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2-CYANO Δ^3 PIPERIDEINES—IX[1]

GENERAL STRATEGIES FOR THE SYNTHESIS OF CORYNANTHÉ-STRYCHNOS TYPE INDOLE ALKALOIDS

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Résumé—La synthèse de trois systèmes indoliques de type Corynanthé-Strychnos illustre l'utilité des cyano-2-Δ^3-pipéridéines **1** comme synthons de caractère général pour la synthèse d'alcaloïdes complexes. La condensation de l'aminonitrile **23** avec l'anion du malonate de méthyle suivie d'une déprotection de l'azote indolique et d'une cyclisation en présence de HCl/MeOH conduit à la *cis* indoloquinolizidine **16a** avec un rendement global de 45%. La réaction de la cyano-2-Δ^3-pipéridéine **30** avec l'anion du β-céto ester **29** donne l'énamine stable **31** (Rdt 91%). La cyclisation de **31** ou de l'aminonitrile correspondant **32** en milieu acide tosylique conduit à **34** qui après décarboxylation fournit la N-méthyl deséthylidène dihydroervitsine **25**. Le traitement du sel le dihydro-pyridinium **42** ou de la cyano-2-Δ^3-pipéridéine **43** par Et_2AlCN dans le benzèze donne la cyano-4-Δ^2-pipéridéine **44** (isolée sous forme de composé d'addition dicyano-2,4 **45** avec un rendement de 37%).

Une réaction de Mannich entre **45** et l'indole fournit les nitriles épimères **46a** et **46b** (Rdt: 65%). Ces composés sont traités séparément avec CH_3Li pour donner les cétones **49** et **51** (Rdt: 90%).

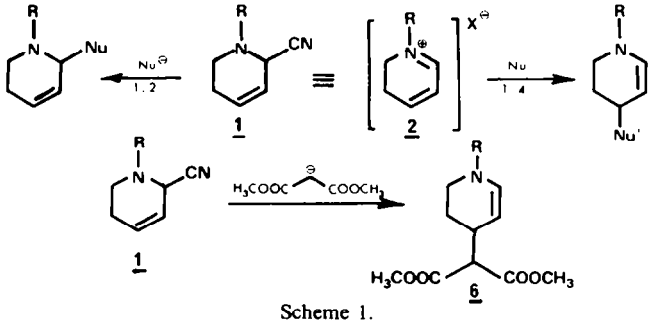
Les composés **49** et **51** donnent tous deux l'épi-20 uléine **36** par cyclisation en présence d'acide 10-camphosulfonique.

Abstract—The syntheses of three Corynanthé-Strychnos type indole systems illustrate how 2-cyano Δ^3 piperideines **1** can be used as synthons for a general approach to the construction of complex alkaloids. By condensation of amino-nitrile **23** with sodium dimethylmalonate and subsequent deprotection of indole N and ring closure in HCl/MeOH, the *cis* indoloquinolizidine **16a** was prepared in 45% overall yield. The reaction of 2-cyano-Δ^3-piperideine **30** with the anion of β-ketoester **29** gave the stable enamine **31** (Y: 91%). Cyclization of **31**, or its corresponding aminonitrile equivalent **32** under acidic conditions (TsOH) gave **34**. Decarboxylation of **34** gave N-methyldesethylidene dihydroervitsine **25**. Treatment of dihydropyridinium salt **42**, or 2-cyano-Δ^3-piperideine **43** with Et_2AlCN in benzene gave 4-cyano-Δ^2-piperideine **44** (isolated as its 2, 4-dicyano adduct **45** in 37% yield). Mannich condensation of **45** with indole gave the epimeric nitriles **46a** and **b** (Y: 65%). These compounds were reacted separately with CH_3Li giving ketones **49** and **51** (Y: 90%). Reaction of both **49** and **51** with 10-camphorsulfonic acid gave 20-epiuleine **36**.

In a recent series of papers,[2-6] we have described the preparation and chemistry of the 2-cyano-Δ^3-piperideines **1**, a new class of compounds which show considerable synthetic potential as "5, 6-dihydropyridinium salt equivalents".[2] In contrast to the unstable 5,6-dihydropropyridinium salt **2** which can exist only under a very restricted set of conditions (i.e. acidic media) their cyano adducts **1** are stable, readily isolable entities. These new synthons retain the reactivity of the parent dihydropyridinium system **2** with respect to nucleophilic addition at the C-2 or C-4 positions without the inconveniences associated with its instability (Scheme 1).

In this paper we wish to further illustrate how 2-cyano-Δ^3-piperideines can be used as synthons for a general approach to the construction of complex alkaloids. In this regard the indole alkaloids are particularly interesting as synthetic targets as the vast majority of these natural products contain within their structure, a substituted piperidine ring. Our present efforts have been directed towards the synthesis of three Corynanthé-Strychnos type indole systems: (i) the tetracyclic indoloquinolizidine system **3**, typical of early members of the Corynanthé alkaloids; (ii) the novel 2-acyl-indole system of ervitsine **4**,[15] and (iii) the indole system **5** of the uleine group (Fig. 1).

In each of these molecules the indole and piper-



Scheme 1.

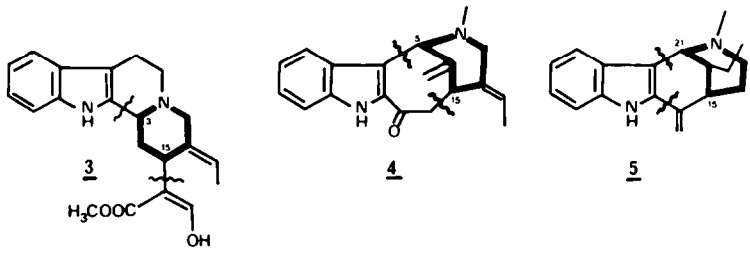


Fig. 1.

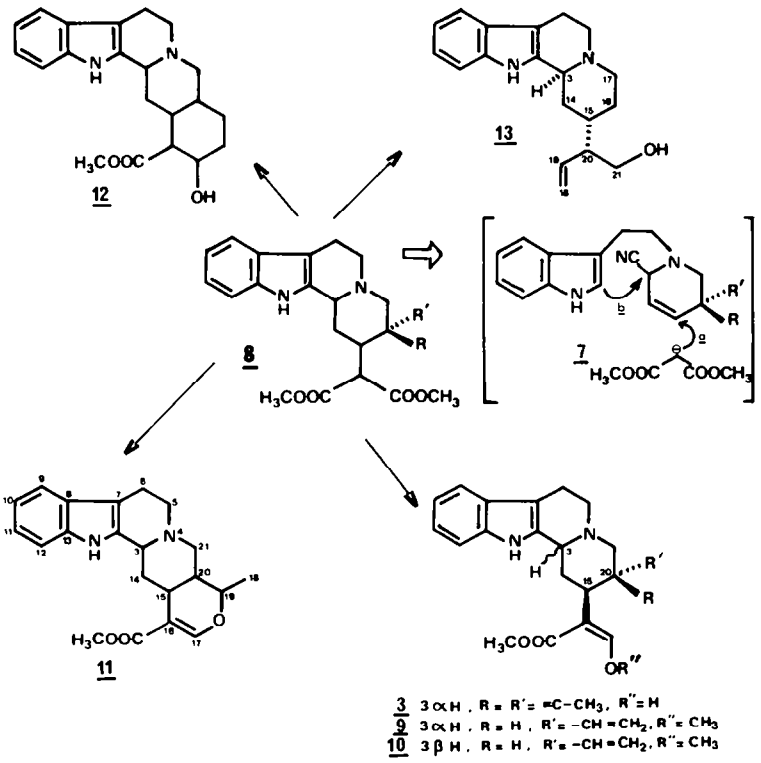
idine portions are joined by bonds connecting the α- and γ-(2 and 4) positions of the piperidine ring (outlined in bold type).[7] This common element forms the basis for the approach to their synthesis using 2-cyano-Δ^3-piperideines.

Indoloquinolizidine synthesis

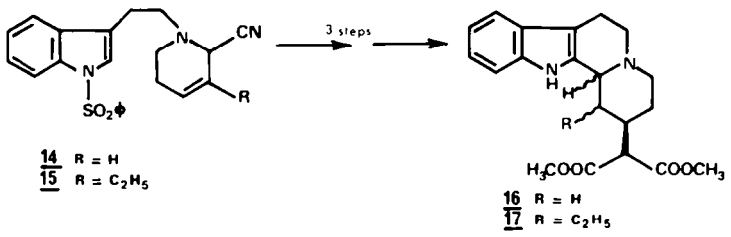
Following the finding that 2-cyano Δ^3 piperideines **1** react cleanly with β-dicarbonyl anions to give C-4 substituted enamines **6**[2] in high yield we envisaged a concise, two steps strategy for the synthesis of the C-15 substituted indoloquinolizidine skeleton of the Corynanthé type indole alkaloids (scheme 2). As illustrated in the retrosynthetic analysis, the transformation **7**→**8** would involve, a) condensation of malonate anion at C-15 of aminonitrile **7**, and b) closure of the C-ring. The subsequent elaboration of the key intermediate **8** to a number of natural alkaloids **3**, **9**–**12** has been previously described.[9–11]

Unfortunately, using our general method[2] the aminonitrile **7** with a substituent at C-20 was unavailable. Therefore, rather than embark upon the development of an entirely new route to this compound it was decided to investigate the feasilbility of the above sequence using the readily available aminonitriles **14** and **15**. As recently reported[6] we were able to show that the indoloquinolizidine systems **16** and **17** could be prepared in 51% and 18% yields respectively (3 steps, including deprotection) from these dihydropyridinium equivalents (scheme 3).

