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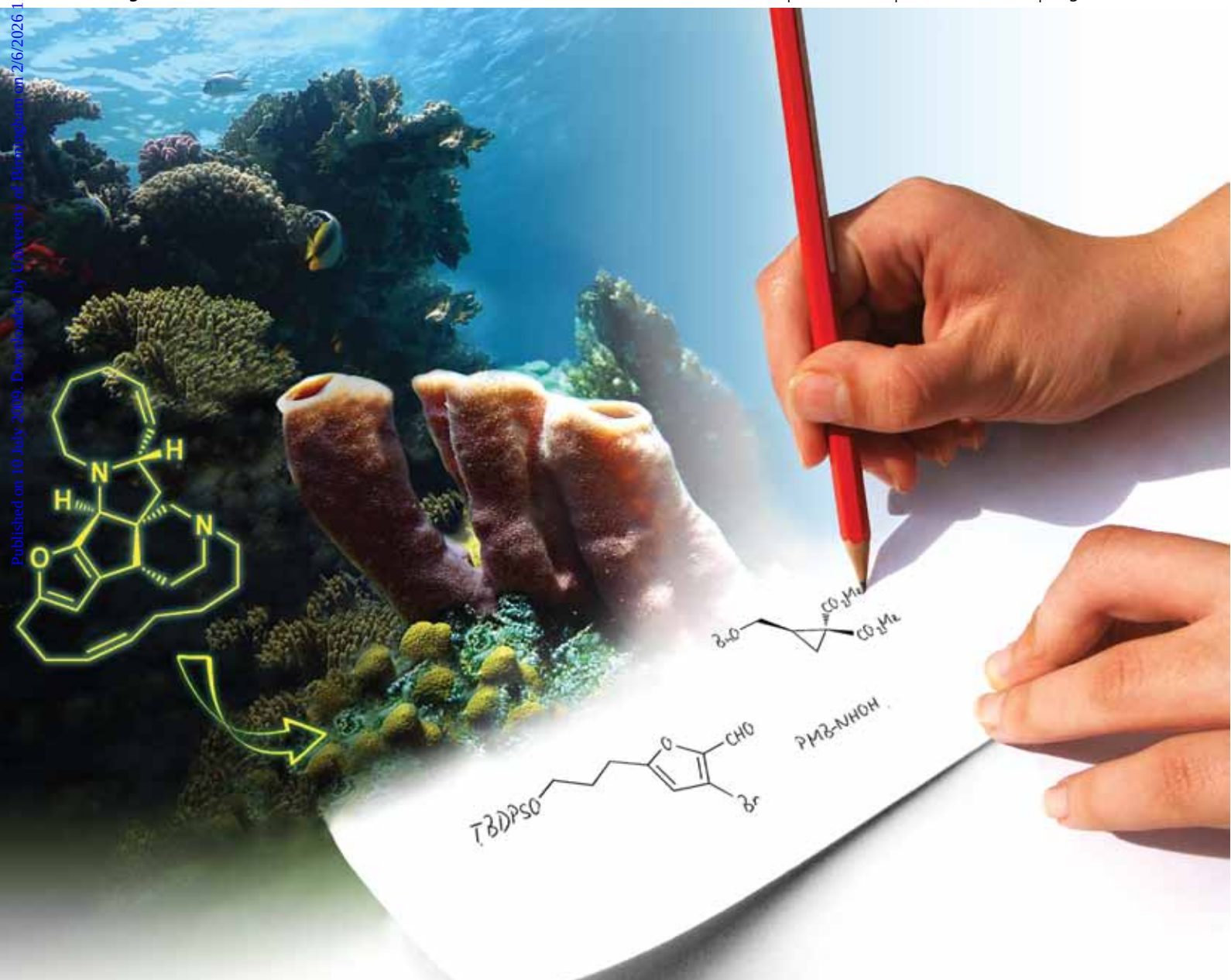

Themed issue: Rapid formation of complexity in organic synthesis

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Rapid Formation of Molecular Complexity in Organic Synthesis issue

Reviewing the latest advances in reaction development and complex, target-directed synthesis

Guest Editors Professors Erik J. Sorensen and Huw M. L. Davies

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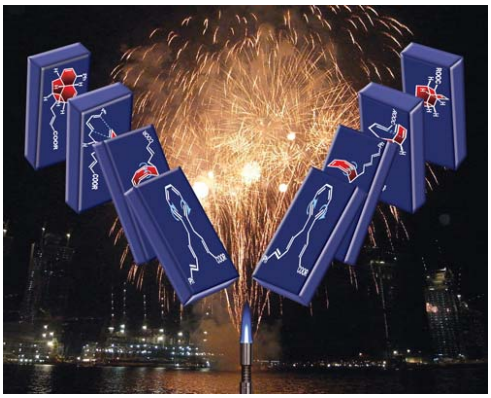

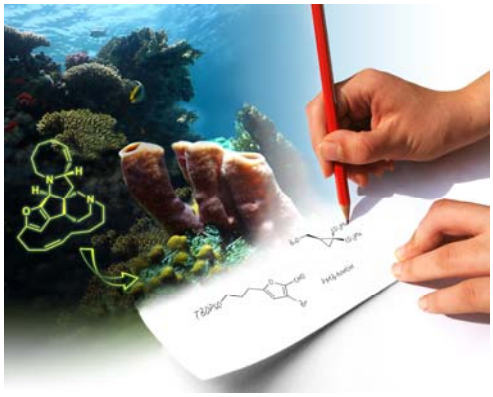

Heterocycles from cyclopropanes: applications in natural product synthesis†

Cheryl A. Carson and Michael A. Kerr*

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The construction of heterocyclic compounds from activated cyclopropane derivatives offers an alternative strategy for the preparation of molecules that may be of interest from a structural or biological standpoint. Several newly developed methods provide access to densely functionalized heterocycles in a manner that can be considered useful for both diversity- and target-oriented synthetic approaches. This *tutorial review* focuses on the latter, describing recent developments and applications of cyclopropane ring-expansion reactions in natural product synthesis.

Introduction

The unique structure and reactivity of the cyclopropane ring has been a subject of interest to organic chemists for many years. The strained three-membered carbocycle often displays reactivity analogous to that observed for olefins, and reactions with nucleophiles, electrophiles and radical species are well documented.[1] The substantial number of methods for the construction and manipulation of cyclopropanes provides access to useful synthetic intermediates with reactivity that can be tuned by substitution with electron-withdrawing and/or donating groups, and by exposure to Lewis acids. In recent years, ring-expansion reactions of cyclopropane derivatives have been emerging as rapid and versatile methods for the synthesis of a variety of complex heterocyclic systems. An array of dipolar reagents (*e.g.* aldehydes,[2] imines,[3,4] nitrones,[5] diazenes,[6] nitriles,[7] azomethine imines,[8] and others[9]) readily react with cyclopropanes to form five- and six-membered heterocycles. Many of these methods are useful for the construction of diverse libraries of compounds, but their relevance in target-oriented synthesis is also evident. This review highlights recent applications of cyclopropane ring-expansion reactions in natural product synthesis, and includes relevant background information on the various synthetic methods that enabled these accomplishments.

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† Part of the rapid generation of molecular complexity in organic synthesis themed issue.

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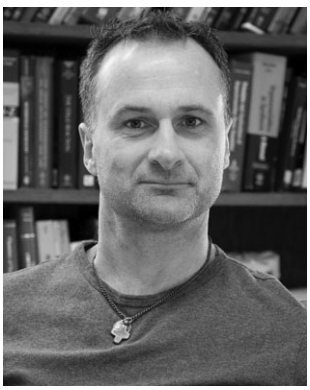

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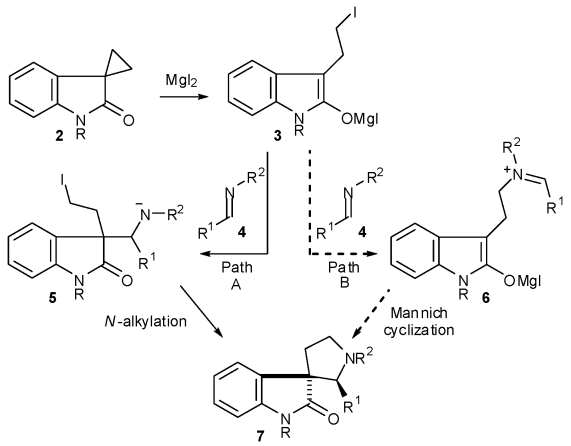
Michael Kerr received his BSc degree in 1985 from the University of Waterloo, where he worked as a research assistant under the supervision of Victor Snieckus. He then moved to the laboratories of Professor Marcus Tius at the University of Hawaii where he was awarded a PhD in 1991. This was followed by two years of post-doctoral study under the guidance of Professor K.C. Nicolaou at the Scripps Research Institute. Professor Kerr began his independent career in 1993 as an Assistant Professor at the primarily undergraduate Acadia University (Nova Scotia, Canada) and was promoted to Associate Professor with tenure in 1998. In 1999, he moved to the more research intensive environment at the University of Western Ontario (London, Ontario), where he is currently Full Professor of Chemistry and Faculty Scholar. Professor Kerr's research focuses on the development of new methods related to heterocyclic chemistry and the application of these methods to the total synthesis of complex targets.

