl) - 3, 4 - dihydropyrrolo [1, 2, 3 - de] - 2H - 1, 4 - benzoxazine (439)



A mixture of N - amino - 7, 8 - dimethoxy - 3 - ethyl - 3, 4 - dihydro - 2H - 1, 4 - benzoxazine (371) (0.89 g, 3.74 mmol) and 5 - phthalimido - 2 - pentanone (0.86 g , 3.74 mmol) in glacial acetic acid (34 ml) was refluxed for 4 hours, then cooled. Water (34 ml) was added, after which the mixture was extracted with ether (3 x 80 ml). The combined extracts were washed with water (2 x 60 ml) and dried ($MgSO_4$). After evaporation of the solvent, the crude product was purified by silica gel column chromatography to give pale yellow needles which on recrystallization from chloroform gave 8, 9 - *dimethoxy* - 3 - *ethyl* - 5 - *methyl* - 6 - (2 - *phthalimidoethyl*) - 3, 4 - *dihydropyrrolo* [1, 2, 3 - de] - 2H - 1, 4 - *benzoxazine* (439) (1.65 g, 75%) as colourless needles, m. p. 135 °C (Found: C, 69.05; H, 5.9; N, 6.3; M^+, m / z 434.18336. $C_{25}H_{26}N_2O_5$ requires C, 69.1; H, 6.0; N, 6.45%; M^+, m/z 434.184159); ν_{max} ($CHCl_3$) 2900, 1712, 1599, 1350, 1120, and 873 cm^{-1}; λ_{max} (MeOH) 215, 270, and 296 nm; δ_H ($CDCl_3$, 90 MHz) 7.75 (4H, m, Ar - H), 6.65 (1H, s, Ar - H), 4.3 (3H, m, $-OCH_2CH-$), 3.9 (3H, s , -OMe), 3.87 (3H, s, -OMe), 3.7 (2H, m, $-CH_2-$), 3 (2H, m, $-CH_2-$), 2.35 (3H, s, $-CH_3$); 1.7 (2H, m, $-C\underline{H}_2CH_3$), and 1 ppm (3H, t, J: 7 HZ, $-CH_2C\underline{H}_3$); m / z (%) 434 (M^+, 35.9), 419 (8), 288 (0.8), 274 (100), 259 (1.2) 174 (2.6), 160

(13.7), 147 (3.1), 146 (1.2), 104 (8), and 77 (7).

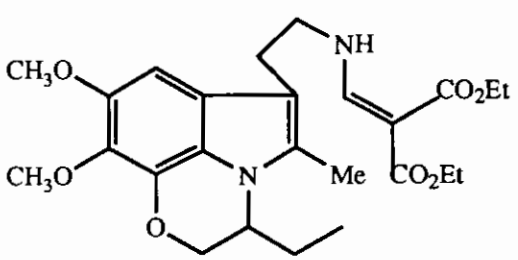
8, 9 - Dimethoxy - 3 - ethyl - 5 - methyl - 6 - (2 - aminoethyl) - 3, 4 - dihydropyrrolo [1, 2, 3 - de] - 2H - 1, 4 - benzoxazine (440)



To a stirred solution of 8, 9 - dimethoxy - 3 - ethyl - 5 - methyl - 6 - (2 - phthalimidoethyl) - 3, 4 - dihydropyrrolo [1, 2, 3 -de] - 2H - 1, 4 - benzoxazine (439) (4.51 g, 10.37 mmol) in ethanol (160 ml) was added hydrazine hydrate (100% aq. sol.; 1.4 g, 0.01 mol) The reaction mixture was refluxed for 20 h. After evaporation of the solvent under reduced pressure, the residue was taken up in 3M hydrochloric acid solution (42 ml). The resulting solution was heated to reflux for 3h, then cooled to 5 °C. The aqueous layer was separated from the phthalhydrazide, concentrated to about 50 ml under reduced pressure, made alkaline with 2M sodium hydroxide solution and then extracted with chloroform (4 x 60 ml). The extract, washed with water (40 ml) and dried over ($MgSO_4$) , was evaporated in *vacuo*. The oily residue was purified by chromatography on silica gel G (25 g) with chloroform - methanol (2%) as the eluent, to give 8, 9 - *dimethoxy* - 3 - *ethyl* - 5 - *methyl* - 6 - (2 - *aminoethyl*) - 3, 4 - *dihydropyrrolo* [1, 2, 3 - de] - 2H - 1, 4 - *benzoxazine* (440) (1.22 g, 39.3%); ν_{max} ($CHCl_3$) 3350 (br) N-H, 2960, 2920, 2870, 2700, 1640, 1590, 1450, 1351, 1115, and 975 cm^{-1}; λ_{max} (MeOH) 220, 276 nm; δ_H ($CDCl_3$, 90 MHz) 6.55 (1H, s, Ar - H), 4.3 (3H, m, CH_2CH),

3.97 (3H, s, -OMe), 3.87 (3H, s, -OMe), 2.9 (4H, m, $-CH_2CH_2-$), 2.3 (3H, s, $-CH_3$), 1.7 (2H, m, $-C\underline{H}_2CH_3$), 1.3 (2H, br s, $N\underline{H}_2$), and 1 ppm (3H, t, J: 7.1Hz, $-CH_3$); m / z (%) 304 (M^+, 15.6), 290 (6.5) [$M^+ - CH_3$], 288 (128), 274 (84.1) [$M^+ - CH_2NH_2$], 260 (100) [$M^+ - CH_2CH_2NH_2$].

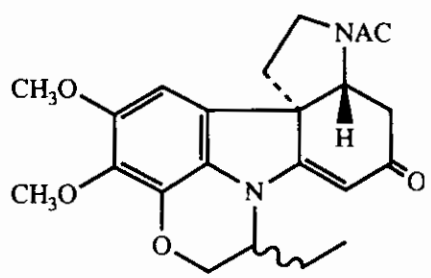
N_b - (2', 2' - Dicarbethoxyvinyl) - 8, 9 - dimethoxy - 3 - ethyl - 5 - methyl - 6 - (2 - aminoethyl) - 3, 4 - dihydropyrrolo [1, 2, 3 - de] - 2H - 1, 4 - benzoxazine (441)



A mixture of the amine (440) (172 mg, 0.56 mmol) and diethyl ethoxymethylenemalonate (2.83 g, 13.1 mmol) in absolute ethanol (13 ml) was heated at a refluxing temperature for 20 h, then cooled. Removal of the solvent under reduced pressure gave a yellow, oily residue which was purified by chromatography on Kieselgel G (25 g) with dichloromethane - ether (7 : 1) as the eluent, to afford N_b - (2', 2' - *dicarbethoxyvinyl*) - 8, 9 - *dimethoxy* - 3 -*ethyl* - 5 - *methyl* - 6 - (2 - *aminoethyl*) -3, 4 - *dihydropyrrolo* [1, 2, 3 - de] - 2H - 1, 4 - *benzoxazine* (441) (147 mg, 92.10%) as a colourless oil (found: M^+, m / z 474.23585. $C_{25}H_{34}N_2O_7$ requires M^+, m/z 474.236583); ν_{max} ($CHCl_3$) 3360, 3280, 3190, 2980, 2870, 1710, 1680, 1640, 1603, 1504, 1120, and 860 cm^{-1}; λ_{max} (MeOH) 226, 274 nm ;

λ_{min} 260 nm.; δ_H ($CDCl_3$, 90 MHz) 9.18 (1H, ap, -NH-), 7.75 (1H, d, J: 14 Hz, C=C<u>H</u>), 6.5 (1H, s, Ar - H), 4.3 (3H, m, -OC<u>H</u>$_2$C<u>H</u>-N_a-), 4.1 (4H, m, 2 x -$CO_2C\underline{H}_2CH_3$), 3.95 (3H, s, -OMe), 3.86 (3H, s, -OMe), 3.5 (2H, m, -CH_2-) 2.9 (2H, m, -CH_2-), 2.2 (3H, s, 5 - CH_3) 1.8 (2H, m, -CH_2 CH_3), 1.3 (6H, m, 2 x - $CO_2CH_2C\underline{H}_3$), and 1 ppm (3H, t, J: 7.1 Hz, -CH3); m / z (%) 474 (M^+, 12.9), 274 (100), 177 (7.6) , 175 (8.6), 154 (3.7), 109 (5.4), 83 (14.5).

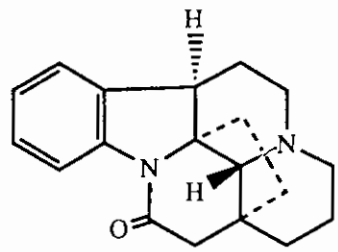
Pentacyclic enaminoketone (442)



A mixture of N_b - (2', 2' - dicarboethoxyvinyl) - 8, 9 - dimethoxy - 3 - ethyl - 5 - methyl - 6 - (2 - aminoethyl) - 3, 4 - dihydropyrrolo [1, 2, 3 - de] - 2H - 1, 4 - bezoxazine (441) (9.27 g, 19.48 mmol), glacial acetic acid (75 ml) and acetic anhydride (114 ml) was heated under reflux for 4 days. The solution was then cooled, diluted to twice its volume with water and then adjusted to pH 12 by addition of 2M sodium hydroxide solution (360 ml).The solution was stirred for 20 minutes and then the product was extracted with chloroform (4 x 200 ml). The combined organic fractions were washed with 2M sodium hydroxide solution (2 x 100 ml), water (100 ml), 2M hydrochloric acid solution (2 x 100 ml), and then with water (2 x 100 ml). The solvent was removed after the solution had been dried (Na_2SO_4) and filtered. Purification by chromatography on Kieselgel G (180 g), using ethyl

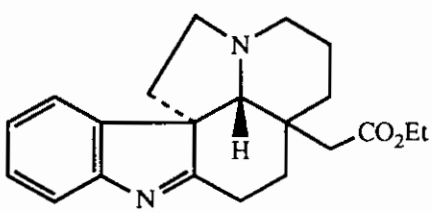
acetate - chloroform (1 : 2) as eluent gave the dimethoxypentacyclic enaminoketone (3.97 g, 52%); ν_{max} ($CHCl_3$) 1645, 1495, 1390, 1260, 1130, and 850 cm^{-1}; λ_{max} (MeOH) 218, 245, 297 and 353 nm; δ_H ($CDCl_3$, 300 MHz) 6.55, 6.5 (1H, 2s, Ar -H), 5.35, 5.3 (1H, 2s), 4.85, 3.8 (6H, m), 3.91, 3.90 (3H, 2s, 2 x -OMe), 3.89, 3.8 (3H, 2s, 2 x -OMe), 3.7, 2.1 (4H, m), 2.18, 2.16 (3H, 2s, 2 x -$COC\underline{H}_3$), 1.8 (2H, m, 2 x -CH_2CH_3), 0.9 (3H, t, J: 7.1 Hz, CH_3); m/z (%) 398 (M^+ , 10), 383 (20.1) [M - CH_3], 355 (5.5), 340 (38.6), 339 (100), 324 (19.6), 310 (15.3), and 43 (90.2).