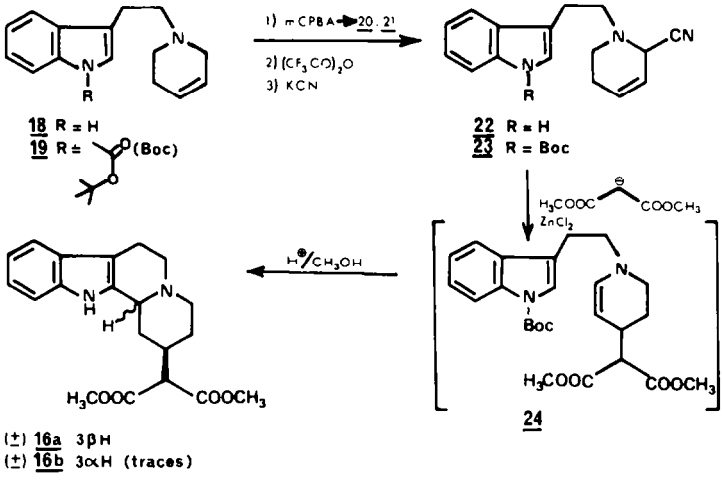
Although successful, the results of this study indicated that some improvements could be introduced, particularly as concerns the protection of the indole N. The removal of the N-benzenesulfonyl group introduced an additional step into the synthesis at a point which required the isolation of fragile intermediates. It was felt that if protection of this N could be avoided, the condensation, and cyclization step could perhaps be carried out with only a change in reaction medium (i.e. THF for MeOH/HCl). This



Scheme 2.



Scheme 3.



Scheme 4.

would hopefully lead to an improvement in product yields, especially where the formation of the tetracyclic system **16** from **14** was concerned.

We therefore returned to the preparation of the unprotected amino-nitrile **22** from tetrahydropyridine **18** (Scheme 4). Formation of the tetrahydropyridine N-oxide **20** (mPCBA, CH_2Cl_2, O°) was achieved without difficulty. However, as previously feared[2,12] reaction of this compound with trifluoroacetic anhydride under a variety of conditions led to formation of a multitude of products from which **22** (detected amongst the more polar components) was isolated in only 4% yield (^{1}H NMR: δ 4.50(s, H-3); 5.96(m, H-14, 15), 7.84(br. s, NH)). Deactivation of the indole N is clearly necessary in order to avoid unwanted side products during the Polonovski–Potier reaction.

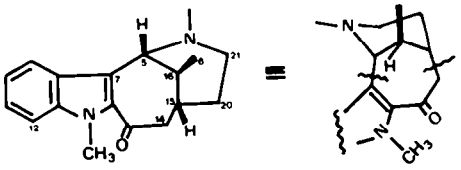
We thus turned our attention towards finding a new protecting group for this N. The t-butyloxycarbonyl protecting group (Boc) was chosen for the present work as it is (a) sufficiently electron withdrawing to prevent side reactions during amino-nitrile formation, (b) its presence would not interfer with the condensation step, and (c) it is acid labile being readily cleaved by treatment with HCl at room temperature.[13] This later feature was particularly attractive as it means that cyclization and deprotection could be achieved in the same operation.

Boc-tetrahydropyridine **19** was prepared from **18** using the phase transfer technique described by Illi.[14] By reaction of **18** in benzene −50% NaOHaq with di-t-butyl carbonate for exactly 20 min, the desired Boc derivative **19** was isolated in 89% yield (IR: 1715 cm^{-1}, ^{1}H NMR: δ 1.68, ^{13}C NMR 27.1, 80.1). Greatly reduced yields due to hydrolysis of the protecting groups in the strongly basic media occurred if longer reaction time were employed.

As above, no difficulties were encountered when **19** was reacted with *m*-chloroperbenzoic acid. N-oxide **21** was obtained pure (74%) after removal of coloured non polar impurities by filtration through an alumina column.

By reaction of N-oxide **21** with trifluoroacetic anhydride at −15°, and treatment of the resultant dihydropyridinium salt with aqueous KCN (buffered to pH 4.0) also at −15° (warming slowly to room temp over 30 min) the desired aminonitrile **23** was obtained. This product proved to be unstable to normal chromatography on alumina, however as the major impurities were more polar materials it could be obtained in essentially pure form (colourless oil, 43%) by rapid filtration under pressure through a short column of alumina. In the ^{1}H NMR spectrum of **23** the singlet resonance at δ 4.25 was attributed to H-3 and the multiplets at δ 5.72 and 6.04 to the olefinic protons H-14 and 15. As previously observed[6] the signals for the bridging methylene protons (H-5 and H-6) were overlapped giving an apparent singlet at δ 2.94. Present in the ^{13}C NMR spectrum were signals at δ 55.2, 51.4 and 83.6 assigned to carbons-3,-14 and the quaternary carbon of the t-Bu group.

The reaction of **23** with sodium dimethylmalonate



25

Fig. 2.

was next studied using $ZnCl_2$ in the place of $AgBF_4$ to catalyse the condensation.[5] By heating **23** and dimethylmalonate anion in the presence of 15 mol % anhydrous $ZnCl_2$ for 8 hr, then evaporating the solvent, the surprisingly stable Boc-enamine **24** was obtained in quantitative yield (^1H NMR examination of the crude product mixture). By subsequently heating the crude enamine **24** in MeOH/HCl for an additional 8–10 hr loss of Boc and cyclization to the desired tetracyclic indoloquinolizidine **16** occurred (reaction at room temp for 2 days did not lead to complete cyclization). The *cis*-quinolizidine (H-3, 15 *trans*) compound **16a** with the configuration typical to antirhine **13** was obtained pure (pale yellow oil, HCl salt m.p. 206–208°) (45%) after preparative layer chromatography on silica gel. The spectral data for this product were identical with those previously recorded.[6] Trace amounts of the *trans*-quinolizidine isomer **16b** were detected using TLC, however this product was not isolated.

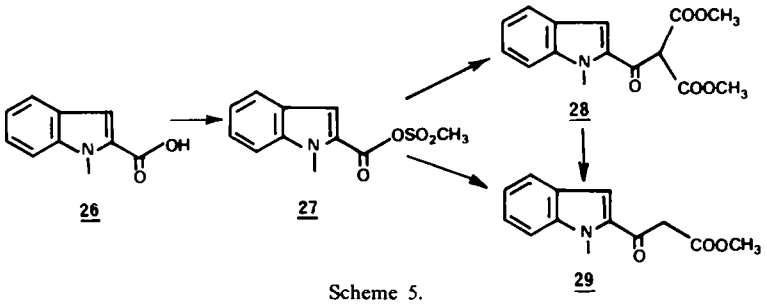
We were thus able to realize the construction of the C-15 substituted indoloquinolizidine system **16** from **23** in two reaction steps, involving in the intermediate work-up stage a simple change in solvent medium. A net increase in the overall yield of **16** was achieved using this new procedure based upon the elimination of an acid labile N_a protecting group (*cf* with ref. 6; 18%).

The yield could certainly be further improved since substantial losses are incurred during chromatographic purification of the only moderately stable tetracyclic product **16**.

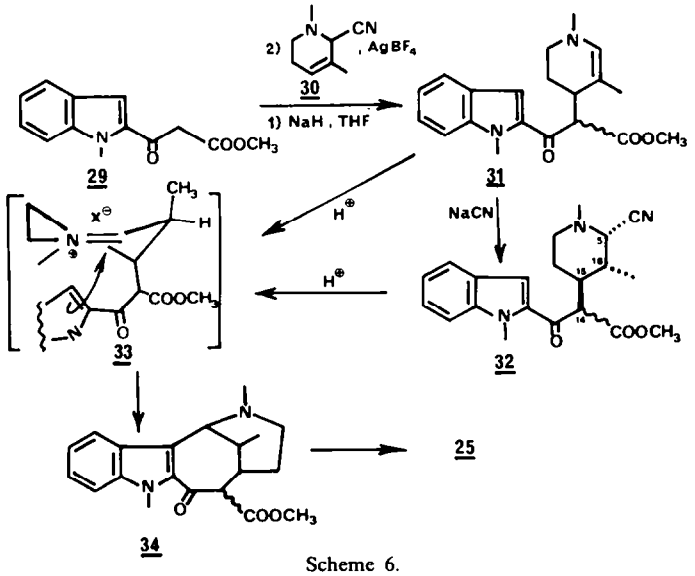
Ervitsine series

Ervitsine **4** is a novel 2-acylindole alkaloid which was isolated in our laboratories from the root barks of *Pandaca boiteaui* (Apocynaceae)[15] (Fig. 1). Strong support exists for the proposed biogenesis of this series by rearrangement of the Corynanthé alkaloid vobasine.[8,15] As this rearrangement occurs without fragmentation of the monoterpene unit ervitsine is considered as belonging to the Corynanthé-Strychnos group. For the sake of simplicity, we first directed our attention towards the preparation of its desethylidene dihydro derivative **25** (Fig. 2) as the required aminontrile **30** is readily prepared from 3-picoline.[2,3] The strategy for the synthesis of this compound resembles closely that used for the formation of the indoloquinolizidine system **16**, i.e. the reaction of a keto ester anion with the γ-(C–4) position of the aminonitrile **30** followed by closure of the C-ring under acidic conditions (Mannich reaction) (Scheme 6).

