SYNTHESIS OF CORYNANTHE ALKALOIDS CORYNANTHEINE, HIRSUTEINE, AND THE ISOSITSIRIKINES*

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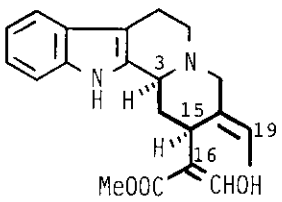
Abstract--Total syntheses of corynanthe alkaloids including eight possible stereoisomers of isositsirikines along with corynantheine and hirsuteine according to two different approaches are described, thereby unambiguously solved the pending problems on the stereochemistry of these alkaloids.

1 GENERAL INFORMATION

The corynanthe-type alkaloids are of particular interest to the synthetic chemist for various reasons. First of all they represent a quite large subgroup of the indole alkaloids which additionally is of special interest from the biogenetic point of view,[1,2] as they are very early located in the biogenetic sequence (Scheme 1). Compounds like geissoschizine **1** and ajmalicine **2** still very nicely reflect the combination of tryptamine or tryptophan with the terpenoid C-10 unit secologanin (**3**). A more detailed discussion on the relationship between the configuration and conformation of crucial biogenetic precursors and the design of key intermediates for this synthetic project as well as the stereoselectivity and stereospecificity of their decisive transformations will be postponed, however, to a later stage after the outcome of these processes has been revealed.



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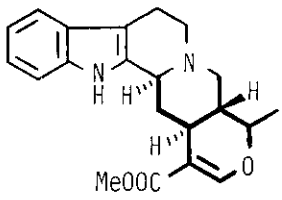

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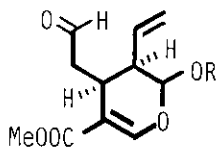

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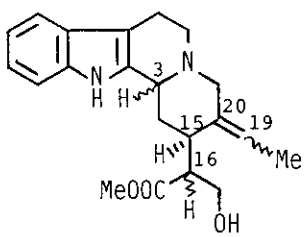
Scheme 1

Last not least a very characteristic feature of this group of alkaloids including isositsirikines, as summarized in Table 1, is the existence of a wide variety of stereoisomers[3] with changing configurations at sp^3 centres (carbon atoms 3, 15 and 16) and sp^2 centres (exocyclic double bond). As this particular double bond is exocyclic and additionally trisubstituted, these details do represent quite a challenge from the view point of stereoselective synthesis, particularly of eight possible stereoisomers of isositsirikines.

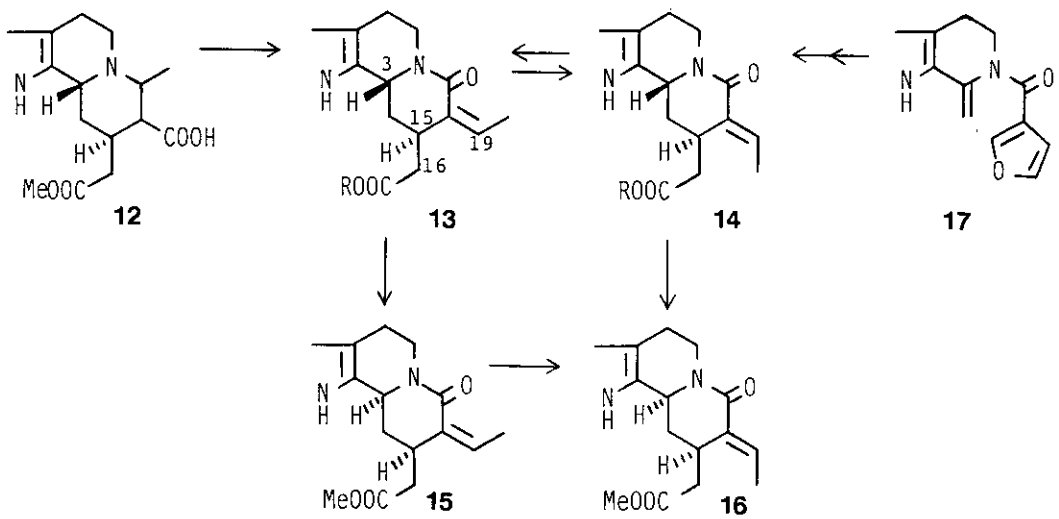
Table 1. The Isositsirikines (**4-11**)



3-H	16-H	19-Me	Alkaloids	
α	β	E	Isositsirikine----------	**4**
α	α	E	16-Epi-isositsirikine-------	**5**
β	β	E	Rhazimanine (proposed)------	**6**
β	α	E	Bhimberine (proposed)-------	**7**
α	β	Z	16R-19,20-Z-isositsirikine--	**8**
α	α	Z	16-Epi-Z-isositsirikine-----	**9**
β	β	Z	unknown----------	**10**
β	α	Z	unknown----------	**11**

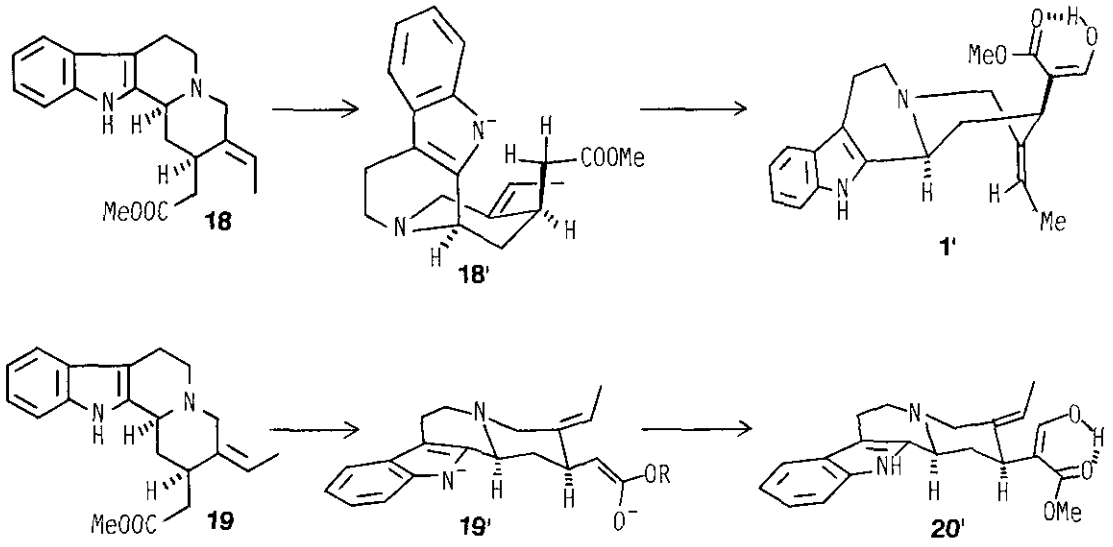
Suffice it to say that at the beginning of synthetic efforts in this direction no stereoselective method was available to solve this problem in the quinolizidine series. In the meantime particularly owing to synthetic efforts aiming at geissoschizine[4~6] this situation has been changed completely as very efficient and reliable techniques have been developed particularly by Overman[7] while the methylene-lactam rearrangement of **12** to **13** developed particularly by our Hannover group[b] proved to be very useful in this field[8,8] (Scheme 2). Recently, an efficient method[9,10] for construction of the stereoisomer **14** has been established by

combination of two interesting reactions which are enamide photocyclization and elimination-addition reaction of furopyridone by the Kobe group.[a] Additionally, the Kobe group has very recently established the useful olefinic isomerization from the stable E-isomer **14** even to the unstable Z-isomer **13** though the Hannover group had already reported[3,4] one-way isomerization of the unstable Z-olefin **13a** to the stable E-olefin **14**. Thus the importance of the two lactams **13** and **14** as key and versatile intermediates in the synthesis of target alkaloids has become clear. It is assumed that the ethylidene-lactams having E- or Z-configuration at the exocyclic double bond would be converted into the respective Z- or E-counterparts, upon olefinic isomerization and additional epimerization at the C-3 position from β to α (**13**→ **15** and **14**→ **16**) would furnish two sets of isomeric lactams depending on the configurations at C-3 and C-19, thereby providing the possibility to synthesize all eight stereoisomers of isositsirikines with respect to C-3, 15, 16, and 19 from either **13** or **14**.



Scheme 2

A systematic preparation of all stereoisomers including those with E- and Z-configurations at the exocyclic double bond accompanied by a detailed investigation of their spectroscopic properties as well as the stereospecificity of their transformations was expected to yield interesting informations not only on the relationship between configuration and conformation of indoloquinolizidines in general but also on the conformation depending stereoselectivity and regioselectivity of stereospecific reactions in this field.



Scheme 3

As was shown by Potier's group[12] and us[13] a few years ago already, geissoshizine **1** having the exocyclic E-double bond populates exclusively in the cis twist-boat conformation **1'** to avoid severe 1,3-strain while the 19Z-geissoschizine isomer **20**, prepared in both groups,[10,14] was shown to behave in the "normal" way strongly preferring conformation **20'** (Scheme 3).

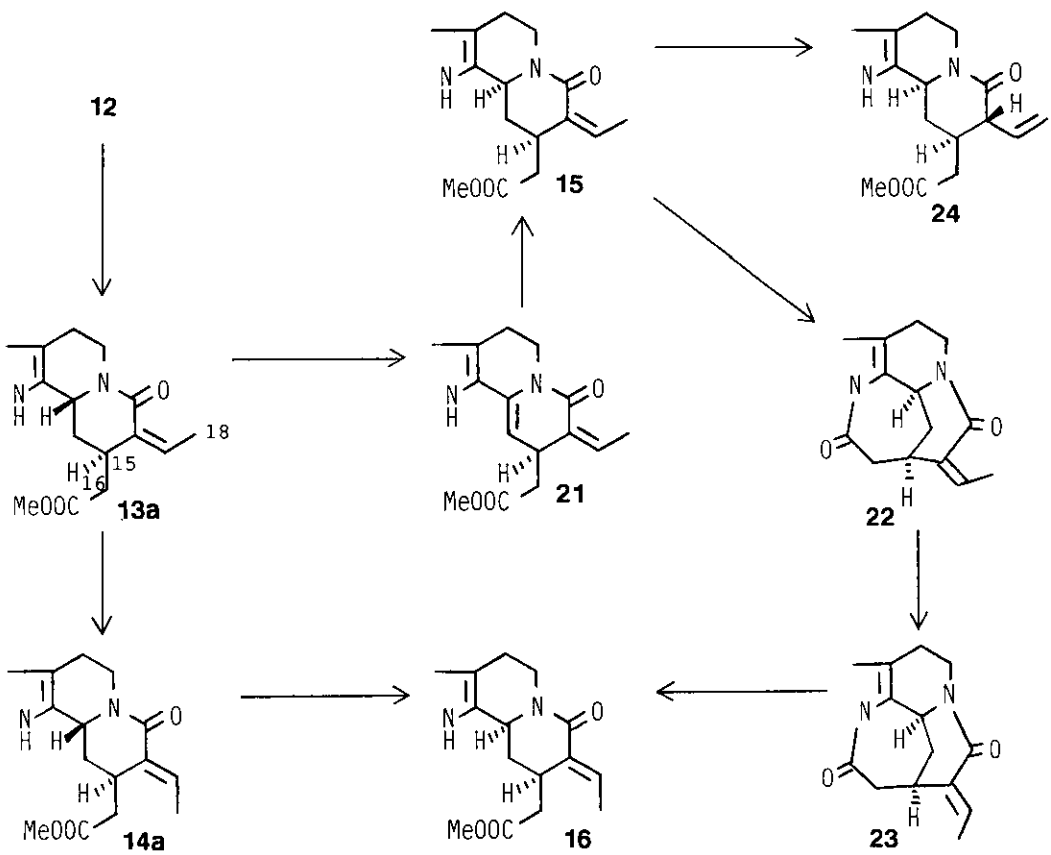
One would not be surprised at all if this very strong dependence of conformation on double bond configuration would turn out to be responsible for the quite different chemical behaviour of the E- and Z-series. A first example of this type was encountered in the synthesis of 19Z-geissoshizine **20**.[10,14] Formylation of the ester **18** (E-series) can simply be started with sodium hydride since the conformation **18'** allows fast transprotonation between indole-nitrogen and the α-ester-carbon atom. On the other hand the formation of a dianion **19'** is a prerequisite for successful formylation in the Z-series.

In this paper, the Hannover group describes further examples of the study on the configuration and conformation depending stereo- and regioselectivities of stereospecific reactions in total synthesis of corynanthe alkaloids while the Kobe group presents full details on the synthesis of this group of alkaloids.

2. GENERAL SYNTHETIC ROUTE I: SYNTHESIS OF KEY INTERMEDIATES 13, 14, 16, AND 17 BY THE HANNOVER GROUP

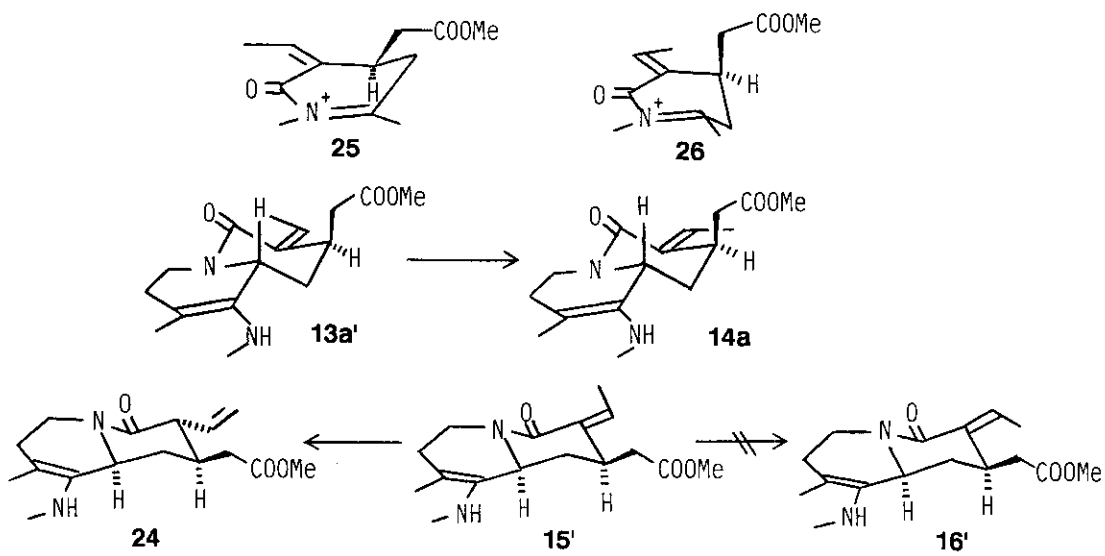
All the four synthetic intermediates **13**, **14**, **15**, and **16** were prepared from the central 19Z-ethylidene-lactam **13a** which was subjected to olefinic isomerization from unstable Z-isomer to stable E-isomer coupled with epimerization at C-3 from β -configuration to α - as shown in the Scheme 4.

As mentioned above the enantiomerically pure lactam **13a** is obtained as a kinetically controlled reaction product from the methylene-lactam rearrangement of the acid **12** described earlier,[6] but if the process is driven to completion it would be accompanied by the stereoisomers **14a**, **15**, and **16**, which can all be separated by chromatography. Additionally to this, however, stereoisomers **14a**, **15**, and **16** can also be prepared in well defined ways starting from the lactam **13a**. Though these have in principle been published[5,6] some interesting comparisons merit closer inspection at this stage having all the results at hand.



Scheme 4

The copperII and ironIII catalyzed hydroxylation of **13a**[6] leads under acidic conditions to the unsaturated lactam **21** (dehydration) which is cleanly reduced by borohydride to the 3α -isomer **15**, the reduction obviously being directed by the configuration of C-15. If, however, the same procedure is applied to the corresponding E-lactam **14a** this reduction gives rise to a 1:1 mixture of **14a** and **16**. The formation of **16** is therefore much more efficiently achieved via cyclization of **15** to the acylindole **22** which isomerizes under the reaction conditions very quickly and with very high selectivity exclusively to form the pentacyclic intermediate **23**. Subsequent methanolysis of the acylindole finally yields pure **16**. Similarly LDA-treatment of **13a** followed by kinetically controlled reprotonation gave rise to the E-isomer **14a** as the main reaction product, while exactly the same conditions on the lactam **16** resulted in the formation of the deconjugated unsaturated lactam **24** preferentially. This product is of course the intermediate of choice for an enantioselective synthesis of corynantheine **46** (see below).
These examples indicate a very high dependence of stereo- and regioselectivity on their configuration which is in every case very probably due to non-bonding interactions of the C-15 side chain with substituents at the exocyclic double bond.[15,16] This type of steric strain which is quite typical for substituents of this kind determines to a very large extent the configurational and conformational behaviours of these compounds. Since, however, with the help of nmr data, the conformation of geissoschizine and some of its stereoisomers could be established, these principles are reliable guideline for the mechanistic understanding of stereospecific transformations in this field.
In the case of the above mentioned reductions the non-bonding interactions are minimized in conformation **25** for the Z-double bond favoring α-attack of hydride ions from configurational as well as conformational reasons (folding of the ring!). On the other hand with the E-configuration, conformation **26** with an axial substituent (avoiding B-strain) will favor α -attack from configurational reasons while ring folding would rather encourage β -attack thus giving rise to a mixture of diastereomers in this case.[17]

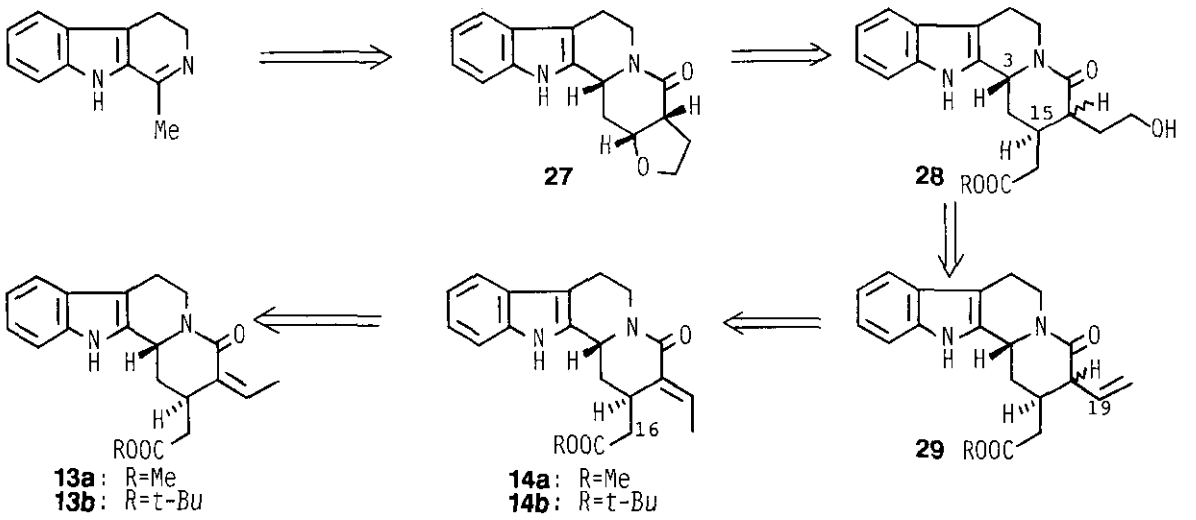


Scheme 5

As far as the double bond isomerization is concerned reprotonation of the conjugated enolate generated from **13a** gives rise mainly to **14a**. The carbonyl-methyl interaction is removed in this process (see **13a'**) and as the ester side chain is held in a pseudo-axial position no severe hindrance with this group is to be expected. In the case of **15** (see **15'**) the formation of the E-configuration would lead from bad to worse (see **16'**) and so in this case protonation α to the carbonyl group deconjugates the system but secures the 15/20-trans configuration of the lactam **24** corresponding to the most stable conformation possible for a disubstituted indoloquinolizidine of this type. (Configuration assignment see below). The lactam **24** offers itself as the starting material of choice for the enantioselective synthesis of corynantheol **52** and corynantheine **46**.

