Strategies towards the synthesis of calyciphylline A-type Daphniphyllum alkaloids

Baldip Kang, Pavol Jakubec and Darren J. Dixon*

Covering: up to September 2013

The Daphniphyllum alkaloids are a diverse family of natural products rich in number and structural diversity that have been known for many decades. However, the structurally unique subclass of calyciphylline A-type alkaloids has only recently been discovered and is relatively unexplored. Several noteworthy core syntheses and the development of a wide range of novel synthetic strategies have been achieved. This includes strategies based on intramolecular Michael addition, Pd-catalysis, cycloaddition, and Mannich-type reactions. This review will provide an overview of these synthetic studies.

1 Introduction

The Daphniphyllum alkaloids are a structurally diverse family of natural products isolated from the genus Daphniphyllum that consists of dioecious evergreen trees and shrubs endemic to Asia.1 Since the first isolation of a Daphniphyllum alkaloid in 1909 by Yagi,2 over 200 Daphniphyllum alkaloids have been discovered in over 15 species.1,3 Structurally, these alkaloids can be classified into fourteen major classes based on the unusual ring systems present (e.g., 1–6, Fig. 1).3

In addition, some of these alkaloids have shown interesting biological activities against a variety of diseases.4 Together, the structural complexity and biological properties exhibited by these natural products has garnered significant attention from the synthetic chemistry community.

In 1973, Yamamura and co-workers conducted feeding experiments on the leaves of D. macropodum and fruits of D. teijsmannii using $^{14}$C-labelled mevalonic acid (7), followed by degradation studies, to determine the biosynthesis of the Daphniphyllum alkaloids.5 Through these studies they determined that daphnilactone B (14)b could be biosynthesised from mevalonic acid (7) via a squalene intermediate 8 (Scheme 1).

Despite this established biosynthetic route to Daphniphyllum alkaloids, it was not until the 1980s that Heathcock and co-workers demonstrated the power of biomimetic synthesis in assembling complex molecular structures by synthesising Daphniphyllum alkaloids.6 Heathcock et al. proposed that proto-daphniphylline could be accessed from squalene, which must determined that daphnilactone B (14)b could be biosynthesised from mevalonic acid (7) via a squalene intermediate 8 (Scheme 1).

Despite this established biosynthetic route to Daphniphyllum alkaloids, it was not until the 1980s that Heathcock and co-workers demonstrated the power of biomimetic synthesis in assembling complex molecular structures by synthesising Daphniphyllum alkaloids.6 Heathcock et al. proposed that proto-daphniphylline could be accessed from squalene, which must...
undergo four C–C bond unions and a nitrogen insertion
between C-10 and its methyl group.6

Thus, in 1988, Heathcock et al. confirmed this hypothesis in
the biomimetic synthesis of rac-methyl homosecodaphniphyllate (25, Scheme 2).7 This synthesis was initi-
ated with a highly convergent conjugate addition/enolate
alkylation sequence with amide 15, α,β-unsaturated ester 16,
and iodide 17 to deliver ester amide 18. A straightforward
conversion to diol 19 in four steps set the stage for a Swern
oxidation (19 → 20) and condensation with ammonia, which
initiated a cascade reaction. The cascade included an in situ
intramolecular aza-Diels–Alder reaction (22 → 23), and an aza-
Prins reaction to afford pentacyclic amine 24. Completion of
the total synthesis required a few functional group transformations
resulting in an efficient synthesis of the natural product in a
44% overall yield over nine steps. This foundational biomimetic

Baldip Kang obtained his B.Sc. Honours in Chemistry from the
University of British Columbia. During his final year he worked
under the guidance of Prof. Jennifer Love developing catalytic
alkyne hydrothiolation reactions. In 2006, he joined the laboratory
of Prof. Robert A. Britton at the Simon Fraser University as a
Ph.D. student. During his studies he developed novel applications
of optically pure α-chloroaldehydes toward the synthesis of natural products. He is
currently a Marie Curie Fellow at the University of Oxford in the
group of Prof. Darren Dixon, where he is involved in the develop-
ment and applications of organocatalysis toward the synthesis of
complex natural products.

Pavol Jakubec received his PhD degree from the Slovak Univer-
sity of Technology in 2005, working under the supervision of
Prof. Dušan Berkeš. In 2006 he joined the group of Prof. Darren
Dixon at the University of Manchester, where he participated in
the development of bifunctional organocatalysts and their appli-
cation in the total synthesis of nakadomarin A. In 2008, he
moved to the University of Oxford, where he worked on total syntheses of several manzamine
alkaloids. His current research focuses on the application of
bifunctional iminophosphoranes in the total syntheses of natural
products.