The keto ester component **29** was prepared directly by reaction of the mixed anhydride **27** (CH_3SO_2Cl,



Scheme 5.



Scheme 6.

Et_3N, THF, $-50°$) of 1-methylindole-2-carboxylic acid **26**[16] with the anion of methyl acetate (72%) or alternatively by a two steps sequence involving reaction of **27** with sodium dimethylmalonate (81%), and monodecarboxylation (Al_2O_3, aq. THF) of the resultant keto diester **28** (87%) (Scheme 5).

Reaction of the anion of keto ester **29** with aminonitrile **30** in the presence of $AgBF_4$ led to the formation of the condensation product, enamine **31**, as a (6:4) mixture of isomers (91%). Enamine **31**, a stable yellow oil, displayed strong absorptions in its IR spectrum at 1650 and 1715 cm^{-1} for the keto + enamine and ester systems respectively. In the ^1H NMR spectrum singlets (6:4 ratio) were observed at δ 2.55 and δ 2.53 for the N_b-Me groups of the two isomers. Similarily pairs of singlets were observed at δ 1.45, δ 1.58 for the C-16 Me group, at δ 3.68, δ 3.67 for the two Me groups, at δ 4.07, δ 4.09 for the N_aCH_3 substituents, and finally at δ 5.60, δ 5.70 for the two H-5 enamine protons.

This compound could be cyclized directly to the tetracyclic 2-acylindole **34**, or converted first to its aminonitrile equivalent **32** (NaCN, pH 4.0). Compound **32** was also obtained as a mixture of isomers ($\sim$4:1) from which the major isomer **32a** was obtained crystalline from ethyl acetate (m.p. 161–162°). It was observed that on attempted purification of the minor isomer **32b** by preparative layer chromatography a mixture of **32a** and **b** was always obtained. Under these conditions it is unlikely that isomerization of the C-5 center occurs, thus these two products are likely epimers at C-14. Isomer **32a** displayed strong absorptions of equal intensity in its IR spectrum at 1650 and 1715 cm^{-1} for the keto and ester carbonyls. In the ^1H NMR spectrum of **32a** doublet resonances were observed at δ 4.47 ($J_{14,15} = 4$ Hz), δ 3.77 ($J_{5,16} = 4$ Hz) and δ 1.20 ($J_{6,16} = 7$ Hz) for hydrogens -14 and -5, and the protons of the C-16 Me group. The small $J_{5,16}$ coupling suggested an axial-equatorial relationship between the cyano and Me groups, and the small $J_{14,15}$ coupling indicated that a rotation of the keto ester unit away from the H_{14}–H_{15} anti position has occurred. On irradiation, the H-15 signal δ 2.37 (t, t) collapsed to triplet of doublets ($J_{15,20ax} = J_{15,16} = 12$ Hz, $J_{15,20eq} = 4$Hz) demonstrating that H-15 and H-16 were both axial. Taken together the data indicated that isomer **32a** adopted a conformation where in the cyano group was positioned axial and the keto ester and Me groups were equatorial.[17]

Intramolecular cyclization of **31** or **32** under acidic conditions (TsOH, MeC_6H_5 Δ) gave the tetracyclic product **34** in good yield (Y: 65% from **31**; 75% from **32**). The loss of the signal for the idole β proton in the ^1H NMR spectrum of **34** and the determination that C-7 was a quaternary center in the off resonance ^{13}C NMR spectrum strongly supported the formation of compound **34**.

Finally, by heating **34** in aqueous THF in the presence of basic alumina, decarboxylation occurred giving N-methyldesethylidene dihydroervitsine **25** in 95% yield (structure **25** was confirmed by X-Ray diffraction).[3]

The formation of the bridged system in **34** (and hence **25**) by cyclization of the iminium salt **33** requires that the C-5 and C-15 substituents be *cis*-diaxial and that the corresponding hydrogens be equatorial. The small coupling constant $J_{5,16} \simeq 1$ Hz observed for the H-5 proton (δ 4.35) in the ^1H NMR spectrum of **25** was a direct indication therefore that the bridge Me group (C-16) was in the axial orientation. The origin of this axial orientation of the Me group can be understood if one considers that protonation of the enamine **31** occurs primarily under thermodynamic conditions from the axial direction (or the face of the enamine containing the keto ester substituent) which leads to an iminium salt where the C-16 and C-15 substituents are equatorial. Ring inversion so as to allow the approach of the C-7 and C-5 centers (structure **33**) then places both substituents, and in particular the methyl groups in an axial orientation.

Cyclization of aminonitrile **32** requires its prior decomposition, and ring inversion to the same iminium salt **33**.

20-*Epiuleine synthesis*

Uleine **35**, 20-epiuleine **36**, dasycarpidone **37**, as well as their desalkyl, and dihydroforms, isolated principally from *Aspidosperma* sp.[18] constitute a small family of Strychnos type indole alkaloids which lack the usual two carbon chain derived from tryptophan (Figure 3).[19] A likely pathway for their biogenesis has been proposed involving fragmentation, loss of car-

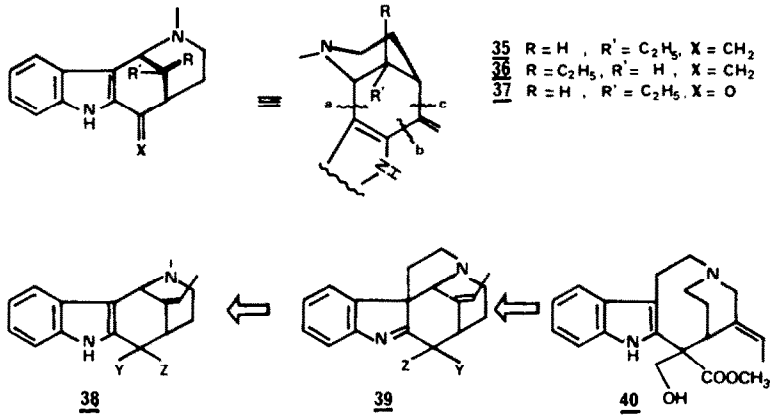


Fig. 3.

bon, and recyclization from the key biosynthetic intermediate stemmadenine **40**.[20] Developing simple methods for the preparation of uleine and related systems **38**, becomes important if one considers the reverse process, i.e. the use of uleine or **38** as a precursor of the more complex bridged alkaloids **39** and ultimately stemmadenine **40** itself.[21]

On examining the uleine skeleton one sees that the indole component is connected directly to the α-position (C-21) of the piperidine ring and bonded to the γ-position (C-15) through a two carbon vinyl unit. Considering this viewpoint two strategies for the construction of this molecule from a 2-cyano-Δ^3-piperideine become apparent: (i) formation of bonds between a 2-cyano-Δ^3-piperideine and an indole component containing the two carbon unit (connections *a* and *c*), or (ii) prior formation of a C-15 substituted piperidine component and its subsequent reaction with indole (connections *a* and *b*). In the present study we have investigated the latter pathway.

A number of syntheses of the uleine (and dasycarpidone **37**) systems have appeared in the literature following this approach.[22] In each case formations of the C-15 substituted piperidine component required a relatively large number of reaction steps.

In our approach to its synthesis we addressed ourselves to the problem of 1,4-vs the normal 1,2-addition[2] of cyanide ion to the dihydropyridinium salt **42** in order to introduce functionality at C-15 (Scheme 7). A C-15 cyano group would act as a potential two carbon unit as reaction with methyllithium leads readily to the corresponding methyl ketone. Unfortunately, reaction of **42** with KCN leads only to the kinetic product 2-cyano-Δ^3-piperideine **43**. To equilibrate **43** to the thermodynamically more stable 1,4 addition product **44** we thus needed an agent which would promote the removal of the cyano group of **43** without removing it completely from the reaction medium. The work of Nagata *et al.*[23] on the 1,4-addition of CN^- to conjugated aldimines using Et_2AlCN suggested a solution to this problem.

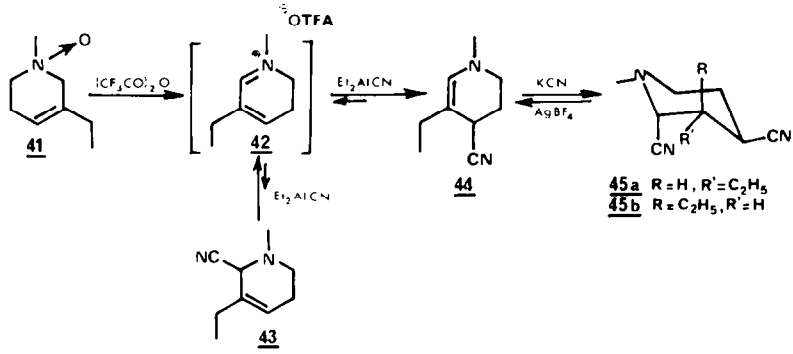
By reaction N-oxide **41**, thoroughly dried under vacuum with trifluoroacetic anhydride in CH_2Cl_2 followed by removal of the solvent and remaining anhydride, the dihydropyridinium salt **42** was obtained in essentially quantitative yield. Reaction of **42** with Et_2AlCN (commercial, Alpha) in THF for 2 hr led to the formation of aminonitrile **43** only. However, if the reaction was allowed to continue overnight complete equilibration of **43** to 4-cyano-Δ^2-piperideine **44** occurred (TLC examination). In contrast, when the reaction was carried out in benzene rapid equilibration of the initial product **43** to **44** occurred, the formation of the enamine **44** being complete in less than 2 hr.[24] The cyanoenamine **44** was isolated as its cyano adduct **45** (4:1 mixture of isomers **45a** and **b**). This isomer mixture was purified by column chromatography on alumina (37%) and a single isomer **45a** (colourless crystals, m.p. 48–59°) was subsequently obtained by crystallisation from ether-hexane.

