ELABORATION OF THE ETHYLIDENE SUBSTITUENT IN THE SYNTHESIS OF INDOLE ALKALOIDS

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Abstract - Some indole alkaloids have a C-20 ethylidene substituent as a common structural feature. All methods for the elaboration of this exocyclic, E-configurated double bond developed in indole alkaloid synthesis are reviewed.

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1. Introduction and biogenetic considerations
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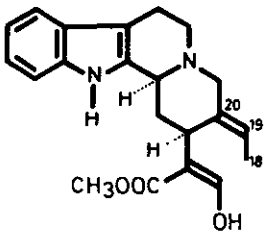
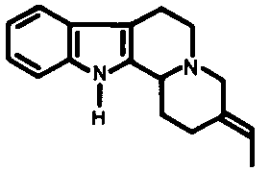
1. INTRODUCTION AND BIOGENETIC CONSIDERATIONS

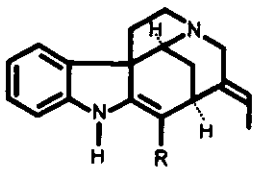
Although the majority of indole alkaloids which are biogenetically derived from strictosidine have a C-20 ethyl group,[1] a quite reduced number of them have, as a common structural feature, a C-20 ethylidene substituent. These alkaloids belong to heterogeneous groups such as *Corynanthe* (geissoschizine), *Strychnos* (akuammicine, norfluorocurarine, condylocarpine), sarpagine (gardnerine), 2-acylindole (ervitsine, vobasine, ochropine, methuenine), mavacurine (C-mavacurine, C-fluorocurine, pleiocarpamine and its tetracyclic analogue vinoxine), usambarane (usambarensine), and akagerine (akagerine, kribine). Further examples of indole alkaloids bearing a C-20 ethylidene group are deplancheine, apparicine, strictamine, and akuammine.[2] On the other hand, in some indole alkaloids (ellipticine, olivacine, strychnine) the 19,20-double bond is included in a ring system, whereas in *Yohimbe* and heteroyohimbine-type alkaloids these carbon atoms are found saturated belonging to the E-ring.



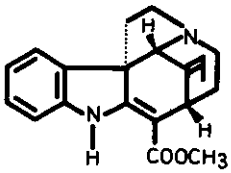
GEISSOSCHIZINE



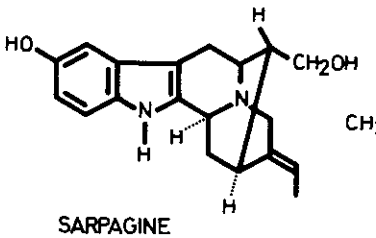
DEPLANCHEINE



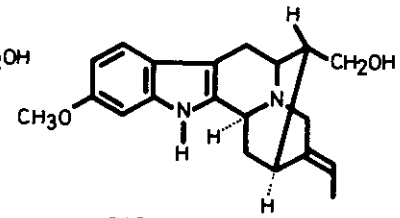
R=CHO , NOR - FLUOROCURARINE
R=COOCH3 , AKUAMMICINE



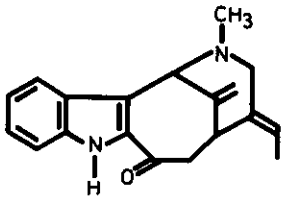
CONDYLOCARPINE



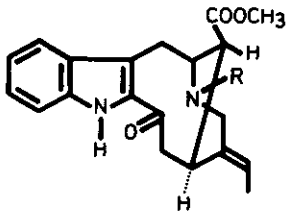
SARPAGINE



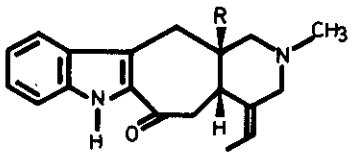
GARDNERINE



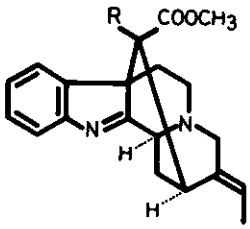
ERVITSINE



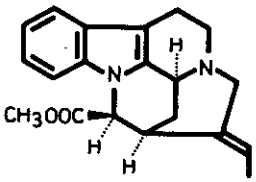
R=CH3 , VOBASINE
R=H , PERIVINE



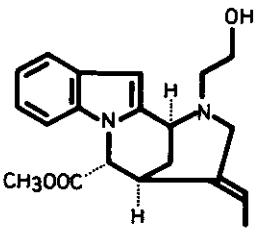
R=H , METHUENINE
R=COOCH3 , DEHYDROERVATAMINE



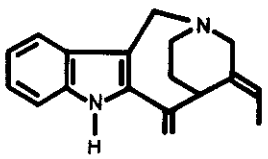
R=CHO , STRICTAMINE
R=CH2OAc , AKUAMMILINE



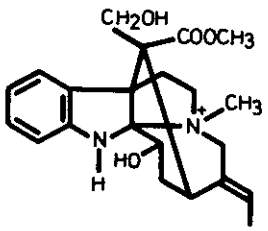
PLEIOCARPAMINE



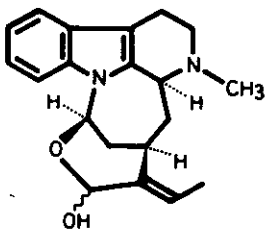
VINOXINE



APPARICINE

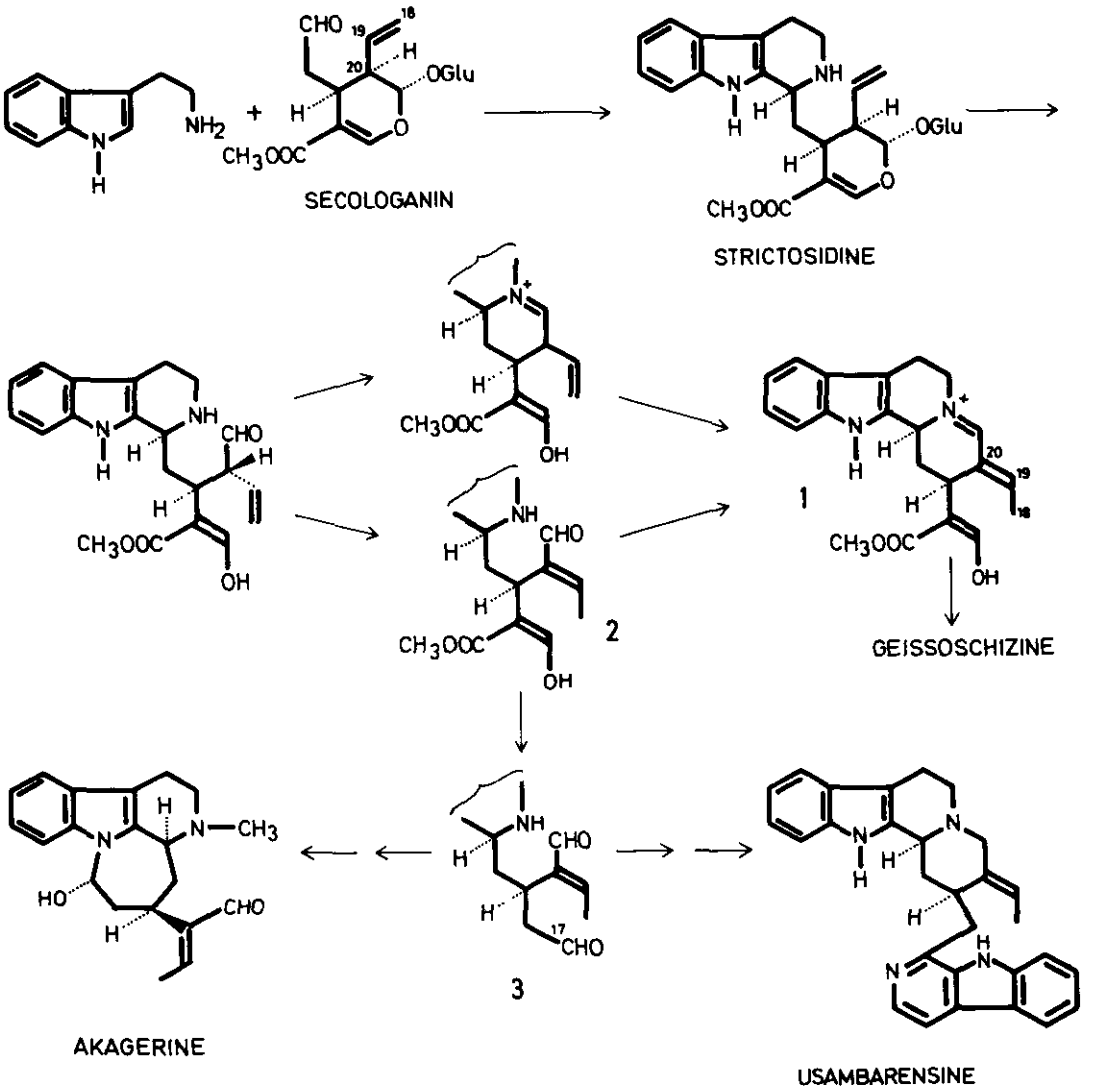


ECHITAMINE



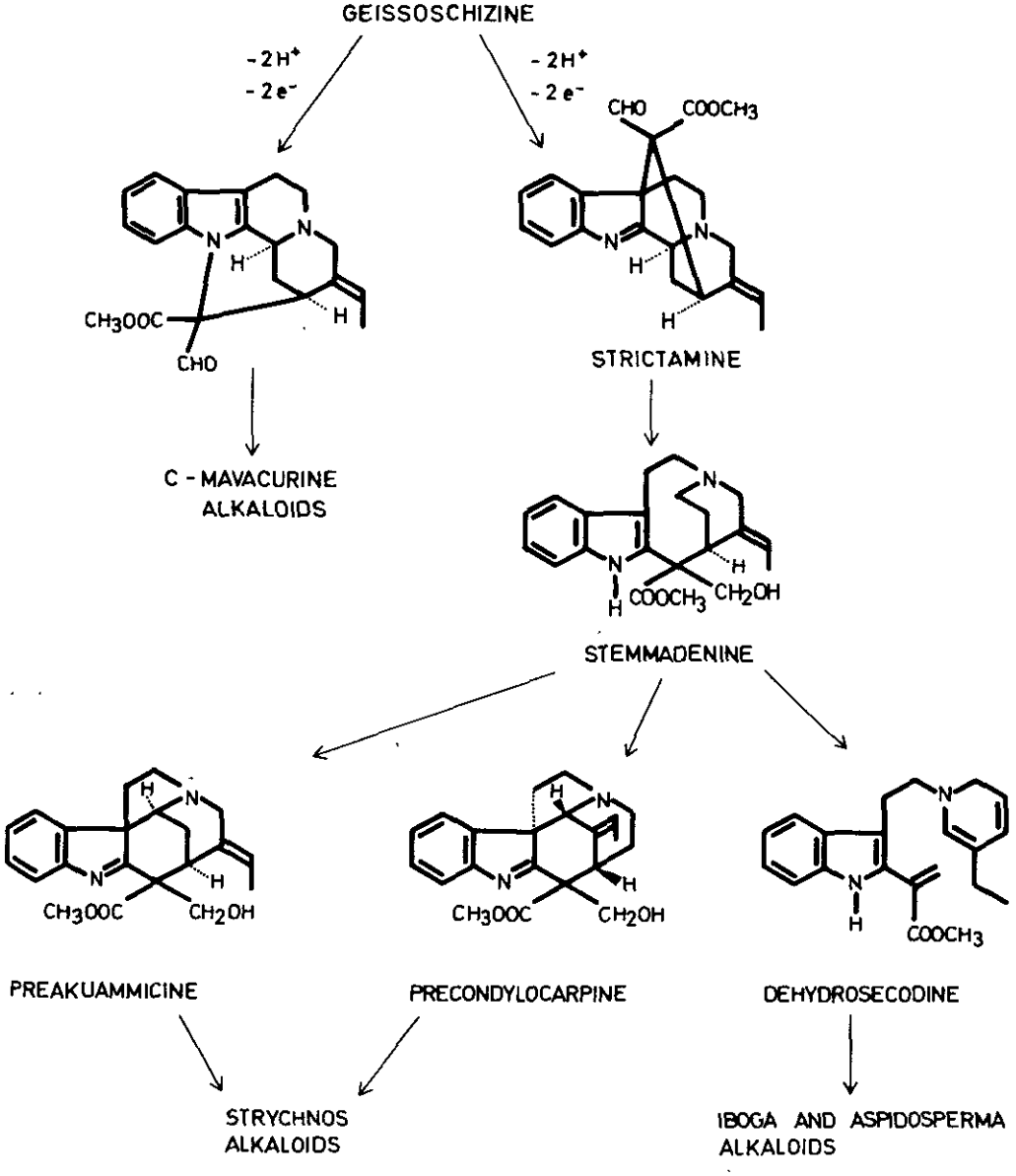
KRIBINE

This two-carbon side chain has its biogenetic origin in secologanin,[3] where it is included as a vinyl substituent. Condensation of secologanin and tryptamine gives strictosidine, a key intermediate in the biosynthesis of indole alkaloids. Hydrolysis of strictosidine followed by cyclization and isomerization of the vinyl double bond or, alternatively, by isomerization to an α,β-unsaturated aldehyde and further cyclization, gives the iminium salt 1, whose reduction leads to the *Corynanthe* alkaloid geissoschizine. It is at this stage when the C-20 ethylidene group is formed. On the other hand, decarbethoxylation of the hypothetical intermediate 2 to 3 followed by closure of ring D and reaction with tryptamine would yield



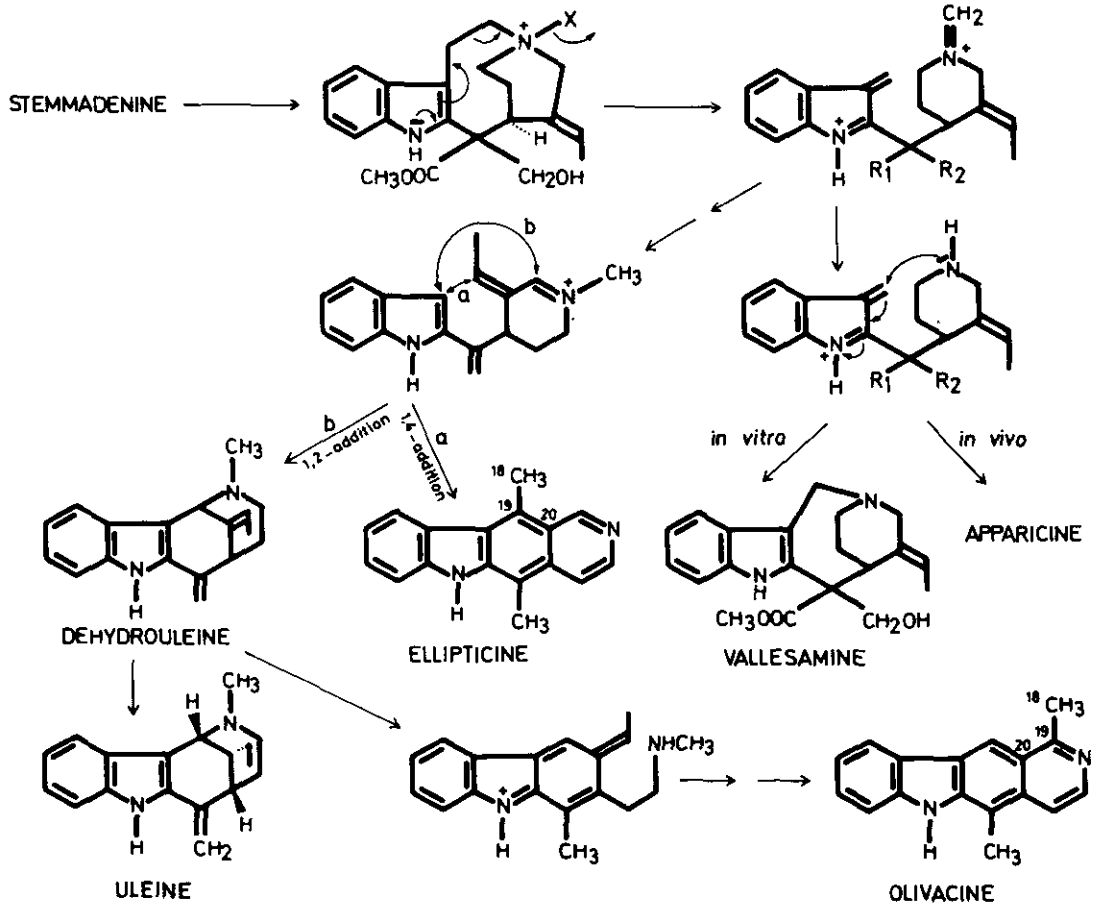
usambarane bases having a C-20 ethylidene group such as usambarensine, whereas ring closure between the C-17 aldehyde group and N_a would lead to alkaloids of the akagerine group (akagerine, kribine).[4]

Geissoschizine can be transformed, *via* strictamine and stemmadenine, into the *Strychnos* alkaloids by oxidative cyclization upon the indole 3-position followed by rearrangement. Similarly, the alkaloids of the C-mavacurine group formally arise from geissoschizine by oxidative ring closure between C-16 and the indole nitrogen.[3,5] In turn, the *Iboga* and *Aspidosperma* alkaloids are derived from stemma-



