CHAPTER 1[†]

Cyathane Diterpenoid Natural Products:

Isolation, Activity, and Previous Synthetic Efforts

1.1 INTRODUCTION

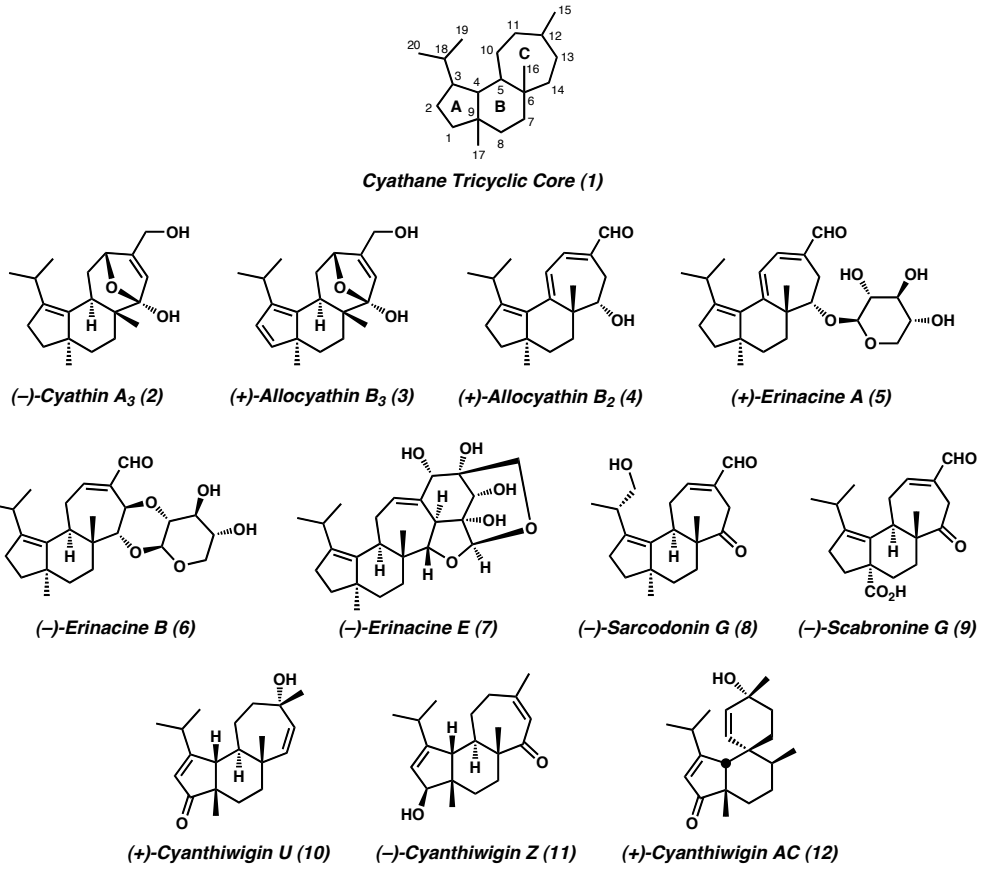
The following chapter is intended to present an overview of the isolation, bioactivity, and synthetic efforts published concerning the cyathane diterpenoid natural products. For the purpose of comprehensive review and comparison, all known completed total syntheses will be presented below, with a specific focus on the ring-forming and stereocenter-forming strategies employed therein.[1] The work summarized herein includes only those reports of cyathane core syntheses disclosed past 2000. All preceding work toward cyathane core preparation has been previously summarized in a review by Wright, which can be consulted for further detail.[2]

[†] Portions of this chapter have been reproduced from *Nat. Prod. Rep.* **2009**, *26*, 661–680.

1.2 OVERVIEW OF THE CYATHANE DITERPENOID NATURAL PRODUCTS

The cyathane molecules are a class of diterpene natural products, which are isolated from a diverse variety of fungi, sponges, and fruiting plants. However, despite their myriad natural sources, all cyathanes are unified by the presence of a characteristic fused 5-6-7 tricarbocyclic structure (1, Figure 1.1).

Figure 1.1 Representative cyathane diterpenoid natural products



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 that 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).

1.2.1 ISOLATION

In 1970, 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.[3] 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 they named cyathin A_3 (**2**) and allocyathin B_3 (**3**).[4] Numerous other cyathin and allocyathin natural products were discovered subsequent to this report, including allocyathin B_2 (**4**),[5] a cyathane diterpenoid that 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 erinaceum* were erinacine A (**5**), erinacine B (**6**), and the more structurally complex erinacine E (**7**).[6]

In 1989 Nakayama and coworkers published the isolation and structural assignment of eight new cyathane molecules from the fungus *Sarcodon scabrosus* that they named the sarcodonins A–H.[7] These compounds possess the conserved 5-6-7 tricyclic core found in all other cyathane natural products, but are distinct from the larger family in that they display further oxidation of the C(19) carbon, as can be observed in sarcodonin G (**8**). Beyond the sarcodonin molecules, an additional class of cyathane diterpene compounds were eventually identified from extracts of the same *Sarcodon scabrosus* fungus. In 1998, by Oshima and coworkers reported the isolation and characterization of the scabronines A–F. Six years later, Liu *et al*. disclosed the isolation of two more compounds of this type from the same source, including scabronine G (**9**).[8] Structural elucidation of the scabornine natural products revealed the presence of a carboxyl group at C(17), a feature that marks these terpenoids 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 obtained from the marine sponge *Epipolasis reiswigi*, cyanthiwigins A–D were structurally assigned, including their absolute configurations, via NMR, X-ray, and Mosher ester analysis.[9] A decade later the laboratories of Hamann isolated an additional 23 compounds of this class from a decoction of the Jamaican sea sponge *Myrmekioderma styx*. This isolation included the products cyanthiwigin U (**10**) and cyanthiwigin Z (**11**). In the years subsequent to their

initial report, Hamann and coworkers have detailed the isolation and characterization of additional cyanthiwigin molecules AB–AG, including the structurally unique spirocyclic cyanthwigin AC (**12**).[10]

1.2.2 BIOACTIVITY

The biological activity of the cyathane natural products varies widely among the different molecules within the class. Many of these diterpene compounds possess both antibiotic and antimicrobial activity, such as the previously discussed cyathin A_3 (**2**) and allocyathin B_3 (**3**). Indeed, almost all of the subcategories of cyathane molecules display mild activity in this regard.[3,5,10] In addition to serving an antibiotic function, some members of the cyanthiwigin compounds exhibit limited cytotoxic activity against human primary tumor cells, P388 murine leukemia cells, and A549 lung tumor cells.[10,11]

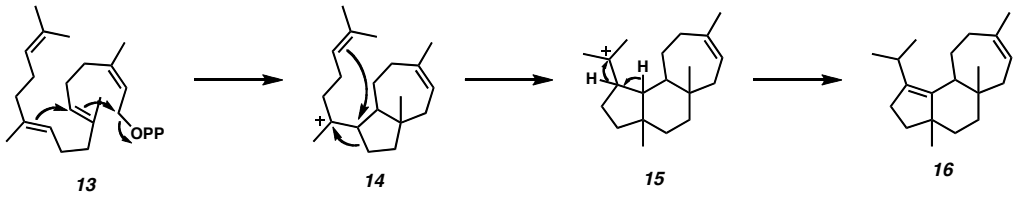
However, the most significant facet of biological activity reported among these diterpenoid molecules is their powerful ability to encourage the synthesis of nerve growth factor (NGF). Both the erinacine and the scabronine natural products have displayed considerable potency in the stimulation of NGF synthesis,[6,8b] a capacity that implicates their potential use as therapeutic agents to treat neurodegenerative ailments such as Alzheimer's or Parkinson's disease.[12]

1.2.3 BIOSYNTHESIS

The details of cyathane diterpenoid biosynthesis have been covered in Wright's review, and as such will only be briefly summarized here.[2] 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 isotopically enriched 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 phosphate (**13** through **16**, Scheme 1.1).[13]

Scheme 1.1 Biosynthesis of the cyathane core tricycle from geranylgeranyl phosphate



1.3 PREVIOUS SYNTHETIC EFFORTS

Since the first isolation of these diterpene natural products in the early 1970s, numerous research groups have endeavored to synthesize the cyathanes. A multitude of diverse strategies have been documented in the literature, and many of these approaches are presented below in schematic form. The synthetic efforts reported to date can be roughly categorized by their key transformations, all of which can be classified as either transition metal-mediated reactions (Scheme 1.2), or akylation/aldol reactions (Scheme 1.3).

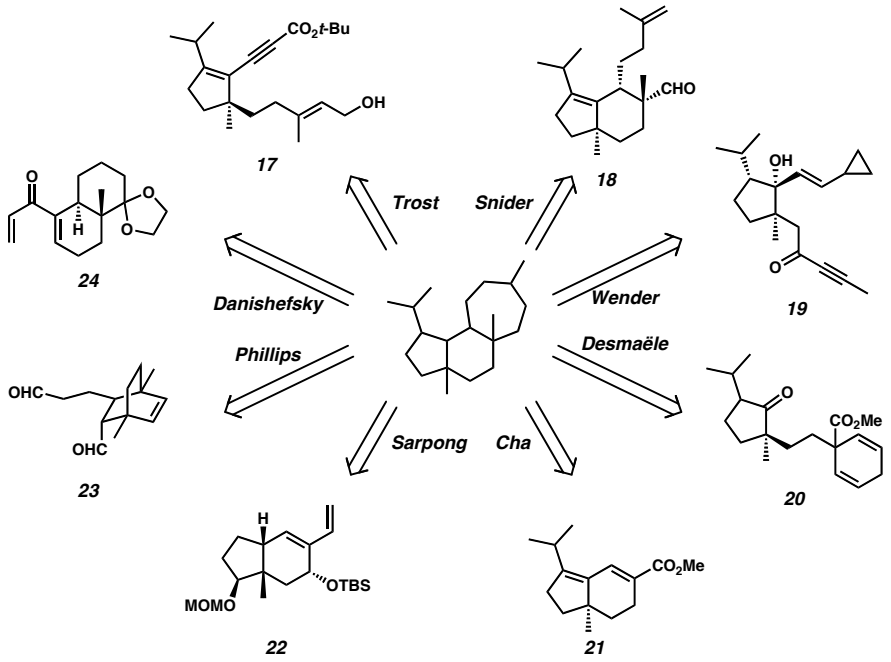
1.3.1 STRATEGY SUMMARY

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*. employs a Ru-catalyzed cycloisomerization to close the central B-ring of the cyathane core, an approach that leads back to allylic alcohol **17** (Figure 1.2). Similarly, Desmaële's route relies upon a Pd-catalyzed intramolecular Heck cyclization to construct the core B-ring, invoking diene **20** 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 **24**. 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 utilizes an Al-catalyzed carbonyl-ene reaction for C-ring construction from bicyclic aldehyde **18**. The laboratories of Cha *et al*. have constructed the seven-membered cyathane C-ring via ring-closing metathesis, thus invoking bicycle **21** as a critical precursor. Sarpong and coworkers seal the C-ring via a novel parallel kinetic resolution, which allows for the use of racemic diene **22** in an enantiodivergent approach toward the cyathin core tricycle.