It was observed that enamine **44** could be readily regenerated from **45** by reaction with $AgBF_4$ in THF. Enamine **44** (IR: 2210, 1660 cm^{-1}; ^1H NMR: δ 2.60 (s, NCH_3), 5.60 (s, H-21) proved to be remarkably stable to extractive work up and column chromatography on alumina.[25]

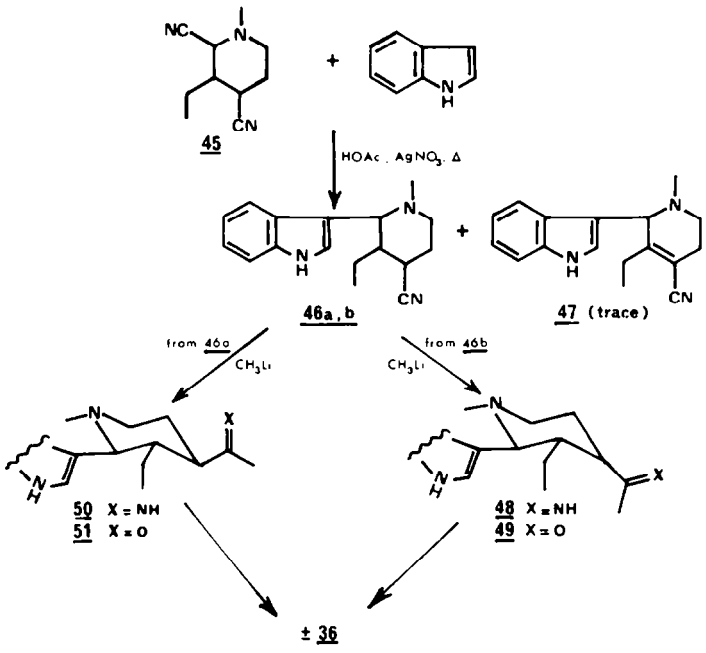
Having developed a short method for the introduction of a substituent at the C-15 position of the piperidine component the intermolecular Mannich condensation between **45a** and indole was studied (Scheme 8). Contrary to previous results[4,22d] this reaction proceeded sluggishly and even after heating at 60–80° for several days would not go to completion. However, if silver nitrate was also present in the medium condensation was complete in less than 16 hr.

The formation of two major components was observed. These products were obtained pure after careful column chromatographic separation from two impurities of similar polarity, present in trace amounts (the least polar of these impurities was identified as compound **47**).[26] The IR, MS, ^1H NMR data indicated that these products were epimers **a** and **b** of the C-21 indole substituted piperidine **46**. Determination of the configuration of the three piperidine ring substituents of the two epimers was hindered by extensive overlapping of the ^1H NMR signals for hydrogens $-14_{ax,eq}$, 20, and -21. The ^1H NMR spectrum of **46b** was sufficiently well resolved however to attribute the signal at δ 3.22 (J = 4 Hz) to H-15. Since no large coupling of H-15 with its neighbors was observed it was concluded that the cyano group of this epimer was in an axial orientation.

An important point to be commented on further below is that the same mixture of isomers **46a** and **b**



Scheme 7.



Scheme 8.

was obtained when the mixture of dicyano adducts **45a** and **b** was used in the condensation with indole. It was apparent that this reaction was independent of the configuration of **45**.

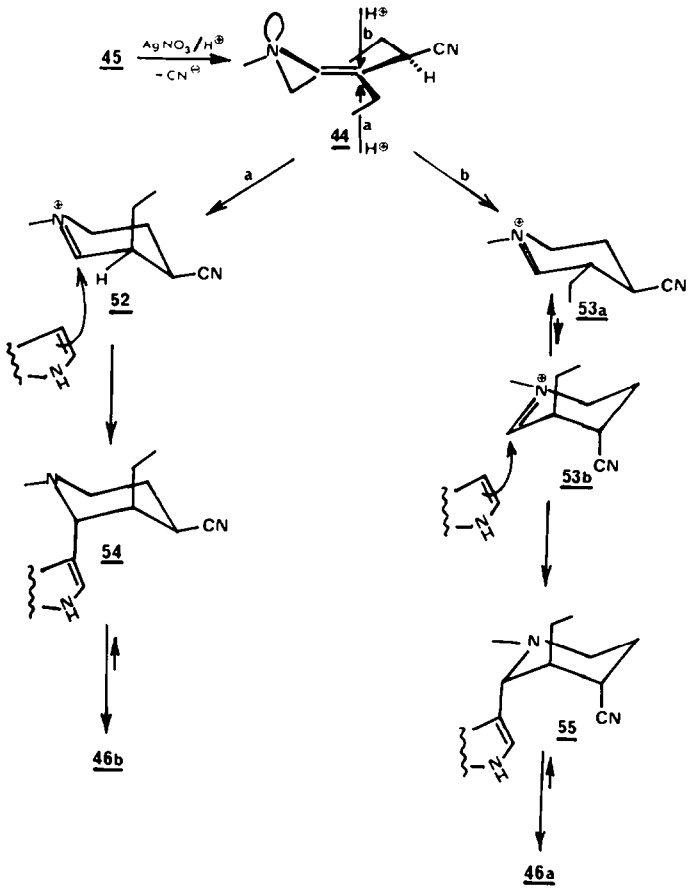
Reaction of isomers **46a** and **b** separately with MeLi in ether led to formation of the epimeric imines **50** and **48** respectively in quantitative yield (TLC determination). Imine **48** (IR: 1640 cm^{-1}; ^1H NMR: δ 1.92 (s, $CH_3C=NH$), 2.05 (s, NCH_3), 4.18 (d, H-21) was hydrolyzed to the ketone **49** (IR: 1700 cm^{-1}) by treatment with aqueous acid (Y: 91% after purification). However it was subsequently found that acidic hydrolysis was unnecessary. On purification of crude imine **50** (IR: 1630 cm^{-1}; ^1H NMR: δ 2.00 (s, $CH_3=NH$), 2.04 (s, NCH_3) by simple filtration through an alumina column complete conversion to the corresponding ketone **51** was observed (90%).

The ^1H NMR spectra of ketones **49** and **51** were well resolved permitting the assignment of all the piperidine ring protons. In the ^1H NMR spectrum of **49** the signal for H-21 appeared as a doublet at δ 3.86. The large $J_{21,20} = 10$ Hz coupling constant indicated that both the indole and ethyl side chains adopted equatorial positions. A quartet resonance (δ 3.10, $J = 4$ Hz) was observed for H-15 which indicated that the acetyl side chain was in the axial position. In the ^1H NMR spectrum of **51** a broadened doublet absorption at δ 3.04 ($J_{21,20} = 10$ Hz) was observed for H-21 and a triplet of doublets resonance at δ 3.61 ($J_{15\text{-}14ax} = J_{15,20ax} = 12$ Hz, $J_{15,14eq} = 4$ Hz) was found for H-15. The large $J_{21,20}$ and $J_{15,20}$ coupling constants indicated that all three substituents occupied equatorial positions.[27]

The two ketones **49** and **51** were thus found to be epimers at the C-15 position. Since there was no epimerization of this center on reaction of nitrile **46b** with methyllithium it is justifiable to assume that the nitriles **46a** and **b** and their corresponding ketones **51** and **49** have identical configurations at the C-20 and 21 centers.

It was clear from the structures of ketones **49** and **51** that on cyclization and dehydration of both compounds 20-epiuleine **36** would be produced. Naturally an epimerization of the C-15 center of **49** would have to take place before cyclization could occur. This final step was accomplished by reacting **49** and **51** in $CHCl_3$ with p-toluenesulfonic acid or 10-camphorsulfonic acid. At present this reaction is not optimized and typical yields are in the order of 35–56%.

