NPR

REVIEW

Strategies towards the synthesis of calyciphylline A-type *Daphniphyllum* alkaloids

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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.

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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. teijsmanni* 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 daphniphylline,[5a] codaphniphylline,[5a] and daphnilactone B (**14**)[5b] 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

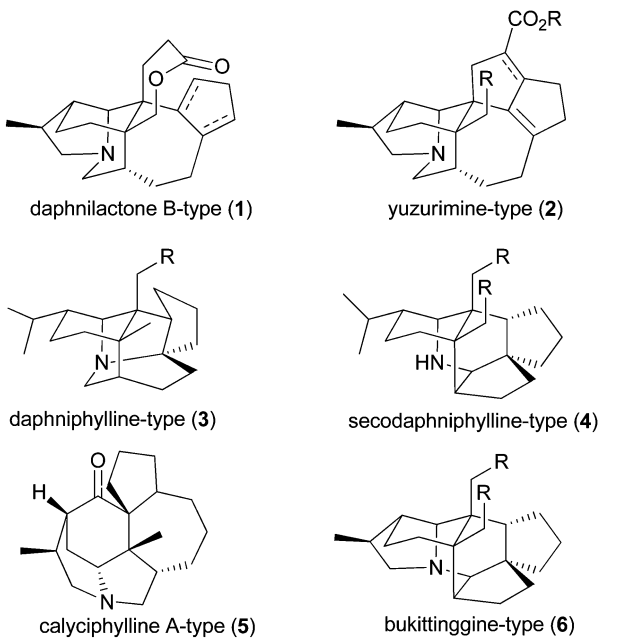


Fig. 1 Representative classes of *Daphniphyllum* alkaloids.

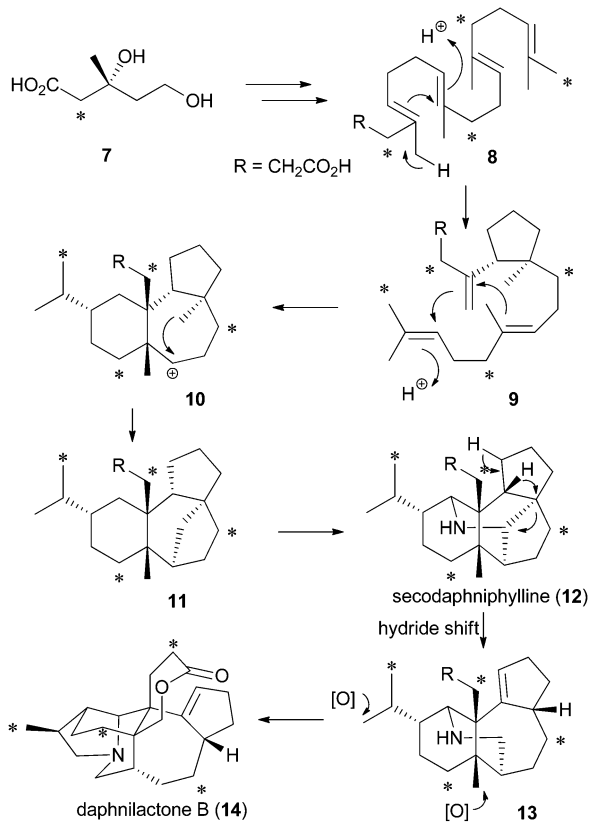
undergo four C–C bond unions and a nitrogen insertion between C-10 and its methyl group.[6]

Thus, in 1988, Heathcock *et al.* confirmed this hypothesis in the biomimetic synthesis of *rac*-methyl homosecodaphniphyllate (**25**, Scheme 2).[7] This synthesis was initiated 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 synthesis stands as an important advance in *Daphniphyllum* alkaloid synthesis.

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 development and applications of organocatalysis toward the synthesis of complex natural products.

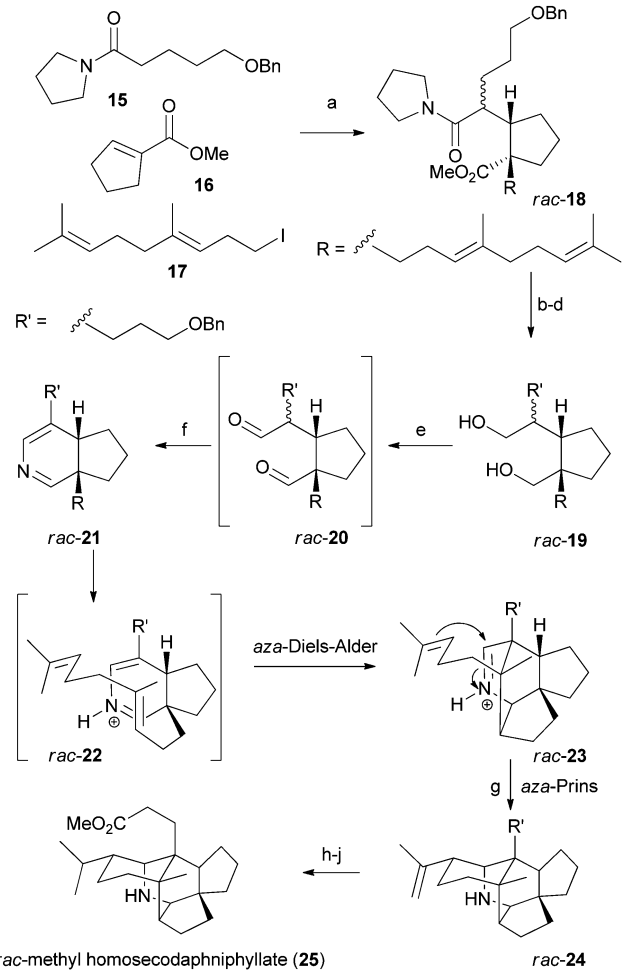
Pavol Jakubec received his PhD degree from the Slovak University of Technology in 2005, working under the supervision of Prof. Dušan Berkeš. In 2006 he joined the group of Prof. Darren Dixon at the University of Manchester, where he participated in the development of bifunctional organocatalysts and their application 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 Chemisty'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.

