Synthetic efforts toward cyathane diterpenoid natural products

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An overview of synthetic efforts toward cyathane diterpenoid natural products from the year 2000 to present is provided. The emphasis of this review is the various ring-constructing and stereoforming strategies employed in these synthetic routes.

1 Introduction

This review is intended to present an overview of synthetic efforts published toward the cyathane diterpenoid natural products. The work summarized here represents an update to the previous review on this topic which was reported in 2000, and as such will only cover cyathane core syntheses described in the literature past this date.[1] For the purpose of comprehensive review and comparison, however, all known completed total syntheses will be detailed herein. The focus of this review is centered upon the strategies used for ring formation and the introduction of stereochemistry en route to cyathane natural products.

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2 Overview of the cyathane diterpenoids

The cyathane diterpene natural products are isolated from a diverse variety of fungi, sponges, and fruiting plants. However, despite their myriad natural sources, all are unified by the presence of a characteristic 5–6–7 tricarbocyclic fused core structure (**1**, Fig. 1). Within this class of natural products can be found the cyathins, the allocyathins, the erinacines, the sarcodonins, the scabronines, the striatals, the cyanthiwigins, and the cyafrins, all of which display the conserved carbon scaffold of the cyathane skeleton (**1**). Of the twenty carbons that comprise this cyathane framework, the C(6) and C(9) carbons present all-carbon quaternary stereocenters, which bear angular methyl groups at the points of ring fusion. Almost all of the compounds within the cyathane class display these methyl groups with an anti relative stereochemical relationship, though the cyanthiwigin natural products possess a syn arrangement. The cyathane core structure is additionally characterized by the presence of an isopropyl side chain at C(3) and an exocyclic carbon atom connected to C(12).

2.1 Isolation

In 1971, Ayer and Brodie published a report in which an extract from the bird's nest fungus *Cyathus helenae* was scrutinized to better understand its antimicrobial activity. Though no full structural assignment was made for any compound within the extract, the active components of the mixture were separated *via* chromatography. After isolation and elemental analysis, the compounds responsible for the observed antimicrobial activity were named (without structural elucidation) as cyathin A_3, A_4, B_3, B_4, C_5, and allocyathin A_4.[2] The first fully characterized cyathane diterpene natural products were subsequently reported by Ayer and coworkers in 1972, when the substance previously identified as cyathin A_3 was found to be a mixture of isomeric compounds, which were then named cyathin A_3 (**2**) and allocyathin B_3 (**3**).[3] Numerous other cyathin and allocyathin natural products were discovered subsequent to this report, including

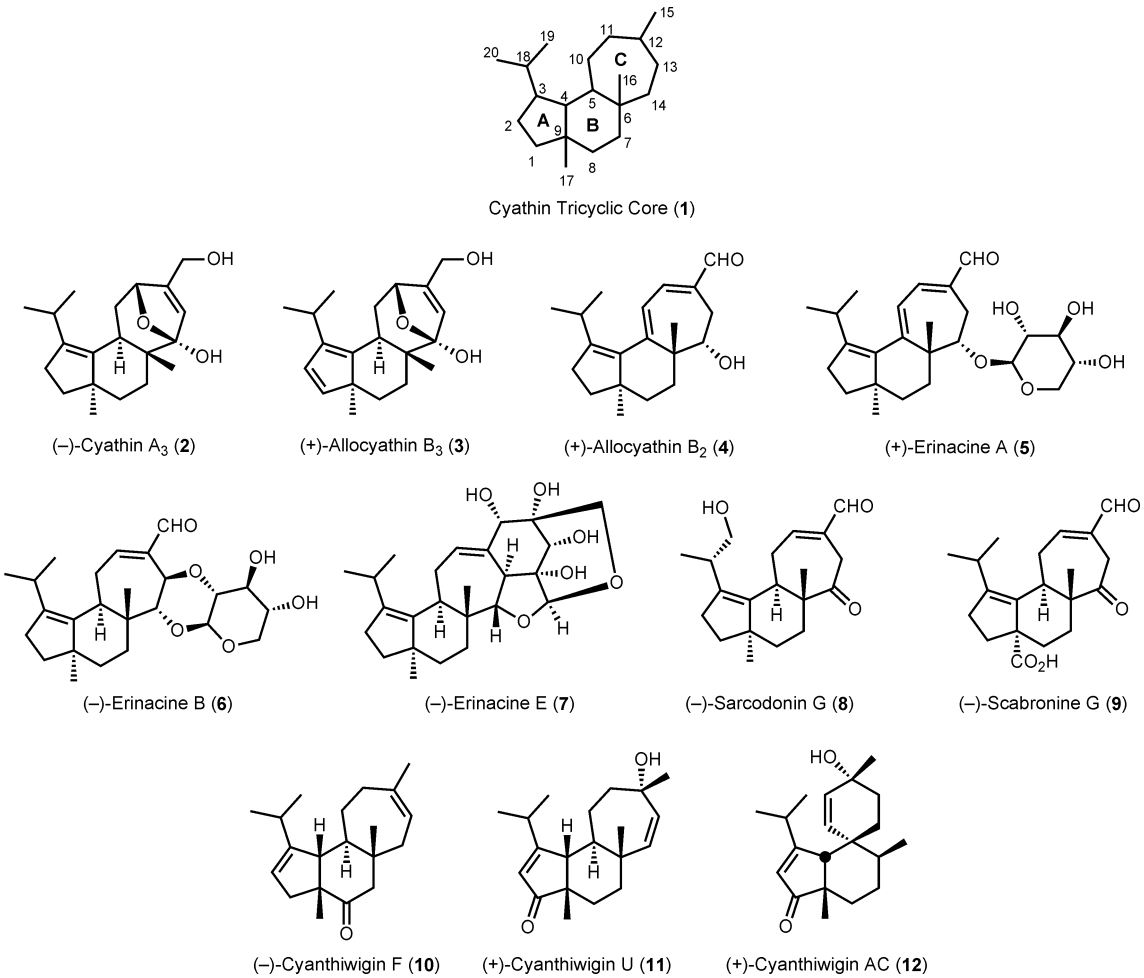

Fig. 1 Representative cyathane diterpenoid natural products.

allocyathin B_2 (**4**),[4] a cyathane diterpenoid which has since become the focus of numerous synthetic studies.

Following the identification of the primary cyathin diterpenoids, several structurally related compounds were isolated from additional natural sources. It was discovered that the fruiting bodies of *Hericium erinaceum* contained a number of glycosylated allocyathin B_2 analogues, which were eventually named the erinacines. Among the compounds obtained from *Hericium*

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erinaceum were erinacine A (**5**), erinacine B (**6**), and the more structurally complex erinacine E (**7**).[5]

In 1989 Nakayama and coworkers published the isolation and structural assignment of eight new cyathane molecules from the fungus *Sarcodon scabrosus* which they named the sarcodonins A–H.[6] These compounds possess the conserved 5–6–7 tricyclic core found in all other cyathane natural products, but are distinct in that they display additional oxidation at the C(19) position, such as is observed with sarcodonin G (**8**). An additional class of cyathane diterpene compounds was later identified from the same *Sarcodon scabrosus* fungus by Oshima in 1998, when isolation and characterization of scabronine A–F were disclosed.[7] Six years later, Liu *et al.* reported the isolation of two additional scabronine molecules from the same source, including scabronine G (**9**).[7] Structural elucidation of these natural products revealed the presence of a carboxyl group at C(17), a feature which marks the scabronines as distinct from the remainder of the cyathanes.

In 1992, Kashman and coworkers published a report detailing the isolation and characterization of the first cyanthiwigin molecules. Initially isolated from the marine sponge *Epipolasis reiswigi*, cyanthiwigins A–D were fully characterized and assigned absolute configuration *via* NMR, X-ray, and Mosher ester analysis.[8] A decade later the laboratories of Hamann isolated the same four cyanthiwigins, plus an additional 23 compounds of this class, from the Jamaican sea sponge *Myrmekioderma styx*. This isolation included the products cyanthiwigin F (**10**) and cyanthiwigin U (**11**). In years subsequent to their initial report, Hamann and coworkers have isolated and characterized the additional natural products cyanthiwigin AB–AG, including the structurally unique spirocyclic cyanthiwigin AC (**12**).[9]

2.2 Bioactivity

The biological activities of the cyathane natural products vary widely among the different molecules within the class. Many of these diterpene compounds, such as the previously discussed (−)-cyathin A_3 (**2**) and (+)-allocyathin B_3 (**3**), possess antibiotic or antimicrobial activity. Indeed, almost all of the subcategories of cyathane molecules display mild activity in this regard.[2,4,9] In addition to serving an antibiotic function, some members of the cyanthiwigin compounds have displayed limited cytotoxic activity against human primary tumor cells, as well as P388 murine leukemia cells and A549 lung tumor cells.[9,10]

However, the most significant biological activity reported among these diterpenoid molecules is their powerful ability to encourage the synthesis of Nerve Growth Factor (NGF). Both the erinacine and the scabronine natural products have displayed considerable potency in the stimulation of NGF synthesis,[5,7b] a capacity that implicates their potential as therapeutic agents to treat neurodegenerative ailments such as Alzheimer's or Parkinson's disease.[11]

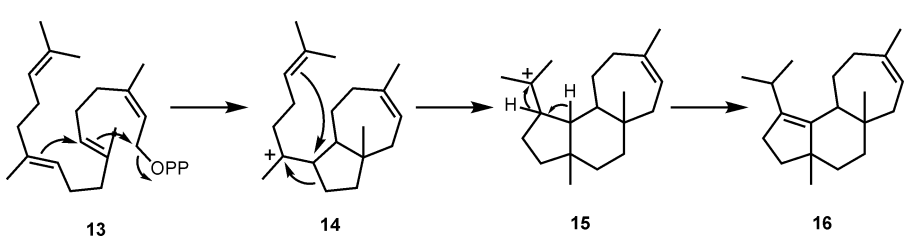
2.3 Biosynthesis

The details of cyathane diterpenoid biosynthesis have been covered in Wright's review, and as such will only be briefly summarized here.[1] Subsequent to his isolation of the parent cyathins, Ayer conducted an in-depth study to scrutinize the biosynthetic origin of the cyathane diterpenoid core. By growing *Cyathus earlei* in the presence of ^{13}C-labelled sodium acetate, Ayer was able to isolate and examine the cyathin molecules produced by these fungal bodies. Analysis of these compounds *via* ^{13}C NMR allowed Ayer to conclude that the biosynthetic pathway toward the cyathane core tricycle involves cascade cyclization and subsequent rearrangement of geranylgeranyl diphosphate (Scheme 1).[12]

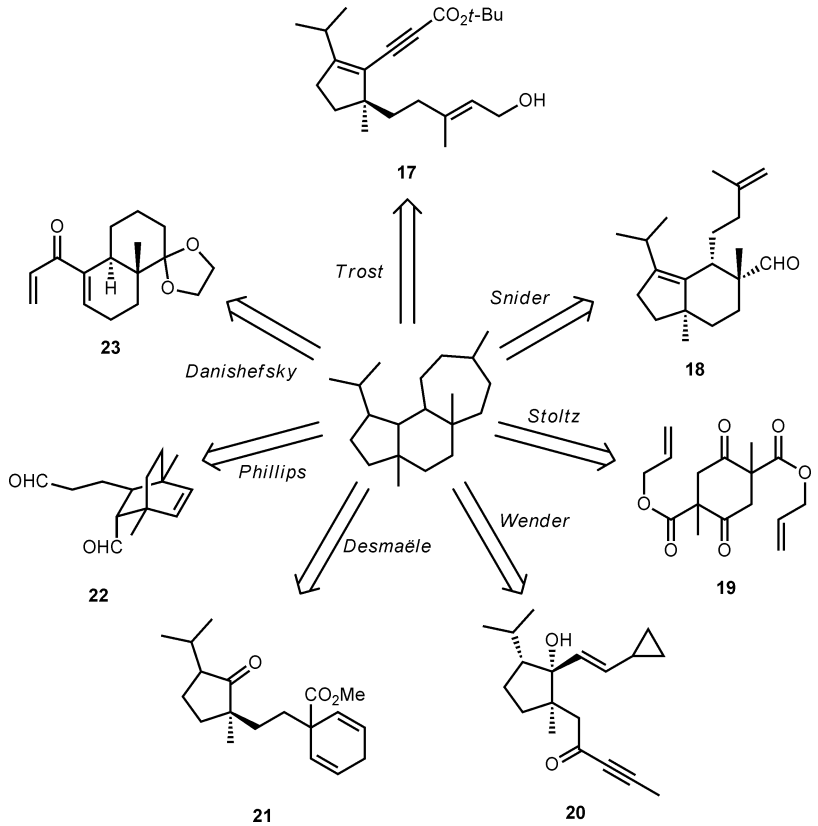
3 Strategy summary

Since the isolation of the first cyathane natural products in the early 1970s, numerous research groups have endeavoured to synthesize these compounds. A multitude of differing strategies have been documented in the literature, and many of these approaches are presented here in schematic form. The synthetic efforts reported to date can be roughly categorized by their key transformations, which are further divided as either metal-mediated reactions (Scheme 2), or alkylation/aldol reactions (Scheme 3).