2.2 APPROACHES TO THE SYNTHESIS OF STREMPELIOPINE

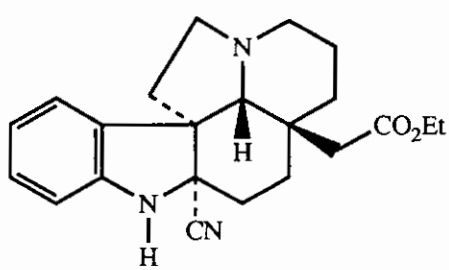


(**447**) Strempeliopine

2.2.1 Synthesis of 1, 2 - dehydro - 19 - carbethoxy - 19 - demethyl - aspidospermidine (270)



(270)



(271)

A stirred mixture of 19 - carbethoxy - 19 - demethylvincadifformine (267) (1.8 g, 4.5 mmol) and sodium cyanide (4.5 g, 91.8 mmol) in dry hexamethylphosphoramide (HMPA, 225 ml) was heated at 75 °C for 4.5 days under nitrogen. After cooling the mixture was diluted with water (400 ml) and then extracted with ether (5 x 250 ml). The combined extracts were washed with water (5 x 400 ml), dried (anhydrous Na_2SO_4), and then concentrated under reduced pressure. The residue was purified by chromatography on silica gel (100 g) with chloroform as the eluent, to give 2 - cyano - 19 - carbethoxy - 19 - demethylaspidospermidine (271) (0.78 g, 47.3%), which was recrystallized from aqueous methanol and obtained as colourless prisms, m. p.113 - 114 °C (lit., [57]114.5

- 115.7 °C) (Found: M^+, m / z 365.19768. $C_{22}H_{27}N_3O_2$ requires M^+, m / z 365.210315) ν_{max} (nujol) 3340 (NH), 2940, 2860, 2795, 2735, 2220 (-CN), 1064, 1590, 1482, and 1174 cm^{-1}; λ_{max} (EtOH) 204, 239, 290 nm; δ_H ($CDCl_3$, 90 MHz) 7 (2H, m, Ar - H), 6.8 (2H, m, Ar - H) 4 (2H, q, J: 7 Hz, $-CO_2C\underline{H}_2CH_3$), 3.4 - 1.3 (18H, m), and 1.2 ppm (3H, t, J: 7Hz , $CO_2CH_2C\underline{H}_3$); m / z (%) 365 (M^+, 4.9), 338 (20.6) [M^+ - HCN], 320 (3.1) - EtO, 277 (13.9), 250 (18.2), 210 (4.5), 182 (100), 154 (16.2), 109 (9.1).

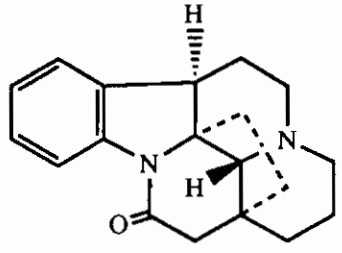
The second fraction eluted with chloroform - methanol (1%) contained 1, 2 dehydro 19 - carbethoxy - 19 - demethylaspidospermidine (270) (0.32 g, 21 %) as an orange oil (lit.,[57] unstable).ν_{max} ($CHCl_3$) 3000, 2850, 2730, 1720, 1570, 1460 and 1185 cm^{-1}; λ_{max} (EtOH) 220, 225, 259 nm; δ_H ($CDCl_3$, 90 Mz) 7 - 7.6 (4H, m, Ar - H), 3.95 (2H, q, J: 7 Hz, $-CO_2C\underline{H}_2CH_3$), 3.29 - 1.2 (17H, m), and 1.1 (3H ,t, J: 7Hz, $CO_2CH_2C\underline{H}_3$); m / z (%) 338 (M^+, 100), 294 (7.9), 268 (40.2), 250 (84.7), and 251 (57).

Conversion of 2 - cyano - 19 - carbethoxy - 19 - demethylaspidospermidine (271) into 1, 2 - dehydroindole (270)

Silver tetrafluoroborate (31 mg, 0.15 mmol) in dry tetrahydrofuran (10 ml) was added, dropwise by syringe, to a solution of 2 - cyano -19 - carbethoxy - 19 - demethylaspidospermidine (270) (48 mg, 0.12 mmol) in dry tetrahydrofuran (20 ml) under a nitrogen atmosphere. The resulting black suspension was stirred at room

temperature for 4 h, then the reaction mixture was diluted with dilute aqueous ammonia solution (7 ml) and extracted with dichloromethane (3 x 30 ml). The combined organic fractions were washed with dilute aqueous ammonia (3 x30 ml) and water (2 x 30 ml), filtered through a short column of Celite, dried (Na_2SO_4), and then concentrated under reduced pressure. The crude product was purified by chromatography on Kieselgel G (15 g) using chloroform as eluent, which gave 1.2 - dehydro -19 -carbethoxy - 19 - demethylaspidospermidine (15 mg, 33.8%) as a colourless oil (Found: C, 74.55, H, 7.55; N, 8.5. $C_{21}H_{26}N_2O_2$ requires C, 74.0; H, 7.70; N, 8.30); ν_{max} ($CHCl_3$) 3000, 2850, 2800, 2730, 1720, 1570, 1460, 1185, 1050, and 920 cm^{-1}; λ_{max} (EtOH) 260, 225, 220 nm; m / z (%) 338 (M^+, 100), 294 (5.3) 268 (35.5), 250 (60.2), 251 (44.4), and 182 (42.9).

2.2.2 Strempeliopine (447)



A suspension of silver tetrafluroborate (0.75 g, 3.82 mmol) in dry tetrahydrofuran (20 ml) was added dropwise to a stirred solution of the cyano compound (271) (0.78 g, 2.1 mmol) and indolenine (270) (0.32 g , 0.94 mmol) in dry tetrahydrofuran (41 ml), kept in the dark and under a nitrogen atmosphere. After 15 minutes the solution became dark and stirring at room temperature was continued for 4 h, then the solvent was removed under reduced pressure. The

resulting product was taken up in glacial acetic acid (126 ml). Zinc dust (12.56 g) and cupric sulphate pentahydrate ($CuSO_4$, 5 H_2O, 61.46 mg) were added to the solution under a nitrogen atmosphere. The reaction mixture was heated to 105 °C and kept at this temperature for 6 h. After 3h reaction time, more zinc (7.29 g) and $CuSO_4$, 5 H_2O (41.79 mg) were added. The mixture was filtered while hot and washed with hot acetic acid. The organic layer was concentrated under reduced pressure and the residue partitioned between ether (550 ml and 250ml) and 7% aqueous ammonia (340 ml). The combined extracts were washed with water (250 ml), brine (200 ml), dried over anhydrous sodium sulphate and concentrated. The residue was purified by chromatography on neutral alumina (grade 1) (20 g), using benzene / benzene - chloroform (100, 10 : 1) as eluent. Four main fractions were obtained:

The first fraction was identified as N_a - *ethyl* - 19 - *carbethoxy* - 19 - *demethylaspidospermidine* (461) (267 mg, 16%) (Found: C, 75.0; H, 8.85; N, 7.85; M^+, m / z 368.24633. $C_{23}H_{32}N_2O_2$ requires C, 75.0; H, 8.7; N, 7.6%; M^+, m / z 368.246365); ν_{max} ($CHCl_3$) (NH, absent), 2930, 2840, 2780, 2715, 1720, 1600, 1480, 1460, 1370, 1270, and1170 cm^{-1}; λ_{max} (MeOH) 226, 258, 304 and λ_{min} 236, 280 nm; δ_H ($CDCl_3$, 300 MHz) 7.5 - 6.4 (4H, m, Ar - H), 4 (2H, q, J: 7.5 Hz, -$CO_2C\underline{H}_2CH_3$), 3.6 - 1.2 (23H, cmplex), and 1.2 (3H, t, J: 7.5 Hz, -$CO_2CH_2C\underline{H}_3$); m / z (%) 368 (20.2), 340 (4.2), 295 (2.6), 294 (3.3), 252 (1), 210 (10.9), 182 (100), 144 (3.5), 130 (5.4).

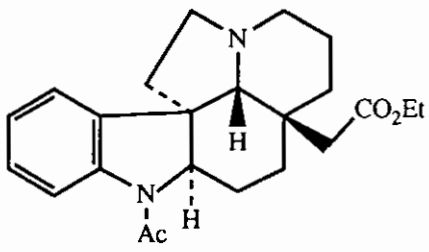
The second fraction was the *strempeliopine* (447), which was obtained as yellow oil (186 mg, 14%) (Found M^+, m/z 294.17311 $C_{19}H_{22}N_2O$ requires M^+, m / z 294.173204); ν_{max} ($CHCl_3$), 2920, 2800, 2740, 1660 (C=O), 1598, 1485, 1460, 1400, 1370, 1040 cm^{-1}; λ_{max} (MeOH) 210, 255 (sh), 280, 290 nm; δ_H ($CDCl_3$, 300 MHz) 8.0 (1H, br d, J: 8 Hz; 12 - H), 7.3 - 7.0 (3H, m , Ar - H), 3.2 (1H, t, J: 7 Hz, 7 - H) , 3.0 (1H, m, 5 - H), 2.8 (1H, m, 3 - H), 2.55 (1H, d, 19 - H), 2.38 (1H, dd, 19 - H'), 2.21 (1H, dt, 3 - H'), 2.08 (1H, dq, 6 - H), 2.04 (1H, ddd, 5 - H'), 2.0 (1H, s, 21 - H), and 1.9 (1H, m, 6 - H'); m / z (%) 295 (M+1, 28.9), 294 (M^+, 76.2), 293 (3.5), 266 (1.4), 265 (1.9), 251(5.2) 249 (1.6), 238 (0.3), 237 (2.3), 160 (3.9), 144 (10.6), 143 (5.7), and 130 (7.3).

