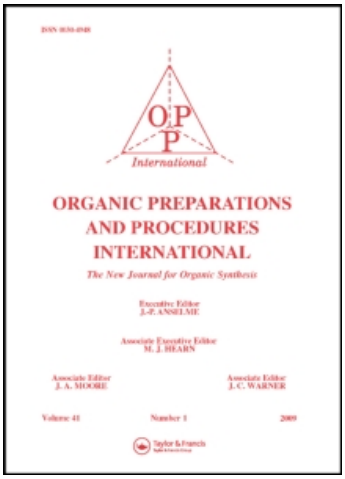

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RECENT PROGRESS ON THE SYNTHESIS OF CYATHANE TYPE DITERPENES. A REVIEW

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INTRODUCTION

The complex molecular structure and exciting biological activity of the cyathane diterpenes has prompted several investigations into their synthesis. Ayer and co-workers isolated the first natural product of this class in 1971 and several additional members of this family were discovered throughout the 1970's.[1-8] The parent cyathins were isolated from the extract of *Cyathus sp.* using bioassay guided fractionation methods based on the antibiotic activity of the extracts. More recently, Kawagishi[9-11] isolated the analogous erinacines from *Hericium erinaceum* and the scabronines[12-14] and sarcodonins[15] were isolated from *Sarcodon scabrosus*. Many of the more recently discovered compounds were shown to be potent stimulators of nerve growth factor (NGF) *in vitro*.[9-14] In this report, we will briefly review the isolation and biological activity of these diterpenes and then focus primarily on the different strategies directed toward the synthesis of these complex natural products.

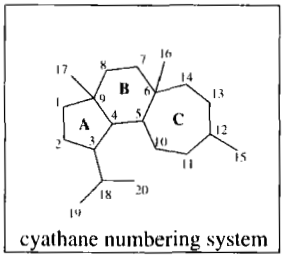
I. ISOLATION, CHARACTERIZATION AND BIOLOGY OF THE CYATHANES

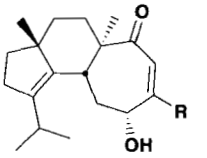
The cyathins were first reported, without full characterization, owing to the antibiotic activity of the crude extracts from the fungus *Cyathus helenae*. The principal components of the extract were determined to be diterpenoid in nature and a trivial nomenclature system was suggested based primarily on the degree of unsaturation present in the compound.[1] Isolated C20 compounds with 30 hydrogen atoms were classified as cyathin A derivatives, 28 hydrogens as cyathin B derivatives and those with 26 hydrogens as members of the cyathin C class. An additional descriptor was added in the form of a subscript after the letter that refers to the number of oxygen atoms present in the molecule. As an example, cyathin A_3 (**1**) contains 30 hydrogen and 3 oxygen atoms. When a structural isomer of a known cyathin was discovered it was given the *allo* prefix as in allocyathin B_3 (**2**), which shares the same empirical formula as cyathin B_3 (**3**). This nomenclature system was somewhat limited and as additional members of this diterpenoid family were discovered, new classifications such as cyafrin, erinacine and scabronine were coined.

1. Isolation and Characterization of the Cyathins

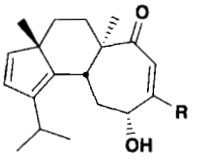
Cyathin A_3(**1**) and allocyathin B_3(**2**) were the first of these natural products to yield to structural determination.[2] The diterpenoids were determined to possess a twenty carbon skeleton composed of a 5-6-7 fused tricyclic core which was assigned the numbering scheme depicted in figure 1. Two carbons are present as angular methyl groups at C9 and C6 located at the AB and CB ring junctions respectively. A pendant carbon is present at C12 (many times in the form of an alcohol or aldehyde)

and the final three carbons take the form of an isopropyl substituent located at C3. An x-ray crystallographic study was ultimately used to determine both the relative and absolute stereochemical assignments.[3-4] Determination of structures of cyathin B_3(**3**) and cyathin C_3(**4**) soon followed through spectroscopic and chemical correlation methods.[3]