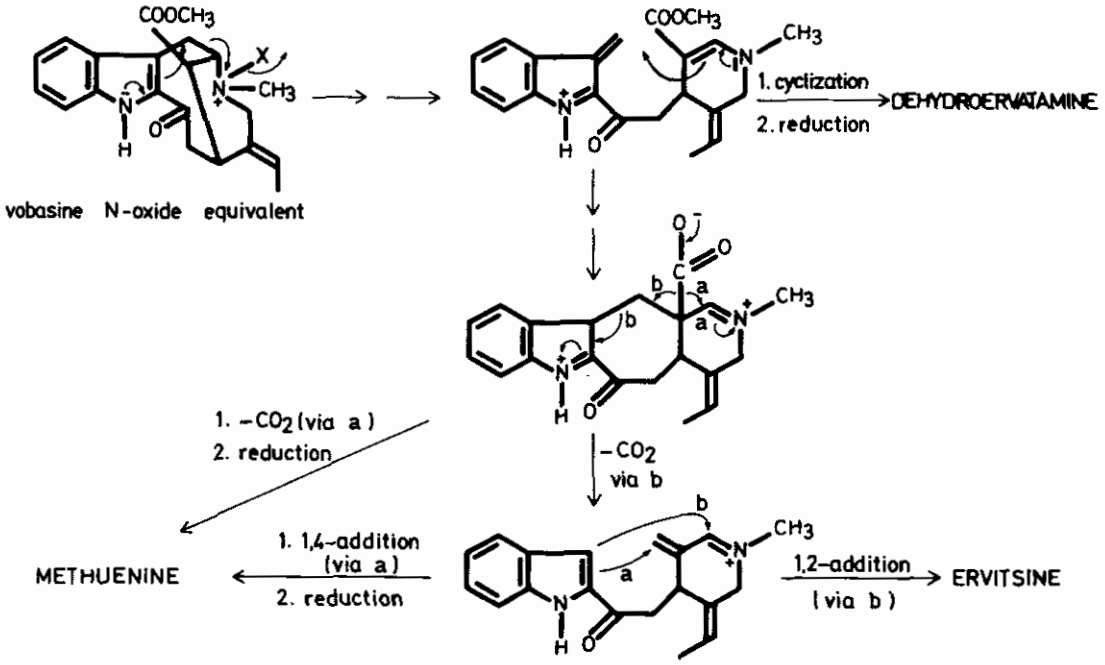
denine by intermediance of dehydrosecodine.[3,6] The presence of an ethyl substituent in these alkaloids can be explained by considering the isomerization of the *exocyclic double* bond which occurs during the transformation of stemmadenine into dehydrosecodine. On the contrary, the *Strychnos* alkaloids have in their origin an ethylidene substituent, the ethyl group being formed in further stages by reductive processes.

Stemmadenine is also the biogenetic precursor of a small group of indole alkaloids exemplified by vallesamine,[7] apparicine,[7,8] uleine, ellipticine,[9] and olivacine,[9] whose common structural feature is the absence of the two carbon atoms of the tryptamine bridge. The biogenetic route suggested by Potier for these alkaloids[10] involves the operation of a biological equivalent of the modified Polonovski reaction.[11] The ethylidene substituent, unchanged in the two former alkaloids, has been reduced to an ethyl group in uleine and has been incorporated to the tetracy-

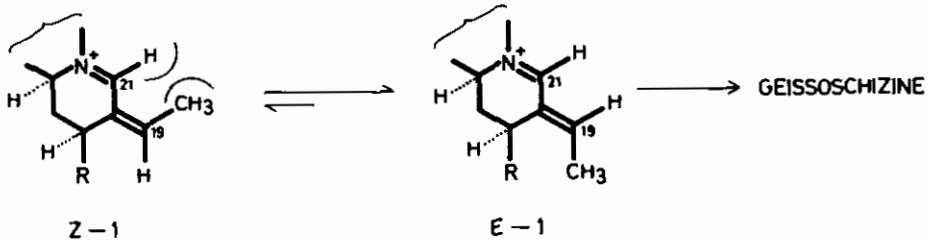


clic ring system of ellipticine and olivacine through cyclization of a conjugated iminium salt.

A modified Polonovski reaction applied to the alkaloids of the vobasine group also allows to explain the biosynthesis of the C-20 ethylidene containing alkaloids dehydroervatamine,[12] methuenine,[13] and ervitsine.[13] The first transformation[12] as well as the correlation between ervitsine and methuenine[13] has been verified *in vitro*.



As a consequence of its biogenetic origin, reduction of an iminium salt conjugated to the exocyclic double bond, the ethylidene substituent present in indole alkaloids has an *E*-configuration. The steric interactions between C_{21}-H and C_{19}-CH_3 in the iminium salt with a *Z* configuration are greater than those between C_{21}-H and C_{19}-H in the *E* iminium salt.



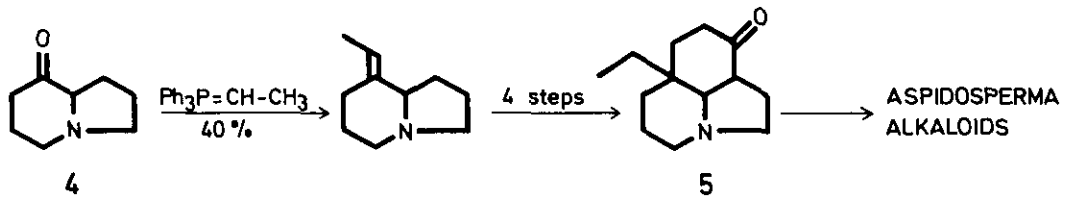
Z — 1 E — 1

In the synthesis of indole alkaloids, the introduction of the exocyclic, E-configurated ethylidene group generally implies an additional difficulty. Likely, by this reason only few syntheses of indole alkaloids having a C-20 ethylidene group have been reported. Among those synthesized up to now are geissoschizine, whose biogenetic interest has stimulated the development of several synthetic ways; deplancheine, probably derived from the former by lossing the C-15 side chain; some pentacyclic *Strychnos* alkaloids; C-mavacurine; 16-epipleiocarpamine; and some structural analogues of 2-acylindole alkaloids.

This review about the methods of forming an exocyclic ethylidene group deals only with those developed in indole alkaloid synthesis

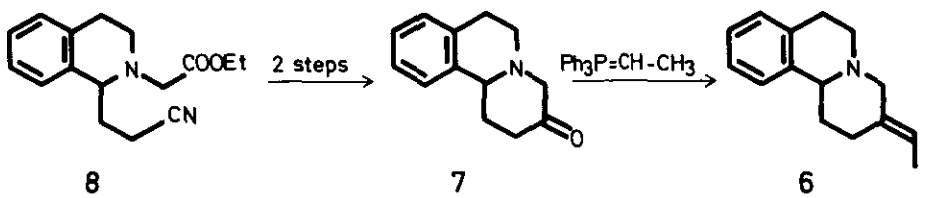
2. WITTIG REACTION

The Wittig reaction[14] is a general method to obtain olefins, which has received considerable attention in carbocyclic and heterocyclic chemistry. An example is the integration of an ethylidene group from indolizidone 4 in the synthesis of the tricyclic ketone 5, a precursor of some *Aspidosperma* alkaloids.[15]



4 5

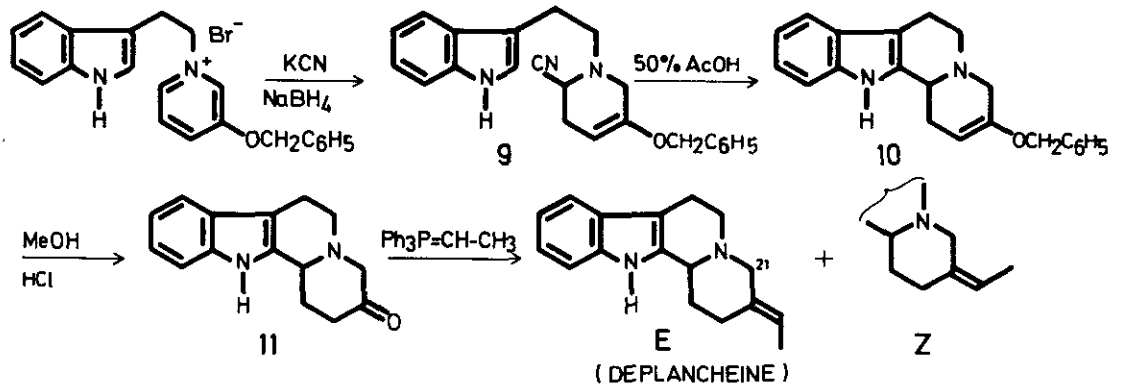
The application of this reaction to the elaboration of the ethylidene group present in some indole alkaloids implies starting from a suitable 3-piperidone. One of the most general methods for the preparation of these systems is the Dieckmann cyclization or related reactions. Thus, in a synthesis of 3-ethylidenebenzo[a]quinolizidine 6, the ethylidene substituent was formed by a Wittig reaction from 3-piperidone 7, which, in turn, was obtained by cyclization of cyano ester 8.[16]



8 7 6

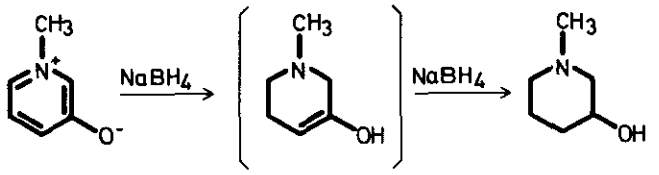
The required 3-piperidone system is also easily attainable by sodium borohydride reduction of 3-alcoxypyridinium salts followed by acid hydrolysis of the enol ether moiety in the resulting tetrahydropyridine.[17]

This synthetic strategy constitutes the basis of a recent synthesis of the alkaloid deplancheine from a 3-benzyloxypyridinium salt.[18] In this case, the reduction of the pyridinium salt was carried out in the presence of cyanide ions[19] to give the 2-cyanotetrahydropyridine 9. Cyclization of this α-amino nitrile upon the 2-position of the indole nucleus was effected, *via* the corresponding iminium salt,[20] on acid treatment. Further acid hydrolysis of the enol ether 10 led to the 3-piperidone 11, upon which the ethylidene group was integrated. The stereoselectivity of the Wittig reaction is low since it furnishes both isomers, E (corresponding to the natural product) and Z, in a nearly equimolecular ratio.

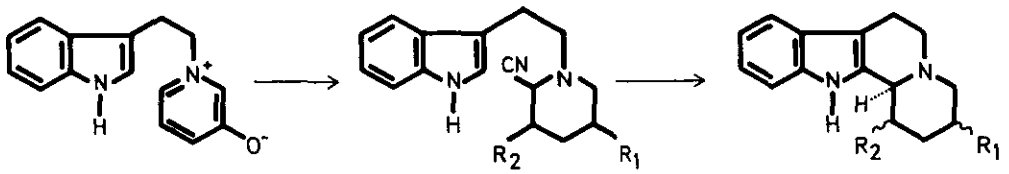


Both isomers can be differentiated by H^1-nmr. In the Z isomer a doublet at δ3.9 (J=12 Hz) due to the equatorial C-21 proton, at considerably lower field than any aliphatic proton signal shown by the E isomer, is observed. Further, the unnatural Z isomer has a higher field olefinic proton signal (δ5.4 compared to δ5.5) and a lower field methyl signal (δ1.8 compared to δ1.7) than the natural geometrical isomer.

When sodium borohydride reduction is done from a 3-hydroxypyridinum salt, the enol intermediate is again reduced, through its ketone tautomer, by an hydride ion to provide a 3-hydroxypiperidine,[21] which can be later oxidized to a 3-piperidone.[22]



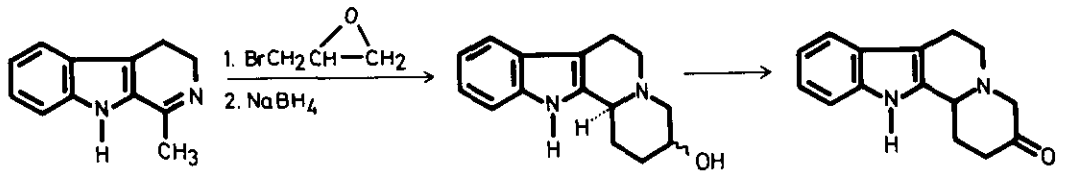
Likewise, sodium borohydride reduction of 1-[2-(3-indolyl)ethyl]-3-oxidopyridiniums in the presence of sodium cyanide gave a mixture of cyano alcohols, which were further cyclized by treatment with aqueous acetic acid.[21]



a. R_1 = OH , R_2 = H

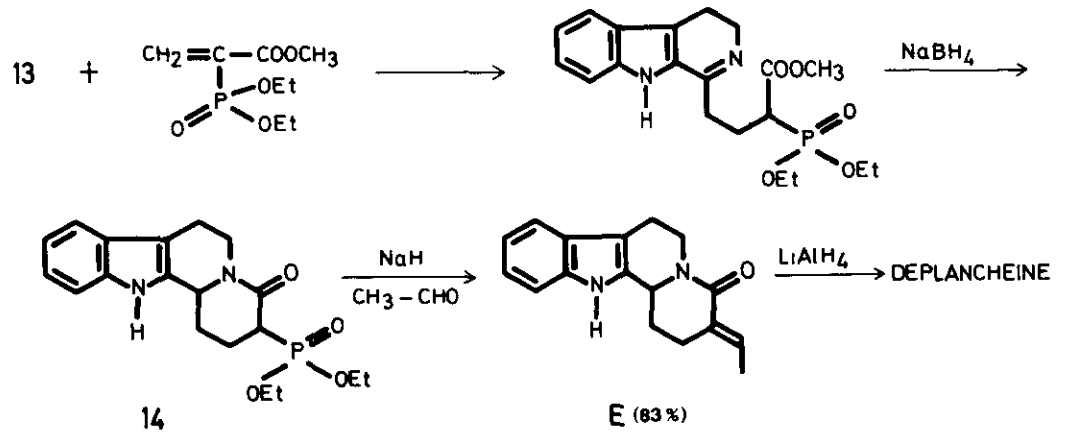
b. R_1 = H , R_2 = OH

An alternative synthetic approach to the indoloquinolizidin-3-ols 12a utilizes the alkylation of imine-enamine 13 with 1-bromo-2,3-epoxypropane followed by reductive work-up as the key ring-forming step. Oxidation (DMSO, DCC, orthophosphoric acid) of the resulting 1:1 diastereomeric mixture furnishes 3-piperidone 11, a precursor of deplancheine.[22]



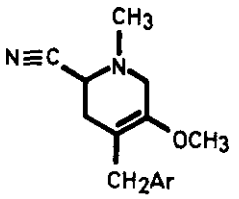
13 12 a 11

The reactivity of the imine 13 as ambident nucleophile allows the synthesis of the amido phosphonate 14, from which a stereoselective synthesis of deplancheine has been developed by Wittig-Horner reaction with acetaldehyde and subsequent reduction of the enamide carbonyl group.[22]



14 E (83%)

In the context of our studies on the synthesis of vinoxine,[23] we have observed some limitations of the Wittig approach to the ethylidene group: cyanotetrahydropyridine 15 failed to give any 3-piperidone by acid treatment, whereas the Wittig reaction on 3-piperidone 16 did not afford the expected 3-ethylidene derivative.[24]



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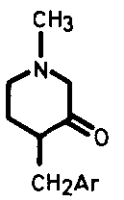
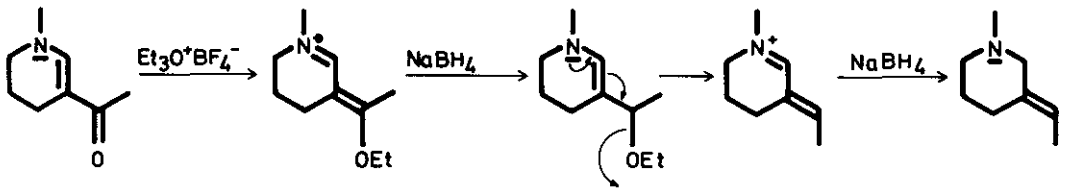


16

Ar = 1 - indolyl

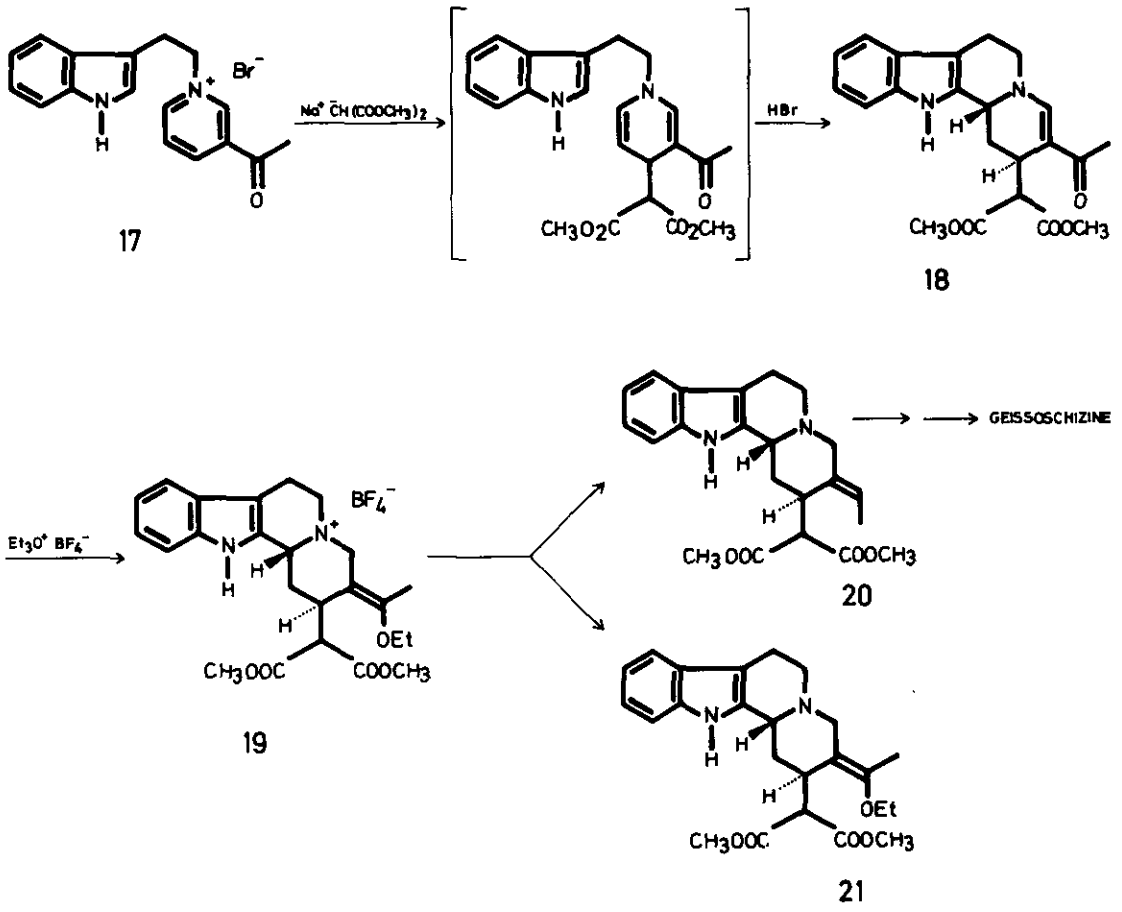
3. FROM 3-ACETYL-2-PIPERIDEINES AND RELATED COMPOUNDS

The reduction of a tertiary amide, either directly with lithium aluminum hydride or through its corresponding imino ether with sodium borohydride, takes place by an initial attack of an hydride ion followed by elimination to give an iminium salt, which is subsequently reduced by an hydride ion.[25] When these reactions are carried out on 3-acetyl-2-piperideines, which are vinylogous amides, the procedure is excellent to prepare 3-ethylidenepiperidines.

