Recent Advances in the Chemistry of Macroline, Sarpagine and Ajmaline-related Indole Alkaloids

Simon E. Lewis

Department of Chemistry, Imperial College London, South Kensington Campus, London SW7 2AZ, U.K.
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Abbreviations list: Ac, acetyl; butyrylcarbonyl; Ba, butyl; Bz, diazabicyclo[4.3.0]non-5-ene; D dihydroidine; DIBAL-H, diisobutylaluminium hydride; DBN, 1.5-azabicyclo[4.3.0]non-5-ene; DBU, 1.5-azabicycloundec-5-ene; DBN; DBU; DBH, diisobutylborane; DDQ, 2,3,5,6-tetrachlorobenzo-1,4-dione; DMAP, 4-(dimethylamino)pyridine; DME, 1,2-dimethoxyethane; DMS, dimethyl sulfide; DMSO, dimethyl sulfoxide; dr, diastereoisomeric ratio; EA, ethylaluminium hydride; EDCI, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; ee, enantiomeric excess; Et, ethyl; h, hours; IBX, 2-iodoxybenzoic acid; IMDA, intramolecular Diels–Alder; LDA, lithium diisopropylamide; Me, methyl; min, minutes; N, normal; NBS, N-bromosuccinimide; NMO, N-methylmorpholine-N-oxide; Np, naphthalene; o-Ns, ortho-nitrophenylsulfonl; Ph, phenyl; PHAL phthalazine; p-TSA, para-toluenesulfonic acid; py, pyridine; rt, room temperature; SiMe3BH, dimethylborane; SM, starting material; TBAF, tetrabutylammonium fluoride; TBDMS, tert-butyldimethylsilyl; TES, triethylsilyl; Tf, trifluoromethanesulfon; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TIPS, trimethylsilyl; TMS, trimethylsilyl; TPAP, tetrapropylammonium perhydro; Ts, para-toluenesulfonyl; Z, zusammen.

* Corresponding author. Tel.: +44-207-994-5822; fax: +44-207-994-5868; e-mail: simon.lewis@imperial.ac.uk
1. Introduction and Scope

A huge variety of indole alkaloids are known,\textsuperscript{1-7} many of which have been submitted to total synthesis. This review concerns the chemistry of indole alkaloids related to macroline 1, sarpagine 2 and ajmaline 3. The structures of these three species are shown in Scheme 1.

The skeletal numbering shown is the biogenetic numbering proposed\textsuperscript{8} by LeMen and Taylor and is used throughout this review. It may be seen that there is significant structural similarity between the three compounds. All possess an indole-annulated azabicyclo[3.3.1] structure and various efforts towards this structural motif are detailed below. Macroline-related alkaloids are defined as those having the same skeletal connectivity as macroline. They crucially do not possess an N4-C21 linkage. Sarpagine-related alkaloids are defined as those having the same skeletal connectivity as sarpagine, specifically with an N4-C21 linkage and the C16-(R) configuration shown. Ajmaline-related alkaloids are defined as those having the same skeletal connectivity as ajmaline, also with an N4-C21 linkage but with the C16-(S) configuration epimeric to that of sarpagine as shown. Alkaloids with a quaternary C16 are known and are included herein. There also may or may not possess a C7-C17 linkage, the quaternary C7 implied thus rendering the C2-C7 bond saturated. Additionally, the compounds under consideration may or may not be N1- and N4-substituted and may or may not possess indole ring oxygenation. Bis(indole) alkaloids in which one or both of the subunits consist of a macroline/sarpagine/ajmaline indole base are also included in this review.

It must be noted that, unlike ajmaline and sarpagine, macroline has not been isolated from natural sources. Many macroline-related alkaloids have, however, been isolated and it is believed that macroline, or an equivalent, is a likely biosynthetic precursor of various sarpagine alkaloids.

The field of macroline, sarpagine and ajmaline-related alkaloids was reviewed extensively by Cook\textsuperscript{9,10} in 1993 and 1994 and again by Lounasmaa\textsuperscript{11,12} in 1999 and 2001. As well as detailing reported synthetic endeavours relevant to the field, these excellent reviews give a comprehensive account of the species from which these alkaloids have been isolated (mostly genera \textit{Rauvolfia} and \textit{Alstonia}) and an overview of their biology, pharmacology, spectroscopic characteristics and proposals for their biosyntheses. Only chemistry of particular relevance, as well as that reported subsequent to these prior reviews or that not covered therein, is included here.

2. Cook’s Syntheses

Cook and co-workers have published extensively in the area of indole alkaloids and, in the last decade, have reported the partial and total syntheses of more than 40 macroline/sarpagine/ajmaline-related alkaloids, as well as bis(indole) alkaloids and related degradation products. These syntheses are detailed in this section and are grouped by the methodology used, as opposed to the final targets in question.

2.1. The tetracyclic ketone

Fundamental to Cook’s syntheses is the tetracyclic ketone intermediate 10. Its synthesis has been reviewed before,\textsuperscript{9,11} but will be detailed here also due to its relevance to the following sections. The overview of the synthesis is shown in Scheme 2.

Scheme 1.

\[ \text{COOH} \]
\[ \text{H} \]
\[ \text{NH}_2 \]
\[ 1) \text{Na/MeOH, 80\% (2 steps)} \]
\[ \text{Me} \]
\[ 2) \text{HCl/MeOH, \Delta, 80\%} \]
\[ \text{H} \]
\[ \text{N} \]
\[ \text{Bn} \]
\[ \text{COOMe} \]
\[ \text{Me}\text{HCO}\text{O, MeOH, NaBH}_4, -5^\circ\text{C, 88\%}} \]
\[ \text{Me} \]
\[ \text{N} \]
\[ \text{Bn} \]
\[ \text{COOMe} \]
\[ \text{NaH/MeOH, PhMe, 92\%} \]
\[ \text{Me} \]
\[ \text{N} \]
\[ \text{Ph} \]
\[ \text{H} \]
\[ \text{COOMe} \]
\[ \text{H} \]
\[ \text{Ph} \]
\[ \text{H} \]
\[ \text{COOMe} \]
\[ \text{AcOH/H}_2\text{O, \Delta, 91\%} \]

Scheme 2.
The synthesis outlined above, whilst only seven steps, has been the subject of extensive study and optimisation. The individual steps merit consideration in detail. Starting from unnatural D-tryptophan 4, N1-methylation and esterification were routine. The reductive amination to protect N4, however, required careful control. After stirring 5 with benzaldehyde for 2 h at room temperature to form the imine, sodium borohydride was added at –5 °C and allowed to react for 3 h. Longer reaction times or higher reaction temperatures led to erosion of the ee of 11 by imine isomerisation to 13 via 12 (Scheme 3).

Scheme 3.

The Pictet–Spengler condensation (and subsequent esterification) shown in Scheme 2 is represented as affording solely the C3,C5-trans tetrahydro-β-carboline 8. In fact a more complex series of events was occurring. As shown in Scheme 4, the initial Pictet–Spengler cyclisation proceeded to give a diastereoisomeric mixture of tetrahydro-β-carboline diacids 14. These underwent decarboxylation as shown and it was therefore the protonation upon rearrangement of intermediate 15 that determined the diastereoisomeric ratio in the product, not the inherent selectivity in the Pictet–Spengler reaction.

Scheme 4.

If the tetrahydro-β-carboline monoacid intermediates 16 were isolated, the diastereoisomeric ratio was found to be C3,C5-trans:trans=42:58. Alternatively, if methyl 3-formylpropionate 17 was used in place of 2-ketoglutaric acid 7, the diastereoisomeric ratio in 21 was found to be C3,C5-cis:trans=28:72 (Scheme 5). This enhanced diastereoisomeric ratio was observed due to the lack of a post-cyclative decarboxylation step; in this instance, the ratio is a true representation of the inherent selectivity of the Pictet–Spengler cyclisation.