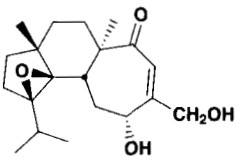




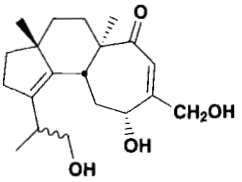
1 cyathin A_3 (R=CH_2OH)
3 cyathin B_3 (R=CHO)



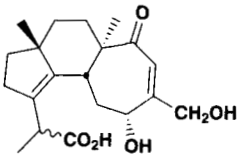
2 allocyathin B_3 (R=CH_2OH)
4 cyathin C_3 (R=CHO)



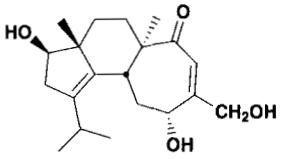
5 neoallocyathin A_4



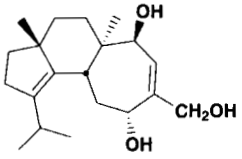
6 cyathin A_4



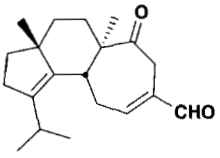
7 cyathin C_5



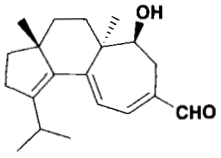
8 cyafrin A_4



9 cyathatriol



10 cyathin B_2



11 allocyathin B_2

Fig 1. Structures of the Cyathin Diterpenes

Further investigations by Ayer and co-workers led to the isolation of other cyathane compounds from a variety of fungal sources.[4-8] Many of these compounds were isolated from either *C. africanus* or *C. earlei* and in some instances both species. The structures that were determined for these components are presented in figure 1, as well as the trivial numbering system that is used for all of the cyathanes. The solution NMR spectra of compounds **1-8** were complicated because they exist as an equilibrium mixture of the hydroxyketone and an internal hemiketal (*Fig. 2*).

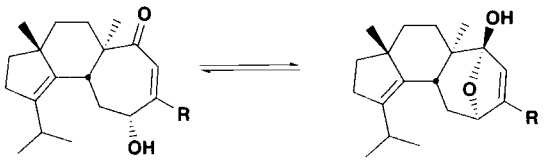
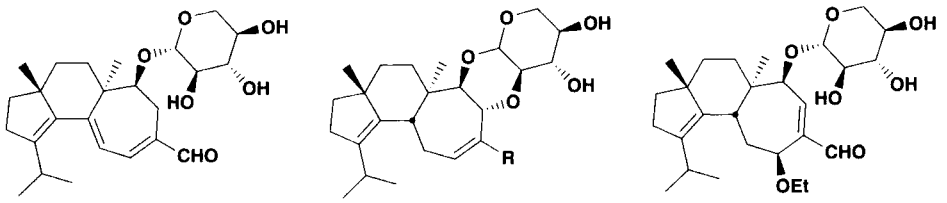


Fig 2. Internal Ketone-Hemiketal Equilibrium in Cyathins

2. Isolation and Characterization of the Erinacines

A related family of glycosylated cyathanes has been recently isolated from the mycelia of the fungus *Hericium erinaceum* and were termed erinacines A-F (**12-17**). These compounds are essentially a D-xylose moiety anchored onto the cyathane framework. In the simplest case, erinacine A (**12**), the compound is the β-D-xyloside of allocyathin B_2(**11**). This family now includes six different isolated structures with extensive modifications of the pendant xylose residue (*Fig. 3*). Erinacine A and F are isomers, but the stereochemistry of erinacine F has not yet been determined.

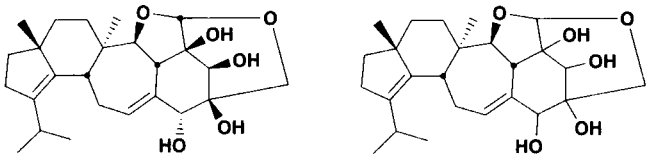
The erinacines were isolated and characterized by Kawagishi and co-workers in Japan. Standard spectroscopic methods as well as chemical correlation determined their structures. The cleavage of the glycosidic linkage in **12** by β-glucosidase provided both **11** and D-xylose, which provided a convenient structure proof for **12**.[9] The absolute stereochemistry of **13** was determined using a comparison of the CD spectra of **12** and **13**, and the stereochemistry of **14** was proven by the conversion of **14** into **13** by DDQ oxidation.