A majority of the cyathane syntheses published to date leverage various metal-catalyzed transformations to accomplish difficult or complicated ring-forming reactions. For example, the strategy employed by Trost *et al.* relies upon Ru-catalyzed cycloisomerization to close the central B-ring of the cyathane core, an approach which leads back to allylic alcohol **17**. Similarly, Desmaële's route relies upon a Pd-catalyzed intramolecular Heck cyclization to construct the core B-ring, invoking diene **21** as a critical retrosynthetic precursor. Danishefsky's approach to the tricycle implements an Fe-catalyzed Nazarov cyclization for construction of the five-membered A-ring, allowing for strategic disconnection back to dienone **23**. Beyond the A- and B-rings, metal-catalyzed methodology has also been used to target the seven-membered C-ring of the cyathane core. For example, Snider's method toward these diterpene molecules employs an Al-catalyzed carbonyl-ene reaction for C-ring construction from bicyclic aldehyde **18**. The power of transition-metal catalysis has also enabled routes that employ a strategy of simultaneous



Scheme 1 Biosynthesis of the cyathane core tricycle from geranylgeranyl diphosphate.



Scheme 2 Transition metal and Lewis acid-catalyzed retrosynthetic disconnections toward the cyathane diterpenoid tricyclic core.

multicyclic construction. For example, Phillips employs an efficient Ru-catalyzed ring-opening ring-closing metathesis strategy to build both the A- and C-rings of the cyathane core in tandem, thus invoking bridged bicycle **22** as a retrosynthetic precursor. Wender's [5 + 2] cycloaddition approach toward the cyathane skeleton allows for cascade construction of both the B- and C-rings simultaneously, thus retrosynthetically disconnecting the core backward to ynone **20**. The strategy employed by Stoltz relies upon Ru-catalyzed C-ring construction, but more imperatively, implements Pd-catalyzed alkylation for quaternary stereocenter formation. This invokes bis-β-ketoester **19** as a critical retrosynthetic precursor.

Another unifying approach by which the cyathane tricycle has been targeted is that of an alkylation strategy, often specifically in the form of an aldol reaction. In order to construct the C-ring of the tricyclic diterpene core, Ward and his group employ an ozonolysis and aldol sequence. This ring-expanding strategy invokes tricycle **28** as an important synthetic precursor (Scheme 3a). Tori implements a similar technique to C-ring formation in his synthesis, in which bis-aldehyde **26** is invoked *via* a disconnection of the cyathane core by means of an intramolecular aldol reaction. The cyathane C-ring has also been targeted *via* a unique [3 + 4] annulation reaction developed by Takeda, which employs **25** as a bicyclic precursor to the larger tricyclic skeleton. A convergent strategy targeting the B-ring of the cyathane core is carried out in Nakada's approach toward these natural products. By disconnecting the central ring of the tricycle, Nakada envisions tethered system **27** as the critical substrate for an intramolecular aldol reaction. Non-aldol alkylation procedures have also played a role in cyathane synthetic design. Reddy disconnects the smaller six-membered C-ring of cyanthiwigin AC *via* an enolate spiro-alkylation strategy to invoke bicycle **29** as a precursor (Scheme 3b). An anionic alkylation approach has also been employed with a focus upon construction of the five-membered cyathane A-ring. Piers' retrosynthetic analysis opens the A-ring to vinyl iodide **24**, a structure, which after lithium-halogen exchange and ketone trapping, is closed to give a tricyclic system.

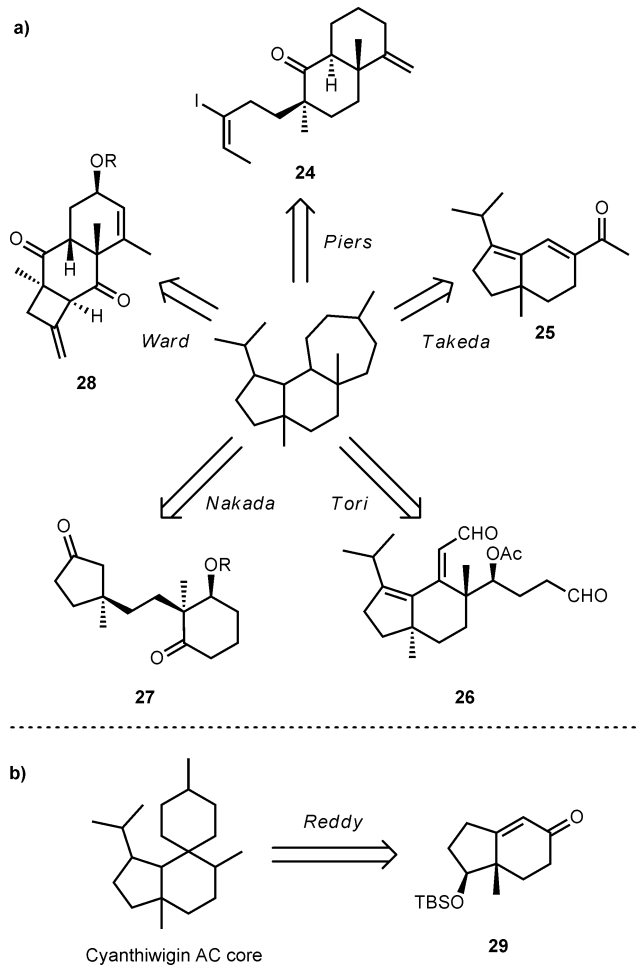
4 Cyathane core syntheses

The section detailed below is intended as an update to the review published in 2000. As such, only cyathane core syntheses published after this date will be summarized here.

Several groups have devised efficient strategies toward the cyathane tricyclic core, with possible extensions toward multiple completed cyathane natural products. These efforts have focused upon preparation of the tricyclic framework found in the typical cyathane molecules.

4.1 Wender's cyathane core synthesis

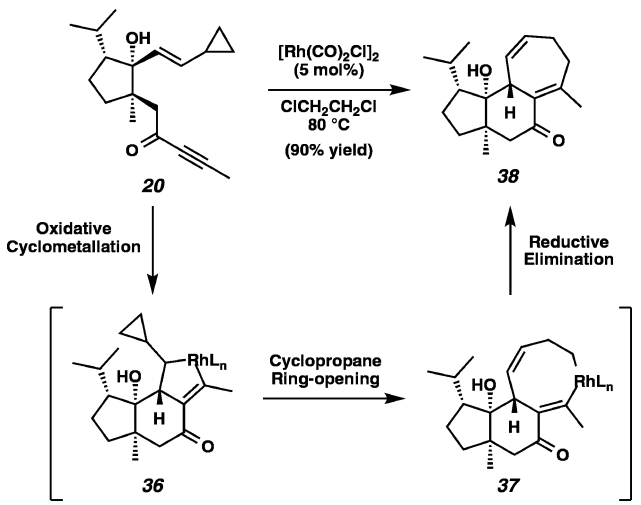
A general route toward the construction of the 5–6–7 tricyclic diterpene core was reported by the laboratories of Wender in 2001 by implementation of a [5 + 2] Rh-catalyzed cycloaddition reaction.[13] Beginning with (−)-limonene (**30**), hydrogenation, oxidative olefin cleavage, and intramolecular aldol condensation afforded enal **31** (Scheme 4). After reduction and vinyl ether



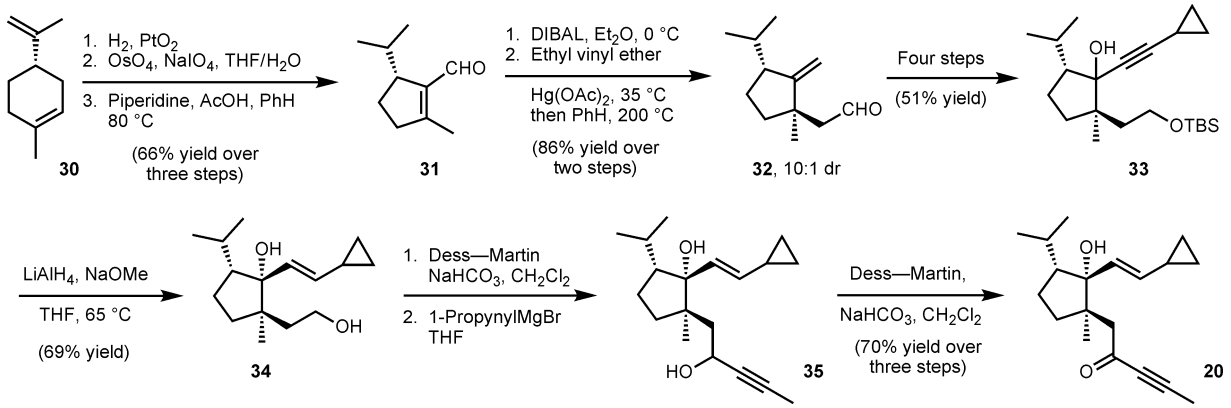
Scheme 3 (a) Alkylation and aldol retrosynthetic disconnections of the cyathane diterpenoid tricyclic core. (b) Reddy's retrosynthetic disconnection of the cyanthiwigin AC core.

formation, a thermal Claisen rearrangement yielded aldehyde **32** as a 10:1 mixture of inseparable diastereomers. Cyclopentane **32** was thereafter advanced along four steps, including ozonolysis of the exocyclic methylene and addition of lithium cyclopropylacetylide, to furnish cyclopentanol **33** as a mixture of diastereomers. Stereoselective reduction of cyclopropyl alkyne **33** allowed access to diol **34**, which was oxidized, then exposed to 1-propynylmagnesium bromide to generate propargyl alcohol **35**. Attempts to execute a [5 + 2] cycloaddition reaction using alcohol **35** as the starting material were unfortunately unsuccessful, and yielded only a complicated mixture of products. For this purpose, enyne **35** was oxidized to conjugated ketone **20** before executing the [5 + 2] cycloaddition reaction.

Upon exposure of vinylcyclopropane **20** to 5 mol% of $[Rh(CO)_2Cl]_2$, the desired cycloaddition reaction proceeded in high yield to provide tricycle **38** as a single diastereomer (Scheme 5).[14] The critical [5 + 2] cycloaddition reaction initiates with complexation of the rhodium catalyst to both the alkyne moiety and the vinylcyclopropane group. This is then followed by oxidative cyclometallation to form an intermediate metallocyclopentane (**36**), which in turn undergoes strain-driven cyclopropane ring-opening and ring-expansion to generate a transient metallocyclooctadiene species (**37**). Reductive elimination of rhodium from **37** thereafter yields tricyclic structure **38**, representing a completed cyathane core. The structure of tricyclic enone **38** was verified by single-crystal X-ray crystallography. Overall, this strategy allows access to a completed 5–6–7 tricyclic structure in 14 steps and 13% overall yield.



Scheme 5 Wender's [5 + 2] cycloaddition reaction to construct the cyathane core tricycle.



Scheme 4 Preparation of the critical [5 + 2] cycloaddition precursor.

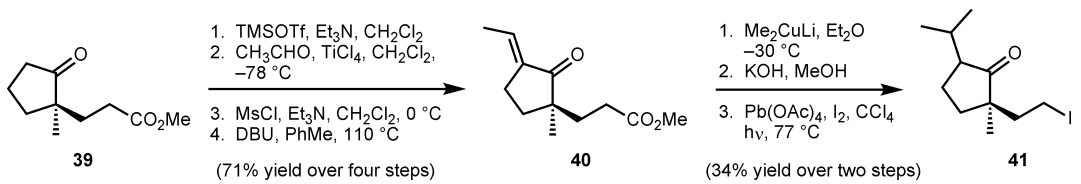
4.2 Desmaële's cyathane core synthesis

A generalized synthetic route toward the tricyclic cyathane core structure was developed by Desmaële and coworkers in 2002, and an updated version of this strategy was later published in 2005.[15] When addressing the challenges present in constructing the tricyclic cyathane framework, Desmaële states that establishing the anti relationship between the methyl groups of C(6) and C(9) represents the most significant obstacle. In order to solve this stereochemical issue, the strategy envisioned employs late-stage construction of the central B-ring of the tricycle *via* intramolecular Heck reaction between tethered A- and C-ring fragments.

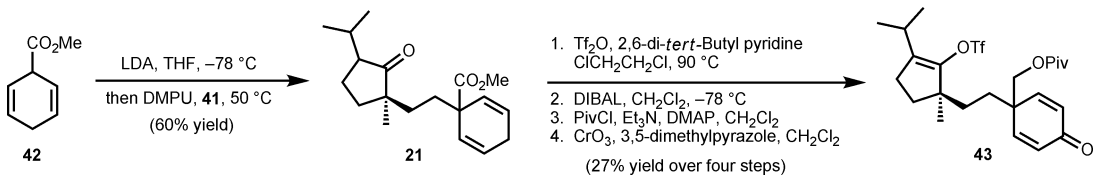
The synthesis was initiated from known, enantioenriched keto-ester **39** (Scheme 6).[16] Mukaiyama aldol reaction with acetaldehyde, followed by dehydration and isomerization, yielded enone **40**. After cuprate addition to and saponification of ester **40**, the intermediate keto-acid obtained was then subjected to the Kochi modification of the Hunsdiecker reaction to afford primary iodide **41**. Displacement of iodide **41** with the lithium enolate of methyl ester **42** then provided tethered intermediate **21**, which was subjected to a four step sequence to access the critical Heck cyclization precursor **43** (Scheme 7). Notably, prior attempts at an intramolecular Heck cyclization involving a seven-membered ring dienone proved quite difficult to advance along this synthetic path, and for this reason Desmaële opted to employ a six-membered ring to serve as a surrogate for the cyathane C-ring.