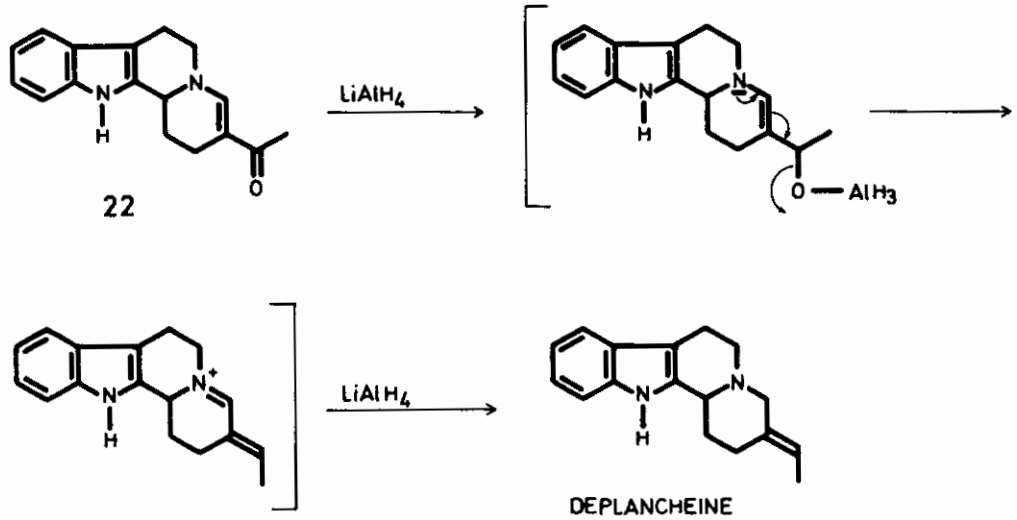


Thus, treatment of 3-acetyl-2-piperideines with triethyloxonium tetrafluoroborate followed by sodium borohydride reduction has been applied to form the ethylidene group in a synthesis of geissoschizine.[26] The required 3-acetyl-2-piperideine 18 was obtained from 3-acetylpyridinium salt 17 by nucleophilic attack of dimethyl sodiomalonate upon the 4-position of the pyridine ring[27] followed by protonation of the non conjugated enamine moiety in the resulting 1,4-dihydropyridine and cyclization upon the 2-position of the indole nucleus. Exposure of vinylogous amide 18 to triethyloxonium tetrafluoroborate yielded iminium salt 19 which, on sodium borohydride reduction, gave a mixture of the desired E-olefinic diester 20, its double bond stereoisomer (in minor amount), and the enol ether 21 formed by a 1,2-reduction process. Diester 20 was converted into geissoschizine through two alternative reaction sequences,[27] one of them constitutes a formal total synthesis of the alkaloid by vir-

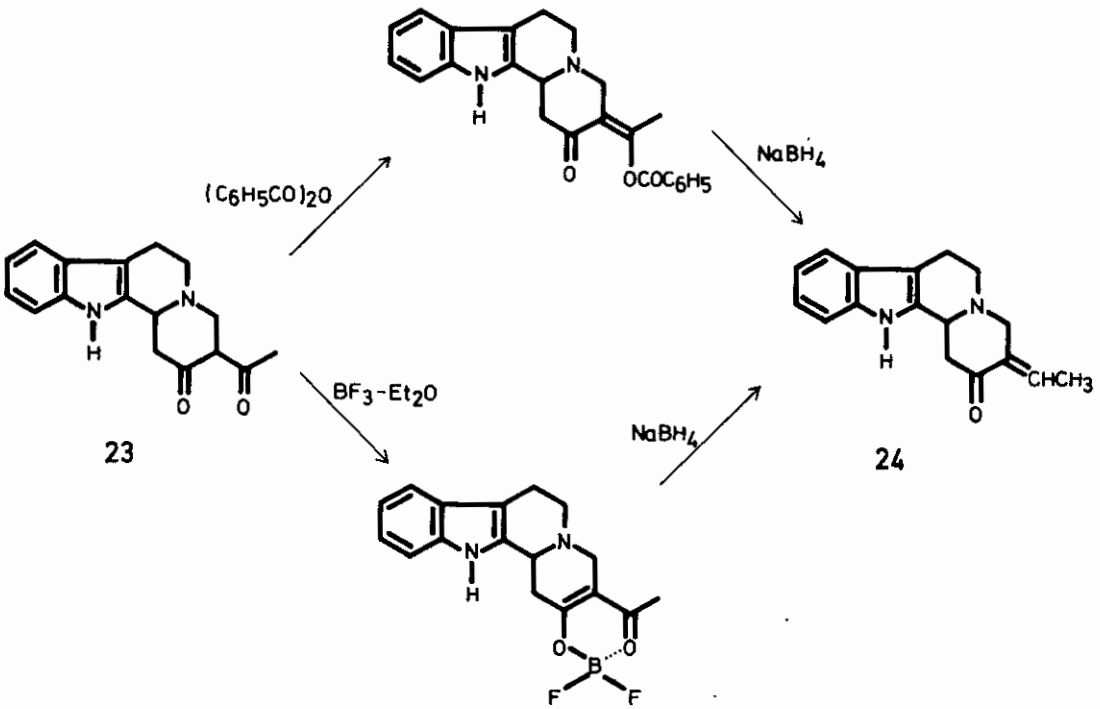
tue of a connection with an earlier synthesis.[28]



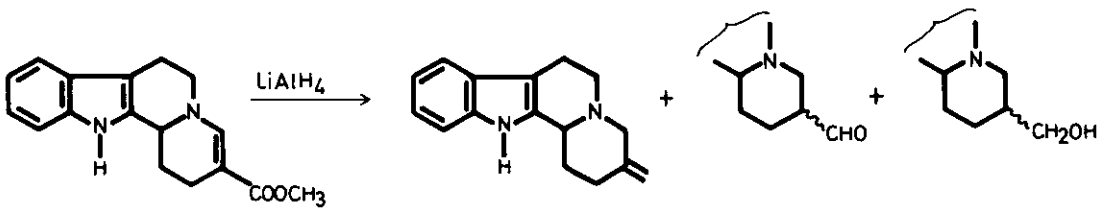
Similarly, lithium aluminum hydride reduction of 3-acetyl-2-piperideines leads, in a single step, to 3-ethylidenepiperidines. This procedure has been applied by Lounasmaa to the synthesis of deplancheine,[29] and provides an easy route to create an *E*-configurational ethylidene side chain at the 3-position of the *indolo*[2,3-*a*]quinolizidine skeleton (corresponding to the 20 position in the biogenetic numbering).[1] The required 3-acetyl-2-piperideine 22 was obtained[30] by sodium dithionite reduction[31] of 3-acetylpyridinium salt 17 followed by acid cyclization of the intermediate 1,4-dihydropyridine.



A related synthetic strategy is based on the sodium borohydride reduction of enol esters[32] or boron difluoride complexes[33] from 1,3-dicarbonyl compounds. 3-Acetyl-4-piperidone 23, prepared by Dieckmann cyclization of the appropriate amino keto ester,[32] was converted into 3-ethylidene-4-piperidone 24 by two alternative sequences as depicted in the following scheme.

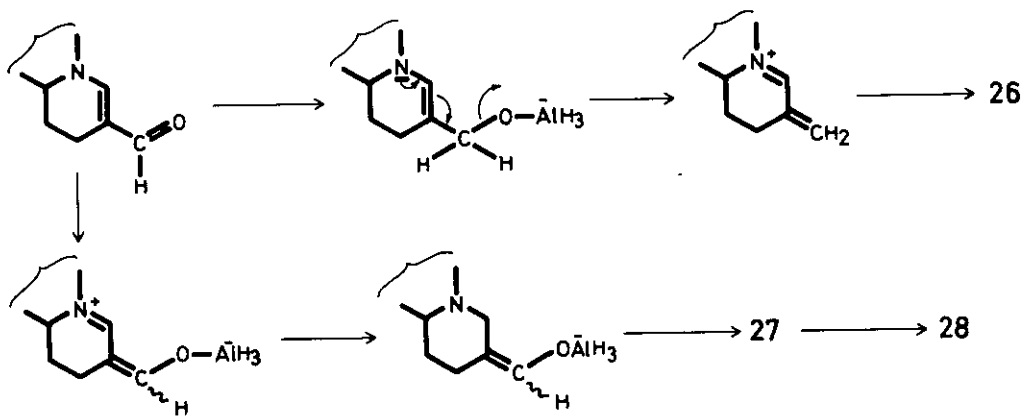


Recently, lithium aluminum hydride reduction of vinylogous urethanes has been studied in order to prepare exocyclic methylene substituents in piperidine derivatives.[34] When 25 was treated with lithium aluminum hydride four products were formed: the methylene derivative 26 (20%) (18-nordeplancheine), the aldehyde 27 (8%), and two epimeric alcohols 28 (33%).

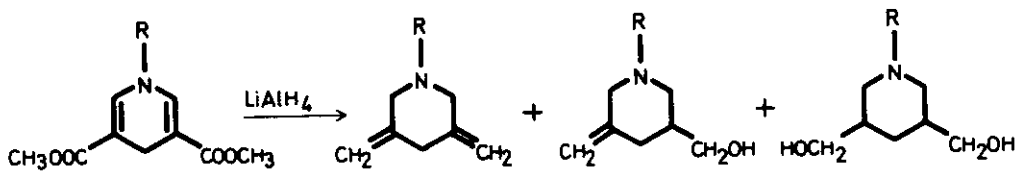


25 26 27 28

This transformation can be explained by the initial reduction of the methoxycarbonyl group to the corresponding aldehyde, which can be further reduced by two alternative paths:



Similar treatment from 29 gave a mixture of dimethylene-, monomethylene, and bis-(hydroxymethyl)piperidines (30, 31, and 32, respectively).

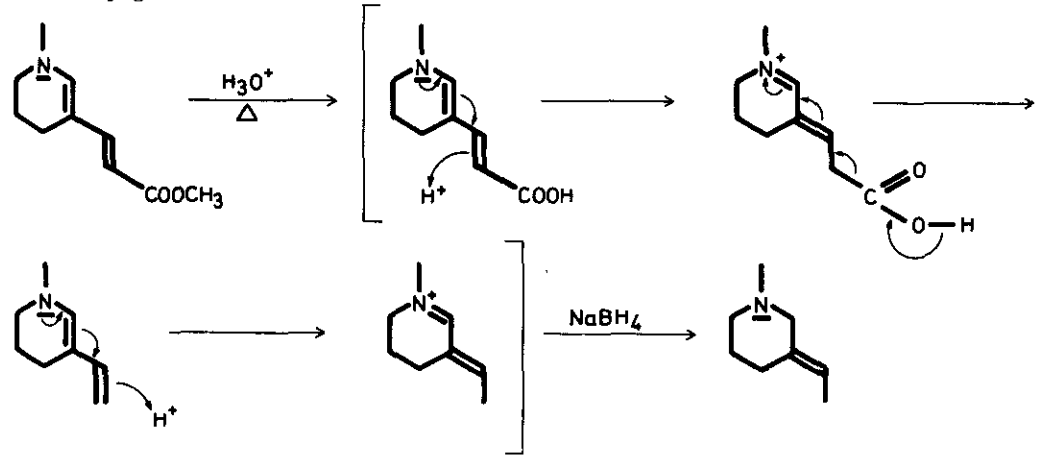


29 30 31 32

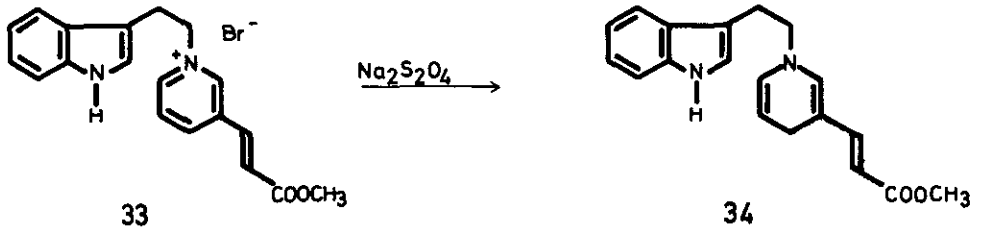
a. R = 2-(3-indolyl)ethyl

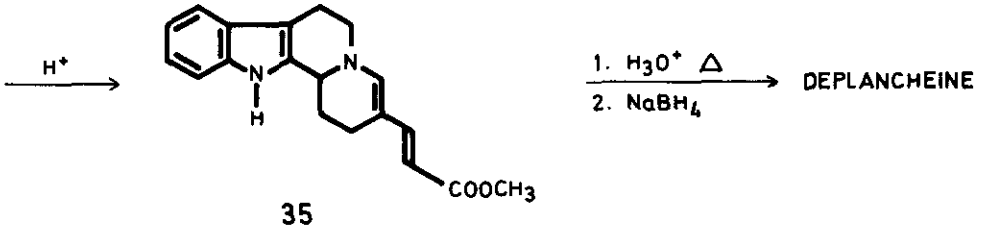
b. R = CH_3

On the other hand, alkyl β-(1,4,5,6-tetrahydro-3-pyridyl)acrylate systems,[35] which are doubly vinylogous urethanes, can be transformed into 3-ethylidenepiperidines by a synthetic sequence implying acid hydrolysis of the ester function followed by decarboxylation of the resulting acid to give an iminium salt, which was subsequently reduced by sodium borohydride. 3-Ethylidenepiperidines prepared in this way have the natural E double bond configuration because of their formation by reduction of a conjugated iminium salt

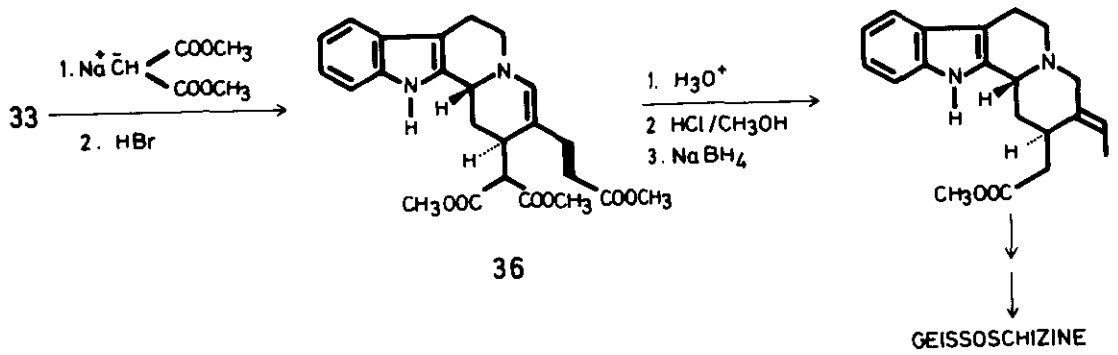


This methodology constitutes the basis of a synthesis of deplancheine.[36] The requisite 2-piperideine 35 was obtained by sodium dithionite[31] reduction of the pyridinium salt 33 followed by acid cyclization of the intermediate 1,4-dihydropyridine 34.