3. GENERAL SYNTHETIC ROUTES II: SYNTHESIS OF KEY INTERMEDIATES 13 AND 14 BY THE KOBE GROUP

The Kobe group has also accomplished the stereoselective synthesis of the same key intermediates **13b** and **14b** for the total synthesis of the isositsirikines. The overall strategy is based on (1) use of the furopyridone **27** as a common precursor to all of the alkaloids, (2) introduction of a two-carbon unit to C-15 into the indoloquinolizine skeleton by an elimination-addition reaction,[18,19] and (3) development of the stereoselective conversion of the stable 19E-lactam **14b** into the unstable 19Z-isomer **13b**[19] (Scheme 6).

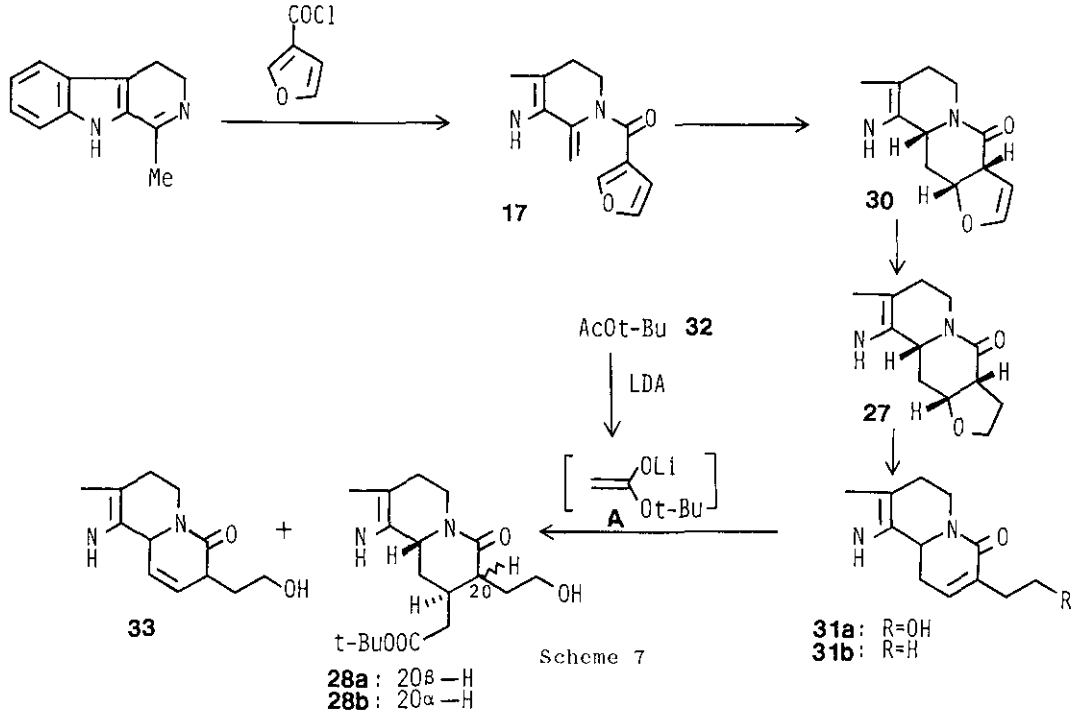


Scheme 6

Stereoselective Preparation of the 19E-Lactam 14b

Acylation of harmalane with 3-furoyl chloride in the presence of triethylamine gave the unstable enamide **17** in quantitative yield which without purification was subjected to irradiation[20] in the presence of sodium borohydride in acetonitrile-methanol (9:1) to afford the photocyclized lactam **30** homogeneously in 77% yield. This is the basic skeletal structure of *indoloquinolizidine alkaloids* substituted with a two-carbon substituent at C-3. Relative configuration between 3a-, 12b-, and 13a-positions as being cis-syn was deduced by comparison of the nmr spectrum [δ 4.76, dd, J= 12 and 3 Hz, 12b-H), 4.46 (ddd, J= 12, 9, and 5 Hz, 13a-H), and 1.70 (1H, q, J= 12 Hz, 13-Hax)] with that of the analogous furoindoloquinolizine [21] which had been firmly characterised by spectral and X-ray analyses. Introduction of a two-carbon unit to C-2 was investigated by developing a quite

efficient elimination-addition sequence based on the inherent reactivity of the β-alkoxycarbonyl group in the corresponding tetrahydrofuropyridone **27** (Scheme 7). Catalytic hydrogenation of **30** in the presence of platinum dioxide afforded the tetrahydrofuropyridone **27** quantitatively which was then treated with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78°C to give the α,β-unsaturated lactam **31a** in 71% yield as a result of β-elimination reaction in the β-alkoxycarbonyl system. The lactam **31a** exhibited the characteristic ir and nmr spectra [ν 3420 and 1630 cm^{-1}; δ 6.40 (br d, J= 5 Hz, 2-H)], which established the structure **31a** as depicted in Scheme 7.



Scheme 7

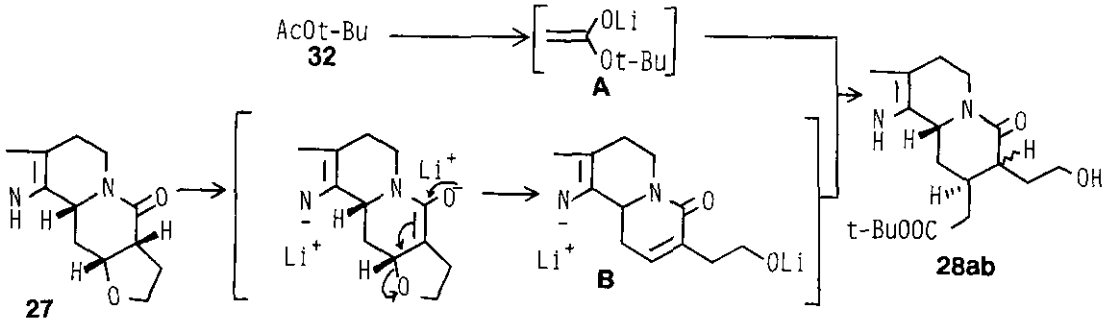
The Michael addition to the α,β-unsaturated lactam **31a** with the lithium enolate **A** was investigated in spite of the fact that a very similar acceptor **31b** has been reported to be reluctant to the Michael reaction.[22] The results are summarized in Table 2.

Table 2. The Michael Addition to the α,β-Unsaturated Lactam **31a**

	Equiv.				Yield (%)	
	31a	**32**	LDA	Temp.	**28ab**	**33**
entry 1	1	6	6.3	-78° ⟶ 0°C	18	--
2	1	6	8.5	〃	80	--
3	1	6	11.0	〃	--	23

Treatment of the α,β-unsaturated lactam **31a** with the lithium enolate **A**, prepared in situ from 6 equiv. of t-butyl acetate **32** and 6.3 equiv. of LDA, gave a 1:1 mixture of the desired trans-anti and cis-anti adducts **28a** and **b** in 18% yield (entry 1). Interestingly, the yield of the adducts **28a** and **b** was improved dramatically to 80% by increasing the amount of LDA (8.5 equiv.)(entry 2), while the Michael reaction using a large excess of LDA (11.0 equiv.) was unsuccessful again and gave the deconjugated β,γ-unsaturated lactam **33** as an only isolated product in 23% yield. The stereochemistry of the adducts **28a** and **b** was deduced by comparison of their nmr spectra [**28a**: δ 4.87 (dd, J= 9.5 and 4 Hz, 3-H) and 2.13 (br t, J= 11 Hz, 14-Hax); **28b**: δ 4.93 (dd, J= 9 and 5 Hz, 3-H) and 2.09 (br t, J= 9 Hz, 14-Hax)] with those of analogous benzoquinolizines previously reported[1a] and unambiguously established by the conversion of the former adduct **28a** into the alkaloid, hirsuteine, as described in the following section 5.

Expecting that the lithium alkoxide **B** having an α,β-unsaturated lactam structure, which would be formed in situ by β-elimination of the starting furopyridone **27** could react as a Michael acceptor, search for a practical procedure was carried out for the preparation of the adducts **28a** and **b** from **27** without isolating the intermediary unsaturated lactam **31** (Scheme 8).

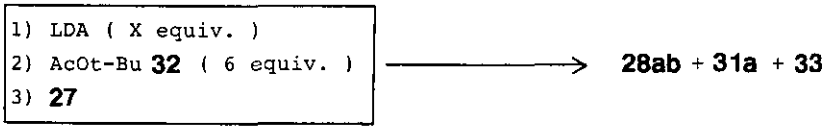


Scheme 8

Thus, the Michael addition reaction of the lithium enolate **A** prepared as above to the lithium alkoxide **B**, prepared in situ by treatment of the furopyridone **27** with LDA at -78°C, was carried out and gave a 1:1 mixture of the desired adducts **28a** and **b** in 53% combined yield. As this reaction sequence apparently consists of two steps of β-elimination reaction of the β-alkoxycarbonyl group and then addition of nucleophile, these two steps reaction was designated as the elimination-

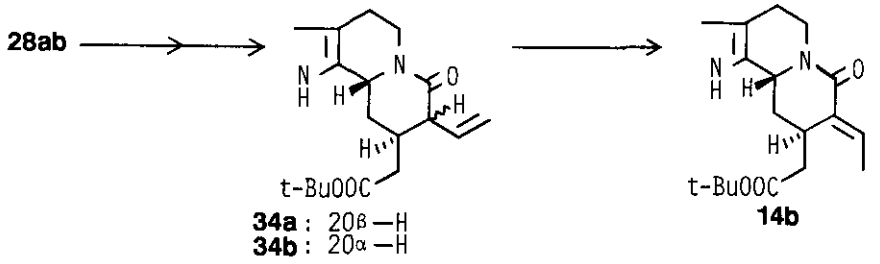
addition reaction. Finally, the most convenient procedure for this elimination-addition sequence was established by carrying out the reaction in one vessel throughout the whole steps. Several reaction conditions investigated by altering the reaction temperature, amount of base, and order of the addition of either receptor or acceptor suggested that the amount of base appears to play a most important role for the successful preparation of the adducts **28a** and **b**.

Table 3. The Elimination-Addition Reaction of the Tetrahydrofuran **27**



		X equiv.	28ab	31a	33
entry	1	8.3	2 %	--	--
	2	11.2	67	7	--
	3	12.8	28	30	6
	4	14.4	2	43	14

As shown in Table 3, the combination of t-butyl acetate (6.0 equiv.) and LDA (8.3 equiv.) resulted in the recovery of a large amount of unchanged furopyridone **27** besides only 2% of the desired adducts **28a** and **b**. Use of 11.2 equiv. of LDA gave a mixture of two adducts **28a** and **b** in a 1:1 ratio in 67% isolated yield. The reaction using a large excess of LDA (12.8-14.4 equiv.) gave a mixture of the adducts **28a** and **b** as minor and the α,β - and β,γ -unsaturated lactams **31** and **33** as major products (entries 3 and 4).



Scheme 9

Thus, a convenient procedure was established for a simple preparation of the desired 3,15-anti disubstituted indoloquinolizidines **28a** and **b** by using a one-pot procedure for the elimination-addition reaction as shown in Table 3, (entry 2). The adducts **28a** and **b** were then converted into the 19E-lactam **14b** by conventional methods (Scheme 9).

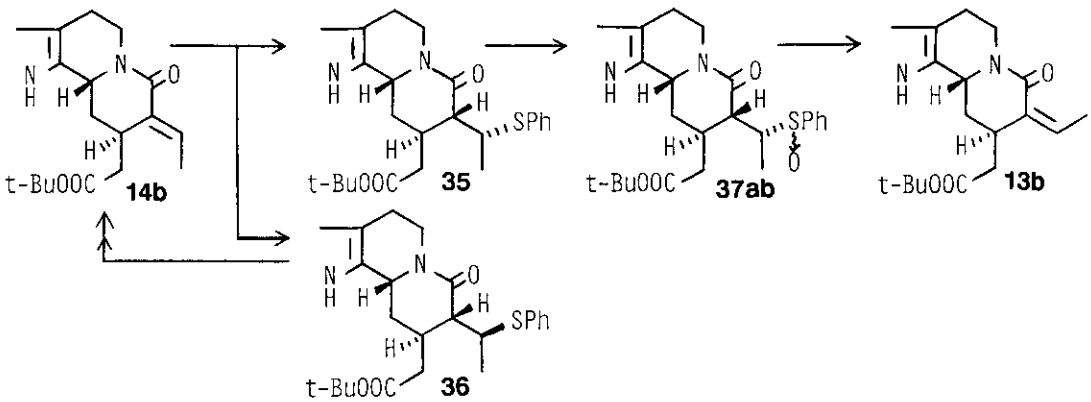
Treatment[23] of the trans-anti alcohol **28a** with o-nitrophenylselenocyanate in the presence of tributylphosphine followed by oxidation of the resulting alkylarylselenide with *m*-chloroperbenzoic acid at 0°C afforded the trans-anti olefin **34a** in 72% yield from **28a**, which exhibited nmr signals at δ 5.72 (ddd, J= 17.5, 10, and 7 Hz, 19-H) and 5.28-5.06 (m, 18-H_2). Similarly, the cis-anti alcohol **28b** was converted into the cis-anti olefin **34b** *in 74% yield from* **28b**. *Conversion of* the olefins **34a** and **b** into the 19E-lactam **14b** was readily accomplished by treatment with base. Treatment of the trans-anti olefin **34a** with either sodium hydride at room temperature or LDA at -78°C afforded the stable 19E-lactam **14b** as a sole product in 83 or 86% yield respectively which has no steric hindrance between 19-methyl and lactam carbonyl group. The stereochemistry of the ethylidene group in **14b** was deduced by comparison of the nmr spectrum [δ 7.08 (q, J= 7 Hz, 19-H) and 1.86 (d, J= 7 Hz, 19-Me)] with those of analogous compounds **13a**[6] and **14a**[14] which are the pair of 19E- and 19Z-isomers prepared by the Hannover group. In the same manner, the cis-anti olefin **34b** was converted into the identical lactam **14b** in 83-91% yield.

Stereoselective Preparation of the 19Z-Lactam **13b**

The synthesis of another key intermediate, 19Z-lactam **13b**, was then investigated via the route involving isomerization of the 19E-isomer **14b**. Direct isomerization of the stable 19E-lactam **14b** into the unstable 19Z-isomer **13b** seemed difficult though the 19Z-lactam **13a** had been already converted back into the 19E-one **14a** by the Hannover group as described in section 2.

Therefore, stereoselective conversion of the 19E-lactam **14b** into the 19Z-isomer **13b** was investigated via the route involving the addition-elimination reaction employing *thiophenol (Scheme 10)*.

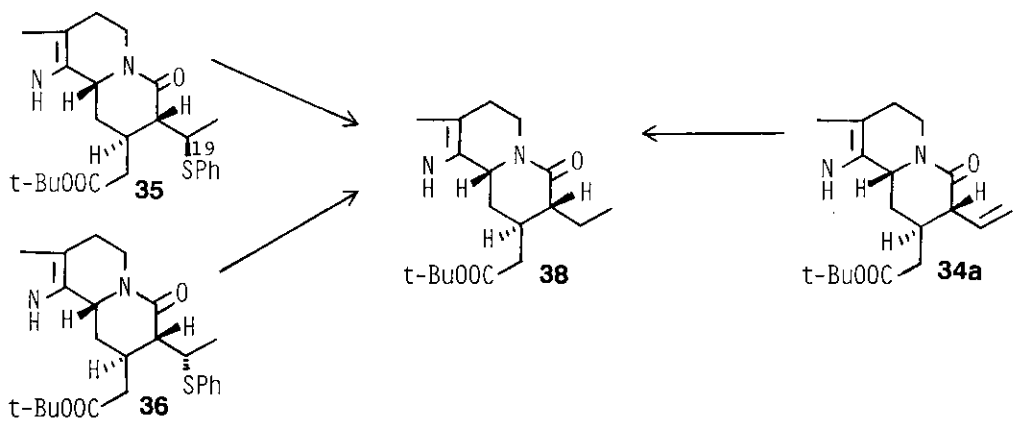
Treatment of the 19E-lactam **14b** with 3 equiv. of lithium thiophenoxide in the presence of 3 equiv. of thiophenol in THF at 70°C gave stereoselectively the adduct **35** in 86% yield in addition to 6% *yield of the adduct* **36**. *The structures of* the adducts **35** and **36** were deduced from spectral data [**35**: m/z: 490 (M^+), δ 3.86



Scheme 10

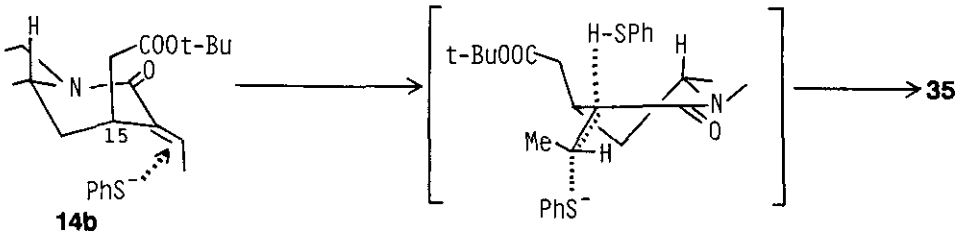
(dq, J= 7 and 5 Hz, 19-H) and 2.53 (br d, J= 5 Hz, 20-H); **36**: m/z: 490 (M^+); δ 4.21 (qd, J= 7 and 3.5 Hz, 19-H) and 2.43 (br t, J= 6 Hz, 20-H)] and firmly established by the following chemical evidences (Scheme 11).