Several attempts to cyclize precursor **43** *via* intramolecular Heck reaction under standard conditions were met with difficulty, with most attempts yielding either undesired acetate addition products or incorrect relative stereochemistry.[15a] Eventually, further optimization of this reaction lead Desmaële to discover that exposure of triflate **43** to 20 mol% of $Pd(OAc)_2$ in the presence of PPh_3 and *n*-Bu_4NBr could execute the desired Heck reaction to yield tricycle **44** in 73% yield and a 19:1 diastereomeric ratio based on the newly formed stereocenter at C(6) (Scheme 8). This transformation constructed the central B-ring of the cyathane core while simultaneously establishing the necessary all-carbon quaternary stereocenter at C(6) *via* desymmetrization of the pendent C-ring precursor.[15b,c]

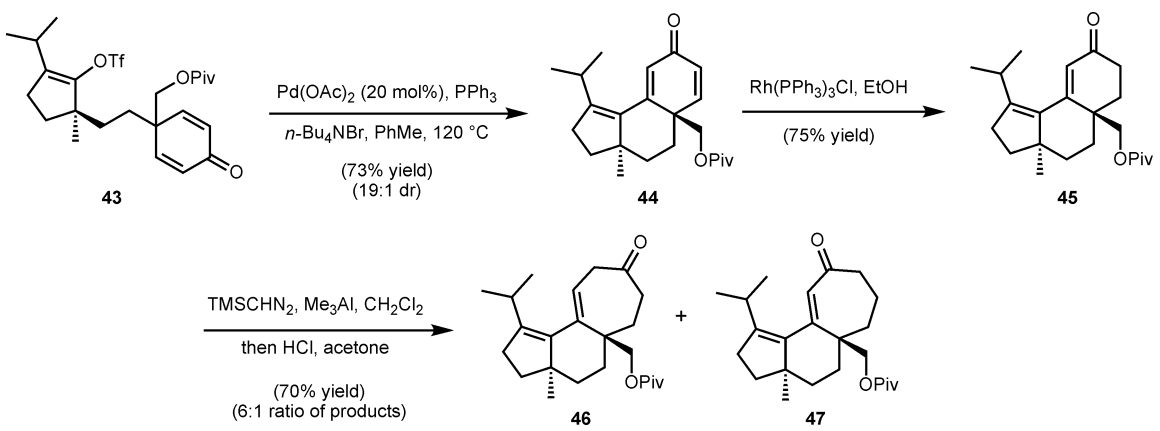
Elaboration of tricyclic dienone **44** toward the cyathane core structure proceeded *via* hydrogenation of the disubstituted olefin using Wilkinson's catalyst to give enone **45**. This reduction was then followed by treatment of tricycle **45** with trimethyl



Scheme 6 Synthesis of Desmaële's alkyl iodide coupling partner.



Scheme 7 Preparation of the crucial Heck cyclization precursor.



Scheme 8 Heck cyclization and aluminium-promoted ring expansion reactions to target the cyathane tricycle.

aluminium and trimethylsilyl diazomethane to effect an organoaluminium-promoted ring expansion.[17] This reaction afforded the completed 5–6–7 tricyclic framework as a 6:1 mixture of ketone (**46**) and enone (**47**) isomers. By obtaining these tricyclic structures, Desmaële accomplished the construction of the cyathane core tricycle over 15 steps and an overall combined yield of 1.4% for both isomers obtained.

4.3 Takeda's cyathane core synthesis

A synthesis of the cyathane core leveraging a [4 + 3] annulation strategy was disclosed by Takeda and coworkers in 2000.[18] Starting from known racemic enone **48**, addition of ethynyl Grignard was followed by a Rupe rearrangement to give extended conjugated enone system **25** (Scheme 9). Formation of the lithium enolate of **25** was followed by addition to acyl silane **49**. Initial nucleophilic addition of the enolate of **25** to **49** produces intermediate alkoxide **50**, which undergoes Brook rearrangement and nucleophilic addition to form cyclopropane **51**. Divinyl cyclopropane species **51** subsequently undergoes spontaneous [3,3] sigmatropic rearrangement, a mechanism which is accelerated by the presence of an alkoxide. After rearrangement occurs, the completed cyathane core structure **52** is afforded as a single diastereomer.[19]

Continued functionalization of tricycle **52** was accomplished by diastereoselective DIBAL reduction, a process which provided the isomerically pure silyl enol ether **53** (Scheme 10). Notably, the stereochemistry imparted by this reduction afforded the alcohol epimer analogous to allocyathin B_2 at C(14).[19] Takeda and coworkers thereafter concluded their efforts with oxidation of the enol silane present in **53** and subsequent cleavage of the C-bound trimethylsilyl group. This provided **54** as the final product of the synthetic sequence.

Beginning from known enone **48**, the des-methyl cyathane core was established in three steps and 19% yield, while the more elaborated cyathane analog **54** was produced in 11% yield over five steps.

5 Cyathane total syntheses

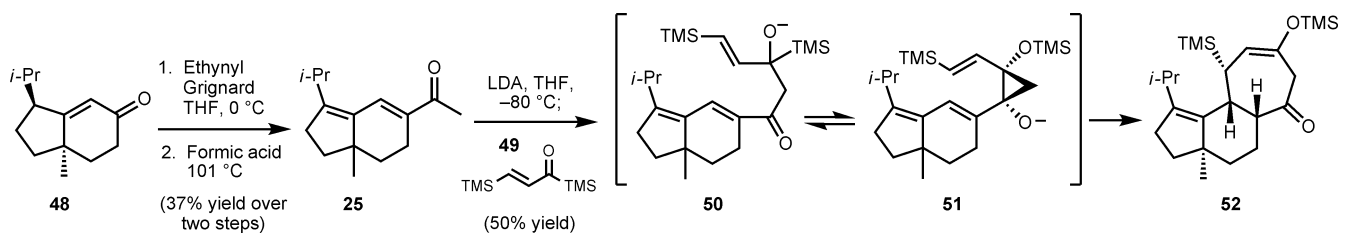
The following section is intended as a comprehensive review of all disclosed total syntheses of cyathane diterpenoid natural products published to date.

5.1 Snider's (±)-allocyathin B_2 and (+)-erinacine A

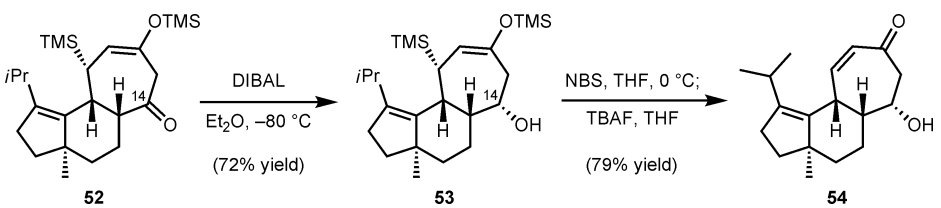
The first total synthesis of any cyathane diterpenoid natural product was accomplished by Snider and coworkers in 1996 with their preparation of allocyathin B_2.[20] Snider's synthetic plan invoked the use of a carbonyl-ene reaction to target the cyathane core, and this strategy was later extended beyond allocyathin B_2 in order to achieve the synthesis of (+)-erinacine A *via* glycosylation.

Beginning with known racemic enone **48**,[21] triflate formation, palladium-catalyzed carbonylation, and oxidation state manipulation allowed access to enal **55** (Scheme 11). Conjugate addition of a cuprate species generated from Grignard reagent **56** to the β-position of extended unsaturated system **55** provided aldehyde **57**, which was subsequently methylated at the α-position to afford bicycle **18**. At this point in the synthesis, Snider's route called for construction of the C-ring *via* intramolecular carbonyl-ene reaction of aldehyde **18**. In the event, treatment of **18** with Me_2AlCl initiated rearrangement to give a single isomer of alcohol **58** in excellent yield, thus completing the final ring of the tricyclic natural product.[22]

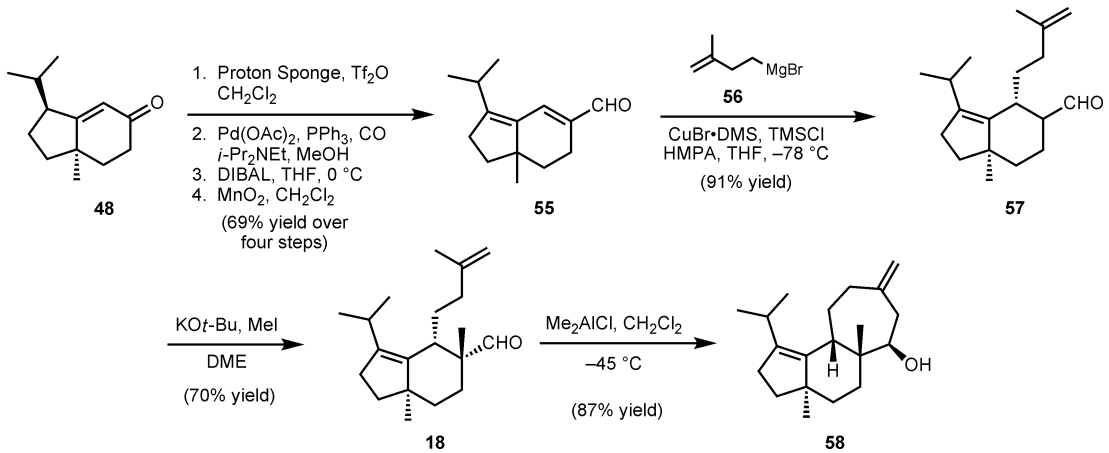
The synthesis was completed over ten additional transformations, which involved protecting group manipulation, oxidation state modification, and palladium-catalyzed carbonylation starting from tricycle **58** (Scheme 12). The completed natural product (±)-allocyathin B_2 (**4**) was thus attained from precursor **48** in 17 steps and 6.4% overall yield. Because allocyathin B_2 represents an aglycone substrate for the erinacine natural products, Snider and coworkers were well equipped at this point to address the total synthesis of the erinacine compounds. As such, glycosylation of (±)-allocyathin B_2 with 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide (**59**) and successive global



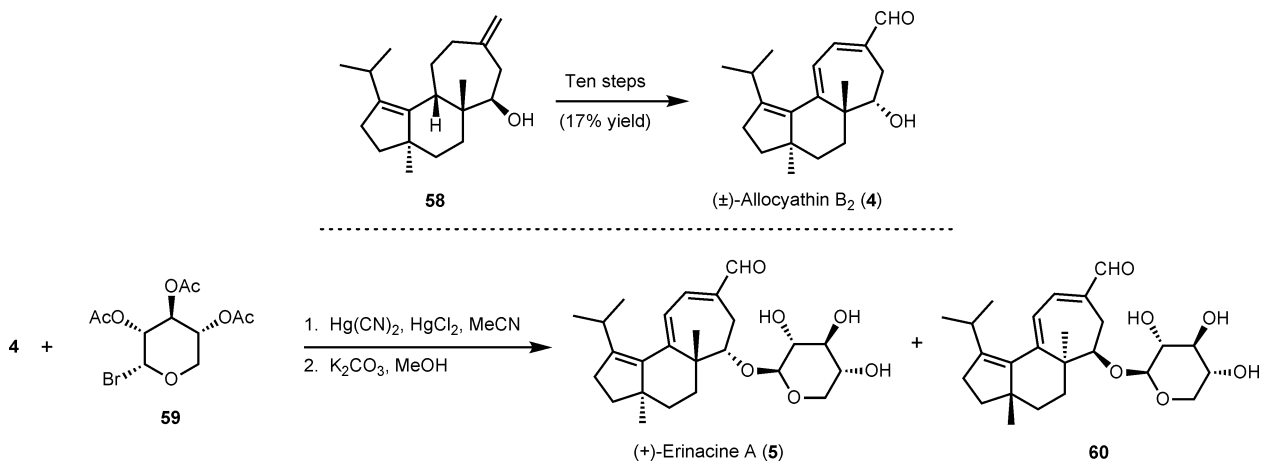
Scheme 9 Takeda's key [4 + 3] annulation to target the C-ring of the cyathane core.



Scheme 10 Advancement of Takeda's cyathane core structure.



Scheme 11 Snider's carbonyl-ene strategy toward the cyathane tricycle.