Spiro[pyrrolidine-3,3′-oxindole] alkaloids

Magnesium iodide-catalyzed ring-expansion reactions

The reaction of spiro[cyclopropan-1,3′-oxindoles] and imines provides an efficient means for the preparation of spirofused pyrrolidines (**1**, Fig. 1).[3] This structural feature is present in a number of cytostatic agents including vincristine and vinblastine, important chemotherapeutics. The total syntheses of three spiro[pyrrolidine-3,3′-oxindole] alkaloids (horsfiline, strychnofoline and spirotryprostatin B) have been achieved using this cyclopropane ring-expansion reaction.[10]

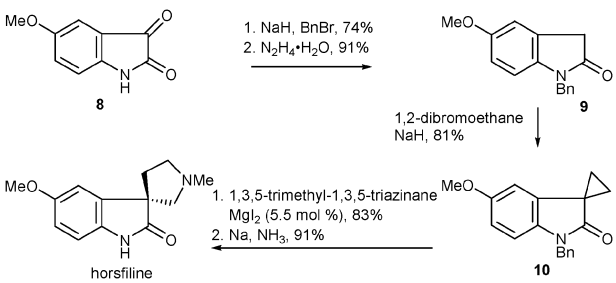
The transformation is promoted by magnesium iodide, and the bifunctional nature of the catalyst is invoked in the proposed mechanism of the reaction (Scheme 1). Ring-opening of cyclopropane **2** by the catalyst would provide a reactive intermediate **3** that could engage an imine **4** in a nucleophilic or electrophilic capacity. The authors prefer mechanistic pathway A, particularly for electrophilic imines (such as *N*-toluenesulfonyl imines), which are generally more reactive substrates. In most cases, good diastereoselectivity was observed in favour of the isomer depicted in Scheme 1.



Scheme 1 Magnesium iodide-catalyzed reaction of imines and spiro[cyclopropan-1,3′-oxindoles].

Total synthesis of (±)-horsfiline

The simplest naturally occurring alkaloid to be prepared using the Carreira method was horsfiline[11] (Fig. 1), an oxindole isolated from the leaves of *Horsfieldia superba* (a tree indigenous to Malaysia).[12] The route presented is succinct, requiring five steps from commercially available isatin **8** and producing (±)-horsfiline in 41% overall yield (Scheme 2). The MgI_2-catalyzed cyclopropane ring-expansion reaction used to prepare the spiro[pyrrolidine-3,3′-oxindole] scaffold was notable not only as the first application of the reaction in total synthesis but also because it demonstrated the feasibility of employing an *N*-alkylmethanimine equivalent in the ring-forming process. Accordingly, the method can be considered viable for the preparation of both simple and highly



Scheme 2 Total synthesis of horsfiline.

functionalized spirofused pyrrolidine derivatives (as illustrated by the syntheses of strychnofoline and spirotryprostatin B).

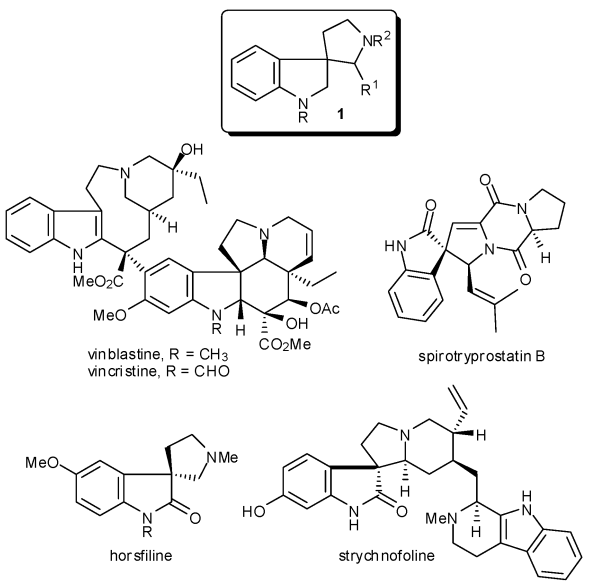
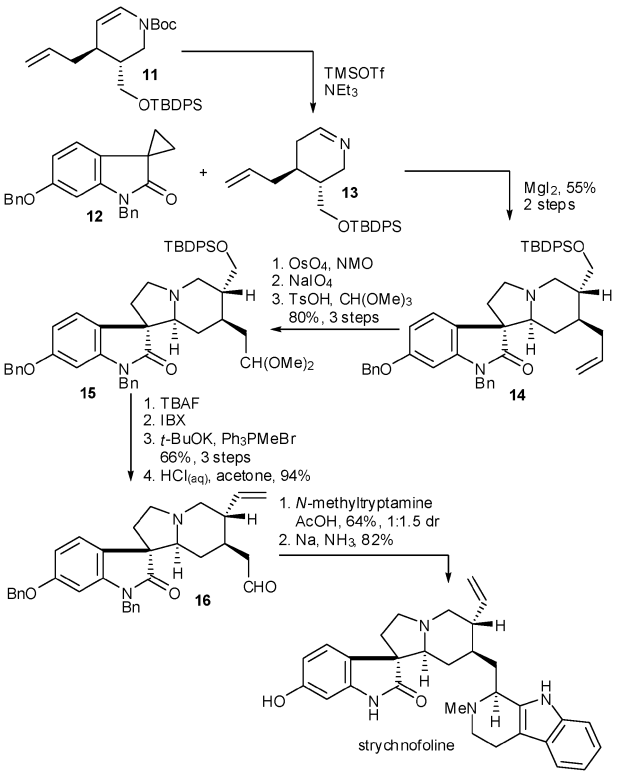


Fig. 1 Spiro[pyrrolidine-3,3′-oxindole] and related alkaloids.

Total synthesis of (±)-strychnofoline

Strychnofoline (Fig. 1) is an alkaloid isolated from the leaves of *Strychnos usambarensis* displaying antimitotic biological activity.[13] The first total synthesis of the natural product was accomplished using the MgI_2-catalyzed reaction of a spiro[cyclopropan-1,3′-oxindole] derivative **12** and a cyclic imine **13** (Scheme 3).[14] This was a valuable extension of the originally published synthetic method as it raised the issue of stereocontrol with regard to imine substitution. Accordingly, treatment of cyclopropane **12** with MgI_2 and imine **13** (which is unstable and was therefore used crude) resulted in the recovery of pyrrolidine **14** as a single stereoisomer in 55% yield from *N*-Boc enamine **11**.

A short series of functional group manipulations provided a substrate onto which the required *N*-methyl tetrahydrocarboline side chain could be appended. Oxidative olefin cleavage of key intermediate **14**, followed by protection of the resulting aldehyde garnered compound **15** in 80% yield over the three steps. Deprotection and oxidation of the primary alcohol gave an aldehyde that was homologated using a Wittig olefination. Liberation of the remaining aldehyde proceeded in high yield to give intermediate **16**, which underwent a Pictet–Spengler reaction with *N*-methyltryptamine. The reaction did not prove to be stereoselective, although this was largely anticipated. The desired diastereomer (the minor isomer of a 1 : 1.5 diastereomeric mixture) was successfully carried on to the



Scheme 3 Total synthesis of strychnofoline.