The power of transition-metal catalysis has also enabled strategies that invoke simultaneous 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 **23** as a retrosynthetic precursor. Wender's [5 + 2] cycloaddition approach toward the cyathane skeleton allows

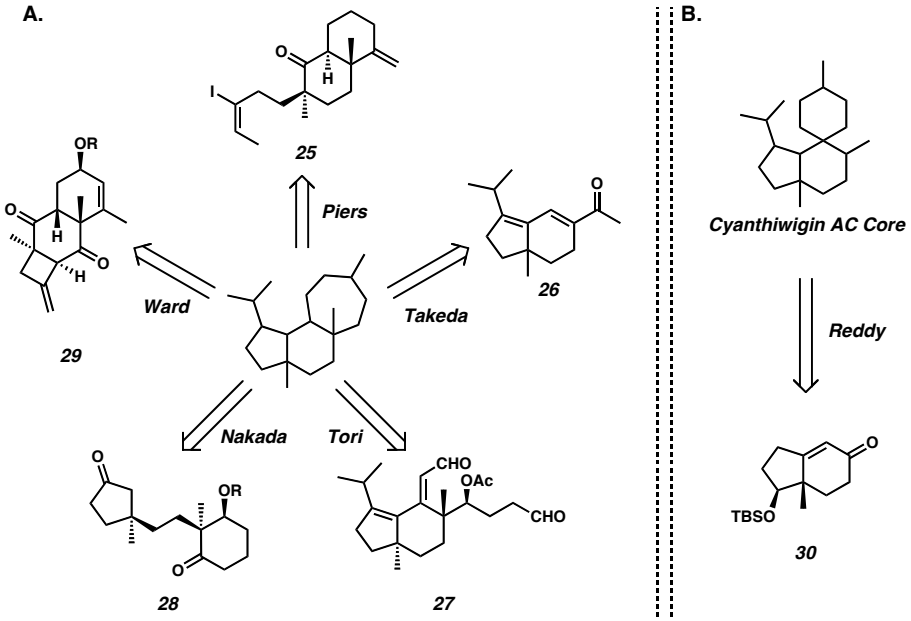
for cascade construction of both the B- and C-rings simultaneously, thus retrosynthetically disconnecting the core backward to ynone **19**.

Figure 1.2 Transition metal and Lewis acid-catalyzed retrosynthetic disconnections toward the cyathane diterpenoid tricyclic core



Another unifying approach by which the cyathane tricycle has been targeted is that of an aklyation 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 **29** as an important synthetic precursor (Figure 1.3A). Tori implements a similar technique to C-ring formation in his synthesis, wherein bis-aldehyde **27** is invoked via a disconnection of the cyathane core by means of an intramolecular aldol reaction.

Figure 1.3 (A) Alkylation and aldol retrosynthetic disconnections of the cyathane diterpenoid tricyclic core (B) Reddy's retrosynthetic disconnection of the cyanthiwigin AC core



The cyathane C-ring has also been constructed via a unique [3 + 4] annulation reaction developed by Takeda, which employes **26** as a bicyclic precursor to the larger tricyclic skeleton. A convergent strategy targeting the B-ring of the cyathane core can be found in Nakada's approach toward these natural products. By disconnecting the central ring of the tricycle, Nakada invokes tethered system **28** 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 **30** as a precursor (Figure 1.3B). Moreover, an anionic alkylation approach has also proven fruitful for construction of the five-membered cyathane A-ring. In this regard, Piers' retrosynthetic analysis of the cyathane core opens the A-ring to vinyl iodide **25**, a

structure that, after lithium-halogen exchange and ketone trapping, closes to give a tricyclic system.

1.3.2 CYATHANE CORE SYNTHESES

Several groups have devised efficient strategies toward preparation of partial cyathane diterpenoid molecules, all of which possess potential divergent extensions to the synthesis of multiple natural products. For the purpose of this chapter, core syntheses will entail those efforts toward cyathane molecules that have successfully attained a completed tricyclic scaffold.

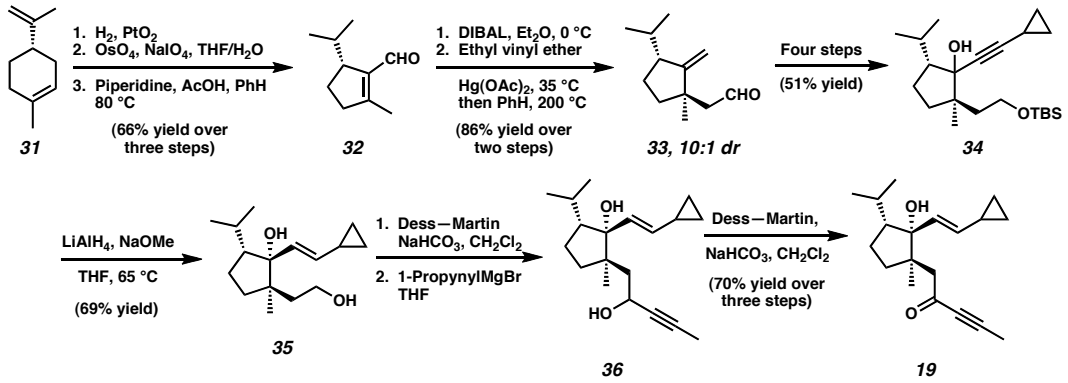
The section below is intended as an update to the review published in 2000.[2] As such, only cyathane core syntheses published after this date will be summarized here.

1.3.2.1 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.[14] Beginning with (–)-limonene (**31**), hydrogenation, oxidative olefin cleavage, and intramolecular aldol condensation afforded enal **32** (Scheme 1.2). After reduction and vinyl ether formation, a thermal Claisen rearrangement yielded aldehyde **33** as a 10:1 mixture of inseparable diastereomers. Cyclopentane **33** was thereafter advanced along four steps, including ozonolysis of the exocyclic methylene and addition of lithium cyclopropylacetylide, to furnish cyclopentanol **34** as a mixture of diastereomers. Stereoselective reduction of cyclopropyl

alkyne **34** allowed access to diol **35**, which was oxidized, then exposed to 1-propynylmagnesium bromide to generate propargyl alcohol **36**. Attempts to execute a [5 + 2] cycloaddition reaction using alcohol **36** as the starting material were unfortunately unsuccessful, and yielded only a complicated mixture of products. Due to this difficulty, enyne **36** was oxidized to conjugated ketone **19** before executing the [5 + 2] cycloaddition reaction.

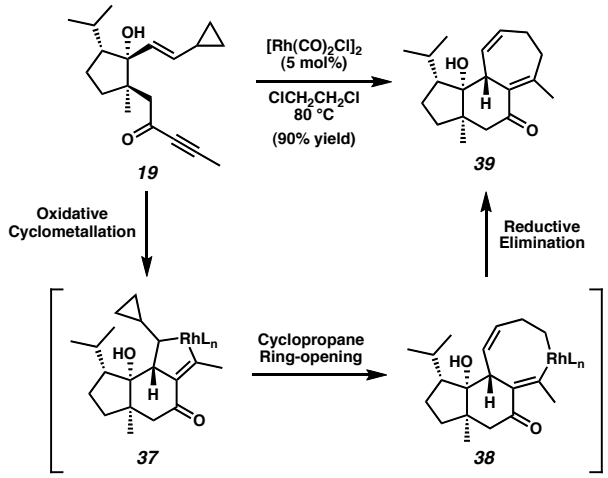
Scheme 1.2 Preparation of the critical [5 + 2] cycloaddition precursor



Upon exposure of vinyl cyclopropane **19** to 5 mol% of $[Rh(CO)_2Cl]_2$, the desired cycloaddition reaction proceeded in high yield to provide tricycle **39** as a single diastereomer (Scheme 1.3).[15] The critical [5 + 2] cycloaddition reaction initiates with complexation of the rhodium catalyst to both the alkyne moiety and the vinyl cyclopropane group. This is then followed by oxidative cyclometallation to form an intermediate metallocyclopentane (**37**), which in turn undergoes strain-driven cyclopropane ring-opening and ring-expansion to generate a transient metallocyclooctadiene species (**38**). Reductive elimination of rhodium from **38** thereafter yields tricyclic structure **39**, representing a completed cyathane core. The structure of

tricyclic enone **39** 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.

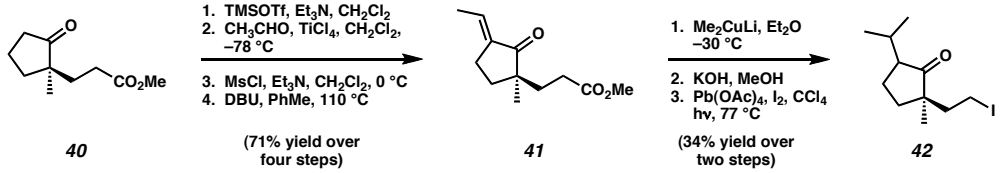
Scheme 1.3 Wender's [5 + 2] cycloaddition reaction to construct the cyathane core tricycle



1.3.2.2 DESMAËLE'S CYATHANE CORE SYNTHESIS

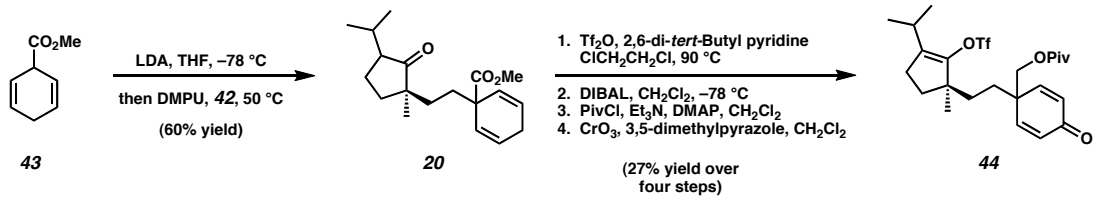
A generalized synthetic route toward the tricyclic cyathane core skeleton was developed by Desmaële and coworkers in 2002, and an updated version of this strategy was later published in 2005.[16] When addressing the challenges present in constructing the tricyclic cyathane framework, Desmaële posits 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, his envisioned strategy involves late-stage construction of the central B-ring of the tricycle via intramolecular Heck reaction between tethered A- and C-ring fragments.

Scheme 1.4 Synthesis of Desmaële's alkyl iodide coupling partner



The synthesis was initated from known, enantioenriched keto-ester **40** (Scheme 1.4).[17] Mukaiyama aldol reaction with acetaldehyde, followed by dehydration and isomerization, yielded enone **41**. After cuprate addition to and saponification of ester **41**, the intermediate keto-acid obtained was then subjected to the Kochi modification of the Hunsdiecker reaction to afford primary iodide **42**. Displacement of iodide **42** with the lithium enolate of methyl ester **43** then provided tethered intermediate **20**, which was subjected to a four step sequence to access the critical Heck cyclization precursor **44** (Scheme 1.5). Notably, prior attempts at an intramolecular Heck cyclization involving a seven-membered ring dieneone proved quite difficult to advance along this synthetic path, and for this reason Desmaële opted to employ a six-membered C-ring surrogate instead.