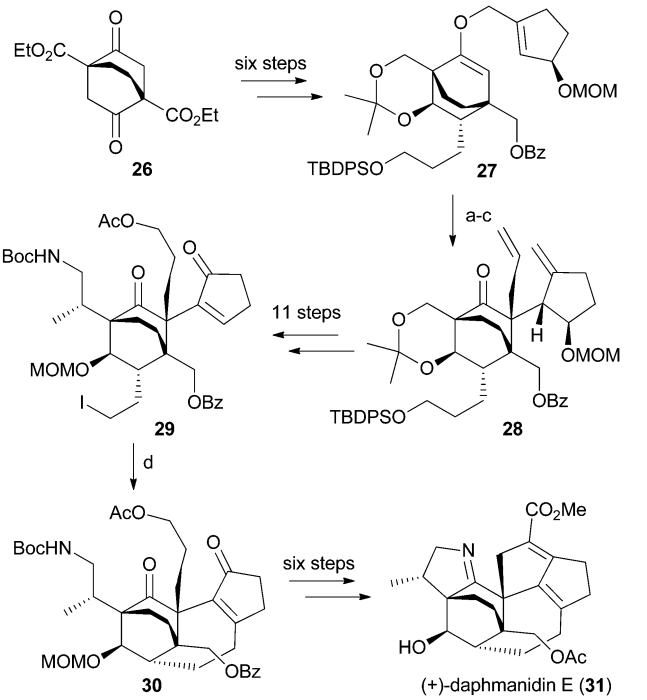


Scheme 1 Biosynthesis of daphnilactone B (**14**) from mevalonic acid (**7**, asterisks indicate ^{14}C-labelling).

Twenty years after the Heathcock group's studies on *Daphniphyllum* alkaloid total synthesis, Carreira and co-workers disclosed a highly stereoselective total synthesis of daphmanidin E (**31**, Scheme 3).[8] Their strategy relied on two consecutive



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, H_2O, EtOH, 95 °C, 80% (two steps); (d) $LiAlH_4$, Et_2O, r.t., 96%; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to 0 °C; (f) NH_3, CH_2Cl_2; (g) AcOH, 70 °C, 77% (from diol **19**); (h) H_2, Pd-C, HCl; (i) CrO_3, H_2SO_4, H_2O, $(CH_3)_2CO$; (j) MeOH, H_2SO_4, 85% (three steps).



Scheme 3 Synthesis of (+)-daphmanidin E (**31**). *Reagents and conditions*: (a) 155 °C, nonane, 10 : 1 d.r., 86%; (b) KHMDS, 18-crown-6, allylbromide, THF, −20 °C, 83%; (c) *o*-xylene, 165 °C, 40%; (d) cobaloxime[8] (25 mol%), iPr_2NEt, blue LED, MeCN, 23 °C, 93%.

Claisen rearrangements (**27** → **28**) and an intramolecular 7-membered alkyl Heck coupling (**29** → **30**). Whilst further synthetic efforts toward *Daphniphyllum* alkaloids have been reported,[8,9] 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,[4b] 24 calyciphylline A-type alkaloids have been isolated (Fig. 2): daphniglaucins D–H (**32a** and **33–36**) (leaves of *D. glaucescens*),[10] subdaphmanidine A (**32b**) (leaves of *D. subverticillatum*),[4j] longistylumphylline A (**37**) (leaves of *D. longistylum*),[11] daphnilongeranins A–C (**38a**, **39**, **40**) (stems and leaves of *D. longeracemosum*),[12] paxiphylline E (**38b**) (twigs and leaves of *D. paxianum*),[13] daphniyunnines A–E (**41–45**)[14] (stems and leaves of *D. yunnanense*[15] and leaves of *D. longeracemosum*[16]), daphnipaxianines A–C (**46–48**) (leaves and fruits of *D. paxianum*),[17] daphlongamines E–G (**49–51**) (leaves of *D. longeracemosum*),[18] calyciphylline A (**52**) (leaves of *D. calycinum*),[4f] and demethyl calyciphylline (fruits of *D. longeracemosum*).[19] 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**).[4b] 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.[15]

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,[20] She,[21] Liang,[22] and most recently Li[23] with a total synthesis of daphenylline, 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,[24,25] cycloaddition,[26–28] and