Desulfurization of **35** with Raney nickel afforded the trans-anti ethyllactam **38** which was identical with the sample prepared by catalytic reduction of the trans-anti olefin **34a**. Similarly, upon desulfurization the minor adduct **36** was converted into the identical trans-anti ethyllactam **38**. Relative configuration at C-19 of **35** and **36** was deduced from the result of syn-elimination of phenylsulfenic acid giving the expected olefins **13b** and **14b** as described later. Attempted addition of selenyl group instead of sulfur group was unsuccessful under similar reaction condition.



Scheme 11

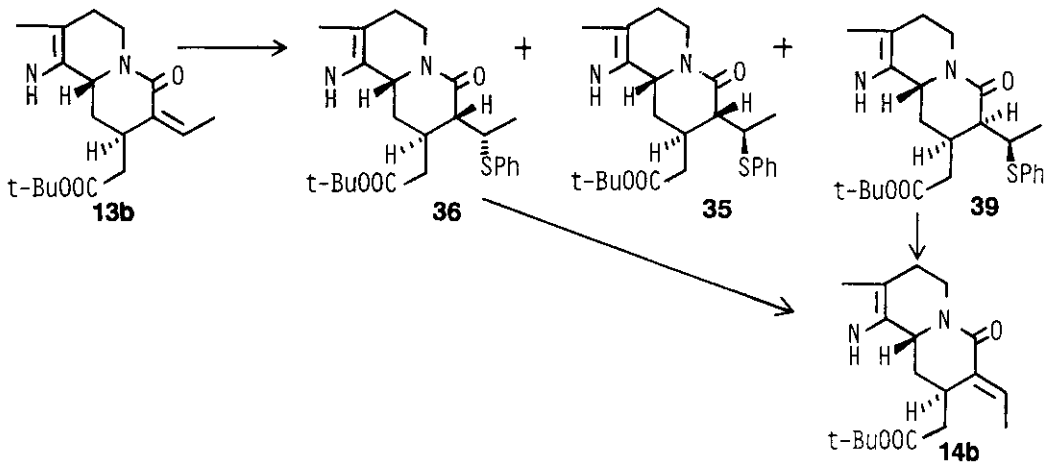
High selectivity for a preferential formation of the product **35** over **36** in the above addition reaction can be explained as follows. Nucleophilic attack of lithium thiophenoxide and electrophilic attack of a proton from thiophenol to the double bond would occur concomitantly from the opposite faces of an olefin as a result of the preferred trans-addition (Scheme 12).[24]



Scheme 12

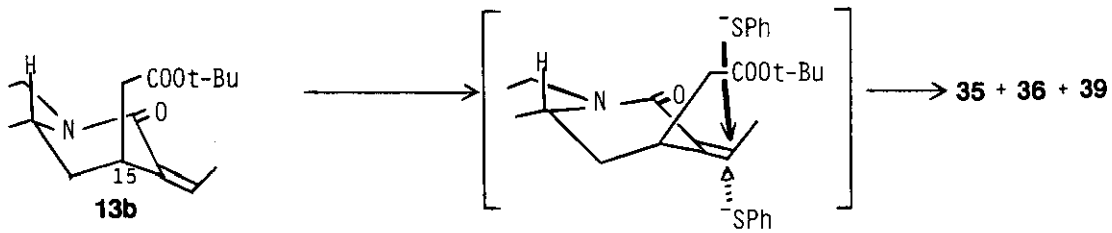
The elimination reaction of the sulfur group was then investigated via the corresponding sulfoxides (Scheme 10). Oxidation of the major product **35** with m-chloroperbenzoic acid at 0°C gave a 1:1 mixture of two sulfoxides **37a** and **b** in quantitative yield which was readily separated by medium-pressure column chromatography. The stereostructures of two sulfoxides **37a** and **b** have remained to be determined. Next, pyrolysis of respective sulfoxides was carried out in boiling toluene. The polar sulfoxide **37a** required 1 h for complete pyrolysis while with the less polar isomer **37b**, this took 2 h. Both gave rise to the identical 19Z-ethylidene-lactam **13b** in quantitative yield. Its structure was deduced by comparison of the nmr spectrum [δ 6.06 (q, J= 7 Hz, 19-H) and 2.17 (d, J= 7 Hz, 19-Me)] with those of the corresponding 19E-isomer **14b** and analogous compounds **13a** and **14a**. The minor adduct **36** upon similar treatments reverted back to the starting **14b** in good yield.

Similarly, olefinic isomerization was successfully applied to the 19Z-lactam **13b** for its stereoselective conversion into the 19E-isomer **14b** (Scheme 13). Treatment of the 19Z-lactam **13b** with lithium thiophenoxide under the same conditions gave three adducts, **35**, **36**, and **39** in 10, 53, and 10% yields respectively, of which the latter two adducts **36** and **39** were respectively converted into the identical 19E-ethylidene-lactam **14b** upon pyrolysis of the corresponding sulfoxides in good yield. Lower selectivity of the addition reaction of sulfur group than in the case of the 19E-lactam **14b** can be explained as follows (Scheme 14). Since the



Scheme 13

conformation of the 19Z-lactam **13b** would be deformed owing to the steric hindrance between 19-methyl and the lactam carbonyl groups, thiophenol would attack from both α - and β - sides to give three adducts **35**, **36**, and **39**.



Scheme 14

Thus, we have also succeeded in the stereoselective preparation of two key intermediates **14b** and **13b** for the total synthesis of alkaloids having an ethylidene group at C-20 via the route involving the newly developed olefinic isomerization.

4. CONVERSION OF KEY COMPOUNDS TO ALKALOIDS

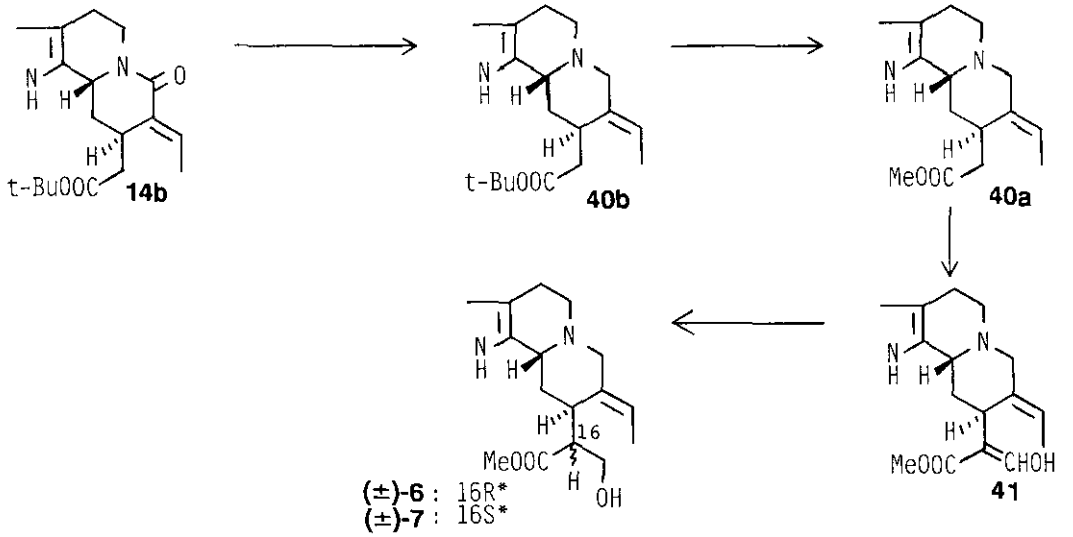
The Hannover group has already described experimental details[8,11,14] on the enantioselective synthesis of all isositsirikines (**4-11**) from the chiral 19E-lactam **14a** and the 19Z-isomer **13a** according to the general reaction sequence which consists of the following three reactions.

1. Borch reduction[8] of the lactam carbonyl group
2. Deprotonation and formylation to yield geissoschizine (**1**) and all its stereoisomers
3. Borohydride reduction, which finally transformed all these isomers into the corresponding isositsirikines (**4-11**)

The Kobe group now reports full details of the synthesis of (±)-isositsirikines (**4-11**) from two key intermediates **14b** and **13b** by the modified procedure of the above three reactions reported by the Hannover group.

Synthesis of (±)-Isositsirikines (4-7) with a 19E-Ethylidene Group[8]

At first, the 19E-lactam **14b** was converted into two 3β ,19E-isositsirikines (**6** and **7**) which had been reported as alkaloids from Rhazia stricta and designated as rhazimanine (**6**)[25a] and bhimberine (**7**)[25b] respectively (Scheme 15).



Scheme 15

Chemoselective reduction of the lactam carbonyl group in the lactam **14b** with aluminum hydride at -50°C gave the corresponding amine **40b** in 50% yield which was then treated with methanol in the presence of conc. sulfuric acid at 20°C to give the methyl ester **40a** in a quantitative yield. Finally, formylation of the methyl ester **40a** with ethyl formate in the presence of LDA at -40°C gave the formyl ester **41**, which was then reduced with sodium borohydride to afford a 2:3 mixture of the epimeric hydroxy esters **6** and **7** upon separation by chromatography on silica gel. They were respectively identical with the chiral samples R-**6**[11] and S-**7**[11] prepared by the Hannover group upon comparison of their spectral data. The structures of these two hydroxy esters **6** and **7** were confirmed by the respective nmr spectrum and further unambiguously by the single crystal X-ray analysis (Figure 1) of the former isomer **6**. However, comparisons of the nmr spectra of natural rhazimanine[25a] and bhimberine[25b] with those of the synthetic compounds **6** and **7** and R-**6** and S-**7** showed their non-identity.

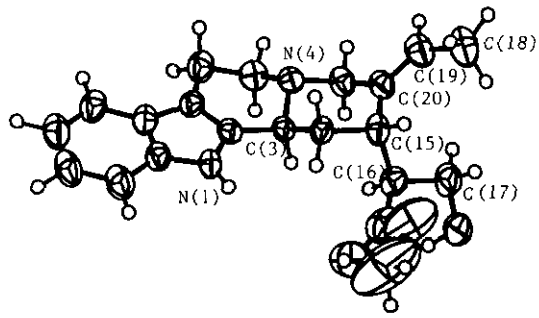
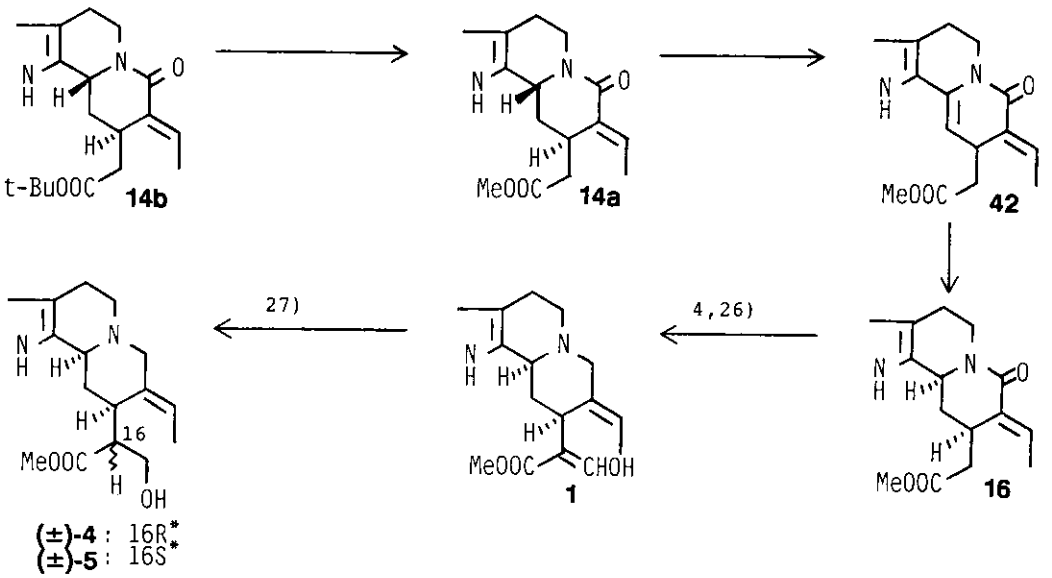


Figure 1. The Crystal Structure of (±)-**6**

Next, total synthesis of isositsirikines **4** *and* **5** *with 3α* -H (3,15-syn) configuration was accomplished by applying the known inversion reaction from *β* to *α* of the configuration at C-3 in the lactam **14b** (Scheme 16). Thus, autooxidation[5] of **14a**, prepared by transesterification of **14b**, in trifluoroacetic acid in the presence of copper acetate at room temperature gave the enamine **42** in 66% yield. The nmr spectrum of **42** exhibited a peak due to olefinic proton at δ 5.55 (d, J= 7 Hz, 14-H). Reduction of **42** with sodium borohydride in acetic acid at 5-10°C gave a 1:1 mixture of the desired 3,15-syn lactam **16** and the starting 3,15-anti lactam **14a** in 90% yield. The former **16** showed identical spectral data with those of the authentic sample[4] prepared by the Hannover group. The reaction sequence involving

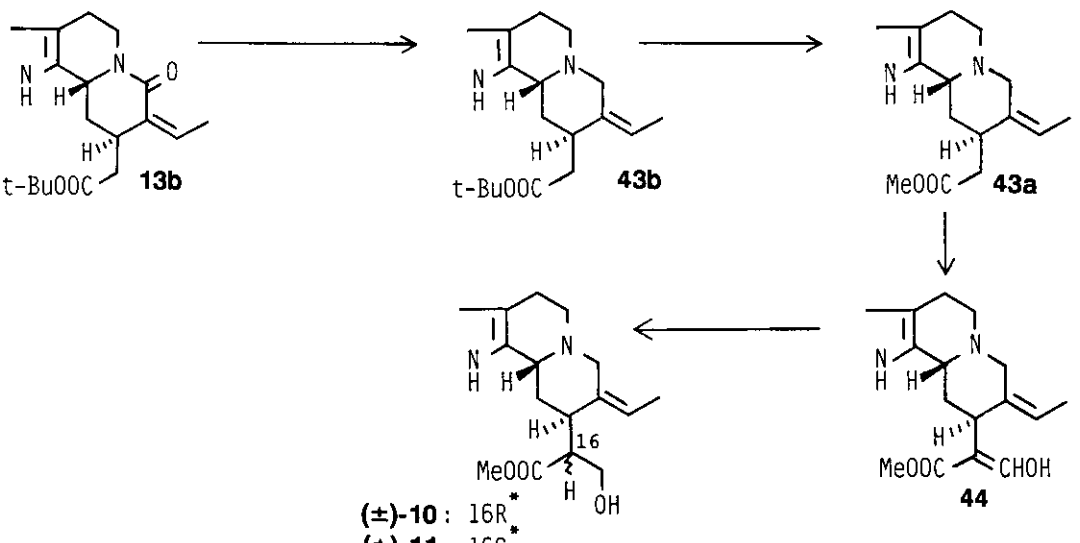
three steps of reduction of the lactam carbonyl group of **16** followed by formylation, and reduction of the formyl ester had already given (±)-isositsirikine (**4**) and the 16-epimer **5**.[4,26,27]



Scheme 16

Synthesis of (±)-Isositsirikines **8-11** with 19Z-Ethylidene Group[10]

Further, the 19Z-lactam **13b** was also converted into natural Z-isositsirikines (**8**[28] and **9**[28]) and their 3β-isomers **10** and **11** according to the similar reaction sequence employed in the synthesis of the 19E-alkaloids (Scheme 17).



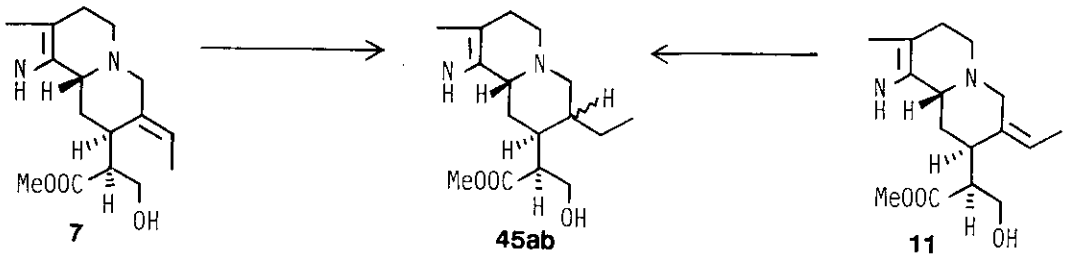
Scheme 17

Chemoselective reduction of the lactam carbonyl group of **13b** followed by transesterification, formylation, and finally reduction afforded a 5:1 mixture of the epimeric 3,15-anti hydroxy esters **10** and **11** upon separation by chromatograpy on alumina. Relative configurations at C-16 of **10** and **11** were deduced from comparison of their nmr spectra with those of the respective 19E-isomers **6** and **7** whose structures were confirmed by the single crystal X-ray analysis of **6** as described above. The nmr spectral data for **6**, **7**, **10**, and **11** are summarized in Table 4.