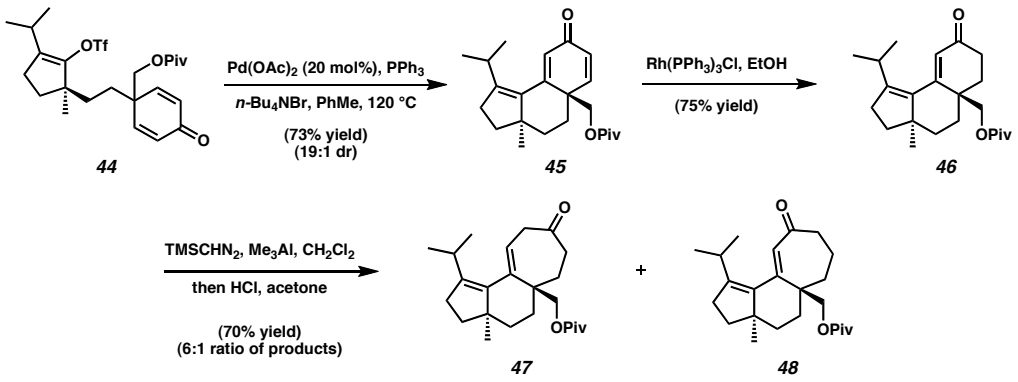
Scheme 1.5 Preparation of the crucial Heck cyclization precursor



Several attempts to cyclize precursor **44** via intramolecular Heck reaction under standard conditions were complicated by either undesired acetate addition to, or incorrect

relative stereochemistry of, the resulting products.[16a] Eventually, further optimization of this reaction led Desmaële to discover that exposure of triflate **44** 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 **45** in 73% yield and a 19:1 diastereomeric ratio (Scheme 1.6).[18] 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.[16b,c]

Scheme 1.6 Heck cyclization and aluminum-promoted ring expansion reactions to target the cyathane tricycle

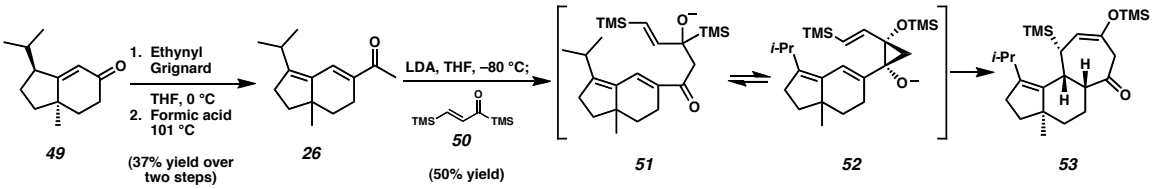


Elaboration of tricyclic dienone **45** toward the cyathane core structure proceeded via hydrogenation of the disubstituted olefin using Wilkinson's catalyst to give enone **46**. This reduction was then followed by treatment of tricycle **46** with trimethyl aluminum and trimethylsilyl diazomethane to effect an organoaluminium-promoted ring expansion.[19] This reaction afforded the completed 5-6-7 tricyclic framework as a 6:1 mixture of ketone (**47**) and enone (**48**) isomers. By obtaining these tricyclic structures, Desmaële accomplished the construction of the cyathane core tricycle over 15 steps and in an overall combined yield of 1.4% for both isomers obtained.

1.3.2.3 TAKEDA'S CYATHANE CORE SYNTHESIS

In 2000, Tekada and coworkers disclosed a synthesis of the cyathane core that leveraged a unique [4 + 3] annulation strategy for tricycle construction.[20] Starting from known racemic enone **49**, addition of ethynyl Grignard was followed by a Rupe rearrangement to give extended conjugated enone system **26** (Scheme 1.7). Formation of the lithium enolate of **26** was followed by addition to acyl silane **50**. Initial nucleophilic addition of the enolate of **26** to **50** produces intermediate alkoxide **51**, which undergoes Brook rearrangement and subsequent intramolecular nucleophilic carbonyl addition to form cyclopropane **52**. Divinyl cyclopropane species **52** thereafter undergoes spontaneous divinyl cyclopropane rearragement to form the cyathane C-ring, a process that is accelerated by the presence of an alkoxide. After this sigmatropic rearrangement occurs, the completed cyathane core structure **53** is afforded as a single diastereomer.[21]

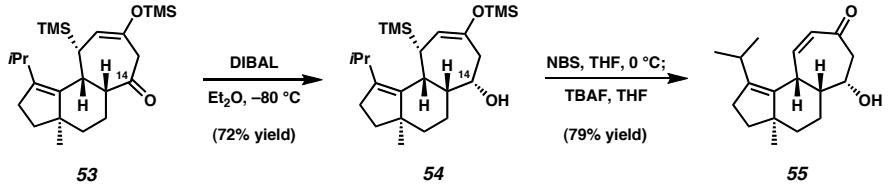
Scheme 1.7 Takeda's key [4 + 3] annulation to target the C-ring of the cyathane core



Continued functionalization of tricycle **53** was accomplished by diastereoselective DIBAL reduction, a process which provided the isomerically pure silyl enol ether **54** (Scheme 1.8). Notably, the stereochemistry yielded by this reduction at C(14) gave the alcohol epimer analogous to that of allocyathin B_2.[21] Takeda and coworkers thereafter concluded their efforts with oxidation of the enol silane present in **54** and subsequent

cleavage of the C-bound trimethylsilyl group. This furnished **55** as the final product of the synthetic sequence.

Scheme 1.8 Advancement of Takeda's cyathane core structure



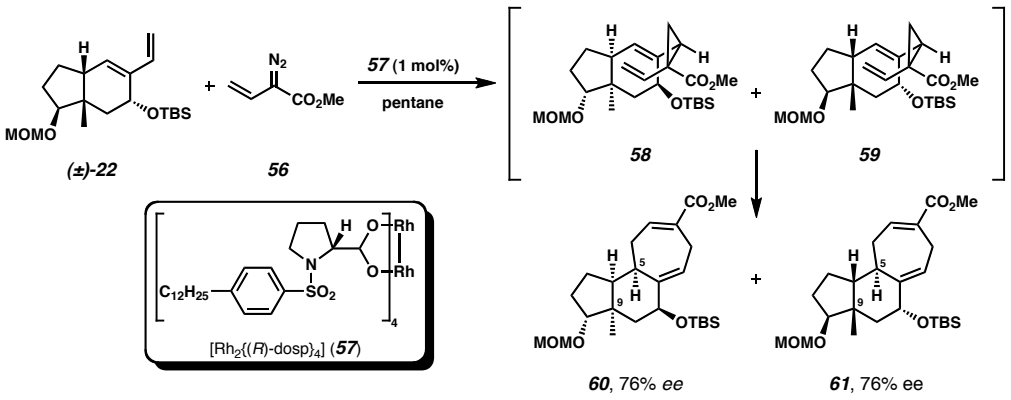
53 ***54*** ***55***

Beginning from known enone **49**, the des-methyl cyathane core was established in three steps and 19% yield, while the more elaborated cyathane analog **55** was produced in 11% yield over five steps.

1.3.2.4 SARPONG'S CYATHANE CORE SYNTHESIS

Sarpong *et al*. have described a unique parallel kinetic resolution method to target the cyathane core tricycle.[22] Bicyclic diene **22**, 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 **22** to vinyldiazoacetate **56** in the presence of Davies' chiral dirhodium tetraprolinate complex **57** proceeded with good catalyst control and facial selectivity (Scheme 1.9).

Scheme 1.9 Sarpong's parallel kinetic resolution method for divergent cyathane tricycle construction



The immediate products of the cyclopropanation were presumably the diastereomeric divinylcyclopropanes **58** and **59**, structures that quickly undergo rearrangement to produce completed cyathane tricycles **60** and **61** in enantioenriched form. Notably, the use of a chiral catalyst and a racemic substrate in this parallel kinetic resolution afforded divergent products that were both well suited toward elaboration into cyathane diterpeniods. Tricycle **60** 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 **61** possesses an *anti* relationship between these same groups, an arrangement that can be found in the cyanthiwigin natural products. By leveraging the exceptional catalyst selectivity of **57**, this parallel kinetic resolution allowed efficient, enantioselective access to two variants of the cyathane core structure from a single racemic starting material.

1.3.3 CYATHANE TOTAL SYNTHESES

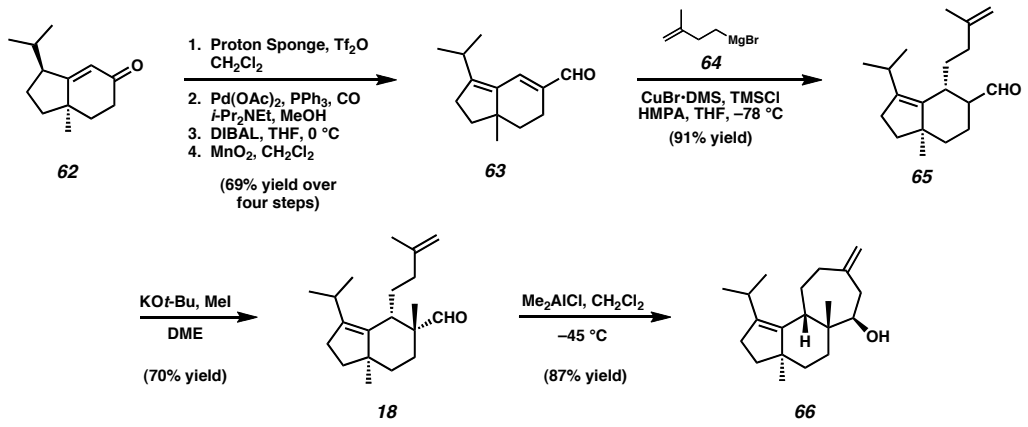
The following section represents a comprehensive overview of all cyathane diterpenoid total syntheses published to date.

1.3.3.1 SNIDER'S (±)-ALLOCYATHIN B_2 AND (–)-ERINACINE A SYNTHESES

The first total synthesis of any cyathane diterpenoid natural product was the preparation of allocyathin B_2 by Snider in 1996.[23] 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 E via glycoslyation.