12 erinacine A

13 erinacine B (R=CHO)
14 erinacine C (R=CH_2OH)

15 erinacine D



16 erinacine E

17 erinacine F

Fig 3. Structures of the Erinacines

3. Isolation of the Sarcodonins and Scabronines

Other cyathane congeners were isolated from the extracts of the mushroom *Sarcodon scabrosus*. The first of these were the sarcodonins A-H, discovered by Hirota[15] and co-workers, however, only the structures of sarcodonin A (**18**) and G (**19**) have been established. Ohta and co-

workers[12-14] discovered five other cyathanes termed scabronines A-G (**20-26**). The major difference between these compounds and the cyathins is the oxidation state of C20 in the case of the sarcodonins and C17 in the scabronines.

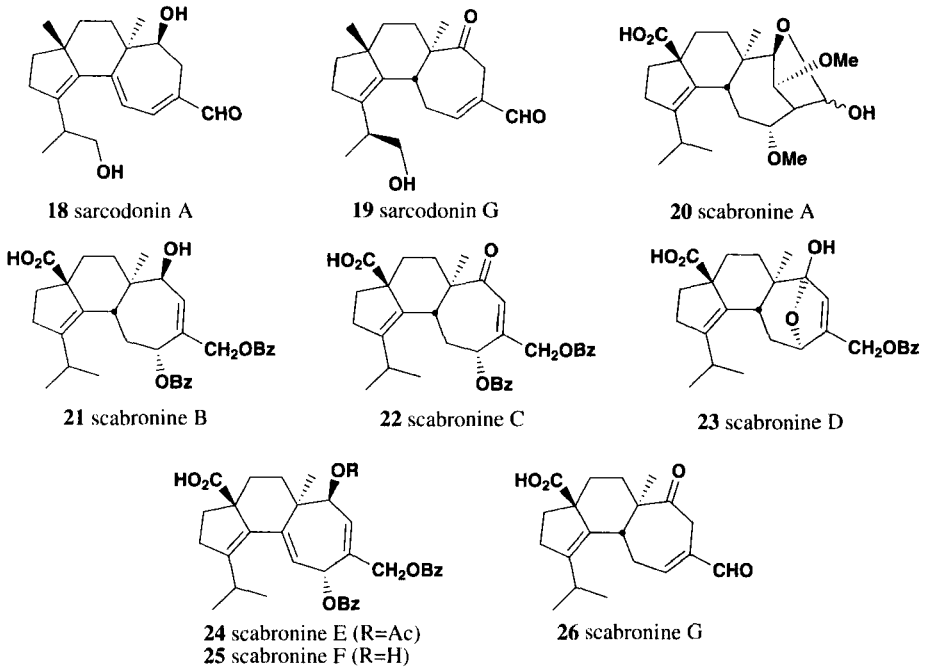
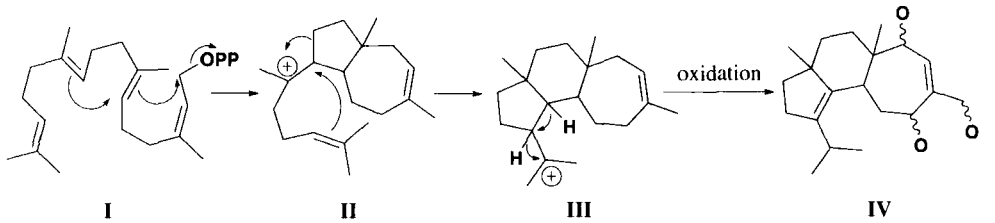


Fig 4. Structures of the Scabronines and Sarcodonins

4. Cyathane Biosynthesis

Ayer and co-workers also investigated the biogenesis of the cyathanes through labeling studies.[16] Since the cyathanes are diterpenes, they should be derived from acetate with geranylgeranyl pyrophosphate serving as the acyclic C20 precursor. Their studies involved feeding ^{13}C-labelled acetate to *C. earlei* and studying the ^{13}C-NMR spectrum of the isolated cyathatriol(**9**). The proposed biogenesis pathway (*Scheme 1*) accounts for the unusual position of the C6 and C9 angular methyl groups, which are disposed in a 1,4-relationship. The postulated transformation from geranylgeranyl pyrophosphate **I** involves an initial cationic closure of the seven membered C-ring and a five



Scheme 1

membered B-ring to give the hydroazulene-like cation **II**. A Wagner-Meerwein migration (**II** → **III**) expands the B-ring to a six membered ring that is followed by a final cationic cyclization with the isopropylidene group to close the five membered A-ring. Final conversion to the natural products takes place through a series of peripheral oxidative transformations.