In retrospect, as only 20-epiuleine **36** was formed from the two ketones the entire synthesis could be repeated without the separation of epimeric products at each reaction step. Interestingly, on the basis of previous results,[6] it was originally felt that the condensation of **45** with indole would lead to a mixture of epimeric nitriles **46** from which both uleine **35** and 20-epiuleine **36** would be produced. This can be understood by considering the mechanism of the condensation reaction (Scheme 9). Heating dicyanopiperidine **45** in HOAc in the presence of $AgNO_3$ results in formation of the enamine **44**. All stereochemistry is lost in this process which explains why it is unimportant to conduct this reaction with pure **45a** or the mixture of isomers **45a** and **b**. Protonation of enamine **44** in the weakly acidic medium can, and does occur from both faces of the molecule (directions **a** and **b**) leading to iminium salts **52** and **53a**. Condensation of **52** with indole from the axial direction would then lead to the diaxial product **54** which prefers to populate the more energetically favourable conformation of **46b** with one axial substituent. Considering the alternate pathway **b**, it was



Scheme 9.

anticipated that indole would react with the iminium salt **53a** to give a condensation product which would eventually lead to uleine **35**. However, it is apparent that steric hindrance to approach of the incoming indole was sufficiently large to inhibit this reaction. Rather, it was the unhindered diaxial conformer **53b** (probably present in small concentrations) which reacted with indole to give a triaxial product **55** which prefers to exist in the all equatorial conformation of **46a**.[28] The 2:1 ratio of products **46b/a** produced in this reaction probably reflects the difference in concentration of iminium salts **52** and **53b**, and to a lesser extent the direction of protonation of enamine **44**.

Thus, from N-oxide **41**, or 2-cyano-Δ^3-piperideine **43** the natural alkaloid 20-epiuleine **36** was prepared in four steps. The key step in this approach was the substitution of a preformed piperidine synthon at the γ- or C-15 position.

EXPERIMENTAL

IR spectra were recorded in $CHCl_3$ soln on a Perkin–Elmer 297 Spectrophotometer. IR absorption bands are expressed in reciprocal centimeters (cm^{-1}) using polystyrene calibration. Peaks yielding structural information are reported. UV spectra were run in MeOH solon on a Bausch and Lomb Spectronic 505 spectrophotometer. ^1H NMR spectra were recorded in $CDCl_3$ (TMS as internal standard $\delta = 0$) at 400 MHz using a Brüker WM 400 instrument. Chemical shift data are reported in ppm downfield from TMS where s, d, dd, t, q, qn, h, o and m designate singlet, doublet, doublet of doublets, triplet, quartet, quintet, hextet, octet and multiplet respectively. ^{13}C NMR spectra were recorded in $CDCl_3$ (δ, ppm, Me_4Si) on either a Brüker HX 90E (22.63 MHz) or WP 60 (15.08 MHz) instrument. High resolution mass spectrometry was performed on a Kratos MS 80 RF instrument. Column and thin layer chromatography were done using Aluminoxid 90 or Silica gel-60 (Merck, n.9385).

Preparation of t-butyloxycarbonyl indole **19**

A soln of 50% NaOHaq (10 ml) was added to a suspension of **18**[6] (1.00 g, 4.42 mmol) in benzene (20 ml) containing tetrabutylammonium hydrogenosulfate (0.450 g) and the resultant two phase medium was stirred rapidly for 5 min at room temp. under an atmosphere of argon. Di-t-butyl dicarbonate (2.01 g, 8.84 mmol) in benzene (10 ml) was then added dropwise over 10 min, and stirring was continued for exactly 10 min. The benzene layer was then separated and the aqueous layer was washed with CH_2Cl_2 ($\times$ 3). The combined organic fractions were then washed with H_2O, dried over Na_2SO_4 and concentrated to give a viscous orange oil. The crude product mixture was separated by column chromatography on alumina ($\sim$ 50:1) eluting with CH_2Cl_2:hexane (1:1). The desired product **19** was obtained pure as a colourless oil (1.24 g, 89%). IR : ν_{max} 1715 cm^{-1} NCOOR; UV (MeOH): λ_{max} 265,288,298 nm; ^1H NMR ($CDCl_3$): δ 1.68 (s, 9 H, $C(CH_3)_3$), 2.25 (m, 2 H, H-20), 2.70 (t, J = 7 Hz, 2 H, H-21), 2.80 (m, 2 H, H-6), 2.97 (m, 2 H, H-5), 3.12 (m, 2 H, H-3), 5.73, 5.80 (2 m, 1 H each, H-14, 15), 7.43 (s, 1 H, H-2), 8.14 (br.s, 1 H, H-12); ^{13}C NMR ($CDCl_3$): δ 22.0, 25.2, 27.1, 48.2, 50.7, 56.1, 80.1, 110.8, 114.3, 114.5, 117.6, 117.9, 119.5, 120.4; MS m/e (rel. intensity): 326 ($M^{+\cdot}$, 40%), 311 (5%), 269 (10%), 252 (10%),

199 (12%), 143–44 (15%), 130 (25%), 98–96 (100%); Exact mass: *m/e* 326.1963 (Calc for $C_{20}H_{26}N_2O_2$: *m/e* 326.1994).

Preparation of N-*oxide* **21**

m-Chloroperbenzoic acid (90%) (3.32 g, 17.4 mmol) was added in portions over several minutes to a stirred solution of **19** (5.00 g, 15.8 mmol) in CH_2Cl_2 (200 ml) and the resultant reaction mixture was stirred at 0° for 1 hr. Solid K_2CO_3 (excess) was then added and stirring was continued for 15 min. After this period the mixture was suction filtered through a celite bed, and the filtrate was concentrated giving a tan coloured foam. The crude product mixture was separated by column chromatography on alumina (30:1) CH_2Cl_2:hexane (1:1)→(CH_2Cl_2:MeOH 2%). N- oxide **21** (3.87 g, 74%) was obtained pure as a colourless foam. This compound was carried directly through to the following step.

Preparation of aminonitrile **23**

N-oxide **21** (0.460 g, 1.38 mmol) was dissolved in CH_2Cl_2 (30 ml) and stirred at −15° under argon. Trifluoroacetic anhydride (1.0 ml, 5 equiv) was then added dropwise to this soln over a 10 min period. After stirring for an additional 1 hr at −15° an aqueous soln of KCN (buffered to pH 4.0 with citric acid and sodium acetate) was added, cooling was discontinued, and the two phase mixture was stirred vigorously for 0.5 hr. The two layers were then separated and the aqueous phase extracted with CH_2Cl_2 (× 3). The combined CH_2Cl_2 layers were then washed with water, dried over Na_2SO_4 and concentrated to give a pale yellow oil. The crude product mixture was separated by rapid column chromatography on alumina (1:50) under medium pressure (~ 100 mbar) using CH_2Cl_2:hexane (1:1) as eluant. Minimal loss of the desired product was observed if the crude product mixture was first absorbed into a thick layer of sand above the alumina bed, and then quickly absorbed onto the alumina, and flushed through the column. Essentially pure **23** (0.200 g, 43%) was obtained as a colourless viscous oil which foamed radily under vacuum. IR: ν_{max} 1710 cm^{-1}; UV (MeOH): λ_{max} 265, 288, 298 nm; ^{1}H NMR ($CDCl_3$): δ 1.68 (s, 9 H, $C(CH_3)_3$), 2.12 (dt, J ≃ 16, 4 Hz, 1 H, H-20 eq.), 2.39 (m, 1 H, H-20 ax), 2.66 (td, J ≃ 12, 4 Hz, 1 H, H-21 ax), 2.94 (apparent s, 5 H, H-5, 6, 21 eq.), 4.25 (br.s, 1 H, H-3), 5.72 (m, 1 H, H-14), 6.04 (m, 1 H, H-15), 7.45 (s, 1 H, H-2), 8.12 (br.s, 1 H, H-12); ^{13}C NMR ($CDCl_3$): δ 23.0, 25.9, 28.2, 46.9, 51.4, 55.2, 83.6, 115.4, 116.1, 118.2, 119.0, 120.7, 122.6, 123.2, 124.5, 130.3, 130.7, 135.6; MS *m/e* (rel. intensity): 351 (M^+, 25%) 324 (15%), 294–95 (15%), 278 (12%), 267, 269 (10%), 251 (30%), 143 (15%), 130 (25%), 121 (100%); Exact mass: *m/e* 351.1953 (Calc for $C_{21}H_{25}N_3O_2$: *m/e* 351.1946).

Condensation of **23** with sodium dimethylmalonate:

Formation of **16a** *by cyclization of enamine* **24.** Anhydrous $ZnCl_2$ (0.1 mmol) in THF (1 ml) was added *via* syringe to a soln of **23** (0.280 g, 0.80 mmol) in THF (4 ml) stirred at room temp under argon. After several min a soln of sodium dimethylmalonate (1.64 mmol) in THF (5 ml) was added to the mixture and the resultant reaction was stirred at 60° for 8 hr. The cooled reaction was then centrifuged and the supranatent concentrated giving a pale yellow viscous oil containing enamine **24**. IR: ν_{max} 1640, 1705–1740 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$): δ 2.52 (s, 9 H, $C(CH_3)_3$), 4.15 (dd, J ≃ 10, 4 Hz, 1 H, H-3), (dd, J = 10, ~ 1.5 Hz, 1 H, H-14).

Enamine **24** was subsequently redissolved in dry MeOH (10 ml) presaturated with HCl, and the soln heated at 60° under argon for 8–10 hr. The cooled reaction was then diluted with ice water, and the aqueous soln was neutralized by the addition of Na_2CO_2, and extracted with CH_2Cl_2 (× 5). The combined CH_2Cl_2 extracts were then washed with water, dried over Na_2SO_4, and concentrated giving an orange foam. The tetracyclic indole **16a** was isolated pure (0.130 g, 45%) as a pale yellow oil after preparative layer chromatography of the crude product mixture on silica (EtOAc: MeOH: Et_3N (96:3:1)). The spectral data for **16a** was identical to those reported.[6] Product **16a** HCl: Found: C, 60.85%; H, 6.42%; N, 7.05%; Calc for $C_{20}H_{25}N_2O_4Cl$; C, 61.14%; H, 6.41%; N, 7.13%.