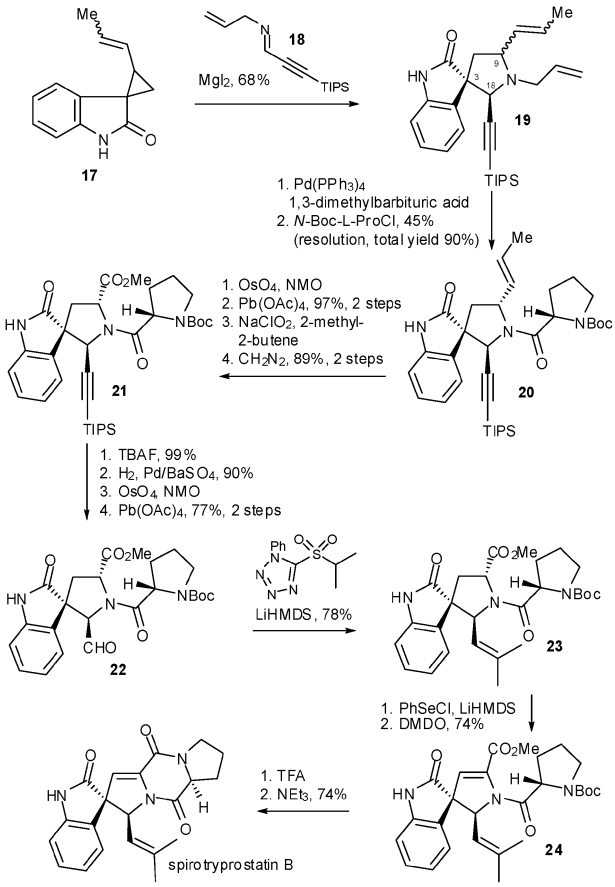
natural product by removal of the benzyl protecting groups to complete the first total synthesis of (±)-strychnofoline.

Total synthesis of (−)-spirotryprostatin B

Spirotryprostatin B was first isolated in small amounts from the fermentation broth of *Aspergillus fumigatus* BM939.[15] Beyond its appealing molecular architecture, the compound displays cytotoxicity in human leukaemia cells lines through inhibition of the G2/M phase of the cell cycle. These factors make it an intriguing target for total synthesis. Much like the syntheses of horsfiline and strychnofoline, the preparation of spirotryprostatin B required an extension of the MgI_2-catalyzed cyclopropane ring-expansion reaction.[16] Specifically, the use of 2-substituted spiro[cyclopropan-1,3′-oxindoles], which in turn produce 2,5-disubstituted pyrrolidines, was addressed.

The reaction of cyclopropane **17** (which was prepared as an inconsequential mixture of isomers) with alkynyl imine **18** produced pyrrolidine **19** as a 6 : 1 mixture of diastereomers in favour of the desired relative stereochemistry between C3 and C18 (Scheme 4). C9 epimers and *E*/*Z* isomers could be separated and carried on to the natural product independently, however, for clarity a single isomer is shown. Removal of the *N*-allyl protecting group and acylation with the acid chloride of *N*-Boc proline both incorporated another ring of the natural product and permitted resolution of the enantiomeric mixture.

Completion of the synthesis required manipulation of the substituents at the C18 and C9 positions. A synthetic sequence involving dihydroxylation, Criegee oxidation, Pinnick oxidation and esterification was used to convert the C9 olefin to a methyl ester (**21**). Removal of the triisopropylsilyl group,



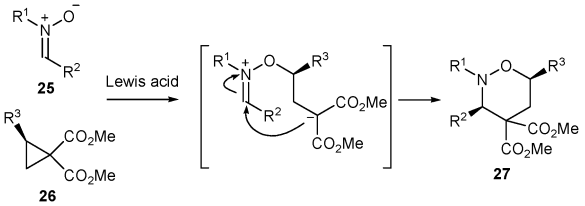
Scheme 4 Total synthesis of spirotryprostatin B.

semi-hydrogenation, dihydroxylation and Criegee oxidation converted the C18 alkyne to aldehyde **22**. A Kocienski-modified Julia–Lythgoe olefination successfully incorporated the C18 trisubstituted olefin (**23**), which was followed by a selenoxide elimination to introduce the desired unsaturation in the spirofused pyrrolidine core (**24**). All that remained was to remove the *N*-Boc protecting group of the proline subunit and cyclize the resulting secondary amine onto the methyl ester substituent. This proceeded smoothly to complete the synthesis of (−)-spirotryprostatin B in 15 steps from cyclopropane **17**.

Securinega alkaloids

The reaction of nitrones and cyclopropanes

Tetrahydro-1,2-oxazines can be prepared in an efficient manner using the reaction of nitrones with cyclopropanes (Scheme 5).[5] The transformation is highly regioselective, with nucleophilic attack occurring at the position of the



Scheme 5 The reaction of nitrones and cyclopropanes.

cyclopropane best able to stabilize a developing positive charge. The products are usually obtained as single stereoisomers bearing a *cis* relationship between their C3 and C6 substituents, with inversion of configuration occurring at chiral centre of the cyclopropane.[17,18] Catalytic asymmetric variations of this reaction have also been developed.[19,20]

Since nitrones can be prepared *in situ* through the condensation of an aldehyde with a hydroxylamine, a three-component version of the reaction was developed (Scheme 6). Using this method, a diverse library of tetrahydro-1,2-oxazines can be prepared.[21] The molecular complexity created can be increased further by manipulation of the tetrahydro-1,2-oxazine products. For instance, the use of *o*-iodophenyl hydroxylamine **28** in the reaction permits the formation of skeletal congeners of FR900482 in a simple, two-step sequence. FR900482, which is related to the mitomycin class of alkaloids, is of interest because of its potent anti-tumour properties. If desired, compounds such as **32** can be elaborated to form pyrrolo[1,2-*a*]indoles.[22] While this strategy has not been applied to natural product synthesis, the preparation of biologically significant structural patterns is easily accomplished. The successful use of the reaction of nitrones in the context of total synthesis was first demonstrated in the synthesis of phyllantidine. The subsequent application of the reaction to the total synthesis of nakadomarin A, as well as the conversion of tetrahydro-1,2-oxazines to pyrrolidines, emphasize the more widespread synthetic utility of the transformation.

Total synthesis of (+)-phyllantidine

Phyllantidine is a member of the *Securinega* alkaloids, which are isolated from plants of the Euphorbiaceae family (Fig. 2).[23] These alkaloids contain a characteristic azabicyclo[3.2.1]octane ring system, and have received considerable attention from the synthetic community. Securinine has well-established biological activity including antagonism of the γ-aminobutyric acid receptor,[24] and many plants of this family have found use in traditional folk medicine. Phyllantidine and the more recently isolated secu'amamine D[25] are unique members of this alkaloid class in that they contain a tetrahydro-1,2-oxazine ring.

The reaction of nitrones with cyclopropanes has successfully been applied to the first total synthesis of (+)-phyllantidine (Scheme 7).[26] Construction of the tetrahydro-1,2-oxazine core (**35**) of the alkaloid was achieved using the three-component

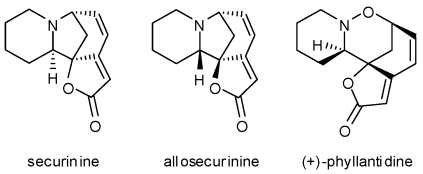
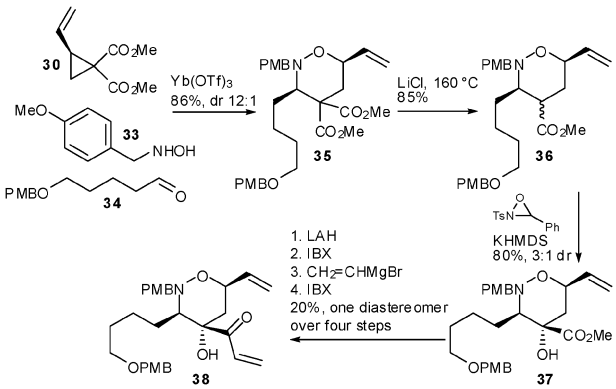


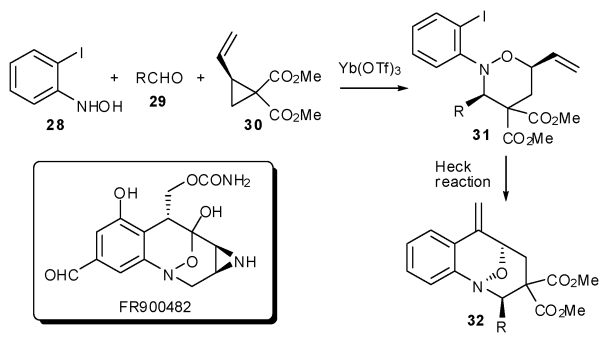
Fig. 2 Representative *Securinega* alkaloids.