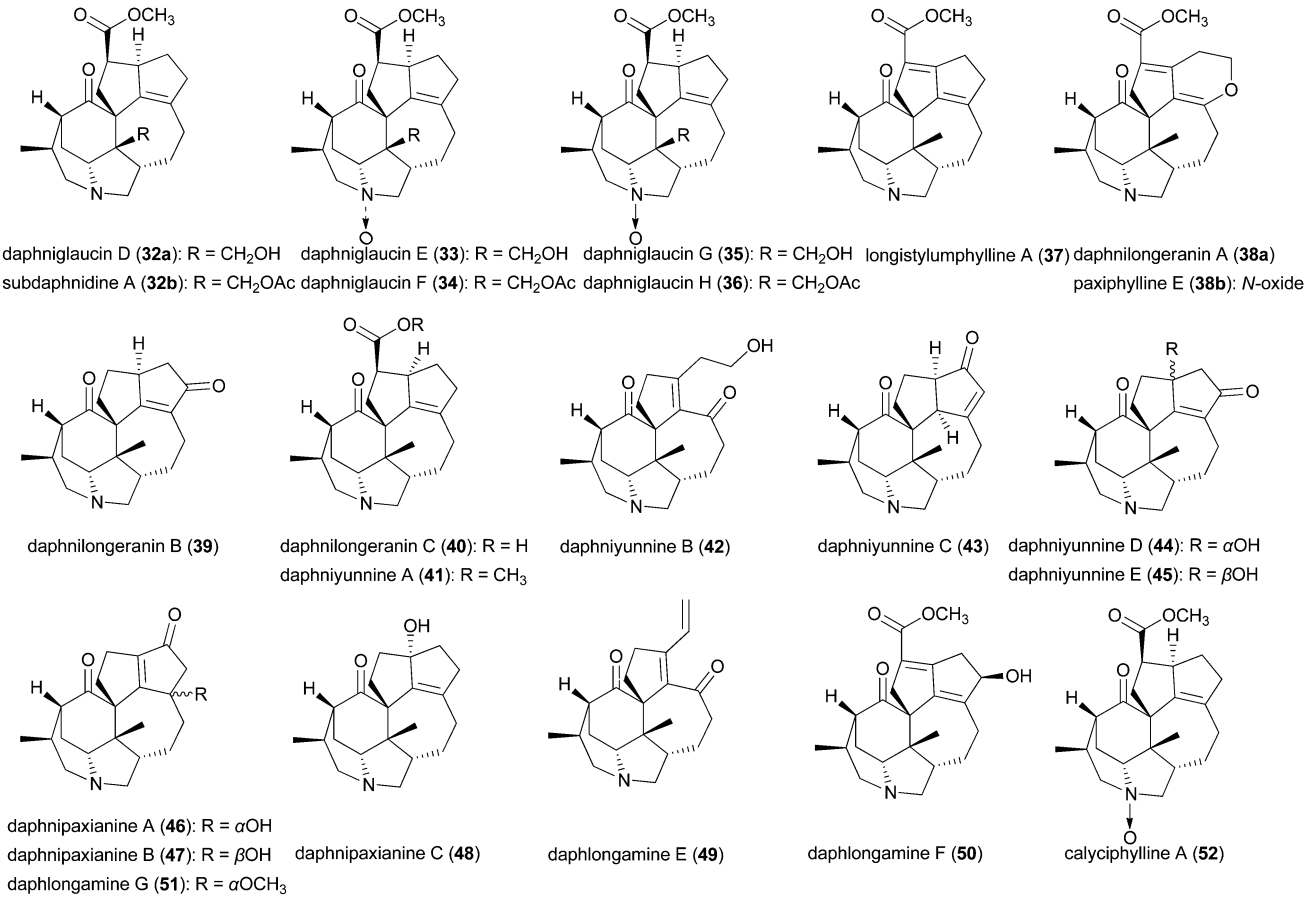


Fig. 2 The known calyciphylline A-type alkaloids.

Mannich-type[9b] strategies have also been reported. While further synthetic approaches and total syntheses are envisaged this review will focus on these aforementioned studies.

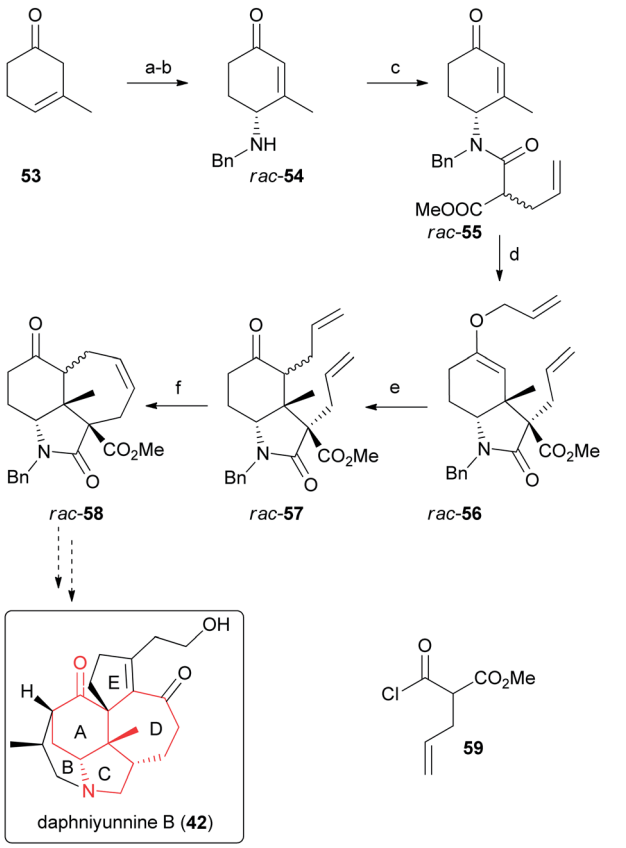
2 Intramolecular Michael addition strategies toward the synthesis of calyciphylline A-type alkaloids

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

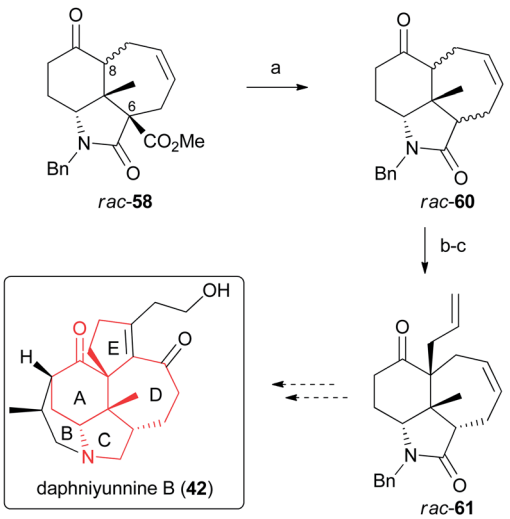
An efficient, robust, and scalable strategy toward the ACD tricyclic [6-5-7] skeleton of calyciphylline A-type alkaloids was developed by Dixon and co-workers based on an intramolecular Michael addition as the key transformation (Schemes 4 and 6).[20] This novel disconnection tactic allows for advancement 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*).[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 KHMDS 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.



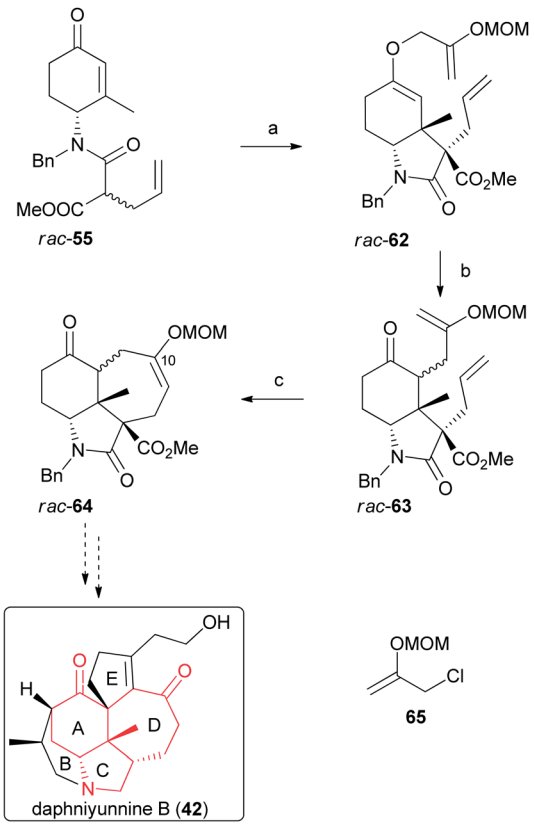
Scheme 4 An intramolecular Michael addition approach to the ACD tricyclic [6-5-7] core of daphniyunnine B (**42**). *Reagents and conditions*: (a) (i) LHMDS, THF, −78 °C, (ii) I_2, −78 °C; (b) $BnNH_2$, DMSO, r.t., 56% (three steps); (c) **59**, Et_3N, CH_2Cl_2, 76–91%; (d) KHMDS, THF, 0 °C to r.t., then allyl *p*-toluenesulfonate, 18-crown-6, 78%; (e) mesitylene, reflux, 6 : 1 d.r., 63%; (f) Grubbs I (5 mol%), CH_2Cl_2, 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, H_2O, DMSO, 170 °C, 73%; (b) KHMDS, THF, then allyl *p*-toluenesulfonate, 18-crown-6, 89%; (c) mesitylene, reflux, 58%.