Preparation of **28**

The mixed anhydride derivative **27** was prepared first by the addition of a soln of methanesulfonyl chloride (0.383 g, 3.36 mmol) in THF (1 ml) to a soln of **26** (0.553 g, 3.16 mmol) and Et_3N (0.515 g) in THF (20 ml) at −25° (under N_2). The mixture was stirred at −25° for 1 hr (noted immediate formation of a colourless ppt).

Secondly the enolate anion of dimethylmalonate was prepared by the addition of dimethylmalonate (0.600 g, 4.54 mmol) in THF (1 ml) to a suspension of NàH (0.200 g, hexane washed) in THF (15 ml). The mixture was stirred for 30 min under N_2. The mixed anhydride soln was then added (*via* transfer under N_2 pressure through a syringe needle equipped with a filter paper) to the anion soln. THF was added to the non-transferred residue, and this in turn was transferred under N_2 pressure. The resultant mixture was stirred for 45 min at room temp after which time it was poured into a soln of aq. HCl/NaOAc (pH 4.0) and the product extracted with CH_2Cl_2 (× 3). The combined organic fractions were then washed with water, dried over Na_2SO_4 and concentrated affording crystals (0.855 g). Trituration of the crude product mixture with hexane furnished pure **28** (0.624 g, 81%). m.p. 137° (EtOAc); IR: ν_{max} 1670, 1740–1760 cm^{-1}; UV (MeOH): λ_{max} 236, 312 nm; ^{1}H NMR ($CDCl_3$): δ 3.80 (s, 6 H, OCH_3), 4.05 (s, 3 H, NCH_3), 5.37 (s, 1 H, CH); ^{13}C NMR ($CDCl_3$): δ 32.1, 53.2, 62.4, 110.6, 113.0, 121.4, 123.4, 125.9, 127.1, 133.3, 140.9, 165.4, 181.6; MS *m/e* (rel. intensity) 289 (M^+; 25%), 175 (100%), 158 (100%), 130 (30%), 89 (40%); Exact mass *m/e* 289.0927 (Calc for $C_{15}H_{15}NO_5$ *m/e* 289.0950); Found: C, 62.03%; H, 5.08%; N, 4.98%; Calc: C, 62.28%; H, 5.23; N, 4.84%.

Monodecarboxylation of **28**

Preparation of ketoester **29**. A well stirred mixture of **28** (0.110 g, 0.38 mmol), H_2O (0.1 ml) and Merck basic alumina (2 g) in THF (10 ml) was treated at reflux for 4 hr. The alumina was then separated from the mixture by suction filtration and washed repeatedly with CH_2Cl_2. The combined organic fractions were finally concentrated affording pure **29** (0.080 g, 87%). The spectral data for this product were identical with that described below.

Preparation of ketoester **29** from **26**

The mixed anhydride derivative **27** was prepared first by the addition of a soln of methane sulfonylchloride (0.387 g, 3.39 mmol) in THF (1 ml) to a soln of **26** (0.551 g, 3.15 mmol) and Et_3N (0.516 g) in THF (20 ml) at −40° (under N_2). The mixture was stirred at −40° for 45 min, then warmed slowly to 0°.

Secondly, the anion of MeOAc was prepared by the dropwise addition of MeOAc (0.75 ml, ~ 3.20 mmol) over 2 min to a soln of LDA (diisopropylamine, 1.29 ml; n-BuLi, 1.23 M, 7.32 ml) at −78°. The resultant mixture was stirred under N_2, for 30 min. The mixed anhydride soln was then added (*via* transfer under pressure of N_2 through a syringe needle equipped with a filter paper) to the anion soln. THF was added to the non-transferred residue, and this in turn was transferred under N_2 pressure. The mixture was stirred over 10 min at −78°, then allowed to warm to 0° over 50 min. after which time it was diluted with water and extracted with CH_2Cl_2 (× 3). The combined organic fractions were washed with dil HCl aq, dried over sodium sulfate and concentrated (0.674 g).

Trituration of the crude product mixture with EtOAc /hexane afforded pure **29** (0.497 g, 22%). m.p. 106–106.5° (EtOAc); IR: ν_{max} 1660, 1715 cm^{-1}; UV (MeOH): λ_{max} 236, 312 nm. ^{1}H NMR ($CDCl_3$): δ 3.70 (s, 3 H, OCH_3), 3.90 (s, 2 H, CH_2), 4.05 (s, 3 H, NCH_3), 7.35 (s, 1 H, H-7), 7.70 (d, 1 H, H-12); ^{13}C NMR ($CDCl_3$): δ 32.2, 46.8, 110.4, 112.8,

121.0, 123.2, 125.8, 126.5, 133.8, 140.6, 167.9, 185.2; MS *m/e* (rel. intensity): 231 ($M^{+\cdot}$, 30%), 158 (100%); Exact mass *m/e* 231.0894 (Calc for $C_{13}H_{13}NO_3$ *m/e* 231.0895).

Preparation of enamine **31a** *and* **b**

The enolate anion of β-ketoester **29** was generated first by the addition of a soln of **29** (0.224 g, 0.97 mmol) in THF (1 ml) to a suspension of NaH (37 mg, hexane washed) in THF (5 ml). Anion formation was complete after stirring at room temp (under N_2) for 30 min.

Secondly the silver complex of **30** was formed by the addition of a soln of $AgBF_4$ (0.191 g, 1.0 mmol) in THF (2 ml) to a soln of **30** (0.165 g, 1.21 mmol) also in THF (4 ml). The resultant mixture was stirred for 5 min (under N_2) after which time the soln of the anion of **29** was added to it in one portion. After 30 min at room temp the reaction was stopped by the addition of aqueous ammonia and the mixture extracted with CH_2Cl_2 (× 4). The combined organic layers were washed with dilute ammonia, and water, then filtered through a bed of celite, dried over Na_2SO_4 and concentrated. Compound **31** , a ~ 6: 4 mixture of isomers, was obtained in 91% yield (0.298 g). IR: ν_{max} 1715, 1650 cm^{-1}; UV (EtOH): λ_{max} 310 nm; ^1H NMR ($CDCl_3$) (major isomer): δ 1.45 (s, 3 H, CH_3), 2.55 (s, 3 H, N_bCH_3), 3.15 (m, 1 H, H-15), 3.68 (s, 3 H, OCH_3), 4.07 (s, 3 H, $NaCH_3$), 4.43 (d, J = 4 Hz, 1 H, H-14), 5.60 (s, 1 H, H-5); (minor isomer): δ 1.58 (s, 3 H, CH_3), 2.53 (s, 3 H, N_bCH_3), 3.67 (s, 3 H, OCH_3), 4.09 (s, 3 H, N_aCH_3), 4.37 (d, J = 4 Hz, 1 H, H-14), 5.70 (s, 1 H, H-5); MS *m/e* (rel. intensity): 340 ($M^{+\cdot}$, 30%), 231 (20%), 158 (40%), 110 (100%); Exact mass *m/e* 340.1773 (Calc for $C_{20}H_{24}N_2O_3$ *m/e* 340.1786).

Preparation of aminonitriles **32a** *and* **b**

An aqueous soln of NaCN (0.40 g in 20 ml H_20) was added to a soln of crude product **31** (0.298 mg, ~ 0.87 mmol) in CH_2Cl_2 (20 ml). The aqueous phase was adjusted to pH 4.0 by the addition of solid citric acid and the two phase system was stirred vigourously for 45 min. The aqueous phase was then basified with Na_2CO_3 soln and separated from the CH_2Cl_2 layer. After several extractions with further quantities of CH_2Cl_2 the combined organic fractions were washed with water, dried over Na_2SO_4, and concentrated (0.303 g, 94%).

Pure **32a** was obtained by crystallization of the product mixture (EtOAc) and by chromatography of the mother liquors (SiO_2: CH_2Cl_2/MeOH 2%). Attempts to isolate the minor isomer **32b** led to its obtention mixed with **32a** (isomer ratio; 32a/32b ~ 4:1). m. p. 161–162° (EtOAc): IR: ν_{max} 1715, 1650 cm^{-1}; UV (MeOH): λ_{max} 240, 315 nm: ^1H NMR ($CDCl_3$): δ 1.20 (d, J = 7 Hz, 3 H, CH_3), 2.37 (tt, overlapped, J = 12 Hz, 1 H, H-15), 2.40 (s, 3 H, N_bCH_3), 3.73 (s, 3 H, OCH_3), 3.77 (d, J = 4 Hz, 1 H, H-5), 4.10 (s, 3 H, N_aCH_3), 4.47 (d, J = 4 Hz, 1 H, H-14), 7.32 (s, 1 H, H-7), 7.67 (d, 1 H, H-12); ^{13}C NMR ($CDCl_3$): δ 16.6, 27.8, 32.2, 36.7, 38.3, 43.7, 52.2, 55.9, 62.4, 110.5, 111.5, 114.8, 121.0, 123.2, 125.7, 126.5, 134.0, 140.5, 169.1, 189.1; MS *m/e* (rel. intensity): 367 ($M^{+\cdot}$, 5%), 340 (10%), 232 (40%), 200 (40%), 151, 148 (35%), 110 (100%); Exact mass *m/e* 367.1902 (Calc for $C_{21}H_{25}N_3O_3$ *m/e* 367.1895).