The third fraction , a colourless oil, corresponds to N_a - *acetyl* - 19 - *carbethoxy* - 19 - *demethylaspidospermidine* (462) (0.312 g, 18%) (Found: C, 72.15; H, 7.8; N, 7.2%; M^+, m / z 382.2262. $C_{23}H_{30}N_2O_3$ requires C, 72.25; H, 7.85; N, 7.3% M^+, m / z 382.225630); ν_{max} 3020, 3000, 2920, 2860, 2800, 2738, 1720, 1640, 1600, 1475, 1455, 1400, 1170, and 1040 cm^{-1}; λ_{max} (MeOH) 210, 251, 278, 288, λ_{min} 224 nm; δ_H ($CDCl_3$, 300 MHz) 8.15 (1H, m, Ar 12 - H), 7.27 - 7 (3H, m, Ar - H), 4.1 (2H, q, J: 7 Hz , $CO_2C\underline{H}_2CH_3$), 4.0 (1H, dd, J: Hz, 2 - H), 3.3 - 2.9 (2H, m), 2.53 (1H, s, 21 - H), 2.26 (3H, s, -$COCH_3$), 2.4 - 1.2 (14H, m), and 1.2 ppm (3H, t, J: 7 Hz, -$CO_2CH_2C\underline{H}_3$); δ_C 171.4 (C - 18), 168.38 (N -

$\underline{C}OCH_3$), 140.8 (C - 13), 137.34 (C - 8), 127.8 (C - 11), 124.33 (C - 9), 122.23 (C - 10), 118.35 (C - 12), 69.15 (C - 21), 67.56 (C - 2), 60.52 ($-CO_2\underline{C}H_2CH_3$), 53.33 (C - 7), 52.8 (C - 3), 52.23 (C - 5), 42.47 (C - 19), 39.22 (C - 6), 35.84 (C - 20), 34.54 (C - 14), and 14.25 ($-CO_2CH_2\underline{C}H_3$); m/z (%) 382 (M^+, 15.9), 340 (3.5), 337 (5.6), 295 (32), 294 (88.1), 293 (4.5), 251 (4.2), 210 (4.8), 182 (100), 144 (6), 130 (11.5), 43 (8.2).

The fourth fraction contained 19 - *carbethoxy* - 19 - *demethylaspidospermidine* (463) (0.169, 11%), a colourless oil (Found: C, 74.4; H, 8.25; N, 8.1 ; M^+, m/z 340.21571. $C_{21}H_{28}N_2O_2$ requires C, 74.1; H, 8.20; N, 8.20; M^+, m/z 340.21506); ν_{max} ($CHCl_3$) 3380 (br, NH), 3050, 2930, 2850, 2780, 2710, 1720, 1630, 1604, 1480, 1460, 1365, and 1170 cm^{-1}; λ_{max} (MeOH) 210, 244, 295 and λ_{min} 226, 275 nm; δ_H ($CDCl_3$, 300 MHz) 7.1 - 6.9 (2H, m, Ar - H), 6.7 - 6.6 (2H, m, Ar - H), 4.0 (2H, q, J: Hz , $-CO_2\underline{C}H_2CH_3$), 3.5 (1H, dd, J: 11, 10 Hz,), 3.1 (2H, m,), 2.9 - 1.3 (16H, m), and 1.2 (3H, t, J: 7 Hz, $CO_2CH_2\underline{C}H_3$); m / z (%) 340 (M^+, 14.9), 312 (7.2) 295 (21)[M^+ - EtO], 252 (52.5), 210 (5.9), 182 (100), 144 (16.9), 130 (15.6); λ_C 171.7 (C - 18), 149.6 (C - 13), 134.30 (C - 8), 127.5 (C - 11), 122.7 (C - 9), 119.1 (C - 10), 110.58 (C - 12), 69.83 (C - 21), 64.80 (C - 2), 59.8 ($CO_2\underline{C}H_2CH_3$), 53.52 (C - 7), 53.5 (C - 3), 52.5 (C - 5), 42.4 (C - 19), 38 (C - 6), 36.13 (C - 20), 34.9 (C - 15), 28.1 (C - 16), 24.3 (C - 17), 21.55 (C - 14), and 14.2 ppm ($CO_2CH_2CH_3$).

2.2.3 N_a - Acetyl - 19 - carbethoxy - 19 - demethylaspidoaspermidine



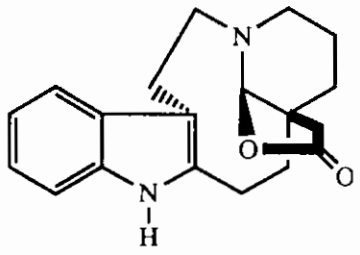
(462)

Cupric sulphate pentahydrate ($CuSO_4$, $5H_2O$, 1.67 mg, 0.006 mmol) and zinc dust (0.35 g, 5.1 mmol) were added to a stirred solution of 2 - cyano - 19 - carbethoxy - 19 - demethylaspidospermidine (31 mg, 0.08 mmol) in acetic acid (4ml), under an atmosphere of nitrogen. The mixture was refluxed for 6 h between 105 - 110 °C. After 4 h further zinc (150 mg) and cupric sulphate pentahydrate (0.5 mg) were added. The mixture was filtered while hot, then washed with hot acetic acid (1.5 ml). The solvent was removed under reduced pressure and the residue partitioned between ether (20 ml and 12.5 ml) and 7% aqueous ammonia (12.5 ml). The combined layers were washed with water (20 ml), brine (20 ml), and dried ($MgSO_4$). The crude product was purified by column chromatography on Kieselgel G (15 g). Elution with chloroform - methanol (3%) afforded N_a - *acetyl* - 19 - *carbethoxy* - 19 - *demethylaspidospermidine* (462) (15 g, 53%) as a clear oil (Found: M^+, m / z 382.18767 $C_{22}H_{26}N_2O_4$ requires m / z 382.189245); ν_{max} ($CHCl_3$) 3000, 2950, 2840, 2800, 2740, 1730, 1650, 1600, 1480, 1400, and 1175 cm^{-1}; λ_{max} (MeOH) 212, 251, 278, 288 nm, λ_{min} 236; δ_H ($CDCl_3$, 400 MHz) 8.1 (1H, m, 12 - H), 7.2 - 7 (3H, m, Ar - H), 4 (2H, q, J: 7 Hz, $-CO_2\underline{CH_2}CH_3$), 3.7 (1H, dd, J: 5 Hz, 11 Hz), 3.25 (2H, m), 2.7 (1H, s, 21 - H), 2.26 (3H, s,

-CO_2CH_3), 2.4 - 1.2 (14H, m), 0.3 (3H, t, J: 7Hz -$CO_2CH_2\underline{C}H_3$); m / z (%) 382 (M^+, 0.9), 340 (1.2), 338 (5.3), 337 (10.6), 295 (1.5), 294 (4), 293 (9.4), 251 (4.1), 210 (16.3), 182 (29.4), 144 (7), 130 (7.2), 43 (18).

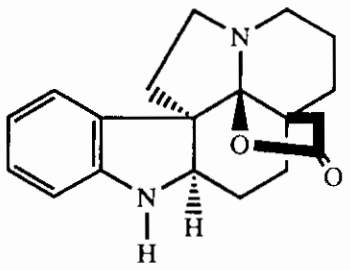
APPROACHES TO THE SYNTHESIS OF CIMICINE DERIVATIVE

Preparation of pentacyclic lactone (466)



A solution of 19 - carbethoxy - 19 - demethylvincadifformine (1.57 g, 3.9 mmol) in 0.5 M ethanolic potassium hydroxide solution (31.4 ml) was refluxed for 6 h, then cooled to 0 °C. After neutralisation by 0.5 M hydrochloric acid solution, the mixture was extracted with cold ether (3 x 100 ml). The combined extracts were washed with water (100 ml), dried ($MgSO_4$), and then kept at 0 °C overnight. Concentration of the solvent under reduced pressure gave a brown oily residue, which was purified by flash chromatography using chloroform as eluent to give the pentacyclic lactone (466) (0.5 g, 42%) as a colurless oil (lit.,[57] unstable oil), ν_{max} ($CHCl_3$) 3480 (NH), 3100, 1740 (lactone), 1610, 1470, 1190, and 900 cm^{-1}; λ_{max} (EtOH) 221, 270 and 290 nm; δ_H ($CDCl_3$, 90 MHz), 8.2 (1H, br s, -NH-), 7.6 - 7.05 (4H, m, Ar - H), 5.1 (1H, s, 21 - H), and 3.4 - 1.1 ppm (16H, m); m / z (%) 310 (M^+, 2.3), 251 (11.4), 240 (3.8), 194 (6.9), 168 (18.9), and 154 (20.2).

2.3.1 Attempted transannular cyclisation to generate the cimicine - derivative (467)



Method A. *via* 1, 2 - dehydro - indolenine lactone (479)

A stirred solution of the pentacyclic lactone (466) (113 mg, 0.36 mmol) in anhydrous benzene (20 ml) was treated in small portions with m - chloroperbenzoic acid (0.139 mg, 0.8 mmol, 2.2 equiv.) at room temperture. Stirring was continued for 24 h in a nitrogen atmosphere. The benzene was then removed under reduced pressure and the residue was taken up in deuteriochloroform (2.5 ml). The solution was cooled to 0 °C, after which trifluoroacetic anhydride (0.152 g, 0.72 mmol, 2 equiv.) was added dropwise *via* syringe. The resulting reaction mixture was allowed to stand at 0 °C for 90 minutes, then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel G (10 g) with chloroform as the eluent, to give a white solid (120 mg), m. p. 138 °C, which was not fully characterized; ν_{max} (Nujol) 2990 - 2800, 1690, 1565, 1450, 1370, 1300, 740, and 710 cm^{-1}; λ_{max} (EtOH) 220, 230, 275, and 285 nm. The resulting unstable indolenine (479) (120 mg, 0.38 mmol) was immediately taken up in methanol (5 ml) and sodium cyanoborohydride (27 mg, 0.43 mmol) was added under a nitrogen atmosphere. After being stirred overnight at ambient temperture, the

reaction mixture was diluted with dichloromethane (50 ml), washed with saturated aqueous sodium bicarbonate solution (20 ml), saturated aqueous sodium chloride solution (20 ml), and dried over magnesium sulphate. The solvent was removed under reduced pressure to provide a very polar compound which was not characterised.