Scheme 12 Completion of (±)-allocyathin B_2 and glycosylation to achieve (+)-erinacine A.

deprotection generated the natural product (+)-erinacine A (**5**) and isomeric structure **60** as a 1:1 mixture of diastereomers.

Erinacine A was prepared in 19 steps and 1.0% yield. The cyathane core framework was constructed in seven steps and 38% overall yield.

5.2 Tori's (±)-allocyathin B_2

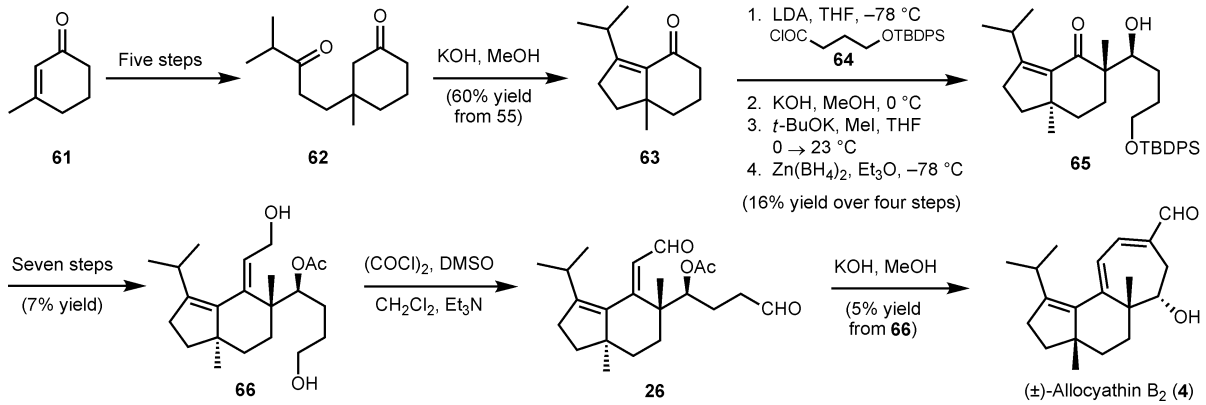
In a report published by Tori and coworkers in 1998, an intramolecular aldol strategy targeting the synthesis of the natural product allocyathin B_2 was described.[23]

Starting from 3-methyl cyclohexenone (**61**), conjugate addition, ozonolysis, and oxidation yielded diketone **62** after five steps (Scheme 13). Intramolecular aldol condensation of cyclohexanone **62** afforded bicyclic enone **63**, a structure containing the completed five-membered A-ring of allocyathin B_2, including the requisite isopropyl group. Subsequent acylation of **63** with acid chloride **64** was followed by methylation and a highly optimized diastereoselective reduction employing $Zn(BH_4)_2$ to afford keto-alcohol **65**.[24] Additional transformations over seven steps provided access to allylic alcohol **66**, which was readily oxidized under Swern conditions to give bis-aldehyde **26**. Upon exposure of **26** to methanolic KOH, a final intramolecular aldol condensation completed the cyathane C-ring and produced (±)-allocyathin B_2 (**4**). Overall, both (±)-allocyathin B_2 and the cyathane core structure were synthesized in 19 steps and 0.5% yield, starting from **61**.

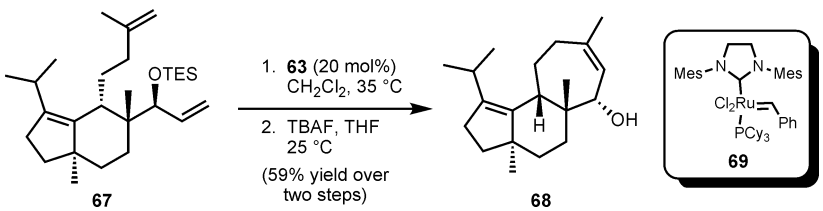
Subsequent to the preparation of (±)-allocyathin B_2, Tori also disclosed a different strategy toward the construction of the cyathane tricyclic core *via* ring-closing metathesis.[25] Modification of their route toward (±)-allocyathin B_2 allowed access to bicyclic intermediate **67** (Scheme 14). Upon treatment of this material with 20 mol% of Grubbs second-generation metathesis catalyst (**69**) and subsequent deprotection, completed cyathane tricycle **68** was obtained as the sole product of reaction.

5.3 Piers' (±)-sarcodonin G

The first total synthesis of (±)-sarcodonin G was described by Piers in 2000.[26] Their approach to this cyathane diterpenoid addressed the tricyclic core with an alkylation and ring-expansion strategy, and employed late-stage installation of the peripheral functionality. Piers' synthesis began from known ketone **70** (introduced as a mixture of diastereomers),[27] which was subject to hydrazone formation, epimerization at the ring fusion, and nucleophilic attack on alkyl iodide **71** to afford vinyl



Scheme 13 Tori's strategy toward (±)-allocyathin B_2.



Scheme 14 Tori's ring-closing strategy toward construction of the seven-membered C-ring and completion of the cyathane core.

germane **72** (Scheme 15). Further transformation of germane **72** eventually produced the vinyl iodide species **24**.

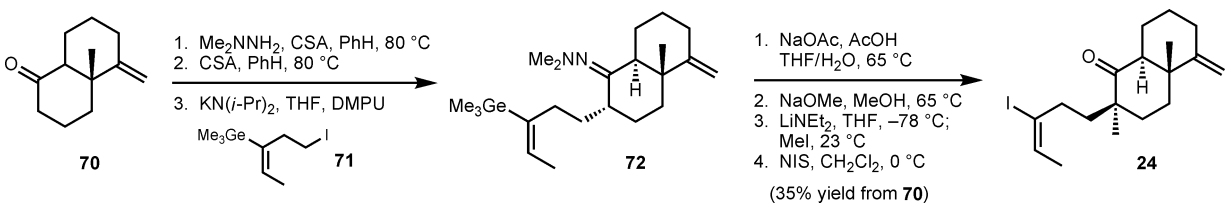
Upon treatment of **24** with *n*-BuLi, lithium-halogen exchange and intramolecular trapping of the ketone moiety constructed the five-membered A-ring of the natural product (Scheme 16). After deprotonation with KH and addition of Bu_3SnCH_2I, ether **73** was isolated as the major product. From this ether intermediate, a Still-Mitra [2,3]-sigmatropic rearrangement provided tricycle **74**, which contains the primary hydroxyl group at C(19) required for sarcodonin G.[28]

Additional synthetic transformation of **74** over four steps yielded β-ketoester **75**, which bears an α-alkyl iodide group well suited for ring-expansion methodology developed by Hasegawa (Scheme 17).[29] Upon exposure to SmI_2 in THF, alkyl iodide **75** is converted in 71% yield to the one-carbon ring expanded product **76**. This process smoothly forms the seven-membered C-ring, and thus completes the tricyclic cyathane core. The total synthesis is thereafter concluded in six steps to yield (±)-sarcodonin G (**8**).

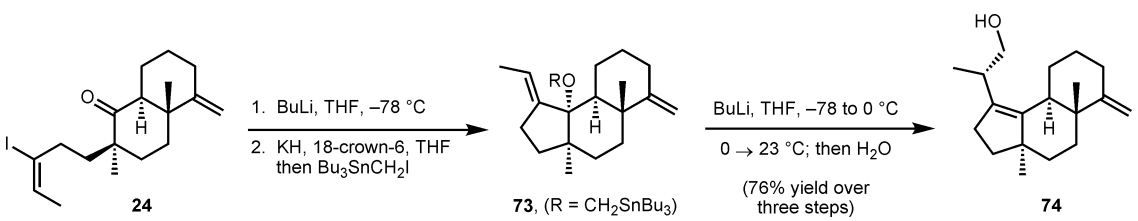
Overall the synthesis of (±)-sarcodonin G (**8**) was accomplished in a total of 21 steps and 4.0% yield. The cyathane tricyclic core was attained in 15 steps and 7.0% overall yield.

5.4 Ward's (±)-allocyathin B_3

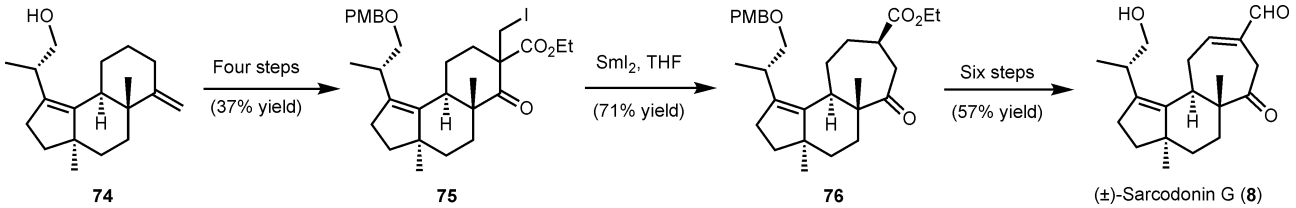
The total synthesis of (±)-allocyathin B_3 was achieved by Ward and coworkers in 2000 by leveraging an interesting cycloaddition strategy for rapid construction of the central B-ring.[30] The



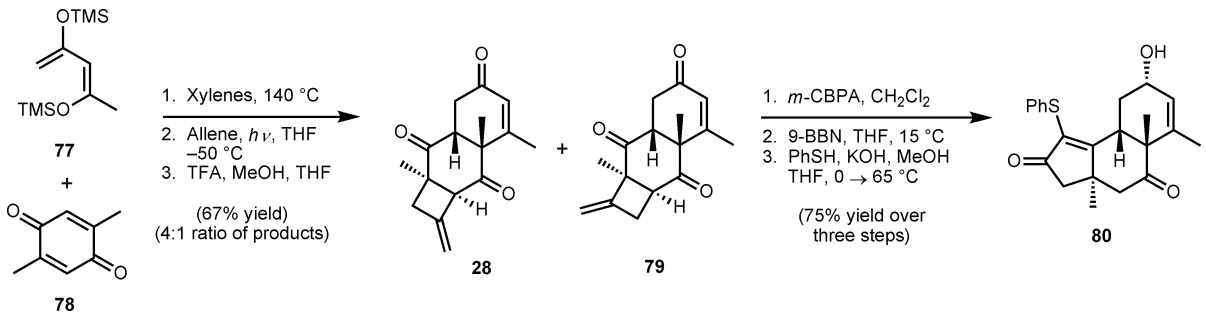
Scheme 15 Vinyl iodide construction in Pier's sarcodonin synthesis.



Scheme 16 Still-Mitra [2,3] sigmatropic rearrangement to construct the A-ring of (±)-sarcodonin G.



Scheme 17 Ring expansion and endgame for (±)-sarcodonin G.



Scheme 18 Ward's cycloaddition strategy toward tricyclic formation.

synthesis was initiated with a Diels–Alder cycloaddition between 2,5-dimethyl-*p*-benzoquinone (**78**) and 2,4-bis(-trimethylsilyloxy)-1,3-pentadiene (**77**, Scheme 18). Subsequent [2 + 2] cycloaddition with allene and exposure to acidic conditions thereafter afforded a 4–6–6 tricyclic system as a 4:1 mixture of structural isomers (**28** to **79**), wherein each was produced as a single diastereomer.[30a]

Though only isomer **28** was desired, the 4:1 mixture of **29** and **79** was epoxidized, reduced at the enone moiety, and then treated with benzenethiol at reflux under basic conditions to effect closure of the cyathane core A-ring. This furnished α-thiophenyl enone **80** in excellent yield, in a sequence that required only a single purification.[30b]

Desulfurization, deoxygenation, protection, and epimerization over nine steps then allowed access to 5–6–6 allylic benzoyl ester **81** (Scheme 19). The six-membered ring olefin of this intermediate provided the reactivity required to construct the seven-membered C-ring of the natural product. Ozonolysis of enone **81** in the presence of Sudan III indicator generated a sensitive keto-aldehyde intermediate which was subjected to aldol reaction, transacylation, and successive trapping *via O*-methylation to afford 5–6–7 tricycle **82**. This three step sequence completed the core framework and simultaneously established the trans-annular ketal bridge present in allocyathin B_3.

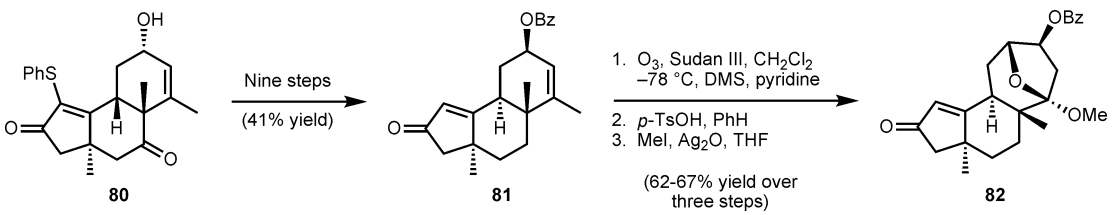
In order to install the necessary isopropyl side-chain appended to the A-ring of the natural product, intermediate **82** was then transformed to propargyl ether **83** (Scheme 20). Treatment of alkyl bromide **83** with AIBN in the presence of Ph_3SnH and subsequent hydrogenation produced the cyclized tetrahydrofuran **84**. Upon exposure to mild acid, tetracycle **84** was opened to tricycle **85**, a structure which contains all of the carbon atoms required for completion of the A-ring. From this point, the total synthesis was completed in eleven steps to yield (±)-allocyathin B_3 (**3**).