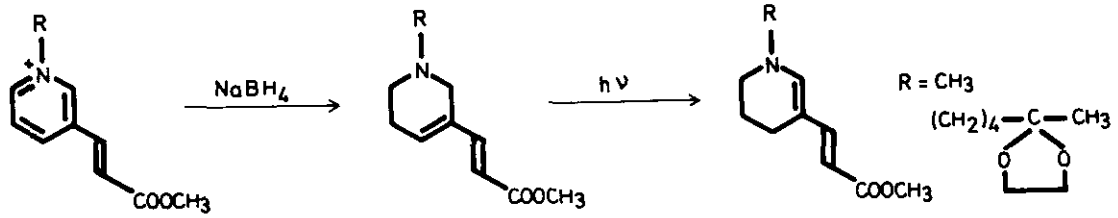


The ethylidene substituent of geissoschizine has been formed in a similar way[26] from 2-piperideine 36. This was prepared from the above pyridinium salt 33 in a two step sequence consisting in reaction with dimethyl sodiomalonate[27] and subsequent acid cyclization.



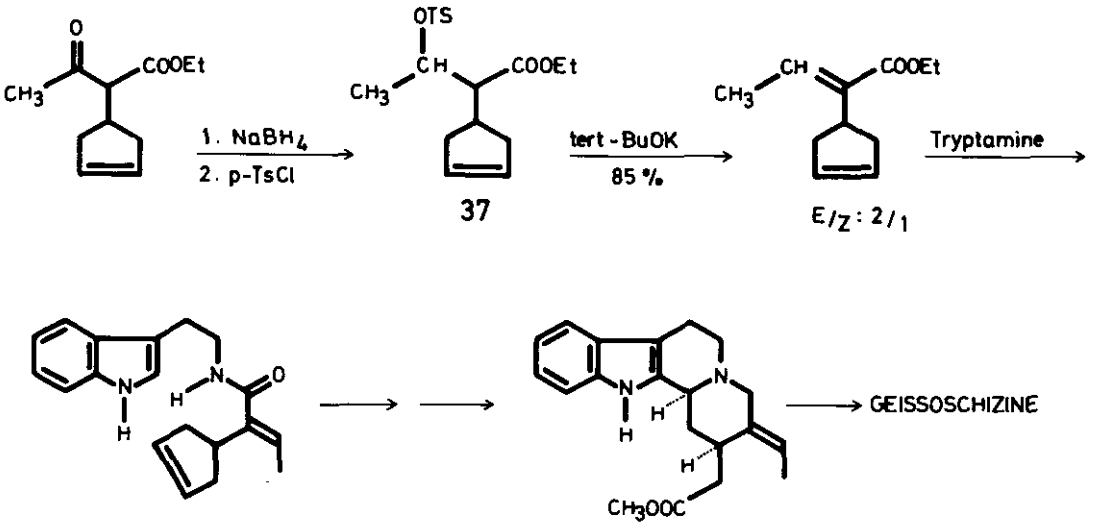
36

Alternatively, the required β-(1,4,5,6-tetrahydro-3-pyridyl)acrylate system can be prepared by photochemical isomerization of appropriate 3-piperideines[37] which, in turn, are easily accessible by sodium borohydride reduction of pyridinium salts.[38]

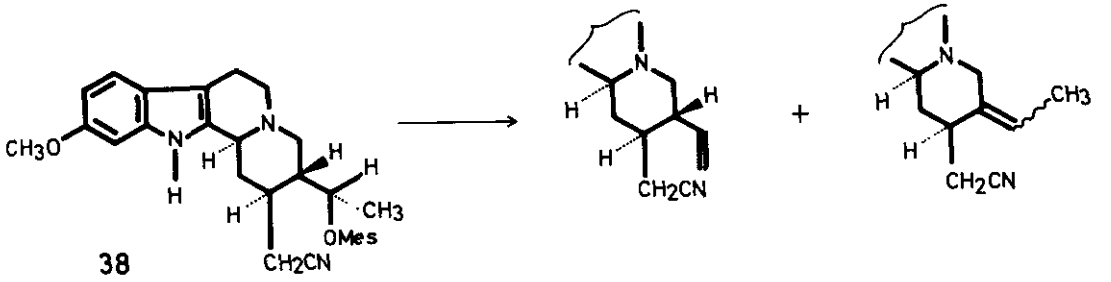


4. ELIMINATION PROCESSES

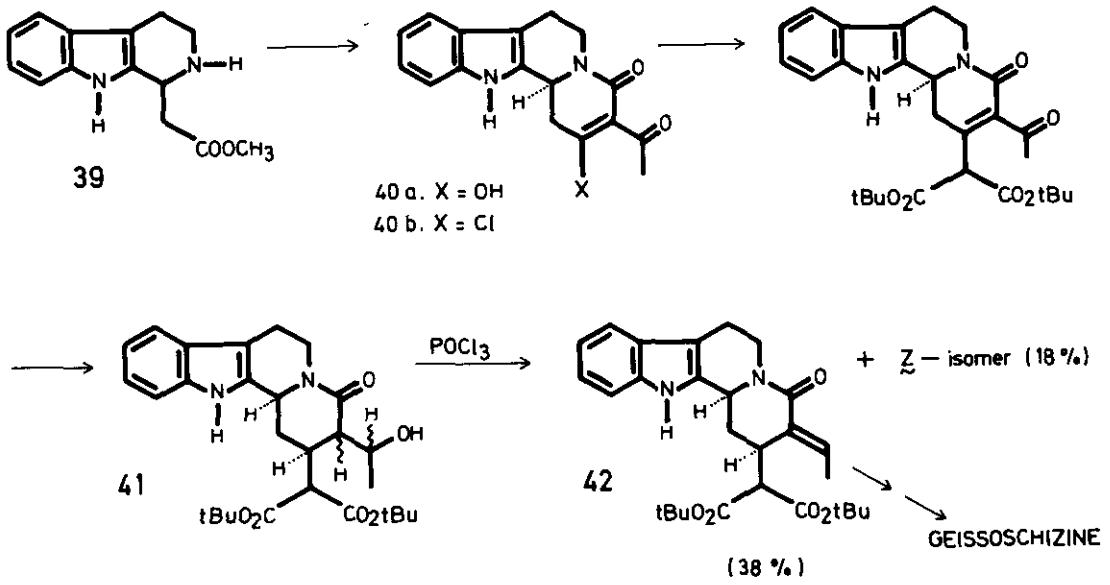
β-Elimination reactions constitute a general method to obtain olefins and, consequently, they have been widely applied to the elaboration of the ethylidene substituent found in a variety of indole alkaloids. Thus, in the first total synthesis of geissoschizine,[28] the ethylidene group was formed in an early synthetic step by base catalyzed elimination of tosylate 37, previously to the formation of the piperidine ring.



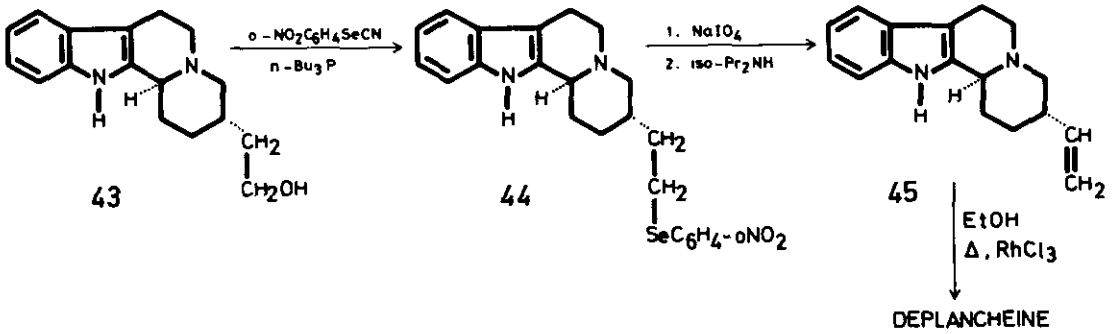
A related elimination occurred when mesylate 38, a product derived from tetraphylline, was treated with DBU: a mixture of vinyl (9%) and ethylidene (9%) compounds was obtained.[39]



The exocyclic, E-configurated double bond of geissoschizine has been also installed by an elimination process from the stereoisomeric mixture of alcohols 41.[40] Thus, reaction of tetrahydrocarboline 39 with diketene followed by cyclization with potassium *tert*-butoxide gave the piperidinedione 40a, bearing the required 20-acetyl group. Michael addition of di-*tert*-butyl malonate upon the chloride 40b and subsequent reduction of the carbon-carbon double bond (1,4-addition with calcium borohydride) and the ketone carbonyl group (sodium borohydride treatment) furnished the alcohols 41. Dehydration of 41 was effected with phosphoryl chloride in pyridine to afford a 2:1 mixture of the desired E-ethylidene lactam 42, which was further converted to geissoschizine, and the unnatural Z-isomer.[40]

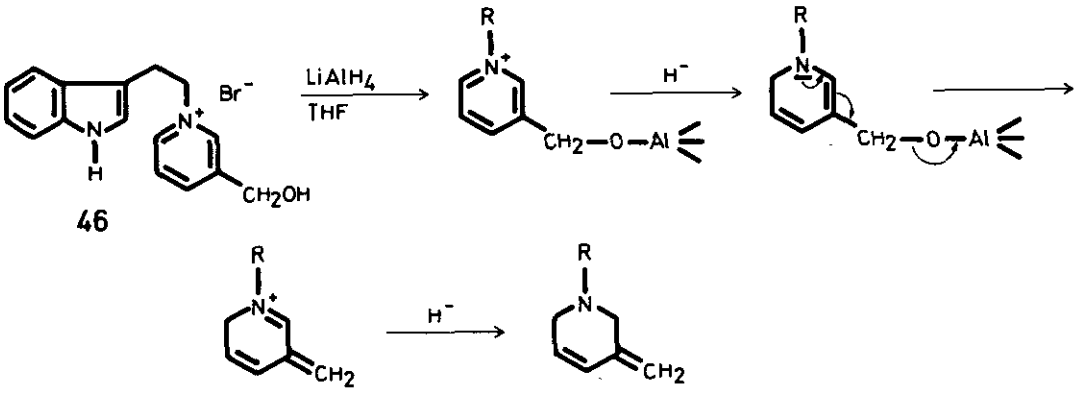


The trisubstituted olefinic linkage *in deplancheine* has been elaborated with low selectivity in 58% overall yield from alcohol 43, *via* a three-step sequence involving an elimination reaction to form a double bond and its subsequent isomerization.[22] Alcohol 43 was prepared from imine 13 by reaction with α-methylene-γ-butyrolactone followed by lithium aluminum hydride reduction, according to the same imine-enamine annelation methodology used in the preparation of 12a and 14 (see section 2). In this synthesis, alcohol 43 was converted to the selenide 44, whose subsequent oxidation and base-induced elimination gave rise to the vinylquinolizidine 45. Finally, 45 underwent double bond migration by heating in ethanol in the presence of catalytic rhodium trichloride trihydrate. A 6:3:1 mixture of deplancheine, its Z-isomer, and unreacted material was obtained.



In this section, reductive eliminations and base catalysed thermal decomposition of tosylhydrazones deserve special attention.

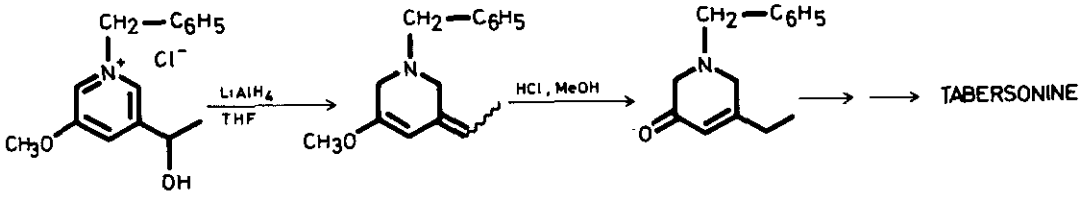
When 3-hydroxymethylpyridinium salt 46 was reduced with lithium aluminum hydride in tetrahydrofuran a reductive elimination occurred to give a diene.[41]



46

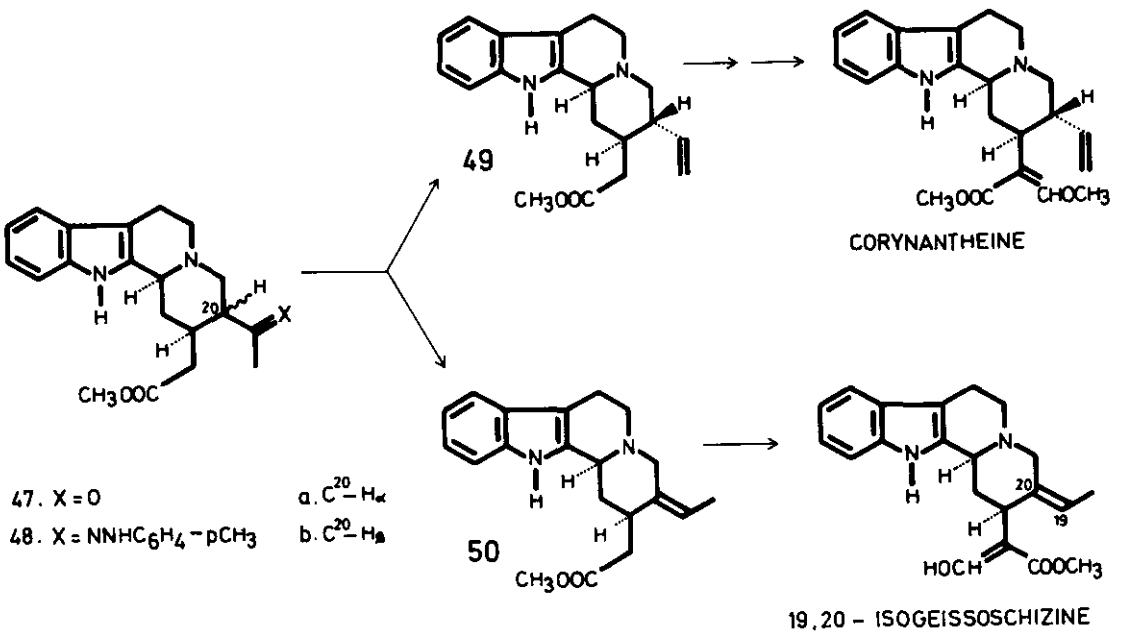
R = 2 - (3 - indolyl) ethyl

This observation was later useful for the formation of the ethyl substituent of tabersonine[42] in early steps of the synthesis.

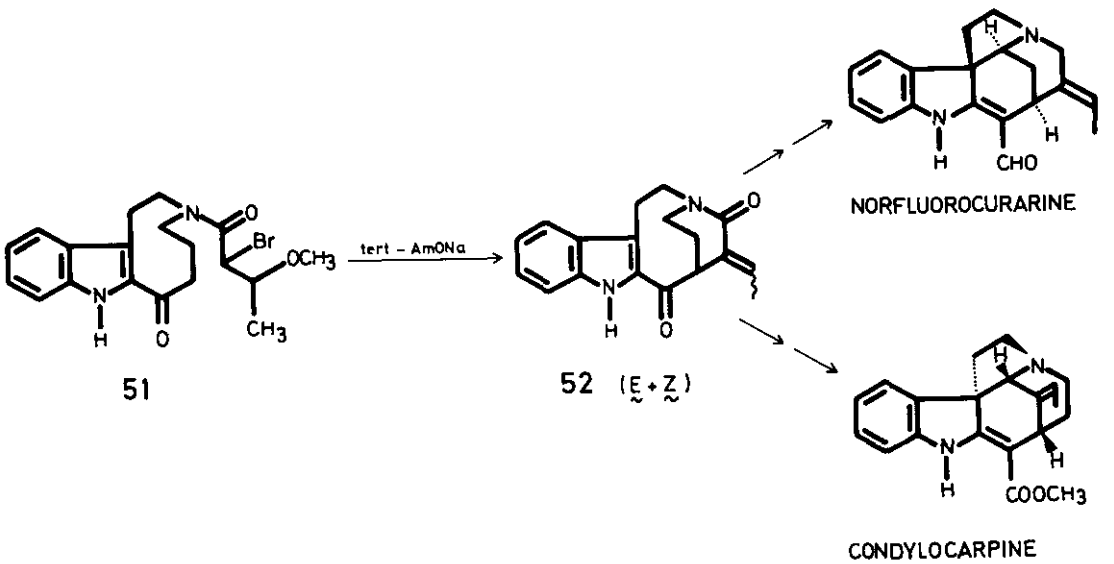


On the other hand, the thermal decomposition of sulfonylhydrazone salts is known to produce olefinic compounds.[43] Use of this reaction for carrying out the conversion of keto ester 47 to unsaturated compounds has found application to the first total synthesis of corynantheine and to that of a related base in the geissoschizine family.[44] The epimeric mixture of keto esters 47 was converted to a mixture of the corresponding toluenesulfonylhydrazones 48, which could be separated. When the *trans*-isomer 48b was refluxed in diglyme in the presence of sodium methoxide, two major products, vinyl- and Z-ethylidenepiperidines 49 and 50, respectively, were obtained. In contrast, decomposition of the *cis*-isomer 48a produced a more complex mixture. One of the extra products can be accounted for as the E-diatereomer of 50. The difference in behavior of the two isomeric tosylhydrazones 48 upon decomposition is probably due to steric factors. Formylation of the vinyl ester 49 followed by treatment with diazomethane gave corynantheine, whereas formylation of the

ethylidene derivative 50 gave the Z-isomer of geissoschizine.[44]