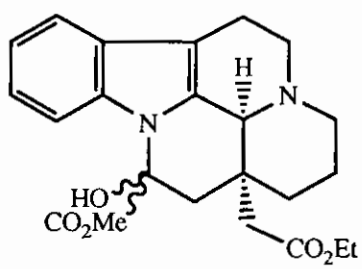
Method B. A solution of the pentacyclic lactone (466) (0.3 g, 1 mmol) and mercuric acetate (0.56 g, 2.07 mmol) in glacial acetic acid (40 ml) was stirred at room temperature under a nitrogen atmosphere, for 24 h. The precipitated mercurous acetate was filtered off and the filtrate was diluted with glacial acetic acid (10 ml). The resulting solution was refluxed , with stirring under nitrogen, for 6 h. After cooling, the reaction mixture was filtered and the solvent removed under reduced presssure leaving a brown, oily residue, which was not purified, but immediately taken up in dry methanol (25 ml) and reduced overnight with sodium borohydride (70 mg, 1.11 mmol) under a nitrogen atmosphere with stirring. This provided after filtration a brown oil (0.5 g), which showed ν_{max} ($CHCl_3$) 3450 - 2900 (br), 2680, 2600 1750, 1600, 1400, 1320, 1040 and 940 cm^{-1}; λ_{max} (MeOH) 206, 222, and 277 nm; m / z (%) 324 (M^+, 8.4), 310 (0.4), 282 (0.6), 264 (6.2), 237 (9.2), 209 (22.8), 166 (3.5), 152 (0.8), 144 (1.5)

Method C . A solution of the pentacyclic lactone (466) (310 mg, 1 mmol) and mercuric acetate (0.66 g, 2.07 mmol) in glacial acetic acid (40 ml) was stirred under a nitrogen atmosphere at room temperature for 24 h. The precipitated mercurous acetate was filtered off and the filtrate was diluted with glacial acetic acid (10 ml). The resulting solution was refluxed under a nitrogen atmosphere for 6 h. After cooling, the reaction mixture was filtered and sodium cyanoborohydride

(70 mg, 1 mmol) was added to the filtrate at 10 °C. Stirring was continued overnight, then the acetic acid was removed under reduced pressure. The residue was diluted with water (10 ml) and ether (80 ml). The organic extract was washed with water (30 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The brown residue was purified by chromatography on neutral alumina (15 g) with acetone - petroleum ether (30 - 40 °C) (2 : 8) as the eluent to afford the *rhazinilam derivative* (487) (138 mg, 42%) as an orange oil (Found M^+, m / z 324.1470 . $C_{19}H_{20}N_2O_3$ requires M^+, m / z, 324.147383); ν_{max} ($CHCl_3$) 3440 (br), 2900, 2860, 1780, 1735, 1600, 1450, 1350, 1100 and 900 cm^{-1}; λ_{max} (EtOH) 228, 274 nm ; δ_H ($CDCl_3$, 90 MHz) 7.9 (1H, s), 7.45 - 7.05 (4H, m, Ar - H), 6.25 and 5.6 (2H, d, 5 - H and 6 - H), and 3.85 - 1.2 (12H, complex); δ_C 171.16, 136.23, 121.8, 119.25, 118.5, 111.16, 64.27, 63.5, 63.29, 53.36, 36.45, 31.9, 29.67, 29.34, 27.38, 22.67, 20.98, 16.23, 14.11; m / z (%) 324 (M^+, 17.6), 323 (1.8), 296 (3)[M^+ - CO], 280 (0.8)[M^+- COOH], 265 (3.8) [M^+ - CH_2CO_2H].

2.4 APPROACHES TO THE SYNTHESIS OF VINCAMINE DERIVATIVES

2.4.1 Attempted synthesis of 19 - carbethoxy - 19 - demethylvincamine (503a) and 16 - epivincamine analogue (503b)

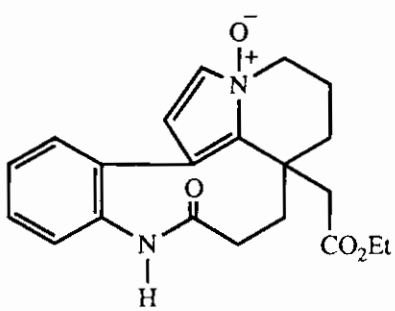


MethodA. A stirred solution of 19 - carbethoxy -19 - demethylvincadifformine (267) (310 mg, 0.783 mmol) in dry benzene (6 ml) was treated in small portions with m - chloroperbenzoic acid (0.3 g, 1.72 mmol, 2.2 equiv.) at ambient temperature. Stirring was continued for 16 h. The solvent was removed under reduced pressure and the residue taken up in dilute acetic acid (20 ml). After extraction with ether , the aqueous phase was basified, saturated with sodium chloride, and extracted with ethyl acetate (4 x 50 ml). The organic extract was dried over magnesium sulphate and concentrated under reduced pressure to give the 19 - *carbethoxy* - 19 - *demethyl* - 1, 2 - *dehydro* - 16 - *hydroxy* - N_b - *oxyvincadifformine* (505); ν_{max} ($CHCl_3$) 1738, 1570, 1390, 1300, 1200 (N^+- O^-), 1020, and 640 cm^{-1}; λ_{max} (MeOH) 223, 270 nm.

The 16 - hydroxy - N_b - oxy compound (505) was taken up in dry acetone (100ml) and hydrogenated at room temperature and pressure using 5% palladium on

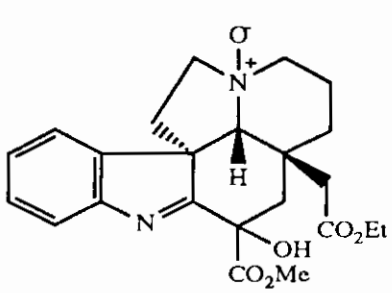
barium sulphate (30 mg) for 3 h . The catalyst was removed by filtration through a pad of Celite and the solvent was then removed under reduced pressure. The residue was dissolved in acetic acid (20 ml) and water (30 ml) and the mixture was stirred at room temperture for 12 h. The solution was basified by the addition of 2M sodium hydroxide solution and then extracted with dichloromethane to give a brown oily product. Analysis of the reaction mixture by t.l.c. showed that the crude product contained only very polar material. But the mass spectroscopy consisted of a mixture of at least of four products.

Compound one (507): m / z (%) 442 (M^+, 2%), 440 (3.1), 426 (8.9)[M - 16], 425 (3.6) [M - 17], 383 (5.6) [M - CO_2Me], 369 (10)[M - CO_2Et], 355 (1.3) [M - CH_2CO_2Et] corresponds to the rhazinilam derivative (507).



(507)

Compound two (505): m / z (%) 428 (M^+, 17), 412 (10.4) [M - 16], 410 (22) [M - H_2O], 411 (8.8) [M - 17], 341 (8.4) [M - , -CH_2CO_2Et], 369 (10) [M - CO2Me], 355 (1.3) [M - CO_2Et]. Corresponds to the indolenine N_b - oxide



(505)

Compound three : m /z (%) 396 (M^+, 7.8), 367 (3.7), 351 (2.3), 309 (6.8), 308 (5.7), 182 (56). Corresponds to starting material (267).

Compound four : corresponds to vincamine derivative (503a,b) m / z (%) 412 (M^+, 10.4), 394 (6.3), 353 (7.1), 342 (2.5), 337 (7.7), 325 (13.8),324 (13.1), 283 (4), 282 (4.9), 279 (6), 278 (2.3), 265 (11.3), 264 (8.1), 251 (11), 249 (6.9), 248 (14.9), and 237 (22.1)

I.R. recorded for crude product ν_{max} ($CHCl_3$) 3550 - 3330, 2960 -2880, 2430, 1750 - 1650, 1600;

U.V. λ_{max} (EtOH) 204, 232, 290, 322 nm.

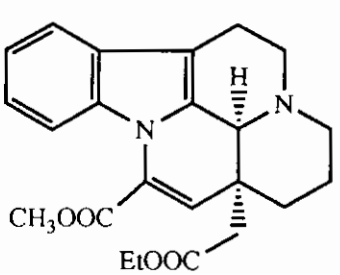
Method B. To a stirred solution of 19 - carbethoxy - 19 - demethylvincadifformine (267) (1.29 g, 3.7 mmol) in dry benzene (190 ml) m - chloroperbenzoic acid (1.22 g, 7.4 mmol, 2 equiv.) was added in small portions over 20 minutes at room temperature. Stirring was continued for 24 h under nitrogen. The solution was then concentrated under reduced pressure ($t° < 40$ °C), after which the residue was dissolved in a mixture of acetic acid - water (9 : 1) and triphenylphosphine (1.27 g, 4.8 mmol) was added in small portions. After being stirred for 3 days in the dark at room temperature, the aqueous phase was washed with benzene (4 x 250 ml), basified with sodium carbonate solution, extracted with dichloromethane (4 x 200 ml), washed with water, dried over magnesium sulphate, and then concentrated under reduced pressure. The residue was chromatographed on Kieselgel G (20 g) using chloroform - methanol (4%) as eluent, which gave an oily product which was not fully characterized ν_{max} ($CHCl_3$) 3500 (OH), 2920, 1780 - 1720, 1610, 1580, 1450, 1380, 1020, 920, 850, and 650 cm^{-1}; λ_{max} (MeOH) 206,

224, 277, 290, 302 nm; δ_H ($CDCl_3$) 7.7 - 7.2 (4H, m), 4.15 (2H, q, J: 7.2 Hz, -$CO_2C\underline{H}_2CH_3$), 3.8 (3H, s, -CO_2Me), 1.2 (3H, t, J: 7.2 Hz, -$CO_2CH_2C\underline{H}_3$).

Attempted " one pot " method of converting 19 - carbethoxy - 19 - demethylvincadifformine (267) into vincamine (503a) and epivincamine (503b) derivatives

A stream of ozone was bubbled through a 5% w / v solution of 19 - carbethoxy - 19 - demethylvincadifformine (0.2 g, 0.5 mmol) in 0.87 N sulphuric acid - methanol (3 : 1) (4 ml) at 60 °C during 10 min. This resulted in a very polar material not easy to extract even at different pH with different solvents. The analysis showed that no significant product was isolated.