Overall, Ward's strategy toward (±)-allocyathin B_3 comprises 34 steps and is concluded in 0.1% yield. The tricyclic cyathane core was attained in 18 steps and 11% overall yield.

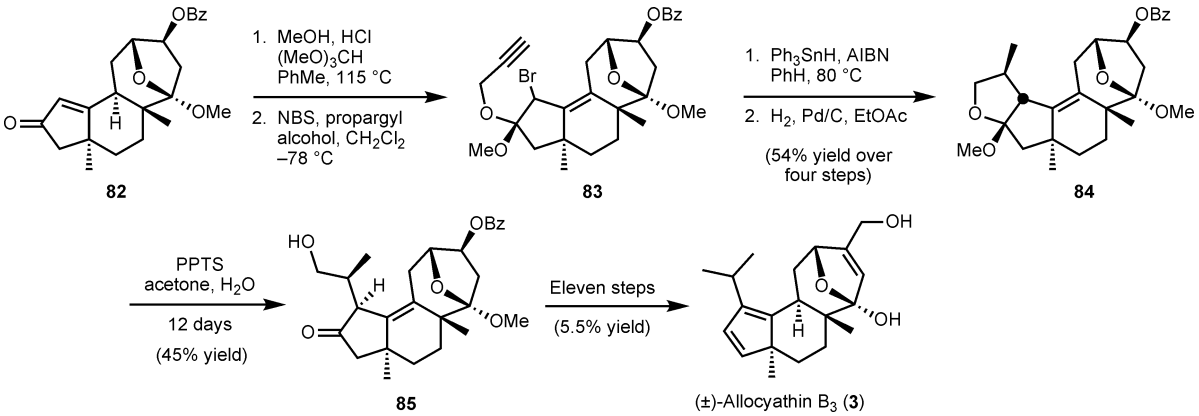
5.5 Ward's (−)-cyathin A_3

A variant of Ward's (±)-allocyathin B_3 strategy was later rendered enantioselective to achieve the total synthesis of the related diterpene natural product (−)-cyathin A_3.[30,31]

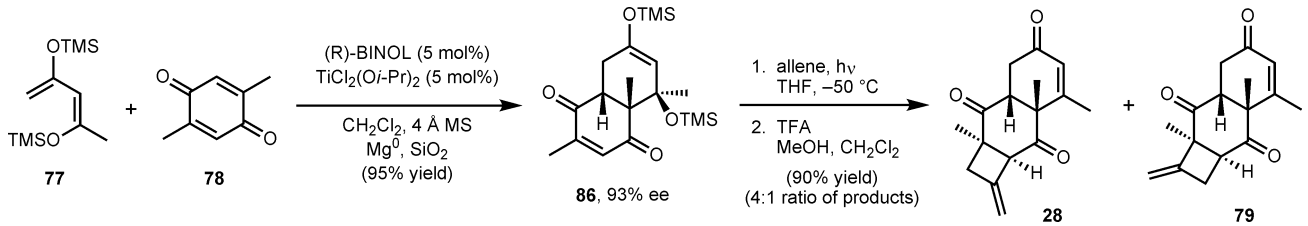
The initial Diels–Alder reaction between 2,5-dimethyl-*p*-benzoquinone (**78**) and 2,4-bis(trimethylsilyloxy)-1,3-pentadiene (**77**) was made asymmetric by employing Mikami's titanium-based BINOL catalyst (Scheme 21).[32] After extensive optimization of this cycloaddition, Ward and coworkers found that addition of Mg powder and silica gel afforded cycloadduct **86** in 90% yield and 93% ee. With **86** in hand, [2 + 2] cycloaddition and acidic hydrolysis proceeded as in the case of Ward's (±)-allocyathin B_3 synthesis to furnish **28** and **79** as a 4:1 mixture of structural isomers.



Scheme 19 Ring expansion *via* ozonolysis and aldol reaction to target the cyathane core.



Scheme 20 Ward's (±)-allocyathin B_3 endgame strategy.

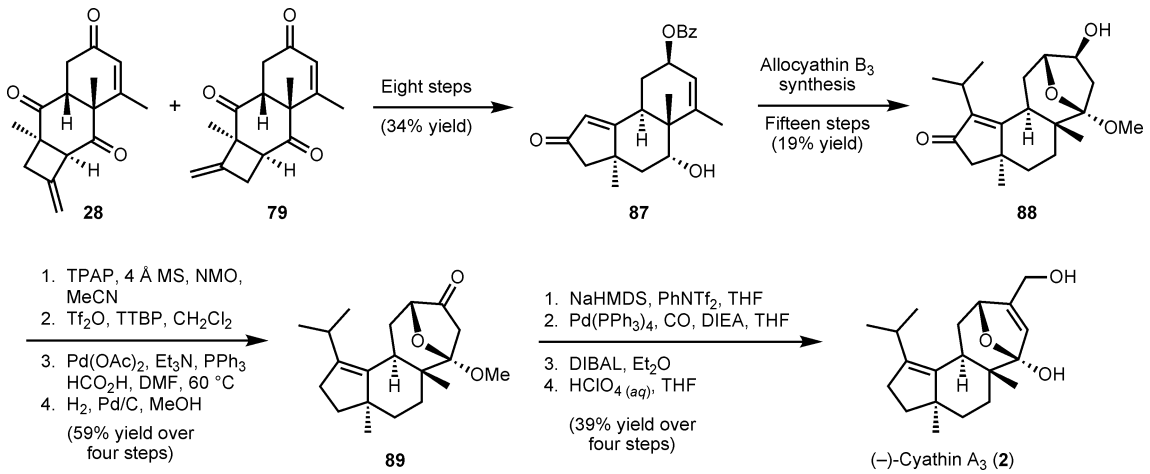


Scheme 21 Catalytic enantioselective Diels–Alder approach to intermediates **86** and **29**.

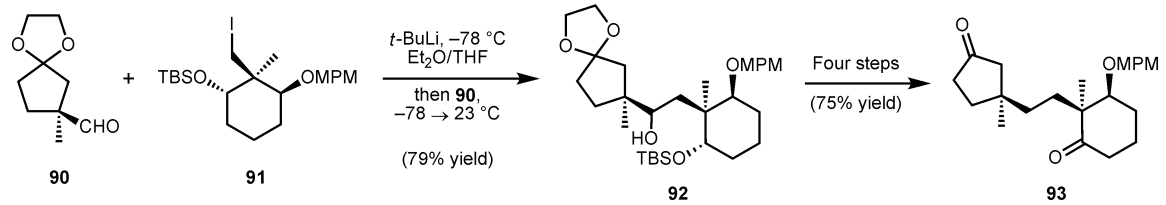
From the isomeric mixture of **28** and **79**, eight additional steps lead to enone **87**, and thus allow Ward to follow his previously reported route (Scheme 22). Advancement of tricycle **87** along fifteen steps (including ozonolysis and aldol reaction for ring expansion) afforded the completed cyathane core in the form of acetal **88**. From this enone, oxidation, triflate formation, reductive deoxygenation, and hydrogenation produced tricycle **89** with the A-ring completed. With this material in hand, Ward was able to conclude the synthesis with four additional reactions, thus furnishing (−)-cyathin A_3 (**2**) in 34 steps and 1.0% overall yield. The cyathane core structure was attained in 17 steps and 15% overall yield.

5.6 Nakada's (+)-allocyathin B_2

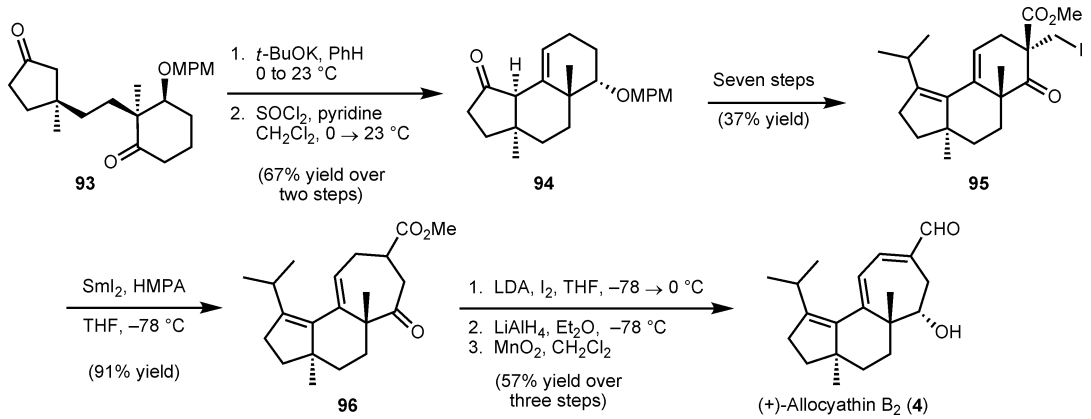
The first enantioselective total synthesis of (+)-allocyathin B_2 was described by the laboratories of Nakada in a report published in 2004.[33] In order to target this cyathane diterpenoid molecule, Nakada envisioned a convergent strategy starting with aldehyde **90** and alkyl iodide **91** (Scheme 23). Both fragment **90** and fragment **91** were prepared in enantioenriched form based on previous work published by Nakada and coworkers.[34,35] After lithium-halogen exchange was performed on iodide **91**, the resulting alkyl lithium was added to a solution of aldehyde **90** to provide access to alcohol **92**. Deoxygenation, deprotection, and oxidation of this structure afforded diketone **93**.



Scheme 22 Endgame synthesis for (−)-cyathin A_3 (TTBP = 2,6-di(*tert*-butyl)-4-methylpyridine).



Scheme 23 Fragment coupling to prepare the tethered aldol precursor.



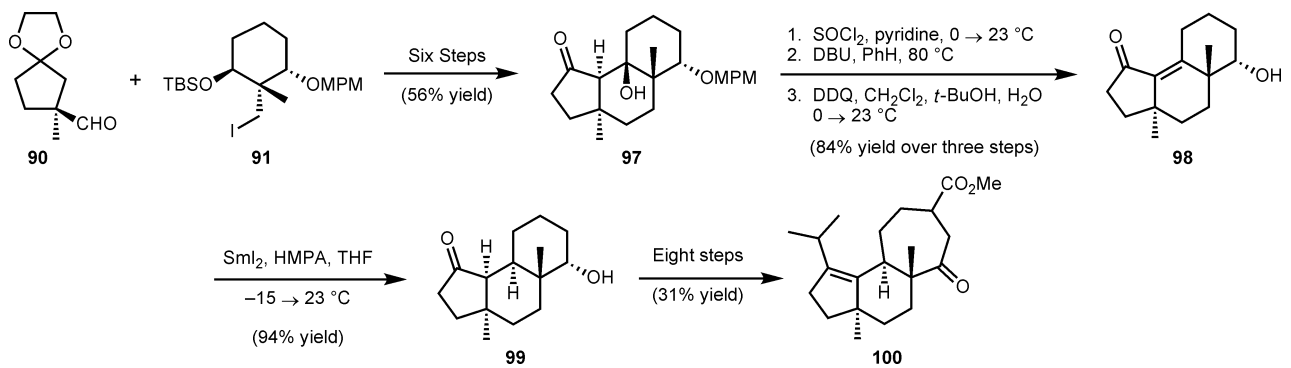
Scheme 24 Intramolecular aldol reaction and ring expansion to complete the total synthesis of (+)-allocyathin B_2.

The tethered diketone **93** was subsequently cyclized *via* intramolecular aldol reaction upon treatment with potassium *tert*-butoxide (Scheme 24). This nucleophilic attack served to form the C(5)–C(4) bond, thus constructing the central B-ring of the natural product. After dehydration, tricycle **94** was isolated as the major product of the reaction sequence. In seven additional steps ketone **94** was transformed into alkyl iodide **95**, an intermediate designed to undergo the samarium-mediated one-carbon ring expansion developed by Hasegawa in a process similar to that employed by Piers for the synthesis of sarcodonin G (Scheme 17, Section 5.3).[29] When **95** was exposed to SmI_2 in the presence of HMPA, the expected migratory ring-expansion occurred in excellent yield to generate the completed cyathane core structure in the form of γ-keto ester **96**.