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,[33] 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 stereocentres of which two are contiguous and fully substituted.

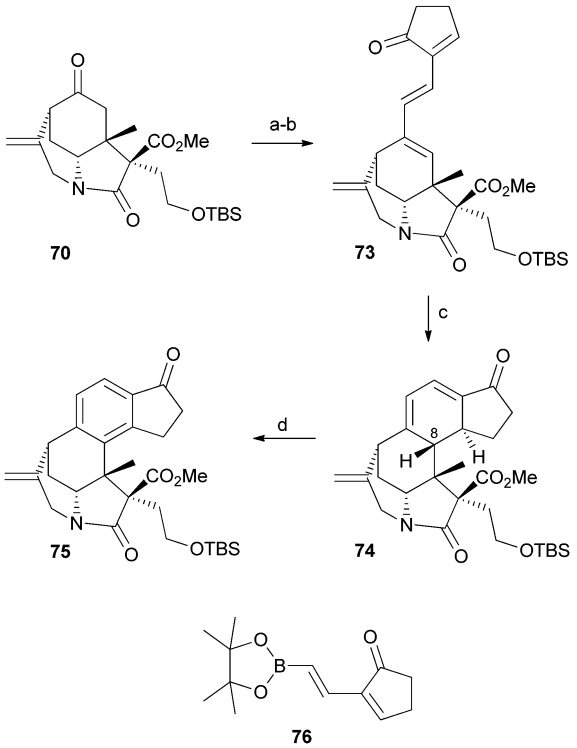
The formidable challenge posed by the structural intricacies present in the *Daphniphyllum* alkaloids, especially the calyciphylline A-type members, has limited total synthetic efforts. Only recent efforts have led to advances toward the total synthesis of a closely related relative of the calyciphylline 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**)[23]—a structurally unique 22-nor-calyciphylline A-type *Daphniphyllum* alkaloid isolated from *D. longeracemosum*,[34] and the only known *Daphniphyllum* alkaloid to contain an arene motif.



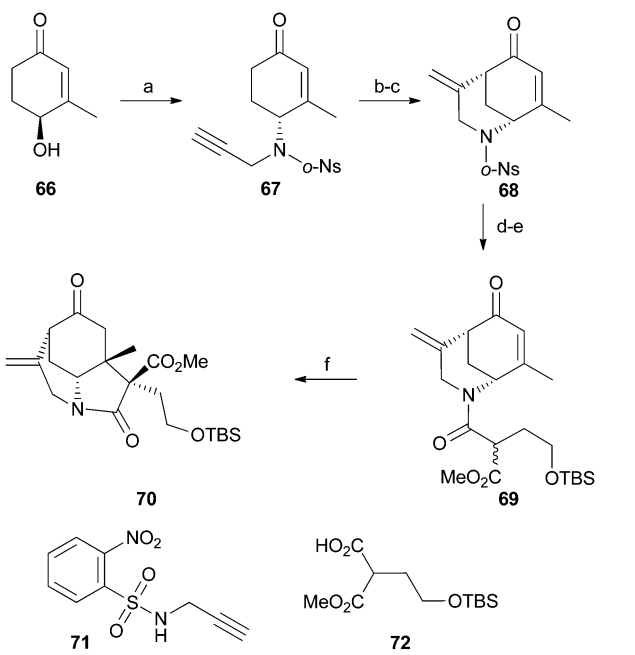
Scheme 6 An intramolecular Michael addition approach to the ACD tricyclic [6-5-7] core of daphniyunnine B (**42**). *Reagents and conditions*: (a) KHMDS, THF, 0 °C to r.t., then **65**, 18-crown-6, 52%; (b) mesitylene, reflux, 53%; (c) Grubbs-Hoveyda II (10 mol%), toluene, 85 °C, 70%.

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 *m*-methylanisole (98% ee))[35] and sulfonamide **71** under Mitsunobu conditions to provide **67** in 86% yield. A Au-catalysed 6-*exo*-dig cyclisation,[36] *via* a silyl enol ether, gave access to the AB ring system **68** of daphenylline. Subsequent nosyl 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**).[20,37]

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[38] and Lewis acid[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.



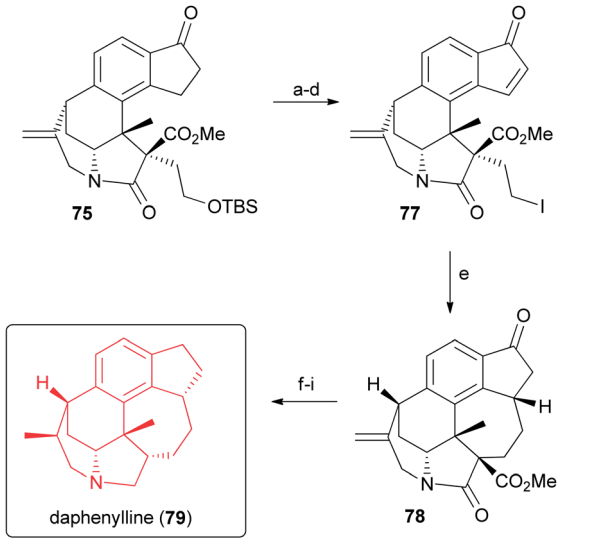
Scheme 8 A photoinduced olefin isomerisation/6π-electrocyclisation cascade approach to the ABCEF pentacyclic core of daphenylline (**79**). *Reagents and conditions*: (a) KHMDS, $PhNTf_2$, −78 °C; (b) **76**, $Pd(PPh_3)_4$, K_2CO_3, 60 °C, 73% (two steps); (c) *hν* (Hg lamp 500 W), 0 °C, 71%; (d) DBU, air, 60 °C, 67%.