5. Biological Activity

The initial members of this diterpenoid class were isolated because of significant antibiotic properties.[1] Several of the cyathin compounds exhibited antibiotic activity against Gram positive and Gram negative bacteria as well as actinomycetes. A renewed interest in this class of natural products was initiated by the discovery that members of the erinacine and scabronine class stimulate the biosynthesis of nerve growth factor (NGF) and other neurotrophic agents.[9-14,17,18] The discovery of small peptide hormones termed neurotrophic factors has initiated investigations into a new mode of treatment for neurodegenerative disorders.[19] These factors are key players in the early development of the embryonic central nervous system where developing neurons compete for low concentrations of the growth factors. This results in a selection process that ensures that effective neuronal connections have been established. Although expressed at much lower concentrations in adults, these factors still play an important role in phenotypic maintenance and cell regulation. Despite the exciting biological profile of NGF and encouraging results obtained in cell culture, clinical applications of NGF have primarily failed due to the unfortunate pharmacological profile.[20] The most critical drawback of NGF is the inability to penetrate the blood-brain barrier (BBB).[21] Compounds that are administered systemically have little chance of passing into the CNS unless they can diffuse through the endothelial cells of the BBB. [22] This necessitates a direct delivery into the CNS typically by infusion into the cerebral spinal fluid (CSF).[23] This has many severe drawbacks including inconvenient medical implantation, rapid turnover of the CSF, and high local concentrations of drug. Since NGF is an endogenous compound that is synthesized *in vivo*, it was reasoned that if the regulatory mechanisms controlling its expression could be stimulated, a method of controlling the endogenous production could be found. The search for compounds that could stimulate the basal production of NGF has led to the isolation of over a dozen structurally unique natural products with this function.[24] These small-molecules can serve as an alternative to NGF delivery by enhancing the basal synthesis of NGF and indirectly increasing the concentration of the peptide. These molecules should show much greater stability toward metabolism and their lipophilic nature and small size make them good candidates to penetrate the BBB.[25]

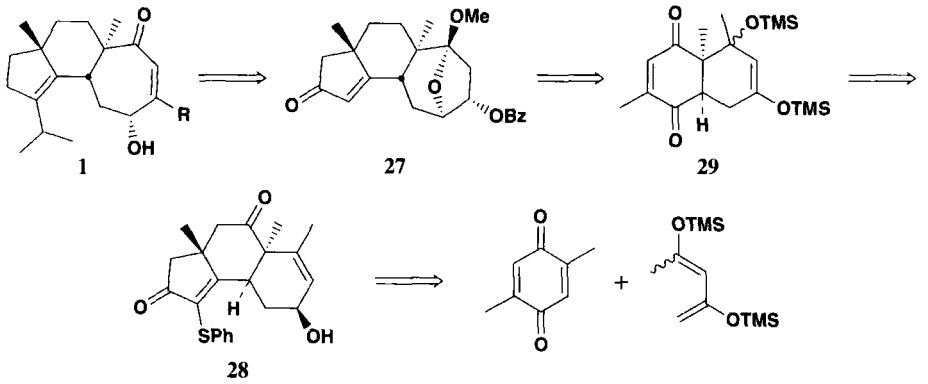
II. APPROACHES TO THE CYATHANE SKELETON

Prior to 1994, only two approaches to the cyathane skeleton had been reported. Owing to the renewed interest in these natural products, this has grown to a total of seven different approaches, including three total syntheses. The most synthetically challenging structural features of the cyathanes are the 5-6-7 tricyclic ring system, the *anti*-1,4 quaternary methyl groups at C6 and C9, the extensive oxygenation on ring-C and the *trans* 6-7 ring fusion. Several novel approaches have been studied for

the synthesis of the cyathin core structure relying on the use of key cyclizations, cycloadditions and rearrangements.