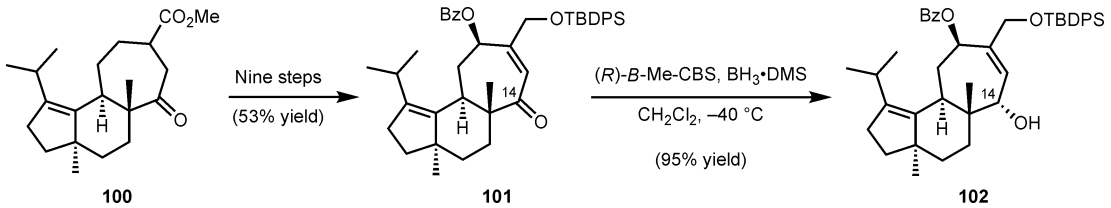
The route toward (+)-allocyathin B_2 was thereafter concluded with three additional oxidation state manipulations, finishing the synthesis in a total of 18 synthetic operations and 7.6% overall yield. The tricyclic cyathane core was attained in 15 steps and 13.4% overall yield. Additionally, this synthetic approach has been adapted toward a number of other cyathane natural products.[36]

5.7 Nakada's (−)-erinacine B

In 2007 Nakada and coworkers extended their synthetic route targeting (+)-allocyathin B_2 toward the preparation of (−)-erinacine B.[37] Following their previous synthetic efforts, it was possible to couple enantioenriched alkyl iodide **91** and aldehyde **90** to furnish, after elaboration, hydroxy ketone **97** (Scheme 25).[35] After dehydration and deprotection to generate intermediate enone **98**, the envisioned synthetic route called for reduction of the α,β-unsaturation present across the central B-ring. Though numerous Birch reduction methods were attempted, it was discovered that such techniques provided mostly over-reduced



Scheme 25 Adaptation of Nakada's (+)-allocyathin B_2 route to (−)-erinacine B.



Scheme 26 Establishing the desired stereochemistry at C(14).

diol products instead of the desired hydroxy ketone. Ultimately, this challenge was overcome *via* diastereoselective olefin reduction with SmI_2 in the presence of HMPA, which provided access to the desired tricycle **99**. This reduction was found to produce a single diastereomer of product, establishing the critical C(5)α-H stereochemistry required for (−)-erinacine B. From this point Nakada was able to once again draw from his synthesis of allocyathin B_2. Over eight steps, including SmI_2-mediated ring-expansion, tricycle **100** was prepared.

Continued synthesis from ester **100** over nine additional steps allowed access to the protected allylic alcohol **101** (Scheme 26). From this point, reduction of the ketone moiety of **101** was required to establish the stereochemistry found in (−)-erinancine B. Unfortunately, all achiral reagents employed for the purpose of diastereoselective reduction afforded only the undesired epimer at C(14). Because of this difficulty, the ketone of **101** was reduced using the (*R*)-CBS catalyst, which set the desired relative stereochemistry with high selectivity to afford allylic alcohol **102**.

This material was thereafter glycosylated with a previously prepared xylose analog **103** to furnish glycone **104** (Scheme 27). After full deprotection of the carbohydrate ring, this material was treated with triethylamine and lithium bromide to effect an S_n' addition into the allylic alcohol. This provided (−)-erinacine B (**6**) as the sole product in enantioenriched form.

Overall, the synthesis was accomplished in 33 steps and 3.0% yield from **90** and **91**. The cyathane core structure was established in 18 steps and 14% overall yield.

5.8 Nakada's (−)-erinacine E

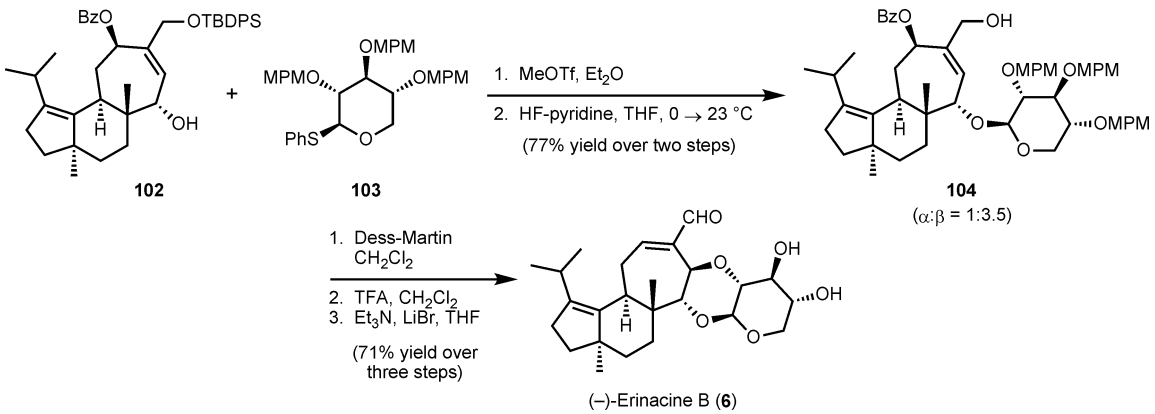
One year subsequent to their report of (−)-erinacine B, Nakada and coworkers disclosed a beautiful modification of their synthetic strategy to target (−)-erinacine E, arguably the most complex cyathane diterpenoid molecule isolated to date.[38] Starting from agylcone molecule **102**, glycosylation with thioglycoside **105** and deprotection provided access to intermediate **106** (Scheme 28). After additional protecting group manipulation, Swern oxidation generated ketone **107**, an intermediate which spontaneously undergoes conjugate addition-elimination to form pentacyclic structure **108**.

Treatment of enal **108** with DBU in benzene at room temperature initiated an intramolecular aldol reaction between the enolate generated at C(4′) and the aldehyde present at C(15) (Scheme 29). This aldol reaction is followed by spontaneous benzoate ester migration, thus producing protected (−)-erinacine E analog **109** as the final product of the sequence. Further deprotection, oxidation, and diastereoselective carbonyl reduction thereafter complete the total synthesis of (−)-erinacine E (**7**).

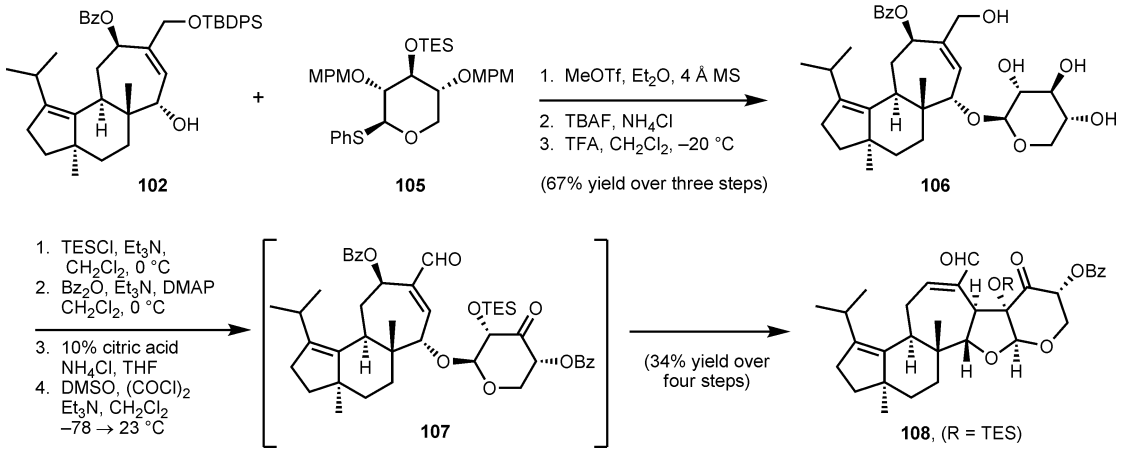
Overall, erinacine E was prepared in 39 steps from iodide **91** and aldehyde **90**, in a total yield of 0.9%.

5.9 Trost's (+)-allocyathin B_2

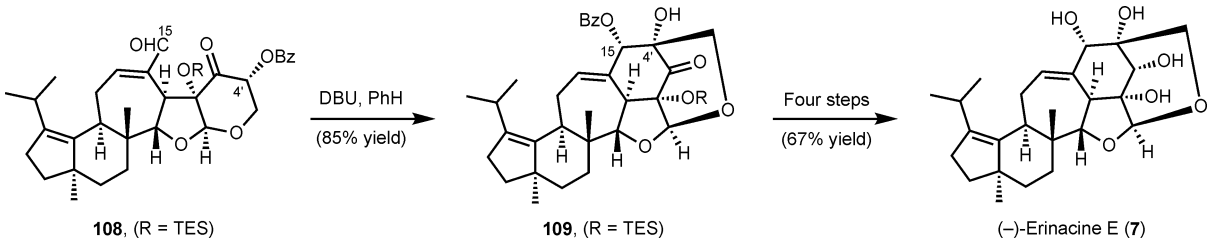
Trost and coworkers have recently reported a unique Ru-catalyzed cycloisomerization strategy for the total synthesis of the cyathane diterpenoid molecule allocyathin B_2.[39] The synthesis was initiated with a Pd-catalyzed asymmetric allylic alkylation. Racemic ketone **110** was alkylated in the presence of $[(\eta^3\text{-}C_3H_7)PdCl]_2$ and chiral ligand (*S,S*)-**112** to afford enantioenriched α-quaternary cyclopentanone **111** (Scheme 30).[40] The high-yielding allylation establishes an all-carbon quaternary stereocenter in 95% ee. This transformation not only set the configuration required at C(9) of the natural product, but also provided the stereochemical basis upon which all subsequent diastereoselective transformations were leveraged.



Scheme 27 Completion of (−)-erinacine B.



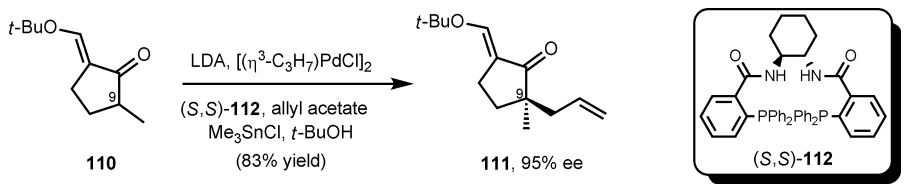
Scheme 28 Synthesis of **108** from allocyathin precursor **102** *via* conjugate addition-elimination.



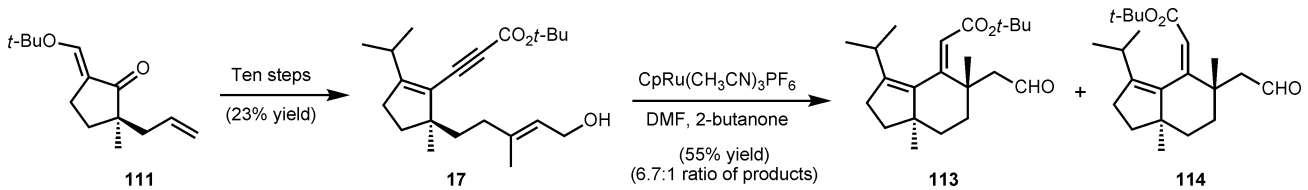
Scheme 29 Intramolecular aldol reaction for Nakada's endgame of (−)-erinacine E.

Further elaboration of the allyl side-chain of **111**, as well as manipulation of the ketone moiety, eventually produced propargyl ester **17** (Scheme 31). With this material, Trost and coworkers planned to seal the central B-ring of (+)-allocyathin B_2 *via* an intramolecular ruthenium-mediated cycloisomerization reaction. In the event, treatment of allylic alcohol **17** with $CpRu(CH_3CN)_3PF_6$ initiated cyclization of the conjugated alkyne onto the trisubstituted olefin with concomitant oxidation of the primary alcohol.[41]

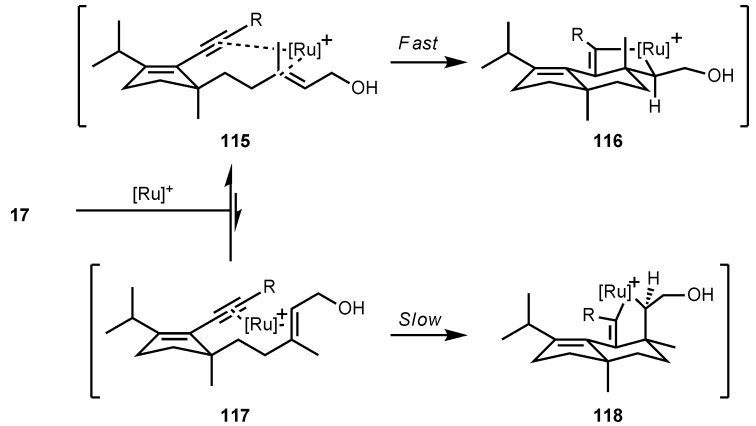
Notably, the cycloisomerization reaction proceeded with high diastereoselectivity. Both products obtained from this transformation possessed the desired anti relationship between the two all-carbon quaternary stereocenters, and no products bearing a syn arrangement were observed. Trost hypothesizes that initial ruthenium complexation to both the alkyne and alkene moieties of **17** can occur to from either a syn-coplanar orientation (**115**) or an orthogonal orientation (**117**, Scheme 32). Because the orbital overlap of the syn-coplanar arrangement is likely more conducive to cycloisomerization, ruthenacycle formation from intermediate **115** to give **116** is expected to be much faster than the alternative formation of **118** from **117**. After β-hydride elimination occurs from ruthenacycle **116**, reductive



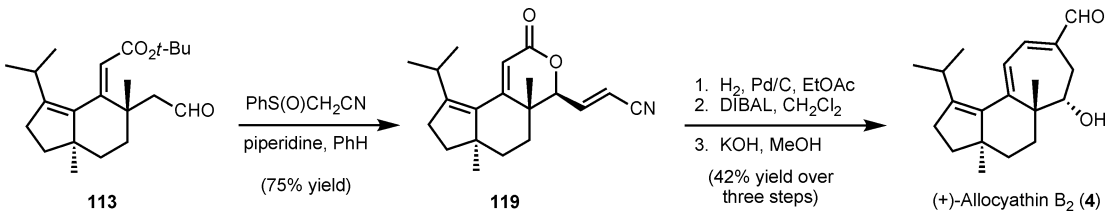
Scheme 30 Asymmetric allylic alkylation to establish stereochemistry at C(9).