Darren J. Dixon is a Professor of Organic Chemistry at the
University of Oxford. He obtained his first degree and D. Phil from Oxford, where he
worked with Professor Stephen Davies. He moved to Cambridge to post-doc with Professor Steven
V. Ley. In 2004 he took a Senior Lecturership at The University of
Manchester and was promoted to Reader in 2007. In 2008, he
moved to his current post where
he holds the Knowles-Williams Tutorial Fellowship at Wadham
College. He was the recipient of a 5-year EPSRC Leadership
Fellowship, the Royal Society of Chemistry’s Catalysis in Organic
Chemistry Award and the AstraZeneca Research Award. He is a
Director of the EPSRC CDT in Synthesis for Biology and Medicine.
Review NPR

Scheme 2 Synthesis of rac-methyl homosecodaphniphyllate (25). Reagents and conditions: (a) LDA, THF, 15 then 16 and then 17, −78 °C to r.t., 87%; (b) DIBAL-H, toluene, −78 °C to r.t.; (c) KOH, H2O, EtOH, 95 °C, 80% (two steps); (d) LAH, Et2O, r.t., 96%; (e) (COCl)2, DMSO, Et3N, CH2Cl2, −78 °C to 0 °C; (f) NH2, CH2Cl2, (g) AcOH, 70 °C, 77% (from diol 19); (h) H2, Pd-C, HCl; (i) CrO3, H2SO4, H2O, (CH3)2CO; (j) MeOH, H2SO4, 85% (three steps).

Claissen rearrangements (27 → 28) and an intramolecular 7-membered alkyl Heck coupling (29 → 30). Whilst further synthetic efforts toward Daphniphyllum alkaloids have been reported, a significant new interest in the construction of alkaloids from the structurally distinct calyciphylline A-type subclass has recently been observed and this will be the target for this review.

1.1 Calyciphylline A-type alkaloids

Since the first report of their isolation in 2003, 24 calyciphylline A-type alkaloids have been isolated (Fig. 2): daphniglaucins D–H (32a and 33–36) (leaves of D. glaucescens), subdaphmanidine A (32b) (leaves of D. subverticillatum), longistylyphylline A (37) (leaves of D. longistylium), daphnilongeranins A–C (38a, 39, 40) (stems and leaves of D. longeracemosum), paxiphillyne E (38b) (twigs and leaves of D. paxianum), daphniyunnines A–E (41–45) (stems and leaves of D. yunnanense15 and leaves of D. longeracemosum46), daphnixaxanines A–C (46–48) (leaves and fruits of D. paxianum), daphlongamines E–G (49–51) (leaves of D. longeracemosum), calyciphylline A (52) (leaves of D. calycinum), and demethyl calyciphylline (fruits of D. longeracemosum). These compounds all have a characteristic structural backbone consisting of four fused rings [6-6-5-7]. Based on the Heathcock group’s biosynthetic models it is thought that the biogenetic origin of the calyciphylline A-type Daphniphyllum alkaloids is via a yuzurimine-type alkaloid (e.g., 2). The limited amount of material available from the natural sources has hindered a thorough biological evaluation; however, preliminary studies have shown that these molecules exhibit cytotoxicity against a variety of human cancer cell lines.

The inimitable structural complexity of the calyciphylline A-type alkaloids natural products ultimately serves as a canvas on which to develop unique and novel synthetic strategies. This, along with the understudied biological evaluation of these alkaloids has led to the recent surge in interest from the synthetic community regarding their synthetic preparation. The challenge presented by these molecules has led to a variety of powerful synthetic strategies being developed: for example, an intramolecular Michael addition strategy has been employed in the synthesis of the calyciphylline core by the groups of Dixon, She, Liang, and most recently Li with a total synthesis of daphniphylline, a 22-nor-calyciphylline A-type Daphniphyllum alkaloid. In addition, other notable synthetic endeavours toward these molecules using a variety of powerful complementary synthetic methods using Pd-catalysis, cycloaddition, and...
Mannich-type\textsuperscript{9} strategies have also been reported. While further synthetic approaches and total syntheses are envisaged this review will focus on these aforementioned studies.

2 Intramolecular Michael addition strategies toward the synthesis of calyciphylline A-type alkaloids

First discovered by Komnenos\textsuperscript{29} and Claisen\textsuperscript{30} and further developed by Michael,\textsuperscript{31} the Michael addition reaction is an important C–C bond forming process in natural product synthesis.\textsuperscript{32} For example, in the past decade many powerful intramolecular Michael additions have been developed to synthesise miscellaneous cores of calyciphylline A-type alkaloids.