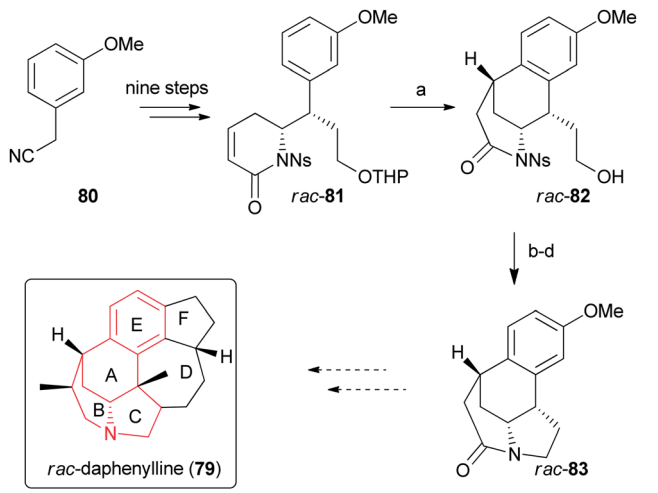
Scheme 7 Li and co-workers' synthesis of the ABC tricyclic [6-6-5] ring system of daphenylline (**79**) using Dixon and co-workers intramolecular Michael addition strategy. *Reagents and conditions*: (a) **71**, PPh_3, DIAD, 0 °C, 86%; (b) TBDPSOTf, 2,6-lutidine, −78 °C; (c) $Au(PPh_3)Cl$, AgOTf, MeOH, 70% (two steps); (d) K_2CO_3, *p*-thiocresol; (e) **72**, HOBt, EDC·HCl, Et_3N, 72% (two steps); (f) K_2CO_3, 100 °C, 86%.

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,[40] followed by a desilyation and iodination to afford iodide **77**. A radical cyclisation was initiated using AIBN and $(TMS)_3SiH$ 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.[20] 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.[21] A Brønsted acid promoted intramolecular Friedel–Crafts type Michael addition of a δ-benzyl α,β-unsaturated δ-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

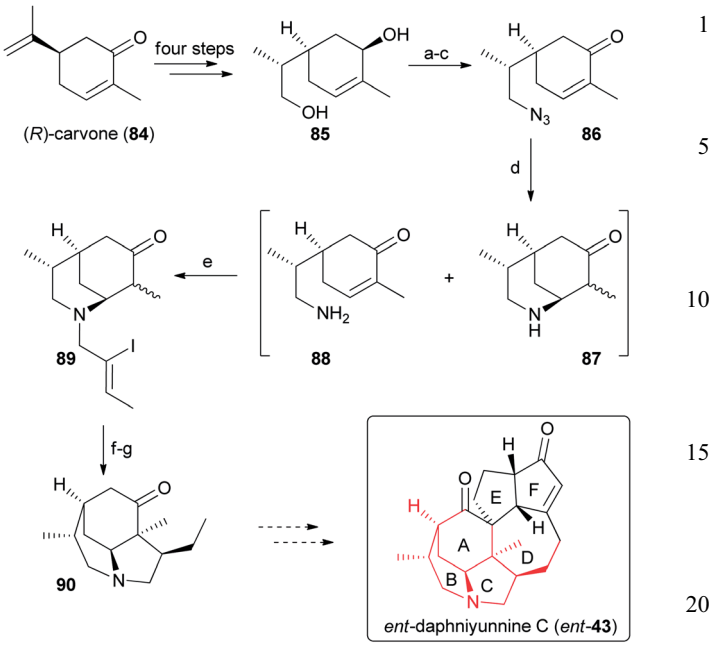


Scheme 9 Completion of the synthesis of daphenylline (**79**). *Reagents and conditions*: (a) TMSOTf, Et_3N, −78 °C; (b) $Pd(OAc)_2$, 81% (two steps); (c) HF·pyr, 0 °C; (d) I_2, PPh_3, imidazole, 93% (two steps); (e) $(TMS)_3SiH$, AIBN, 75 °C, 98%; (f) H_2, Crabtree's catalyst; (g) $LiCl{\bullet}H_2O$, DMSO, 160 °C, 86% (two steps); (h) Pd/C, MeOH; (i) $LiAlH_4$, 40 °C, 66% (two steps).



Scheme 10 An intramolecular Friedel–Crafts type Michael addition to the ABCE core of daphenylline (**79**). *Reagents and conditions*: (a) TfOH, 50 °C, $ClCH_2CH_2Cl$, 71%; (b) PhSH, K_2CO_3, DMF, 66%; (c) MsCl, Et_3N, DMAP, CH_2Cl_2, 98%; (d) NaH, DMF, 77%.

prepared in nine steps from commercially available *m*-methoxyphenyl acetonitrile **80**.[41] After a thorough optimisation of the key intramolecular Friedel-Craft type Michael addition, She and co-workers found that using a variety of Lewis acids (*e.g.*, SBr_4, $TiCl_4$, $BF_3{\cdot}OEt_2$, $FeCl_3$, BCl_3, BBr_3, $AlBr_3$, TMSOTf) or protic acids (*e.g.*, *p*-TsOH, CF_3COOH) 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



Scheme 11 An *aza*-Michael addition and a Pd-catalysed enolate α-vinylation strategy toward the ABC core of *ent*-daphniyunnine C (*ent*-**43**). *Reagents and conditions*: (a) TsCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 76%; (b) NaN_3, DMF, 90 °C, 95%; (c) PCC, CH_2Cl_2, 91%; (d) PPh_3, THF/H_2O; (e) (*Z*)-1-bromo-2-iodobut-2-ene, K_2CO_3, MeCN, reflux, 89% (two steps); (f) $Pd(PPh_3)_4$ (5 mol%), *t*-BuOK, THF, reflux, 84%; (g) 10% Pd/C, H_2 (1 atm), MeOH, 97%.

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).[22] This robust approach involved an *aza*-Michael addition and a Pd-catalysed enolate α-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 α-vinylation reaction. Tricycle **90** was produced as a single diastereomer when **89** was treated with $Pd(PPh_3)_4$/*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