Preparation of **34** *by cyclization of enamine* **31**

A mixture of crude product **31** (0.404 g, ~ 1.18 mmol), and TsOH (0.5 g) was refluxed in toluene (using a Dean-Stark apparatus) for 22 hr under an atmosphere of N_2. The mixture was then cooled, basified with NH_4OH aq, and extracted with CH_2Cl_2 (× 3).

The combined organic fractions were washed with water, dried over Na_2SO_4, and concentrated to dryness (0.296 g).

Pure **34** (0.240 g, 64%) was obtained by trituration of the crude product with MeOH and by chromatography of the mother liquors (Silica, CH_2Cl_2/MeOH 5%). m.p. 166° (MeOH); IR: ν_{max} 1660, 1720 cm^{-1}; UV (EtOH): λ_{max} 240, 315 nm; ^1H NMR ($CDCl_3$): δ 1.49 (d, J = 7 Hz, 3 H, CH_3), 2.00 (s, 3 H, N_bCH_3), 3.63 (s, 3 H, OCH_3), 3.72 (d, J = 4 Hz, 1 H, H-14), 3.94 (s; 3 H, N_aCH_3), 4.26 (s, 1 H, H-5), 7.38 (s, 1 H, H-7), 7.70 (d, 1 H, H-12). ^{13}C NMR ($CDCl_3$): δ 21.0, 25.7, 31.7, 34.3, 36.5, 44.1, 45.7, 52.4, 58.5, 65.7, 110.3, 116.8. 120.2, 121.9, 125.3, 127.2, 135.8, 138.6, 170.5, 194.0; *MS m/e* (rel. intensity): 340 ($M^{+\cdot}$, 100), 309 (10), 297 (10), 283 (25), 281 (15), 270 (15), 255 (50), 251 (30), 242 (30); Exact mass *m/e* 340.1792 (Calc for $C_{20}H_{24}N_2O_3$ 340.1786); Found: C, 70.36%; H, 7.12%; N, 8.37%; Calc: C, 70.56%; H, 7.10%; N, 8.22%.

Preparation of **34** *by cyclization of* **32**

The mixture of **32a, b** (0.030 g, 0.82 mmol) and TsOH (50 mg) was refluxed in toluene (using a Dean-Stark apparatus) for 22 hr under an atmosphere of N_2. The mixture was then cooled, basified with NH_4OH aq. and extracted with CH_2Cl_2 (× 3). The combined organic fractions were washed with water, dried over Na_2SO_4 and concentrated to dryness (0.032 g). The desired product **34** (0.024 g, 74%) was obtained pure after separation from polar impurities by thick layer chromatography on silica gel (CH_2Cl_2/MeOH 5%). The spectral data for this product were identical with that described above.

Preparation of **25**

Compound **34** (0.710 g, 2.08 mmol) was dissolved in a mixture of AcOH (10 ml), H_2O (10 ml), conc. H_2SO_4 (1 ml) and treated at reflux for 5 hr. The mixture was then cooled, basified with NH_4OH aq, and extracted with CH_2Cl_2 (× 3). The combined organic fractions were washed with water, dried over Na_2SO_4 and concentrated to dryness. Near colourless crystals of the desired product **25** were obtained (0.563 g, 95%). m.p. 179–180° (MeOH); IR: ν_{max} 1630 cm^{-1}; UV (EtOH): λ_{max} 236, 318 nm; ^1H NMR (240 MHz, $CDCl_3$) δ 1.55 (d, J = 7 Hz, 3 H, CH_3), 2.00 (s, 3 H, N_bCH_3), 2.95, 3.15 (dd, J_{AB} = 12 Hz, J_{AX} = 4 Hz, 2 H, H 14), 3.95 (s, 3 H, N_aCH_3), 4.35 (s, 1 H, H-5); ^{13}C NMR ($CDCl_3$) δ 21.0, 26.1, 32.0, 34.4, 37.6, 44.2, 45.9, 53.6, 58.9, 110.2, 117.5, 120.1, 121.1, 125.2, 127.4, 135.2, 138.2, 198.3; MS *m/e* (rel. intensity) 282 ($M^{+\cdot}$, 100) 254, 251 (10), 239 (10), 225 (25), 210 (20), 199 (100), 184 (45); Exact mass *m/e* 282.1773 (Calc for $C_{18}H_{22}N_2O$: 282.1732); Found: C, 76.56%; H, 7.89%, N, 9.92%; Calc: C, 76.56%; H, 7.85%; N, 9.92%.

Preparation of N*-methyl-2, 4-dicyano-3-ethylpiperidines* **45a** *and* **b**

N-oxide **41**[2] (6.18 g, 43.8 mmol) was dissolved in THF (100 ml) and reacted at 0° under argon with trifluoroacetic anhydride (9.2 ml, 1.5 equiv) (added *via* syringe over a 5 min period). After stirring for 1 hr at 0° the THF and residual anhydride were removed under high vacuum. The mixture containing intermediate **42** was then diluted with benzene (50 ml), and reacted (with cooling) with diethylaluminium cyanide (1.8 M in toluene, 24.3 ml, 43.8 mmol). The resultant mixture was stirred at room temp for 2 hr, then poured into a two phase medium (CH_2Cl_2–H_2O containing KCN, buffered to pH 4.0). After stirring vigourously for 30 min the two phases were separated, and the aqueous phase was washed with CH_2Cl_2 (× 3). The combined organic fractions were then washed with H_2O, dried over Na_2SO_4, and concentrated to give a red coloured oil. The crude product mixture was separated by column chromatography on alumina (200 g) (CH_2Cl_2–hexane, 1:1). Compound **45**, a colourless oil was obtained as a 4:1 mixture of isomers (2.85 g, 37.0%). The major isomer **45a** crystallized from ether-hexane mixtures as colourless cubes; m.p. 58–59°. IR: ν_{max} 2210 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.37 (t, J = 7.5 Hz, 3 H, CH_3), 1.81 (m, 1 H, CH_2), 2.18 (qd partly overlapped, J = 12, 4 Hz, 1 H, H-5 ax), 2.25 (m, 2 H, H-3, CH_2), 2.35(dq, J = 12, 3 Hz, 1 H-5 eq), 2.61 (td partly overlapped, J = 12, 3 Hz, 1 H, H-6 ax), 2.66 (s, 3 H, NCH_3), 2.69 (td overlapped, J = 12, 4 Hz, 1 H, H-4 ax), 3.00 (dm, J = 12.5 Hz, 1 H, H-6 eq), 4.06 (d, J = 4 Hz, 1 H, H-2); ^{13}C NMR ($CDCl_3$): δ 10.7, 23.8, 28.8, 30.4, 42.2, 44.0, 48.9, 57.6, 113.4, 120.3; MS *m/e* (rel. intensity): 177 ($M^{+\cdot}$, 35%), 176 (30%), 162 (27%), 150–148 (25%), 137 (30%), 135

(100%), 123 (40%), 121 (20%), 109 (15%); Found; C, 67.76%; H, 8.53%; N, 23.70%; Calc for $C_{10}H_{15}N_3$: C, 67.87%; H, 8.59%; N, 23.69%. In the ^{1}H NMR spectrum of the minor isomer **45b**, peaks observed at : 2.00 (m), 2.64 (s, NCH_3), 2.77 (m), 3.28 (dt, J = 12.5 Hz), 3.73 (br.s, H-2); ^{13}C NMR: δ 11.6, 20.0, 25.0, 28.3, 41.0, 44.2, 49.7, 56.2.

Condensation of **45** *with indole*

Preparation of products **46a, b** *and* **47**. Silver nitrate (1.40 g, 7.91 mmol) was added in one portion to a soln of **45** (1.40 g, 7.91 mmol) and indole (2.77 g, 23.7 mmol) in 50% aqueous AcOH (10 ml) and the resultant heterogeneous mixture was heated for 24 hr at 60° (argon atmosphere). After this period the mixture was cooled, diluted with 6N HCl (4 ml), stirred for an additional 10 min and finally poured into a separatory funnel containing 10% aq HCl. The aqueous mixture was extracted with ether (× 3), then neutralized with Na_2CO_3 and reextracted with CH_2Cl_2 (× 5). The combined CH_2Cl_2 extracts were washed with water, dried over Na_2SO_4 and concentrated to give a tan foam (1.72 g). Two minor components were isolated after column chromatography of the crude product mixture on silica gel (75 g) eluting with EtOAc/MeOH/Et_3N (93:3:2).

The least polar compound **47** was isolated in only trace amounts. IR: ν_{max} 3490 cm^{-1} NH, 2220 cm^{-1} (S) CN; ^{1}H NMR ($CDCl_3$): δ 0.98 (t, J = 7.5 Hz, 3 H, H-18), 1.93 (m, 1 H, H-19), 2.72 (apparent s, 3 H), 2.40, 2.53 (2m, ~ 5 H), 2.88 (m, 1 H), 4.37 (s, 1 H, H-21), 7.03 (d, 1 H, H-2), 8.30 (br.s, 1 H, NH); ^{13}C NMR ($CDCl_3$): δ 13.3, 27.47, 27.55, 43.4, 47.8, 60.4, 105.11, 111.4, 112.4, 118.6, 119.6, 120.2, 122.5, 124.4, 127.4, 136.5, 137.2; MS *m/e* (rel. intensity): 265 ($M^{+\cdot}$, 60%), 250 (20%), 236 (100%), 221 (10%), 192 (20%); Exact mass *m/e* 265.1544 (Calc for $C_{17}H_{19}N_3$ *m/e* 265.1578).