An efficient, robust, and scalable strategy toward the ACD tricyclic [6-5-7] skeleton of calyciphylline A-type alkaloids was developed by Dixon and co-workers based on an intramolecular Michael addition as the key transformation (Schemes 4 and 6).\textsuperscript{20} This novel disconnection tactic allows for advancement of Daphniphyllum alkaloid synthesis, and has been employed in the first total synthesis of a calyciphylline A-type alkaloid by Li and co-workers (vide infra).\textsuperscript{23}

This approach (Scheme 4) initiated from ketone 53, which was subjected to a sequence involving enolate formation, γ-iodination and alkylation of benzylamine to give 54. Acylation with acid chloride 59 provided amide 55. At this time, the key intramolecular Michael addition was thoroughly studied and it was found that upon treatment of 55 with KHMD in THF the cis-fused Michael adduct (not shown) could be obtained with complete stereocontrol. However, it was quickly realised that an in situ quench of the enolate with allyl p-toluenesulfonate and 18-crown-6 cleanly generated the Claisen precursor 56 in 78% yield. A subsequent Claisen rearrangement afforded 57 as a 6 : 1 diastereomeric mixture, which subsequently underwent a ring-closing metathesis with the Grubbs I catalyst to afford >6 g of a 6 : 1 diastereomeric mixture of ACD tricyclic [6-5-7] core 58 of the Daphniphyllum alkaloid daphniyunnine B (42).

To further advance the tricyclic scaffold, Dixon and co-workers chose to address the possibility of installing two crucial stereocentres at C-6 and C-8 (Scheme 5). Thus, 58 was subjected to a Krapcho demethoxycarbonylation with wet DMSO-LiCl producing 60 as a diastereomeric mixture at both C-6 and C-8. The stereo- and regioselective alkylation at C-8 proved problematic with standard Michael acceptors (e.g., MVK, methyl acrylate) under a variety of conditions. Pleasingly, this was overcome by performing an O-alkylation of 60 followed by a Claisen rearrangement to give three diastereomers from which 61 was isolated as the major component in 58% yield. Notably, this sequence was carried out on the gram scale.
This efficient protocol was further elaborated (Scheme 6) to target a route that would allow oxidation at C-10, which is present in daphniyunnine B (42). To accomplish this, the key Michael addition/allylation cascade on amide 55 (vide supra) was performed with enol ether 65 resulting in 62 in 52% yield. A Claisen rearrangement (62 → 63) followed by an atypical enol ether ring-closing metathesis, rarely found in the construction of 7-membered rings, afforded the C-10 oxygenated ACD tricycle 64. This practical and scalable route to the core of calyciphylline A-type alkaloids, based on a key intramolecular Michael addition, allowed the construction of four stereo-centres of which two are contiguous and fully substituted.

The formidable challenge posed by the structural intricacies present in the Daphniphyllum alkaloids, especially the calyciphylline A-type members, has limited total synthetic efforts. Only recent efforts have led to advances toward the total synthesis of a closely related relative of the calyciphylline A-type natural product. Inspired by the work of Dixon and co-workers on the highly diastereoselective Michael addition in the construction of the ABC tricyclic system, Li and co-workers devised an elegant synthesis of daphenylline (79)—a structurally unique 22-nor-calyciphylline A-type Daphniphyllum alkaloid isolated from D. longeracemosum, and the only known Daphniphyllum alkaloid to contain an arene motif.

Scheme 4  An intramolecular Michael addition approach to the ACD tricyclic [6-5-7] core of daphniyunnine B (42). Reagents and conditions: (a) (i) LHMDS, THF, −78 °C, (ii) I2, −78 °C; (b) BnNH2, DMSO, r.t., 56% (three steps); (c) 59, Et3N, CH2Cl2, 76–91%; (d) KHMDS, THF, 0 °C to r.t., then allyl p-toluenesulfonate, 18-crown-6, 78%; (e) mesitylene, reflux, 6 : 1 d.r., 63%; (f) Grubbs I (5 mol%), CH2Cl2, reflux, 6 : 1 d.r., 98%.

Scheme 5  Installation of stereocentres at C-6 and C-8 of tricycle 61. Reagents and conditions: (a) LiCl, H2O, DMSO, 170 °C, 73%; (b) KHMDS, THF, then allyl p-toluenesulfonate, 18-crown-6, 89%; (c) mesitylene, reflux, 58%.

Scheme 6  An intramolecular Michael addition approach to the ACD tricyclic [6-5-7] core of daphniyunnine B (42). Reagents and conditions: (a) KHMDS, THF, 0 °C to r.t., then 65, 18-crown-6, 52%; (b) mesitylene, reflux, 53%; (c) Grubbs-Hoveyda II (10 mol%), toluene, 85 °C, 70%.
In the synthesis of daphenylline \(79\), Li and co-workers start (Scheme 7) with the coupling of the known hydroxy enone \(66\) (six steps from \(n\)-methylanisole (98% ee))\(^\text{15}\) and sulfonamide \(71\) under Mitsunobu conditions to provide \(67\) in 86% yield. A Au-catalysed 6-exo-dig cyclisation,\(^\text{46}\) via a silyl enol ether, gave access to the AB ring system \(68\) of daphenylline. Subsequent noryl cleavage and condensation of the resulting amine with carboxylic acid \(72\) produced amide \(69\). Following the disconnection strategy developed by Dixon and co-workers, amide \(69\) was subjected to a base-promoted intramolecular Michael addition to afford the ABC tricyclic [6-6-5] ring system \(70\) of daphenylline \(79\).