Beginning with known racemic enone **62** triflate formation, palladium-catalyzed carbonylation, and oxidation state manipulation allowed access to enal **63** (Scheme 1.10).[24] Conjugate addition of a cuprate species generated from Grignard reagent **64** to the β-position of extended unsaturated system **63** provided aldehyde **65**, 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 **66** in excellent yield, thus completing the final ring of the tricyclic natural product.[25]

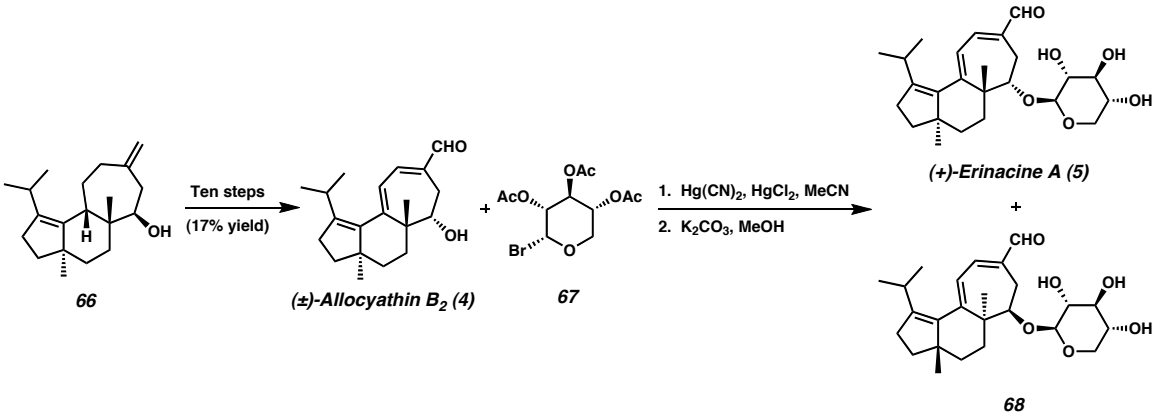
Scheme 1.10 Snider's carbonyl-ene strategy toward the cyathane tricycle



The synthesis was finalized over ten additional transformations, which involved protecting group manipulation, oxidation state modification, and palladium-catalyzed carbonylation starting from tricycle **66** (Scheme 1.11). The completed natural product (±)-allocyathin B_2 (**4**) was thus attained from precursor **62** 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 these more complicated compounds. As such, glycosylation of allocyathin B_2 with 2,3,4-tri-*O*-acetyl-α-D-xylopyranosyl bromide (**67**) and successive global deprotection generated the natural product (–)-erinacine A (**5**) and isomeric structure **68** as a 1:1 mixture of diastereomers.

Following Snider's route, erinacine A was prepared in 19 steps and 1.0% yield. The cyathane core framework was constructed in seven steps and 38% overall yield.

Scheme 1.11 Completion of (+)-allocyathin B_2 and glycosylation to achieve (–)-erinacine A

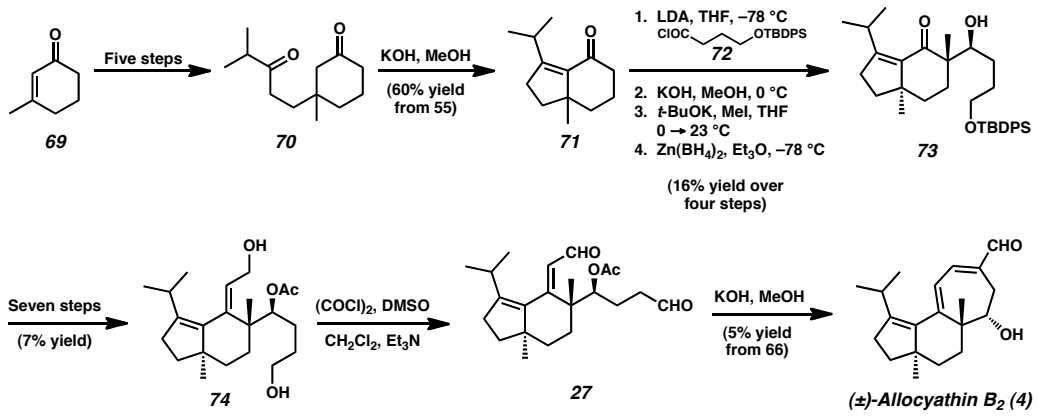


1.3.3.2 TORI'S (±)-ALLOCYATHIN B_2 SYNTHESIS

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.[26]

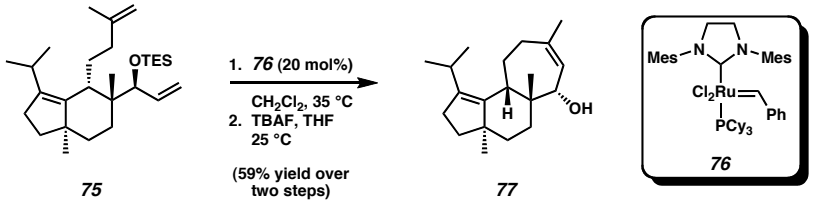
Starting from 3-methyl cyclohexenone (**69**), conjugate addition, ozonloysis, and oxidation yielded diketone **70** after five steps (Scheme 1.12). Intramolecular aldol condensation of cyclohexanone **70** afforded bicyclic enone **71**, a structure containing the completed five-membered A-ring of allocyathin B_2, complete with the requisite isopropyl group. Subsequent acylation of **71** with acid chloride **72** was followed by methylation and a highly optimized diastereoselective reduction employing $Zn(BH_4)_2$ to afford keto-alcohol **73**.[27] Additional transformations over seven steps provided access to allylic alcohol **74**, which was readily oxidized under Swern conditions to give bis-aldehyde **27**. Upon exposure of **27** to methanolic KOH, a final intramolecular aldol condensation was executed to complete the cyathane C-ring and produce allyocyathin B_2 (**4**). Overall, both allocyathin B_2 and the cyathane core structure were synthesized in 19 steps and 0.5% yield, starting from **68**.

Scheme 1.12 Tori's strategy toward allocyathin B_2



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.[28] Modification of their previous synthetic route allowed access to bicyclic intermediate **75** (Scheme 1.13). Upon treatment of this material with 20 mol% of Grubbs second-generation metathesis catalyst (**76**), completed cyathane tricycle **77** was obtained as the sole product of reaction.

Scheme 1.13 Tori's ring-closing strategy toward construction of the seven-membered C-ring and completion of the cyathane core

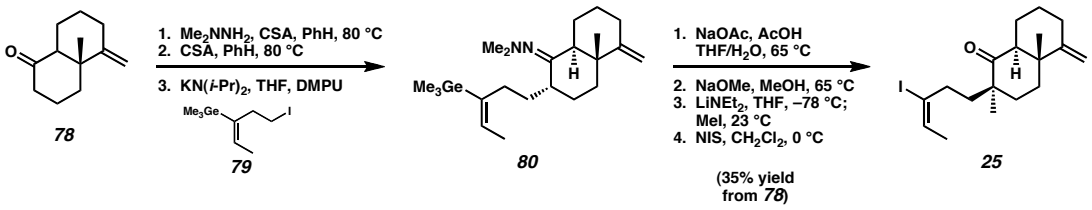


1.3.3.3 PIERS' (±)-SARCODONIN G SYNTHESIS

The first total synthesis of sarcodonin G was described by Piers *et al*. in 2000.[29] Their approach to this cyathane diterpenoid targeted the tricyclic core with an alkylation

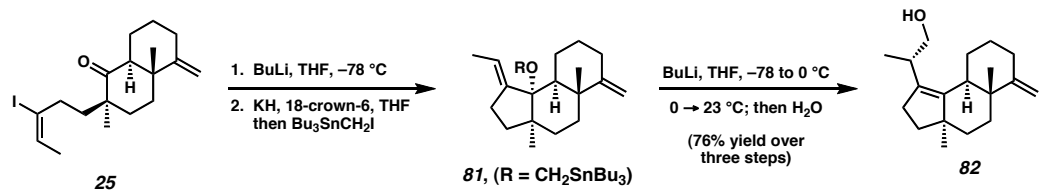
and ring-expansion strategy, and employed late-stage installation of the peripheral functionality. Piers' synthesis began from known ketone **78** (introduced as a mixture of diastereomers),[30] which was subjected to hydrazone formation, epimerization at the ring fusion, and nucleophilic attack on alkyl iodide **79** to afford vinyl germane **80** (Scheme 1.14). Further transformation of germane **80** eventually produced the vinyl iodide species **25**.

Scheme 1.14 Vinyl iodide construction in Pier's sarcodonin synthesis



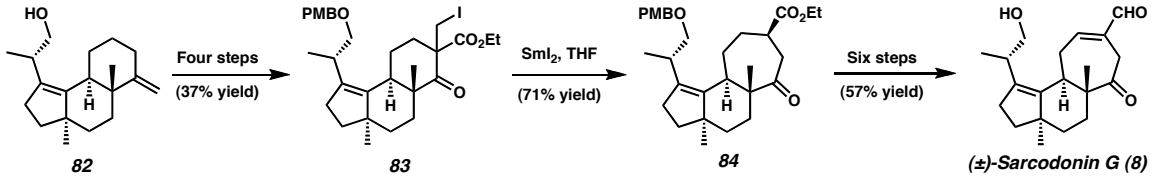
Upon treatment of **25** with *n*-BuLi, lithium-halogen exchange and intramolecular trapping of the ketone moiety constructed the five-membered A-ring of the natural product (Scheme 1.15). After deprotonation with KH and addition of Bu_3SnCH_2I, ether **81** was isolated as the major product. From this ether intermediate, a Still–Mitra [2,3]-sigmatropic rearrangement provided tricycle **82**, which contains the primary hydroxyl group at C(19) required for sarcodonin G.[31]

Scheme 1.15 Still-Mitra [2,3] sigmatropic regarrangement to construct the A-ring of sarcodonin G



Additional synthetic transformation of **82** over four steps yielded β-ketoester **83**, which bears an α-alkyl iodide group well suited to engage in ring-expansion methodology developed by Hasegawa (Scheme 1.16).[32] Upon exposure to SmI_2 in THF, alkyl iodide **83** was converted in 71% yield to the one-carbon ring expanded product **84**. This process smoothly formed the seven-membered C-ring, and thus completed the tricyclic cyathane core. The total synthesis was thereafter concluded in six steps to yield sarcadonin G (**8**).

Scheme 1.16 Ring expansion and endgame for sarcodonin G



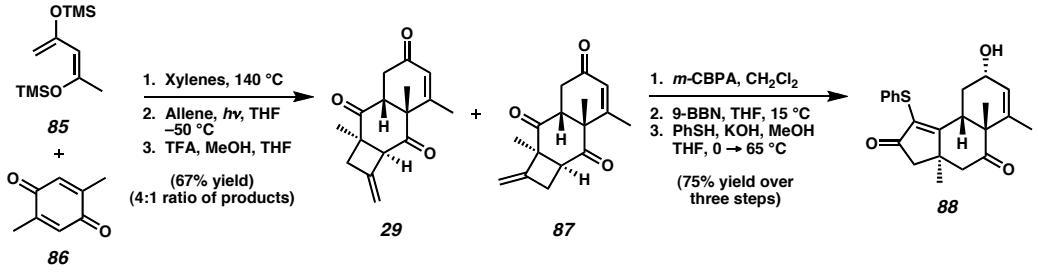
Overall the synthesis of sarcodonin G (**8**) was accomplished in a total of 21 steps and 4.0% yield. The cyathane tricyclic core was attained in 15 steps and 7.0% overall yield.