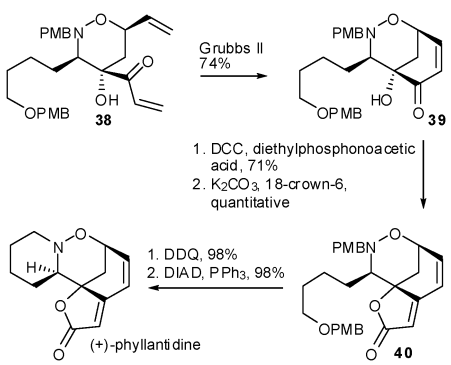
Scheme 7 Application of the reaction of nitrones and cyclopropanes to the total synthesis of phyllantidine.

variant of the reaction. Incorporation of an oxygen atom at the position of the geminal diester functionality was required for elaboration to the natural product, and this was achieved *via* a Krapcho demethoxycarbonylation reaction and subsequent treatment with potassium bis(trimethylsilylamide) and the Davis oxaziridine. Unfortunately, the stereoselectivity of the enolate oxidation reaction was low (a 3 : 1 mixture in favour of the desired stereoisomer **37**). The diastereomeric compounds could be separated once the remaining ester was converted to an α,β-unsaturated ketone **38**, a task that was accomplished in a four-step sequence.

The peripheral rings of the natural product were then assembled in an efficient fashion (Scheme 8). Treatment of oxazine **38** with Grubbs' second-generation catalyst promoted ring-closing metathesis to provide compound **39**. The butenolide ring was accessed by acylation of the alcohol of **39** with diethylphosphonoacetic acid and treatment with base to promote an intramolecular Horner–Emmons reaction. Weinreb had previously demonstrated the feasibility of this strategy for



Scheme 6 Three-component coupling and preparation of FR900482 skeletal congeners.



Scheme 8 Completion of the synthesis of phyllantidine.

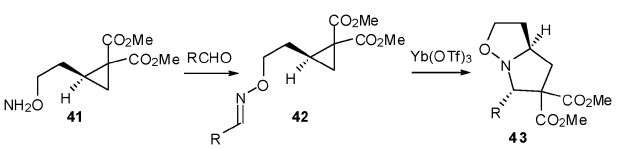
the formation of the butenolide ring of other *Securinega* alkaloids.[27] Removal of the *p*-methoxybenzyl protecting groups then provided a substrate that readily underwent a Mitsunobu-type ring closure to complete the target.

The complete synthetic sequence required 12 operations from the formal nitrone–cyclopropane cycloaddition reaction and provided (+)-phyllantidine in roughly 6% yield. A modification of this synthetic strategy would later be applied to the total synthesis of allosecurinine, which highlights a novel stereodivergent method for the construction of pyrrolo-isoxazolidines.

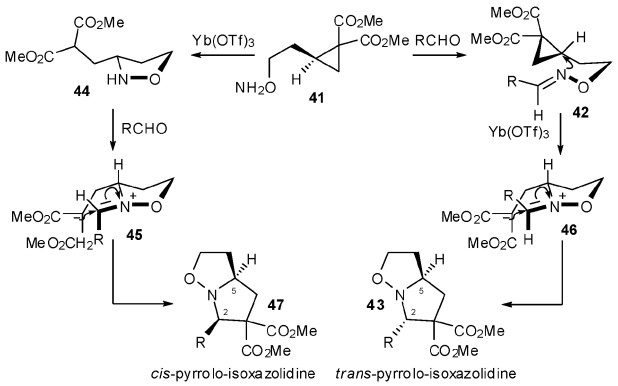
Intramolecular oxime ether annulations

A method for the preparation of pyrrolo-isoxazolidines (**43**) *via* an intramolecular annulation reaction of a cyclopropane and an oxime ether has been reported (Scheme 9).[28] The intramolecular reaction was investigated because the intermolecular reaction of oxime ethers and cyclopropanes proved to be sluggish and narrow in substrate scope. Gratifyingly, the intramolecular process was found to be exceptionally facile and highly stereoselective. Much like the reaction of nitrones and cyclopropanes, inversion of configuration was observed at the chiral centre of the cyclopropane. The relative stereochemical outcome across the pyrrolidine ring, on the other hand, turned out to be an interesting issue in terms of reaction design.

The 2,5-*cis* or *trans* relationship present in the pyrrolidine ring was found to be governed to the *E*/*Z* geometry of the parent oxime ether. When *E*-oxime ethers were treated with a Lewis acid, *trans*-pyrrolo-isoxazolidines **43** would result (Scheme 10). This was clear because *Z*- and *E*-oxime ethers could be separated and subjected to Lewis acid catalysis independently. While *Z*-oxime ethers were found to give rise to exclusively *cis*-products (**47**), the *Z*-oximes were only obtained as minor isomers (if formed at all) from the condensation of aldehydes with alkoxylamine **41**. An appealing aspect of this chemistry is that the *cis* stereoisomers can easily be accessed from the same starting materials by simply changing the order of addition of the aldehyde and Lewis acid. The proposed mechanistic rationale for why this should occur invokes the nucleophilic ring-opening of the cyclopropane by the pendent alkoxylamine prior to oxime ether formation. One might expect the *Z*-oxime ether **45** to be formed preferentially from cyclic alkoxylamine **44**, which could then undergo ring closure to provide the *cis*-pyrrolo-isoxazolidine products **47**. Both methods are high yielding and amenable to the use of a broad range of aldehyde substrates (including aryl, olefinic, and aliphatic). Pyrrolidines can easily be prepared using this method by N–O bond cleavage of the pyrrolo-isoxazolidine products. As pyrrolidine rings are present in a large number of natural products, this method could potentially be applied to a variety of synthetic targets.



Scheme 9 Preparation of pyrrolo-isoxazolidines from cyclopropanes.



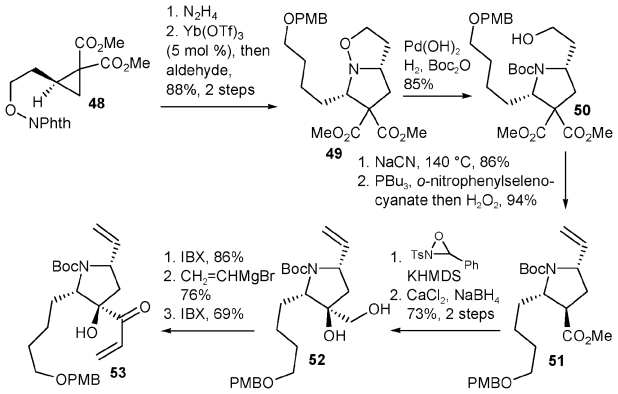
Scheme 10 Rationale for *cis* and *trans* stereoselectivity.

Total synthesis of allosecurinine

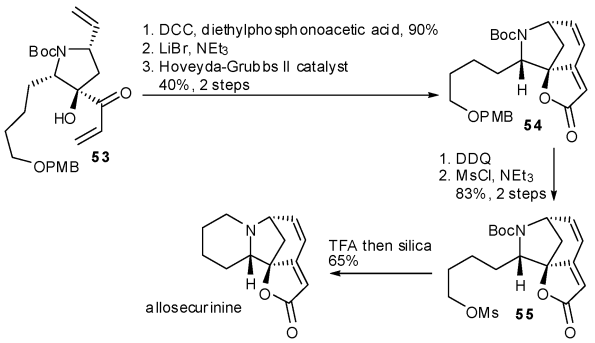
Allosecurinine (Fig. 2),[29] the C2 epimer of securinine, was first isolated in 1962 from the leaves of *Securinega suffruticosa*. Its enantiomer, viroallosecurinine, has also been isolated.[30,31] There are currently two total syntheses of allosecurinine,[32] the first of which employed a cyclopropane–oxime ether annulation reaction for the preparation of the central pyrrolidine structural feature.[33]

The *cis*-selective pyrrolo-isoxazolidine synthetic method was used to construct compound **49** in good yield (Scheme 11). Cleavage of the N–O bond with concomitant *N*-Boc protection then provided pyrrolidine **50**. As a ring-closing metathesis reaction was planned to form of the cyclohexene ring of the natural product, the ethyl alcohol side chain was converted to an olefin (**51**) using Grieco's procedure for selenoxide elimination. As was the case in the total synthesis of phyllantidine, removal of one of the esters and incorporation of an oxygen atom at the C3 position of the pyrrolidine ring was required for elaboration to the natural product. This was achieved in a similar fashion, however, in this case the enolate oxidation was completely selective for the desired stereoisomer. The α,β-unsaturated ketone of **53** was formed *via* a comparable four-step sequence, although a calcium borohydride reduction was used as opposed to lithium aluminium hydride to avoid reduction of the nitrogen protecting group.

The formation of the butenolide ring proved to be difficult once the ring-closing metathesis reaction had been performed.



Scheme 11 Application of an intramolecular cyclopropane–oxime ether annulation to the total synthesis of allosecurinine.