With tricycle \(70\) in hand, Li and co-workers focussed on the construction of the tetrasubstituted arene (Scheme 8). This was accomplished by first converting \(70\) with KHMDs and PhNTf\(_2\) to the corresponding vinyl triflate, which was subsequently treated under Suzuki conditions with trans-boronate \(76\) to afford the desired triene \(73\). The second key step in the synthesis was a well-designed photoinduced olefin isomerisation/6π-electrocyclisation/aromatisation sequence. Notably, the authors found that the 6π-electrocyclisation was reluctant both under thermal\(^\text{38}\) and Lewis acid\(^\text{39}\) conditions, and generally led to decomposition. Furthermore, while the conrotatory pathway was possible under irradiation with a 500 W Hg lamp small amounts of \(O_2\) led to unproductive side products. With preclusion of \(O_2\), this reaction afforded pentacycle \(74\) in 71% yield. At this time, the pentacycle \(74\) was oxidised to the arene scaffold \(75\) using the inherent acidity of the C-8 proton with DBU in the presence of air.

The end-game to the synthesis of daphenylline \(79\) required construction of the seven-membered ring, a selective facial reduction of the exocyclic alkene, and a Krapcho demethoxycarbonylation (Scheme 9). To achieve this, arene \(75\) was first converted to an enone using the Saegusa-Ito oxidation procedure,\(^\text{40}\) followed by a desilylation and iodination to afford iodide \(77\). A radical cyclisation was initiated using AIBN and (TMS)\(_3\)SiH providing hexacycle \(78\) in 98% yield. Hydrogenation of the exocyclic olefin was realised using Crabtree’s catalyst in the presence of \(H_2\) to provide a >30:1 d.r. favouring the desired C-18 diastereomer. This late-stage material was then subjected to a Krapcho demethoxycarbonylation akin to conditions used by Dixon and co-workers.\(^\text{28}\) To complete the synthesis of the natural product, a deoxygenation promoted by Pd/C under a \(H_2\) atmosphere was performed, followed by the reduction of the lactam with LiAlH\(_4\). In short, daphenylline \(79\) was synthesised in 25 steps featuring an intramolecular Michael addition strategy and a photoinduced olefin isomerisation/6π-electrocyclisation/aromatisation sequence.

The versatility of the intramolecular Michael addition toward the synthesis of the core of \(Daphniphyllum\) alkaloids was also realised by She and co-workers.\(^\text{38}\) A Bronsted acid promoted intramolecular Friedel–Crafts type Michael addition of a \(\delta\)-benzyl \(\alpha,\beta\)-unsaturated \(\delta\)-lactam \(81\) was harnessed in the construction of the ABCE tetracyclic [6-6-5-6] core of daphenylline \(79\) (Scheme 10). This key intermediate, lactam \(81\), was
prepared in nine steps from commercially available m-methoxymethyl phenyl acetonitrile. After a thorough optimisation of the key intramolecular Friedel-Crafts type Michael addition, She and co-workers found that using a variety of Lewis acids (e.g., SbF5, TiCl4, BF3·OEt2, FeCl3, BCl3, Br2, AlBr3, TMSOTf) or protic acids (e.g., p-TsOH, CF3COOH) resulted in little or no conversion. However, treating lactam 81 with TfoH resulted in the intramolecular Friedel-Crafts type Michael addition and concomitant deprotection of the OTHP to afford tricycle 82 in 71% yield. With tricycle 82 in hand, removal of the nosyl group, mesylation of the primary alcohol, and a subsequent N-cyclisation furnished tetracycle 83. This concise synthesis to the ABCE tetracyclic [6-6-5-6] ring system of daphenylline (79) was achieved in 7.5% overall yield over 13 steps.