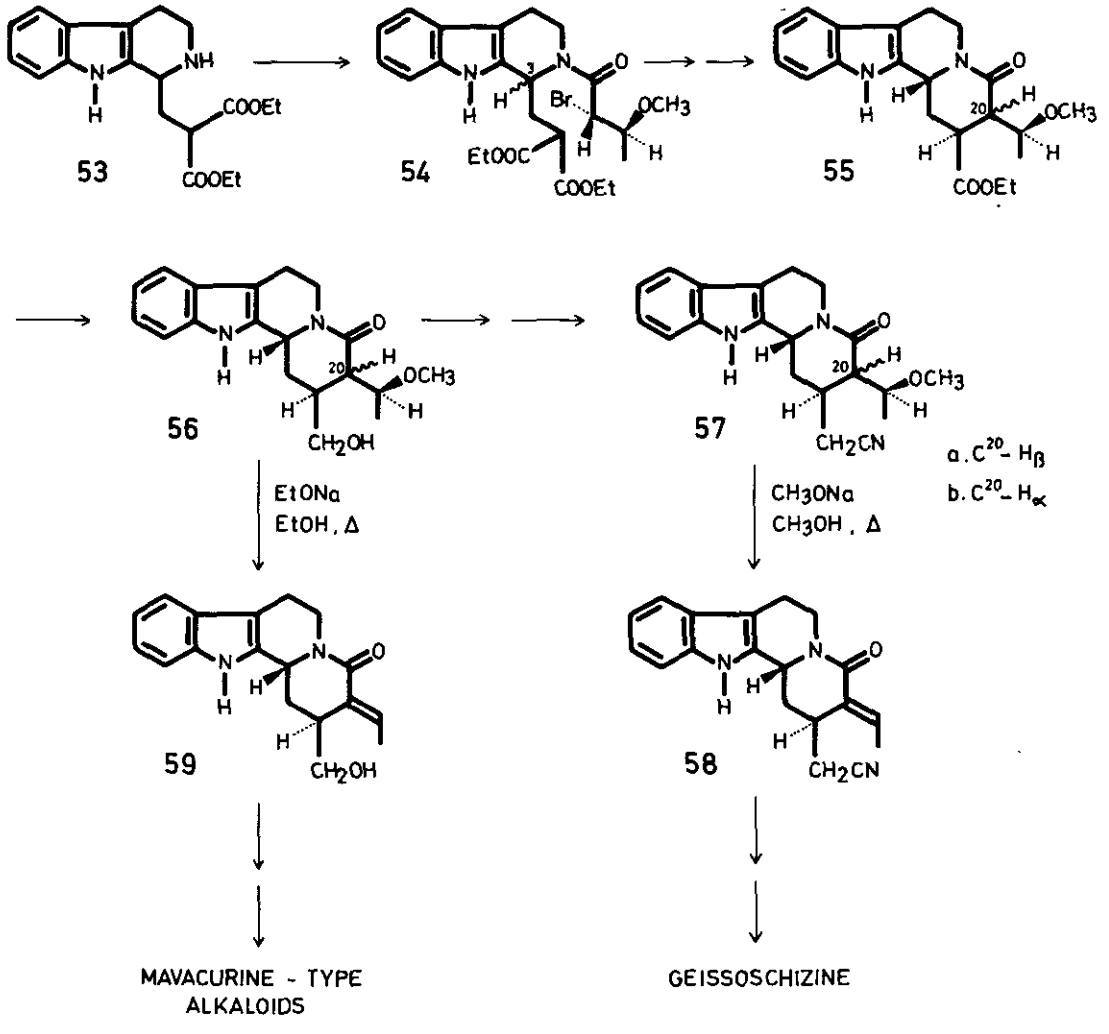


A general method for introducing the E-ethylidene substituent, based on an elimination process, has been developed by Harley-Mason for the synthesis of the pentacyclic *Strychnos* alkaloids norfluorocurarine[45,46] and condylocarpine.[45] The ethylidene group of these alkaloids was formed simultaneously to the piperidine ring closure by base catalyzed elimination of methanol. On treatment with excess of sodium



tert-amyloxide in tetrahydrofuran, keto amide 51 underwent a cyclization-elimination process to give a mixture of E and Z keto lactams 52. The unnatural Z-isomer was not wasted, since it can be equilibrated with the natural one on treatment with sodium methoxide by an addition-elimination process.[45]

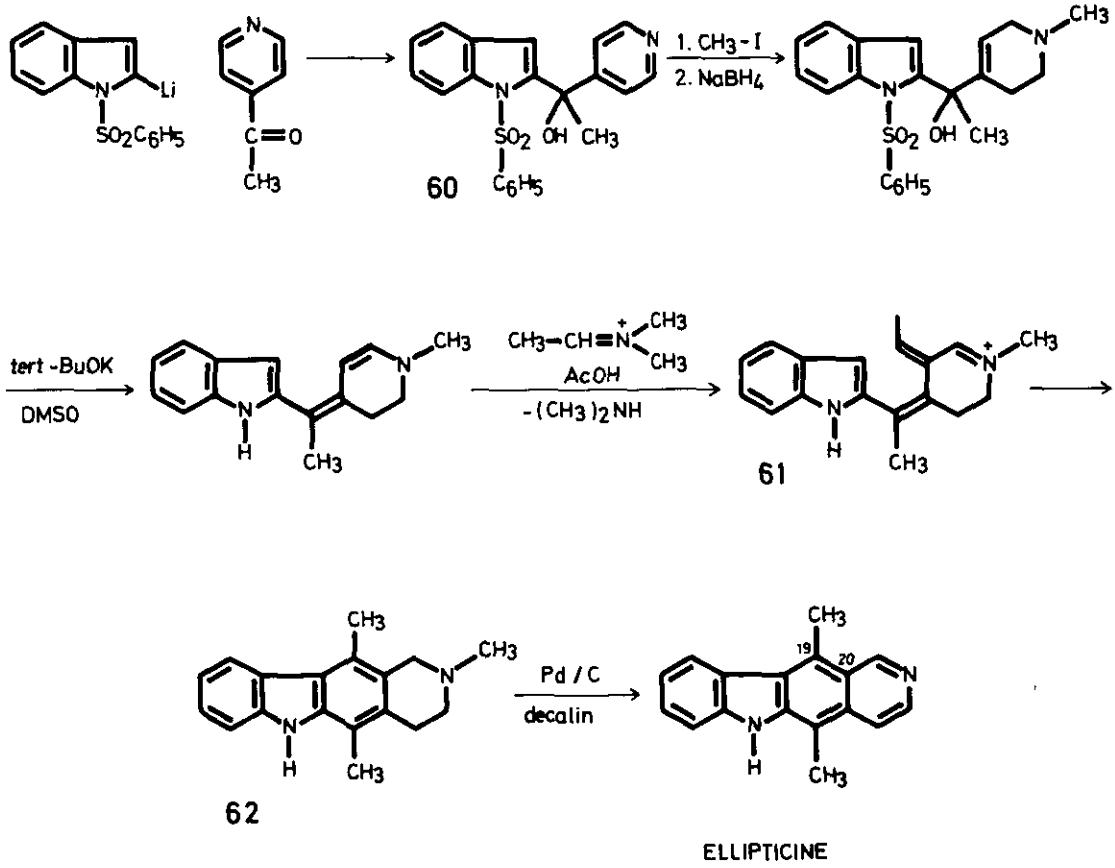
This strategy has been used in establishing a new synthesis of geissoschizine[47] and the first total synthesis of alkaloids of the C-mavacurine group[48] from common intermediates. Condensation of amino diester 53 with *erythro*-2-bromo-3-methoxybutyryl chloride gave the bromo amide 54 as a mixture of C-3 epimers. Cyclization of this mixture with sodium hydride followed by hydrolysis and decarboxylation gave a nearly equimolecular mixture of C-20 epimeric lactam esters 55, which were separated, reduced to the C-20 epimeric alcohols 56, and then converted to the nitri-



les 57. From nitrile 57a an entirely stereospecific elimination of methanol was then induced by heating with sodium methoxide in methanol, giving the E-ethylidene-bearing nitrile 58 in 68% yield. The use of the isomer 57b was shown to give the same product 58, which was converted to geissoschizine.[47]

Similarly, elimination of methanol from the mixture of alcohols 56 by heating with sodium ethoxide in ethanol gave in 79% yield the E-ethylidene-bearing alcohol 59 (again each C-20 epimer was separately found to give only this product),[47] from which the first total synthesis of C-mavacurine, *via* epipleiocarpamine and normavacurine (epipleiocarpaminol), together with a total synthesis of ε_2-dihydromavacurine has been reported.[48]

Finally, it is worth commenting upon a biomimetic synthesis of ellipticine effected by Husson *et al.*[49] This alkaloid lacks the 20-ethylidene substituent since the exocyclic 19,20-double bond[1] has been included into the ring C through cyclization of a conjugated iminium salt. The synthesis implies preparation of a conjugated, ethylidene-bearing iminium salt which spontaneously cyclizes upon the indo-

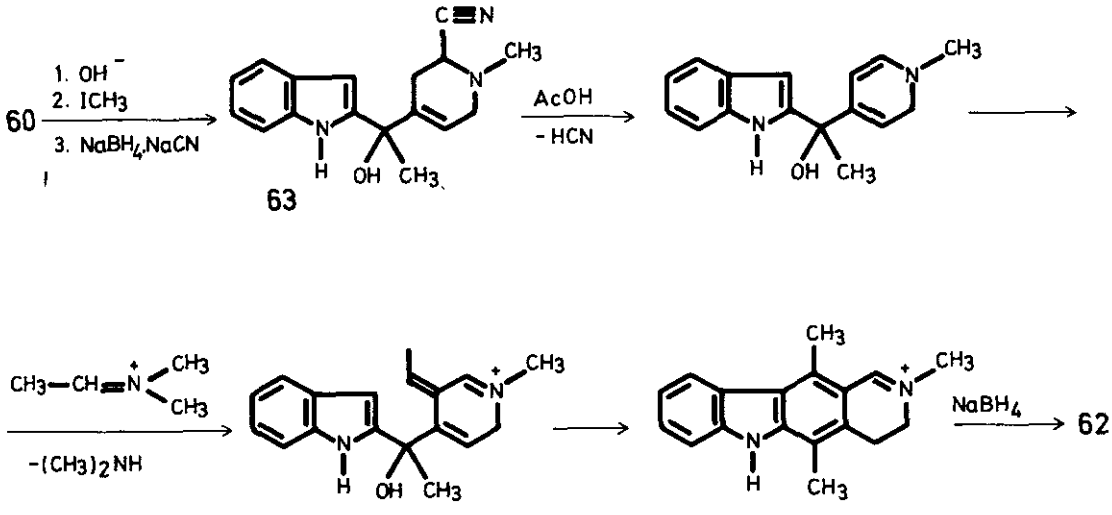


le nucleus.

The ethylidene substituent was introduced by reaction between an appropriate dienamine and the Mannich reagent prepared from acetaldehyde and dimethylamine. The required dienamine was obtained as a mixture of isomers from carbinol 60 in a three-step sequence as illustrated in the above Scheme.

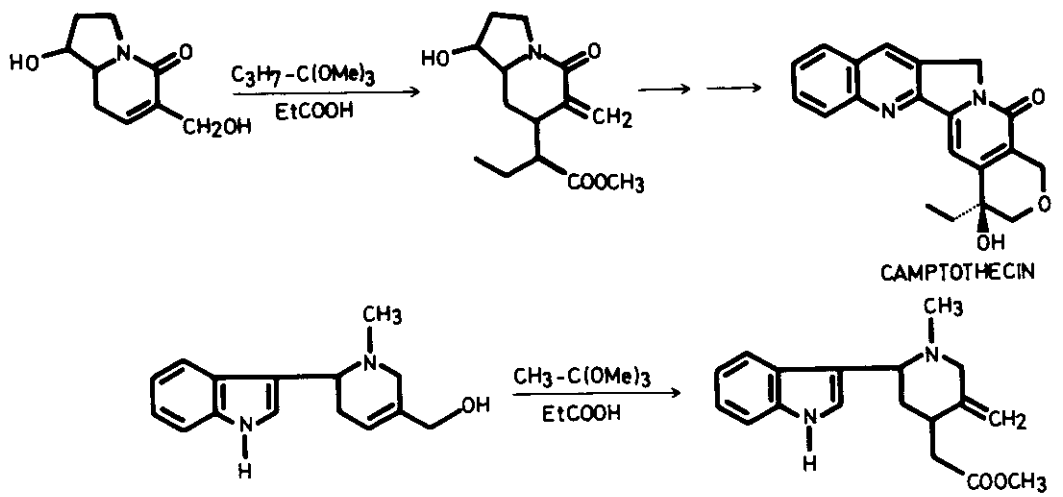
After electrophilic attack of the Mannich reagent, an elimination of dimethylamine occurs to give the intermediate iminium salt 61, whose cyclization led to *N*-methyltetrahydroellipticine (62).

The same compound 62 was obtained in 24% yield by a similar Mannich reaction from 2-cyanotetrahydropyridine 63, followed by sodium borohydride reduction.

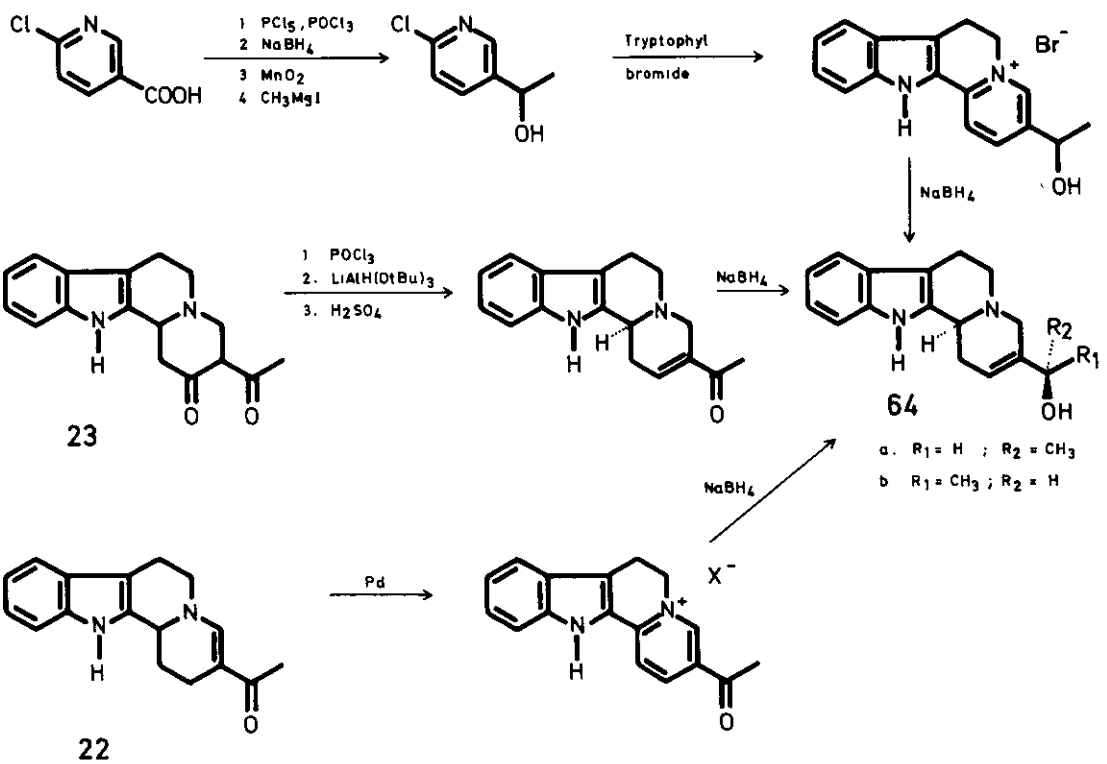


5. CLAISEN REARRANGEMENT

The [3,3]-sigmatropic rearrangement of allyl vinyl ethers, known as the Claisen rearrangement,[50] has been frequently employed in alkaloid synthesis.[51] Thus, the Claisen rearrangement has been effectively utilized in the total synthesis of the *Aspidosperma* alkaloid tabersonine[42] as well as to introduce an exocyclic methylene substituent at the 3-position of the piperidine ring in a synthesis of camptothecin[52] and in the context of synthetic approaches to ervitsine.[53]