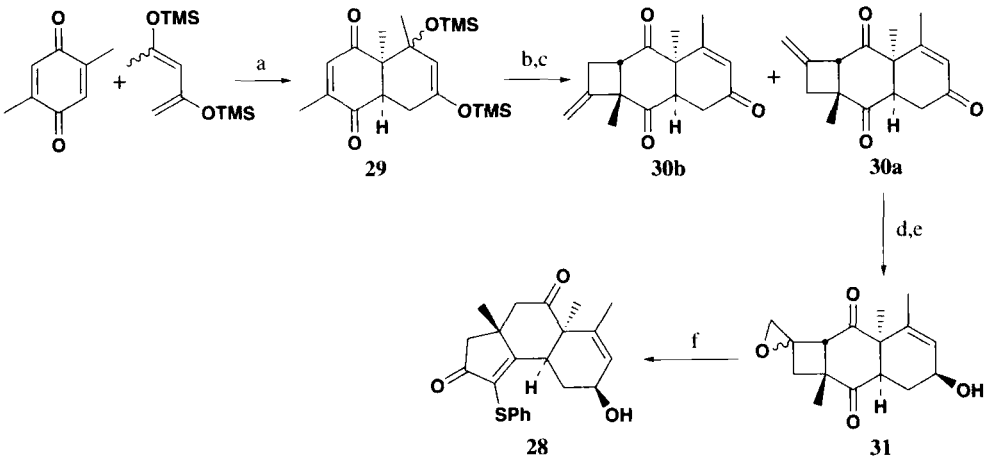
1. Ayer and Ward's Approach

The first synthetic approach was disclosed by Ayer and co-workers,[26] which provided a key 5-6-6 tricyclic compound that was ultimately used as a precursor to the carbon skeleton of the cyathins by Ward.[27] The retrosynthetic strategy employed by Ayer and Ward *(Scheme 2)* relies on two key cycloadditions followed by one-atom ring expansion processes for the formation of ring A (4→5 expansion) and ring C (6→7 expansion). This strategy of targeting smaller ring precursors permits the application of key [2+2] and [4+2] cycloaddition strategies. Ayer elected for an early stereoselective introduction of the 1,4 *anti* quaternary methyl groups. This was readily accomplished by the sequential application of cycloaddition reactions whereby an initial [4+2] cycloaddition would control the stereochemistry of a subsequent [2+2] cycloaddition. The cyclobutane would then be expanded to form the A ring and the cylohexene could be oxidatively opened and then closed *via* aldol reaction to form ring C.