Another example in which the intramolecular Michael addition is prominent is in the scalable route to the ABC tricyclic [6-6-5] ring system of calyciphylline A-type alkaloids developed by Liang and co-workers (Scheme 11). This robust approach involved an aza-Michael addition and a Pd-catalysed enolate a-vinylation as the key steps. Starting from the known diol 85,42 the primary alcohol was converted to an azide and the secondary alcohol oxidised to a ketone (85/86). A subsequent Staudinger reaction produced an inseparable mixture of amine 88 and the aza-Michael addition product 87, which was carried forward in an alkylation reaction allowing access to a diastereomeric mixture of bicycle 89. With the desired C–N bond formation completed, attention turned to the Pd-catalysed enolate a-vinylation reaction. Tricycle 90 was produced as a single diastereomer when 89 was treated with Pd(PPh3)4/t-BuOK followed by a stereoselective hydrogenation. This elegant scalable route allows rapid access to the ABC tricycle of ent-daphniyunnine C (ent-43) in 11 steps from (R)-carvone (84).

3 Alternative and complementary strategies toward the synthesis of calyciphylline A-type alkaloids

Although the aforementioned intramolecular Michael addition strategies significantly enhanced the repertoire of available methods for the construction of various scaffolds of...
Daphniphyllum alkaloids and their fruitful advancements ultimately led to the first total synthesis of daphenylline, several alternative and complementary synthetic methods appeared as a result of the intense on-going investigation in the field of Daphniphyllum alkaloids.

Whilst the first members of the calyciphylline A family were isolated in the 1980s, it was not until the pioneering work of Bonjoch and co-workers in 2005 that offered the first route to a racemic tricyclic core of the calyciphylline A-type alkaloids.24 The synthetic adventure towards the ABC tricyclic [6-6-5] core began with suitably protected diketone 91, which was transformed into bicyclic intermediate 94 in 11 steps (91 → 94, Scheme 12). The advanced precursor 94, containing both ketone acidic hydrogens and a tethered vinylbromide moiety, was then submitted to a Pd-catalysed carbocyclisation in the presence of potassium tert-butoxide. The one-pot enolate formation followed by a Pd-catalysed intramolecular vinylation stereoselectively generated the piperidine ring simultaneously with the exo-cyclic double bond, which was perfectly poised to undergo a consecutive hydrogenation.

Direct catalytic hydrogenation of 95 using Pd/C in MeOH led smoothly to the formation of tricycle 96a and generated a new stereogenic centre. However, this heterogeneous and highly stereoselective reduction of 95 generated the undesired configuration of the newly formed stereogenic centre for the synthesis of calyciphylline A-type alkaloids. In order to reverse the stereoselectivity of the reduction an alternative, substrate-directed process was designed; the ketone functionality of 95 was diastereoselectively reduced to alcohol 97, which was followed by protection of the tertiary amine as an amine-borane-ate complex. It was anticipated that the hydroxyl group in 97 would direct delivery of a reducing reagent from the more hindered face and produce the desired epimer 98b. Indeed, this rationally designed approach was proven to be plausible and the use of a Rh-catalysed hydrogenation led to the formation of the desired diastereomer 98b in 56% yield, along with 16% of its epimer 98a. The directing hydroxyl group in 98b was converted back to the ketone moiety in 96b using standard Swern oxidation conditions, thus finishing the first stereoselective synthesis of one of the most challenging ABC [6-6-5] motifs present in the calyciphylline A-type alkaloids.

Another application of Pd-catalysis in synthetic efforts toward calyciphylline A-type alkaloids was reported by Zhang and co-workers in 2012.25 The formation of the racemic ADE tricyclic [6-7-5] core of daphniphylline B (42) involved several noteworthy transformations, especially a sophisticated tandem Lewis acid-promoted semipinacol-type migration/aldol reaction and a Pd-catalysed carbocyclisation (Scheme 13). The multistep tandem reaction between enone 99 and suitably functionalised aldehyde 100 was initiated by MeAlCl2 under mild conditions and furnished an epimeric mixture of spirocyclic ketones 101a and 101b, which correspond to an important and extensively abundant AE structural motif found in the calyciphylline A-type family. The mixture of diastereomers 101a and 101b was accompanied by their cyclic hemiketals 102a,b. Major diastereomer 101a containing its inseparable corresponding hemiketal 102a was isolated by column chromatography and transformed to acetol 103a after a chemoselective reduction of the cyclohexanone moiety and a subsequent acetalisation. Then, the keto-acetal 103a underwent standard triflation and set the stage for the formation of the third ring of daphniphylline B (42). The Pd-catalysed intramolecular carbocyclisation performed under reductive conditions in the presence of formic acid created not only the all-carbon seven-membered ring but also, a suitably substituted exo-cyclic double bond in 105a ready for further elaboration. The same triflation/Pd-catalysed carbocyclisation sequence was also performed on minor epimer 103b. This approach gives access to the tricyclic framework present in the calyciphylline A-type alkaloids from relatively simple starting materials using an impressive sequence of chemical transformation.