Table 4. ^{1}H-nmr Data of **6**, **7**, **10**, and **11** (δ ppm(J in Hz))

	6	**7**	**10**	**11**
3-H	3.78 (br d, J=13)	3.64 (br d, J=13)	3.74 (m)	3.61 (m)
14-Hax	1.82 (td, J=13, 4.5)	1.79 (td, J=13, 5)	1.88 (ddd, J= 13.4, 11, 5.1)	1.85 (ddd, J=13.5, 12.7, 5.4)
14-Heq	2.00 (dt, J=13, 2)	2.28 (br d, J=13)	1.92 (br dt, J= 13.4, 4)	2.18 (br dt, J= 13.5, 1.5)
15-H	3.31 (ddd, J=11.5, 4.5, 2)	3.39 (br dd, J=11, 5)	2.81 (br dd, J=11, 4)	2.75 (br d, J=12.2)
16-H	3.10 (m)	3.14 (m)	3.12 (m)	3.09 (m)
17-H_2	3.80 (d, J=6)	4.02 (dd, J=12, 6) 4.04 (dd, J=12, 4)	3.74 (m)	3.91 (dd, J=11.3, 6.2) 3.94 (dd, J=11.3, 4.1)
COOMe	3.89 (s)	3.68 (s)	3.84 (s)	3.61 (s)

These spectral data suggest that these four compounds exist in the conformation with an axially oriented 15-substituent group and an anti relationship between 15- and 16-hydrogens as shown in Figure 2. Furthermore, comparison of the spectrum of **6** with that of **7** shows that signals due to 17-methylene protons in **6** having 16R* configuration appeared at higher field than those in **7** having 16S*-configuration while signals due to the ester methyl group in **7** appeared at higher field than that in **6** both due to the anisotropic effect of the ethylidene group at C-20. Similarly, comparisons of their nmr spectra, particularly chemical shifts due to 17-methylene protons and ester methyl group, proposed that the 19Z-isomers **10** and **11** would have 16R*- and 16S*-configurations respectively. This proposal was unambiguously established by the chemical conversion of the latter **11** into the dihydro compounds **45a** and **b**, both of which were identical with the authentic samples prepared from the 16S* isomer **7** (Scheme 18).



Scheme 18

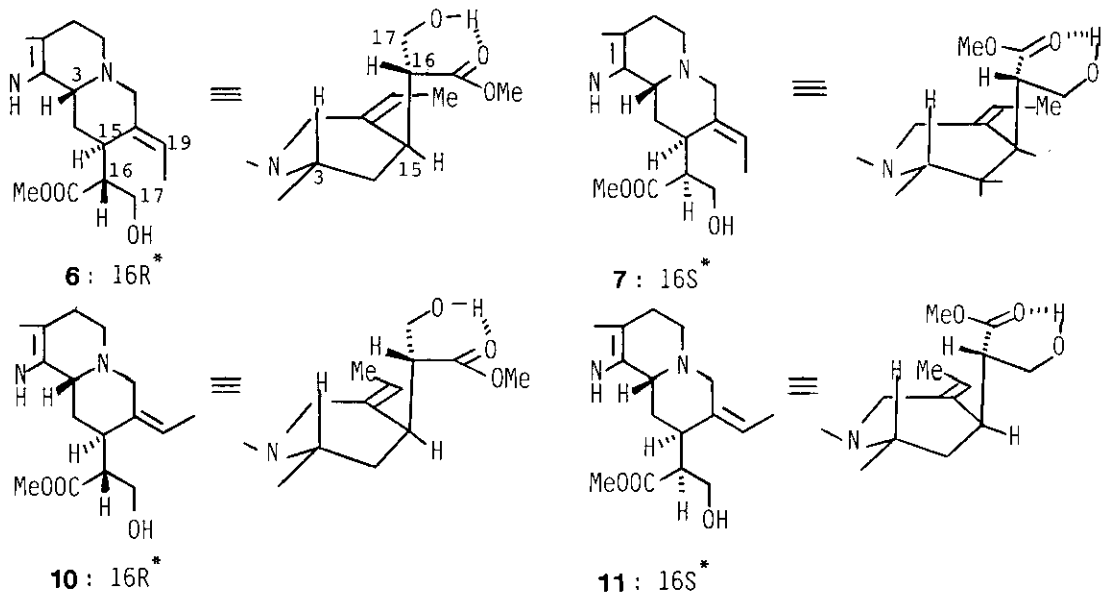
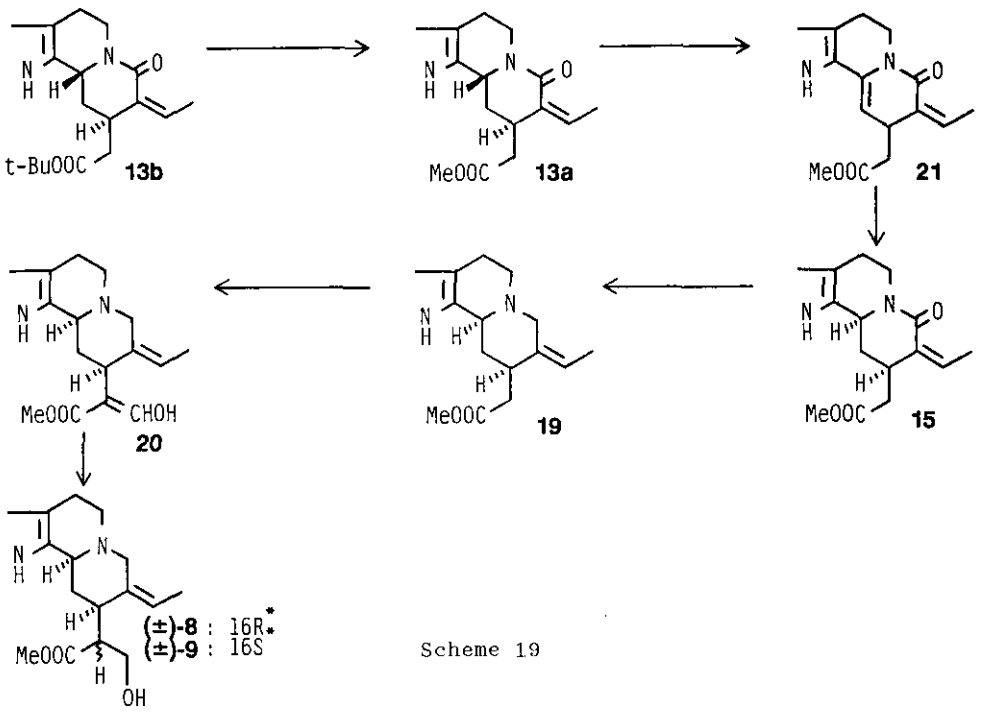


Figure 2. Stereostructures of **6**, **7**, **10**, and **11**

Similarly, total synthesis of alkaloids, (±)-Z-isositsirikine (**8**) and its 16-epimer **9** having 3,15-syn structure was accomplished according to the same reaction sequence employed in the synthesis of isositsirikines (**6**, **7**, **10**, and **11**). Two hydroxy esters **8** and **9** were identical with the respective authentic alkaloids[14] upon comparisons of their nmr spectra and Rf values (Scheme 19).



Scheme 19

In conclusion, we have now succeeded in the total synthesis of all eight stereoisomers of isositsirikine group of alkaloids via a route using the 19E-lactam **14** and the 19Z-isomer **13** as the key intermediates.

5. SYNTHESIS OF RELATED ALKALOIDS

Total syntheses of two alkaloids of corynanthe group, a) hirsuteine (**47**) and b) corynantheine (**46**), according to the completely different approaches by respective groups are described (Figure 3).

Corynantheine and hirsuteine are the corynanthe alkaloids with a 20-vinyl group, have the same planar structure, and are epimeric with respect to the configuration at C-3 as 3β in hirsuteine (**47**) and 3α in corynantheine (**46**).

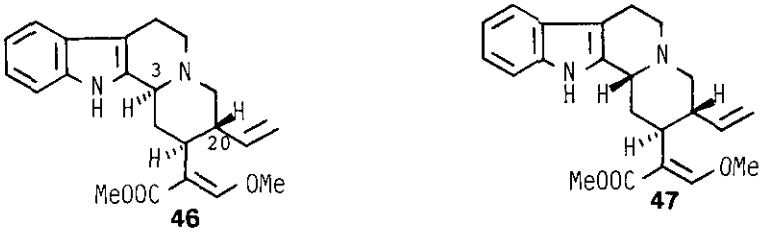
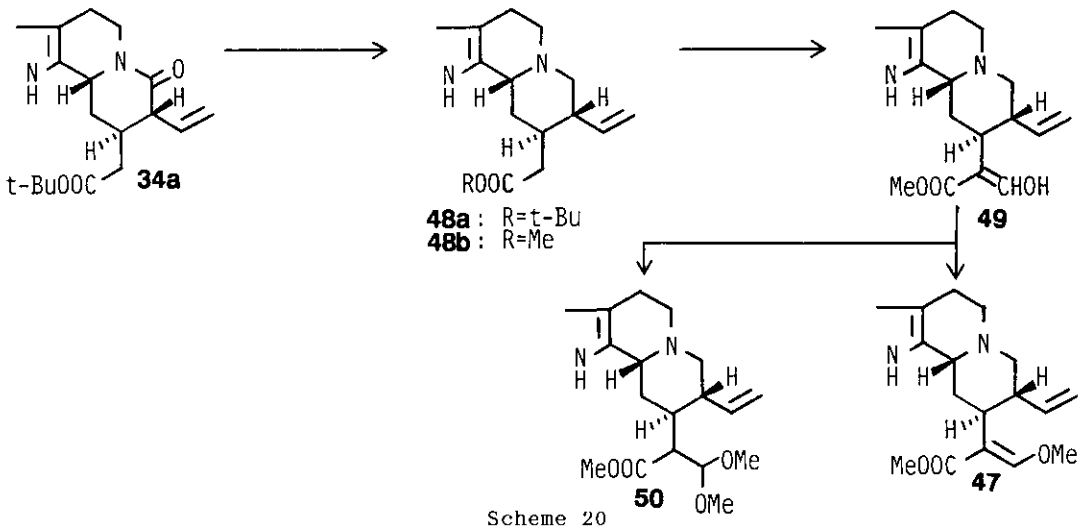


Figure 3. Corynantheine (**46**) and Hirsuteine (**47**)

5-1) Total Synthesis of (±)-Hirsuteine (47)[19]

The effectiveness of our synthetic methodology was also established by the first total synthesis of (±)-hirsuteine (**47**), which had previously been isolated from Mitagyna parvifolia Korth.[30] and Uncaria rhynchophylla Mig[31] (Scheme 20).



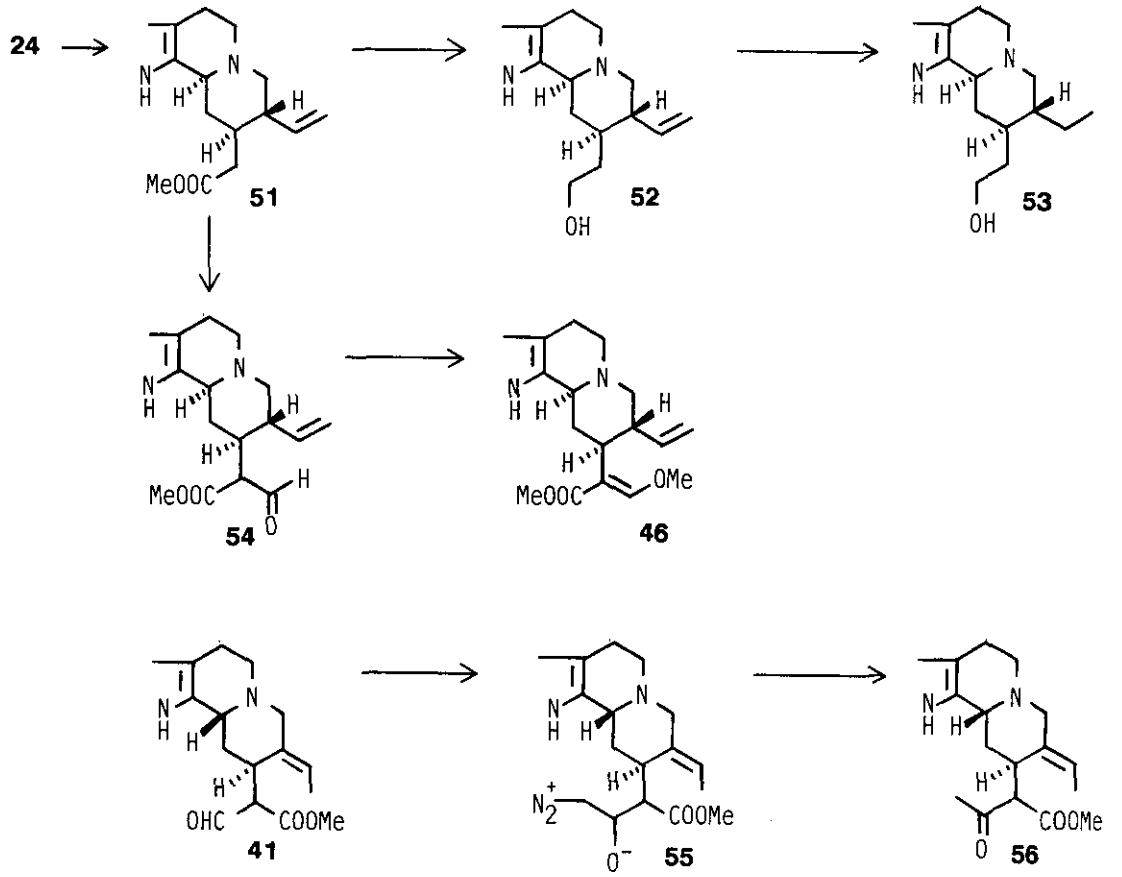
Scheme 20

The 3,15-anti-lactam **34a** with a vinyl group at C-20 was used as a starting compound for the synthesis of hirsuteine. Chemoselective reduction of the lactam carbonyl group in the lactam **34a** with aluminum hydride, transesterification of the t-butyl ester **48a** with methanol-conc. sulfuric acid to the methyl ester **48b**, and then formylation of the ester **48b** with ethyl formate in the presence of LDA at -30~ -20°C gave the α -formyl ester **49** in 70% yield, which without purification was treated with methanol saturated with hydrogen chloride[32] to afford (±)-hirsuteine (**47**) and the acetal **50** in 42 and 25 % yield, respectively. The methoxy ester (**47**) was also obtained by treatment of the acetal **50** with LDA at -78°C and identical with the natural alkaloid[30] upon comparisons of their ir, nmr, and mass spectra, and Rf values. Thus, we succeeded in the first total synthesis of **47**.

5-2). Total Synthesis of Corynantheine (46) and Related Alkaloids

According to expectations, Borch reduction[6] of **6** yielded **51** which on hydride reduction gave rise to corynantheol (**52**) and as no comparison material was available this compound was hydrogenated to generate dihydrocorynantheol (**53**), which proved to be identical in every detail (tlc and ir) with an authentic sample thus proving the β -configuration at C-20 (Scheme 21).[13,33]

Again without any complications deprotonation (LDA) of **51** and subsequent treatment with methyl formate led to the aldehyde **54**. Although nmr and ir data indicated a high ratio of enol to be present in solution we hesitated simply to treat this intermediate with diazomethane as given in the literature. First of all, as Karrer had pointed out,[34] the basic nitrogen may be alkylated under these conditions but additionally unwanted side reactions[1] obviously take place at the 1,3-dicarbonyl moiety. Although van Tamelen used this very sketchily described process in his preparation of corynantheine, Szantay[35] on repeating it ran into serious problems and reported only a poor yield owing to the formation of a number of unwanted byproducts.



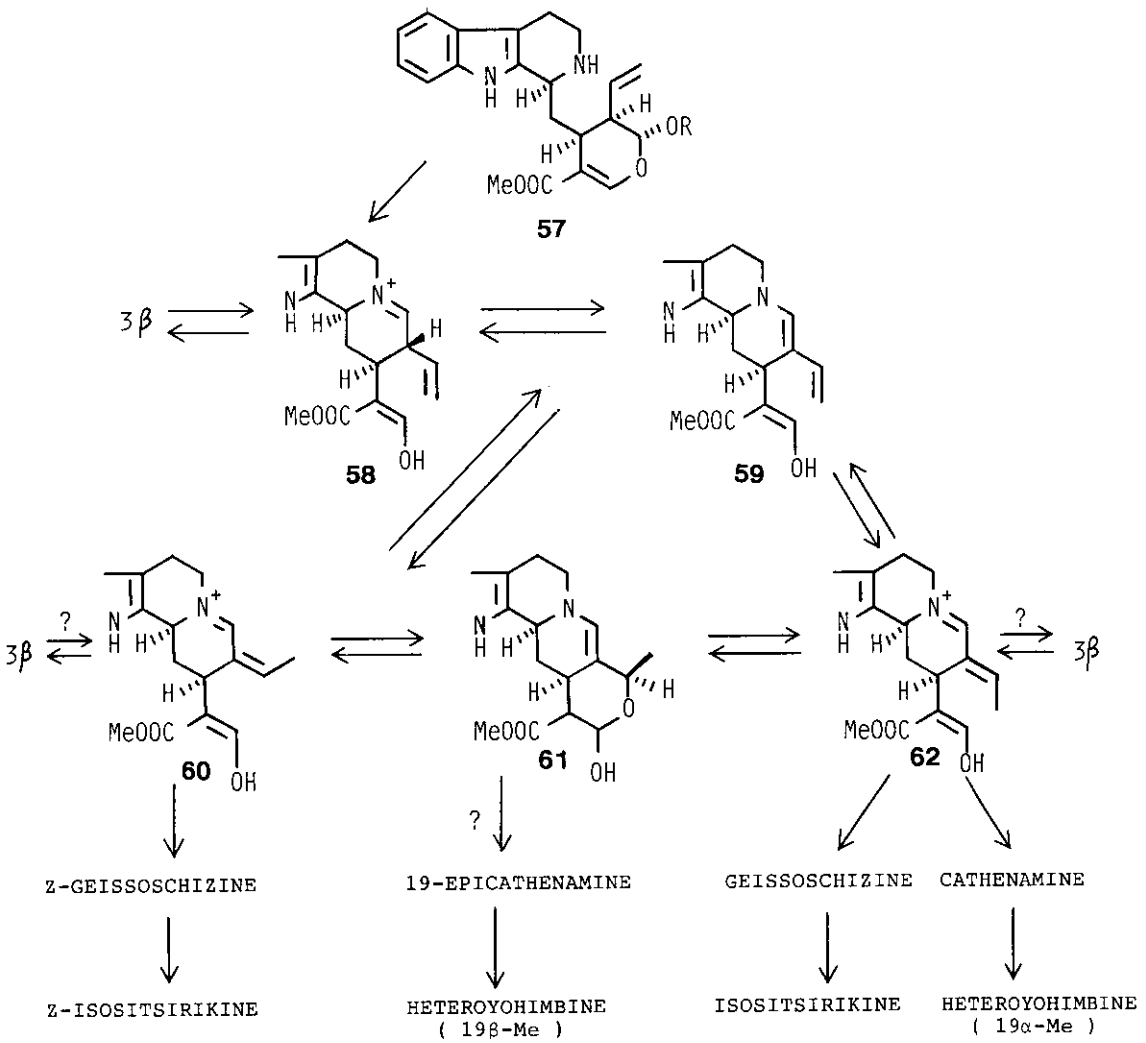
Scheme 21

He probably was right with his suspicion that failure of this reaction may be due to the formation of the corresponding methyl ketone instead of the enol ether, at least when we, using 3β-geissoschizine (**41**) as a model system, treated this aldehyde with diazomethane in methylene dichloride none of the corresponding enol ether was formed, but the main reaction product (51%) turned out to be a mixture of the epimeric β-keto ester **56** which is very probably formed by nucleophilic attack to aldehyde and subsequent hydride shift. Fortunately, conventional esterification of **54** using a stoichiometric amount of methanol[36] solved the problem and gave rise to **46** *which was proved to be identical (ir, nmr data and Rf values)* with a sample of natural corynantheine kindly provided by Professor P. Potier and Dr. F. Khuong-Huu.