Scheme 5.

Whilst the reaction of methyl 3-formylpropionate 17 with 6 increased the diastereoselectivity in the formation of 21 via 18-20, total selectivity was desired in order that tedious chromatography might be avoided and the sequence might be executed on a large scale. This was achieved by acid-catalysed isomerisation of the C3,C5-cis isomer to the more stable C3,C5-trans isomer, simply by treating the diastereoisomeric mixture 16 or 21 with methanolic HCl (for 16, this also effected esterification). The isomerisation of 22 is thought to proceed via a C3-N4 bond cleavage and formation of stabilised C3 cation 23 (Scheme 6).

Scheme 6.

With pure 8 in hand, Dieckmann condensation to the tetracyclic system 9 was effected with sodium methoxide. The C3,C5-trans-configured tetrahydro-β-carboline 8 is unable to attain a conformation suitable for cyclisation, and so base-induced epimerisation of C5 must occur prior to cyclisation. Whilst the cis tetrahydro-β-carboline 24 is the less stable diastereoisomer (as established in Scheme 6), the small amount formed is irreversibly transformed to the tetracycle, the equilibrium then replenishes the amount of 24 present and so all material is eventually transformed into tetracycle 9 (Scheme 7). The epimerisation prior to Dieckmann cyclisation is the reason Cook’s synthesis commences with the unnatural amino acid antipode. This
(incorrect) initial C5 configuration induces the correct C3 configuration which, in turn, induces complete epimerisation at C5 to the correct configuration.

Scheme 7.

The uncontrolled configuration of C15 in 9 is of no consequence as acid-induced decarboxylation leads to key tetracycle 10 (7 steps from D-tryptophan, 47% overall yield). Cook’s group have routinely performed this synthetic sequence on a 100-gram scale. As not all macroline/sarpagine/ajmaline alkaloids are N1-substituted, the tetracyclic ketone 32 has also been prepared from 25 with a free N1-H. The synthesis was complicated by unwanted lactam formation, as shown in Scheme 8.

Scheme 8.

Acid/methanol-induced transformation of 27 to 29 did not occur, probably because the lactam moiety would destabilise the α-aryl cation intermediate. The reaction occurred as desired in the absence of a free carboxyl group, using 28 to give 29. Upon exposure to base, 29 initially formed lactam 26, but eventually gave the desired Dieckmann product 31 via 30. Decarboxylation as before gave 32 (Scheme 9).

Scheme 9.

2.2. α,β-Unsaturated aldehyde formation and Claisen rearrangement: alstonerine, anhydromacrosaline-methine and macrocarpamine

The tetracyclic ketone 10 was elaborated by Cook’s group in the first total synthesis of (−)-alstonerine,15 as shown in Scheme 10. Exchange of the N4-benzyl group for methyl to give 33 and elaboration of the ketone gave α,β-unsaturated aldehyde 36 (via 34 and the intermediate epoxide 35).

Scheme 10.

Studies had shown that intermolecular addition to the C15 position of 36 was not a facile process, so an intramolecular strategy was used. Reduction of 36 to 37 and formation of vinylogous ester 39 using 38 allowed C15 functionalisation via a Claisen rearrangement to give 40 (Scheme 11).

Scheme 11.

Carbonyl reduction and hydroboration gave triol 42 via 41, and then selective tosylation of a primary alcohol and cyclisation gave 43. A modified Swern oxidation17 regenerated the vinylogous ester functionality and so led to (−)-alstonerine 44 (along with 31% dihydroalstonerine) in 8% overall yield from tetracyclic ketone 10 (not considering recycling of material) or 4% overall yield from D-tryptophan (Scheme 12).

Scheme 12.
The strategy detailed above for the synthesis of (–)-alstonerine 44 was later extended by Cook et al. for the synthesis of (–)-anhydromacrosalhine methine 46. Whilst not a natural product, this indole base constitutes the indole unit of the macroline-related bis(indole) alkaloid (–)-macrocarpamine 48. Reduction of (–)-alstonerine 44 gave secondary alcohol 45, which underwent acid-induced elimination to give (–)-anhydromacrosalhine methine 46. Coupling of 46 with a natural sample of pleiocarpamine (Scheme 13) completed the partial synthesis of (–)-macrocarpamine 48 (2% overall yield from D-tryptophan).

Scheme 13.

2.3. Ajmaline and alkaloid G

2.3.1. First-generation syntheses: 1,4-addition, oxyanion-Cope rearrangement and selective oxidations

Cook and co-workers employed the tetracyclic ketone 10 in the first total synthesis of (–)-ajmaline. Ketone 10 was elaborated into α,β-unsaturated aldehyde 49 as before, although the reaction was found to proceed in the absence of the phosphine oxide (also the N4-benzyl group was still in place). As mentioned in Section 2.2, intramolecular C15 functionalisation had been found to be difficult, but it transpired that successful organometallic addition was possible by use of a Barbier–Grignard process. A pseudo-symmetric allyl bromide 50 was used to circumvent ambiguity regarding α- versus γ-addition. A mixture of 1,2- and 1,4-addition products resulted, as shown, but, in an elegant resolution to this problem, Cook was able to transform the undesired 1,2-addition product 51 into the 1,4-addition product 52 by means of an oxyanion-Cope rearrangement (Scheme 14).

Scheme 14.

From the initial Barbier–Grignard reaction, 51 and 52 were formed in a ratio of 51:49. Of this, the 1,4-addition product 52 was formed in a ratio of 52a:52b of 3:1, where 52a was the desired isomer having the (15S) configuration. When 51 underwent an oxyanion-Cope rearrangement, 52a and 52b were isolated in a ratio of 3:2. Subsequent elaboration of 52a was by ethyldiene acetal protection of the aldehyde (giving 53) and oxidative cleavage of the olefin. In order to effect chemoselective cleavage in the presence of the oxidatively-sensitive indole, a stoichiometric osmylation was required, with subsequent periodate cleavage of the resultant diol. At this point in the sequence it was possible to epimerise C20 via the aldehyde enolate, giving a 54a:54b 1:1 epimeric mixture, separable by chromatography. With recycling of the undesired epimer 54b, >80% conversion from 53 was possible (Scheme 15).

Scheme 15.

N4-deprotection allowed formation of the O-acetyl aminal 55. Treatment with HClaq/AcOH, then Ac2O/HCl, effected the final cyclisation to the ajmalan skeleton by electrophilic addition to C7. The resultant C2 hemiaminal 56 was reduced under Lewis acidic conditions to furnish a C2-epimeric mixture, 57a:57b of 2:3. The epimer having the correct C2 configuration, 57a, underwent base-mediated hydrolysis to afford (–)-ajmaline 3 (Scheme 16) in 11% yield from tetracyclic ketone 10 (5% from D-tryptophan). Whilst the formation of only 40% of the desired C2 epimer in the penultimate step is not ideal, Cook notes that 2-epi-diacetyl ajmaline 57b is the thermodynamic product and many reagent systems provide solely 57b.
Hydrolysis of acetal 55 gave 58, which had previously been converted \textit{via} 59 into alkaloid G by Stöckigt and co-workers\textsuperscript{22} (Scheme 17), employing a DDQ oxidation to functionalise the C6 position. Cook’s report therefore constitutes a formal synthesis of alkaloid G\textsuperscript{60} in 10 steps and 12\% yield from tetracyclic ketone 10 (6\% overall yield from D-tryptophan).

Oxyanion-Cope rearrangement of 63 took place as before; in this instance, however, near total selectivity for the desired configurations was observed at C15 and C20 (\textit{c.f.}\ selectivity of 3:2 in Section 2.3.1). At C16, in the first instance, the selectivity was 1:4 for \textit{64a}:\textit{64b} for the undesired sarpagan (16\textit{R}) configuration. Upon prolonged exposure of (16S) \textit{64a} to base, epimerisation to mostly (16\textit{R}) \textit{64b} was observed, implying \textit{64b} was the thermodynamic product (Scheme 19).