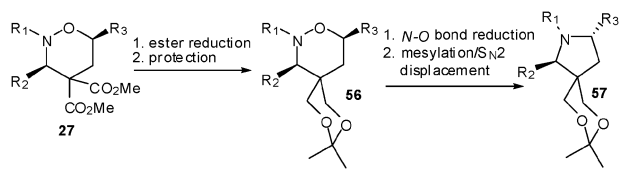
Scheme 12 Completion of the synthesis of allosecurinine.

Consequently, this ring was constructed first using an intramolecular Horner–Emmons reaction (Scheme 12). The intermediate butenolide was subjected to the Hoveyda–Grubbs second-generation catalyst without purification because the material was not stable to column chromatography. This yielded compound **54**, the primary alcohol of which was deprotected and converted to a mesylate (**55**). Removal of the *N*-Boc protecting group, neutralization and treatment with silica successfully closed the final ring *via* an intramolecular substitution reaction. This served to complete the first total synthesis of allosecurinine.

Other pyrrolidine containing alkaloids

Conversion of tetrahydro-1,2-oxazines to pyrrolidines

The tetrahydro-1,2-oxazine ring is not a structural feature commonly found in nature (phyllantidine and FR900482 being two notable exceptions). Accordingly, the synthetic utility of the reaction of nitrones with cyclopropanes was expanded when a straightforward method for the conversion of oxazines to pyrrolidines was developed (Scheme 13).[34] N–O bond cleavage and subsequent S_N2 displacement of the resulting aminoalcohols can provide 2,5-*trans* pyrrolidines (**57**) in a stereospecific manner. This process is complicated in the presence of the geminal diester functionality due to a competing retro-Mannich fragmentation pathway. This can be avoided by reduction, or other manipulation, of the ester groups prior to N–O bond cleavage. In the context of total synthesis, this is not especially problematic since one or both of the esters would likely require modification *en route* to the natural product. This is well illustrated by the total synthesis of nakadomarin A, another example of the application of the reaction of nitrones and cyclopropanes in natural product synthesis.



Scheme 13 Conversion of tetrahydro-1,2-oxazines to pyrrolidines.

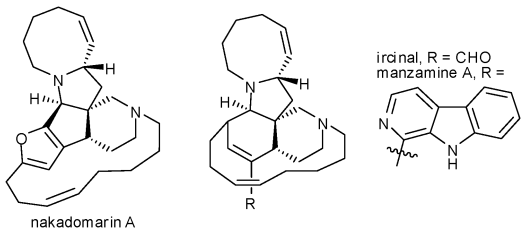


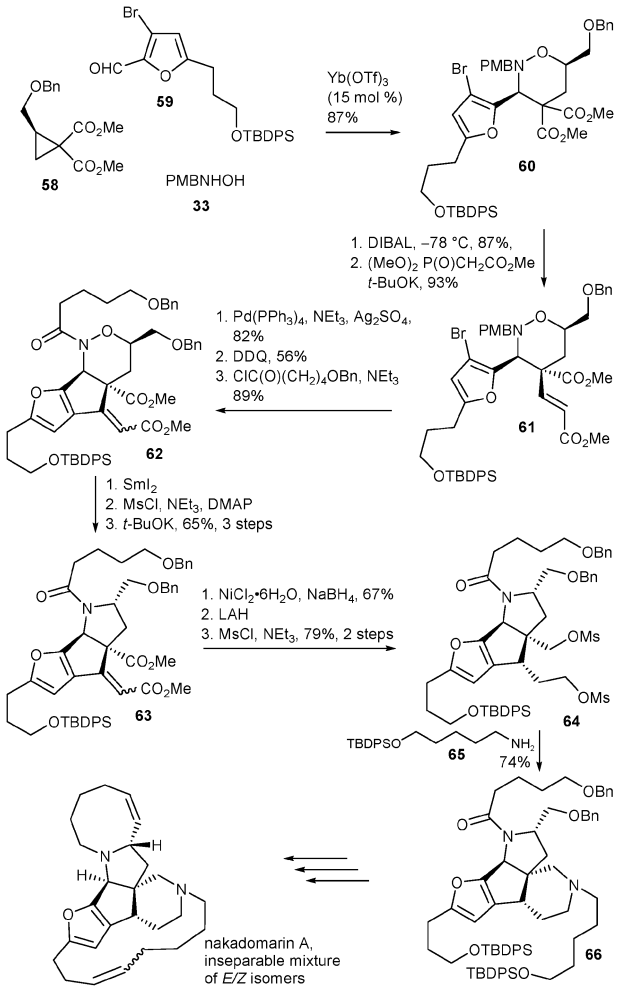
Fig. 3 Representative manzamine alkaloids.

Total synthesis of (+)-nakadomarin A

(−)-Nakadomarin A is a member of the manzamine class of alkaloids, first isolated by Kobayashi from an Okinawan sea sponge (Fig. 3).[35] The structure of the natural product consists of an angularly fused 6/5/5/5 core ring system decorated with an eight-membered ring and bridging 15-membered macrocycle. To date there have been few total syntheses of nakadomarin A, the first of which was disclosed by the Nishida group. Nishida completed the synthesis of both (−)-nakadomarin A[36] and its unnatural enantiomer[37] according to different routes. Subsequent to these seminal publications, a total synthesis of (+)-nakadomarin A utilizing the reaction of nitrones with cyclopropanes was developed.[38]

The three-component variation of the nitrone–cyclopropane formal cycloaddition was used to couple aldehyde **59**, hydroxylamine **33**, and cyclopropane **58**, yielding a tetrahydro-1,2-oxazine **60** that was appropriately functionalized for elaboration to (+)-nakadomarin A (Scheme 14). Treatment of **60** with DIBAL reduced one of the esters and set the quaternary stereocentre of the natural product with complete selectivity. The intermediate aldehyde was then elongated using a Horner–Wadsworth–Emmons reaction to provide **61**. An intramolecular Heck cyclization was used to form the cyclopentane ring as a single double bond isomer, the identity of which was not determined. At this point the PMB group was removed and the oxazine was acylated to provide compound **62**. Acylation was required because the N–O bond of oxazines bearing *N*-alkyl substitution proved resistant to reduction. This is why hydroxylamine **33** (which incorporates a readily cleaved protecting group) was used in the synthesis as opposed to a suitable longer chain aliphatic hydroxylamine (such as $BnO(CH_2)_5NHOH$), which would appear to be a more direct route.

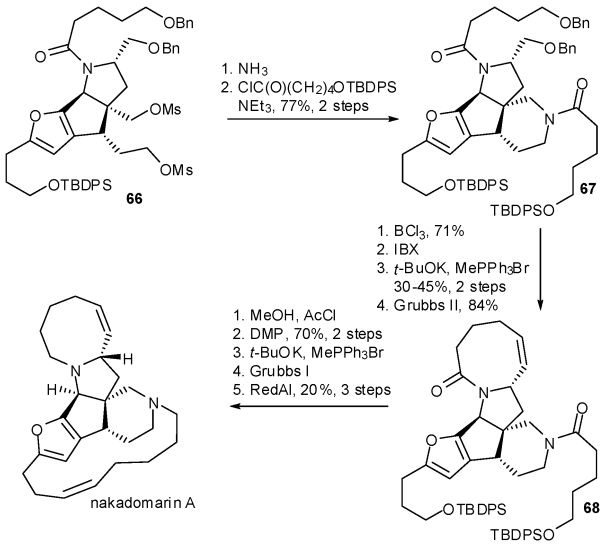
The conversion of oxazine **62** to pyrrolidine **63** was achieved by reduction of the N–O bond with samarium diiodide, mesylation of the resulting primary alcohol, and treatment with potassium *tert*-butoxide. Nickel boride was used to reduce the double bond of **63** with greater than 9 : 1 selectivity for the desired stereoisomer. Reduction of the two methyl esters and subsequent mesylation provided compound **64**, a suitable substrate from which to construct the piperidine ring of nakadomarin A. Initially, this was achieved by displacement of bis-mesylate **64** with amine **65**. This route ultimately led to the successful completion of the target molecule, however, the penultimate ring-closing metathesis reaction resulted in a mixture of double bond isomers that proved inseparable. In order to prepare a pure sample of nakadomarin A, the route was altered to converge with Nishida's earlier report in which



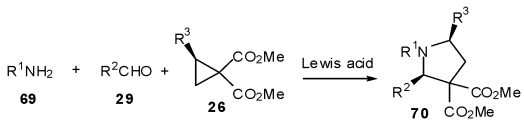
Scheme 14 Application of the reaction of nitrones with cyclopropanes to the total synthesis of nakadomarin A.

the *E*/*Z* isomers were separable by column chromatography. This entailed only a small modification; the incorporation of a carbonyl on the alkyl chain of the piperidine ring.