Scheme 31 Ru-catalyzed cycloisomerization to establish the central B-ring of (+)-allocyathin B_2.



Scheme 32 Diastereoselectivity considerations in the ruthenium catalyzed cycloisomerization.



Scheme 33 Completion of allocyathin B_2 *via* hydroxylative Knoevenagel and intramolecular aldol reactions.

elimination forms **113** and **114** as the major products of reaction. Because only **113** was desired, ultimately it was determined that increasing the size of the alkynyl ester to a bulky *tert*-butyl provided preferential formation of Z olefin isomer **113** in a 6.7:1 ratio with isomer **114**.[39b]

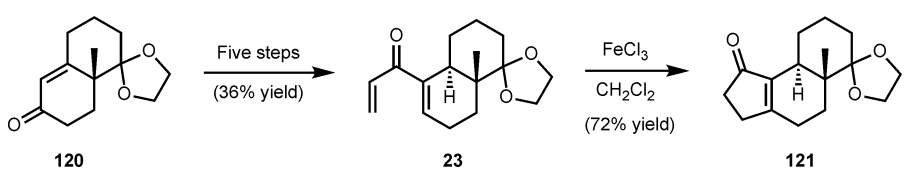
From **113**, a hydroxylative Knoevenagel reaction was performed to access lactone **119** as a single diastereomer (Scheme 33).[42] The final stages of the synthesis involved hydrogenation and nitrile/lactone reduction, followed by an intramolecular aldol reaction to yield (+)-allocyathin B_2 (**4**). Following this sequence, the natural product (+)-allocyathin B_2 (and the cyathane core) was synthesized in sixteen steps and 5.2% overall yield.

5.10 Danishefsky's (−)-scabronine G

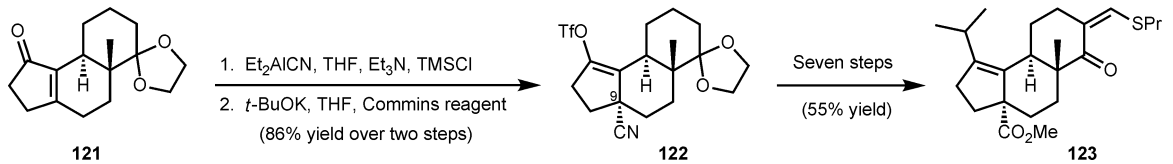
In 2005, Danishefsky and coworkers reported the first total synthesis of the cyathane diterpenoid (−)-scabronine G (**9**).[43] In order to target this bioactive compound, they approached the synthesis with "the pleasingly simple idea that scabronine G can be viewed as an annulated, one-carbon ring-expanded version of the (−)-Wieland–Miescher ketone". The initial transformations of the synthesis commenced from the protected ketone **120** (Scheme 34). Over five steps, including kinetic enolate trapping and palladium-catalyzed carbonylation, acetal **120** was converted to dienone **23**. Construction of the five-membered A-ring of scabronine G was then accomplished *via* Lewis acid-promoted Nazarov reaction. Upon treatment of dienone **23** with $FeCl_3$, cyclization proceeded smoothly to afford enone **121** in good yield. Notably, this tetracyclic product was obtained as a single tetrasubstituted olefin isomer.

The enone of tricycle **121** was then subsequently leveraged in order to install the critical all-carbon quaternary stereocenter present at C(9) of (−)-scabronine G. Conjugate addition of Nagata's reagent was observed to occur with high axial diastereoselectivity, and the resulting enolate was trapped with TMSCl (Scheme 35).[44] The intermediate silyl enol ether obtained from this sequence was then converted to a vinyl triflate species to provide nitrile **122**. Further synthetic elaboration over seven steps allowed for the conversion of vinyl triflate **122** to thiopropylmethylidene **123**.

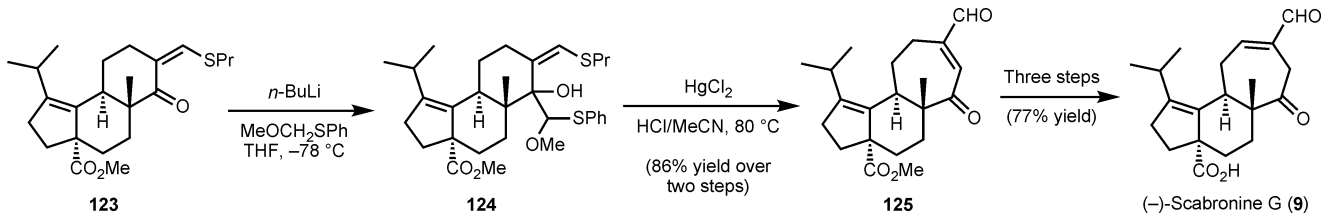
In order to access the 5–6–7 tricyclic cyathane core, vinylogous thioester **123** was first treated with the lithium anion of methoxymethyl phenyl sulfide to produce intermediate tertiary alcohol **124** as a combination of diastereomers (Scheme 36). Subsequent exposure of this mixture to $HgCl_2$ effected a one-carbon ring



Scheme 34 Danishefsky's Nazarov strategy for cyathane A-ring construction.



Scheme 35 Advancement toward Danishefsky's ring-expansion precursor.



Scheme 36 Ring expansion and endgame to complete (−)-scabronine G.

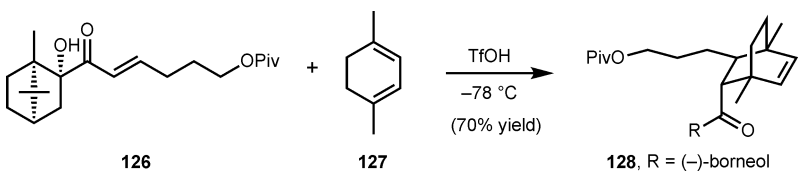
expansion reaction to furnish tricycle **125** and the seven-membered C-ring, thus completing the cyathane framework.[45] With ring-expanded aldehyde **125** in hand Danishefsky and coworkers were able to complete (−)-scabronine G (**9**) in three additional transformations, accomplishing the total synthesis in 20 steps and 8.2% overall yield. The cyathane core framework was constructed in 17 steps and 11% yield.

5.11 Phillip's (+)-cyanthiwigin U, (+)-cyanthiwigin W, and (−)-cyanthiwigin Z

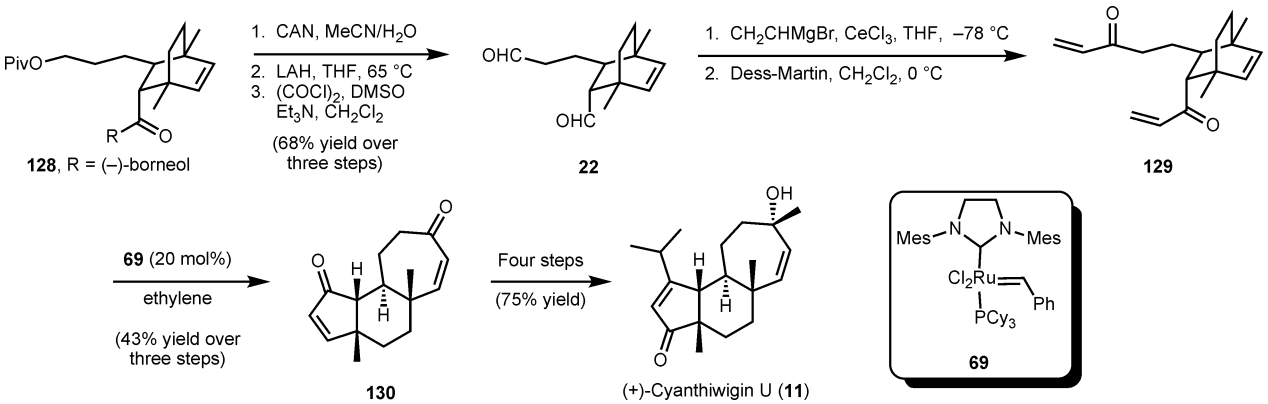
The first report of the total synthesis of any member of the cyanthiwigin sub-class of natural products was published by Phillips and coworkers in 2005.[46] Phillips' strategy for targeting (+)-cyanthiwigin U focused upon construction of the tricyclic cyathane core *via* simultaneous construction of both the A- and C-rings, and employed late-stage installation of the peripheral functionality.

The synthesis was initiated with an asymmetric Diels–Alder reaction between 1,4-dimethyl cyclohexadiene (**127**) and (−)-borneol-appended enone **126** (Scheme 37).[47] This cycloaddition reaction proceeded smoothly to give a single diastereomer of **128**, thus establishing both quaternary stereocenters of the natural product in a single synthetic operation. After cleavage of the chiral controller, deprotection, and further functional group manipulation, this sequence provided access to bridged bicyclic bis-aldehyde **22** (Scheme 38).

Addition of vinyl Grignard to bis-aldehyde **22** was followed by oxidation to bis-enone **129**. The bicyclo[2.2.2]octene system of **129** was designed to be well suited to the planned synthetic



Scheme 37 Auxiliary-mediated Diels–Alder reaction to establish the quaternary stereocenters of (+)-cyanthiwigin U.



Scheme 38 Completion of (+)-cyanthiwigin U *via* ring-opening ring-closing metathesis.

strategy of "two-directional" tandem ring-opening, ring-closing metathesis developed by Phillips in prior reports.[48] By treating this bis-enone with 20 mol% of Grubbs' second-generation metathesis catalyst (**69**) under an atmosphere of ethylene, ring-opening metathesis of the strained bridging olefin was rapidly followed by two sequential ring-closing events. This reaction established both the five- and seven-membered rings of the cyathane core, providing tricycle **130** as the ultimate product of the cascade. From this point, the synthesis of (+)-cyanthiwigin U (**11**) was completed in four steps involving oxidation state manipulation, as well as addition of the isopropyl and methyl groups. Phillip's route produces the cyathane core in eight synthetic operations and 19% yield, and in total, the synthesis comprises only 12 steps and is accomplished in 17% overall yield.

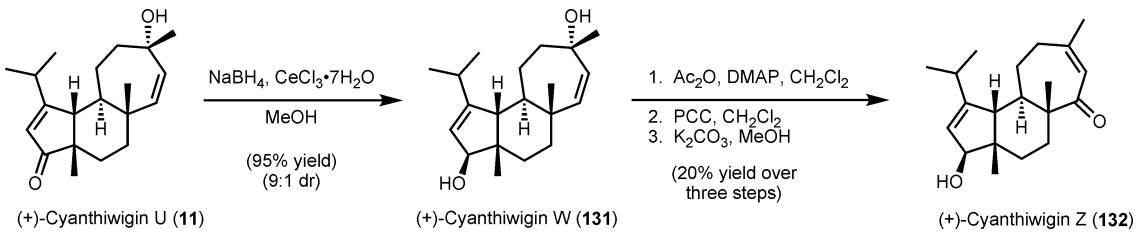
Very recently, the laboratories of Phillips have reported the synthesis of additional cyanthiwigin natural products based on an extension of their route toward (+)-cyanthiwigin U.[49] Treatment of (+)-cyanthiwigin U (**11**) under Luche reduction conditions afforded the natural product (+)-cyanthiwigin W in 9:1 dr (**131**, Scheme 39). Protection of the resulting secondary hydroxyl group was then followed by allylic transposition and alcohol oxidation *via* PCC. After deprotection, this sequence furnished (−)-cyanthiwigin Z (**132**).

5.12 Reddy's (+)-cyanthiwigin AC

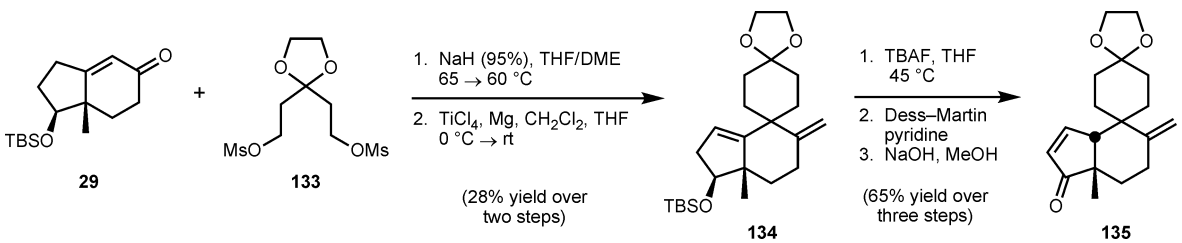
The structure of cyathane diterpenoid (+)-cyanthiwigin AC is unique in comparison to other cyathane molecules in that it does not possess a 5–6–7 fused tricyclic core. Instead, the natural product contains both a 5–6 fused bicycle and a 6–6 spirocyclic junction. The first total synthesis of this natural product was reported in 2006 by Reddy and coworkers.[50]

Starting from the (+)-Hajos–Parrish ketone derivative **29**, double-alkylation with bis-mesylate **133** was effective to install the spiro-annulation of the natural product (Scheme 40). After methylenation of the resulting compound, spirocyclic intermediate **134** was isolated as the major product of this two-step sequence. Deprotection, oxidation, and isomerization then furnished enone **135** in preparation for installation of the isopropyl sidechain to the five-membered A-ring.