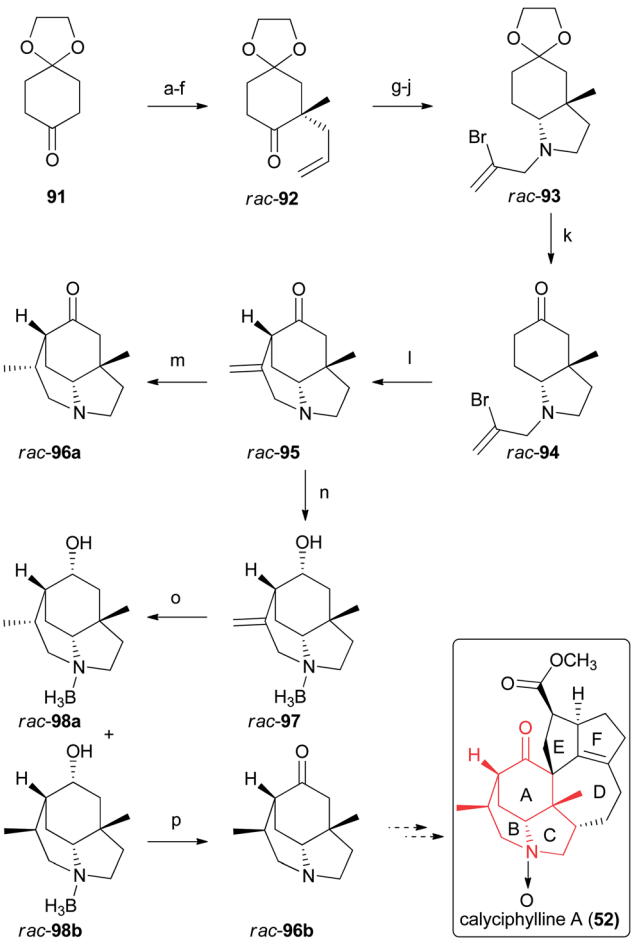
Although the aforementioned intramolecular Michael addition strategies significantly enhanced the repertoire of available methods for the construction of various scaffolds of

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 α-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.

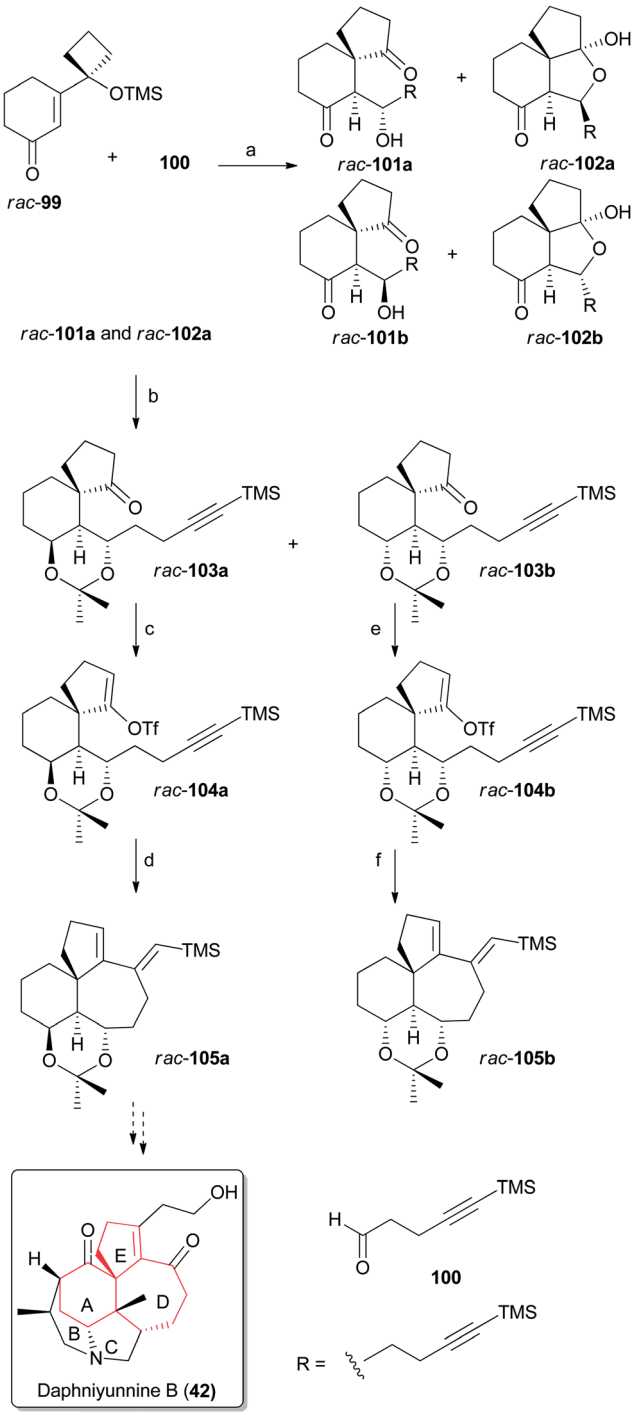
Another application of Pd-catalysis in synthetic efforts toward calyciphylline A-type alkaloids was reported by Zhang and co-workers in 2012.[25] The formation of the racemic ADE tricyclic [6-7-5] core of daphniyunnine B (**42**) involved several noteworthy transformations, especially a sophisticated 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 $MeAlCl_2$ 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



Scheme 12 A Pd-catalysed intramolecular vinylation strategy to the ABC core of calyciphylline A (**52**). *Reagents and conditions*: a) NaH, $(MeO)_2CO$; b) NaH, allylbromide 80% (two steps); c) LiI, 135 °C, DMF, 88%; d) $(iPr)_2NMgBr$, Et_2O; e) TMSCl, Et_3N, HMPA; f) MeLi, THF then MeI, HMPA, 85% (three steps); g) O_3, CH_2Cl_2; h) $BnNH_2 \cdot HCl$, $NaBH_3CN$, 59% (two steps); i) H_2, $Pd(OH)_2$, EtOAc, 88%; j) 2,3-dibromopropene, K_2CO_3, KI (cat.), CH_3CN, 55%; k) HCl, 89%; l) PhOK, $Pd(PPh_3)_4$, THF, 45%; m) H_2, Pd/C, 80%; n) $NaBH_4/CeCl_3$, 62%; o) [Rh(NBD)(DIPHOS-4)]BF_4, H_2 (400 psi), NaH, THF, 56% of desired diastereomer **98b**, 16% of its epimer **98a**; p) DMSO, $(COCl)_2$, Et_3N, then HCl, 50%.