1.3.3.4 WARD'S (±)-ALLOCYATHIN B_3 SYNTHESIS

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.[33] The synthesis was initiated with a Diels–Alder cycloaddition between 2,5-dimethyl-*p*-benzoquinone (**86**) and 2,4-bis(trimethylsilyloxy)-1,3-pentadiene (**85**, Scheme 1.17). Subsequent [2 + 2] cycloaddition with allene and exposure to acidic conditions

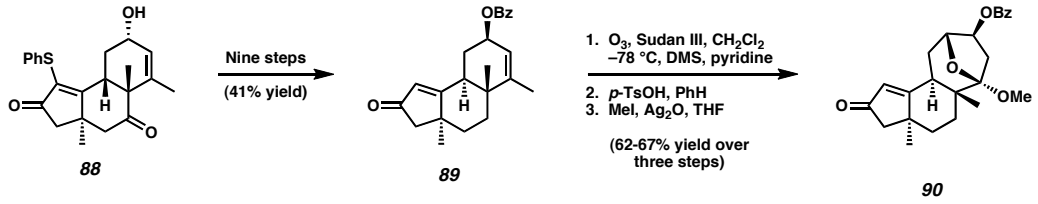
thereafter afforded a 4-6-6 tricyclic system as a 4:1 mixture of structural isomers (**29** to **87**), wherein each was produced as a single diastereomer.[33a]

Scheme 1.17 Ward's cycloaddition stragety toward tricyclic formation



Though only isomer **29** was desired, the 4:1 mixture of **29** and **87** 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 **88** in excellent yield, in a sequence that required only a single purification.[33b]

Scheme 1.18 Ring expansion via ozonolysis and aldol reaction to target the cyathane core

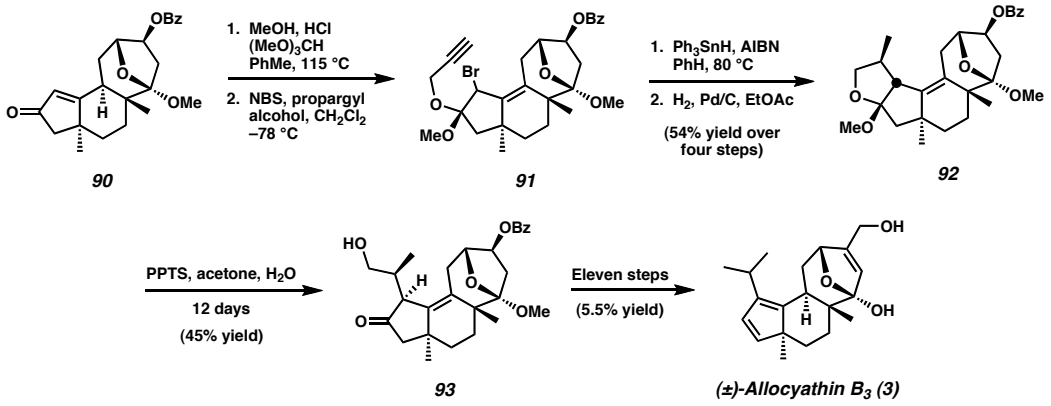


Desulfurization, deoxygenation, protection, and epimerization of **88** over nine steps then allow access to 5-6-6 allylic benzoyl ester **89** (Scheme 1.18). The six-membered ring olefin of this intermediate provided a reactive handle with which to construct the seven-membered C-ring of the natural product. Ozonolysis of enone **89** in the presence of Sudan III indicator generated a sensitive keto-aldehyde intermediate that was subjected

to aldol reaction, transacylation, and successive trapping via *O*-methylation to afford 5-6-7 tricycle **90**. 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 **90** was then transformed into propargyl ether **91** (Scheme 1.19). Treatment of alkyl bromide **91** with AIBN in the presence of Ph_3SnH was followed by subsequent hydrogenation to produce cyclized tetrahydrofuran **92**. After extended exposure to mild acid, tetracycle **92** was opened to tricycle **93**, a structure which contains all of the carbon atoms required for completion of the cyathane A-ring. From this point, the total synthesis was completed in 11 steps to yield allocyathin B_3 (**3**).

Scheme 1.19 Ward's allocyathin endgame strategy

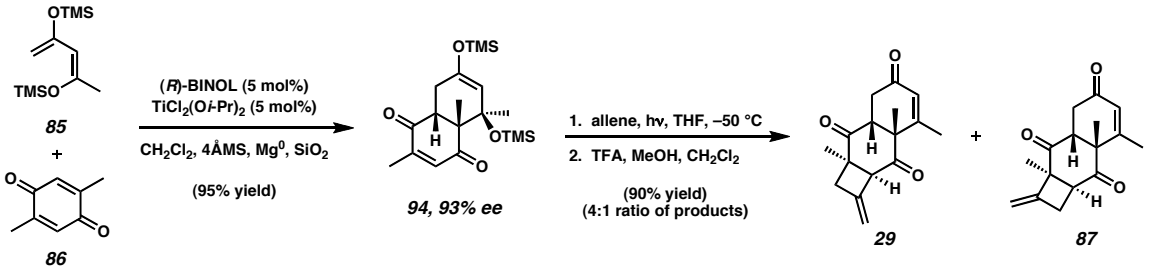


Overall, Ward's strategy toward allocyathin B_3 comprises 34 steps and is concluded in 0.1% yield. The tricyclic cyathane core was attained in 18 steps and 11% overall yield.

1.3.3.5 WARD'S (+)-CYATHIN A_3 SYNTHESIS

A variant of Ward's allocyathin A_3 strategy was later rendered enantioselective to achieve the total synthesis of the related diterpene natural product cyathin A_3.[33,34]

*Scheme 1.20 Catalytic enantioselective Diels–Alder approach to intermediates **29** and **87***

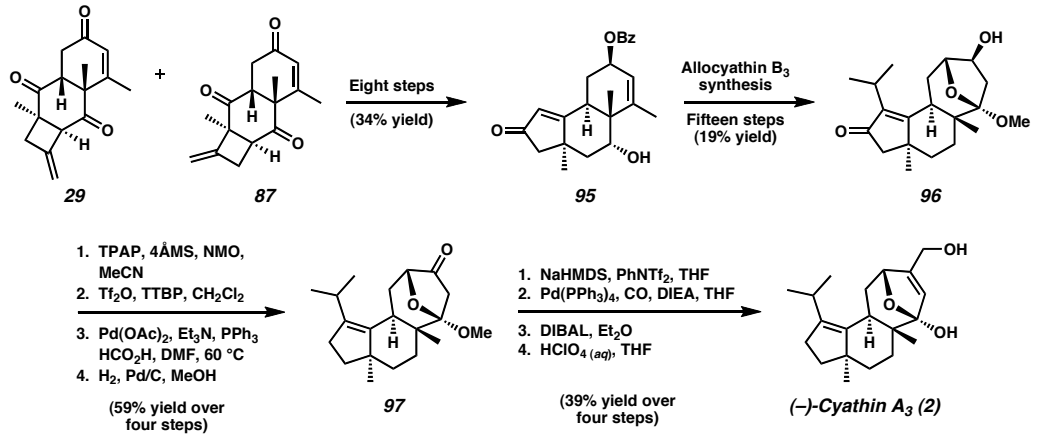


The initial Diels–Alder reaction between 2,5-dimethyl-*p*-benzoquinone (**86**) and 2,4-bis(trimethylsilyloxy)-1,3-pentadiene (**85**) was made asymmetric by employing Mikami's titanium-based BINOL catalyst (Scheme 1.20).[35] After extensive optimization of this cycloaddition, Ward and coworkers found that addition of Mg powder and silica gel afforded cycloadduct **94** in 95% yield and 93% ee. With **94** in hand, [2 + 2] cycloaddition and acidic hydrolysis proceeded as in the case of Ward's allocyathin B_3 synthesis to furnish **29** and **87** as a 4:1 mixture of structural isomers.

From the isomeric mixture of **29** and **87**, eight additional steps were taken to access enone **95** (Scheme 1.21). This then allowed Ward to follow his previously published procedure reported route. Advancement of tricycle **96** along 15 steps (including ozonolysis and aldol reaction for ring expansion) afforded the completed cyathane core in the form of acetal **96**. From this enone, oxidation, triflate formation, reductive deoxygenation, and hydrogenation produced tricycle **97** 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.

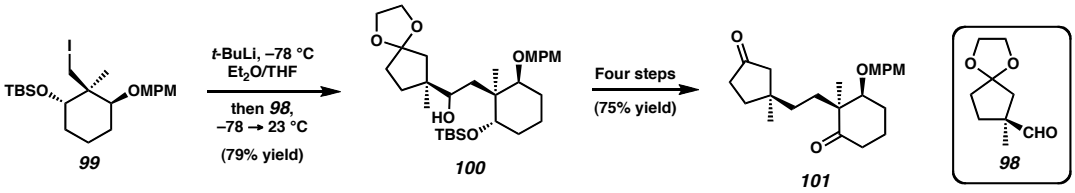
Scheme 1.21 Endgame synthesis for cyathin A_3 (TTBP = 2,6-di(tert-butyl)-4-methylpyridine)



1.3.3.6 NAKADA'S (+)-ALLOCYATHIN B_2 SYNTHESIS

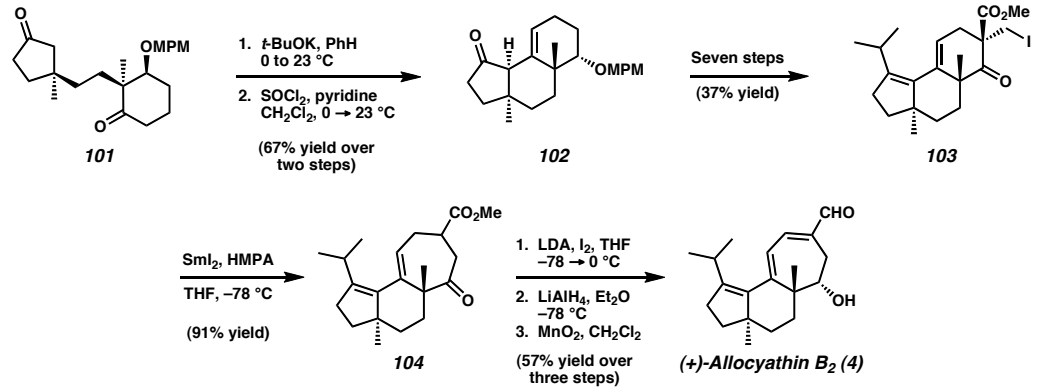
The first enantioselective total synthesis of allocyathin B_2 was described by the laboratories of Nakada in a report published in 2004.[36] In order to target this cyathane diterpenoid molecule, Nakada envisioned a convergent strategy starting with aldehyde **98** and alkyl iodide **99** (Scheme 1.22). Both fragment **98** and fragment **99** were prepared in enantioenriched form based on previously reported work.[37,38] After lithium-halogen exchange was performed on iodide **98**, the resulting alkyl lithium was added to a solution of aldehyde **99** to provide access to alcohol **100**. Deoxygenation, deprotection, and oxidation of this structure afforded diketone **101**.