Scheme 2

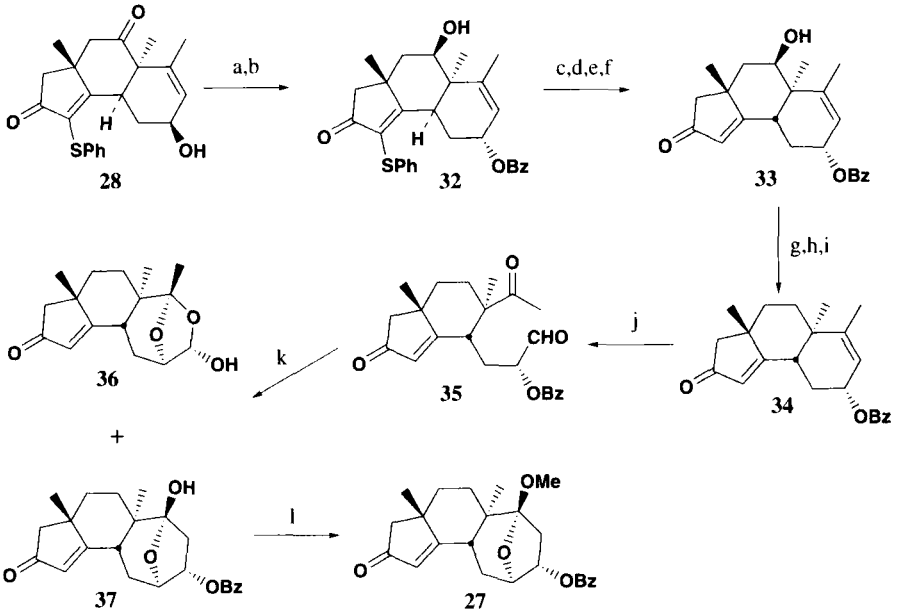
The synthetic approach commenced with a Diels-Alder reaction of a 1,3-disiloxydiene with 2,5 dimethyl bezoquinone that proceeded in boiling xylene to provide **29** with the key C6 angular methyl installed. The cycloadduct was then treated with allene under photochemical conditions to provide a 4:1 mixture of isomeric methylene cyclobutanes and importantly the remaining C9 angular methyl group with the correct relative stereochemistry. Fortunately, the desired isomer (**30a**) was the major isomer formed after hydrolysis of the silyenolether. This was followed by selective epoxidation of the exocyclic methylene and selective 1,2 reduction of the enone to provide epoxide **31**. Attempts to open the cyclobutane epoxide with lithium diisopropylcuprate met in failure, but opening of the epoxide with thiophenol under basic conditions served to cleave open the cyclobutane and form the cyclopentenone **28** in one operation. This reaction proceeds by opening of the epoxide at the least hindered site, followed by a retro-aldol of the resulting β-hydroxy ketone. The 1,4 dione can then undergo an alternative mode of aldol closure to form the A-ring cyclopentenone.



(a) xylene, reflux; (b) allene, hυ; (c) MeOH/THF, Rexyn 101 acidic ion exchange resin; (d) 9-BBN; (e) *m*CPBA; (f) PhSH, 5% aq. KOH.

Scheme 3

Ward extended this work in an attempt to construct the complete cyathin framework (*Scheme 4*). The hydroxyl function at C11 was inverted under Mitsunobo conditions to give **32** with the natural configuration. Attempts to directly epimerize the C5 stereocenter, after selective reduction



(a) $PhCO_3H$, Ph_3P, DEAD; (b) $NaBH_4$, $MeOH/CH_2Cl_2$, -78°C; (c) NaOH, $MeOH/H_2O$; (d) RaNi, MeOH; (e) NaOH, MeOH, reflux; (f) PhCOCl, Et_3N, DMAP, CH_2Cl_2; (g) MsCl, pyridine; (h) DBU, $PhCH_3$, reflux; (i) H_2, $(Ph_3P)_3RhCl$, PhH; (j) O_3, Sudan III, CH_2Cl_2, -78°C; (k) *p*-TsOH, PhH; (l) CH_3I, NaH, THF.