Intermediate **67** was prepared by treatment of **66** with ammonia in ethanol–THF and acylation of the resulting piperidine (Scheme 15). The two pendent benzyl ether protected alcohols of **67** were converted to olefins *via* a double deprotection–oxidation–Wittig reaction sequence. Ring-closing metathesis then garnered the desired eight-membered ring (**68**). A similar double deprotection–oxidation–Wittig reaction protocol provided a synthetic intermediate previously prepared by Nishida. Ring-closing metathesis resulted in a mixture of *E*/*Z* isomers that could be separated by column chromatography, as reported, and reduction of the two amides completed the synthesis of (+)-nakadomarin A. The entire synthetic sequence required 22 linear steps from the nitrone–cyclopropane formal cycloaddition, or 29 linear steps from D-mannitol (the precursor to cyclopropane **58**).



Scheme 15 Completion of the synthesis of nakadomarin A.



Scheme 16 The reaction of imines and cyclopropanes.

The reaction of imines and cyclopropanes

Another synthetic method, comparable to that reported by Carreira, involves the reaction of imines with 1,1-cyclopropanediesters to form pyrrolidine products (Scheme 16).[4] These heterocycles are similar in structure to those obtained from the conversion of tetrahydro-1,2-oxazines to pyrrolidines (Scheme 13) except that the 2,5-*cis* isomers (**70**) are usually obtained as the major products. In this sense, the two methods can be considered complimentary. It is often useful to prepare the imine *in situ* from the condensation of an aldehyde and an amine to avoid unnecessary isolation and purification steps.

This method is less general than those discussed thus far in terms of substrate scope and stereoselectivity. The diastereoselectivity ranges from poor (nearly 1 : 1) to excellent (>99 : 1 in favour of the *cis* isomer) depending on the substrates employed. Furthermore, the reaction is largely restricted to the use of aromatic/heteroaromatic aldehydes or formaldehyde equivalents. These factors serve to limit the utility of the reaction in natural product synthesis. Attempts to apply the reaction of imines and cyclopropanes to a total synthesis of FR901483 were initially unsuccessful, however, the development of an intramolecular variation of the transformation ultimately enabled the construction of the alkaloid.

Total synthesis of FR901483

FR901483 is a potent immunosuppressive alkaloid isolated from the fermentation broth of *Cladobotryum sp.* by the Fujisawa Pharmaceutical Company (Fig. 4).[39] There has been

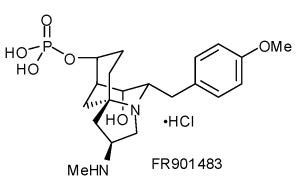
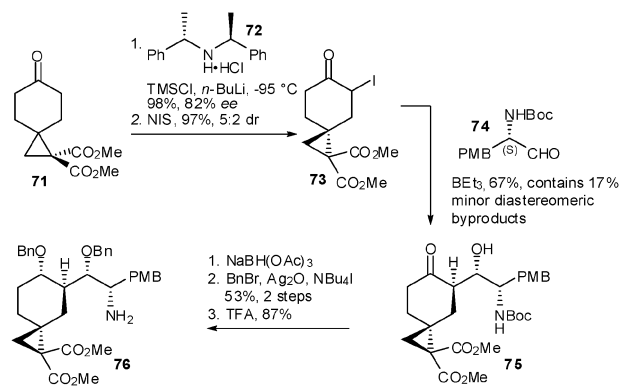


Fig. 4 Structure of FR901483.

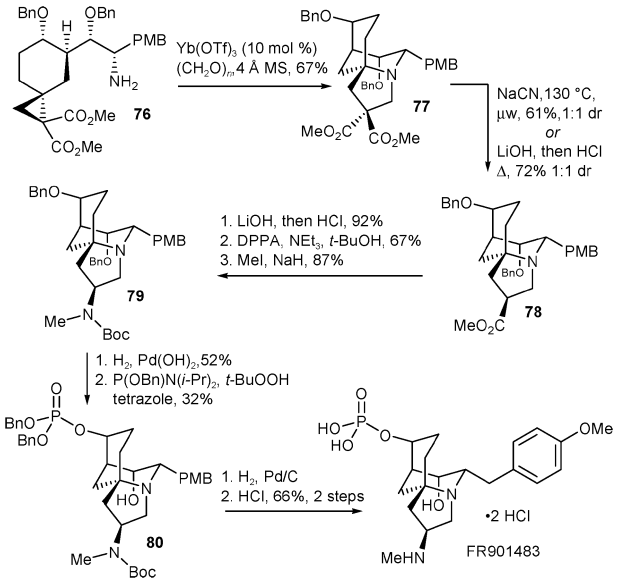
a large amount of synthetic work regarding this compound, owing to its biological activity and compact structure. Numerous total syntheses have been reported,[40] the most recent of which employs an intramolecular variation of the reaction of imines with 1,1-cyclopropanediesters.[41]

The synthesis of a suitable substrate for the intramolecular imine–cyclopropane annulation reaction was not trivial (Scheme 17). The natural product contains a complicated arrangement of stereocentres that can be difficult to prepare selectively. The early stages of the synthesis involved the coupling of chiral aldehyde **74** (derived from L-tyrosine) and the enolate of prochiral cyclohexanone derivative **71**. Because the deprotonation of cyclohexanone **71** generates a new stereocentre, a chiral base (**72**) was used to impart enantioselectivity. The highest diastereoselectivity for the coupling of the two chiral fragments was achieved when **71** was first derivatized as the α-iodoketone **72**. Treatment of **72** and **74** with triethylborane promoted a Reformatsky-like reaction to join the two segments in acceptable yield, although the material (**75**) was contaminated with some minor diastereomeric byproducts. The ketone of **75** was then reduced and the resulting diol was protected as the bis-benzyl ether. Removal of the *N*-Boc protecting group gave the amine **76** that was required for the cyclopropane ring-expansion reaction.

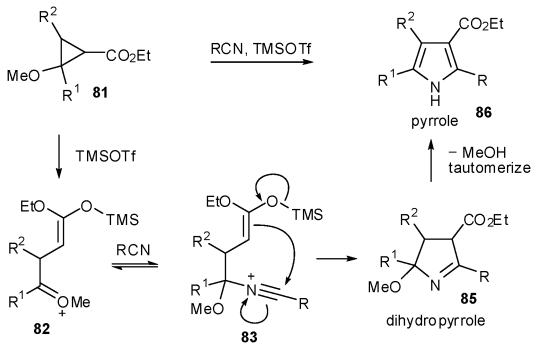
The key reaction in the synthesis was the formation of pyrrolidine **77** from amine **76** and paraformaldehyde (Scheme 18). This reaction represents the first example of an intramolecular imine–cyclopropane annulation reaction and demonstrates that while the reaction may be narrow in substrate scope, it is still potentially useful in a synthetic context. Once one of the superfluous esters was removed, a Curtius rearrangement and subsequent alkylation reaction provided compound **79**, which had been previously prepared by the Brummond group. The target was completed using the conditions reported by Brummond and Hong[40f] (for the removal of the benzyl groups and phosphorylation) and Sorensen *et al.*[40b] (for global deprotection).



Scheme 17 Preparation of amine **76**.



Scheme 18 Total synthesis of FR901483.



Scheme 19 The reaction of nitriles and cyclopropanes.

Aspidosperma alkaloids

The reaction of nitriles and cyclopropanes

Cyclopropanes have been shown to react with nitriles to form either dihydropyrroles or pyrroles (Scheme 19).[7] When cyclopropanes such as **81** are treated with nitriles and trimethylsilyl triflate, pyrroles **86** will result after dehydration and tautomerization of the intermediate dihydropyrroles **85**. The substrate scope encompasses aliphatic, aryl and α,β-unsaturated nitriles, permitting the regioselective preparation of a diverse set of di-, tri-, and tetra-substituted pyrroles. The use of a suitable cyclopropane permits the preparation of tetrahydroindoles, which can be oxidized reliably to indoles. This strategy has been applied to the total synthesis of two members of the *Aspidosperma* alkaloids, goniomitine and quebrachamine.

Total synthesis of (±)-goniomitine

The appealing structure and biological activity of various members of the *Aspidosperma* alkaloids (Fig. 5) have made them the subjects of extensive synthetic study by organic chemists.