Scheme 1.22 Fragment coupling to prepare the tethered aldol precursor



The tethered diketone **101** was subsequently cyclized via intramolecular aldol reaction upon treatment with potassium *tert*-butoxide (Scheme 1.23). 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 **102** was isolated as the major product of the reaction sequence. In seven additional steps ketone **102** was transformed into alkyl iodide **103**, an intermediate designed to undergo the samarium-mediated one-carbon ring expansion developed by Hasegawa and employed by Piers for the synthesis of Sarcodonin G (Scheme 1.16, Section 1.3.3.3).[32] When **103** 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 **104**.

Scheme 1.23 Intramolecular aldol reaction and ring expansion to complete the total synthesis of allocyathin B_2

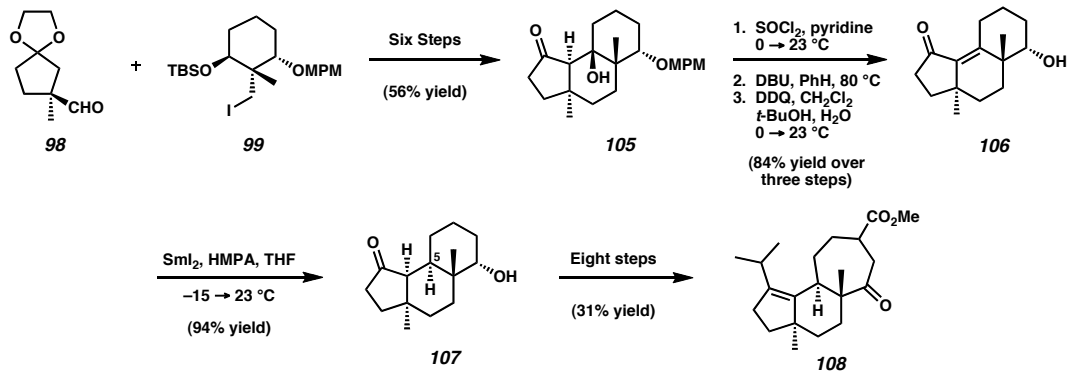


The route toward allocyathin B_2 was thereafter concluded with three additional oxidation state manipulations, affording natural product **4** in a total of 18 synthetic operations and 7.6% overall yield. The tricyclic cyathane core was attained in 15 steps and 13.4% overall yield. Notably, this synthetic approach has been adapted toward a number of other cyathane natural products.[39]

1.3.3.7 NAKADA'S (–)-ERINACINE B SYNTHESIS

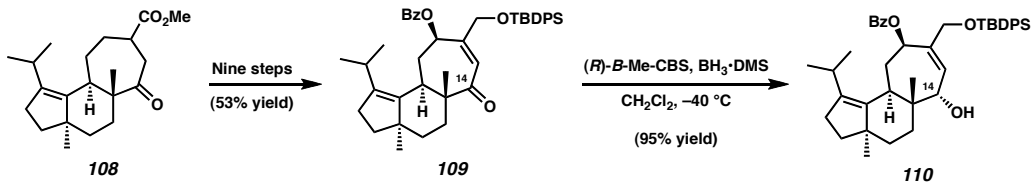
In 2007 Nakada and coworkers extended their synthetic route targeting allocyathin B_2 toward the preparation of erinacine B.[40] Following their previous synthetic efforts enantioenriched alkyl iodide **99** was coupled to aldehyde **98** to furnish, after elaboration, hydroxy ketone **105** (Scheme 1.24).[38] After dehydration and deprotection to generate intermediate enone **106**, 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 diol products instead of the desired hydroxy ketone. Ultimately, this challenge was overcome via diastereoselective olefin reduction using SmI_2 in the presence of HMPA, which provided access to the desired tricycle **107**. These conditions were found to produce a single diastereomer of product, and established 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 **108** was prepared.

Scheme 1.24 Adaptation of Nakada's allocyathin B_2 route to erinacine B



Continued synthesis from ester **108** over nine additional steps allowed access to the protected allylic alcohol **109** (Scheme 1.25). In order to proceed, reduction of the ketone moiety of **109** 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 alcohol epimer at C(14). Because of this difficulty, the ketone of **109** was reduced using the (*R*)-CBS catalyst, which set the desired relative stereochemistry with high selectivity to afford allylic alcohol **110**.

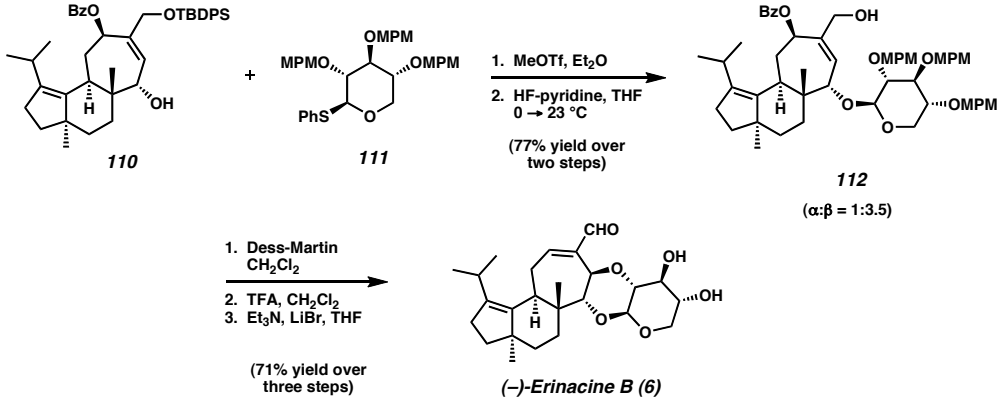
Scheme 1.25 Establishing the desired stereochemistry at C(14)



Tricyclic intermediate **110** was thereafter glycosylated with a previously prepared xylose analog **111** to furnish glycone **112** (Scheme 1.26). 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.

Scheme 1.26 Completion of (–)-erinacine B

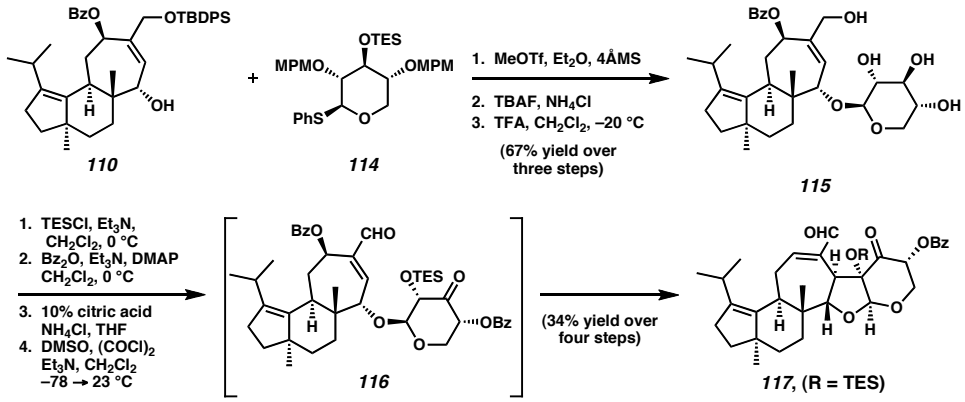


Overall, the synthesis was accomplished in 33 steps and 3.0% yield from **98** and **99**. The cyathane core structure was established in 18 steps and 14% overall yield.

1.3.3.8 NAKADA'S (–)-ERINACINE E

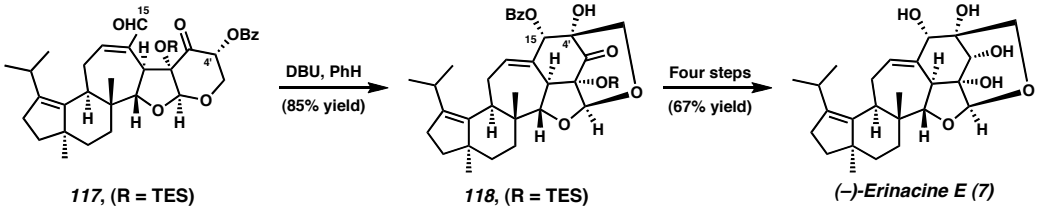
One year subsequent to their report of erinacine B, Nakada and coworkers disclosed a beautiful modification of their synthetic strategy to target (–)-erinacine E, which remains the most complex cyathane diterpenoid molecule isolated to date.[41] Starting from agylcone molecule **110**, glycosylation with thioglycoside **114** and deprotection provided access to intermediate **115** (Scheme 1.27). After additional protecting group manipulation, Swern oxidation generated ketone **116**, an intermediate that spontaneously undergoes conjugate addition-elimination to form pentacyclic structure **117**.

*Scheme 1.27 Synthesis of **117** from allocyathin precursor **110** via conjugate addition-elimination*



Treatment of enal **117** 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 1.28). This aldol reaction is followed by spontaneous benzoate ester migration, thus producing protected erinacine E analog **118** as the final product of the sequence. Further deprotection, oxidation, and diastereoselective carbonyl reduction thereafter completed the total synthesis of (–)-erinacine E (**7**).

Scheme 1.28 Intramolecular aldol reaction for Nakada's endgame of (–)-erinacine E

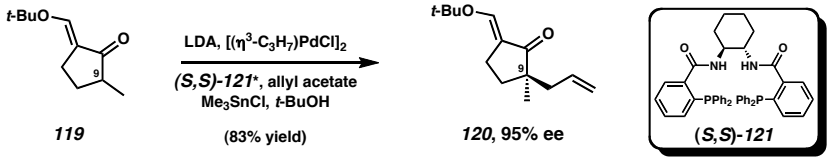


Overall, erinacine E was prepared in 39 steps from iodide **99** and aldehyde **98**, in a total yield of 0.9%.