The 3D structure (Scheme 20) of the enolate resulting from the oxyanion-Cope rearrangement suggested that the \textit{α}-face might be less hindered and as such \textit{64a} might be the kinetic product. After optimisation, it was found that quenching the oxyanion-Cope rearrangement with 1 N trifluoroacetic acid at low temperature favoured the formation of \textit{64a}. After the rearrangement had gone to completion, THF was added, allowing the reaction mixture to be cooled below the melting point of dioxane. At –100 °C in dioxane:THF, addition of 1 N trifluoroacetic acid in THF afforded \textit{64a}:\textit{64b} in a ratio of 43:1.

The ability...
to vary reaction conditions to favour either 64a or 64b permits stereospecific entry to either the macroline/sarpagine (16R) series or the ajmaline (16S) series. Aldehyde 64a was protected as the ethylidene acetal and then N1-methylated to converge on the (−)-ajmaline synthesis detailed in Section 2.3.1. The second-generation synthesis was thus completed in 9% overall yield from D-tryptophan methyl ester, an appreciable improvement. In completing the second-generation synthesis of alkaloid G, Cook’s laboratory reports a significant improvement to the DDQ-mediated α-aryl oxidation step – performing the reaction in wet THF leads to a yield of 94% of 42 (one diastereoisomer only). The improved alkaloid G synthesis was therefore completed in 25% overall yield from D-tryptophan methyl ester.

2.4. Selenium chemistry and an unusual pyrolytic rearrangement: talpinine, talcarpine, alstonerine and anhydromacrosalmine-methine

Cook et al. have reported syntheses26,27 of the two structurally related macroline/sarpagine alkaloids, (−)-talcarpine 65 and (−)-talpinine 66. They employ much of the methodology used for the synthesis of (−)-ajmaline and alkaloid G. It may be seen (Scheme 21) that 65 and 66 are epimeric at C20 and that 66 lacks the N4-methyl group, but has a hemiaminal moiety containing a C21-N4 linkage.

Scheme 21.

The synthetic sequence was executed as per Section 2.3.2, this time from the N1-unsubstituted tetracyclic ketone 32. As the sarpagan configuration (16R) was required in this instance, the enolate deriving from the oxynion-Cope rearrangement was quenched under thermodynamic conditions, simply by adding MeOH to the reaction mixture and stirring at room temperature for 2 h to give 64b. After N1-methylation, the aldehyde moiety was reduced and oxidative olefin cleavage (as previously) this time afforded a diastereoisomeric mixture of lactols 68, which were then dehydrated (Scheme 22).

Conversion of 72a into 72b is simply base-induced epimerisation to the thermodynamic product. The pyrolytic conversion29 of 72b into 72a is not fully understood mechanistically. Conversion of 72a into talpinine (10% from D-tryptophan, Scheme 25) was effected simply by N4-debenzylation (with spontaneous hemiaminal formation). Conversion of 72b into talcarpine (10% from D-tryptophan, Scheme 25) was effected by N4-debenzylation with concomitant N4-methylation, a transformation speculated to involve in-situ formaldehyde formation.

A key feature of this synthesis is the use of N-(phenylseleno)phthalimide to effect the addition of selenium28 and a methoxy group across the enol ether, giving 709, followed by selenium oxidation and elimination with rearrangement to afford a mixture of exocyclic olefin geometries (Scheme 23) in a ratio 71a:71b of 4:1 (where 71a is the desired isomer).

Scheme 23.

The desired isomer 71a was treated with 5% H2SO4 for 3 days, which induced acetal opening. C15-C20 bond rotation and Michael addition, to generate saturated C20-aldehydes as a C20 epimeric mixture. 3:5 of 72a:72b. Aldehyde 72a (20R configuration) is the precursor of talpinine and, similarly, 72b (20S configuration) is the precursor of talcarpine. The two epimeric precursors may, in fact, be interconverted (Scheme 24).

Scheme 24.
The methodology detailed above has also been employed in the second-generation syntheses\(^{27}\) of anhydromacrosalhine-methine and alstonerine. The geometric mixture of olefins (71a and 71b) was subjected to hydroboration, Swern oxidation, elimination of methanol and N4-debenzylation/methylation to furnish (–)-alstonerine \(^{44}\) (Scheme 26) via 73 and 74 in an improved 12% overall yield from D-tryptophan (c.f. Section 2.2).

Scheme 26.

Anhydromacrosalhine-methine 46 was synthesised from 69 (Scheme 27), by N4-debenzylation/methylation at an earlier stage, then selenium introduction, oxidation and elimination as before, followed by acid-induced elimination to the vinylogous enol ether product 46 via 75 and 76 (14% from D-tryptophan, c.f. Section 2.2).

Scheme 27.

2.5. Pyridine formation: norsuaveoline

Cook’s laboratory has also reported the synthesis of the pyridyl macroline alkaloid, norsuaveoline.\(^{21,30}\) This synthesis has much in common with Cook’s earlier synthesis of suaveoline.\(^{31}\) From the N1-unsubstituted tetracyclic ketone 32, the synthesis proceeded as per the ajmaline synthesis in Section 2.3.2. Cook and co-workers opted to use the sarpagan C16-configured oxyanion-Cope product, although, in this instance, the configurations of C15, C16 and C20 are of less concern, since all are ultimately incorporated into the pyridine ring. Ethylidene acetal formation and oxidative olefin cleavage were executed as before to give 77. In this case, however, the acetal was deprotected to furnish a 1,5-dialdehyde 78. This was treated with ethanolic hydroxylamine hydrochloride to access the pyridine ring directly; N4-debenzylation of 79 afforded norsuaveoline 80 in 28% yield from D-tryptophan methyl ester (Scheme 28).

Scheme 28.
with success when he employed a palladium-mediated cyclisation. The key reaction may be illustrated with the example of Cook’s total synthesis $^{32,33}$ of (+)-vellosimine $^{85}$. The iodoalkene $^{82}$ (which has been employed by other workers $^{34-40}$) was reacted with the N1-unsubstituted, N4-debenzylated tetracyclic ketone $^{81}$ to give $^{83}$ (Scheme 29).

Scheme 29.

Ketone $^{83}$ was elaborated to the corresponding \(\alpha,\beta\)-unsaturated aldehyde $^{84}$, as previously. One can envisage that transmetallation and Michael addition would give access to the sarpagan skeleton, but, in fact, this approach was unsuccessful. Instead, it was found that a radical-mediated coupling could effect C15-C20 bond formation. This occurred with scrambling of the C19-C20 olefin geometry, however, and the desired (+)-vellosimine $^{85}$ was the minor product in a ratio $^{85} : ^{86}$ of 1:3 (Scheme 30).

Scheme 30.

In view of the failure of both metallate and radical methods, the desired stereospecific cyclisation of $^{84}$ was attempted under Pd$^{0}$ catalysis. The unexpected product $^{87}$ was isolated (as a single geometric isomer), presumably arising from the enolate of $^{84}$. Such a cyclisation had been previously observed in other systems. $^{41}$ By inference from this result, it followed that $^{83}$ might undergo cyclisation to the desired vellosimine skeleton. Ketone $^{83}$ did, indeed, give $^{88}$ stereospecifically under the same conditions. This was transformed into (+)-vellosimine $^{85}$ via a masked aldehyde, which was unmasked and epimerised to the more stable C16 sarpagan configuration (Scheme 31). The first total synthesis of this sarpagine alkaloid was therefore completed in 27% overall yield from D-tryptophan methyl ester.

Scheme 31.