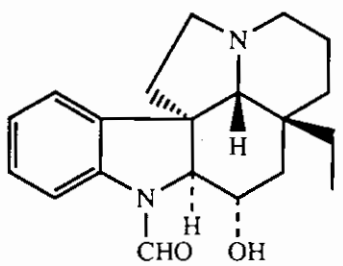
2.4.2 Synthesis of 19 - Carbethoxy - 19 - demethylapovincamine (504)



A solution of 19 - carbethoxy - 19 - demethylvincadifformine (267) (0.2 g, 0.5) and N - chlorosuccinimide (66 g, 0.5 mmol) in dry trifluoroacetic acid (20 ml) was stirred at room temperature for 4 h in a nitrogen atmosphere, then heated at reflux for 3 h. The solution was concentrated under reduced pressure, The residue was taken up in ethyl acetate, washed with 2M sodium hydroxide, and dried (anhydrous $MgSO_4$). The crude product was chromatographed on kieselgel G (35 g), using

ethyl acetate as eluent, which gave 19 - *carbethoxy* - 19 - *demethylapovincamine* (105 mg, 55.3%) as a colourless oil (Found: C, 69.75; H, 6.8; N, 6.85. M^+, m/z 394.1905. $C_{23}H_{26}N_2O_4$ requires M^+, m/z 394.1893 C, 70.05; H, 6.60; N,7.1%); ν_{max} ($CHCl_3$) 1720 (-CO_2Et), 1638 (-CO_2Me), 1618, 1410, 1280, and 735 cm^{-1} [3320 (NH) was absent]; λ_{max} (EtOH) 202, 226, 272, 313 and λ_{min} 215, 244, 294; δ_H ($CDCl_3$, 400 MHz) 7.47, 7.1 (4H, m, Ar - H), 6.47 (1H, s, =CH), 4.28 (1H, br s, 21 - H), 4.18 (2H, q, J: 7 Hz, -$CO_2C\underline{H}_2CH_3$), 3.94 (3H, s, -CO_2Me), 2.17 (2H, s, -$C\underline{H}_2CO_2$Et), 3.3 - 1.2 (10H, m), and 1.28 ppm (3H, t, J: 7Hz, $CO_2CH_2C\underline{H}_3$); δ_C 171.36 (-$\underline{C}O_2$Et), 163.64 (-$\underline{C}O_2$Me),134.128 (C -13), 130.33 (C - 2), 128.9 (C - 8), 127.61 (C - 16), 126.86 (C - 17), 122.07 (C - 11), 120.32 (C - 10), 118.26 (C - 9), 112.52 (C - 12), 108.97 (C - 7), 60.44 ($C\underline{H}_2CH_3$), 56.32 (C - 21) 52.47 (-OMe), 51.40 (C - 5), 44.70 (C - 3), 39.52 (C - 20), 36.8 (C - 15), 29.31 (C - 19), 20.42 (C - 14), 16.35 (C - 6), and 14.26 ($CO_2CH_2\underline{C}H_3$); m / z (%) 394 (M^+, 3.8), 324 (1.6), 321 (1.2), 307 (24.7), 306 (47.3), and 248 (0.7).

2.5 APPROACHES TO THE SYNTHESIS OF STRICTANINE (507)



Preparation of aldimine (155)

Cyclohexylamine (49.59 g , 0.5 mmol) was placed in 250 ml three - necked, round bottomed flask fitted with thermometer, mechanical stirrer, and an addition funnel, then cooled to -5 °C in an ice salt bath. Butyraldehyde (36.05 g, 0.5 mol) was carefully added dropwise at such a rate that the temperature remained below 5 °C. Stirring was continued for 30 minutes. The solution was then allowed to warm to room temperature. The reaction mixture was poured into a separatory funnel, and the water produced during the reaction was removed. The solution was allowed to stand for 24 h in the presence of potassium carbonate (16 g) and potassium hydroxide pellets (16 g). This allowed the reaction to go to completion. Filtration followed by distillation gave the desired aldimine (65 g, 68%) as a colourless liquid, b. p. 80 - 84 °C / 20 mm Hg; δ_H ($CDCl_3$, 90 Mz) 7.7 (1H, t, J: 5.14 Hz, :C<u>H</u>-), 3 - 1.2 (14H, m), and 1ppm (3H, t, J: 7.4 Hz, -CH_3).

Preparation of lithium diethylamide

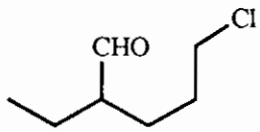
A solution of diethylamine (7.31 g, 0.1 mol), dry hexamethylphosphoramide (17.92 g, 0.1 mol), dry benzene (20 ml), and lithium (0.69 g, 0.1 atomg) was

stirred vigorously between 20 and 25 °C for 3 h.

Lithium salt of the imine

Lithium diethylamide solution in dry tetrahydrofuran (15 ml) was cooled to - 60 °C and imine (155) (15.3 g, 0.1 mol) was added *via* a syringe at such a rate that the temperature remained between - 60 and - 65 °C during the addition. After 30 min stirring the reaction mixture was allowed to warm to - 10 °C for 2 h.

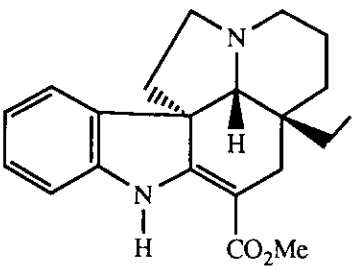
Synthesis of chloroaldehyde (156)



To a stirred solution of 1 - bromo - 3 - chloropropane (15.74 g, 0.1 mol) in anhydrous tetrahydrofuran (200 ml), cooled to - 70 °C, lithium salt of the aldimine in solution was added dropwise by syringe. After the addition was complete, the resulting reaction mixture was allowed to warm to - 10 °C and kept there for 2 h. Stirring was continued overnight at room temperature. The reaction mixture was treated with hydrochloric acid (3 N) at - 20 °C, then stirred at room temperature for 5h. The mixture was extracted with ether (3 x 150 ml). The combined ethereal layers were washed with sodium carbonate (40 ml), dried (Na_2SO_4), and then concentrated under reduced pressure. The residue was purified by chromatography on Kieselgel G (180 g) using ethyl acetate as eluent, which gave 5 - chloro - 2 - ethyl - pentanal (156) (11.49 g, 89 - 77.37%) as a colourless oil, b. p. 100 °C/ 0.5mm Hg; ν_{max} ($CHCl_3$) 1720 (-CHO), 650 cm^{-1}; δ_H ($CDCl_3$, 90 MHz) 9.5

1H,d, J: 2.5Hz, -CHO), 3.5 (2H, m, $-CH_2Cl$), 2.4 (2H, m), 1.8 (4H, m), and 0.9 (3H, t, J: 7.2 Hz, $-CH_3$).

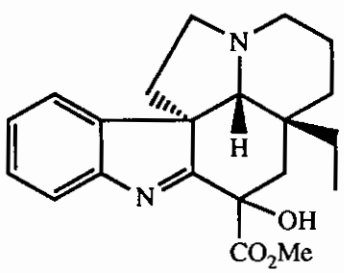
Preparation of (±) - vincadifformine (5)



A mixture of 1 - carbomethoxy - 1 - methyl - 1, 2, 3, 4 - tetrahydro - β - carboline (152b) (5 g, 20.4 mmol), p - toluenesulphonic acid and 5 - chloro - 2 - ethyl - pentanal (156) (3.66 ml, 24.9 mmol) in toluene (420 ml) was refluxed for 100 h under an atmosphere of nitrogen in a Dean - Stark apparatus. To the hot solution, diazabicycloundecene (DBU) (6.33 ml, 49.9 mmol) was added and heating continued for 18 h. The reaction mixture was allowed to cool to room temperature, then concentrated under reduced pressure. The brown residue was purified by chromatography on Kieselgel G (180 g), using dichloromethane - ether (7 : 1) as eluent; this gave (±) vincadifformine (5) (5.83 g, 81.2%), which was recrystallised from acetonitrile and obtained as colourless prisms; m. p. 125 °C (lit., [33] 124 - 125 °C) (Found: C, 74.65; H, 7.75; N, 8.3. calc. for $C_{21}H_{26}N_2O_2$: C, 74.55; H, 7.7; N, 8.3 %); ν_{max} ($CHCl_3$) 3380 (NH), 1720 (CO_2Me), 1670, 1610, 1360, 1050, 750, and 610 cm^{-1}, λ_{max} (MeOH) 222, 296, 324 nm, and λ_{min}

256, 304 nm; δ_H ($CDCl_3$, 300 MHz) 8.9 (1H, br s, -NH-), 6.65 - 7.2 (4H, m, Ar - H), 3.75 (3H, s, $-CO_2C\underline{H}_3$), 3.2 - 0.7 (15H, m), and 0.6 ppm (3H, t, J: 7 Hz, $-C\underline{H}_3$); δ_C (169.05 ($-\underline{C}O_2Me$), 167.61 (C - 2), 143.17 (C - 13), 137.77 (C - 8), 127.36 (C - 11), 120.29 (C - 9), 120.43 (C - 10), 109.23 (C - 12), 92.52 (C - 16), 72.5 (c - 21), 55.42 (C - 7), 51.69 (C - 3), 50.9 ($-O\underline{C}H_3$), 50.56 (C - 5), 45.1(C - 6), 38.08 (C - 20), 32.8 (C - 5), 25.57 (C - 17), 29.31 (C - 19), and 7.09 ppm (C - 18); m / z (%) 338 (M^+, 5.6), 144 (0.4), 143 (0.5), 130 (0.6), 125 (9.4), 124 (100), and 96 (1.9).