Most of the methodologies devoted to the synthesis of the calyciphylline alkaloids’ cores have targeted the ABC [6-6-5] and ACD [6-5-7] structural motifs. Much less attention has been
given to the DEF [7-5-5] ring of the alkaloids. Interestingly, in 2011 Wang et al. envisioned that the EF [5-5] bicyclic unit could be constructed through a Pauson–Khand annulation/double bond shift tandem reaction. This hypothesis was successfully confirmed by Dixon and co-workers in 2012. Their approach to the DEF tricyclic [7-5-5] core of calciphylline A-type alkaloids employed three key late-stage steps: an intramolecular Pauson–Khand reaction, base-mediated double bond isomerisation and an allylic oxygenation. A suitable precursor 108 for the key transformations was constructed in five straightforward steps from inexpensive cycloheptanone (106, Scheme 14). Standard alkoxy carbonylation of cycloheptanone (106) with diethyl carbonate followed by a Michael addition of the resulting keto ester to acrolein and subsequent Bestmann–Ohira reaction afforded the keto-ester 107 in three steps. The ketone 107 was then successfully transformed into alkene 108, by a Luche reduction and elimination of the resulting alcohol. With alkyne 108 containing perfectly positioned multiple bonds in hand the envisaged Pauson–Khand reaction was tested under various conditions. After a relatively extensive screen of conditions, it was found that exposure of 108 to dicobalt octacarbonyl in

Scheme 13 Lewis acid-promoted semipinacol-type migration/aldol and Pd-catalysed carbocyclisation strategy to the ADE core of daphniyunnine B (42). Reagents and conditions: a) MeAlCl2, CH2Cl2, 0 °C, 89%, (101a + 102a):(101b + 102b) 4.7 : 1; b) NaBH(OAc)3, AcOH, (MeO)2CMe2 then PTSA, DMF, 41% of 103a and 17% of 103b; c) KHMS, PhNTf2, THF, –78 °C, 86%; d) Pd(OAc)2, Ph3P, DIPEA, HCOOH, 60 °C, DMF, 90%; e) KHMS, PhNTf2, THF, –78 °C, 83%; f) Pd(OAc)2, Ph3P, DIPEA, HCOOH, 60 °C, DMF, 86%.

Scheme 14 Construction of the DEF of daphniyunnine D using a Pauson–Khand strategy. Reagents and conditions: (a) NaH, (EtO)2CO, 100 °C, toluene, 98%; (b) acrolein, Et3N, r.t., DMF, 85%; (c) Ohira–Bestmann reagent, K2CO3, EtOH, 0 °C to r.t., EtOH, 85%; (d) CeCl3·7H2O, NaBH4, 0 °C, MeOH, 78%; (e) MsCl, pyridine, RT then reflux, 72%; (f) Co2(CO)8, CH2Cl2, RT; (g) NMO, CH2Cl2, r.t., 58%; 3.7 : 1 d.r; (h) K2CO3, EtOH, r.t., 92%; (i) AIBN, O2, t-BuOOH, 60 °C then SnCl2, r.t., 34%.
dichloromethane at room temperature resulted in the formation of cobalt-alkyne complex 109, which after promotion with NMO, underwent the desired cyclisation and afforded an epimeric mixture of two carboxyclic ketones 110. Whilst the desired carbon skeleton was rapidly assembled in just seven steps, two more transformations were needed to adjust the position of the internal double bond and introduce a hydroxy group. First, the thermodynamically driven double bond isomerisation was achieved by a treatment of 110 with potassium carbonate in ethanol. The subsequent allylic oxygenation of the resulting single diastereomer of 111 under radical oxygenation conditions gave rise to desired tricyclic core 112. Overall, the described strategy demonstrated the feasibility of a late stage Pauson–Khand reaction/double bond migration/allylic oxygenation sequence and could become a valuable tool for the end game in total syntheses of countless members of the calyciphilhylline A-type alkaloids considering their ubiquitous nature.

Before Li and coworkers’ first total synthesis of daphenylline (79) (Schemes 7–9) she had already disclosed an alternative approach to its synthetically demanding ABCE tetracyclic [6-6-5-6] core in 2012 (Schemes 15). Unlike Li and co-workers’ strategy, where the benzene ring of daphenylline was formed at a late stage, She and co-workers introduced the aromatic ring at the beginning of their synthetic sequence from the substituted iodobenzene 114. This was used as a pro-nucleophile in a highly stereoselective Michael addition to substituted cyclohexenone 113, which afforded lactone 115. Successive manipulation of the lactone 115 involved a ring opening with hydroxylamine, protection of primary alcohol and a low-temperature DIBAL-H reduction to generate aldehyde 116. According to Pearson’s protocol, aldehyde 116 was condensed with (aminomethyl) tributylstannane which generated imine 117. Then, with the key intermediate available, the imine was treated with n-butyllithium and the in situ formed allyl anion 118 smoothly underwent a [3 + 2] cycloaddition thus generating the pyridoline ring of tricycle 119 in a highly stereoselective manner. Single diastereomer of 119 was further elaborated to tetracyle 120 via removal of the TBS-protecting group, Appel reaction of the liberated alcohol and a 6-exo-tet ring closure. The latter transformation offered an alternative, attractive route to the formation of the substituted piperidine ring of calyciphilline A-type alkaloids, and could be applied to the synthesis of miscellaneous members of the Daphniphyllum family.