Several more sarpagine alkaloids $^{33,42}$ were, in turn, synthesised from (+)-vellosimine $^{85}$ (Scheme 32). Reduction of the aldehyde in $^{85}$ gave (+)-normacusine B $^{89}$ (24% from D-tryptophan methyl ester). Conversely, oxidation of the aldehyde in $^{85}$ and esterification gave $^{90}$, quaternisation of which with methyl iodide (to furnish $^{91}$) and subsequent anion exchange gave (−)-alkaloid Q3 $^{92}$ (18% from D-tryptophan methyl ester). Ester hydrolysis of $^{92}$ and neutralisation gave zwitterionic (−)-panarine $^{93}$ (16% from D-tryptophan methyl ester).

Scheme 32.

The same synthetic sequence used to prepare (+)-vellosimine was applied to the N1-methyl tetracyclic ketone $^{10}$ to produce (+)-N-methylvellosimine $^{94}$ (29% overall yield from D-tryptophan, Scheme 33). Oxidation and esterification provided (+)-N-methyl-16-epipericyclivine $^{95}$ (27% overall yield from D-tryptophan). Reduction of the aldehyde in $^{94}$ provided (+)-affinisine $^{95}$.

Scheme 33.
Tetrahedron

97 (26% overall yield from D-tryptophan). Cook’s group also executed the entire synthetic sequence from L-tryptophan, via 96, thus providing ent-97 (+)-affinisine,43 the enantiomer of the natural product (Scheme 33). This ent-affinisine was required for the synthesis of “mismatched” unnatural bis(indole) alkaloids, to probe their biological activities and SAR. As LeQuesne had previously reported44,45 partial syntheses of macroline 1 and alstonerine 44 from affinisine, Cook’s work constitutes formal syntheses of the antipodes of these alkaloids also.

Scheme 33.

A slightly different approach was used to access sarpagine alkaloids possessing the opposite configuration at C16 (ajmaline configuration). From sarpagan C16 ketone 88, Wittig methylation and selective hydroboration of the disubstituted olefin from the less hindered face gave 16-epi-normacusine B 99 (26% from D-tryptophan methyl ester). In the N1-methyl series, from sarpagan C16 ketone 100, the same Wittig methylation and selective hydroboration gave 16-epi-affinisine 101 (25% from D-tryptophan methyl ester). DDQ-mediated α-aryl oxidation gave dehydro-16-epi-affinisine 102 (24% from D-tryptophan methyl ester), as shown in Scheme 34.

Scheme 34.

The palladium-mediated cyclisation was less facile than in previous examples with the opposite (E) olefin geometry – despite much optimisation, on reaction of 106 significant amounts of dealkylated product 81 were isolated along with the desired 107. Completion of the synthesis (Scheme 36) was via hydroboration of 108 as for the other C-16-epi alkaloids, in 21% yield from D-tryptophan methyl ester.

Scheme 36.

2.7. Selective hydroboration: trinervine

The sarpagine alkaloid trinervine 113, a cyclic hemiacetal, was synthesised from (+)-normacusine B 89, the synthesis of which is detailed in Section 2.6. Silylation of the alcohol was followed by attempts at selective hydroboration of the trisubstituted C19-C20 olefin (Scheme 37). Surprisingly, the initial selectivity (at 0 °C) for the secondary hydroxyl product 111 over the tertiary regioisomer was only 7:3. It was postulated that this may be due to complexation of the first equivalent of borane to N4, thus altering the electronic characteristics of the olefin. A detailed optimisation study
was carried out28 – use of bulky hydroborating agents resulted in no reaction, but increased selectivity was observed by using 110 (with R = TIPS) at room temperature, furnishing the desired regioisomer in a ratio of 25:1. This was oxidised, in turn, to the ketone and upon deprotection of the hydroxyl group in 112 (and cleavage of the borane adduct), spontaneous cyclisation gave trinervine 113 (20% from tetracyclic ketone 32).

Scheme 37.

2.8. Indole oxygenation

As alluded to in the introduction, many macroline/sarpagine/ajmaline alkaloids possess indole ring oxygenation. Cook has synthesised many of these and the key to these syntheses has been the optimisation of routes to the relevant oxygenated tryptophan derivatives. Cook has successfully introduced oxygenation in the C10-, C11- and C12-positions. In each instance, the Schöllkopf chiral auxiliary was used to introduce the correct amino acid stereochemistry. The precise details vary depending on the ring substitution pattern, however, and so will be discussed individually.

2.8.1. C10 oxygenation: majvinine, 10-methoxyaffinisine, N-methylsarpagine and macralstonidine

p-Anisidine was employed as a starting material for a synthesis50,51 that Cook’s laboratory has executed on a > 600-gram scale (Scheme 38). Fischer indole formation via a Japp–Klingemann azo-ester intermediate52,53 formed from 114 and 115 gave the trisubstituted indole 116. C2-Decarboxylation to give 117 was followed by N1-protection, either with a Boc group (giving 118) or as a sulfonamide (only the Boc series is considered here). Optimisation of the brominating conditions was required to access the desired α-aryl brominated product 119 and avoid indolyl C2-bromination.

Scheme 38.

Cook has studied the effect of the leaving group and other parameters on the diastereoselectivity of the reaction with Schöllkopf auxiliaries.54,55 Bromide 119 was coupled with the Schöllkopf auxiliary 120 (derived from L-valine) to give 121 as a single diastereoisomer. The Boc group was cleaved thermolytically, followed by N1-methylation in one pot, giving 122. The auxiliary was removed under conditions of acidic hydrolysis to furnish 123, the C10-methoxy analogue of D-tryptophan ethyl ester (Scheme 39).

Scheme 39.

The ring-oxygenated amino acid 123 was amenable to the chemistry developed by Cook and co-workers detailed in Sections 2.1 to 2.7. Thus, the synthesis of C10-methoxy tetracyclic ketone 124 was high yielding (although it was necessary to avoid harshly acidic conditions in the Pictet–Spengler and C3-isomerisation steps, otherwise decomposition of the indole occurred). The conversion of 124 to the sarpagan skeleton via the palladium enolate methodology described previously was similarly high yielding (Scheme 40). Synthesis of (+)-majvinine 125 (28% yield from C10-methoxy D-tryptophan ethyl ester analogue 123) was executed as per N-methylvellosimine 94.
(majvinine is simply the C10-methoxy analogue of 94). Reduction of the aldehyde moiety in 125 gave

Scheme 40.

(+)-10-methoxyaffinisine 126 (25% yield from 123). For the synthesis of (+)-N-methylsarpagine 128, a C10-hydroxy group was required as opposed to a C10-methoxy group. Therefore, (+)-majvinine 125 was demethylated with boron tribromide (giving 127) prior to reduction to (+)-N-methylsarpagine 128 (20% yield from 123).

Cook also reported the first total synthesis of the bis(indole) alkaloid, (+)-macralstonidine 129, from the coupling 45 of synthetic N-methylsarpagine 128 with synthetic macroline 1 (Scheme 41).

Scheme 41.

2.8.2. C11 oxygenation: gardnerine, gardnutine, 11-methoxyaffinisine and 16-epi-N-methylgardneral

Synthesis of a C11-oxygenated tryptophan analogue would have been subject to regiochemical ambiguity if attempted via a Fischer indole formation. Cook and co-workers accessed this series by means of a Larock heteroannulation.57 The order of events is reversed from that in Section 2.8.1, in that reaction of 130 with the Schöllkopf auxiliary occurs prior to indole formation with 132 to give 133 (Scheme 42). The formation of 131 in high de is due in part to the choice of phosphonate leaving group.58 The Larock heteroannulation has been carried out on a 300-gram scale.