6. BIOSYNTHETIC CONSIDERATIONS

The general planning of this stereoselective and enantioselective approach to the complete corynanthe group was mainly governed by the fact that the configuration at C-15, which biosynthetically is introduced from secologanin (**3**) thus giving rise to the very "early" intermediates strictosidine (**58**), is not changed throughout the whole biogenetic sequence.

This observation was of some importance for the synthetic strategy and for the choice of the enantiomerically pure lactam **13a** as our starting material. The sequence given in Scheme 22 calls for an early introduction of this particular configuration if one wants to benefit from the directing capacity of this centre. Very simple explanations for the configurational changes at C-3 (sp^3) and C-19 (sp^2) result from the proven existence of dehydrogeissoschizine **62** as an important intermediate en route to the various stereoisomers.[37,38] Via its enamine form **59** the Z-configuration as shown in **60** is easily established and the very important intermediate **61** which was reported by Kan-Fan and Husson[39] and which may operate as a precursor for cathenamine as well as 19-epi-ajmalicine indicates the possibilities for configurational changes at C-19. Additionally the three iminium salts **58**, **60**, and **62** provide sufficient activation of the hydrogen bond at C-3 to trigger epimerization at this centre too. One set of results, however, still warrants a closer inspection. As Scheme 22 indicates the E-isositsirikines are formed from geissoschizine or dehydrogeissoschizine in a reductive process and the observation that these isositsirikines may be obtained from geissoschizine by treatment with cell-free extracts[27] may be taken as strong evidence for geisso-



Scheme 22

schizine to operate as a direct precursor for these alkaloids. In analogy one could expect Z-geissoschizine to be the intermediate leading to the corresponding Z-isositsirikines particularly as dehydro-Z-geissoschizine (**60**) may easily result by stereoselective protonation from **59** or by elimination from **60**. To the best of our knowledge, however, 19-Z-geissoschizine although synthetically prepared recently was never observed in nature. As E/Z-double bond isomerization is hardly to be expected at the hydrogenated stage of the E-isositsirikines and as intermediate **61** opens the road to dehydro-Z-geissoschizine (**60**), one possible explana-

tion for this dilemma could be a comparatively high reaction rate for aldehyde reduction in **60**, thus allowing only for dehydro-Z-isositsirikines (**60**) as precursors for these stereoisomers. Again the above discussed conformational preferences could offer the decisive argument. As very probably E-dehydrogeissoschizine will prefer the twist boat conformation **1'** (see Scheme 3) the 1,3-dicarbonyl group is certainly more shielded than the one in **20'** which is in an equatorial position and thus more prone to reduction processes.

ACKNOWLEDGEMENTS

Constant supports from the DFG (Deutsche Forschungsgemeinschaft) and the Fonds der Chemischen Industrie to E. W. and The Grant-in-Aids from the Ministry of Culture and Education, Japan to I. N. and T. N. are gratefully acknowledged. We are also grateful to Professor S. Sakai (Chiba University, Japan) for gifts of authentic sample and the spectral data of natural hirsuteine and his helpful discussion.

EXPERIMENTAL

^{1}HNmr spectra were measured with JEOL PMX-60, Varian XL-200 and XL-500, and Bruker AM 300 instruments for solutions in deuteriochloroform unless otherwise stated (tetramethylsilane as internal reference), mass spectra with Hitachi M-80 instruments, and ir spectra for solutions in chloroform on a Hitachi 270-30 spectrophotometer. Mps were determined with a Kofler-type hot-stage apparatus. The extracts from the reaction mixture were dried over anhydrous sodium sulfate. Photochemical reactions were carried out by irradiation with a high-pressure (100 or 300 W) mercury lamp through a Pyrex filter (Eikosha, Osaka, Japan, PIH-100 or PIH-300); during irradiation, the solutions were kept at 5-10°C whilst being stirred and treated with bubbling nitrogen. All other reactions were carried out in a nitrogen stream. Thin layer chromatography (tlc) was performed on pre-coated Silica gel 60F-254 (0.25 mm thick, Merck) and alumina (Aluminiumoxid 150 F_{254} (Typ T), Merck) and preparative thin layer chromatography (plc) on pre-coated Silica gel 60F-254 (0.25 mm thick, Merck), and spots were detected by ultraviolet (uv) irradiation of the plate at 254 and 300 nm. Medium-pressure column chromatography (mcc) was undertaken on a 530-4-10V apparatus (Yamazen) using Lobar grosse B (310-25, Lichroprep Si60, Merck) as a column. Short column chromatography (short cc) was undertaken using silica gel (Kieselgel 60 F_{254} (Typ T), Merck) under reduced pressure. Ether refers to diethyl ether.

Methyl 18,19-Didehydro-21-oxocorynan-17-oate **24**--To a solution of LDA (8.70 mmol) in THF (7.0 ml), HMPT (1.80 ml) was added and after 30 min a solution of the lactam **15** (294 mg, 0.869 mmol) in THF (8.5 ml). After 2 h at -78°C the reaction mixture was poured into aqueous acetic acid, neutralized with concentrated sodium bicarbonate solution and extracted with methylene dichloride. The solvent was removed under reduced pressure and the residue was separated by flash chromatography (petroleum ether-ethyl acetate=2:3). One recovers the starting lactam **15** (162 mg, 55%) and the vinyl lactam **24** (80 mg, 27%) which was recrystallized from petroleum ether-ethyl acetate and melts with decomposition. Ir ν_{max} cm^{-1} 3470 (NH), 1727 (COOMe), and 1628 (NCO). Nmr (300 MHz) δ : 5.75 (1H, ddd, J= 16.9, 10, and 9.7 Hz, 19-H), 5.35 (1H, d, J= 10 Hz, 18-H), 5.22 (1H, d, J= 16.9 Hz, 18-H), 5.13 (1H, m, 5-Heq), 4.85 (1H, dd, J= 11.3 and 3.8 Hz, 3-H), 3.71 (3H, s, COOMe), and 1.56 (1H, q, J= 12.2 Hz, 14-Hax). Ms m/z 338 (M^+). Anal. Calcd $C_{20}H_{22}N_2O_3$. $0.6H_2O$: C, 68.79; H, 6.70; N, 8.02. Found: C, 68.73; H, 6.74; N, 8.31.

2,3,4,9-Tetrahydro-2-(3-furoyl)-1-methylene-1H-pyrido[3,4-b]indole **17**--A solution of 3-furoyl chloride(0.95 g, 7.3 mmol) in benzene (20 ml) was added dropwise to an ice-cooled, stirred solution of harmalane (1.23 g, 6.7 mmol) and triethylamine (2.5 ml) in benzene (70 ml). After being stirred at room temperature for 2 h, the solution was filtered to remove triethylamine hydrochloride. The filtrate was evaporated to give the unstable enamide **17** (1.82 g, 98%) as a pale yellow glass. Ir $\nu_{max}$$cm^{-1}$ 1632 (NCO). Nmr (60 MHz) δ : 5.37 and 4.90 (each 1H, d, J=1 Hz, H_2C=C), which was used for irradiation without further purification.

Reductive Photocyclization of Enamide **17** --Sodium borohydride (3.0 g, 80 mmol) and methanol (100 ml) were added successively to a stirred solution of the enamide **17** (1.82 g, 6.6 mmol) in acetonitrile (900 ml) at 5-10°C. When the added sodium borohydride had dissolved, the resulting solution was irradiated for 2 h. The reaction mixture was then evaporated at room temperature under reduced pressure. Water was added to the residue and the separated oil was extracted with methylene dichloride. The extract was washed, dried, and evaporated to give a solid which was recrystallized from ether-methanol to give the lactam **30** (1.4 g, 77%) as colorless crystals, mp 237-239°C (decomp.). Ir $\nu_{max}$$cm^{-1}$ 3480 (NH) and 1635 (NCO). Nmr (200 MHz) δ : 6.32 (1H, t, J=3 Hz, 2-H), 5.28 (1H, t, J=3 Hz, 3-H), 5.11 (1H,

m, 6-Heq), 5.03 (1H, td, J=11, 6 Hz, 13a-H), 4.77 (1H, br dd, J=11, 2 Hz, 12b-H), 4.00 (1H, dt, J=11, 2.5, 3a-H), 2.58 (1H, ddd, J=13, 6, 3 Hz, 13-Hax), and 1.96 (1H, br q, J=12 Hz, 13-Hax). Anal. Calcd $C_{17}H_{18}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.85; H, 5.88; N, 9.70.

Catalytic Hydrogenation of the Dihydrofuran **30**--A solution of the dihydrofuran **30** (2 g) in methanol (150 ml) was catalytically hydrogenated over platinum dioxide (400 g) under a hydrogen atmosphere at room temperature for 2 h. Work-up gave a solid which was recrystallized from methanol to afford the tetrahydrofuran **27** (2 g, 99%) as colorless crystals, mp 115-116°C(Et_2O-MeOH). Ir $\nu_{max}^{cm^{-1}}$ 3480 (NH), 1628 (NCO). Nmr (200 MHz) δ : 5.14 (1H, m, 6-Heq), 4.76 (1H, dd, J=12, 3 Hz, 12b-H), 4.46 (1H, ddd, J=12, 9, 5 Hz, 13a-H), 3.95 (1H, td, J=9, 6.5 Hz, 2-H), 3.81 (1H, td, J=9, 6.5 Hz, 2-H), 3.20 (1H, q, J=9 Hz, 3a-H), 2.64 (1H, ddd, J= 12.5, 5, 3.5 Hz, 3-H), 2.16 (1H, dq, J=12, 9 Hz, 3-H), and 1.70 (1H, q, J=12 Hz, 13ax-H). Anal. Cacld $C_{17}H_{18}N_2O_2$: C, 68.77; H, 7.05; N, 8.90. Found: C, 68.69; H, 7.00; N, 8.98.

Elimination-Addition Reaction of the Furopyridone **27**--According to the following procedure using 11.2 equiv. of LDA, other elimination-addition reactions of **27** were carried out under the reaction condition as summarized in Table 2 and all results obtained are collected in the same Table.

tert-Butyl acetate (0.4 ml, 3 mmol) was added with stirring at -78°C to an LDA solution, prepared from diisopropylamine (0.8 ml, 5.6 mmol) and butyllithium (10% solution in hexane)(3.6 ml, 5.6 mmol) at -78°C. After being stirred at -78°C for 15 min, a solution of the furopyridone **27** (140 mg, 0.5 mmol) in THF (15 ml) was added and the resulting solution was stirred for 1 h whilst being warmed up to 0°C. After addition of water, the reaction mixture was extracted with methylene dichloride. The extract was dried and evaporated to give a residue which was purified by mcc to give the products.

28b: colorless crystals, mp 210-211°C (Et_2O-MeOH). Ir $\nu_{max}^{cm^{-1}}$: 3490 (NH), 3350 (OH), 1720 (COOtert-Bu), 1618 (NCO). Ms m/z: 398 (M^+). Nmr(200 MHz) δ :5.09 (1H, m, 5-Heq), 4.93(1H, dd, J=9, 5 Hz, 3-H), 3.90-3.62 (2H, m, 18-H_2), 2.09 (1H, br t, J=9 Hz, 14-Hax), 2.04-1.88 (1H, m, 19-H), 1.72-1.58 (1H, m, 19-H), 1.48 (9H, s, COOtert-Bu). Anal. Calcd $C_{23}H_{30}N_2O_4$: C, 69.32; H, 7.59; N, 7.03. Found: C, 69.09; H, 7.67; N, 6.90.

28a: pale yellow crystals, mp 91-93°C(Et_2O-hexane). Ir $\nu_{max}cm^{-1}$: 3490 (NH), 3300 (OH), 1720 (COOtert-Bu), 1618 (NCO). Ms m/z: 398 (M^+). Nmr (200 MHz) δ :5.14 (1H, m, 5-Heq), 4.87 (1H, dd, J=9.5, 4 Hz, 3-H), 3.78 (2H, br q, J=5Hz, 18-H_2), 2.13 (1H, br t, J=11 Hz, 14-Hax), 2.00-1.66 (2H, m, 19-H_2), 1.49 (9H, s, COOtert-Bu). Anal. Calcd $C_{23}H_{30}N_2O_4$ 2/5H_2O:C, 69.01; H, 8.00; N, 6.54. Found: C, 68.78; H, 7.82; N, 6.54.

31a: colorless crystals, mp 224.5-225.5°C (MeOH). Ir $\nu_{max}cm^{-1}$: 3480 (NH), 3420 (OH), 1630 (NCO). Ms m/z: 282 (M^+). Nmr (60 MHz) δ :6.40 (1H, br d, J=5 Hz, 2-H). Anal. Calcd $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.26; H, 6.43; N, 9.79.

33: very unstable oil. Nmr (200 MHz) δ :6.12 (1H, br d, J=10 Hz, 1- or 2-H), 5.86 (1H, br d, J=10 Hz, 1- or 2-H), 5.49 (1H, br s, 12b-H), 5.17 (1H, m, 6-Heq), 3.82 (2H, br t, J=6.5 Hz, CH_2CH_2OH), 1.96 (2H, m, CH_2CH_2OH).

tert-Butyl (3β,20α)-(±)-18,19-Didehydro-21-oxocorynan-17-oate **34b**--According to the literature,[23] selenation of the cis-adduct **28b** (1.62 g, 4 mmol) with o-nitrophenylselenocyanate (1.29 g, 5.6 mmol), tributylphosphine (1.4 ml, 5.6 mmol) gave the selenide (2.05 g, 86%). Ir $\nu_{max}cm^{-1}$: 3476 (NH), 1720 (COOtert-Bu), 1630 (NCO). Nmr (200 MHz) δ :8.30 (1H, dd, J=7, 1 Hz, 3'-H), 5.12 (1H, m, 5-Heq), 4.94 (1H, br dd, J=10, 5 Hz, 3-H), 3.20-3.06 (2H, m, 18-H_2), 1.46 (9H, s, COOtert-Bu). Oxidation of the selenide (500 mg, 0.86 mmol) with 80% m-chloroperbenzoic acid (mCPBA)(200 mg, 0.9 mmol) in methylene dichloride (50 ml) at 0°C afforded the olefin **34b** (294 mg, 86%) as pale yellow crystals, mp 201-202°C (AcOEt). Ir $\nu_{max}cm^{-1}$: 3485 (NH), 1718 (COOtert-Bu), 1628 (NCO). Ms m/z: 380 (M^+). Nmr (200 MHz) δ :5.49 (1H, ddd, J=17, 11, 8 Hz, 19-H), 5.42-5.24 (2H, m, 18-H_2), 5.06 (1H, m, 5-Heq), 4.96 (1H, br s, 3-H), 3.14 (1H, dd, J=8, 3 Hz, 20-H), 1.46 (9H, s, COOtert-Bu). Anal. Calcd $C_{23}H_{28}N_2O_3$: C, 72.60; H, 7.42; N, 7.37. Found: C, 72.44; H, 7.47; N, 7.42.

tert-Butyl (3β)-(±)-18,19-Didehydro-21-oxocorynan-17-oate **34a**--According to the procedure given for **34b**, selenation of the trans-adduct **28a** (1.62 g) followed by oxidation of the resulting selenide gave the olefin **34a** (1.11 g, 72%) as pale yellow crystals, mp 193-194°C (CH_2Cl_2-Et_2O). Ir $\nu_{max}cm^{-1}$: 3485 (NH), 1718 (COOtert-Bu), 1628 (NCO). Ms m/z: 380 (M^+). Nmr (200 MHz) δ :5.72 (1H, ddd, J=17.5, 10, 7 Hz, 19-H), 5.28-5.06 (2H, m, 18-H_2), 5.12 (1H, m, 5-Heq), 4.92 (1H, br t, J=7 Hz,

3-H), 1.48 (9H, s, COOtert-Bu). Anal. Calcd $C_{23}H_{28}N_2O_3$: C, 72.60; H, 7.42; N, 7.37. Found: C, 72.48; H, 7.51; N, 7.35.

Isomerization of the Olefins **34a** and **34b**--(a) By using sodium hydride. Sodium hydride (300 mg, 12 mmol) was added with stirring at 0°C to a solution of the cis-olefin **34b** (1g, 2.6 mmol) in THF (100 ml). After being stirred at room temperature for 30 min, water and then 10% hydrochloric acid were added. The mixture was extracted with methylene dichloride. The extract was dried and evaporated to give a residue which was purified by short cc to give tert-butyl (3β,19E)-(±)-19,20-didehydro-21-oxocorynan-17-oate **14b** (880 mg, 88%) as pale yellow crystals, mp 226.5-227°C (Et_2O-MeOH). Ir $\nu_{max}cm^{-1}$: 3500 (NH), 1720 (COOtert-Bu), 1663 (NCO). Ms m/z: 380 (M^+). Nmr (200 MHz) δ :7.08 (1H, q, J=7 Hz, 19-H), 5.24 (1H, m, 5-Heq), 5.03 (1H, dd, J=5, 2 Hz, 3-H), 3.49 (1H, m, 15-H; 18% intensity increase upon irradiation at 1.86), 2.58 (1H, ddd, J=14.5, 5, 3.5 Hz, 14-Heq), 2.50 (1H, dd, J=15.5, 10 Hz, 16-H), 2.43 (1H, dd, J=15.5, 6 Hz, 16-H), 1.90 (1H, ddd, J=14.5, 12, 5 Hz, 14-Hax), 1.86 (3H, d, J=7 Hz, 19-Me), 1.53 (9H, s, COOtert-Bu). Anal. Calcd $C_{23}H_{28}N_2O_3$: C, 72.60; H, 7.42;N, 7.37. Found: C, 72.36; H, 7.52; N, 7.40.

Similar treatment of the trans-olefin **34a** (1 g) with sodium hydride followed by purification of the crude product gave the identical E-olefin **14b** (803 mg, 83%) obtained above.