1.3.3.9 TROST'S (+)-ALLOCYATHIN B_2 SYNTHESIS

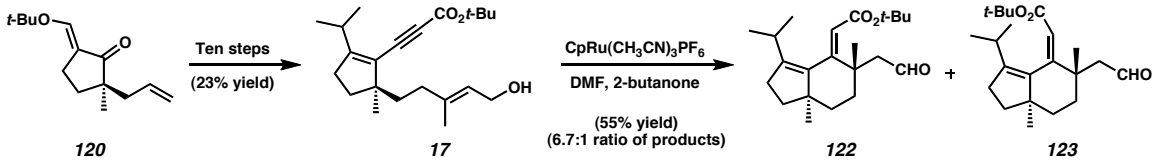
Trost and coworkers have recently reported a unique Ru-catalyzed cycloisomerization strategy for the total synthesis of the cyathane diterpenoid molecule allocyathin B_2.[42] The synthesis was initiated with a Pd-catalyzed aysmmetric allylic alkylation. Racemic ketone **119** was alkylated in the presence of $[(\eta^3\text{-}C_3H_7)PdCl]_2$ and chiral ligand (*S,S*)-**121** to afford enantioenriched α-quaternary cyclopentanone **120** (Scheme 1.29).[43] This high-yielding allylation established an all-carbon quaternary stereocenter in 95% ee. The transformation not only served to 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 1.29 Asymmetric allylic alkylation to establish stereochemistry at C(9)



Further elaboration of the allyl side-chain of **120**, as well as manipulation of the ketone moiety, eventually produced propargyl ester **17** (Scheme 1.30). 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.[44]

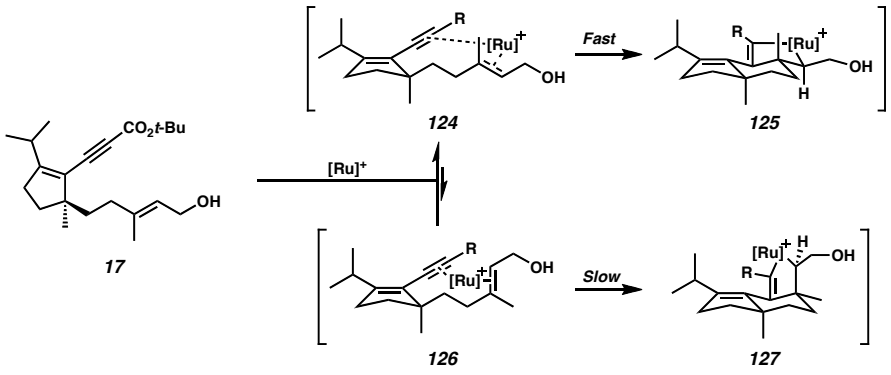
Scheme 1.30 Ru-catalyzed cycloisomerization to establish the central B-ring of allocyathin B_2



120 *17* *122* *123*

Notably, the cycloisomerization reaction proceeds 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 form either a syn-coplanar orientation (**124**) or an orthogonal orientation (**126**, Scheme 1.31). Because the orbital overlap of the syn-coplanar arrangement is likely more conducive to cycloisomerization, ruthenacycle formation from intermediate **124** to give **125** is expected to be much faster than the alternative formation of **127** from **126**.

Scheme 1.31 Diastereoselectivity considerations in the Ru-catalyzed cycloisomerization



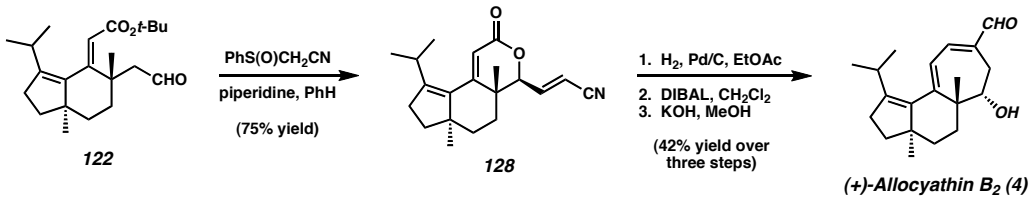
17 *124* *125* *126* *127*

After β-hydride elimination from ruthenacycle **125**, reductive elimination forms **122** and **123** as the major products of reaction. Because only **122** was desired, ultimately the

reaction was optimized by increasing the size of the alkynyl ester to a bulky *tert*-butyl group, thus preferentially forming the Z olefin isomer in a 6.7:1 ratio with isomer **123**.[42b]

From **122**, a hydroxylative Knoevenagel reaction was performed to access lactone **128** as a single diastereomer (Scheme 1.32).[45] The final stages of the synthesis involved hydrogenation and nitrile/lactone reduction, followed by an intramolecular aldol reaction to yield (+)-allocyathin B_2 (**4**). Employing this route, the natural product allocyathin B_2 (and the cyathane core) was synthesized in 16 steps and 5.2% overall yield.

Scheme 1.32 Completion of allocyathin B_2 via hydroxylative Knoevenagel and intramolecular aldol reactions

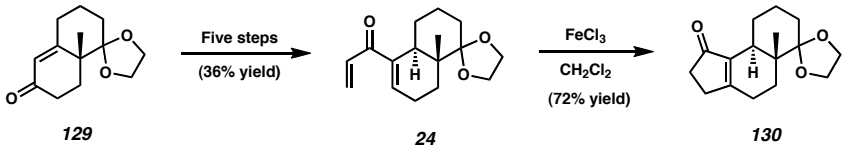


1.3.3.10 DANISHEFSKY'S (–)-SCABRONINE G SYNTHESIS

In 2005, Danishefsky and coworkers reported the first total synthesis of the cyathane diterpenoid scabronine G (**9**).[46] In order to target this bioactive compound, they approached the synthesis with "the pleasingly simple idea that scabronine G [could] 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 **129** (Scheme 1.33). Over five steps, including kinetic enolate trapping and palladium-catalyzed carbonylation, acetal **129** was converted to dieneone **24**. Construction of the five-membered A-ring of scabronine G was then accomplished via

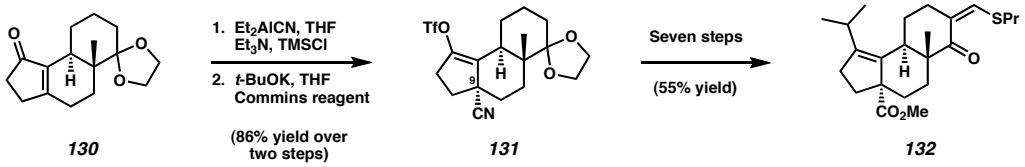
Lewis acid-promoted Nazarov reaction. Upon treatment of dienone **24** with $FeCl_3$, cyclization proceeded smoothly to afford enone **130** in good yield. Notably, this tetracyclic product was obtained as a single tetrasubstituted olefin isomer.

Scheme 1.33 Danishefsky's Nazarov strategy for cyathane A-ring construction



The enone of tricycle **130** was then subsequently leveraged 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 1.34).[47] The intermediate silyl enol ether obtained from this sequence was then converted to a vinyl triflate species to provide nitrile **131**. Further synthetic elaboration over seven steps allowed for the conversion of vinyl triflate **131** to thiopropylmethylidene **132**.

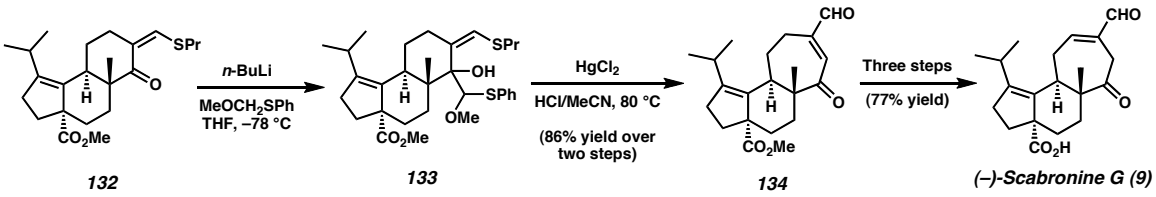
Scheme 1.34 Advancement toward Danishefsky's ring-expansion precursor



In order to access the 5-6-7 tricyclic cyathane core, vinylogous thioester **132** was first treated with the lithium anion of methoxymethyl phenyl sulfide to produce intermediate tertiary alcohol **133** as a combination of diastereomers (Scheme 1.35). Subsequent

exposure of this mixture to $HgCl_2$ effected a one-carbon ring expansion reaction to furnish tricycle **134**, forging the seven-membered C-ring and completing the cyathane framework.[48] With ring-expanded aldehyde **134** 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.

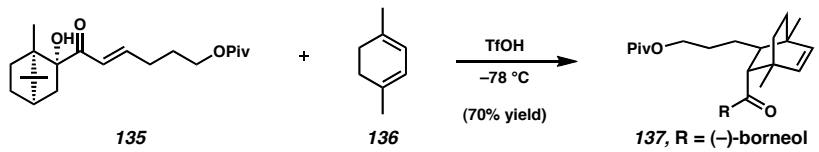
Scheme 1.35 Ring expansion and endgame to complete (–)-scabronine G



1.3.3.11 PHILLIP'S SYNTHESES OF (+)-CYANTHIWIGIN U, (+)-CYANTHIWIGIN W, AND (–)-CYANTHIWIGIN Z

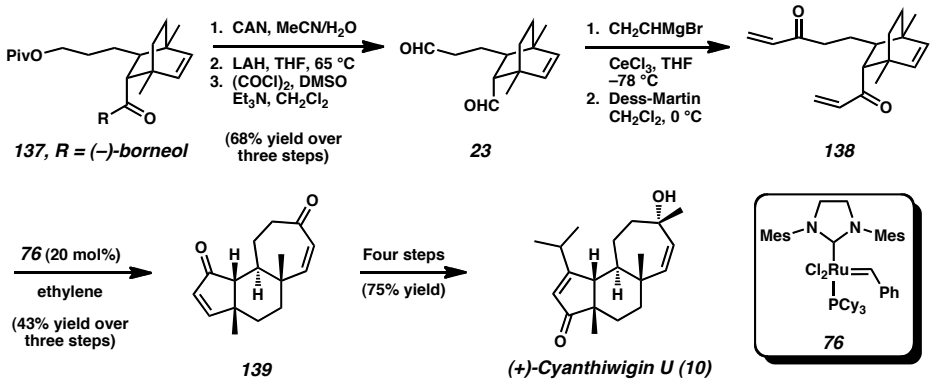
The first report of the total synthesis of any member of the cyanthiwigin subclass of natural products was published by Phillips and coworkers in 2005.[49] Phillips' strategy for targeting cyanthwigin U focused upon construction of the tricyclic cyathane core via simultaneous construction of both the A- and C-rings, with late-stage installation of the peripheral functionality.

Scheme 1.36 Auxiliary-mediated Diels–Alder reaction to establish the quaternary stereocenters of the natural product



The synthesis began with an asymmetric Diels–Alder reaction between 1,4-dimethyl cyclohexadiene (**136**) and (–)-borneol-appended enone **135** (Scheme 1.36).[50] This cycloaddition reaction proceeded smoothly to give a single diastereomer of **137**, 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 **23** (Scheme 1.37).