16 - Hydroxy - 1, 2 - dehydrovincadifformine (294)



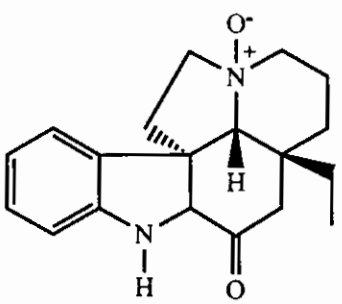
(±) - Vincadifformine (5) (0.5 g, 1.47 mmol) in a solution of Rose Bengal (1.5×10^{-4} M) in methanol - water (6 : 1, 37.5 ml) in the presence of sodium thiosulphate (0.35 g, 2.2 mmol) and sodium hydroxide solution (0.5 ml) was irradiated for 1 h between 20 - 30 °C using two 150 w tungsten lamps in the presence of oxygen. Sodium tetrathionate was filered off and the solvent removed under reduced pressure (t < 40 °C), then the crude product was filtered on a short column of neutral alumina to remove the sensitiser using chloroform - methanol (19 : 1). After removal of the solvent, the crude products were chromatographed on silica gel (15 g), eluting with chloroform - ethyl acetate (2 : 1) to give two main fractions:

The mixture was washed with 10% sodium sulphite solution (30 ml), 5% sodium bicarbonate solution, and water, then dried ($MgSO_4$) and concentrated under reduced pressure ($t°_{bath} < 40$ °C). Chromatography on silicagel G (30 g) using a mixture of benzene - methanol - ether, and ammonia (5 : 3.9 : 1 : 0.1) as eluent afforded *16 - hydroxy - 1, 2 - dehydrovincadifformine N_b - oxide* (496b) (170 mg, 77.9%), which was recrystallised from dichloromethane - ether and obtained as colourless prisms, m . p. 176 - 178 °C (dec.) (Found: C, 67.9; H, 7.1; N, 7.55. Calc. for $C_{21}H_{26}N_2O_4$: C,68.1; H, 7.0; N, 7.6%); ν_{max} ($CHCl_3$) 3450 (OH), 3100 - 2900, 2809, 1738 (unconjugated ester carbonyl), 1570, 1450, 1280 - 1230, and 663 cm^{-1}; λ_{max} (MeOH) 223, 270 nm; δ_H ($CDCl_3$, 90 MHz), 8.0 (1H. m, -OH), 7.6 (1H, dd, 9 - H), 7.5 - 7.1 (3H, m, Ar - H), 3.95 (3H, s, $-CO_2Me$), 2.64 (1H, s, 21 - H), 3.4 - 1.2 (14H, complex), and 0.5 ppm (3H, t, J: 7 Hz, 18 - H), δ_C 180 (C - 2), 171.87 (C - 22), 152 (C - 13), 146 (C - 8), 127.98 (C - 11), 127.79 (C - 10), 124.6 (C - 9), 120.05 (C - 12), 83 (C - 21), 76.6 (C - 16), 67 (C - 3), 65 (C - 5), 58 (C - 7), 53.11 ($CO_2\underline{C}H_3$), 40.62 (C - 17) 36.43 (C - 20), 35.11 (C - 19), 31.46 (C - 15), 18.8 (C - 14), 7.4 (C - 18); m/z (%) 370 (M^+, 10.2), 253 (15.4), 252 (3.3), 267 (5.1), 144 (9.1), 130 (18.2), and 124 (30.9).

The less polar fraction contained vincadifformine - N_b- oxide (36 mg, 18%), m. p. 160 °C (dec.), ν_{max} ($CHCl_3$) 1690 and 1615 cm^{-1}; λ_{max} (MeOH) 227, 297, and 330 nm; δ_H ($CDCl_3$, 90 MHz) 7.65 - 7.2 (4H, m, Ar - H), 3.9 (3H, s,

-CO_2Me), 3.8 (1H, s, 21 - H), 3.45 - 1.2 (15H, m), and 0.5 (3H, t, -CH_3); m/z 354 (M^+, 86), 353 (39.7) [M^+- 17], 295 (34) [M^+- CO_2Me], 294 (6.4), 252 (100), 265 (4.5), 144 (6.3), 143 (12.9), and 124 (21.3).

16 - Oxoaspidospermidine - N_b - oxide (511)

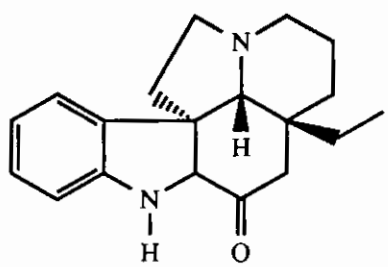


This was prepared according to the procedure of Le Men *et al*[155]

m - Chloroperbenzoic acid (1.128 g, 6.5 mmol) was added in small portions to a stirred solution of vincadifformine (1 g, 2.9 mmol) in dry benzene (150 ml) under a nitrogen atmosphere. The reaction mixture was stirred continuously for 24 h at room temperature in the dark, after which the solvent was removed under reduced pressure (t° < 40 °C). The residue was taken up in 1.25 M sodium hydroxide solution (100 ml) and the resulting solution was stirred at ambient temperature under a nitrogen atmosphere in the dark for 2.5 h. Then the solution was acidified with 1.25 M hydrochloric acid solution to pH 1, and stirred vigorously at 100 °C for 20 minutes under a nitrogen atmosphere. After cooling the mixture was extracted with ether (5 x 60 ml). The aqueous phase was then basified with sodium hydroxide solution, saturated with sodium chloride and extracted with dichloromethane (5 x 60 ml). The combined organic fractions were dried (Na_2SO_4) and evaporated under reduced pressure to give 16 - oxoaspidospermidine - N_b - oxide (511) (0.915 g, 98%) as

yellow, amorphous solid ν_{max} ($CHCl_3$) 3040 - 2880 cm^{-1}, 1700 (-C0), 1610, 1470, 1275, 1110, 920, 715, and 670 cm^{-1}; λ_{max} (MeOH) 218, 243 (sh), and 300 nm; δ_H ($CDCl_3$, 90 MHz) 8.25 (1H, br, NH), 7.5 - 6.5 (4H, m, Ar - H), 5 - 1.1 (16H, complex), and 0.7 ppm (3H, t, J: 6.5 Hz, $-CH_3$), m / z (%) 312 (M^+, 0.9), 296 (6.9)[M^+- 16], 295 (19.2), 294 (100), 293 (59.6), 268 (4), 144 (16.8), 138 (32.3), 130 (34.4), and 124 (20.1).

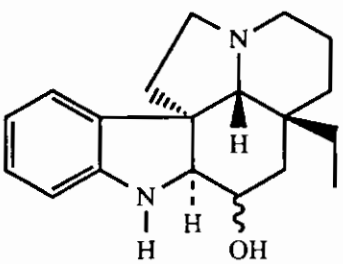
16 - Oxoaspidospermidine (512)



A suspension of 16 - oxoaspidospermidine - N_b - oxide (0.9 g, 2.8 mmol) and platinium (IV) oxide (PtO_2 , 122 mg, 0.53 mmol) in methanol (20 ml) was hydrogenated at room temperature and atmospheric pressure for 3 h. The catalyst was removed by filtration. Concentration under reduced pressure then gave 16 - oxoaspidospermidine (512) (0.75 g, 88%), which was recrystallised from methanol and obtained as clourless prisms m. p. 108 - 112 °C (Found: C, 68.3; H,7.65; N, 7.5. $C_{19}H_{24}N_2O$ requires C, 68.5; H, 7.5; N, 8%); ν_{max} (nujol) 3345, 1720 (CO), 1610, 1475, 1385, and 730 cm^{-1}; λ_{max} (MeOH) 210, 240, 292, λ_{min} 262 nm; δ_H (MeOD, 300 MHz) 7.22 - 6.8 (4H, m, Ar - H), 4.9 (1H, s),

4 - 0.9 (10H, m), and 0.7 ppm (3H, t, J: 7Hz, -CH_3); m / z (%) 296 (M^+, 8.8), 268 (10)[M^+- CO], 144 (18.6), 138 (100), 130 (6.4), and 124 (18.1).

16 - Hydroxyaspidospermidine



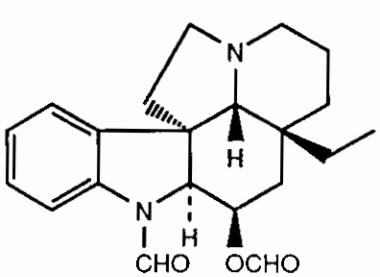
To a solution of 16 - oxoaspidospermidine (512) (1.71 g, 5.7 mmol) in ethanol (400 ml) sodium borohydride (5.97 g, 0.15 mol) was added in portions with stirring at ambient temperature. After the addition was complete, the resulting mixture was refluxed for 4 h, then allowed to cool before being diluted with water. The mixture was concentrated under reduced pressure and the residue was taken up in water (100 ml), then extracted with dichloromethane (3 x 200 ml). The combined organic phases were dried ($MgSO_4$) and then concentrated under reduced pressure. The residue was purified by chromatography on Kieselgel G (40 g) using chloroform - methanol (9 : 1) as eluent, which gave two main fractions:

- The less polar fraction contained 16β - *hydroxyaspidospermidine* (513a) (1.24 g, 72.5%), which was obtained as a colourless plates, m. p. 55 °C (Found: C,76.75; H, 9.05; N, 9.0. $C_{19}H_{26}N_2O$ requires C, 76.5; H, 8.70; N, 9.0); ν_{max} ($CHCl_3$) 3420 (-OH), 3000 - 2705, 1600, 1480, 1460, 1312, 1250, 1030, 900, and 630 cm^{-1}; λ_{max} (MeOH) 212, 244, 300 ; δ_H ($CDCl_3$, 400 MHz) 7.05 (2H,

m, Ar - H), 6.7 (1H, t, J: 7 Hz), 6.55 (1H, d, J: 7, Ar - H), 4.85 (1H, m, 16 - H), 3.77 (1H, d, J: 4 Hz, 2 - H), 3 - 0.8 (17H, m), and 0.55 ppm (3H, t, 7.5 Hz -CH_3); δ_C 150.37 (C - 13), 136.01 (C - 8), 127.61 (C - 11), 123 (C - 9), 118.4 (C - 10), 109.26 (C - 12), 74.49 (C - 21), 71.01 (C - 2), 67.65 (C - 16), 54.1 (C - 7), 53.15 (C - 3), 52.49 (C - 5), 43.0 (C - 6), 36.11 (C - 20), 35.97 (C - 17), 34.7 (C - 15), 34.23 (C - 19), 22.10 (C - 14), and 7.75 ppm (CH_3); m / z (%) 298 (M^+, 5.7), 254 (8.7), 144 (5.3), 138 (1.5), 130 (5.5) and 124 (100)

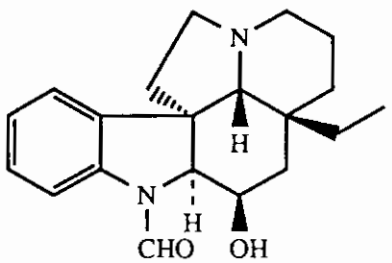
- The more polar fraction corresponds to the second epimer 16α - *hydroxyaspidospermidine* (513b) (212 mg, 12.3%), which was obtained as an amorphous solid; ν_{max} ($CHCl_3$) 3400 cm^{-1} (OH), 3000, 2940, 2860, 2700, 1605, 1480, 1460, and 670 cm^{-1}; λ_{max} 212, 242 and 296 nm; δ_H ($CDCl_3$, 300 MHz) 7.25 - 6.6 (4H, m, Ar - H), 3.6 (1H, m, 16 - H), 4 (1H, s, -OH), 3.5 (1H, m, H - 2), 3.8 - 0.8 (16H, m), 0.6 (3H, t, J: 7 Hz , -CH_3); m / z (%) 298 (M^+, 5.8), 249 (6.2), 168 (18.3), 144 (13.5), 138 (3.1), 130 (16.1), and 124 (100).