(b) By using LDA. A solution of the cis-olefin **34b** (25 mg, 0.066 mmol) in THF (5 ml) was added with stirring at -78°C to an LDA solution, prepared from diisopropylamine (0.03 ml, 0.2 mmol) and butyllithium (10% solution in hexane)(0.13 ml, 0.2 mmol) at -78°C. After being stirred at -78°C for 20 min, water was added and the reaction mixture was extracted with methylene dichloride. The extract was dried and evaporated to give a residue which was purified by short cc (ethyl acetate-methylene dichloride=1:5) to give the E-olefin **14b** (22 mg, 86%). Similar isomerization of the trans-olefin **34a** (25 mg) afforded the identical lactam **14b** (23 mg, 91%). These products **14b** and **14b** were identical (ir spectra and Rf values) with two samples obtained in (a).

Addition Reaction of Thiophenol to E-Ethylidene Lactam **14b** --Butyllithium (10% solution in hexane)(10.1 ml, 15.8 mmol) was added with stirring at 0°C to a solution of thiophenol (3.3 ml, 31.6 mmol) in THF (20 ml) to give a solution of a mix-

ture of thiophenol-lithium thiophenoxide=1:1. To the resulting solution was added the E-ethylidene-lactam **14b** (2 g, 5.3 mmol) and the solution was refluxed for 5 h. After being cooled, the mixture was made alkaline by addition of 1N sodium hydroxide and extracted with methylene dichloride. The extract was dried and evaporated to give a residue which was purified by mcc (ethyl acetate-methylene dichloride=1:9) to afford tert-butyl (3β,19R*)-(±)-19-(phenylthio)-21-oxocorynan-17-oate **35** 2.2 g (86%) as pale yellow crystals, mp 154.5-155.5°C (hexane-Et_2O) and tert-butyl (3β,19S*)-(±)-19-(phenylthio)-21-oxocorynan-17-oate **36** 150 mg (6%) as pale yellow oil.

35: Ir $\nu_{max}cm^{-1}$: 3480 (NH), 1718 (COOtert-Bu), 1624 (NCO). Ms m/z: 490 (M^+). Nmr (500 MHz) δ :7.54-7.12 (9H, m, aromatic H), 5.10 (1H, br dd, J=12.5, 4 Hz, 5-Heq), 4.86 (1H, br dd, J=10.7, 4.7 Hz, 3-H), 3.86 (1H, qd, J=7, 5 Hz, 19-H), 2.86 (1H, m, 15-H), 2.53 (1H, br d, J=5 Hz, 20-H), 2.46 (3H, m, 16-H_2 and 14-Hax), 2.31 (1H, dt, J=13.6, 4.7 Hz, 14-Heq), 1.52 (9H, s, COOtert-Bu), 1.42 (3H, d, J=7 Hz, 19-Me). Anal. Calcd $C_{29}H_{34}N_2O_3S$ 1/3H_2O: C, 70.13; H, 7.04; N, 5.64. Found: C, 70.29; H, 6.95; N, 5.35.

36: Ir $\nu_{max}cm^{-1}$: 3476 (NH), 1718 (COOtert-Bu), 1624 (NCO). Nmr (500 MHz) δ :7.37 (2H, dd, J=6, 0.5 Hz, 2'-and 6'-H), 7.23 (3H, br t, J=6 Hz, 3'-, 4'-, and 5'-H), 5.11 (1H, m, 5-Heq), 4.85 (1H, br dd, J=10.3, 4.5 Hz, 3-H), 4.21 (1H, qd, J=7, 3.5 Hz, 19-H), 2.80 (1H, m, 15-H), 2.43 (1H, br t, J=3.5 Hz, 20-H), 2.30 (3H, m, 16-H_2 and 14-Heq), 1.99 (1H, ddd, J=13.9, 10.3, 4.5 Hz, 14-Hax), 1.17 (3H, d, J=7 Hz, 19-Me). *High resolution Ms m/z: Calcd* $C_{29}H_{34}N_2O_3S$ (M^+) 490.2295. Found: 490.2289.

Oxidation of the Sulfide **35** --mCPBA (80%)(330 mg, 1.53 mmol) was added with stirring at 0°C to a solution of the sulfide **35** (720 mg, 1.47 mmol) in methylene dichloride (30 ml). After being stirred at 0°C for 15 min, the reaction mixture was made alkaline by addition of 5% aqueous sodium bicarbonate and then extracted with methylene dichloride. The extract was dried and evaporated to give a residue which was purified by mcc (ethyl acetate-methylene dichloride=1:1) to afford tert-butyl (3β,19R*)-(±)-19-(phenylsulfinyl)-21-oxocorynan-17-oate **37a** (357 mg, 48%) and **37b** (364 mg, 49%).

37a: pale yellow oil. Ir $\nu_{max}cm^{-1}$: 3472 (NH), 1716 (COOtert-Bu), 1638 (NCO). Ms m/z: 380 (M^+-PhSOH). Nmr (200 MHz) δ :7.76 (2H, m, 2'- and 6'-H), 7.52 (3H, m, 3'-, 4'-, and 5'-H), 5.10 (1H, m, 5-Heq), 4.93 (1H, br t, J=4 Hz, 3-H), 3.28 (1H,

br dd, J=8.5, 3 Hz 20-H), 2.72 (1H, qd, J=7, 3 Hz, 19-H), 2.20 (1H, m, 15-H), 1.45 (9H, s, COOtert-Bu), 0.82 (3H, d, J=7 Hz, 19-Me).

37b: pale yellow oil. Ir $\nu_{max}cm^{-1}$: 3470 (NH), 1718 (COOtert-Bu), 1632 (NCO). Ms m/z: 380 (M^+-PhSOH). Nmr (200 MHz) δ :7.66 (2H, m, 2'- and 6'-H), 7.51 (3H, m, 3'-, 4'-, and 5'-H), 5.15 (1H, m, 5-Heq), 4.93 (1H, br dd, J=9, 5 Hz, 3-H), 3.21 (1H, qd, J=7, 4 Hz, 19-H), 2.60 (1H, m, 15-H), 2.50 (1H, br d, J=4.5 Hz, 20-H), 1.47 (9H, s, COOtert-Bu), 1.20 (3H, d, J=7 Hz, 19-Me).

Pyrolysis of the Sulfoxide **37a**--A solution of the sulfoxide **37a** (690 mg) in toluene (30 ml) was refluxed for 1 h. After evaporation of solvent, the residue was purified by short cc (ethyl acetate-methylene dichloride=1:5) to give tert-butyl (3β,19Z)-(±)-19,20-didehydro-21-oxocorynan-17-oate **13b** (507 mg, 98%) as colorless crystals, mp 210-211°C (Et_2O-MeOH). Ir $\nu_{max}cm^{-1}$: 3476 (NH), 1718 (COOtert-Bu), 1658 (NCO). Ms m/z: 380 (M^+). Nmr (200 MHz) δ :6.06 (1H, q, J=7 Hz, 19-H), 5.22 (1H, m, 5-Heq), 4.94 (1H, br dd, J=12, 5 Hz, 3-H), 3.03 (1H, m, 15-H), 2.48 (2H, d, J=8 Hz, 16-H_2), 2.46 (1H, dt, J=12, 4 Hz, 14-Heq), 2.10 (1H, td, J=12, 4 Hz, 14-Hax), 2.17 (3H, d, J=7 Hz, 19-Me), 1.49 (9H, s, COOtert-Bu). Anal. Calcd $C_{23}H_{28}N_2O_3$: C, 72.60; H, 7.42; N, 7.37. Found: C, 72.63; H, 7.46; N, 7.33.

Pyrolysis of the Sulfoxide **37b**--According to the procedure given for **13b**, pyrolysis of the sulfoxide **37b** (690 mg) in toluene (30 ml) followed by short cc of the crude product gave the Z-ethylidene-lactam **13b** (512 mg, 99%) which was identical (ir spectra and Rf values) with the product **13b** obtained by pyrolysis of **37a**.

Oxidation of the Sulfide **36** and Pyrolysis of the Resulting Sulfoxide--According to the procedure given for **37a**, oxidation of the sulfide **36** (20 mg, 0.04 mmol) with mCPBA (9 mg, 0.042 mmol) followed by pyrolysis of the sulfoxide by refluxing in toluene for 24 h gave the E-ethylidene-lactam **14b** (14.5 mg, 93%) after purification by short cc (ethyl acetate-methylene dichloride=1:5) of the crude product. The olefin **14b** was identical (ir spectra and Rf values) with the olefin **14b** obtained by isomerization of the vinyl lactam **34a**.

Addition Reaction of Thiophenol to Z-Ethylidene Lactam **13b**--According to the procedure given for **35**, addition of thiophenol, using thiophenol (0.07 ml, 0.72 mmol) and butyllithium (10% solution in hexane)(0.23 ml, 0.36 mmol), to the olefin **13b**

(47 mg, 0.12 mmol) followed by purification of the crude product by mcc (ethyl acetate-methylene dichloride=1:9) gave **35** (6 mg, 10%), **36** (32 mg, 53%), and tert-butyl (3β,19R*,20α)-(±)-19-(phenylthio)-21-oxocorynan-17-oate **39** (6 mg, 10%) as pale yellow oil. Two products **35** and **36** were respectively identical (ir spectra and Rf values) with two products **35** and **36** obtained by addition reaction of thiophenol to **14b**.

39: Ir ν_{max} cm^{-1}: 3476 (NH), 1718 (COOtert-Bu), 1632 (NCO). Nmr (500 MHz) δ :7.42 (2H, dd, J=8, 0.5 Hz, 2'- and 6'-H), 7.26 (2H, br t, J=8 Hz, 3'- and 5'-H), 7.19 (1H, tt, J=8, 0.5 Hz, 4'-H), 5.11 (1H, m, 5-Heq), 4.93 (1H, dd, J=10, 5.6 Hz, 3-H), 3.93 (1H, qd, J=7, 4.4 Hz, 19-H), 2.85-2.75 (2H, m, 15- and 16-H), 2.71 (1H, t, J=4.4 Hz, 20-H), 2.62 (1H, dt, J=13.5, 5.6 Hz, 14-Heq), 2.40 (1H, dd, J=15, 11.1 Hz, 16-H), 1.85 (1H, ddd, J=13.5, 10, 3 Hz, 14-Hqx), 1.50 (9H, s, COOtert-Bu), 1.49 (3H, d, J=7 Hz, 19-Me). High resolution ms m/z: Calcd $C_{29}H_{34}N_2O_3S$ (M$^+$) 490.2292. Found: 490.2288.

Oxidation of the Sulfide **39** and Pyrolysis of the Resulting Sulfoxide--According to the procedure given for **37a**, oxidation of the sulfide **39** (20 mg) followed by pyrolysis of the corresponding sulfoxide gave the E-ethylidene-lactam **14b** (14 mg, 91%) which was identical (ir spectra and Rf values) with the olefin obtained by isomerization of the vinyl lactam **34a**.

tert-Butyl (3β)-(±)-21-Oxocorynan-17-oate **38**--(a) By reduction of the 15,20-trans-vinyl lactam **34a**. Catalaytic hydrogenation of the trans-vinyl lactam **34a** (30 mg, 0.078 mmol) in methanol (10 ml) over platinum dioxide (10 mg) under hydrogen atmosphere at room temperature for 1 h. Usual work-up gave the crude solid which was recrystallized from methylene dichloride-hexane to afford the saturated lactam **38** (29 mg, 96%) as pale yellow crystals, mp 162-163°C (n-hexane). Ir ν_{max} cm^{-1}: 3480 (NH), 1718 (COOtert-Bu), 1620 (NCO). Ms m/z: 382 (M$^+$). Nmr (500 MHz) δ :5.13 (1H, m, 5-Heq), 4.83 (1H, dd, J=10, 5 Hz, 3-H), 2.44 (1H, dd, J=18, 10.5 Hz, 16-H), 2.39 (1H, m, 15-H), 2.37 (1H, dd, J=18, 6 Hz, 16-H), 2.23 (1H, dt, J=14, 5 Hz, 14-Heq), 2.22 (1H, m, 20-H), 2.13 (1H, ddd, J=14, 10, 2.9 Hz, 14-Hax), 1.79 (1H, m, 19-H), 1.60 (1H, dquint., J=14, 7 Hz, 19-H), 1.48 (9H, s, COOtert-Bu), 0.94 (3H, t, J=7 Hz, 19-Me). Anal. Calcd $C_{22}H_{30}N_2O_3$: C, 72.22; H, 7.91; N, 7.32. Found: C, 72.14; H, 7.78; N, 7.24.

(b) By desulfurization of the sulfide **35**. Raney-Ni (ca. 2 ml) was added with

vigorous stirring and refluxing to a solution of the sulfide **35** (20 mg) in ethanol (10 ml) whilst the reaction was monitored by tlc. After filtration of the catalyst, the filtrate was condensed to give a solid which was recrystallized from methylene dichloride-methanol to give the ethyl lactam **38** (28 mg, 93%). This product was identical (ir spectra and Rf values) with the sample obtained by catalytic hydrogenation of **34a**.

(c) By desulfurization of the sulfide **36**. According to the procedure described in (b), desulfurization of the sulfide **36** (20 mg) gave the ethyl lactam **38** (29 mg, 96%) which was identical (ir spectra and Rf values) with the sample obtained by catalytic hydrogenation of **34a**.

tert-Butyl (3β,19E)-(±)-19,20-Didehydrocorynan-17-oate **40b**--A solution of aluminum hydride solution, prepared from lithium aluminum hydride (285 mg, 7.5 mmol) and anhydrous aluminum trichloride (335 mg, 2.5 mmol), was added dropwise with stirring at -50°C to a solution of the E-lactam **14b** (200 mg, 0.53 mmol) whilst the reaction was monitored by tlc. After addition of water, the reaction mixture was extracted with methylene dichloride. The extract was dried and evaporated to give a residue which was purified by short cc (methylene dichloride, then ethyl acetate-methylene dichloride=1:1) to give the amine **40b** (107 mg, 56%) as pale yellow oil. Ir ν_{max} cm^{-1}: 3480 (NH), 2852, 2804, and 2744 (Bohlmann band), 1714 (COOtert-Bu). Nmr (200 MHz) δ :5.50 (1H, q, J=7 Hz, 19-H), 3.62 (1H, br d, J=12 Hz, 3-H), 3.46 (1H, m, 15-H), 3.24 (2H, s, 21-H_2), 2.52 (1H, dd, J=14, 6 Hz, 16-H), 2.48 (1H, dd, J=14, 7.5 Hz, 16-H), 2.10 (1H, br d, J=13 Hz, 14-Heq), 1.83 (1H, ddd, J=13, 12, 5 Hz, 14-Hax), 1.66 (3H, d, J=7 Hz, 19-Me), 1.48 (9H, s, COOtert-Bu). High resolution ms m/z: Calcd $C_{23}H_{34}N_2O_2$ (M^+) 366.2302. Found: 366.2305.

Methyl (3β,19E)-(±)-19,20-Didehydrocorynan-17-oate **40a**--A solution of the tert-butyl ester **40b** (200 mg) in 15% sulfuric acid-methanol (20 ml) was stirred at 20°C overnight. After addition of saturated aqueous sodium bicarbonate, the reaction mixture was extracted with methylene dichloride. The extract was dried and evaporated to give a residue which was purified by short cc (ethyl acetate-methylene dichloride=1:4) to give the methyl ester **40a** (173 mg, 98%), mp 123-124°C (Et_2O-n-hexane)(lit.[11,28,32] 134-136°C). Ir ν_{max} cm^{-1}: 3480 (NH), 2852, and 2750 (Bohlmann bands), 1730 (COOMe). Ms m/z: 324 (M^+). Nmr (200 MHz) δ : 5.50 (1H, q,

J=7 Hz, 19-H), 3.78 (3H, s, COOMe), 3.62 (1H, br d, J=13 Hz, 3-H), 3.48 (1H, m, 15-H), 3.24 (2H, s, 21-H_2), 2.68 (1H,dd, J=15, 8 Hz, 16-H), 2.58 (1H, dd, J=15, 7 Hz, 16-H), 2.10 (1H, dt, J=13, 2 Hz, 14-Heq), 1.84 (1H, td, J=13, 5 Hz, 14-Hax), 1.65 (3H, d, J=7 Hz, 19-Me). Anal. Calcd $C_{20}H_{24}N_2O_2$ 1/5H_2O: C, 73.23; H, 7.49; N, 8.54. Found: C, 73.21; H, 7.54; N, 8.56.

Methyl (3β,19E)-(±)-16,17,19,20-Tetradehydro-17-hydroxycorynan-16-caboxylate **41**--A solution of the methyl ester **40a** (75 mg, 0.23 mmol) in THF (5 ml) was added with stirring at -78°C to an LDA solution, prepared from diisopropylamine (0.1 ml, 0.72 mmol) and butyllithium (10% solution in hexane)(0.45 ml, 0.72 mmol) at -78°C. The solution was stirred for 1 h whilst being warmed up to 0°C. After addition of water, the reaction mixture was extracted with methylene dichloride. The extract was dried and evaporated to give a residue which was purified by short cc (methylene dichloride and then ethyl acetate-methylene dichloride=1:1) to afford the ester **41** (53 mg, 65%) as pale yellow oil, identical with the authentic sample by comparison of their spectral data. Ir ν_{max} cm^{-1}: 3480 (NH), 1740, 1717, 1662, and 1623 (CO-CH-COOMe). Nmr (200 MHz) δ :9.81 (1/6H, d, J=3.5 Hz, 17-H of keto form), 9.46 (1/6H, br d, J=3 Hz, 17-H of keto form), 8.04 (2/3H, s, 17-H of enol form), 5.88-5.37 (1H, m, 19-H), 3.90 (1/2H, s, COOMe of keto form), 3.76 (2H, s, COOMe of enol form), 3.74 (1/2H, s, COOMe of keto form), 1.67 (2H, br d, J=7 Hz, 19-Me of enol form), 1.54 (1H, br d, J=7 Hz, 19-Me of keto form). High resolution ms m/z: Calcd $C_{21}H_{24}N_2O_3$ (M^+) 352.1784. Found: 352.1785.

Reduction of the Formyl Ester **41** with Sodium Borohydride--Sodium borohydride (11 mg, 0.3 mmol) was added in small portions with stirring at 0°C to a solution of the formyl ester **41** (95 mg, 0.27 mmol) whilst the reaction was monitored by tlc. After addition of water, the reaction mixture was extracted with methylene dichloride. The extract was dried and evaporated to give a residue which was purified by mcc (ethyl acetate) to afford methyl (3β,16R*,19E)-(±)-19,20-didehydro-17-hydroxycorynan-16-carboxylate **6** (31 mg, 33%) and methyl (3β,16S*,19E)-(±)-19,20-didehydro-17-hydroxycorynan-16-carboxylate **7** (35mg, 37%).