Both N1-methyl and N1-unsubstituted amino acids are easily accessible by this method. Once again, Cook’s previously developed methodology was viable with these C11-oxygenated amino acids (Scheme 43): (+)-16-epi-N-methylgardneral 137 was synthesised via 136 (35% from C11-methoxy, N1-methyl D-tryptophan ethyl ester 135) as per N-methylvellosimine 94 (Section 2.6, 137 is simply the C11-methoxy analogue of 94). Reduction of 137 gave 11-methoxyaffinisine 138 (32% from 91). Note that 137 and 138 have not been isolated from a natural source to date; they are precursors of natural products discussed in Sections 2.11 and 2.12.

Scheme 43.

(−)-Gardnerine 139 and (+)-gardnutine 140 are N1-unsubstituted C11-methoxy sarpagine alkaloids synthesised from C11-methoxy D-tryptophan ethyl ester 134 by Cook and co-workers in a manner analogous to that for 16-epi-normacusine B 99 (Section 2.6, 139 is simply the 11-methoxy analogue of 99). (−)-Gardnerine 139 was synthesised in 20% overall yield from 134. (+)-Gardnutine 140 was synthesised from 139 by DDQ-mediated α-aryl oxidation (18% overall yield from 134, Scheme 44).
2.8.3. C12 oxygenation: fuschiaefoline, 12-methoxyaffinisine and 12-methoxy-N-methylvellosimine

The required C12-methoxy amino acids were prepared by the same process used for the C11-methoxy series (namely a Larock heteroannulation), employing a regioisomeric iodoanisidine 141, giving 142 as a common intermediate for the synthesis of 143 and 144 (Scheme 45).

Scheme 45.

The C12-methoxy amino acids were compatible with Cook’s previously developed methodology, thus permitting the synthesis\(^{59,60}\) of (+)-12-methoxy-N-methylvellosimine 145 (overall yield 40% from 144) and (+)-12-methoxyaffinisine 146 (overall yield 38% from 144) as per the unsubstituted analogues 85 and 97. The quaternary alkaloid (–)-fuschiaefoline 148 was synthesised via 147 (27% yield from 144) in two steps from 145 (Scheme 46).

Scheme 46.

2.9. Hofmann elimination: alstophylline, ent-macroline, 11-methoxymacroline, macralstonine

As mentioned in the introduction, the macroline skeleton may be accessed by Hofmann elimination of the sarpagine skeleton, a transformation used by Cook to synthesise many macroline alkaloids. For example,\(^{61}\) starting from L-tryptophan, Cook et al. synthesised 149, the enantiomer of the N1-methyl analogue of C19-oxo borane adduct 112 from the synthesis of trinervine (Section 2.7). Whereas in the trinervine synthesis 112 was treated with excess acid to effect both dative bond scission and desilylation, in this instance 149 was treated with a small excess of acid, removing the borane, but leaving the silyl group intact to give 150. N4 was quaternised with methyl iodide, then under basic conditions Hofmann elimination occurred with regiospecific N4-C21 bond scission to give O-silylated macroline derivative ent-151. This was stable upon storage, or could be deprotected to give reactive (–)-macroline, ent-1 (Scheme 47), in 12% overall yield from L-tryptophan methyl ester (intended for use in the synthesis of mismatched bis(indole) alkaloid analogues).

Scheme 47.

11-Methoxymacroline 155 was synthesised\(^{56}\) by an entirely analogous route from the (naturally configured) 11-methoxy amino acid ester 134 (detailed in Section 2.8.2) in 14% overall yield. (–)-Alstophylline 158 (the 11-methoxy analogue of alstonerine 44) was also synthesised by this route\(^{62}\) – in this case, two possible pathways were available, only one of which utilised 11-methoxymacroline 155 as an intermediate (via 152, 153 and 154, Scheme 48), the other being via 156. The final step in the synthesis of (–)-alstophylline 158 is an IBX-mediated oxidation of common intermediate 157. Note that the yields are not quoted for all steps (preliminary communication). The bis(indole) alkaloid, macralstonine 159, was synthesised by the protocol of LeQuesne and Cook\(^{63}\) from macroline and alstophylline monomer units (Scheme 49).
2.10. Diastereospecific oxindole formation: alstonisine

Brief consideration will be given to Cook’s synthesis of the macroline-related oxindole (+)-alstonisine 163. Oxindoles may be formed from the corresponding indoles by C2-C7 oxidation, with rearrangement to the C7-spiroyclic skeleton in the case of tetrahydro-β-carbolines. Model studies performed by Cook \(^6\) on the tetracyclic ketone 10 (Scheme 50) led to the discovery that if osmium tetroxide was used as oxidant, a particular diastereoisomer (160 or 161) could be favoured by the presence or absence of a Sharpless ligand (quinuclidine, DHQ-CLB, DHQD-CLB, (DHQ)\(_2\)PHAL and (DHQD)\(_2\)PHAL were used).

Cook applied the findings from the model studies to the synthesis of (+)-alstonisine. Acetal 74 (a late-stage intermediate from the second-generation synthesis of (-)-alstonerine 44, detailed in Section 2.4) was oxidised diastereoselectively to furnish oxindole 162 as the sole diastereoisomer. Cook proposes that coordination of the N4 lone pair to the osmium enhances the selectivity. N4-Debenzylation was followed by elimination to form the vinylogous ester product (+)-alstonisine 163 (12% overall yield from D-tryptophan, Scheme 51).
2.11. Tollens reaction: dehydrovoachalotine, 11-methoxy-17-epi-vincamajine and vincamajinine

Various sarpagine/ajmaline-related alkaloids are known which have a quaternary C16 motif. To access this substitution pattern from tertiary C16 species such as those dealt with in Sections 2.6-2.8, Cook et al. employed the Tollens reaction. For example, in the synthesis of (+)-dehydrovoachalotine 167, N-methylvellosimine 94 was transformed into the 1,3-diol 164 in a yield of up to 90% after optimisation (Scheme 52). DDQ-mediated α-aryl oxidation was high yielding, as before, but oxidation of the neopentyl hydroxyl group in 165 proved problematic; eventually, it was found that a selenium-mediated oxidation furnished the aldehyde 166, which, in turn, could be oxidised to (+)-dehydrovoachalotine 167 (21% overall yield from D-tryptophan).

![Scheme 52](image)

The Tollens reaction was also used by Cook and co-workers in their syntheses of (--)-vincamajinine 172, and (--)-11-methoxy-17-epi-vincamajine 176. The synthesis of 172 (Scheme 53) also commenced with the transformation of N-methylvellosimine into the 1,3-diol 164. To enable cyclisation to the ajmaline skeleton, a selective oxidation to a β-hydroxylaldehyde was needed. In the event, TPAP was able to selectively oxidise the less hindered hydroxymethyl group with diastereoselectivity > 10:1. Treatment of 168 with trifluoroacetic acid and acetic anhydride in a sealed tube effected the C7-C17 cyclisation, giving 169, and then the unwanted C2-hydroxyl was reduced to give 170. Completion of the synthesis of 172 (via 171) required several sequential oxidations and reductions – all attempts to combine these steps resulted in a dramatic drop in yield. (--)-Vincamajinine 172 was obtained in 12% overall yield from D-tryptophan methyl ester.

![Scheme 53](image)

The synthesis of (--)-11-methoxy-17-epi-vincamajine 176 (Scheme 54) was broadly similar to that of 172, except that a ring-oxygenated precursor (N-methyl-16-epi-gardneral 137) was employed. The Tollens reaction has been shown...
to be compatible with both C10 and C11 oxygenation.\(^6\)

(–)-11-Methoxy-17-epi-vincamajine 176 was obtained via 173, 174 and 175 in an overall yield of 8% from 10-methoxy D-tryptophan ethyl ester 123. Cook has also prepared\(^6\) related compounds such as quebranchidine diol, epimeric at C17.