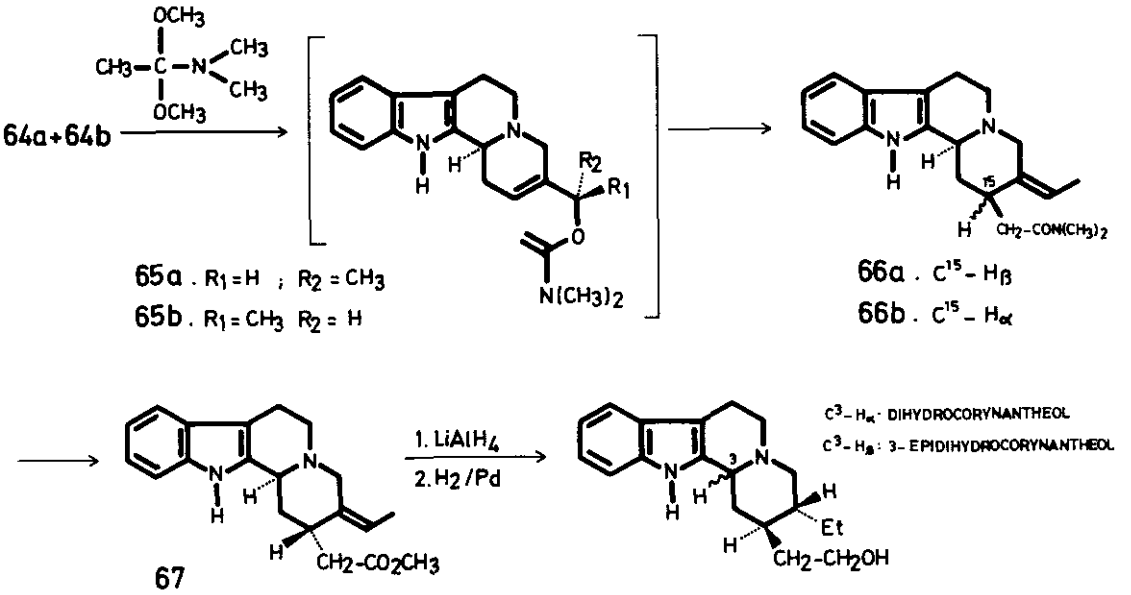


This reaction allows to obtain 3-ethylidenepiperidines bearing a functionalized two carbon chain at the 4-position. In this context, it has been used as a key step in a synthesis of dihydro- and 3-epidihydrocorynantheol in which the 20-ethyl substituent was formed by catalytic hydrogenation of a 2-ethylidene group.[54] The required allylic alcohols 64 were obtained in six steps from 6-chloronicotinic acid. Subsequently, the preparation of the same diastereomeric mixture of alcohols 64 by

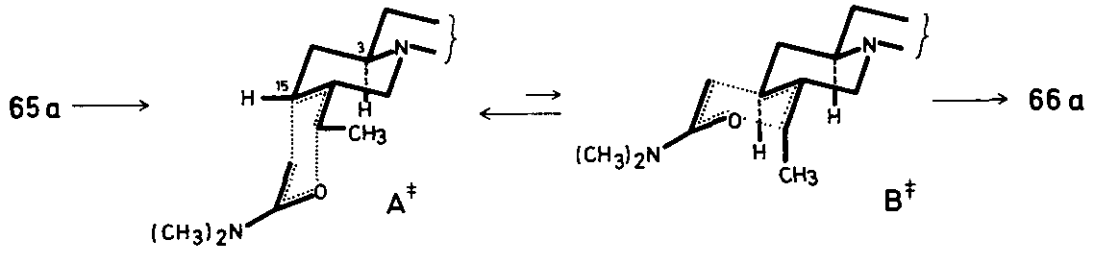


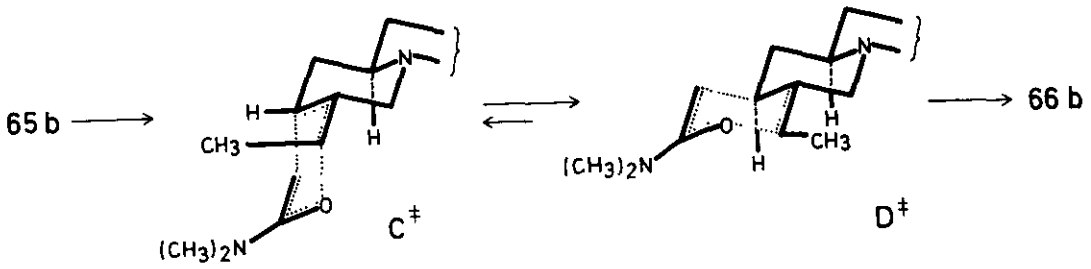
two alternative sequences, from 3-acetyl-4-piperidone 23[32,55] and from 3-acetyl-2-piperideine 22,[30] has been described.

When the mixture of alcohols 64a and 64b was subjected to the Claisen rearrangement employing the technique of Eschenmoser,[56] amides 66a and 66b were obtained.[51,54] The method involves heating an allylic alcohol with dimethylacetamide dimethyl acetal to give the required vinyl ether 65, which rearranges *in situ* to the γ,δ-unsaturated amide 66. Alkaline hydrolysis of 66 followed by esterification afforded 67 which, by hydride and catalytic reduction, provides a mixture of dihydrocorynantheol and its C^3-epimer.

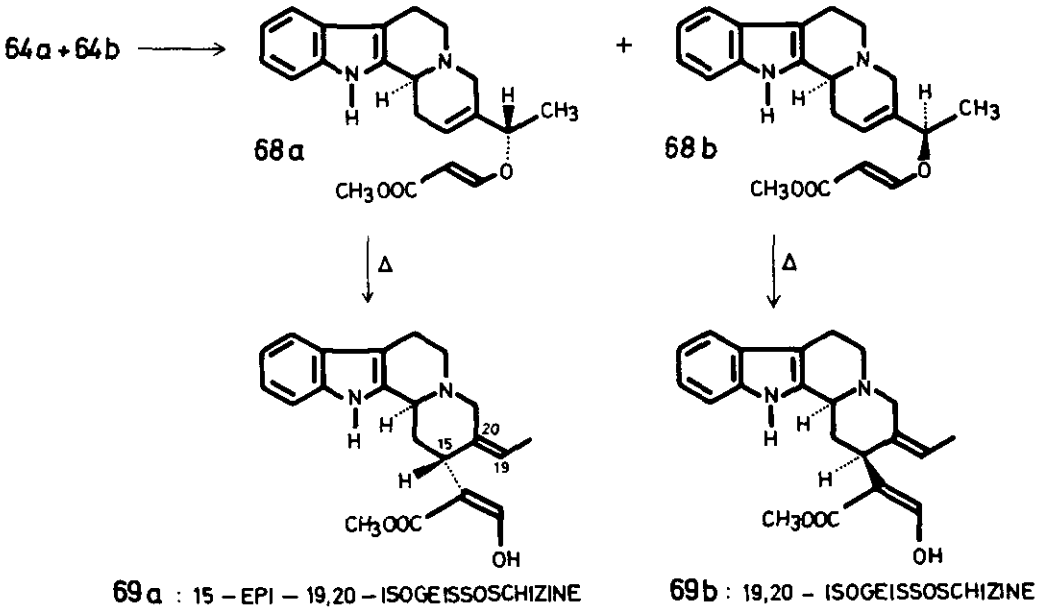


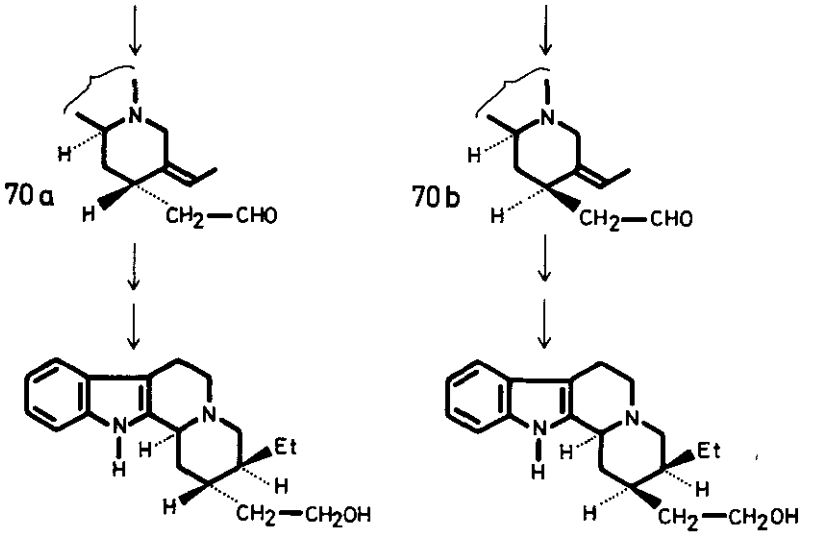
The stereoselectivity in the rearrangement of the above alcohols 64 is high. The possible transition states favor the presence of an equatorial methyl group and a chairlike conformation of the piperidine ring. Thus, transition states $A^{\neq}$ and $D^{\neq}$ are favored over $B^{\neq}$ (which would have led to the correct stereochemistry in geissoschizine) and $C^{\neq}$, respectively, in order to avoid the pseudo 1,3-diaxial interaction between methyl and dimethylamino groups.



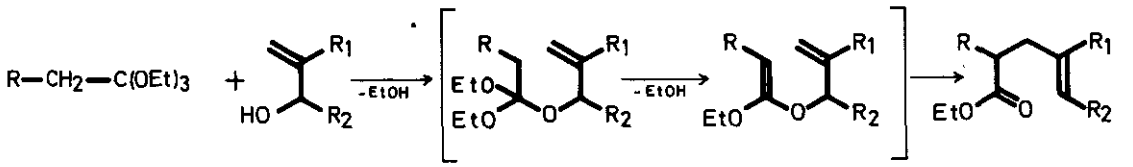


The above results make evident that the correct E-olefin stereochemistry for the ethylidene group cannot be attained by Claisen rearrangement. In this context, Winterfeldt[55] has proved that the exocyclic, Z-configurated double bond of 19,20-isogeissoschizine can be introduced *via* a highly stereoselective and stereospecific Claisen rearrangement. Treatment of the diastereomeric mixture of alcohols 64 with methyl propiolate gave a mixture of enol ethers 68, which undergo a thermal sigmatropic rearrangement to 19,20-isogeissoschizines 69a and 69b, *via* transition states similar to those above depicted. The configuration of the products was proved by correlation to natural products through a three-step sequence involving an hydrolysis-decarboxylation, followed by sodium borohydride and catalytic reductions.
The sterically pure aldehydes 70, as well as the corresponding alcohols, populate the *trans*-quinolizidine conformation exclusively, thus proving that the unnatural double bond configuration is compatible with both C-3 and C-15 configuration combinations.[57]

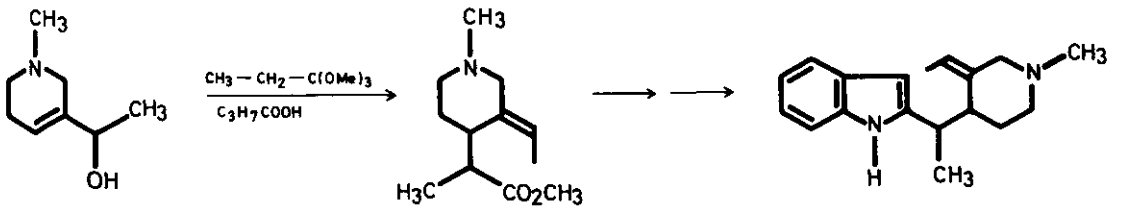




The orthoester version of the Claisen rearrangement[58] consists in heating an allylic alcohol with excess orthoester in the presence of a trace of weak acid. A mixed orthoester is first formed and loses ethanol to give a ketene acetal (vinyl ether) which rearranges to an olefinic ester.



By this procedure, 3-ethylidenepiperidine 71 was obtained as a mixture of diastereomers in a biomimetic synthesis of ellipticine.[59] After Fischer indole synthesis, cyclization to the required tetracyclic ring system was achieved by electrophilic attack of a conjugated iminium salt upon the 3-position of the indole ring.



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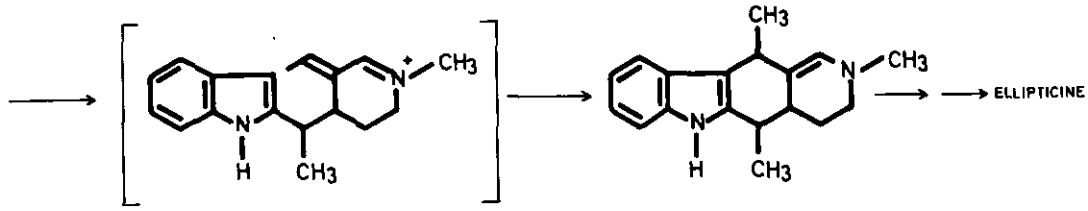
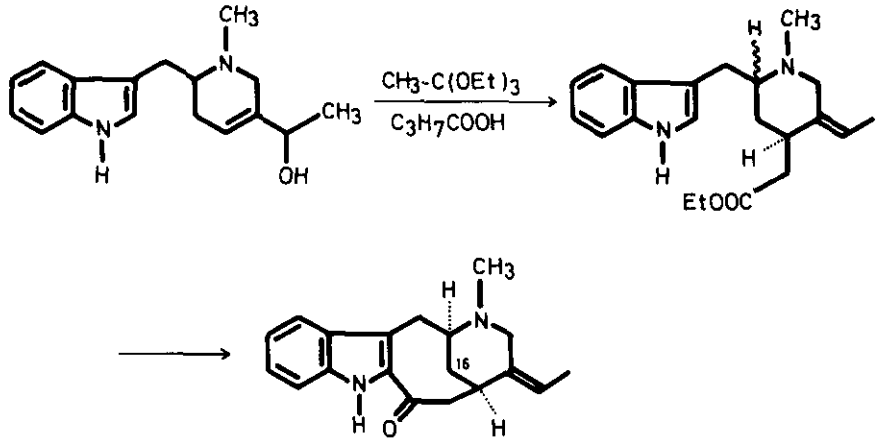
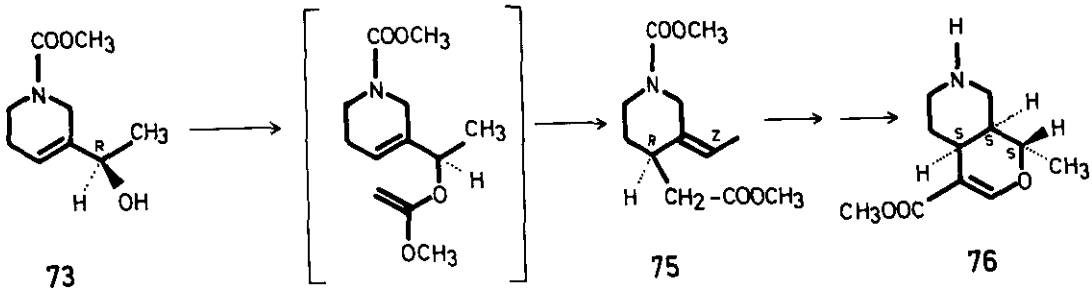


The orthoester Claisen rearrangement has been also utilized[60] to produce the ethylidene group of 16-demethoxycarbonylvobasine 72. This synthesis takes advantage of the resulting ethyl acetate chain at the 4-position of the piperidine ring for the final cyclization to the 2-acylindole system.



72

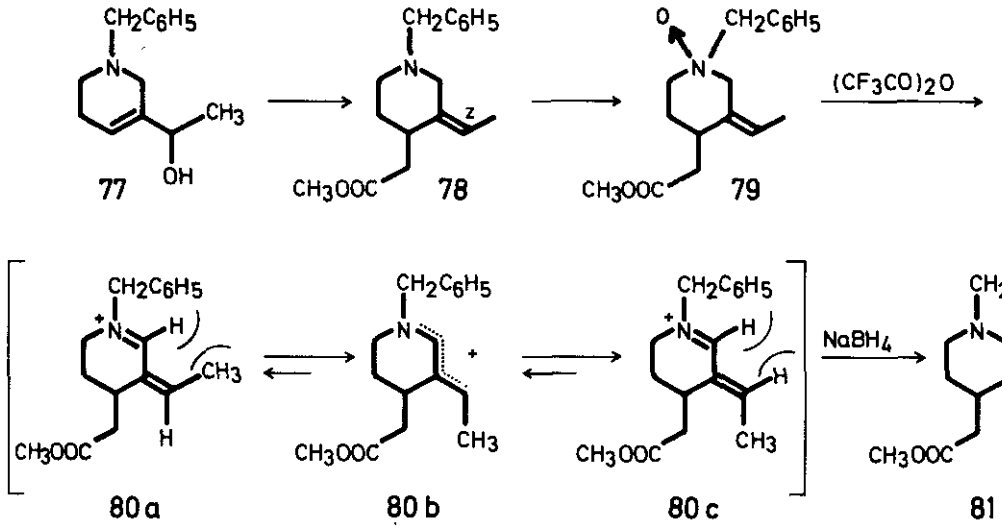
The orthoester Claisen rearrangement constitutes the key step of an asymmetric and stereospecific synthesis of the bicyclic amino ester 76, an important intermediate in the synthesis of natural *allo*-heteroyohimbine alkaloids.[61] The required R-ester 75, bearing a Z-ethylidene group, was prepared from the allylic alcohol 73 by a [3,3]-sigmatropic rearrangement of the intermediate pyro ester 74.



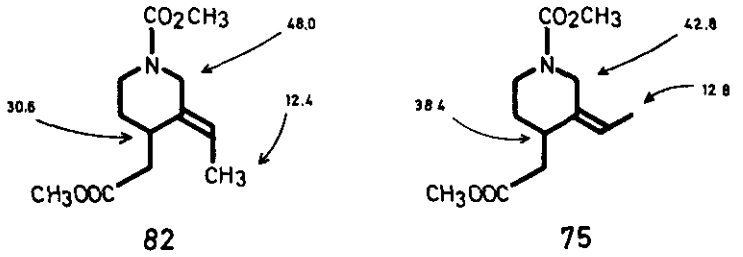
73 74 75 76

The concerted mechanism that operates in this reaction permits the transfer of chirality from the side chain to C-4, through the most stable chair-like transition state having an equatorial methyl group.