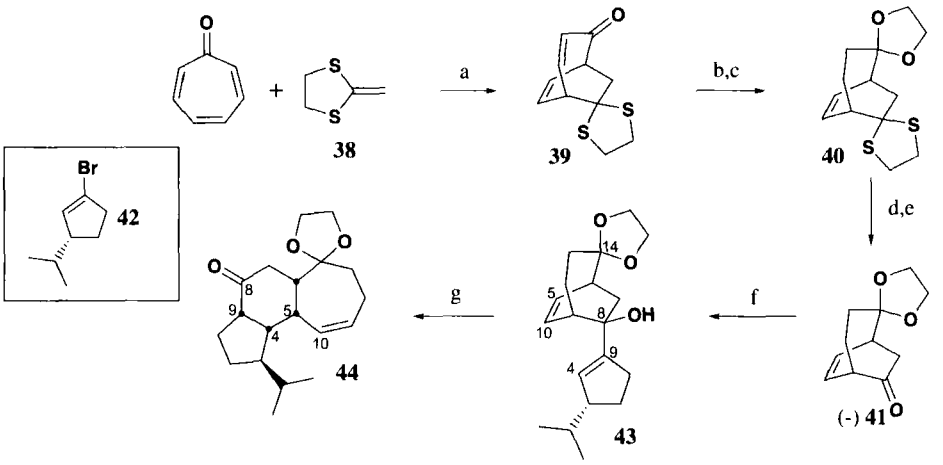
Scheme 4

of the saturated ketone, proved unsuccessful. Attempts to facilitate the desired epimerization by removal of the electron donating phenylthiol group were complicated by the adjacent benzoate ester. Removal of the benzoate allowed the thiol to be successfully reduced with Raney nickel that was followed by near quantitative epimerization to the *trans*-ring fusion. Subsequent reacylation of the alcohol gave the key intermediate **33**. Deoxygenation at C7 was accomplished by mesylation of the alcohol, elimination of the mesylate and regioselective reduction of the resulting olefin to provide **34**. Ozonolysis of the non-conjugated olefin was followed by an acid promoted aldol condensation to give **36** and **37** in a 1:3 ratio. Compound **36** apparently resulted from hydrolysis of the benzoate, followed by formation of the stable internal hemiacetal. The most advanced structure produced in this approach is **27**, isolated after methylation of **37**. Ayer and Ward's approaches provide a compound which has the entire 5-6-7 ring system, the *trans* 6-7 ring fusion and the oxygenation needed, however, the A ring is in need of further elaboration.

2. Paquette's Approach

Paquette and co-workers[28] disclosed an early approach to these ring systems through a key sigmatropic rearrangement process to form the C4-C5 bond. This study succeeded in rapidly assembling a non-racemic 5-6-7 tricyclic system, however, attempts to introduce the *anti* 1,4 methyl groups were unsuccessful. The objective of Paquette's approach was to rapidly provide the enantio-pure ketone **44** and to study various methods of introducing the peripheral carbon and oxygen functionality.

The synthetic sequence to produce ketone **44** (*Scheme 5*) commenced with an inverse electron demand Diels-Alder reaction between tropone and dithioketene acetal **38** to produce the



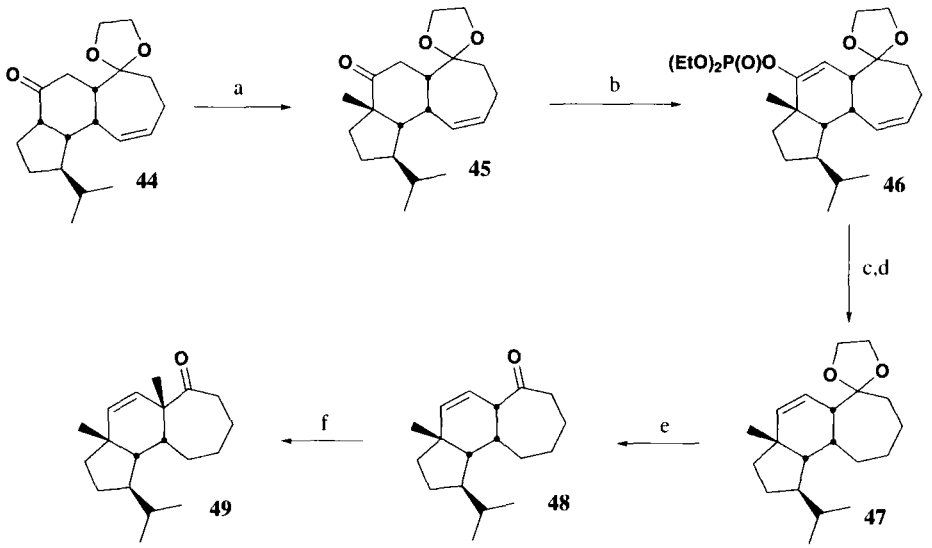
(a) cat. Et_3N, 120°C, 56%; (b) Dibal-H,MeCN,HMPA,THF, 92%; (c) $HO(CH_2)_2OH$, *p*-TsOH, 98%; (d) chloramine-T, acetone, aq. MeOH, 56%; (e) Johnson's sulfoxime resolution, 87%; (f) t-BuLi, **42**, 51%; (g) KH, 18-crown-6, THF, 90°C, 83%.

Scheme 5

bicyclo[3.2.2]nonane system **39**. The enone was subjected to selective 1,4 reduction followed by protection of the ketone as the ethylene glycol ketal **40**. Selective hydrolysis of the thioketal provided the ketone **41**, which was resolved *via* Johnson's sulfoxime technology[29] to provide the levorotatory enantiomer.