N_a - Formyl - 16β - formyloxyaspidospermidine (514a)



To a stirred solution of 16β - hydroxyaspidospermidine (513a) (121 mg, 0.4 mmol) in formic acid (5.47 ml, 6.6 mg, 0.14 mol) at 0 °C, acetic anhydride (0.54 ml, 59 mmol) was added dropwise over 10 minutes. The resulting reaction mixture was stirred at room temperture for 18 h and then concentrated under reduced pressure. The residue was purified by chromatography on Kieselgel G (20 g) with dichloromethane / methanol (2%) as the eluent, to give the N_a - *formyl* - 16β - *formyloxyaspidospermidine* (514a) (130 mg, 90.1%) as colourless plates m. p. 70 - 72 °C (Found: C,71.4; H, 7.6; N, 8; M^+, m/z 354.19138. $C_{21}H_{26}N_2O_3$ requires C, 71.18; H, 7.34; N, 7.9; M^+, m/z 354.1913); ν_{max} ($CHCl_3$) 3019, 2943, 2900, 2800, 2740, 1720, 1670, 1600, 1480, 1460, 1400, 1361, and 1180 cm^{-1}; λ_{max} (MeOH) 210, 250, 282, 290 , λ_{min} 226, 270 nm; δ_H ($CDCl_3$, 300 MHz) 8.9 (1H, s, -CHO), 8.6 (1H, s, -CHO), 7.9 (dd, J: 9.3 and 18Hz, 12 - H), 7.15 - 7 (3H, m, Ar - H), 5.75 (1H, m, 16 - H), 4.6 (1H, d, J = 5Hz 2 - H), 3 (2H, m), 2.4 - 0.8 (13H, m), and 0.7 (3H, t, J: 6 Hz, - CH_3); δ_C 160.187, 160.35 (-NCHO), 160.05, 157.89 (-OCHO), 140.97 (C - 13), 138.46 (C - 8), 127.81, 127.62 (C - 16), 124.79, 124.64 (C - 11), 123.17, 122.28 (C - 9), 116.153 (C - 10), 109.05 (C - 12), 71.05, 70.29 (C - 21), 70.14, 68.8 (C - 2), 66.4, 63.7 (C - 7), 53.32, 52.96 (C - 3), 51.89, 51.76 (C - 5), 41.11, 40.67 (C - 6), 35.04, 34.94 (C - 20) , 34.84, 34.64 (C - 17), 32.76, 32.15 (C - 15), 27.9, 26.61 (C - 19), 21.57, 21.46 (C - 14), and 7.12, 6.95 (-CH_3); m / z (%) 354 (M^+, 1.9), 326 (0.9), 325 (0.9), 282 (3.9), 144 (4.5), 130 (5.2), 124 (100), and 29 (15.9) [CHO].

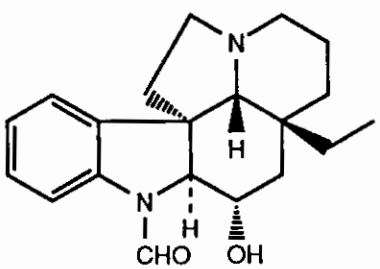
N_a - Formyl - 16β - hydroxyaspidospermidine (515)



To a stirred solution of N_a - formyl - 16β - formyloxyaspidospermidine (76 mg, 0.2 mmol) in methanol (1 ml) sodium carbonate solution (1 ml) was added. The resulting reaction mixture was stirred at room temperature for 15 minutes. Concentration under reduced pressure gave a residue which was taken up in ethyl acetate, washed with water (15 ml), and dried over magnesium sulphate. Removal of the solvent under reduced pressure gave a yellow solid, which was purified by chromatography on Kieselgel G (25 g) using dichloromethane / ether (1 : 1) as eluent, which gave N_a - *formyl* - 16β - *hydroxyaspidospermidine* (68.5 mg, 98%) as colourless plates m. p. 66 - 68 °C (Found: C, 73.40; H, 8.15; N, 8.25. $C_{20}H_{26}N_2O_2$ requires C, 73.6; H, 8.0; N, 8.5%); ν_{max} ($CHCl_3$) 3360 (br, OH), 3010, 2945, 2860, 2798, 2738, 1680, 1600, 1490, 1460, 1365, 1335, 1180, 1080, 908, and 675 cm^{-1}; λ_{max} (MeOH) 210, 253, 260 (sh), 280, 290 nm, and λ_{min} 266, 270 nm; δ_H ($CDCl_3$, 300 MHz) 9, 8.72 (1H, 2s, -NC<u>H</u>O), 8.03 (1H, d, J: 9Hz, 12 - H), 7.2 - 7 (3H, m, Ar - H), 5 (1H, br s, 16 - H), 4.15 (1H, d, J: 4.6 Hz, 2 - H), 3.2 - 0.6 (16H, m), and 0.55 ppm (3H, t, J: 7.4 Hz, $-CH_3$); δ_C 159.82 (N<u>C</u>HO), 142.23 (C - 13), 138 (C - 8), 128.02 (C - 16), 125.11 (C - 11), 124.15 (C - 9), 116 (C - 10), 109.66 (C - 12), 74.09 (C - 21), 71.84 (C - 2),

65.23 (C - 7), 52.9 (C - 3), 52.47 (C - 5), 41.26 (C - 6), 35.79 (C - 20), 35.46 (C - 17), 34.35 (C - 19), 33.62 (C - 15), 21.86 (C - 14), 7.58 (C - 18); m / z (%) 326 (M^+, 5.7), 325 (0.9), 309 (0.2), 298 (0.6), 297 (0.4) 282 (5.4), 149 (6.1),144 (2.8), 143 (1.5), 138 (2.5), 130 (1.9), 124 (100), 122 (1), 110 (1.7), 109 (2.6), 96 (2.3).

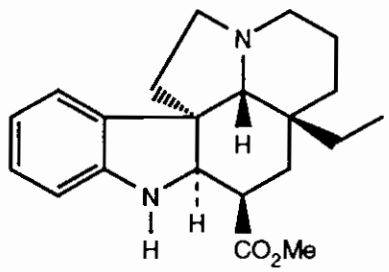
N_a - Formyl - 16α - hydroxyaspidospermidine (507)



To a solution of 16α - hydroxyaspidospermidine (90 mg, 0.3 mmol) in formic acid (4 ml, 4.87, 0.1 mol) at 0 °C, acetic anhydride (0.4 ml, 17.6 mmol) was added dropwise. The mixture was stirred at room temperature for 18 h, then concentrated under reduced pressure. The residue was taken up in methanol (1ml), and sodium carbonate solution (1 ml) was added. The reaction mixture was then stirred for 20 minutes. Removal of the solvent under reduced pressure gave a yellow oily residue which was purified by chromatography on silica gel G (15 g) with dichloromethane / methanol 5% as the eluent, to afford the N_a - *formyl* - 16α - *hydroxyaspidospermidine* (76mg, 77%) as clear, yellow oil (Found: M^+, m/z 326.200. $C_{20}H_{26}N_2O_2$ requires M^+, m/z 326.1994); ν_{max} ($CHCl_3$) 3450 (br, OH), 3010, 2940, 2860, 1660, 1490, 1405, 1125 cm^{-1}; λ_{max} (MeOH) 212, 253,

260 (sh), 280, 290 nm; δ_H ($CDCl_3$, 400MHz) 9, 8.6 (1H, 2s, NCHO), 8.08 (1H, d, J: 9.1 Hz, 12 - H), 7.3 - 7 (3H, m, Ar - H), 4.37 (1H, d, J: 7.5Hz, 2 - H), and 0.7 ppm (3H, t, J: 7Hz, CH_3); δ_C 160.2 (N<u>C</u>HO), 142 (C - 13), 138.62 (C - 8), 127.86 (C - 16), 125.43 (C - 11), 123.52 (C - 9), 110.54 (C - 12), 73.85 (C - 21), 71.39 (C - 2), 64 (C - 7), 53.40 (C - 3), 52.64 (C - 5), 42.23 (C - 6), 36.74 (C - 20), 34.31 (C - 19), 32.78 (C - 15), 31.30 (C - 17), 21.38 (C - 14), and 6.8 (C - 18); m/z (%) 326 (M+, 12.3), 325 (4.3), 309 (6.3), 298 (4.4), 297 (1.8), 282 (8.1), 152 (6.7), 149 (9.4), 144 (36.2), 143 (42.8), 138 (15.8), 130 (51.7), 124 (92.5), 122 (5.1), 110 (18.8) 109 (6.6), 96 (16.4).