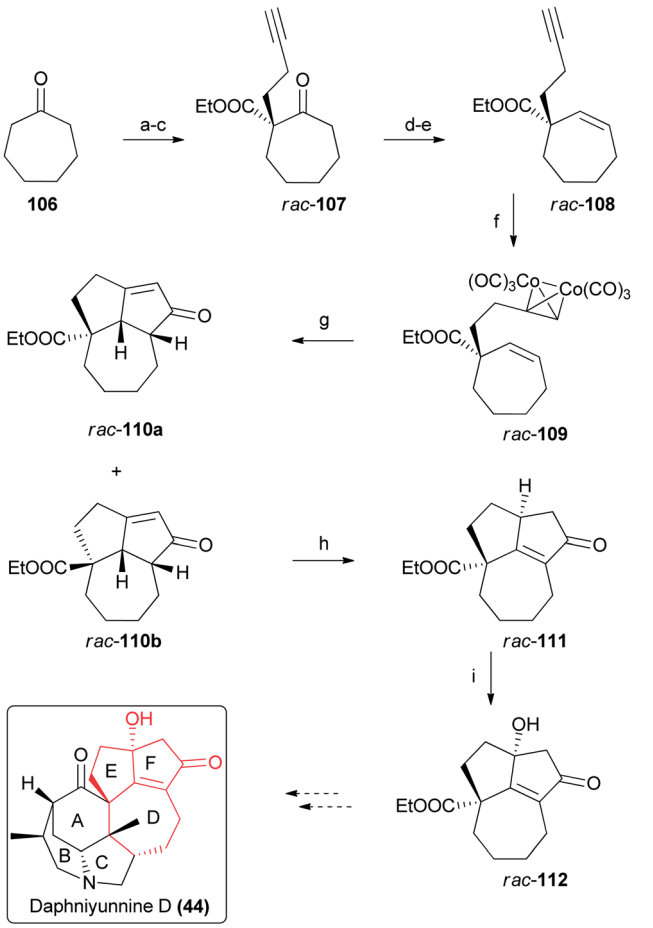
transformed to acetal **103a** after a chemoselective reduction of the cyclohexanone moiety and a subsequent acetalisation. Then, the keto-acetal **103a** underwent standard triflation and set the stage for the formation of the third ring of daphniyunnine B (**42**). The Pd-catalysed intramolecular carbocyclisation[43] 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



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) $MeAlCl_2$, CH_2Cl_2, 0 °C, 89%, (**101a** + **102a**):(**101b** + **102b**) 4.7 : 1; b) $NaBH(OAc)_3$, AcOH; $(MeO)_2CMe_2$ then PTSA, DMF, 41% of **103a** and 17% of **103b**; c) KHMDS, $PhNTf_2$, THF, −78 °C, 86%; d) $Pd(OAc)_2$, Ph_3P, DIPEA, HCOOH, 60 °C, DMF, 90%; e) KHMDS, $PhNTf_2$, THF, −78 °C, 83%; f) $Pd(OAc)_2$, Ph_3P, DIPEA, HCOOH, 60 °C, DMF, 86%.

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.[44] This hypothesis was successfully confirmed by Dixon and co-workers in 2012.[26] Their approach to the DEF tricyclic [7-5-5] core of calyciphylline 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 alkoxycarbonylation of cycloheptanone (**106**) with diethylcarbonate followed by a Michael addition of the resulting ketoester 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-ene **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



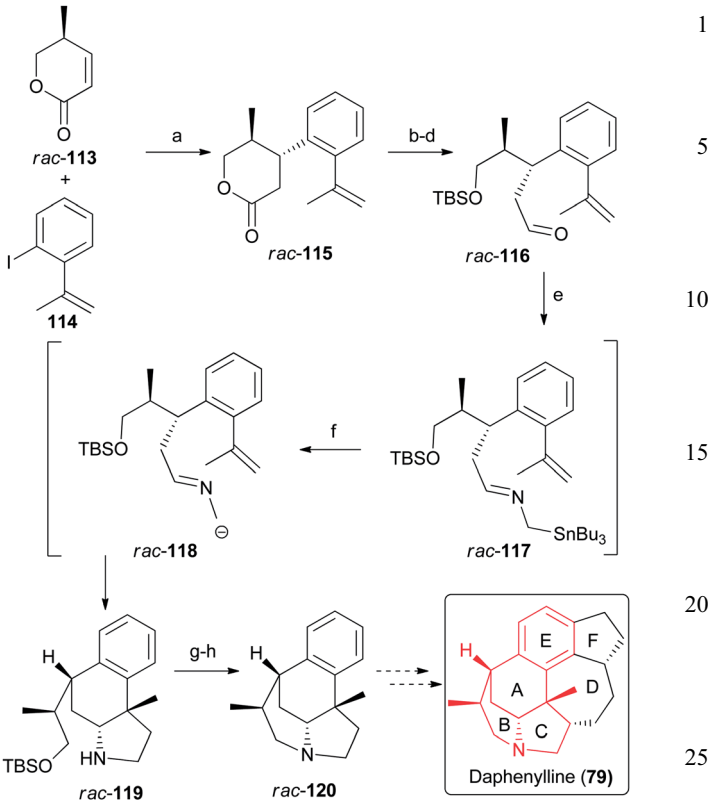
Scheme 14 Construction of the DEF of daphniyunnine D using a Pauson–Khand strategy. *Reagents and conditions*. (a) NaH, $(EtO)_2CO$, 100 °C, toluene, 98%; (b) acrolein, Et_3N, r.t., DMF, 85%; (c) Ohira–Bestmann reagent, K_2CO_3, EtOH, 0 °C to r.t., EtOH, 85%; (d) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, 0 °C, MeOH, 78%; (e) MsCl, pyridine, RT then reflux, 72%; (f) $Co_2(CO)_8$, CH_2Cl_2, RT; (g) NMO, CH_2Cl_2, r.t., 58%, 3.7 : 1.0 d.r; (h) K_2CO_3, EtOH, r.t., 92%; (i) AIBN, O_2, *t*-BuOOH, 60 °C then $SnCl_2$, 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 carbocyclic 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 calyciphylline 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).[27] 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-butyl lithium and the *in situ* formed allyl anion **118** smoothly underwent a [3 + 2] cycloaddition thus generating the pyrolidine 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.