To date, the most advanced core of the calyciphilline A-type alkaloids is synthesised by Wang and co-workers in 2012 and has become an important milestone in the synthesis of the Daphniphyllum alkaloids. This report closely followed their first disclosure from 2011.44 Inspired by Overman et al.,42 Wang and co-workers’ chiral pool approach to the diastere- and enantiomERICally pure diol 121 used naturally occurring (+)-carvone as the starting material (Scheme 16). Having rapidly established the correct configuration of two stereogenic centres in diol 121, the primary alcohol was selectively protected with PMP protecting group and the secondary allylic alcohol was then reacted with trichloroacetonitrile. Thus, the newly formed imidate subsequently underwent an Overman rearrangement and gave trichloroacetamide 122 with the expected configuration of the stereogenic centre bearing the protected amino group. Next, 122 was converted to a carbamate, and then reacted with paraformaldehyde in order to prepare N-acyl iminium precursor 123. The following intermolecular Mannich condensation was found to be efficiently promoted by Sn(NTf$_2$)$_2$, and the reaction yielded 124 containing all carbon atoms for the construction of the tetracyclic core of daphniyunnine B. Before the key intramolecular [2 + 2] cycloaddition/Grob fragmentation sequence could take place, it was necessary to acylate the enol ether with acetyl chloride. Successive exposure of the acetate (not shown) to UV-light facilitated the formation of stable tetracyclic protected amine 126 via a highly stereoselective [2 + 2] cycloaddition. The major, desired product 126 was accompanied by 127, whose formation was attributed to a retro-aldol reaction driven by release of the strain from the cyclobutane moiety. Importantly, the stereochemical outcome of the pericyclic reaction perfectly matched the desired configuration present in the Daphniphyllum alkaloids. Stereoselective reduction of the ketone moiety in 126 followed by mesylation of the resulting alcohol provided a substrate with the necessary stereochemical requirements for the ring expansion. The Grob fragmentation of 127 was triggered by potassium carbonate and afforded the.
heavily functionalised tricyclic core 128. After oxidative cleavage of the PMP protecting group and mesylation of the primary alcohol, subjection of mesylate 129 to TMS iodide and triethylamine resulted in an efficient formation of the synthetically challenging piperidine ring of daphniyunnine B. The last stereogenic centre in tetracycle 130 was installed by a mild heterogeneous Pt-catalysed hydrogenation reaction, thus completing the fascinating synthetic sequence towards the most advanced ABCD core of daphniyunnine B so far. Not only have Wang and co-workers synthesised the most complex core in enantiomerically pure form, but they have also generated an advanced scaffold which possesses four rings of the hexacyclic natural product and provides a suitable handle for further elaboration.

Similar to the previous ABCD [6-6-5-7] core synthesis by Wang, Iwabuchi and co-workers aimed for the synthesis of the BCD [6-5-7] tricyclic core of Daphniphyllum alkaloids. Although Iwabuchi directly targeted the unnatural enantiomer of daphnicyclin A of the daphnicyclin subclass, their synthesis of the heavily functionalised tricyclic BCD [6-5-7] core could be viewed as a tactic towards the calicyphiline A-type alkaloids. Strategically, the chiral pool approach described in Scheme 17 required a convergent combination of two major, enantiomerically pure fragments 133 and 134 derived from D-mannitol (131) and cycloheptanone, respectively. Dissimilar to acidic fragment 133, whose enantiomeric purity is directly derived from naturally occurring D-mannitol, the chirality in amino alcohol 134 was induced by enantiomerically pure (−)-8-phe-nylmenthol auxiliary. With both advanced enantiomerically

---

**Scheme 16** Access to the ABCD core of daphniyunnine B using an intramolecular [2 + 2] cycloaddition/Grob fragmentation sequence. Reagents and conditions. (a) TsCl, pyridine, DMAP, CH$_3$Cl, 58%; (b) NaH, 4-methoxyphenol, DMF, 85%; (c) DBU, CCl$_3$CN, 0 °C; (d) xylene, reflux, 50% (two steps); (e) HCl(OMe)$_2$, PTSA, Na$_2$CO$_3$, 150 °C, MeOH, DMF, 82%; (f) CH$_2$==O, t-BuOK, t-BuOH, r.t., 54%; (g) Sn(NTf$_2$)$_2$, 1,3-cyclopentanediene, MeCN, r.t., 77%; (h) AcCl, Et$_3$N, CH$_2$Cl$_2$, 95%; (i) hv (254 nm), MeCN, 29% of 125, 50% of 126; (j) NaBH$_4$, MeOH, 95%; (k) MsCl, pyridine, DMAP; (l) K$_2$CO$_3$, MeOH, 82%; (m) CAN, MeCN, H$_2$O, 99%; (n) MsCl, Et$_3$N, 95%; (o) TMSI, CH$_2$Cl$_2$; (p) Et$_3$N, CH$_2$Cl$_2$, 80% (two steps); (q) Pd$_2$(dba)$_3$, H$_2$, 94%.