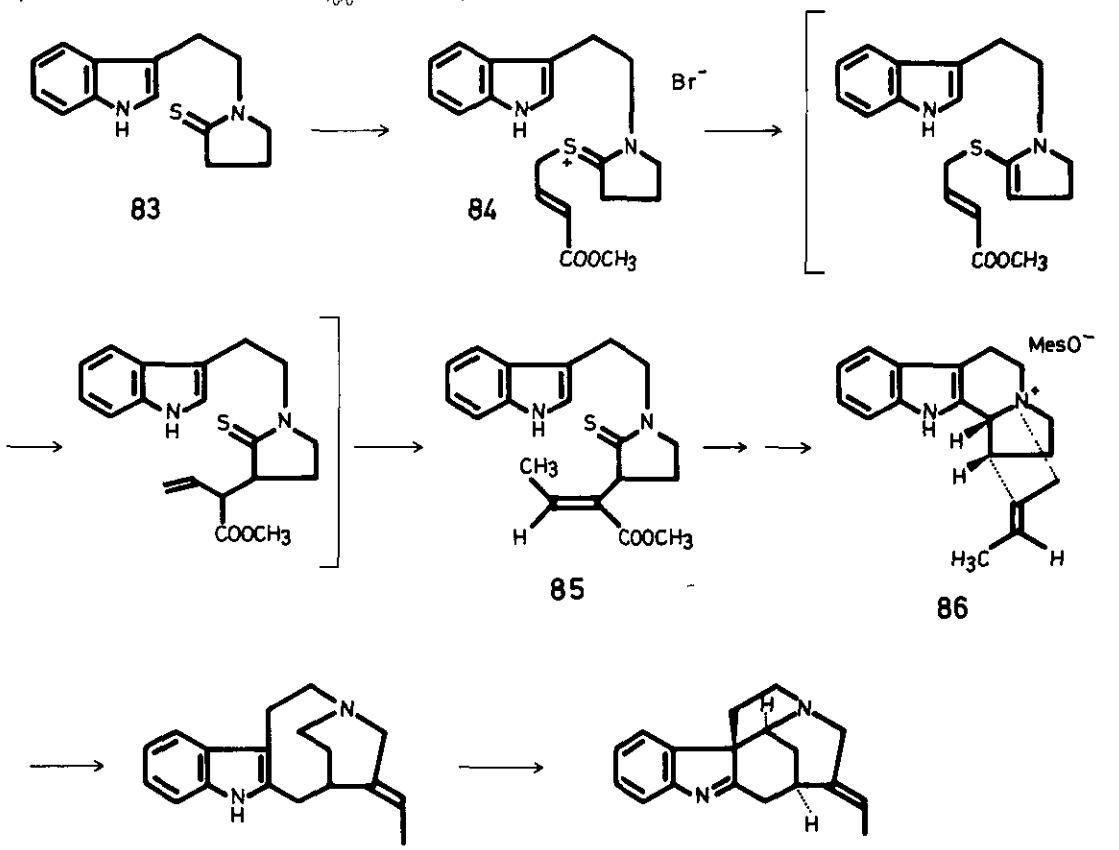
The isomerization of the Z-double bond to the natural E-configuration has been effected[61] on methyl 1-benzyl-3-ethylidenepiperidine-4-acetate (78). The inversion sequence is based on consideration of the difference in steric nonbonding interactions between the C-2 hydrogen and either the allylic methyl in 80a or the vinyl hydrogen in 80c. The racemic Z-olefinic ester 78, prepared from the allylic alcohol 77, was converted to N-oxide 79 and then subjected to the modified Polonovski reaction[11] with trifluoroacetic anhydride to give the conjugated Z-iminium cation 80a, which spontaneously rearranged to the more stable E-isomer 80c. Quenching with sodium borohydride gave the E-olefinic ester 81.



The exchange of N-benzyl group for N-carbomethoxy furnished the E-isomer 82, which was compared with 75 by ^{13}C-nmr spectroscopy.[61]



Recently, a simple and selective route to the *Strychnos*-type alkaloids containing a 19,20-double bond with the requisite stereochemistry has been developed employing the *thio-Claisen rearrangement*.[62] Thio lactam 83 was allowed to react with methyl γ-bromocrotonate to give the sulfonium salt 84, which was treated with sodium methoxide to induce concurrent ketene thioaminoacetal formation, [3,3]-sigmatropic rearrangement, and stereoselective double bond migration, affording the α,β-unsaturated *E*-ester 85 in 83% yield.



83 84 85 86

87 88

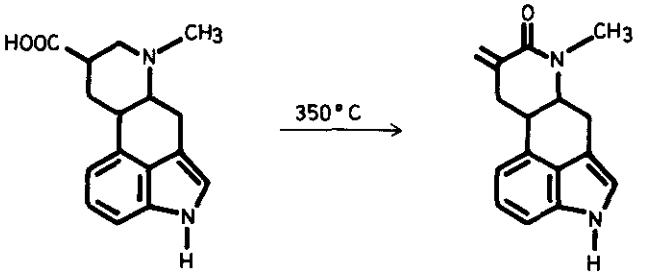
After cyclization of the thio lactam 85 with phosphoryl chloride, sodium borohydride and diisobutylaluminum hydride reductions, methanesulfonation of the resulting allylic alcohol, and spontaneous intramolecular alkylation, the pentacyclic quaternary base 86 was obtained. Treatment of 86 with sodium metal in liquid ammonia furnished the known nine-membered amine 87, from which the synthesis of the saturated *Strychnos* alkaloids tubifoline, tubifolidine, and condyfoline has been already described.[63]

Finally, when the *N*-oxide of this amine was subjected to the modified Polonovski reaction conditions[11] the only isolated product possessed the *Strychnos* framework

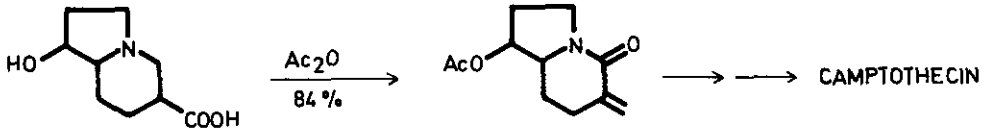
§§ with the requisite E-ethylidene configuration.

6. α-METHYLENELACTAM REARRANGEMENT

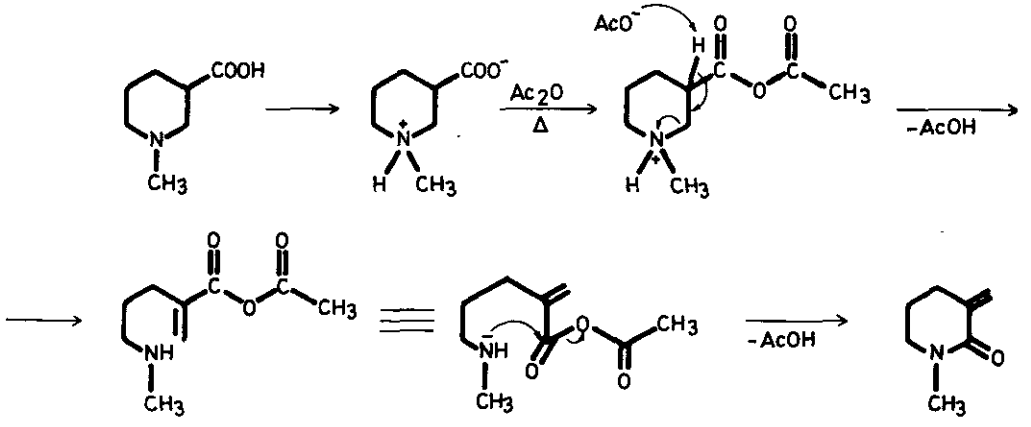
Studies about the rearrangement of cyclic β-amino acids to α-methylenelactams started with a fortuitous observation: an attempt to purify dihydrolysergic acid by sublimation led to dihydrolysergic lactam.[64]



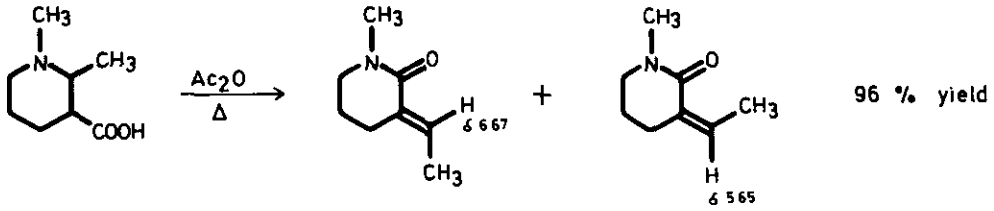
Subsequently, this rearrangement has been effected in good yields by heating with acetic anhydride.[65] Under these conditions it appears to be quite general and occurs with facility to a single product in the six-membered ring systems. Recognition of the synthetic potential of this reaction was achieved when the rearrangement was employed as a key step in the synthesis of camptothecin and structural analogues of this alkaloid.[52]



The rearrangement has been shown[66] to proceed *via* the zwitterion of the amino acid through the protonated amine-mixed anhydride which undergoes β-elimination. Recyclization takes place by nucleophilic attack of the secondary amine on the mixed anhydride function.

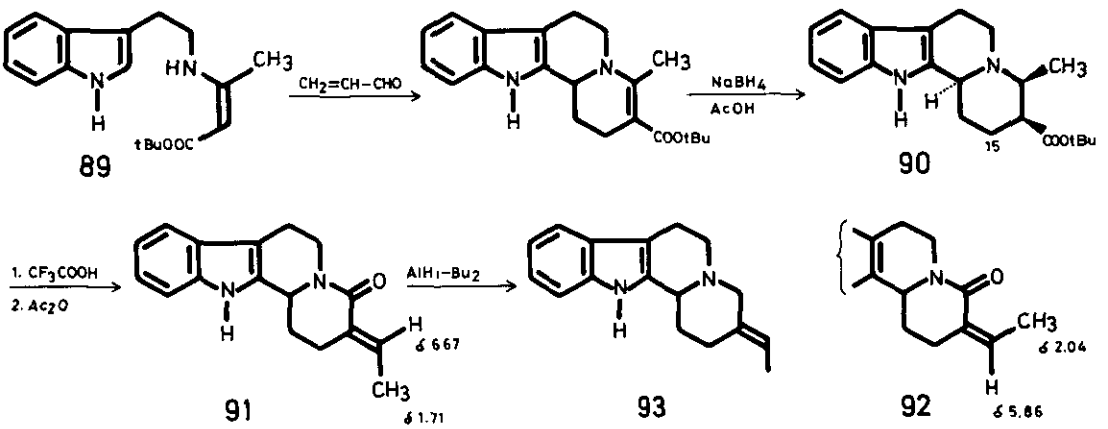


The rearrangement is compatible with a variety of substituents on nitrogen and the α-positions to the nitrogen. When 2-methylnipecotic acid derivatives were treated under the usual reaction conditions, 3-ethylidene-2-piperidones were obtained and, therefore, the rearrangement is potentially useful to incorporate the ethylidene substituent present in some indole alkaloids.

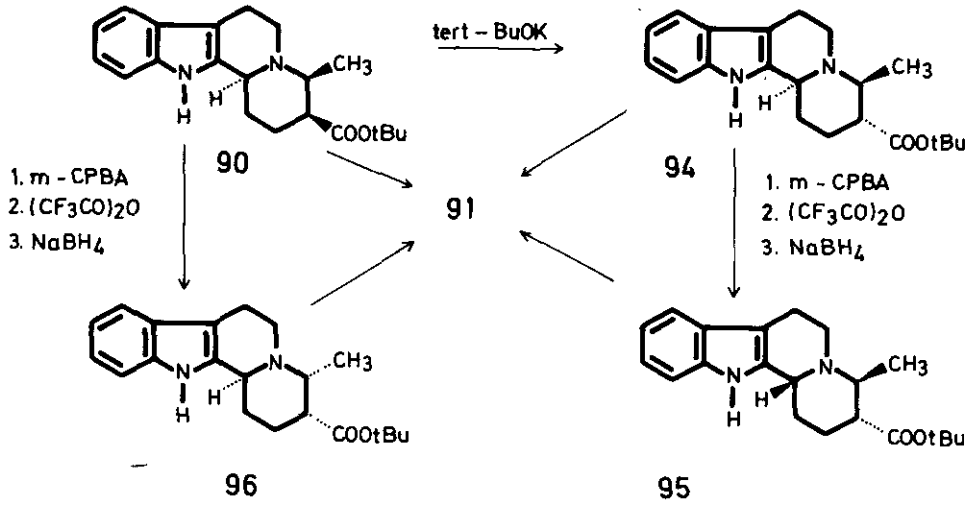


Assignment of E- and Z-configurations are based on the chemical shift of the olefinic proton, which is farther downfield (δ6.67) in the E-isomer (proton *cis* to amide carbonyl) as compared to the Z one (δ5.65).[66]

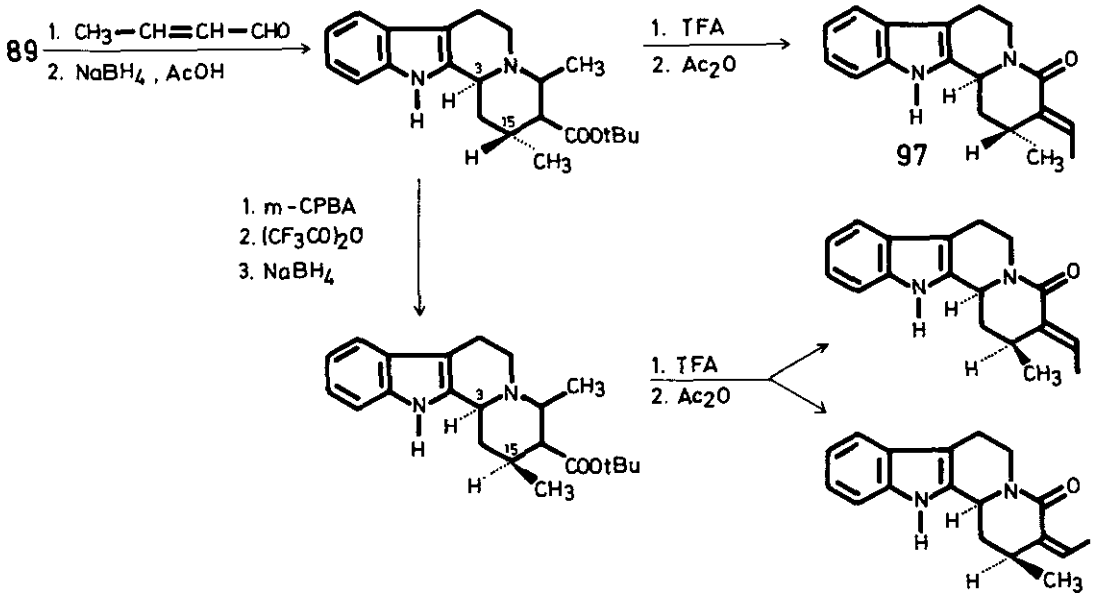
This reaction has been utilized in the synthesis of some ethylidene-containing alkaloids and related structures.[57] Thus, in 1974 it was applied to the synthesis of a tetracyclic compound[67,68] that several years later was found to be the alkaloid deplancheine.[36] When quinolizidine *tert*-butyl ester **90**, prepared from enamine **89** and acrolein as outlined in the following Scheme, was treated with trifluoroacetic acid, and the resulting β-amino acid was heated in the presence of acetic anhydride, an isomeric mixture of E- (62% yield) and Z-(7% yield) ethylidene lactams (**91** and **92**, respectively) was obtained. Diisobutylaluminum hydride reduction of the major lactam **91** afforded the base **93** (deplancheine).



From ester 89, stereoisomeric indolo [2,3-*a*]quinolizidines 94, 95, and 96 were prepared in a stereoselective manner, and then treated according to the methylene-lactam rearrangement. In all cases the same lactam 91 with an exocyclic, *E*-configurated double bond was obtained.[67,68] Therefore, this rearrangement provides a highly stereoselective route to the natural ethylidene configuration, at least in C-15 unsubstituted[1] indolo[2,3-*a*]quinolizidines.