6: pale yellow crystals, mp 191-199°C (EtOH). Ir ν_{max} cm^{-1}: 3480 (NH), 3320 (OH), 2852, 2804, and 2770 (Bohlmann bands), 1720 (COOMe). Nmr (200 MHz) δ : 5.68 (1H, q, J=7 Hz, 19-H), 3.89 (3H, s, COOMe), 3.80 (2H, d, J=6 Hz, 17-H_2), 3.78 (1H, br d, J=13 Hz, 3-H), 3.31 (1H, ddd, J=11.5, 4.5, 2 Hz, 15-H, 10.5% intensity increase

upon irradiation at 1.71), 3.25 (2H, s, 21-H_2), 3.10 (1H, m, 16-H), 2.00 (1H, dt, J=13, 2 Hz, 14-Heq), 1.82 (1H, td, J=13, 4.5 Hz, 14-Hax), 1.71 (3H, d, J=7 Hz, 19-Me, 1.9% intensity increase upon irradiation at 3.80). High resolution ms m/z: $C_{21}H_{26}N_2O_3$ (M^+) 354.1924. Found: 354.1941.

Crystal data of **6**--$C_{25}H_{30}N_2O_4$, M.W. 428.573, monoclinic; a=11.099(5), b=14.098(3), c=16.145(3)A, β = 98.54(2)° , V= 2498(1)A^3, Z= 4, Dx= 1.1395 gcm^{-3}

R value 0.15 for 4263 reflections (Cu Kα , $2\theta_{max}$ < 130°) space group $P2_1/n$

7: colorless crystals, mp 202-203°C (CH_2Cl_2-MeOH). Ir $\nu_{max}cm^{-1}$: 3480 (NH), 3330 (OH), 2852, 2804, and 2750 (Bohlmann bands), 1726 (COOMe). Ms m/z: 354 (M^+). Nmr (200 MHz) δ :5.55 (1H, q, J=7 Hz, 19-H), 4.04 (1H, dd, J=12, 4 Hz, 17-H), 4.02 (1H, dd, J=12, 6 Hz, 17-H), 3.68 (3H, s, COOMe), 3.64 (1H, br d, J=13 Hz, 3-H), 3.39 (1H, br dd, J=11, 5 Hz, 15-H; 9.2% intensity increase upon irradiation at 1.60), 3.34 (1H, br d, J=12.5 Hz, 21-H), 3.22 (1H, d, J=12.5 Hz, 21-H), 3.14 (1H, m, 16-H; 7.1% intensity increase upon irradiation at 3.64), 2.28 (1H, br d, J=13 Hz, 14-Heq; 8.4% intensity increase upon irradiation both at 4.04 and 4.02), 1.79 (1H, td, J=13, 5 Hz, 14-Hax), 1.60 (1H, dd, J=7, 1 Hz, 19-Me). Anal. Calcd $C_{21}H_{26}N_2O_3$ 2/5H_2O: C, 69.74; H, 7.47; N, 7.55. Found: C, 69.87; H, 7.37; N, 7.76.

Methyl (3β,19E)-(±)-19,20-Didehydro-21-oxocorynan-17-oate **14a**--A solution of the E-lactam **14b** (82 mg, 0.22 mmol) in 15% sulfuric acid-methanol (20 ml) was stood at room temperature overnight. The reaction mixture was made alkaline by addition of saturated aqueous sodium bicarbonate and extracted with methylene dichloride. The extract was dried and evaporated to give a residue which was purified by short cc (ethyl acetate-methylene dichloride=3:7) to give the methyl ester **14a** (713 mg, 98%) as colorless crystals, mp 205.5-206.5°C (Et_2O-MeOH)(lit.[15] 192°C). Ir $\nu_{max}cm^{-1}$: 3480 (NH), 1725 (COOMe), 1660 (NCO). Ms m/z: 338 (M^+). Nmr (200 MHz) δ : 7.10 (1H, q, J=7 Hz, 19-H), 5.24(1H, m, 5-Heq), 5.02 (1H, br dd, J=12, 4 Hz, 3-H), 3.77 (3H, s, COOMe), 3.53 (1H, m, 15-H), 2.62 (1H, dd, J=15, 10 Hz, 16-H), 2.60 (1H, dt, J=14, 5 Hz, 14-Heq), 2.54 (1H, dd, J=15, 6 Hz, 16-H), 1.92 (1H, br td, J=13, 4 Hz, 14-Hax),1.84 (3H, d, J=7 Hz, 19-Me). Anal. Calcd $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.28. Found: C, 70.79; H, 6.70; N, 8.30.

Methyl (19E)-(±)-3,14,19,20-Tetradehydro-21-oxocorynan-17-oate **42**--A mixture of the methyl ester **14a** (77 mg, 0.23 mmol) and cupric acetate (100 mg, 0.55 mmol) in trifluoroacetic acid (15 ml) was stirred at room temperature for 5 h whilst dry

oxygen gas was bubbled into the solution. The reaction mixture was made alkaline by addition of saturated aqueous sodium bicarbonate and extracted with methylene dichloride. The extract was dried and evaporated to give a residue which was purified by short cc (ethyl acetate-methylene dichloride=1:4) to afford **42** (51 mg, 66%) as pale yellow oil. Ir ν_{max} cm^{-1}: 3470 (NH), 1730 (COOMe), 1670 (NCO). Nmr (200 MHz) δ :7.02 (1H, q, J=7 Hz, 19-H), 5.55 (1H, d, J=7 Hz, 14-H), 4.89 (1H, dt, J=13, 5 Hz, 5-Heq), 3.95 (1H, m, 15-H), 3.72 (3H, s, COOMe), 2.56 (1H, dd, J=16, 9 Hz, 16-H), 2.48 (1H, dd, J=16, 6 Hz, 16-H), 1.88 (3H, d, J=7, 19-Me). High resolution ms m/z: Calcd $C_{17}H_{18}N_2O_3$ (M^+) 336.1497. Found: 336.1472.

Reduction of the Enamine **42** with Sodium Borohydride--Sodium borohydride (30 mg, 0.8 mmol) was added to a solution of the enamine **42** (30 mg, 0.088 mmol) in acetic acid (10 ml) at 5°C and the solution was stirred at 5°C for 30 min. The reaction mixture was made alkaline by addition of saturated aqueous sodium bicarbonate and then extracted with methylene dichloride. The extract was dried and evaporated to give a residue which was purified by plc (methanol-ether=2:98) to afford **14a** (13 mg, 42%) and methyl (19E)-(±)-19,20-didehydro-21-oxocorynan-17-oate **16** (14.5 mg, 48%) as pale yellow crystals, mp 212-213°C (Et_2O-MeOH)(lit.[4] 212-213°C). Mps and spectral data of **16** were identical with those of the authentic sample prepared by the Hannover group. Ir ν_{max} cm^{-1}: 3476 (NH), 1728 (COOMe), 1658 (NCO). Nmr (200 MHz) δ : 6.92 (1H, q, J=7 Hz, 19-H), 5.12 (1H, m, 5-Heq), 4.85 (1H, br t, J=5 Hz, 3-H), 3.58 (3H, s, COOMe), 3.44 (1H, br dq, J=11, 5 Hz, 15-H), 2.49 (1H, dt , J=15, 6 Hz, 14-H), 2.34 (1H, dt, J=15, 6 Hz, 14-H), 2.28 (1H, dd, J=16, 4.5 Hz, 16-H), 2.14 (1H, dd, J=16, 11Hz, 16-H), 1.84 (3H, d, J=7 Hz, 19-Me). High resolution ms m/z: Calcd $C_{20}H_{22}N_2O_3$ (M^+) 338.1626. Found: 338.1628.

tert-Butyl (3β,19Z)-(±)-19,20-Didehydrocorynan-17-oate **43b**--According to the procedure given for **40b**, reduction of the Z-ethylidene-lactam **13b** (32 mg, 0.084 mmol) with aluminum hydride at -78°C followed by purification of the crude product by mcc (ethyl acetate-methylene dichloride=1:3) gave the amine **43b** (21 mg, 62 %) as pale yellow oil. Ir ν_{max} cm^{-1}: 3480 (NH), 1714 (COOtert-Bu). Nmr (500 MHz) δ :5.39 (1H, q, J=6.8 Hz, 19-H), 3.71 (1H, t, J=7.2 Hz, 3-H), 3.60 (1H, d, J=12.5 Hz, 21-Heq), 3.01 (1H, d, J=12.5 Hz, 21-Hax), 2.72 (1H, m, 15-H), 2.52 (1H, dd, J=14.5, 8 Hz, 16-H), 2.43 (1H, dd, J= 14.5, 7.6 Hz, 16-H), 1.97 (2H, m, 14-H_2), 1.64 (3H, d, J=6.8 Hz, 19-Me), 1.45 (9H, s, COOtert-Bu). High resolution ms m/z:

Calcd $C_{23}H_{30}N_2O_3$ (M^+) 366.2302. Found: 366.2305.

Methyl (3β,19Z)-(±)-19,20-Didehydrocorynan-17-oate **43a**-- According to the procedure given for **40a**, transesterification of the ester **43b** (15 mg) in 15% sulfuric acid-methanol (2 ml) followed by purification of the crude ester by mcc (ethyl acetate-methylene dichloride=1:4) gave the methyl ester **43a** (13 mg, 98%). as pale yellow oil. Ir $\nu_{max}cm^{-1}$: 3480 (NH), 1730 (COOMe). Nmr (200 MHz) δ :5.24 (1H, q, J=7 Hz, 19-H), 3.72 (1H, m, 3-H), 3.72 (3H, s, COOMe), 3.65 (1H, d, J=12.5 Hz, 21-Heq), 3.19 (1H, m, 15-H), 3.02 (1H, d, J=12.5 Hz, 21-Hax), 2.62 (2H, d, J=7 Hz, 16-H_2), 2.02 (2H, m, 14-H_2), 1.68 (3H, d, J=7, 19-Me). High resolution ms m/z: Calcd $C_{20}H_{24}N_2O_2$ (M^+) 324.1810. Found: 324.1835.

Methyl (3β,19Z)-(±)-16,17,19,20-Tetradehydro-17-hydroxycorynan-16-carboxylate **44**--According to the procedure given for **41**, formylation of the ester **43a** (10 mg, 0.031 mmol) using diisopropylamine (0.013 ml, 0.092 mmol) and butyllithium (10% solution in hexane) (0.06 ml, 0.92 mmol) and ethyl formate (0.5 ml, 7.3 mmol) followed by purification of the crude product gave the formyl ester **44** (8.7 mg, 80 %) as pale yellow oil. Ir $\nu_{max}cm^{-1}$: 3480 (NH), 1740, 1718, 1664, and 1630 CO-CH-COOMe). Nmr (200 MHz) δ :5.60 (1H, m, 19-H), 3.87 (9/7H, s), 3.83 (3/7H, s), 3.76 (3/7H, s), and 3.72 (6/7H, s) (COOMe of keto and enol forms), 1.68-1.58 (3H, m, 19-Me). High resolution ms m/z: Calcd $C_{21}H_{24}N_2O_3$ (M^+) 352.1800. Found: 352.1786.

Reduction of the Formyl Ester **44**--According to the procedure given for **6**, reduction of the formyl ester **44** (14 mg, 0.04 mmol) by sodium borohydride (1.7mg, 0.044 mmol) followed by repeated purification of the product by plc (alumina, methanol-ethyl acetate=2:98) gave methyl (3β,16R*,19Z)-(±)-19,20-didehydro-17-hydroxycorynan-16-carboxylate **10** (1.6 mg, 11 %) and methyl (3β,16S*,19Z)-(±)-19,20-didehydro-17-hydroxy-corynan-16-carboxylate **11** (7 mg, 54 %).

10: pale yellow oil. Ir $\nu_{max}cm^{-1}$: 3490 (NH), 3330 (OH), 2850, 2802, and 2750 (Bohlmann bands), 1728 (COOMe). Nmr (500 MHz) δ :5.50 (1H, q, J=6.8 Hz, 19-H), 3.84 (3H, s, COOMe), 3.74 (3H, m, 3-H and 17-H_2), 3.71 (1H, d, J=13 Hz, 21-Heq), 3.12 (1H, m, 16-H), 2.28 (1H, br d, J=13 Hz, 21-Hax), 2.81 (1H, br dd, J=11.4, 4 Hz, 15-H), 1.92 (1H, br dt, J=13.4, 4 Hz, 14-Heq), 1.88 (1H, ddd, J=13.4, 11, 5.1 Hz, 14-Hax), 1.70 (3H, dd, J=6.8, 1.2 Hz, 19-Me). High resolution ms m/z: Calcd $C_{21}H_{26}N_2O_3$ (M^+) 354.1963. Found: 354.1942.

11: pale yellow oil. Ir $\nu_{max}cm^{-1}$:3480 (NH), 3420 (OH), 2852, 2804, and 2764

(Bohlmann bands), 1728 (COOMe). Nmr (500 MHz) δ :5.32 (1H, q, J=6.8 Hz, 19-H), 3.94 (1H, dd, J=11.3, 4.1 Hz, 17-H), 3.91 (1H, dd, J=11.3, 6.2 Hz, 17-H), 3.65 (1H, d, J=12.8 Hz, 21-Heq), 3.61 (1H, m, 3-H), 3.61 (3H, s, COOMe), 3.00 (1H, br d, J=12.8, 21-Hax), 3.09 (1H, m, 16-H), 2.75 (1H, br d, J=12.2 Hz, 15-H), 2.18 (1H, br dt, J=13.5, 1.5 Hz, 14-Heq), 1.85 (1H, ddd, J=13.5, 12.7, 5.4 Hz, 14-Hax), 1.62 (3H, d, J=6.8 Hz, 19-Me). High resolution ms m/z: Calcd $C_{21}H_{26}N_2O_3$ (M^+) 354.1963. Found: 354.1952.

Catalytic Hydrogenation of the Hydroxy Ester **7**--Catalytic hydrogenation of the hydroxy ester **7** (5 mg) in methanol (10 ml) over platinum dioxide (10 mg) under hydrogen atmosphere at room temperature followed by purification of the crude product by plc (ethyl acetate-methanol=98:2) gave two products, methyl (3β,16S*)-(±)-17-hydroxycorynan-16-carboxylates **45a** (2 mg, 43%) and **45b** (2.7 mg, 54%).

45a: pale yellow oil. Ir $\nu_{max}cm^{-1}$: 3470 (NH), 3420 (OH), 2848, 2802, and 2750 (Bohlmann band), 1720 (COOMe). Nmr (500 MHz)δ :3.95 (1H, dd, J=11.5, 10 Hz, 17-H), 3.83 (3H, s, COOMe), 3.68 (1H, dd, J=11.5, 4 Hz, 17-H), 3.21 (1H, br d, J=12 Hz, 3-H), 3.16 (1H, dd, J=11.5, 4 Hz, 21-Heq), 3.00 (1H, m, 16-H), 2.16 (1H, t, J=11.5 Hz, 21-Hax), 1.96 (1H, m, 15-H), 1.94 (1H, br d, J=12.5 Hz, 14-Heq), 1.73 (1H, m, 20-H), 1.69 (1H, m, 19-H), 1.50 (1H, q, J=12.5 Hz, 14-Hax), 1.26 (1H, m, 19-H), 0.96 (3H, t, J=7, 19-Me). High resolution ms m/z: Calcd $C_{21}H_{28}N_2O_3$ (M^+) 356.2082. Found: 356.2098.

45b: pale yellow oil. Ir $\nu_{max}cm^{-1}$: 3470 (NH), 3420 (OH), 1724 (COOMe). Nmr (500 MHz) δ :4.08 (1H, br s, 3-H), 3.95 (1H, dq, J=11.5, 7 Hz, 17-H), 3.84 (1H, dd, J=11.5, 4 Hz, 17-H), 3.78 (1H, s, COOMe), 2.94 (1H, ddd, J=10.5, 7, 4 Hz, 16-H), 2.79 (1H, dd, J=11.5, 4 Hz, 21-Heq), 2.55 (1H, dd, J=11.5, 7.5 Hz, 21-Hax), 2.07 (1H, ddd, J=13.5, 6, 4 Hz, 14-Heq), 1.97 (1H, ddd, J=13.5, 9, 4 Hz, 14-Hax), 1.82 (1H, m, 15-H), 1.52 (1H, m, 19-H), 1.56 (1H, m, 20-H), 1.25 (1H, m, 19-H), 0.85 (3H, t, J=7 Hz, 19-Me). High resolution ms m/z: Calcd $C_{21}H_{28}N_2O_3$ (M^+) 356.2089. Found:356.2097.

Catalytic Hydrogenation of the Hydroxy Ester **11**--According to the procedure given for **45a,b**, catalytic hydrogenation of the hydroxy ester **11** (10 mg) followed by purification of the crude product by plc (ethyl acetate-methanol=98:2) gave **45a** (7 mg, 70%) and **45b** (2 mg, 20%) which were identical (nmr spectra and Rf values) with

those of the products obtained from **7**.

Methyl (3β,19Z)-(±)-19,20-Didehydro-21-oxocorynan-17-oate **13a**--According to the procedure given for **14a**, transesterification of the t-butyl ester **13b** (100 mg) followed by recrystallization of the crude solid from methylene dichloride gave the methyl ester **13a** as colorless crystals, mp 224.5-225.5°C (CH_2Cl_2) (lit.[15] 218°C), (77 mg, 86%) which showed identical spectra with those of the authentic sample. Ir ν_{max} cm^{-1}: 3476 (NH), 1728 (COOMe), 1658 (NCO). Ms m/z: 338 (M^+). Nmr (200 MHz) δ :6.05 (1H, qd, J=7, 1 Hz, 19-H), 5.20 (1H, m, 5-Heq), 4.94 (1H, br dd, J=11, 5 Hz, 3-H), 3.74 (3H, s, COOMe), 3.08 (1H, m, 15-H), 2.59 (2H, d, J=7.5 Hz, 16-H_2), 2.47 (1H, dt, J=13, 5 Hz, 14-Heq), 2.16 (3H,d, J=7 Hz, 19-Me), 2.10 (1H, ddd, J=13, 11, 3 Hz, 14-Hax). Anal. Calcd $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.25. Found: C, 70.95; H, 6.42; N, 8.23.