---

**Scheme 17** Access to the BCD core of the calicyphiline A-type alkaloids using a tandem acyliminium/Mannich-type reaction. Reagents and conditions. (a) EDCI, DMAP, pyridine, CH$_2$Cl$_2$, 80%; (b) TsCl, Et$_3$N, Me$_2$N.HCl, CH$_2$Cl$_2$ then TBAF, 95%; (c) H$_2$, Pd/C, NaHCO$_3$, MeOH, 97%; (d) NaOMe, reflux, MeOH. (e) AcCl, reflux, MeOH then PivCl, Et$_3$N, 32% of 136a (undesired) and 36% of 136b (desired).
pure fragments in hands the key intermediate 135 was accessed after an EDCI mediated coupling followed by a 3-step synthetic manipulation. Upon treatment of 135 with in situ generated HCl the piperidinone and pyrrolidine BC rings of tricyclic core 136 were elegantly assembled in one-pot as a result of several acid-catalysed reactions including a stereoselective acyliminium/Mannich type reaction. Pleasingly, only two enantiomerically pure separable diastereomers 136a and 136b, out of four possible diastereomers, were generated.

4 Conclusions

*Daphniphyllum* alkaloids are a rapidly growing, fascinating family of natural products rich in number and structural diversity. Since the isolation of its first member in 1909, there has been an ever growing interest within the synthetic community to achieve total syntheses of various intriguing and structurally complex members of this heavily branched family of natural products. Several remarkable total syntheses have been accomplished already; Heathcock’s classic synthesis of methyl homosecodaphnyllate (secodaphniphylline subclass) and Carreira’s recent synthesis of daphmanidin E (daphmanidin subclass) represent noteworthy milestones in the total synthesis of these two popular subclasses of the large *Daphniphyllum* family. However, in the past decade, enormous synthetic efforts have also been dedicated to the construction of the relatively unexplored subclass of calyciphylline A-type alkaloids. The unique structural characteristics present in these natural products have led to several noteworthy core syntheses and the development of a plethora of novel synthetic tactics to create the molecular complexity required. This includes strategies based on: Pdcatalysis by Bonjoch and Zhang; cycloadditions by Dixon, She, and Wang; and Mannich-type reactions by Iwabuchi; intramolecular Michael additions by the groups of Dixon, She, and Liang. Recently, building on this founding studies, the asymmetric total synthesis of a structurally exciting member closely related to the calyciphylline A-type alkaloids, daphenylline, was accomplished by Li and co-workers. With various applications of state-of-the-art catalytic methods, significant contributions and advances have been made in the synthesis of *Daphniphyllum* alkaloids. Founded on the recent rapid developments in the synthesis of calyciphylline A-type alkaloids, further exciting endeavours and discoveries are envisaged alongside expected completed total syntheses.66

5 Acknowledgements

This work was supported by the EPSRC (Leadership Fellowship to D.J.D., Postdoctoral Fellowship to P.J.), and the EU (IIF to B.K [PHIF-GA-2011-300137]).

6 Notes and references

14 Daphniyunnine B is also known as longeraclinphyllin B, and daphniyunnine C as longeraclinphyllin A.


32 (a) E. D. Bergmann, D. Ginsburg and R. Pappo, Org. React., 1959, 10, 179;
(b) D. A. Oare and C. H. Heathcock, Top. Stereochem., 1989, 19, 227;

33 For representative examples of cyclic enol ether synthesis through olefin metathesis reactions, see: (a) O. Fujimura, G. C. Fu and R. H. Grubbs, J. Org. Chem., 1994, 59, 4029;
(c) J. S. Clark and J. G. Kettle, Tetrahedron, 1999, 55, 8231;


42 (a) O. Corminboeuf, L. E. Overman and L. D. Pennington, J. Am. Chem. Soc., 2003, 125, 6650;


During the preparation of this manuscript an additional report was published: X. Xiong, Y. Li, Z. Lu, M. Wan, J. Deng, S. Wu, H. Shao and A. Li, Chem. Commun., 2014, DOI: 10.1039/c3cc47873d.