2.12. Modified Wacker oxidation: alstophylline, 6-oxoalstophylline, alstonerine and macralstonine

Cook has recently reported\(^6\) the use of a modified Wacker protocol\(^6\) to improve on the previous syntheses of the above-named alkaloids. For example, in the third generation synthesis of (–)-alstonerine, silylated macroline equivalent 151 (described in Section 2.9) undergoes deprotection and oxidative cyclisation directly to (–)-alstonerine 44 in a palladium-catalysed process employing \(\text{BuOOH}\) as oxidant (Scheme 55). The yield of 60% is the result of optimisation work.

\[
\text{Scheme 55.}
\]

(–)-Alstonerine 44 was synthesised in 9% overall yield from D-tryptophan methyl ester. In a second-generation synthesis of (–)-alstophylline 158 (Scheme 56), the same protocol was applied to the corresponding 11-methoxymacroline equivalent 154, affording 158 directly in 55% yield. (–)-Alstophylline 158 was obtained in 9% overall yield from 11-methoxy amino acid ester 135. This improved synthesis of (–)-alstophylline also constituted a second-generation synthesis of macralstonine 159 (c.f. Section 2.9). Finally, to effect the first total synthesis of (+)-6-oxoalstophylline 181, silylated sarpagan borane adduct 177 underwent N4-B bond scission to give 178, and was then oxidised\(^7\) with excess IBX to effect not only C19, but also C6, ketone formation. Tertiary amine 179 underwent Hofmann elimination as expected, giving 180, and the modified Wacker protocol furnished (+)-6-oxoalstophylline in 10% overall yield from 11-methoxy amino acid ester 135. The mechanism of the modified Wacker oxidation has not yet been fully elucidated.

\[
\text{Scheme 56.}
\]

2.13. Lactol protection: 10-hydroxy-N-methylpericyclivine, 10-methoxy-N-methylpericyclivine, 12-methoxy-N-methylvoachalotine, N-methylakuammidine and N-methylpericyclivine
Certain of Cook’s syntheses have been of sarpagine-related alkaloids that have required protection of C17. For instance, in the synthesis\(^\text{71}\) of N-methylpericyclivine \(185\), formation of the C17 ester was complicated by the fact that C16 epimerisation gave the more stable isomer, N-methyl-16-\(\text{epi}\)-pericyclivine \(95\), under many ester-forming conditions. It was ascertained after experimentation that protection of the C17 aldehyde of \(182\) as a lactol (using the DDQ methodology outlined in Section 2.3.2) permitted oxidation of C17 (in \(183\)) to the correct oxidation state (in \(184\)) with retention of the hydroxyl moiety in the final product as an acetate was also indicated (via \(188-191\), Scheme 58). N-methylakuammidine \(192\) was synthesised in 6\% yield from D-tryptophan.

A similar protection strategy was adopted in Cook’s recent synthesis\(^\text{60}\) of 12-methoxy-N-methylvoachlotine \(198\). In this instance, the protection was at a lower level of oxidation – as a cyclic ether, as opposed to a γ-lactol or lactone. 12-Methoxy-N-methylvellosimine \(145\) was subjected to the Tollens reaction as before to give \(193\), and then to the sequence of transformations effecting the protection \((194)\), transformation \((195\) and \(196)\) and deprotection \((197)\); quaternisation furnished 12-methoxy-N-methylvoachlotine \(198\) in 20\% yield from \(144\), Scheme 59.

In the case of N-methylakuammidine\(^\text{71}\) \(192\), the configuration at the quaternary C16 was retained by the same protection strategy. In this instance, protection of the hydroxyl moiety in the final product as an acetate was also indicated \(\text{via}\) \(188-191\), Scheme 58). N-methylakuammidine \(192\) was synthesised in 6\% yield from D-tryptophan.
3. Martin’s Biomimetic Synthesis of (+)-N-Methylvellosimine

Martin et al. have reported an enantiospecific total synthesis of N-methylvellosimine 94, which differs fundamentally from that of Cook in that formation of the C5-C16 bond is the final C-C bond-forming event (199).

Martin’s synthesis (Scheme 61) commenced with the vinylogous Mannich reaction of dihydro-β-carboline 200 (derived from D-tryptophan and formic acid in 60% yield) with silyl ketene acetal 201 to give tetrahydro-β-carboline 202 with total diastereoselectivity. Introduction of the 4-carbon C18-21 fragment with diketene (and concomitant cyclising Michael addition) gave tetracycle 203. Stepwise borohydride reduction and elimination gave α,β-unsaturated amide 204 as a single geometric isomer. N1-methylation, amide reduction (giving 205) and selective ester hydrolysis gave the potential iminium precursor 206.

It was decided to employ an α-aminonitrile as the actual iminium precursor, as these were known to furnish iminium ions under mild conditions. α-Aminonitrile 207 was thus synthesised by introduction of an amide at the C5 position and its subsequent dehydration (Scheme 62).

Scheme 61.

Scheme 62.
α-Aminonitrile 207 was subjected to imine-generating conditions, but no C5–C16 cyclisation was observed. This was taken to mean that the ester was insufficiently activating and so it was converted into the aldehyde 208. This also was inert to cyclisation, but, upon formation of the corresponding silyl enol ether 209 and treatment with BF₃·OEt₂, cyclisation to the sarpagan skeleton was observed (Scheme 63).

Scheme 63.

The target was obtained as an epimeric mixture (7:3 (+)-N-methylvellosimine:(+)-16-epi-N-methylvellosimine). As the desired natural epimer is the more thermodynamically stable, conversion into pure 94 was achieved by exposure of the mixture to aqueous KOH in MeOH. This elegant synthesis (7% overall yield from D-tryptophan) provides significant evidence for the feasibility of van Tamelen’s original biogenetic pathway. Furthermore, it points to the possibility that the total synthesis of other sarpagine/ajmaline alkaloids might be via such an iminium-induced cyclisation.

4. Martin’s Olefin Metathesis Route to Azabicyclo[3.3.1]nonenes

Martin et al. have conducted an extensive study on olefin metathesis as a method of accessing various azabicyclo[m.n.1] structures (m = 3-5, n = 2-3, with the nitrogen in the 1-atom bridge). Such structural motifs (211-214) are common in alkaloids (Scheme 64).

Scheme 64.

An indole-annulated azabicyclo[3.3.1] structure constitutes the tetracyclic skeleton of the macroline/sarpagine/ajmaline alkaloids and Martin and co-workers have been able to access this skeleton, as shown in Scheme 65.

Scheme 65.

Starting this time from L-tryptophan, the dihydro-β-carboline ent-200 (accessed in 63% yield) was N-protected before aminal formation with in situ esterification. The diastereoisomeric mixture 215 was treated with allyltrimethylsilane 216 and boron trifluoride etherate to afford C₃,C₅-cis tetrahydro-β-carboline 217 in a 5.5:1 diastereoisomeric ratio. The ester was then selectively reduced and the aldehyde reacted with the diazophosphonate shown to afford the alkyne in a one-pot procedure. This alkyne 218 underwent enyne metathesis (Scheme 66) with Grubbs’ first-generation catalyst 219 to give tetracyclic diene 220 in essentially quantitative yield. The monosubstituted olefin of this diene was then selectively cleaved with AD-mix-α⁷⁹ and NaIO₄ to give α,β-unsaturated aldehyde 221.

Scheme 66.

The α,β-unsaturated aldehyde 221 (10% yield from L-tryptophan) is a differentially protected form of the advanced intermediate 61 reported by Cook in the enantiospecific syntheses of macroline/sarpagine/ajmaline alkaloids, as detailed in Section 2. As such, this report from Martin constitutes a useful alternative approach to these natural products, starting, as it does, from L-tryptophan.