Scheme 1.37 Completion of cyanthiwigin U via ring-opening ring-closing metathesis

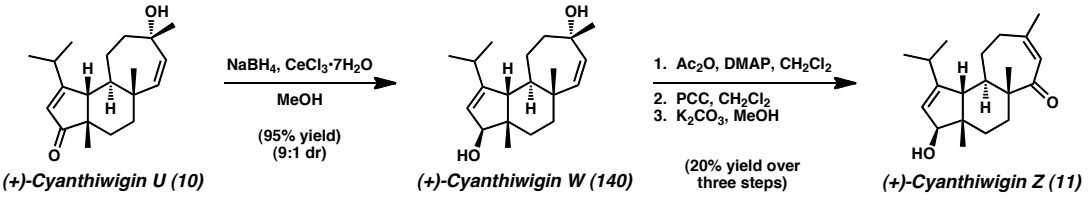


Addition of vinyl Grignard to bis-aldehyde **23** was followed by oxidiation to bis-enone **138**. The bicyclo[2.2.2]octene system of **138** was designed to be well suited to the planned synthetic strategy of "two-directional" tandem ring-opening, ring-closing

metathesis developed by Phillips in prior reports.[51] By treating this bis-enone with 20 mol% of Grubbs' second-generation metathesis catalyst (**76**) under an atmosphere of ethylene, ring-opening metathesis of the strained bridging olefin was rapidly followed by two sequental ring-closing events. This reaction established both the five- and seven-membered rings of the cyathane core, providing tricycle **139** as the ultimate product of the cascade. From this point, the synthesis of (+)-cyanthwigin U (**10**) was completed in four steps involving oxidation state manipulation, as well as addition of the isopropyl and methyl groups. Phillip's route produced the cyathane core in eight synthetic operations and 19% yield, and in total, while the synthesis in total involved only 12 steps 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.[52] Treatment of cyanthiwigin U (**10**) under Luche reduction conditions afforded the natural product cyanthwigin W in 9:1 dr (**140**, Scheme 1.38). 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 (**11**).

Scheme 1.38 Preparation of cyanthiwigin W and cyanthiwigin Z from cyanthiwigin U

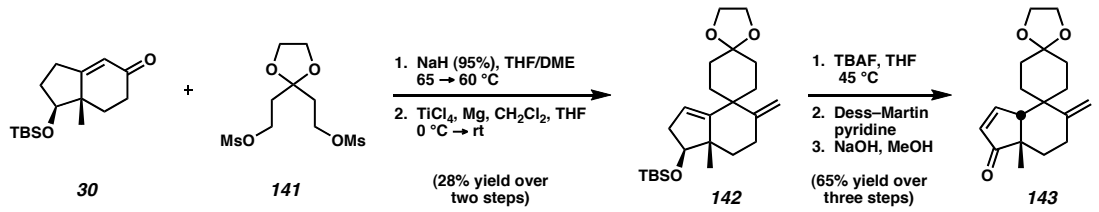


1.3.3.12 REDDY'S (+)-CYANTHIWIGIN AC SYNTHESIS

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.[53]

Starting from the (+)-Hajos–Parrish ketone derivative **30**, double alkylation with bis-mesylate **141** was effective to install the spiro-annulation of the natural product (Scheme 1.39). After methylenation of the resulting compound, spirocyclic intermediate **142** was isolated as the major product of this two step sequence. Deprotection, oxidation, and isomerization then furnished enone **143** in preparation for installation of the isopropyl sidechain to the five-membered A-ring.

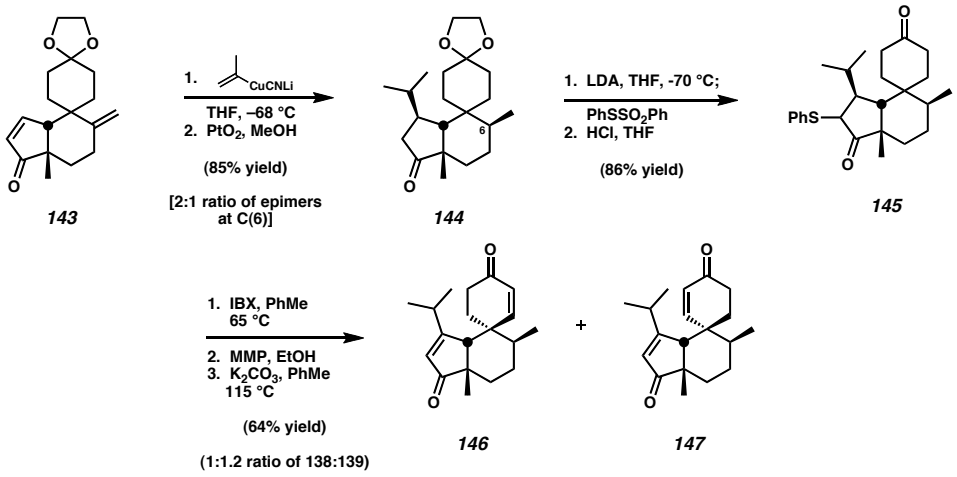
*Scheme 1.39 Spiro-annulation of Hajos–Parrish ketone derivative **30***



Conjugate addition of isopropenyl cyanocuprate to tetracycle **143** was followed by diastereoselective reduction of the exocyclic methylene to set the tertiary methyl stereocenter of the natural product (Scheme 1.40). This process yielded ketone **144** as a 2:1 mixture of epimers at C(6). Further elaboration of this material provided access to thioether **145**, which upon exposure to IBX in toluene underwent oxidation to generate a

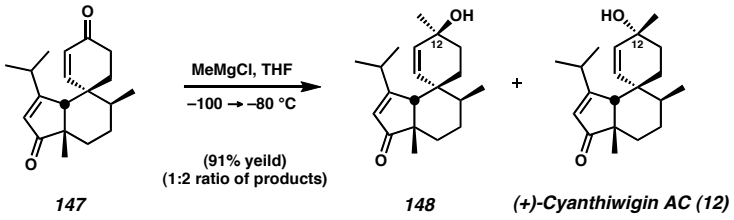
mixture of six-membered ring enones.[54] After sulfoxide formation and dehydrosulfenylation of this intermediate mixture, enones **146** and **147** were obtained in a 1:1.2 ratio of isomers.

Scheme 1.40 Further oxidation and transformation toward cyanthiwigin AC



From this point, the addition of methyl lithium to dienone **147** produced the natural product as a 1:2 mixture of epimers at C(12), favoring the generation of (+)-cyanthiwigin AC (**12**, Scheme 1.41) over isomer **148**. The total synthesis of the natural product was concluded in 13 steps and 2.0% overall yield.

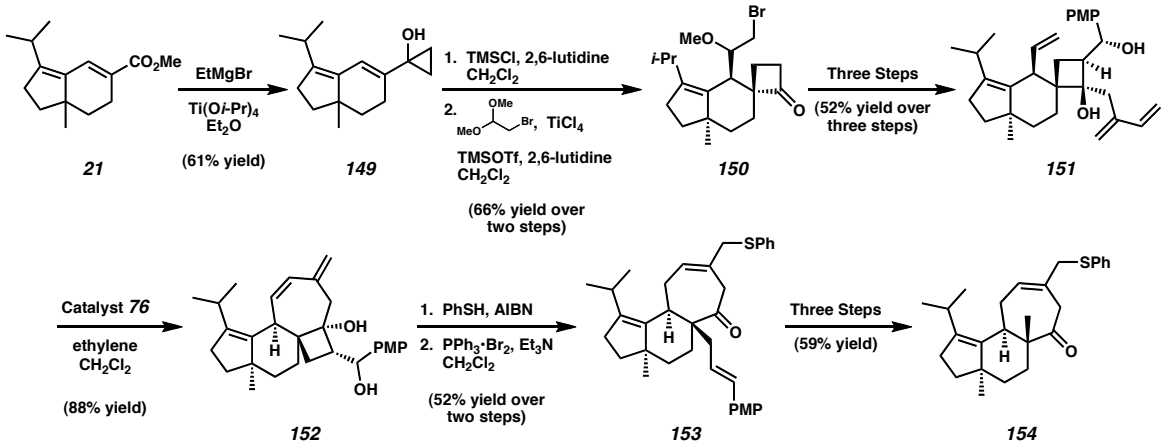
Scheme 1.41 Endgame of cyanthiwigin AC



1.3.3.13 CHA'S SYNTHESIS OF (±)-CYATHIN A_3 AND (±)-CYATHIN B_2

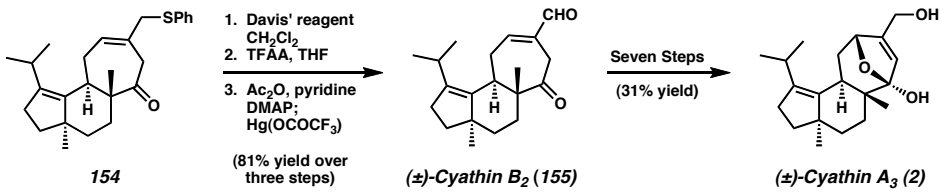
In 2009, the laboratories of Cha disclosed the total syntheses of both cyathin A_3 and cyathin B_2.[55] Starting from racemic conjugated ester **21**, Kulinkovich cyclopropanation afforded access to tricyclic structure **149** (Scheme 1.42). After protection of this tertiary alcohol, treatment with bromoacetaldehyde dimethyl acetal in the presence of titantium(IV) chloride furnished spirocycle **150** as a 1:1 mixture of diastereomers with regard to the methoxy group stereochemistry. Notably, this ring expansion served to set the quaternary sterocenter of the spirocyclic ring fusion, establishing the necessary C(6) stereochemistry required for completion of the natural product. Cyclobutanone **150** was further advanced through three chemical transformations, including aldol addition of a cyclobutene enolate to anisaldehyde, addition to the cyclobutanone carbonyl, and elimination to yield elaborated tricyclic compound **151**. Thereafter, ring-closing metathesis of tetraolefin **151** with Grubbs' catalyst **76** installed the seven-membered C-ring, thus generating the completed cyathane core in the form of tetracyclic diol **152**. Addition of thiophenol to the diene moiety of **152** was then followed by Grob fragmentation of the cyclobutane ring, arriving at tricycle **153**. Excision of the C(6) appended side arm over three steps furnished access to a methyl group at this position, yielding **154** as the final product of the sequence.

Scheme 1.42 Cha's spirocyclic approach to cyathin A_3 and cyathin B_2



Allylic tricyclic ketone **154** was advanced toward the natural product cyathin B_2 via oxidation of the allylic thioether to a sulfoxide moiety (Scheme 1.43). After treatment with trifluoroacetic anhydride and subsequent Pummerer rearrangement, the resulting mixture of isomeric products were exposed to the conditions of acetylation and hydrolysis, yielding the tricyclic natural product cyathin B_2 (**155**) the sole product of reaction. Diterpenoid **155** was further transformed over seven steps to yield cyathin A_3 (**2**). By leveraging this novel ring-expanding technology, Cha and coworkers were able to access the cyathane tricyclic core in seven steps and18% yield. The completed total synthesis of cyathin B_2 was accomplished in 15 steps and 4.7% yield, while cyathin A_3 was afforded over 22 steps and 1.4% overall yield.

Scheme 1.43 Cha's endgame for cyathin B_2 and elaboration to attain cyathin A_3



1.4 CONCLUSIONS

The cyathane diterpenoid natural products have been the focus of numerous total synthetic efforts. Seventeen completed total syntheses of these compounds have been reported, fourteen 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.

1.5 NOTES AND REFERENCES

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