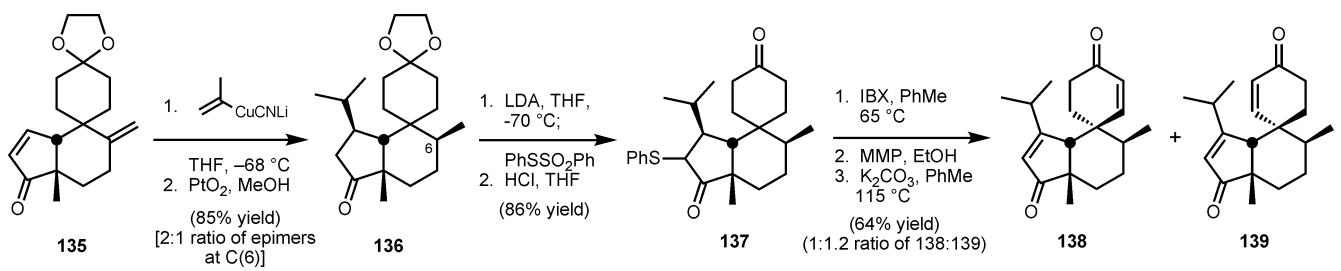
Conjugate addition of isopropenyl cyanocuprate to tetracycle **135** was followed by diastereoselective reduction of the exocyclic methylene to set the tertiary methyl stereocenter of the natural product (Scheme 41). This yielded ketone **136** as a 2:1 mixture of epimers at C(6). Further elaboration of this material provided access to thioether **137**, which upon exposure to IBX in toluene underwent oxidation to generate a mixture of six-membered ring enones.[51] After sulfoxide formation with magnesium



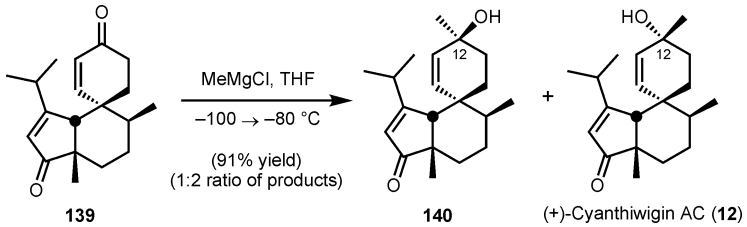
Scheme 39 Preparation of (+)-cyanthiwigin W and (−)-cyanthiwigin Z from (+)-cyanthiwigin U.



Scheme 40 Spiro-annulation of Hajos–Parrish ketone derivative **29**.



Scheme 41 Further oxidation and transformation toward (+)-cyanthiwigin AC.



Scheme 42 Reddy's endgame for (+)-cyanthiwigin AC.

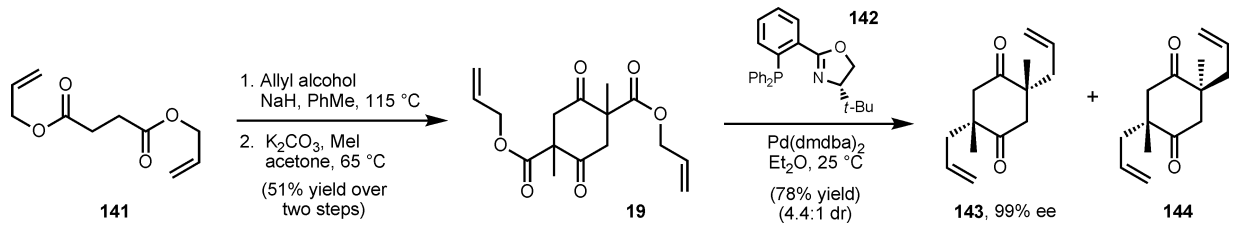
monoperoxyphthalate (MMP) and dehydrosulfenylation of this intermediate mixture, enones **138** and **139** were obtained in a 1:1.2 ratio of isomers.

From this point, the addition of methyl magnesium chloride to dienone **139** produced the natural product as a 1:2 mixture of epimers at C(12), favoring the generation of (+)-cyanthiwigin AC (**12**, Scheme 42) over isomer **140**. The total synthesis of the natural product was concluded in 13 steps and 2.0% overall yield.

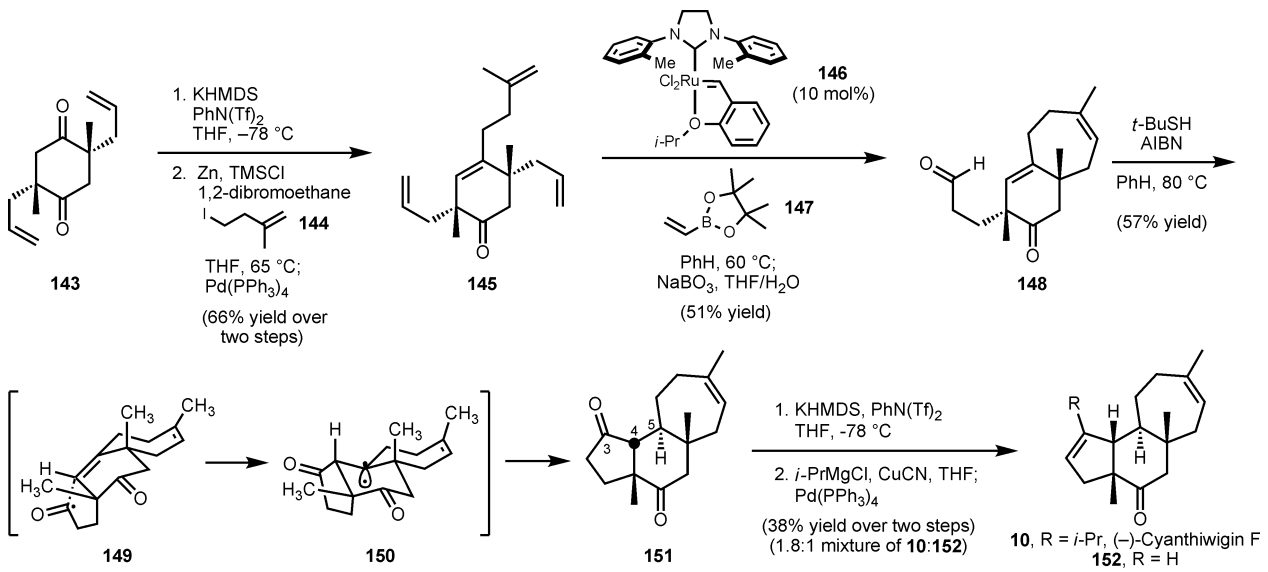
5.13 Stoltz's (−)-cyanthiwigin F

The total synthesis of (−)-cyanthiwigin F *via* a double catalytic enantioselective alkylation was published by Stoltz in 2008.[52] Tandem Claisen condensation and Dieckmann cyclization of diallyl succinate (**141**) were followed by methylation of both α positions to yield bis-β-ketoester **19** (Scheme 43). Treatment of this material with a palladium catalyst precursor and (*S*)-*t*-BuPHOX (**142**) as a ligand initiates a double catalytic enantioselective alkylation reaction to generate both quaternary stereocenters present in the natural product.[53] This reaction affords enantioenriched diketone **143** in 99% ee, as well as the corresponding meso diastereomer **144**, in a 4.4:1 diastereomeric ratio.

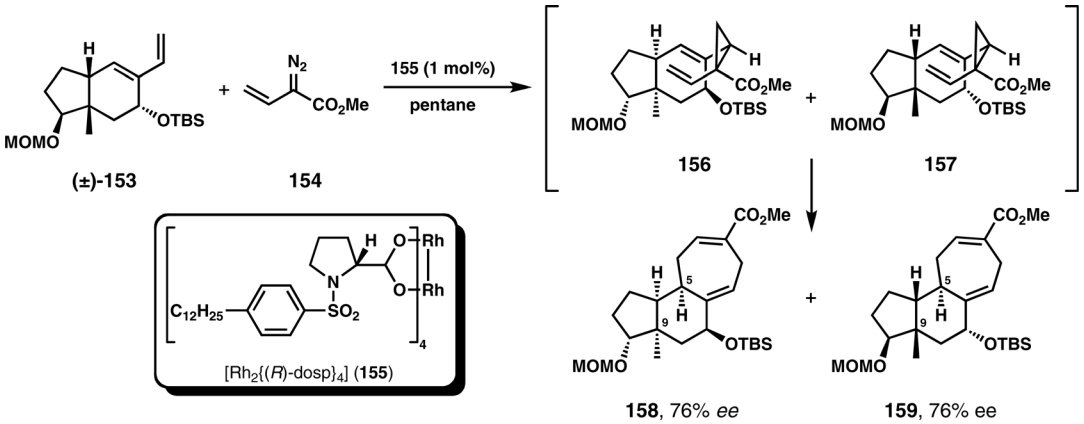
Diketone **143** was subsequently desymmetrized *via* triflate formation and Negishi cross-coupling with alkyl iodide **144** to furnish tetraene **145** (Scheme 44). This material was subjected to ring-closing metathesis by the action of modified Grubbs' catalyst **146** accompanied by cross-metathesis with vinyl boronate **147**. This transformation served to close the seven-membered C-ring of the core scaffold while subsequently functionalizing the remaining allyl side-chain of **145** toward further elaboration. After mild oxidative work-up with aqueous sodium perborate, bicyclic aldehyde **148** was obtained in a single synthetic operation



Scheme 43 Catalytic enantioselective double-alkylation for (−)-cyanthiwigin F.



Scheme 44 Completion of the total synthesis of (−)-cyanthiwigin F.



Scheme 45 Sarpong's parallel kinetic resolution method for divergent cyathane tricycle construction

from **145**. Closure of the final ring of the cyathane framework was then accomplished *via* an acyl radical cyclization in a reaction which yielded a single diastereomer of tricyclic diketone **151**.[54] A potential explanation for the diastereoselectivity of this reaction involves rapid formation of the five-membered A-ring through intermediate acyl radical **149**, followed by external hydrogen atom abstraction by tertiary radical **150** to give diketone **151**. After vinyl triflate formation from this diketone, palladium-catalyzed cross-coupling with a pregenerated isopropyl cyanocuprate species produced both (−)-cyanthiwigin F (**10**) and reduced product **152** in a 1.8:1 ratio.

The total synthesis of (−)-cyanthiwigin F was achieved in nine steps and 1.9% overall yield. The tricyclic cyathane core was accessed in seven steps and 6.2% overall yield.

6 Conclusions

The cyathane diterpenoid natural products have been the focus of numerous total synthetic efforts. Sixteen completed total syntheses of these compounds have been reported, thirteen of which have emerged in the last eight years alone. Because the cyathane natural products have been implicated as important biologically active molecules, particularly in regard to the stimulation of NGF synthesis, continued investigation into and refinement of their laboratory preparation is undoubtedly forthcoming.

Note added in proof

Subsequent to the submission of this review, Sarpong *et al.* described a unique parallel kinetic resolution method to target the cyathane core tricycle (Scheme 45).[55] Bicyclic diene **153**, which was prepared from the Hajos–Parrish ketone, was subjected to a number of rhodium-catalyzed cyclopropanation reactions in order to initiate a divinylcyclopropane rearrangement for construction of the seven-membered C-ring. In the event, exposure of racemic diene **153** to vinyldiazoacetate **154** in the presence of Davies' chiral dirhodium tetraprolinate complex **155** proceeded with good catalyst control and facial selectivity. The immediate products of the cyclopropanation were presumably the diastereomeric divinylcyclopropanes **156** and **157**, structures which immediately underwent rearrangement to produce completed cyathane tricycles **158** and **159** in enantioenriched form. Notably, the use of a chiral catalyst and a racemic substrate in this parallel kinetic resolution afforded divergent products which were both well suited toward elaboration into cyathane diterpenoids. Tricycle **158** displays *syn* relative stereochemistry between the hydrogen atom of C(5) and the methyl group of C(9), which is analogous to the structure of cyathin A_3. Tricycle **159** possesses an *anti* relationship between these stereocenters, as can be found in the cyanthiwigin natural products. By leveraging the exceptional catalyst selectivity of **155**, this parallel kinetic resolution allowed efficient, enantioselective access to two variants of the cyathane core structure from a single racemic starting material.

7 Acknowledgements

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