5. Rassat’s Synthesis of the Tetracyclic Ketone

In 2000, Rassat and co-workers reported a synthesis of Cook’s tetracyclic ketone intermediate 10 (summarized in Scheme 67). The crucial strategic difference in this approach is that formation of the [3.3.1] bicyclic skeleton occurs prior to the introduction of an indole.
Transannular cyclisation of the bis(epoxide) starting material 222 with benzylamine led to a regioisomeric mixture of bicyclic structures. The unwanted [4.2.1]bicycle 223 may be converted into the desired [3.3.1]bicycle 224 under conditions of trifluoroacetate formation and subsequent hydrolysis. Selective monoprotection of the resultant diol to give 225 was followed by a protecting group swap, giving 226. Oxidation to the ketone and deprotection of the other hydroxyl functionality led to the precursor 227 for Fischer indole synthesis of the tetracyclic core. This was effected in good yield with N-methyl-N-phenylhydrazine in acidic methanol at reflux overnight. Reduction to 228 regenerated the original N-benzyl protecting group and oxidation afforded the racemate of Cook’s intermediate 10 in 25% overall yield.

6. Kwon’s Formal Syntheses of (±)-Alstonerine and (±)-Macroline

Kwon and co-workers’ formal syntheses arose from their interest in phosphine-catalysed [4+2] annulations. This key reaction occurred between an indolyl imine dienophile 230 (prepared from 229) and a diene synthetic equivalent, the allenyl diester 233 (prepared from 231 via 232). The synthesis of these two coupling partners is shown in Scheme 68.

Under acidic conditions, the [4+2] product 241 underwent an intramolecular Friedel–Crafts acylation (Scheme 70) to give the tetracyclic macroline skeleton 242. Thiolate-mediated N4-deprotection and subsequent Eschweiler–Clarke N4-methylation both proceeded in essentially quantitative yield to give 243. NaBH₄ and ZnI₂ effected benzylic ketone reduction (along with formation of the N4-borane adduct, 244; the N-B bond was cleaved by heating to reflux in EtOH). DIBAL-H ester reduction gave the tetracyclic allyl alcohol rac-37.

Kuethe and co-workers have also adopted a [4+2] annulation strategy for construction of the tetracyclic macroline core. Adapting the work of Waldmann, they employed Danishefsky’s diene 248 with an imine derived from 245 (via 246 and 247), the connectivity of which was different to that used by Martin, in that it was derived from an indole substituted at the C7-position, not the C2-position. The cyclisation is shown in Scheme 71.

Racemic alcohol rac-37 (31% yield, longest linear sequence) is an advanced intermediate in Cook’s syntheses of alstonerine 44 and macroline 1 (see Sections 2.2 and 2.9).
Kuethe’s group then attempted the synthesis of the desired tetracyclic system under conditions of both transmetallation and radical initiation. In both instances, however, the substrate 249 was simply deiodinated at the indolyl 2-position. The desired cyclisation was eventually effected by the use of palladium, giving 251 (Scheme 72).

The reaction required stoichiometric amounts of Pd(II) – rapid deposition of palladium black was observed during the course of the reaction. The inability of the reaction to go to completion under catalytic Heck conditions is presumed to arise from the lack of an appropriate β-hydrogen for elimination. The proposed intermediate anti-252 (Scheme 73) has no β-hydrogen for syn elimination. Whilst isomerisation via a palladium enolate 253 is feasible, syn elimination still does not occur, presumably since it would entail the formation of a high-energy anti-Bredt bridgehead olefin.

Attempts at performing the catalytic Heck reaction under reductive conditions led only to isolation of the deiodinated by-products 250. When a modified Heck substrate 255 that contained additional β-hydrogens (the extra methyl group in 254 compared to 248) was prepared, this smoothly underwent cyclisation with 10 mol% Pd(0) to give 256 (Scheme 74).

Many ajmaline/sarpagine alkaloids possess a hydroxymethyl group at the C16 position. In order to introduce such a moiety, 249 was hydroxymethylated to give 257 prior to palladium cyclisation, as before, to give 258. Notably, appreciable amounts of α,β-unsaturated ketone 259 were isolated also. This is proposed to arise by elimination from the palladium enolate of type 253. Whilst the use of stoichiometric amounts of palladium has obvious disadvantages, this entry to the tetracyclic macroline skeleton is novel and reasonably succinct (e.g. N-methyl-258, 5 steps, 9% yield, Scheme 75).

Efforts are currently under way to induce asymmetry in the aza-Diels–Alder cyclisation by use of a chiral amine for imine formation. For example, the use of the imine derived from (S)-α-methylbenzylamine 261 and indolyl aldehyde 260 gave rise to dihydropyridone 262 in a diastereoisomeric ratio of 92:8 (Scheme 76).
Like Cook, Bailey and co-workers have made extensive study of the Pictet–Spengler reaction and have utilised it in previously reported formal syntheses of ajmaline, koumidine and suaveoline, amongst others. Unlike Cook, Bailey’s syntheses have as their core strategy the use of C3,C5-cis-specific Pictet–Spengler reactions. This permits the use of L-tryptophan to access various tetrahydro-β-carbolines having the correct configuration at C-3 and C-5 and this approach was used in Bailey’s recent synthesis of raumacline(263, Scheme 77). In contrast, Cook employs D-tryptophan in C3,C5-trans-specific Pictet–Spengler reactions, followed by selective epimerisation at C-5.

Scheme 77.

Bailey et al. employed cyanomethyltryptamine 265 as their Pictet–Spengler substrate. It may be synthesised in 4 steps from the amino acid starting material on a large scale with no need for chromatography – the cyano sulfonamide made from 264 may be purified by crystallisation and the subsequent reductive desulfonylation has been optimised to provide pure 265 (Scheme 78).

Scheme 78.

Pictet–Spengler cyclisation of 265 with a protected β-hydroxyaldehyde 266 gave C3,C5-cis tetrahydro-β-carboline 267 entirely stereoselectively. The factors that influence the selectivity had previously been studied and it had been shown that in general, only for reactions of aryl aldehydes with tryptophan allyl ester was total C3,C5-cis selectivity observed. A C-3 aryl substituent would not have been synthetically useful in the context of raumacline, however. A two-carbon masked aldehyde equivalent was required at the C-3 position, and the use of the silylated hydroxyaldehyde in conjunction with the cyanomethyl group is both synthetically useful and cis-specific. Such a choice of substituents likely arose from extensive optimisation; for example, cyclisation of the same aldehyde 266 with L-tryptophan methyl ester 268 gave 269 with only 3:1 cis-selectivity (Scheme 79).

Scheme 79.

Once formed, tetrahydro-β-carboline 267 was N4-benzylated and N1-methylated without complication, giving 270. It is probably significant that the Pictet–Spengler reaction was performed on the N1,N4-unsubstituted system; Cook has observed that an N4-benzyl substituent (or any bulky substituent) enhances C3,C5-trans selectivity in the cyclisation. Hydroxyl deprotection and oxidation to 271 were routine (Scheme 80).

Scheme 80.

A Horner–Wadsworth–Emmons reaction with 272 furnished 273 (5:3 E,Z) as their substrate for intramolecular Michael cyclisation to the tetracycle. This was induced with LiNEt3, giving 274 as an inseparable mixture of diastereoisomers. C-15 was found to have entirely R configuration as desired and C-16 was found to be 4:1 S,R. No selectivity was observed at C-18 (1:1 S,R). Bailey makes no comment relating the C-18 stereochemistry to olefin geometry or otherwise (Scheme 81).

Scheme 81.