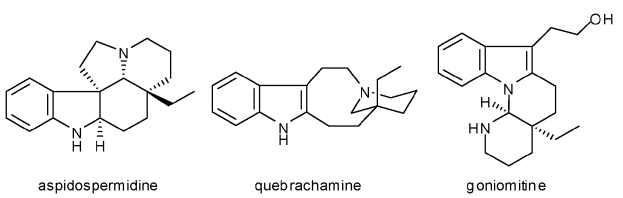


Fig. 5 Representative *Aspidosperma* alkaloids.

Goniomitine, a member of this alkaloid family, was first isolated in 1987 from the root bark of *Gonioma malagasy*.[42] The second reported synthesis of goniomitine used a nitrile–cyclopropane [3 + 2] cyclization to construct a highly functionalized pyrrole that would ultimately form the indole nucleus of the natural product.[43]

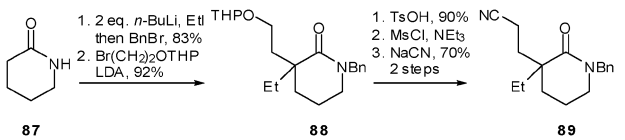
The synthesis began with the preparation of an appropriate nitrile substrate (Scheme 20). The one-pot C and N-alkylation of δ-valerolactam **87** (with ethyl iodide and benzyl bromide, respectively) proceeded smoothly. Treatment of the resulting lactam with lithium diisopropylamide and a suitable alkyl halide provided substrate **88**, which could easily be converted to nitrile **89** once the alcohol was deprotected and converted to an alkyl chloride. Direct alkylation with either acrylonitrile or a 3-halopropionitrile proved to be low yielding and the four-step procedure was preferred, particularly on scale up.

The reaction of cyclopropane **90** with nitrile **89** furnished pyrrole **91** in 74% yield (Scheme 21). This transformation is particularly noteworthy because the nitrile was used in limiting quantities. In general, the reaction of nitriles and cyclopropanes is most readily executed when the nitrile is used in large excess, preferably as the solvent. The authors aptly demonstrate in this synthesis, as well as related investigations of the synthesis of 2,2′-bipyrroles and 2,2′-thienylpyrroles,[44] that more valuable nitriles can be effectively used in smaller amounts. Tetrahydroindole **91** was oxidized to provide indole **92**, which was saponified and decarboxylated using microwave irradiation.

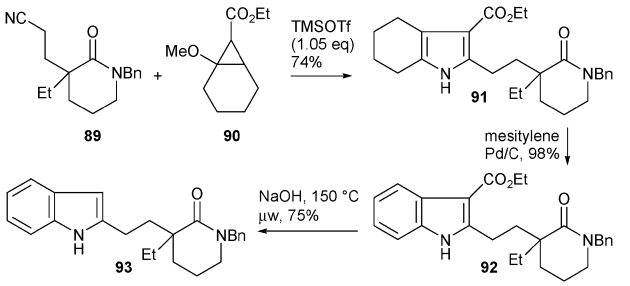
The side chain at the 3-position of the indole was incorporated into substrate **93** *via* a Mannich reaction (Scheme 22). The resulting amine was alkylated and displaced with cyanide to give compound **94**. Removal of the benzyl protecting group provided an intermediate previously prepared by Takano, and its conversion into the natural product was achieved using the conditions previously reported.[45] Accordingly, the tetracyclic core of the natural product **95** was formed by treatment with phosphorus oxychloride and reduction of the resulting amidine. Reduction of the cyano group and epimerization provided the desired *cis*-ring fusion giving goniomitine in an efficient manner. A modification of this synthetic strategy was subsequently applied to the total synthesis of another member of the *Aspidosperma* alkaloids, quebrachamine.

Total synthesis of (±)-quebrachamine

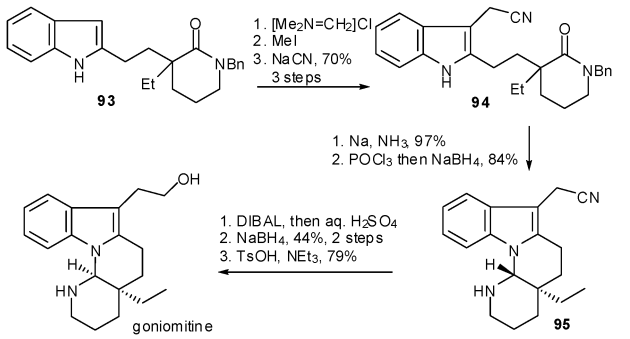
Quebrachamine (Fig. 5) is a molecule with a rich history of synthetic endeavours. Isolated more than a century ago from the bark of the *Aspidosperma quebracho* tree,[46] the first total synthesis of quebrachamine dates back to that of Stork and Dolfini in 1963.[47] The most striking structural feature of the alkaloid, beyond its indolic nature, must be its nine-membered ring, known to pose a significant synthetic challenge.



Scheme 20 Preparation of nitrile **89**.

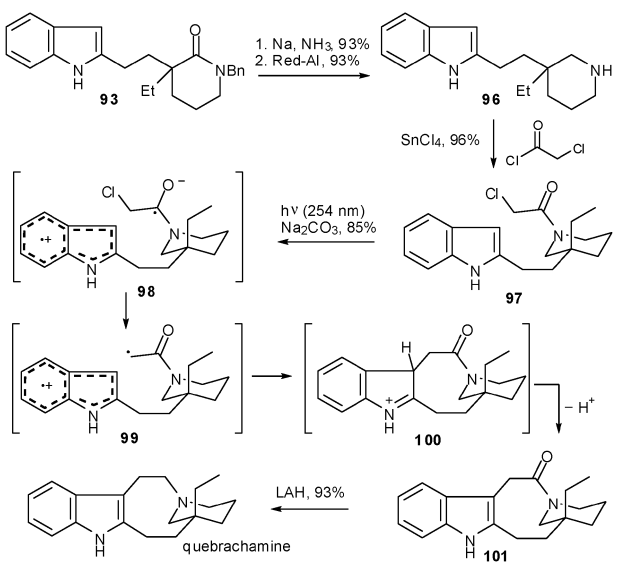


Scheme 21 Application of the reaction of nitriles and cyclopropanes to the total synthesis of goniomitine.



Scheme 22 Completion of the synthesis of goniomitine.

A route toward quebrachamine has been reported using the reaction of nitriles with donor–acceptor cyclopropanes (Scheme 23).[48] The synthetic sequence proceeds through indole **93** (previously used for the synthesis of goniomitine, Scheme 21), illustrating the usefulness of this intermediate for the divergent preparation of members of this alkaloid class. Early attempts to convert **93** into the natural product relied on a variety of Friedel–Crafts and *N*-alkylation strategies, but these methods proved unsuitable for the construction of the nine-membered ring. Ultimately, a successful synthetic sequence employing a chloroacetamide Witkop photocyclization was developed. The required substrate was prepared in a



Scheme 23 Total synthesis of quebrachamine.

succinct manner *via* a three-step procedure. Removal of the benzyl protecting group, amide reduction and acylation with chloroacetyl chloride provided photocyclization substrate **97**. Irradiation of **97** successfully promoted radical closure of the troublesome nine-membered ring in 85% yield. The efficiency of the reaction was exceptional considering only modest yields (15–55%) have been reported for the Witkop photocyclization of similar substrates. All that remained to complete the synthesis was the reduction of amide **101**. The reaction proceeded smoothly to provide (±)-quebrachamine in 17.8% yield over 13 steps from δ-valerolactam **87**.

Conclusions

In summary, the use of cyclopropane derivatives for the construction of complex heterocycles can provide a practical alternative to traditional methods for the preparation of such compounds. The reactions are highly regioselective, often stereoselective, and permit the synthesis of a variety of heterocyclic systems, both saturated and unsaturated. The substrates employed in most cases are simple (and often commercially available) making the methods amenable to the rapid construction of diverse collections of compounds. Finally, the preparation of more elaborate naturally occurring molecular architectures, which can be a demanding challenge in terms of reaction scope, has been clearly demonstrated.