2, 16 - Dihydrovincadifformine (517)



To a solution of (±) vincadifformine (5) (0.23 g, 0.22 mmol) in 10% absolute methanolic sulphuric acid (100 ml) zinc dust (30 g) was added. The reaction mixture was heated for 30 minutes with vigorous stirring. The mixture was filtered and thoroughly washed with methanol. The filtrate was concentrated under reduced pressure, then eluted with water (50 ml). Sodium carbonate was added until the solution became turbid and then ammonia (20 ml, d: 0.88) was added to the solution and the whole immediately extracted with ether (5 x 30 ml). The ether layer was dried (Na_2SO_4) and concentrated. Chromatography on silica gel (30 g) of the residue with chloroform and chloroform - ethyl acetate (2 : 1) as the eluent afforded the 2, 16 - *dihydrovincadifformine* (517) (212 mg, 92 %) as a colourless oil (Found: C, 74.25; H, 8.45; N, 8.4. $C_{21}H_{28}N_2O_2$ requires C, 74.10; H, 8.25; N, 8.25%); ν_{max} ($CHCl_3$) 3400 (NH), 3060, 3040, 2810, 2760, 1720, 1610, 1490, 1150, 1030, 905, 730, and 640 cm^{-1}; λ_{max} (MeOH) 207, 244, 298 nm; δ_H ($CDCl_3$, 400 MHz) 7.05 - 6.4 (4H, m, Ar - H), 4.35 (1H, br, NH), 3.97 (1H, d, J: 2 Hz, 2 - H), 3.92 (1H, m, H - 16), 3.75 (3H, s, -CO_2Me), 3.05 - 0.8 (15H, m), and 0.5 ppm (3H, t, J: 7.2 Hz, -CH_3); δ_C 176.6 (-$\underline{C}O_2Me$), 150 (C -

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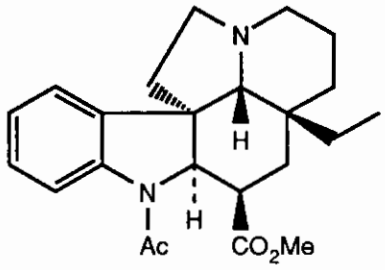
13), 135 (C - 8), 127 (C - 11), 123.21 (C - 9), 118.21 (C - 10), 108.8 (C - 12), 75.32 (C - 21), 67.33 (C - 2), 53.47 (C - 7), 52.47 (C - 3), 52.4 (C - 5), 51.5 (-$CO_2\underline{C}H_3$), 43.22 (C - 6), 39.14 (C - 16), 36.33 (C - 20), 33.93 (C - 17), 33.75 (C - 15), 28.36 (C - 19), 22.10 (C - 14), and 7.47 ppm (C - 18); m/z (%) 340 (M^+, 4), 254 (13), 144 (2.6), 143 (1.8), 130 (3.1), 124 (100).

N_a - Acetyl - 2, 16 - dihydrovincadifformine (522)



2, 16 - Dihydrovincadifformine (517) (0.7 g, 2.2 mmol) was dissolved in a mixture of acetic anhydride (6.8 ml) and pyridine (13.8 ml) in the presence of 4 - dimethylaminopyridine (0.268 g, 2.2 mmol). After 12 h stirring at room temperature under a nitrogen atmosphere water (200 ml) was added, the mixture was basified to pH 9.0 using dilute ammonia, and extracted with dichloromethane. The solvent was removed from the dried ($MgSO_4$) solution under reduced pressure and the residue was purified by chromatography on Kieselgel G (40 g) using chloroform - ethyl acetate (2 : 1) as eluent, which gave two main fractions:

- The less polar fraction contained a by - product (0.42 g, 50%), which was recrystallised from ethyl acetate and obtained as colourless prisms, m. p. 172 - 173 °C; (Found: C, 70.45; H, 7.6; N, 6.3; M^+, m/z 424.23620. $C_{25}H_{32}N_2O_4$ requires C, 70.75; H, 7.5; N, 6.6%; M^+ m/z 424.23437); ν_{max} ($CHCl_3$) 3000, 2940,

2780, 1690, 1630, 1585, 1470, 1395, 1250, 1110, 655 cm^{-1}; λ_{max} (MeOH) 206, 246, 276, 288 nm; δ_H ($CDCl_3$, 400MHz) 8.16 (1H, d, 12 - H), 7.26 - 7.21 (2H, m, Ar - H), 7.1 (1H, t, Ar - H), 4.53 (1H, br s, 2 - H), 3.73 (3H, s, OMe), 3 - 0.65 (complex), and 0.4 (3H, t , J: 7Hz, CH_3); δ_C (C - 22, not recorded)165.4 ($\underline{C}OCH_3$), 141.54 (C - 13), 138.09 (C - 8), 127.9 (C - 11), 124.7 (C - 9), 123.22 (C - 10), 117.57 (C - 12), 73.8 (C - 21) 67.75 (C - 2), 52.83 (C - 5), 52.6 (C - 3), 51.9 ($CO_2\underline{C}H_3$), 44.73 (C - 16), 40.58 (C - 6), 35.09 (C - 20), 34.6 (C - 15), 30.4 (C - 19), 33.7 (C - 17), 27.69 (C - $CO\underline{C}H_3$) 20.23 (C - 14) 7.66 (C - 18); m/z (%) 425 (6.6), 424 (24.8), 423 (6.6), 340 (2), 338 (3.4) 254 (2.1), 144 (1.5), 130 (1), 125 (100), 43 (3.5).

- The more polar fraction contained the desired product N_a - *acetyl* - 2, 16 - *dihydrovincadifformine* (522) (0.21g, 25%), which was obtained as yellow oil; ν_{max} ($CHCl_3$) 2930, 2780, 2710, 1720, 1630, 1595, 1480, 1375, and 1140 cm^{-1}; λ_{max} (MeOH) 208, 250, 280, 288, 302 (sh), and λ_{min} 228, 268 nm. δ_H ($CDCl_3$, 300 MHz) 8.15 (1H, m, 12 - H), 7.4 - 7 (3H, m, Ar - H), 4.5 (1H, m, 16 - H), 3.8 (1H, d, 2 - H), 3.6 (3H, s, -CO_2Me), 2.28 (3H, s, -NCO$\underline{C}H_3$), and 0.6 (3H, t, -CH_3); m / z (%) 382 (M^+, 2.7), 340 (11) [M^+-Ac], 296 (4.7) , 255 (5.5), 254 (26.6), 168 (2.8), 144 (3.2), 130 (2.7), and 124 (100).

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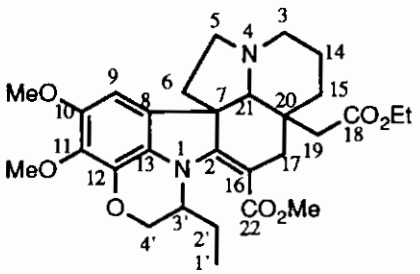

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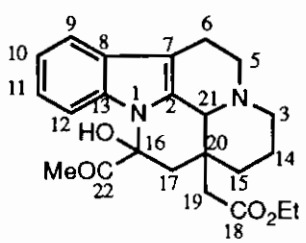

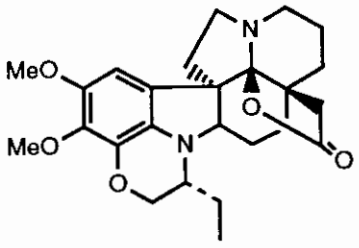

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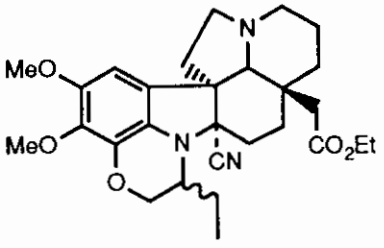

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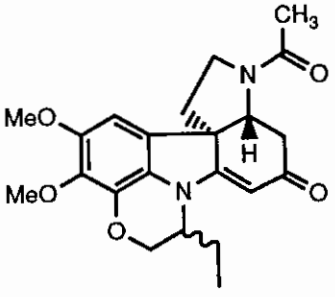

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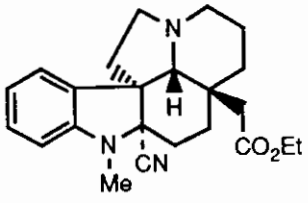

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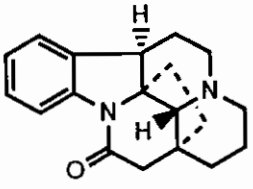

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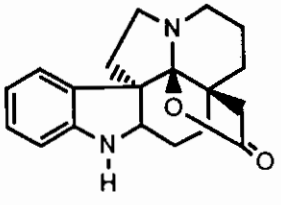

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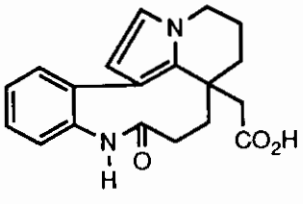

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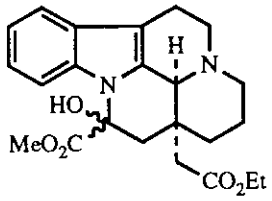

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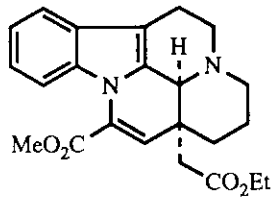

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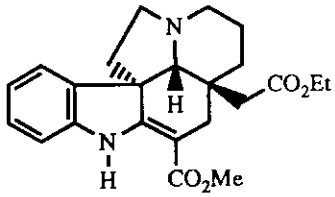

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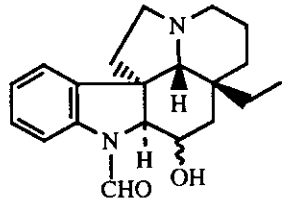

(507) 16α - OH
(515) 16β - OH

A synthesis of two epimers (507) and (515), via 16 - oxoaspidospermidine has also been achieved. (507) is the structure given to the alkaloid strictanine by Atta - Ur - Rahman. However, a comparison of the data for (507) with the very limited published data for strictanine was inconclusive, but certain differences in the spectroscopic data suggest that strictanine does not have the structure (507).

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ABBREVIATIONS

Ar	Aryl
Ac	acetyl
n - BuLi	n - butyl - lithium
DMAP	4 - dimethylaminopyridine
DMF	dimethylformamide
DMS	dimethylsulphide
DMSO	dimethylsulphoxide
THF	tetrahydrofuran
THP	tetrahydropyranyl
HMPA	hexamethylphosphoramide
TsOH	para - toluenesulphonic acid
TFAA	trifluoroacetic anhydride
mCPBA	meta - chloroperbenzoic acid
DMPU	(N, N'- dimethyl - N, N'- propylene urea = 1, 3 - dimethyl - 2 - oxo - hexahydropyrimidine)
DBU	1, 8 - diazabicyclo [5.4.0] undec - 7 - ene
LDPA	lithium diisopropylamide
n.m.r.	nuclear magnetic resonance
u.v.	ultra - violet
i.r.	infra - red
t.l.c.	thin layer chromatography