Intermediate column fractions (0.953 g) contained product **46a** contaminated with **46b** and trace amounts of an unidentified component. Epimer **46a** was obtained pure (0.450 g, 22%) after a second chromatography on silica (EtOAc/MeOH/Et_3N 98:1:1); IR: ν_{max} 3450, 2210 cm^{-1}; UV (MeOH): λ_{max} 278, 283, 292 nm; ^{1}H NMR ($CDCl_3$): δ 0.77 (t, J = 7.5 Hz, 3 H, H-18), 1.30 (m, 1 H, H-19), 1.58 (m, 1 H, H-19), 2.02 (s, 3 H, NCH_3), 2.16–2.25 (m, ~ 4 H), 2.60 (m, 1 H), 3.00 (br. d, J = 12 Hz, 1 H), 3.12 (m, 1 H), 7.80 (br.s, 1 H, H-9), 8.25 (br.s, 1 H, NH); ^{13}C NMR ($CDCl_3$): δ 8.9, 23.4, 29.8, 31.8, 44.5, 56.8, 111.3, 119.5, 721.7, 122.3, 122.7; MS *m/e* (rel. intensity); 267 ($M^{+\cdot}$, 100%), 252 (20%, 238 (10%), 188 (50%), 187 (35%), 174 (45%), 173 (30%), 159 (70%), 158 (75%); Exact mass m/e 267.1724 (Calc for $c_{17}H_{21}N_3$ *m/e* 267.1735). The more polar epimer **46b** was obtained as a colourless foam (0.881 g, 42%). IR: ν_{max} 3450, 2210 cm^{-1}; UV (MeOH): λ_{max} 278, 285, 292 nm.^{1}H NMR ($CDCl_3$): δ 0.75 (t, J = 7.5 Hz, 3 H, H-18), 1.25 (m, 2 H, H-19), 2.07 (s, 3 H, NCH_3), 2.11–2.16 (m, tt, 3-4 H, H-14 ax, H-14 eq, H-20, H-21), 2.61 (m, 1 H, H-3 ax), 3.07 (dt, J = 12, ≃ 4 Hz, H-3 eq), 3.22 (q, J ≃ 4 Hz, 1 H, H-15), 7.80 (br.s, 1 H, H-9), 8.14 (br.s, 1 H, NH); ^{13}C NMR ($CDCl_3$) δ 11.1, 23.6, 28.3, 30.0, 43.9, 44.4, 52.9, 64.7, 111.4, 115.7, 119.6, 120.2, 122.3, 123.2, 136.8; MS *m/e* (rel. intensity); 267 ($M^{+\cdot}$, 100%), 252 (20%), 238 (15%), 186 (95%), 185 (75%), 172 (90%), 157–158 (95%), 143 (50%), 130 (50%); Exact mass *m/e* 267.1729 (Calc for $C_{17}H_{21}N_3$ *m/e* 267.1735).

Preparation of ketone **49** *from nitrile isomer* **46b**

A soln of **46b** (0.300 g, 1.16 mmol) in ether (1 ml) was added dropwise over 5 min to a soln of MeLi (2.40 mmol) in ether (20 ml). The resultant heterogeneous mixture was stirred under argon at room temp for 2 hr. An aqueous 10% soln of HCl (3·5 ml) was then added and vigorous stirring continued for an additional 5 hr. The mixture was then diluted with water, neutralized by the addition of solid K_2CO_3 and extracted with CH_2Cl_2 (× 3). The combined CH_2Cl_2 extracts were subsequently washed with water, dried over Na_2SO_4 and concentrated to give a tan coloured foam. The crude product mixture was separated by column chromatography on alumina (18 g) eluting with CH_2Cl_2–MeOH 1%. Pure **49** was obtained as a colourless foam (0.300 g, 91%). IR: $\nu_{max\ 3480}$, 1700 cm^{-1}; UV (MeOH): λ_{max} 278, 283, 288 nm; ^{1}H NMR ($CDCl_3$): 0.68 (t, J = 7.5 Hz, 3 H, H-18), 1.16 (m, 2 H, H-19), 1.96 (dq, m, overlapped, J = 12, 4 Hz, 1 H each, H-14 eq, 20), 2.05 (s, 3 H, $COCH_3$), 2.10 (m, overlapped, 1 H, H-14 ax), 2.15 (s, 3 H, NCH_3), 2.36 (td, J = 12, 4 Hz, 1 H, H-3 eq), 3.10 (q, J = 4 Hz, 1 H, H-15), 3.86 (d, J = 10 Hz, 1 H, H-21), 8.14 (br.s, 1 H, NH); ^{13}C NMR ($CDCl_3$): δ 12.4, 22.4, 27.0, 30.2, 44.4, 45.6, 46.7, 51.5, 62.1, 111.2, 117.6, 119.3, 120.3, 122.0, 122.5, 127.7, 136.5, 204.5; MS *m/e* (rel. intensity): 284 ($M^{+\cdot}$, 25%), 242 (100%), 198 (60%), 172 (30%); Exact mass *m/e* 284.1886 (Calc for $C_{18}H_{24}N_2O$ 284.1888).

Preparation of ketone **51** *from nitrile* **46a**

MeLi (5% in ether, 2.0 ml) was added dropwise over a 5 min period to a stirred suspension of **46a** (0.200 g, 0.75 mmol) in ether (25 ml) and the resultant mixture was stirred for 3 hr at room temp (argon atmosphere). The reaction was then stopped by the addition of a sat NH_4Cl aq, and the aqueous phase extracted with CH_2Cl_2 (× 3). The combined CH_2Cl_2 layers were washed with water, dried over Na_2SO_4 and concentrated giving a tan coloured foam (0.220 g) containing imine **50**. IR: ν_{max} 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$, 80 MHz); δ 2.00 (s, CH_3C = NH), 2.04 (s, NCH_3).

The crude product mixture containing imine **50** was applied to an alumina column (20 g) and the column was eluted with CH_2Cl_2-MeOH 1%. Hydrolysis of **50** to the desired ketone **51** occurred during the chromatography. The ketone **51** (0.194 g, 90%) was obtained as a colourless foam. IR: ν_{max} 3490, 1700 cm^{-1}; UV (MeOH): λ_{max} 278, 283, 288 nm; ^{1}H NMR ($CDCl_3$): 0.68 (t, J = 7.5 Hz, 3 H, H-18), 1.13 (m, 2 H, H-19), 1.91 (m overlapped, 1 H, H-14 eq), 1.96 (qd overlapped, J = 12, 4 Hz, 1 H, H-14 ax), 2.03 (s, 3 H, CH_3CO), 2.20 (m, overlapped, 1 H, H-3 ax), 2.22 (s, 3 H, NCH_3), 2.35 (m, 1 H, H-20), 2.61 (dt, J = 12, 4 Hz, 1 H, H-15 ax), 3.04 (br.d, J = 10 Hz, 1 H, H-21), 3.12 (dt, J = 12, ~ 4 Hz, 1 H, H-3 eq), 7.82 (br.s, 1 H, H-9), 8.14 (br.s, 1 H, NH); ^{13}C NMR ($CDCl_3$): δ 9.3, 23.2, 28.4, 29.3, 42.8, 44.7, 54.3, 56.5, 64.8, 111.3, 116.5, 119.5, 120.1, 122.1, 122.7, 127.8, 136.5, 204.0; MS *m/e* (rel. intensity): 284 ($M^{+\cdot}$, 40%), 242 (25%), 241 (100%), 198 (40%), 185 (10%), 172 (20%), 157 (15%), 130 (20%);Exact mass *m/e* 284.1900 (Calc for $C_{18}H_{24}N_2O$ *m/e* 284.1888).

Preparation of 20-*Epiuleine* **36**

(i) A mixture of **51** (0.025 g, 0.088 mmol) and *p*-toluenesulfonic acid (0.070 g) was refluxed in $CHCl_3$ (20 ml) for 15 hr after which time the mixture was cooled, basified with NH_4OH, and extracted with CH_2Cl_2 (× 3). The combined organic fractions were wahed with water, dried over Na_2SO_4 and concentrated (0.020 g). 20-epiuleine **36** (0.013 g, 56%) was obtained pure after preparative layer chromatography of the crude reaction mixture on alumina (EtOAc–CH_2Cl_2 (6:2)). The 400 MHz ^{1}H NMR spectrum and the TLC Rf values for **36** were identical with an authentic sample of 20-epiuleine.

(ii) A mixture of **49** (0.19 g, 0.67 mmol) and camphorsulfonic acid (0.600 g) was refluxed in $CHCl_3$ (20 ml) for 24 hr 20-epiuleine **36** (0.062 g, 35%) was obtained after extractive work-up and purification by preparative layer chromatography.

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[28]Compare with compound **31** in ref. 6. For **31** a preference for the triaxial conformation **31** (C 2) was observed in order to reduce interactions between a bulky malonyl substituent at C-15 and an adjacent Et side chain.