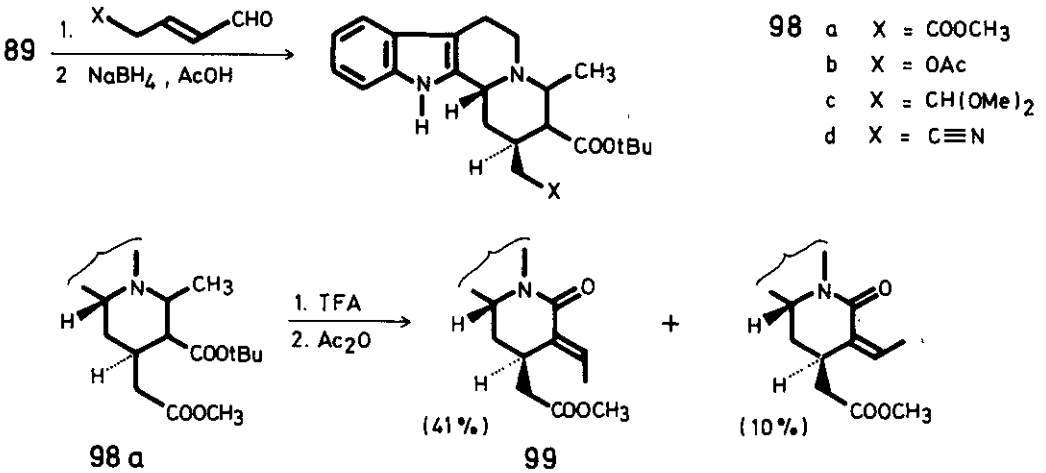


In order to study the stereochemical course of the methylenelactam rearrangement, stereoisomeric 15-methyl-substituted indolo [2,3-a]quinolizidines were prepared as in the above C-15 unsubstituted series, *via* a Pictet-Spengler cyclization followed by sodium borohydride reduction. From the C-3/C-15 *trans* series, *E*-ethylidene lac-



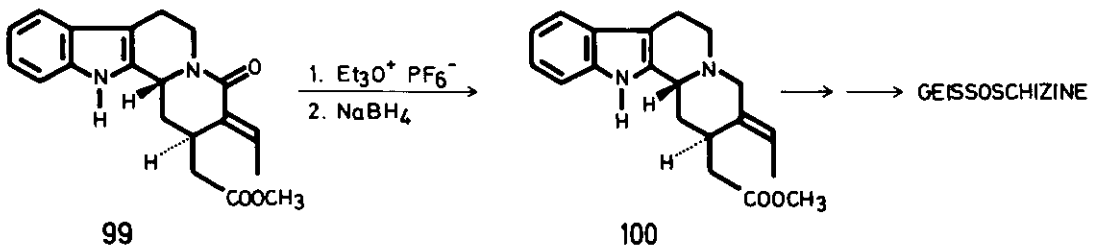
tam 97 was isolated as the only rearranged product (23% yield), whereas from the C-3/C-15 *cis*-series a mixture (20% yield) of the E and Z-ethylidene lactams was obtained.[68]

Similarly, 15-methoxycarbonylmethyl-substituted indoloquinolizidines having *trans*-oriented hydrogens at C-3 and C-15 are shown to rearrange in high stereoselectivity into unsaturated lactams with an E-configurated ethylidene group.[69] Compounds 98a-c were prepared as in the above C-15 methyl series, whereas 98d was obtained in three steps from 98b or 98c.



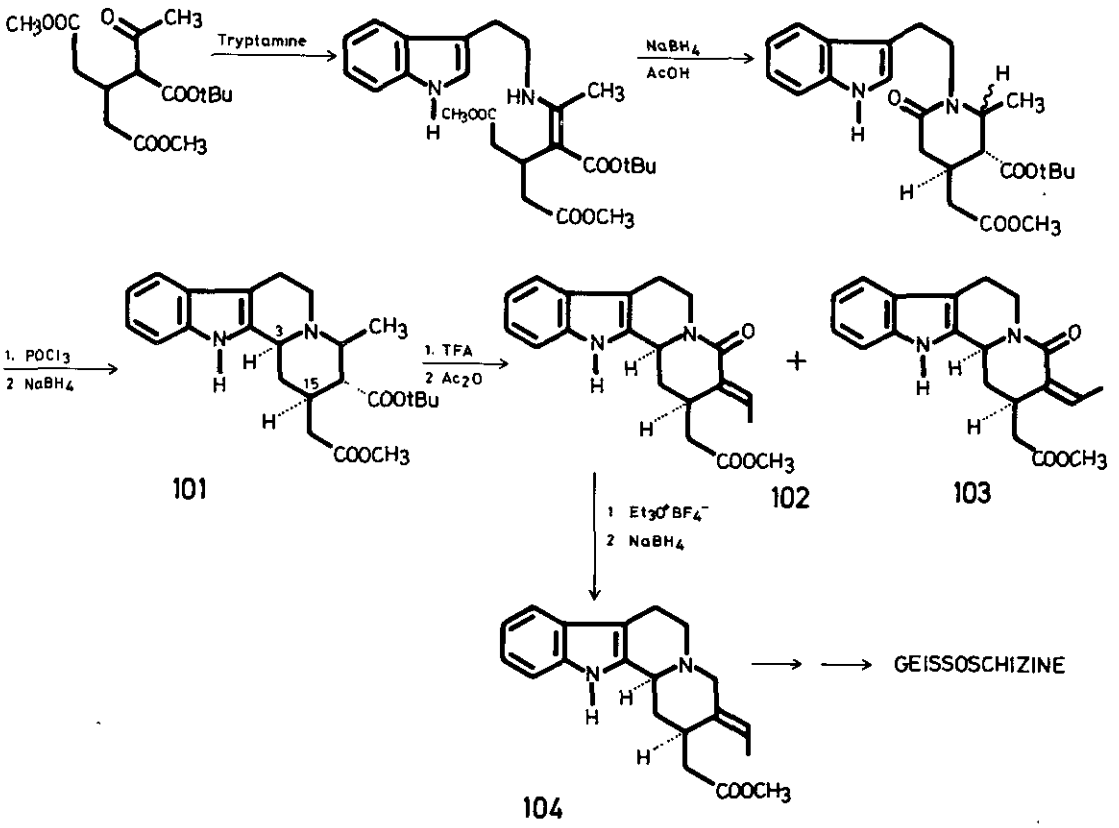
On successive treatment with trifluoroacetic acid and acetic anhydride, the *trans*-isomer 98a gave rise to both double bond configurations although, again, the natural one turned out to be the main product. In a similar fashion, an E-ethylidene lactam was the major product (37% yield) from rearrangement of nitrile 98d.

The lactam 99 was reduced[69] through its imidate salt to the *trans*-ester 100, which constitutes an intermediate in the first total synthesis of geissoschizine.[28]

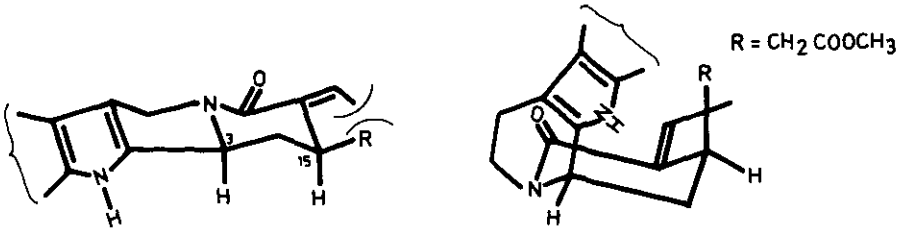


Winterfeldt *et al.* have reported a stereoselective total synthesis of geissoschizine, in which the methylenelactam rearrangement may be regarded as the key reaction.[40] The required 15-methoxycarbonylmethyl-substituted indolo[2,3-*a*]quinolizi-

dine 101, with *cis*-hydrogens at C-3 and C-15, was prepared by Bischler-Napieralski cyclization, as outlined in the following Scheme. Acid hydrolysis of the *tert*-butyl ester and subsequent heating of the intermediate β-amino acid with acetic anhydride afforded a diastereomeric mixture of E-(28% yield) and Z- (12% yield) ethylidene lactams, which could be separated. On treatment with Ac_2O-TFA, the Z-isomer 103 was equilibrated in 57% yield to a 2:1 mixture of 102 and 103, respectively. Reduction of the amide carbonyl group of the E-isomer 102, through the corresponding imidate, led to the ester 104, a known synthetic precursor of geissoschizine.[28]

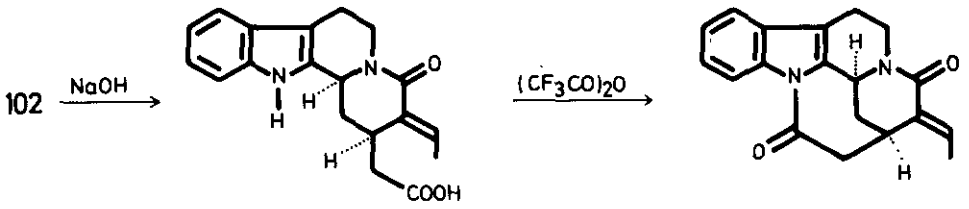


In an attempt to avoid the above separation step, the possibilities of Z-E isomerization were studied.[70,71] Whereas in the case of C-15 unsubstituted lactams such as 91 only the desired E-double bond configuration is formed under kinetically controlled conditions, in the case of the C-15 substituted ones, especially in the C-3/C-15 *cis*-series, competitive formation of the Z-isomer takes place. This fact can be accounted for in terms of the steric interaction between CH_3 and R groups in the most stable conformation 102-A.



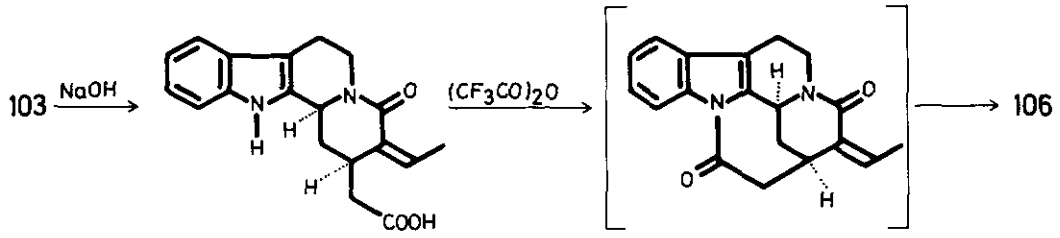
102 - A 102 - B

This interaction would be minimized in the conformation 102-B, which is not populated unless forcefully so by bonding between R and the indole N-atom. This was achieved[70,71] in 82% overall yield by saponification followed by treatment of the resulting lactam acid 105 with trifluoroacetic anhydride.



105 106

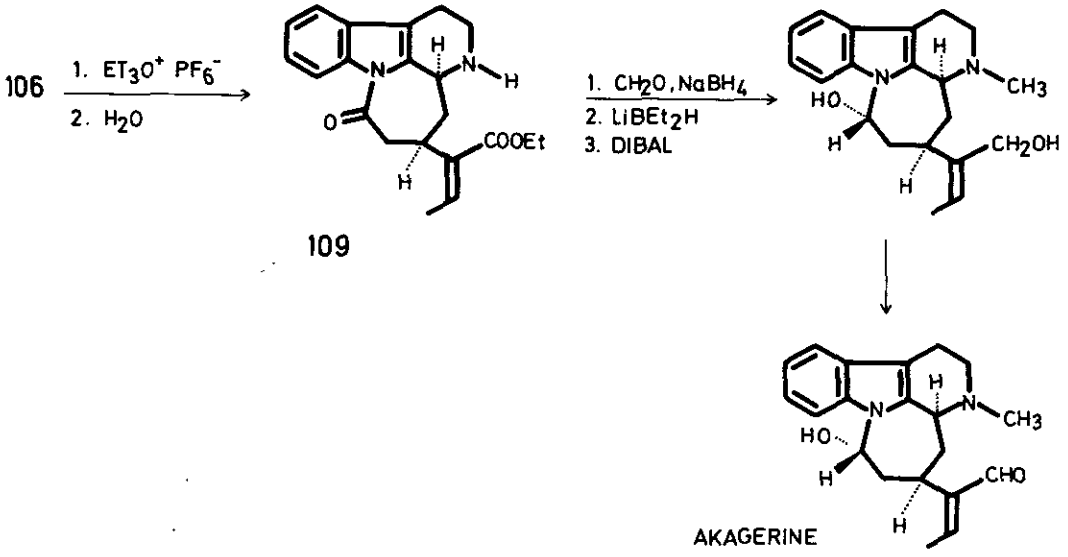
The same pentacyclic dilactam 106, having the natural E-configuration, was obtained in 83% yield from the Z-isomer 103. This ring closure is in fact accompanied by a spontaneous isomerization of the double bond. However, a closer inspection of the cyclization of acid 107 actually did reveal the formation of two lactams, 106 and 108, *after short reaction times*. Since the Z-dilactam 108 on further treatment was cleanly converted into the E-isomer 106, the latter can be safely identified as the product of thermodynamic control in this cyclization reaction.[71]



107 108

Regioselective ring opening of the dilactam 106 with sodium methoxide in methanol led to the desired lactam ester 102 in near quantitative yield.[70] In this way the synthesis becomes stereoconvergent through the intermediate 106. Thus, the mixture of ethylidene lactams 102 and 103 was hydrolyzed without separation to a mixture of lactam acids 105 and 107, which then cyclized to the single dilactam 106.[70]

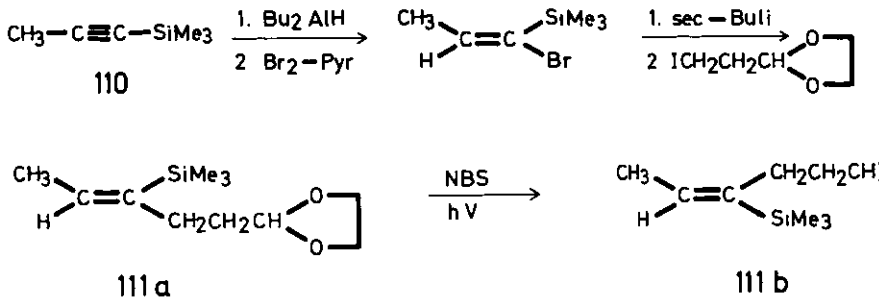
From the pentacyclic dilactam 106 the synthesis of akagerine, a new ethylidene bearing indole alkaloid, has been reported.[71] Ring D was opened in a selective and stereospecific manner by reaction with the Meerwein-reagent followed by treatment with water to give the ester 109. After methylation of the secondary nitrogen atom and reduction of the lactam and ester carbonyl groups a diol was obtained, whose oxidation with nickel peroxide gave rise to akagerine.



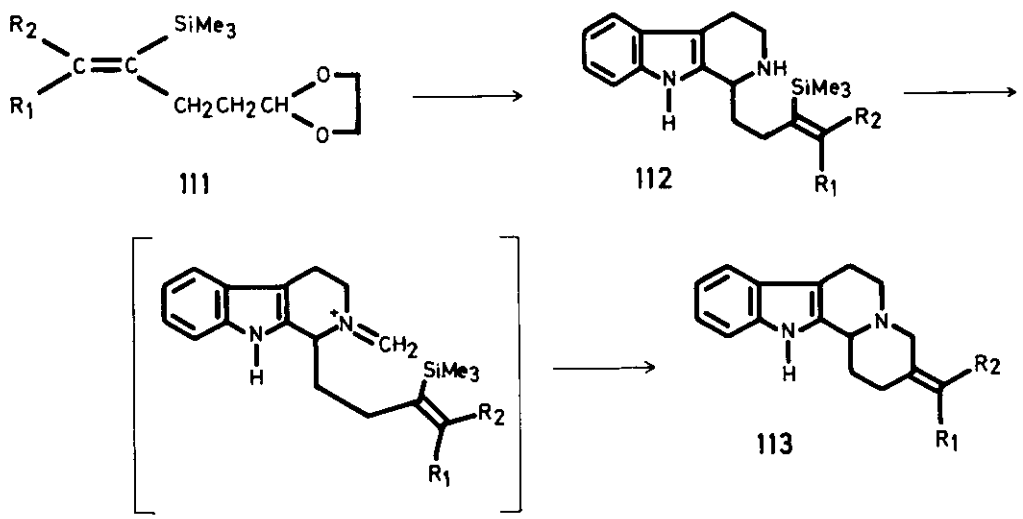
7. IMINIUM ION-VINYLSILANE CYCLIZATIONS

A stereocontrolled synthesis of exocyclic trisubstituted double bonds by stereospecific iminium ion-vinylsilane cyclization has been recently reported.[72] Since a variety of methods are available for the stereoselective synthesis of vinylsilanes,[73] this methodology potentially provides a general stereocontrolled route to 3-alkylidene azabicyclics. It has been successfully applied to the synthesis of ethylideneindolo[2,3-a]quinolizidines 113a and 113b, the latter being the indole alkaloid deplancheine.[36]

The required Z-vinylsilane 111a was prepared in 61% overall yield from the commercially available 1-(trimethylsilyl)propyne 110 as shown in the following Scheme, whereas the more stable E-isomer 111b was obtained by bromide catalyzed isomerization of 111a.



Acid hydrolysis of silyl acetals 111a and 111b followed by Pictet-Spengler condensation of the resulting aldehydes with tryptamine hydrochloride afforded the nearly isomerically pure tetrahydro-β-carbolines 112a and 112b, respectively. The reaction of these Z- and E-trisubstituted vinylsilanes with paraformaldehyde and acid proceeded with >98% retention of configuration to give indoloquinolizidines 113a and 113b, respectively, in excellent yield. In this way, isomerically pure deplancheine 113b was prepared in 26% overall yield from 110. Since the iminium ion-vinylsilane cyclization of both Z- and E-isomers occurs with virtually complete retention of configuration, this reaction provides a convenient route to either exocyclic trisubstituted alkene isomer.



a. R_1 = H ; R_2 = CH_3

b. R_1 = CH_3 ; R_2 = H

Addendum. Recently, a new synthesis of deplancheine has been described.[74] The ethylidene substituent was formed with nearly 100% yield and full stereoselectivity by toluene-tricarbonyl-chrome promoted 1,4-hydrogen addition on 3-vinyl-1,4,6,7,12,12b-hexahydroindolo[2,3-a]quinolizine.

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