References

1 For reviews regarding the chemistry of cyclopropanes see: (*a*) S. Danishefshy, *Acc. Chem. Res.*, 1979, **12**, 66–72; (*b*) H. N. Wong, M.-Y. Hon, C.-W. Tse, Y.-C. Yip, J. Tanko and T. Hudlicky, *Chem. Rev.*, 1989, **89**, 165–198; (*c*) H.-U. Reissig and R. Zimmer, *Chem. Rev.*, 2003, **103**, 1151–1196; (*d*) M. Yu and B. L. Pagenkopf, *Tetrahedron*, 2005, **61**, 321–347.
2 (*a*) P. D. Pohlhaus and J. S. Johnson, *J. Org. Chem.*, 2005, **70**, 1057–1059; (*b*) P. D. Pohlhaus, S. D. Sanders, A. T. Parsons, W. Li and J. S. Johnson, *J. Am. Chem. Soc.*, 2008, **130**, 8642–8650, and references therein.
3 P. B. Alper, C. Meyers, A. Lerchner, D. R. Siegel and E. M. Carreira, *Angew. Chem., Int. Ed.*, 1999, **38**, 3186–3189.
4 (*a*) C. A. Carson and M. A. Kerr, *J. Org. Chem.*, 2005, **70**, 8242–8244; (*b*) Y.-B. Kang, Y. Tang and X.-L. Sun, *Org. Biomol. Chem.*, 2006, **4**, 299–301, and references therein.
5 I. S. Young and M. A. Kerr, *Angew. Chem., Int. Ed.*, 2003, **42**, 3023–3026.
6 V. S. Korotkov, O. V. Larionov, A. Hofmeister, J. Magull and A. de Meijere, *J. Org. Chem.*, 2007, **72**, 7504–7510.
7 (*a*) M. Yu and B. L. Pagenkopf, *J. Am. Chem. Soc.*, 2003, **125**, 8122–8123; (*b*) M. Yu and B. L. Pagenkopf, *Org. Lett.*, 2003, **5**, 5099–5101.
8 C. Perrault, S. R. Goudreau, L. E. Zimmer and A. B. Charette, *Org. Lett.*, 2008, **10**, 689–692.
9 This list and the references cited are in no way comprehensive, but are chosen as recent representative examples.
10 For a brief review of synthetic approaches see: C. Marti and E. M. Carreira, *Eur. J. Org. Chem.*, 2003, 2209–2219.
11 C. Fisher, C. Meyers and E. M. Carreira, *Helv. Chim. Acta*, 2000, **83**, 1175–1181.
12 A. Jossang, P. Jossang, H. A. Hadi, T. Sévenet and B. Bodo, *J. Org. Chem.*, 1991, **56**, 6527–6530.
13 L. Angenot, *Plant. Med. Phytother.*, 1978, **12**, 123–129.
14 (*a*) A. Lerchner and E. M. Carreira, *J. Am. Chem. Soc.*, 2002, **124**, 14826–14827; (*b*) A. Lerchner and E. M. Carreira, *Chem.–Eur. J.*, 2006, **12**, 8208–8219.
15 (*a*) C.-B. Cui, H. Kakeya and H. Osada, *J. Antibiot.*, 1996, **49**, 832–835; (*b*) C.-B. Cui, H. Kakeya and H. Osada, *Tetrahedron*, 1996, **52**, 12651–12666.
16 (*a*) C. Meyers and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2003, **42**, 694–696; (*b*) C. Meyers and E. M. Carreira, *J. Am. Chem. Soc.*, 2005, **127**, 11505–11515.
17 K. Sapeta and M. A. Kerr, *J. Org. Chem.*, 2007, **72**, 8597–8599.
18 A. Karadeolian and M. A. Kerr, *J. Org. Chem.*, 2007, **72**, 10251–10253.
19 M. P. Sibi, Z. Ma and C. P. Jasperse, *J. Am. Chem. Soc.*, 2005, **127**, 5764–5765.
20 Y.-B. Kang, X.-L. Sun and Y. Tang, *Angew. Chem., Int. Ed.*, 2007, **46**, 3918–3921.
21 I. S. Young and M. A. Kerr, *Org. Lett.*, 2004, **6**, 139–141.
22 M. B. Johansen and M. A. Kerr, *Org. Lett.*, 2008, **10**, 3497–3500.
23 Isolation of (+)-phyllantidine: N. H. Lajis, O. B. Guan, M. V. Sargent, B. W. Skelton and A. H. White, *Aust. J. Chem.*, 1992, **45**, 1893–1897. Isolation of (–)-phyllantidine: J. Parello and S. Munavalli, *C. R. Hebd Seances Acad. Sci.*, 1965, **260**, 337–340. Structure revision: Z. Horii, T. Imanishi, M. Yamauchi, M. Hanaoka, J. Parello and S. Munavalli, *Tetrahedron Lett.*, 1972, **13**, 1877–1880.
24 J. A. Beutler, E. W. Karbon, A. N. Brubaker, R. Malik, D. R. Curtis and S. J. Enna, *Brain Res.*, 1985, **330**, 135–140.
25 A. Ohsaki, Y. Kobayashi, K. Yoneda, A. Kishida and H. Ishiyama, *J. Nat. Prod.*, 2007, **70**, 2003–2005.
26 C. A. Carson and M. A. Kerr, *Angew. Chem., Int. Ed.*, 2006, **45**, 6560–6563.
27 G. Han, M. G. LaPorte, J. J. Folmer, K. M. Werner and S. M. Weinreb, *Angew. Chem., Int. Ed.*, 2000, **39**, 237–240.
28 S. K. Jackson, A. Karadeolian, A. B. Driega and M. A. Kerr, *J. Am. Chem. Soc.*, 2008, **130**, 4196–4201.
29 I. Satoda, M. Murayama, J. Tsuji and E. Yoshii, *Tetrahedron Lett.*, 1962, **3**, 1199–1206.
30 S. Saito, T. Iwamoto, T. Tanaka, C. Matsumura, N. Sugimoto, Z. Horii and Y. Tamura, *Chem. Ind.*, 1964, **28**, 1263–1264.
31 T. Honda, H. Namiki, M. Watanabe and H. Mizutani, *Tetrahedron Lett.*, 2004, **45**, 5211–5213.
32 G. G. Bardají, M. Cantó, R. Alibés, P. Bayón, F. Busqué, P. de March, M. Figueredo and J. Font, *J. Org. Chem.*, 2008, **73**, 7657–7662.
33 A. B. Leduc and M. A. Kerr, *Angew. Chem., Int. Ed.*, 2008, **47**, 1–5.
34 I. S. Young, J. L. Williams and M. A. Kerr, *Org. Lett.*, 2005, **7**, 953–955.
35 J. Kobayashi, D. Watanabe, N. Kawasaki and M. Tsuda, *J. Org. Chem.*, 1997, **62**, 9236–9239.
36 K. Ono, M. Nakagawa and A. Nishida, *Angew. Chem., Int. Ed.*, 2004, **43**, 2020–2023.
37 T. Nagata, M. Nakagawa and A. Nishida, *J. Am. Chem. Soc.*, 2003, **125**, 7484–7485.
38 I. S. Young and M. A. Kerr, *J. Am. Chem. Soc.*, 2007, **129**, 1465–1469.
39 K. Sakamoto, E. Tsujii, F. Abe, T. Nakanishi, M. Yamashita, N. Shigematsu, S. Izumi and M. Okuhara, *J. Antibiot.*, 1996, **49**, 37–44.
40 (*a*) B. B. Snider and H. Lin, *J. Am. Chem. Soc.*, 1999, **121**, 7778–7786; (*b*) G. Scheffler, H. Seike and E. J. Sorensen, *Angew. Chem., Int. Ed.*, 2000, **39**, 4593–4596; (*c*) M. Ousmer, N. A. Braun, C. Bavoux, M. Perrin and M. A. Ciufolini, *J. Am. Chem. Soc.*, 2001, **123**, 7534–7538; (*d*) J.-H. Maeng and R. L. Funk, *Org. Lett.*, 2001, **3**, 1125–1128; (*e*) T. Kan, T. Fujimoto, S. Ieda, Y. Asoh, H. Kitaoka and T. Fukuyama, *Org. Lett.*, 2004, **6**, 2729–2731; (*f*) K. M. Brummond and S.-P. Hong, *J. Org. Chem.*, 2005, **70**, 907–916.
41 C. A. Carson and M. A. Kerr, *Org. Lett.*, 2009, **11**, 777–779.
42 L. Randriambola, J.-C. Quirion, C. Kan-Fan and H.-P. Husson, *Tetrahedron Lett.*, 1987, **28**, 2123–2126.
43 C. L. Morales and B. L. Pagenkopf, *Org. Lett.*, 2008, **10**, 157–159.
44 M. Yu, D. Pantos, J. L. Sessler and B. L. Pagenkopf, *Org. Lett.*, 2004, **6**, 1057–1059.
45 S. Takano, T. Sato, K. Inomata and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1991, 462–464.
46 O. Hesse, *Ber. Dtsch. Chem. Ges.*, 1881, **13**, 2308–2309.
47 G. Stork and J. E. Dolfini, *J. Am. Chem. Soc.*, 1963, **85**, 2872–2873.
48 B. Bajtos and B. L. Pagenkopf, *Eur. J. Org. Chem.*, 2009, 1072–1077.