After reduction, heating the resultant diastereoisomeric mixture 275 to reflux with catalytic toluene-4-sulfonic acid hydrate in THF gave a mixture of two lactones 276a/b, diastereoisomeric at C-18. Gratifyingly, both C-16 epimers had been transformed only into (16S) lactones 276a/b. Presumably the (16R) epimer of 275 had initially cyclised to the cis-decalin, before base-induced epimerisation to the trans-decalin structure. That the trans-decalin would be the lower-energy configuration may be seen from the predicted 3D structure of (−)-raumacline (Scheme 82), where the all-equatorial conformation is visible. The C-18 epimeric lactones were separated by chromatography and the isomer having the correct (18S) configuration (276a) underwent Dibal reduction to introduce the lactol 277 (correctly
configured) and hydrogenolytic debenzylation to afford (−)-raumacline 263 (Scheme 82).

The difficulty in exerting control over the C-18 stereochemistry is regrettable, but, nevertheless, in this synthesis of (−)-raumacline (7% overall yield from L-tryptophan), five of the six stereocentres have been effectively controlled, a notable achievement and a significant improvement on previous approaches.

9. Bailey’s Synthesis of (−)-Suaveoline

In addition to the earlier reported formal syntheses88 of suaveoline and ajmaline, Bailey and co-workers have made many and varied additional contributions92 to the field. These have culminated in a recent total synthesis of suaveoline.93 The synthesis employs the same cis-selective Pictet–Spengler cyclisation described in Section 8, but in this instance, cyanoaldehyde 271 was homologated to an unsaturated bis(nitrile) species 279 by means of a Horner–Wadsworth–Emmons reaction. The phosphonate 278 was prepared by in-situ alkylation with ethyl iodide. A vinylogous Thorpe cyclisation was then effected, giving the tetracyclic intermediate 280 (Scheme 83).

Tetracycle 280 was isolated as a mixture of diastereoisomers, all of which were suitable for further elaboration to suaveoline. Completion of the synthesis was by DIBAL-mediated reduction of 280 to an intermediate diimine 281. This was treated with hydroxylamine hydrochloride in ethanol to effect formation of pyridine 282. N4-Deprotection gave suaveoline 80 (6% from L-tryptophan), identical with both the natural product and a sample of semi-synthetic suaveoline prepared from

The total synthesis of (−)-suaveoline reported by Ohba and co-workers94 arose from their interest in oxazole–olefin Diels–Alder reactions as a route to annulated pyridines. Formation of oxazole 284 from N4-Boc-protected L-tryptophan methyl ester 283 occurred without erosion of ee according to their previously reported methodology.95 Temporary removal of the protecting group was necessary for N-acylation (giving 285), Bischler–Napieralski reaction (6 days in neat POCl3, giving 286) and stereoselective hydrogenation (Scheme 85).

Upon re-introduction of the Boc group to give 287, a chemoselective ester to aldehyde reduction was effected followed by Wittig reaction to introduce the ethyl sidechain. The IMDA reaction of 289 was found to work best by heating in xylene at reflux, with addition of 1,5-diazabicyclo[4.3.0]non-5-ene (suggested simply to be a scavenger for H2O), giving pyridine 290 in 69% yield. N1-Methylation and N4-deprotection afforded (−)-suaveoline 80 in 10% yield from 283. The route disclosed above is radically different from those of Bailey and Cook – instead
of relying on a Pictet–Spengler reaction to install the crucial tetrahydro-β-carbol ine stereochemistry, Ohba employs a diastereoselective reduction. Whilst the synthesis was most likely conceived primarily as a showcase for the pyridine-forming IMDA reaction, the aforementioned diastereoselective reduction may be of use for the synthesis of further members of the macroline/sarpagine/ajmaline indole class. It is noteworthy that, in this succinct synthesis, N1-protection was unnecessary (Scheme 86).

Scheme 86.

11. Ohba’s Synthesis of 1-Demethyl-20-deethylsuaveoline

In 1996, Batista et al. isolated selloiine, a macroline-related alkaloid, from the leaves of *Rauvolfia selloii*. For this natural product, they proposed the structure 1-demethyl-20-deethylsuaveoline 294. The methodology of Ohba and co-workers was ideally suited to the synthesis of this structure and they were able to achieve a total synthesis\(^9\) (Scheme 87).

![Scheme 87](image)

Elaboration of aldehyde 288 was by a Wittig reaction to introduce a vinyl sulfide sidechain (it was found that a terminal olefin was not able to undergo the intramolecular Diels–Alder reaction). Thus the removable thiomethyl group was used instead, and the IMDA reaction of 291 gave pyridine 292 in good yield. Removal of the thiomethyl group from 292 by reduction with Raney-nickel (giving 293) and trifluoroacetic acid-induced N4-deprotection gave

![Scheme 87](image)

12. Craig’s Approach to (−)-Alstonerine

Craig and co-workers have recently reported\(^\text{109}\) the results of their studies on the syntheses of (−)-alstonerine 44 by an aziridine-based approach. Using methodology reported by Mioskowski,\(^\text{108}\) they were able to generate anion 296 by reductive desulfonylation of bis(sulfone) 295. This in turn was added to L-tryptophan-derived aziridine 297 to give 298. The cyclopentene in 298 was employed as a dialdehyde surrogate; in order that it could be unmasked, a selective oxidation of the olefin in the presence of the indole was necessary. After optimisation, this was found to be viable with tetra-n-butylammonium permanganate in CH\(_2\)Cl\(_2\), giving 299. Subsequent diol cleavage gave dialdehyde 300, which underwent acid-induced Pictet–Spengler cyclisation via 301 to tetracyclic monoaldehyde 302 as a mixture of diastereoisomers (Scheme 88).

Scheme 88.

Craig’s use of the Pictet–Spengler reaction is strategically different from Cook’s or Bailey’s. In Bailey’s syntheses, *cis* selectivity was achieved in the Pictet–Spengler reaction by careful choice of reaction partners. In the current work, the tetrahydro-β-carbol ine geometry was formed exclusively *cis*, due to the cyclic nature of the iminium intermediate. This reversal of the order of events (formation of the C3-N4-C5-C15-C14 ring prior to this intramolecular Pictet–Spengler cyclisation) neatly avoids stereoch emical ambiguity in the cyclisation step. Monoaldehyde 302 was further elaborated by sulfone elimination and vinylogous silyl enol ether formation. The geometry shown for 303 was observed exclusively. Introduction of C17 was effected by the use of an unusual hetero-Diels–Alder reaction of formaldehyde. Monomeraldehyde 302 was further reacted with Mioskowski’s aziridine methodology to give advanced pentacyclic intermediate 304 (9% from L-tryptophan). It can be seen that introduction of a pendant 2-carbon fragment at C20 would permit access to the complete alstonerine skeleton (Scheme 89).

Scheme 89.
13. Conclusions and Future Prospects

The chemistry detailed herein shows that considerable advances have recently been made in the field of sarpagine/macroline/ajmaline indole alkaloids since the field was last reviewed. The Pictet–Spengler reaction remains a key strategic transformation for the synthesis of molecules of this class, as evidenced by the work of Cook, Bailey and Craig. Nevertheless, a diverse array of other reaction classes have been deployed to access the targets in question. In particular, Cook’s use of a common late-stage tetracyclic intermediate has allowed access to a large variety of natural products by use of varied transformations for the final elaborations. It is anticipated that further advances in the chemistry of macroline/sarpagine/ajmaline indole alkaloids will be reported in due course by many of the laboratories from which the work reviewed here originated.

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Biographical Sketch

Simon E. Lewis was born in London, UK in 1978. He received his MSci degree in 2001 from Imperial College, London, where he earned the SmithKline Beecham award for excellence in organic chemistry and was jointly awarded the Neil Arnott prize. After a short period with GlaxoSmithKline, he returned to Imperial College in 2002 where he was the beneficiary of a generous Pfizer CASE scholarship. He pursued his doctoral studies under the supervision of Professor Donald Craig, on the decarboxylative Ireland–Claisen rearrangement and its application to the synthesis of suaveoline. In 2006 he joined the group of Professor Andrew G. Myers at Harvard University where he is currently working on the synthesis of tetracycline antibiotics.