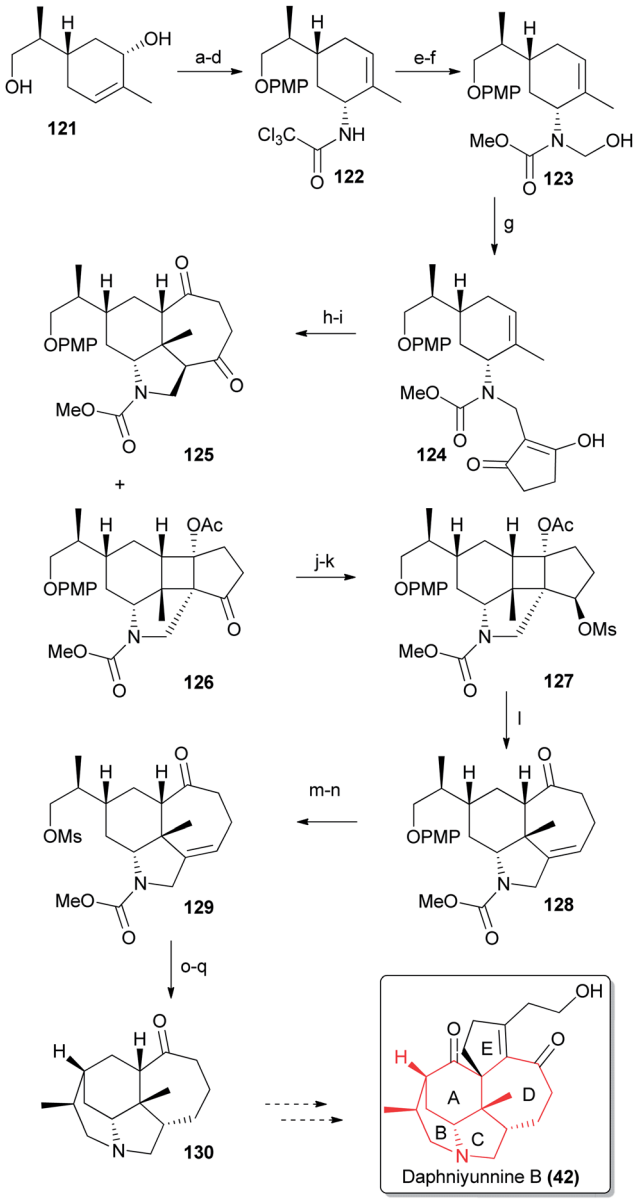
To date, the most advanced core of the calyciphylline A-type alkaloids is synthesised by Wang and co-workers in 2012 and has become an important milestone in the synthesis of the *Daphniphyllum* alkaloids.[28] This report closely followed their first disclosure from 2011.[44]

Inspired by Overman *et al.*,[42] Wang and co-workers' chiral pool approach to the diastereo- and enantiomerically pure diol **121** used naturally occurring (+)-carvone as the starting material (Scheme 16).[28] 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



Scheme 15 A [3 + 2] cycloaddition strategy toward the ABCE core of daphenylline. *Reagents and conditions*. (a) n-BuLi, CuI, $BF_3{\cdot}E_2O$, −78 °C, Et_2O, 69%; (b) Me_3Al, MeNHOMe·HCl, 0 °C, CH_2Cl_2; (c) TBDSCl, Et_3N, 0 °C to r.t., CH_2Cl_2, 89% (two steps); (d) DIBAL-H, −78 °C, THF, 95%; (e) $H_2NCH_2SnBu_3$, 4 Å molecular sieves, r.t., Et_2O; (f) n-BuLi, −78 °C, THF, 60% (two steps); (g) HCl, r.t., MeOH; (h) PPh_3, CBr_4, Et_3N, 0 °C to r.t., CH_2Cl_2, 40% (two steps).

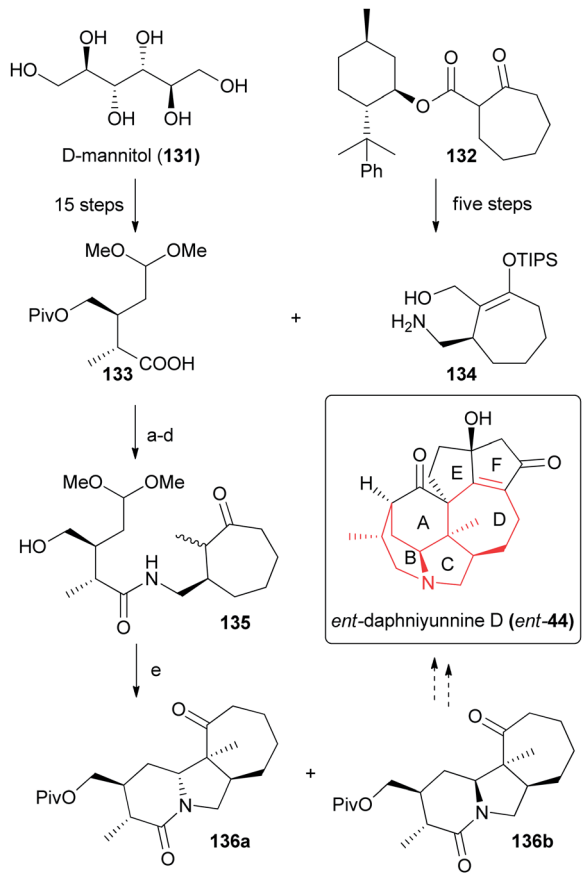
trichloroacetamide **122** with the expected configuration of the stereogenic centre bearing the protected amino group. Next, **122** was converted to a carbamate, and then reacted with paraformaldehyde in order to prepare *N*-acyl iminium precursor **123**. The following intermolecular Mannich condensation was found to be efficiently promoted by $Sn(NTf_2)_4$ 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 **125**, 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



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_3Cl, 58%; (b) NaH, 4-methoxyphenol, DMF, 85%; (c) DBU, CCl_3CN, 0 °C; (d) xylene, reflux, 50% (two steps); (e) $HC(OMe)_3$, PTSA, Na_2CO_3, 150 °C, MeOH, DMF, 82%; (f) CH_2=O, *t*-BuOK, *t*-BuOH, r.t., 54%; (g) $Sn(NTf_2)_4$, 1,3-cyclopentanedione, MeCN, r.t., 77%; (h) AcCl, Et_3N, CH_2Cl_2, 95%; (i) *hv* (254 nm), MeCN, 29% of **125**, 50% of **126**; (j) $NaBH_4$, MeOH, 95%; (k) MsCl, pyridine, DMAP; (l) K_2CO_3, MeOH, 82%; (m) CAN, MeCN, H_2O, 99%; (n) MsCl, Et_3N, 95%; (o) TMSI, CH_2Cl_2; (p) Et_3N, CH_2Cl_2, 80% (two steps); (q) PtO_2, H_2, MeOH, 94%.

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 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.[9b] Although Iwabuchi directly targeted the unnatural enantiomer of daphnicyclidin A of the daphnicyclidin subclass,[45] 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-phenylmenthol auxiliary. With both advanced enantiomerically



Scheme 17 Access to the BCD core of the calyciphylline A-type alkaloids using a tandem acyliminium/Mannich-type reaction. *Reagents and conditions*. (a) EDCI, DMAP, pyridine, CH_2Cl_2, 80%; (b) TsCl, Et_3N, $Me_3N.HCl$, CH_2Cl_2 then TBAF, 95%; (c) H_2, Pd/C, $NaHCO_3$, MeOH, 97%; (d) NaOMe, reflux, MeOH, (e) AcCl, reflux, MeOH then PivCl, Et_3N, 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: Pd-catalysis 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 these 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.[46]

5 Acknowledgements

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