Methyl (19Z)-(±)-3,14,19,20-Tetradehydro-21-oxocorynan-17-oate **21**--According to the procedure given for **42**, autooxidation of **13a** (750 mg) followed by purification of the crude product by mcc (ethyl acetate-methylene dichloride=1:4) gave the enamine **21** (645 mg, 86%) as pale yellow oil, which showed identical spectra with those of the authentic sample.[4] Ir ν_{max} cm^{-1}: 3476 (NH), 1728 (COOMe), 1666 (NCO). Nmr (200 MHz) δ :6.08 (1H, br q, J=7, 19-H), 5.62 (1H, dd, J=6, 1.5 Hz, 14-H), 4.93 (1H, br d, J=13 Hz, 5-Heq), 3.68 (3H, s, COOMe), 2.53 (2H, br d, J=7.5 Hz, 16-H_2), 2.10 (3H, br d, J=7 Hz, 19-Me). High resolution ms m/z: Calcd $C_{20}H_{20}N_2O_3$ (M^+) 336.1452. Found: 336.1472.

Methyl (19Z)-(±)-19,20-Didehydro-21-oxocorynan-17-oate **15**--A mixture of the ester **21** (540 mg, 1.6 mmol) and sodium borohydride (400 mg, 10.5 mmol) in a 5:1 mixture of acetic acid and methanol (150 ml) was stirred at 0°C for 30 min. After being made alkaline by addition of saturated aqueous sodium bicarbonate, the reaction mixture was extracted with methylene dichloride. The extract was dried and evaporated to give a residue which was purified by mcc (ethyl acetate-methylene dichloride=1:9) to afford the ester **15** (497 mg, 91%) as colorless crystals, mp 166-167°C(lit.[4] 158°C) (Et_2O-n-hexane). This ester showed identical spectra with those of the authentic sample. Ir ν_{max} cm^{-1}: 3476 (NH), 1730 (COOMe), 1658 (NCO). Ms m/z: 338 (M^+). Nmr (200 MHz) δ :5.19 (1H, qd, J=7, 1 Hz, 19-H), 5.15 (1H, m, 5-Heq), 4.90 (1H, br dd, J=10, 6 Hz, 3-H), 3.69 (3H, s, COOMe), 3.08 (1H, m, 15-H),

2.64 (1H, dd, J=15.5, 5 Hz, 16-H), 2.54 (1H, dt, J=13, 5 Hz, 14-Heq), 2.49 (1H, m, 14-Heq), 2.32 (1H, dd, J=15.5, 9 Hz, 16-H), 2.15 (3H, dd, J=7, 1 Hz, 19-Me), 1.82 (1H, dt, J=13, 10 Hz, 14-Hax). Anal. Calcd $C_{20}H_{22}N_2O_3$: C, 70.98; H, 6.55; N, 8.25. Found: C, 70.95; H, 6.42; N, 8.23.

Methyl (19Z)-(±)-19,20-Didehydrocorynan-17-oate **19**--According to the procedure given for **40b**, reduction of the lactam **15** (150 mg) with aluminum hydride at -78°C followed by purification of the crude product by mcc (ethyl acetate-methylene dichloride=1:6) gave the amine **19** (83 mg, 58%) as pale yellow oil. Ir $\nu_{max}cm^{-1}$: 3480 (NH), 2850, 2808, and 2752 (Bohlmann bands), 1728 (COOMe). Nmr (200 MHz) δ :5.25 (1H, q, J=7 Hz, 19-H), 3.90 (1H, d, J=12.5 Hz, 21-Heq), 3.75 (3H, s, COOMe), 3.54 (1H, br d, J=12 Hz, 3-H), 2.73 (1H, d, J=12.5 Hz, 21-Hax), 2.31 (1H, dd, J=17, 10 Hz, 16-H), 2.23 (1H, dt, J=12, 4 Hz, 14-Heq), 1.71 (3H, d, J=7 Hz, 19-Me), 1.38 (1H, q, J=12 Hz, 14-Hax). High resolution ms m/z: Calcd $C_{20}H_{24}N_2O_2$ (M^+) 324.1837. Found: 324.1837.

Methyl (19Z)-(±)-16,17,19,20-Tetradehydro-17-hydroxycorynan-16-carboxylate **20**--According to the procedure given for **41**, formylation of the ester **19** (100 mg, 0.31 mmol) using diisopropylamine (0.13 ml, 0.92 mmol), butyllithium (10% solution in hexane)(0.6 ml, 0.92 mmol), and ethyl formate (1 ml, 15mmol) followed by purification of the crude product by mcc (ethyl acetate-methylene dichloride=4:1) gave the formyl ester **20** (83 mg, 77%) as pale yellow crystals, mp 137-138°C (Et_2O-n-hexane). Ir $\nu_{max}cm^{-1}$: 3476 (NH), 1720, 1660, 1610, and 1585 (CO-CH-COOMe). Ms m/z: 352 (M^+). Nmr (200 MHz) δ :9.80 (1/10H, d, J=3 Hz, 17-H of keto form), 9.70 (1/10H, d, J=3, 17-H of keto form), 8.24 (4/5H, s, 17-H of enol form), 5.30-5.18 (1H, m, 19-H), 3.82 (3/10H, s, COOMe of keto form), 3.77 (12/5H, s, COOMe of enol form), 3.70 (3/10H, s, COOMe of keto form), 1.68 (12/5H, br d, J=7 Hz, 19-Me of enol form), 1.58 (3/5H, br d, J=7 Hz, 19-Me of keto form). Anal. Calcd $C_{21}H_{24}N_2O_3 \cdot H_2O$: C, 68.08; H, 7.07; N, 7.56. Found: C, 68.23; H, 6.84; N, 7.52.

(±)-Z-Isositsirikine **8** and (±)-16-Epi-Z-isositsirikine **9**--According to the procedure given for **6**, reduction of the formyl ester **20** (70 mg, 0.2 mmol) with sodium borohydride (8.3mg, 0.22mmol) followed by repeated purification of the crude product by mcc (methylene dichloride-ether-methanol=15:1:2) gave **8** (23 mg, 33%) and **9** (21 mg, 31%). These products were identical (spectral data and Rf values)

with those of the authentic samples prepared by the Hannover group.[14]

8: colorless crystals, mp 188-189°C (CH_2Cl_2-n-hexane). Ir ν_{max} cm^{-1}: 3480 (NH), 3350 (OH), 2850, 2800, and 2749 (Bohlmann bands), 1724 (COOMe). Ms m/z: 354 (M^+). Nmr (500 MHz) δ :5.48 (1H, q, J=7 Hz, 19-H), 3.91 (1H, dd, J=11.5, 7 Hz, 17-H), 3.83 (1H, dd, J=11.5, 5 Hz, 17-H), 3.81 (1H, d, J=12.5 Hz, 21-Heq), 3.73 (3H, s, COOMe), 3.68 (1H, br d, J=12 Hz, 3-H), 2.98 (1H, m, 16-H), 2.92 (1H, d, J=12.5 Hz, 21-Hax), 2.70 (1H, m, 15-H), 2.18 (1H, dt, J=12, 4 Hz, 14-Heq),1.72 (1H, q, J=12 Hz, 14-Hax), 1.71 (3H, d, J=7 Hz, 19-Me). Anal. Calcd $C_{21}H_{26}N_2O_3$ 1/4H_2O: C, 70.27; H, 7.44; N, 7.86. Found: C, 70.33; H, 7.53; N, 7.86.

9: pale yellow oil. Ir ν_{max} cm^{-1}: 3480 (NH), 3412 (OH), 2852, 2804, and 2752 (Bohlmann bands), 1724 (COOMe). Nmr (500 MHz) δ :5.22 (1H, q, J=7 Hz, 19-H), 3.99 (1H, dd, J=11.5, 7 Hz, 17-H), 3.92 (1H, d, J=12, 21-Heq), 3.91 (1H, dd, J= 11.5, 4 Hz, 17-H), 3.79 (3H, s, COOMe), 3.53 (1H, br d, J=10 Hz, 3-H), 2.92 (1H, m, 16-H), 2.84 (1H, d, J=12 Hz, 21-Hax), 2.83 (1H, m, 15-H), 2.26 (1H, dt, J=12, 4 Hz, 14-Heq), 1.72 (3H, d, J=7 Hz, 19-Me), 1.46 (1H, br q, J=12, 14-Hax). High resolution ms m/z: Calcd $C_{21}H_{26}N_2O_3$ (M^+) 354.1916. Found: 354.1941.

tert-Butyl (3β)-(±)-18,19-Didehydrocorynan-17-oate **48a**--According to the procedure given for **40b**, reduction of the vinyl lactam **34a** (190 mg) with aluminum hydride at -78°C followed by purification of the crude product by mcc (ethyl acetate-methanol=95:5) gave the amine **48** (115 mg, 63%) as pale yellow oil. Ir ν_{max}, cm^{-1}: 3480 (NH) and 1714 (COOtert-Bu). Nmr (500 MHz) δ : 5.41 (1H, dt, J= 17, 9 Hz, 19-H), 5.07 (1H, dd, J= 17, 2 Hz, 18-H), 5.01 (1H,, dd, J= 9, 2 Hz, 18-H), 4.37 (1H, br s, 3-H), 3.25 (2H, m, 5-H_2), 2.62 (2H, d, J= 7 Hz, 21-H_2), 2.49 (1H, dd, J= 17, 4 Hz, 16-H), 2.41 (1H, dt, J= 14, 3.5 Hz, 14-Heq), 2.10 (1H, br quint, J= 8 Hz, 20-H), 1.97 (1H, dd, J= 17, 10.5 Hz, 16-H), 1.71 (1H, ddd, J= 14, 11, 5 Hz, 14-Hax), and 1.55 (1H, m, 15-H). High resolution ms m/z: Calcd $C_{23}H_{30}N_2O_2$ 366.2306. Found: 366.2324.

Methyl (3β)-(±)-18,19-Didehydrocorynan-17-oate **48b**--According to the procedure given for **40b**, transesterification of the butyl ester **48a** (600 mg, 1.64 mmol) in 15% sulfuric acid-methanol (2 ml) followed by purification of the crude ester by mcc (ethy acetate-methanol=95:5) gave the methyl ester **48b** (450 mg, 85%) as pale yellow oil. Ir ν_{max}, cm^{-1}: 3476 (NH) and 1726 (COOMe). Nmr (500 MHz) δ : 5.39 (1H, br dt, J= 18, 10 Hz, 19-H), 5.08 (1H, dd, J= 18, 2 Hz, 18-H), 5.02 (1H, dd, J= 10,

2 Hz, 18-H), 4.40 (1H, br s, 3-H), 3.70 (3H, s, COOMe), 2.64 (2H, d, J= 7 Hz, 21-H_2), 2.58 (1H, dd, J= 17, 3 Hz, 16-H), 2.41 (1H, dt, J= 14, 3 Hz, 14-Heq), 2.13 (1H, m, 20-H), 2.07 (1H, dd, J= 17, 11 Hz, 16-H), 1.74 (1H, ddd, J= 14, 11, 5 Hz, 14-Hax), and 1.62 (1H, br qt, J= 11, 3 Hz, 15-H). High resolution mass m/z: Calcd $C_{20}H_{24}N_2O_2$ 324.1837. Found: 324.1837.

Methyl (3β)-(±)-16,17,18,19-Tetrahydro-17-hydroxycorynan-16-carboxylate **49**--According to the procedure given for **41**, formylation of the amino ester **48b** (240 mg, 0.74 mmol) using diisopropylamine (0.36 ml, 2.7 mmol) and butyllithium (10% solution in hexane) (1.74 ml, 2.7 mmol) and ethyl formate (1 ml, 15mmol) followed by purification of the crude product by mcc (triethylamine-methylene dichloride= 1:9 then methylene dichloride-methanol=9:1) gave the formyl ester **49** (183 mg, 70%) as pale yellow glass. Ir ν_{max}, cm^{-1}: 3480 (NH), 1718, 1664, and 1610 (CO-CH-COOMe).

(±)-Hirsuteine (**47**)--According to the literature,[32] methanol (10 ml) saturated with hydrogen chloride was added with stirring at -20°C to a solution of the formyl ester **49** (110 mg, 0.31 mmol) in methylene dichloride (1 ml). After being stirred at -20°C for two days, the mixture was made alkaline by addition of 5% aqueous sodium bicarbonate, and extracted with methylene dichloride. The extract was dried and evaporated to give a residue which was purified by mcc (ether-methanol=9:1) to give the (±)-hirsuteine (**47**)(46 mg, 42%) as colorless glass and methyl (3β)-(±)-18,19-didehydro-17-dimethoxycorynan-16-carboxylate **50** (31 mg, 25%) as colorless glass, of which the former (**47**) was also obtained by treatment of the latter **50** with LDA at -78°C and identical with the authentic natural alkaloid[30] upon comparison of their ir, nmr, and mass spectra and Rf values.
47: Ir ν_{max}, cm^{-1}: 3490 (NH) and 1700 (COOMe). Nmr (200 MHz) δ : 7.34 (1H, s, 17-H), 5.38 (1H, ddd, J= 18, 10.5, 9 Hz, 19-H), 5.08-4.86 (2H, m, 18-H_2), 4.63 (1H, br s, 3-H), 3.82 (3H, s, OMe), 3.72 (3H, s, OMe), 2.64 (1H, br td, J= 14, 5 Hz, 14-Hax), 2.42 (1H, br ddd, J= 13, 11, 3 Hz, 15-H), and 2.10 (1H, br d, J= 14 Hz, 14-Heq). High resolution mass m/z: Calcd $C_{22}H_{26}N_2O_3$ 366.1970. Found: 366.1942.
50: Ir ν_{max}, cm^{-1}: 3472 (NH) and 1728 (COOMe). Nmr(200 MHz) δ : 5.43 (1H, ddd, J= 18, 10, 8 Hz, 19-H), 5.15 (1H, dd, J= 18, 2 Hz, 18-H), 5.09 (1H, dd, J= 10, 2 Hz, 18-H), 4.96 (4/5H, d, J= 9 Hz, 17-H), 4.74 (1/5H, d, J= 9 Hz, 17-H), 4.49 (4/5H, br s, 3-H), 4.42 (1/5H, br s, 3-H), 3.73 (12/5H, s, COOMe), 3.69 (3/5H, s, COOMe),

3.40 (12/5H, s, OMe), 3.39 (3/5H, s, OMe), and 3.18 (3H, s, OMe). High resolution mass m/z: Calcd $C_{23}H_{30}N_2O_4$: 398.2203. Found: 398.2195.

Methyl 18,19-Didehydrocorynan-17-oate **51**--The lactam **24** (340 mg, 1.0 mmol) and triethyloxonium hexafluorophosphate (1 g, 4mmol) were dissolved in dry methylene dichloride (16 ml) and treated with molecular sieve (4 A)(3 g). After 12 h, sodium borohydride (149 mg, 4mmol) was added at 0°C and the mixture was kept at this temperature for 1 h. For workup the mixture was poured into aqueous sodium hydroxide and extracted with methylene dichloride. Then the organic solvent was evaporated and purified by flash chromatography to give the amine **51** (226 mg, 70%). Ir $\nu_{max}cm^{-1}$: 3470 (NH) and 1725 (COOMe). Nmr (200 MHz) δ :5.59 (1H, m, 19-H), 5.23-5.07 (2H, m, 18-H_2), 3.71 (3H, s, COOMe), 3.34 (1H, dd, J= 11, 1.5 Hz, 3-H), and 1.37 (1H, q, J= 12 Hz, 14-Hax). High resolution ms m/z: Calcd $C_{20}H_{24}N_2O_2$ 324.1838 (M^+). Found: 324.1837.

Corynantheol (**52**)--The amine **51** (77.3 mg, 0.25 mmol) was dissolved in THF (5 ml) and treated with lithium aluminum hydride (19 mg, 0.5mmol). The mixture was stirred for 45 min. After slow addition of aqueous sodium hydroxide (2 ml) was added and the reaction product was extracted with methylene dichloride. The solvent was removed under reduced pressure and the residue was purified by flash chromatography to yield corynantheol (**52**) (43 mg, 61%). Ir $\nu_{max}cm^{-1}$: 3410 (NH) and 3257 (OH). Nmr (300 MHz) δ :5.59 (1H, m, 19-H), 5.18-5.09 (2H, m, 18-H_2), 3.73 (2H, m, CH_2OH), and 3.32 (1H, dd, J= 11, 1.3 Hz, 3-H). High resolution ms m/z: Calcd $C_{19}H_{24}N_2O$ 296.1889 (M^+). Found: 296.1889. Catalytic hydrogenation of this compound **52** gave the corresponding dihydrocorynantheol which was identical (two tlc systems) with the authentic sample of dihydrocorynantheine.

Corynantheine (**46**)--The amine (**51**) (73 mg, 0.225 mmol) was dissolved in THF (2 ml) and treated with a solution of LDA (1.8 mmol) in THF at -78°C. After being stirred at -78°C, methyl formate (1 ml, 15mmol) was added and the reaction mixture was then allowed to warm up to room temperature and then poured into water. The reaction mixture was extracted with methylene dichloride. The solvent was evaporated and the residue was separated by flash chromatograpy (chloroform-methanol=10:1) to give the starting material **51** (18 mg, 25%) and the formyl ester (56 mg, 71%) which was dissolved in methylene dichloride (10 ml) and the solution

was saturated with dry hydrogen chloride. After addition of methanol (0.17 mmol), the mixture was left in a refrigerator and after 5 days the same amount of methanol was added. The reaction mixture was left another 5 days at the same temperature. For workup the mixture was poured into aqueous sodium hydroxide and extracted with methylene dichloride. The solvent was removed and the residue was purified by flash chromatography (trichloroethane-methanol=5:1) to yield corynantheine (**46**) (22 mg, 38%) which was proved to be identical with a natural product provided by Professor P. Potier.

Methyl (3β,19E)-16-Acetyl-19,20-didehydrocorynan-17-oate **56**--3-Epi-geissoschizine (30 mg) was dissolved in methylene dichloride (7 ml) and treated with a solution of diazomethane in ether (0.25 M, 4 ml). After 4.5 h at room temperature the solvent was removed with a rotary evaporator and the residue was purified by flash chromatography (methylene dichloride-methanol-t-butyl methyl ether=15:1:2) to yield the keto ester **56** (16 mg, 51%). Ir $\nu_{max}cm^{-1}$: 3475 (NH), 1735 (COOMe), and 1715 (Ac). High resolution ms m/z: Calcd $C_{22}H_{26}N_2O_3$ 366.1941 (M$^+$). Found: 366.1841.

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