The enantiopure organolithium reagent derived from **42**[30] was added to (-)**41** to provide the alcohol **43** as a prelude to a key bond reorganization. An oxyanion accelerated Cope rearrangement occurred upon treatment of the allylic alcohol **43** with potassium hydride/18-crown-6 which closed ring C by formation of the C4-C5 bond while fragmenting the bicyclic system.

With the tricyclic system **44** intact, their next priority was to introduce the key angular methyl groups. The C9 methyl could be installed directly by alkylation of the thermodynamic enolate; the excellent stereocontrol derives from addition to the concave α-face. Unfortunately, the cup-shaped structure resulting from the all *cis* ring fusions precludes direct installation of the α-C6 methyl group by enolate alkylation. Attempted alkylation of ketone **48** delivered the *cis* angular methyl group **49** exclusively.

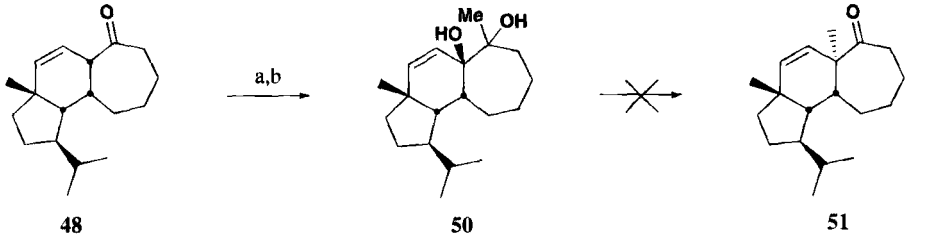


(a) KH, CH_3I, THF, 87%; (b) LHMDS, $ClP(O)(OEt)_2$, THF, 87%; (c) H_2, PtO_2, 90%; (d) Li, $EtNH_2$, EtOH, Et_2O, 95%; (e) HCl, THF, 57%; (f) KH, CH_3I, THF, 59%.

Scheme 6

An indirect method for stereoselective methylation through a pinacol rearrangement was also explored (*Scheme 7*). Oxidation of the enolate derived from **48** with bis trimethylsilyl peroxide occurred on the open face to produce an acyloin. Addition of methyl magnesium bromide to the α hydroxy ketone resulted in a single diastereomer of the diol **50,** although the stereochemistry was not established. It was anticipated that ionization of the tertiary carbinol would lead to the C6 carbonium

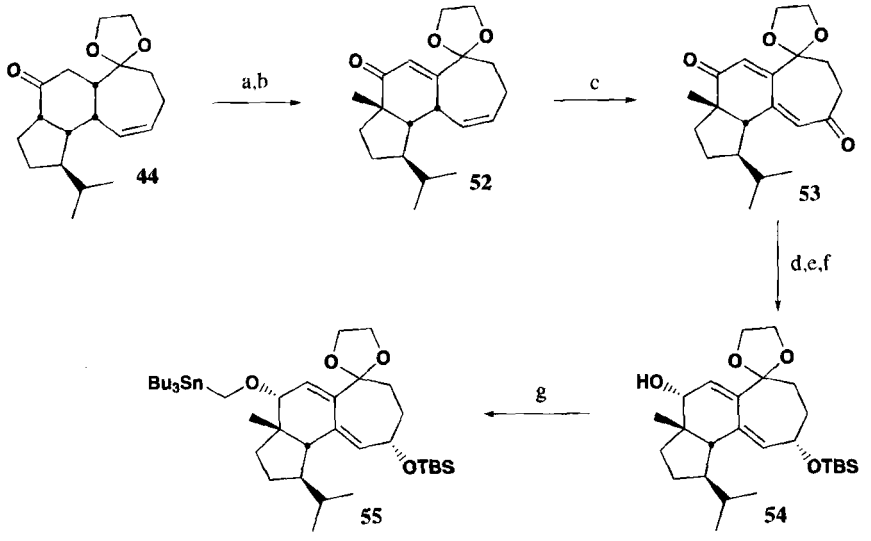
ion which would be followed by a pinacol triggered migration of the methyl group to give the ketone **51**. Unfortunately, under a variety of acidic conditions, this compound failed to undergo the desired rearrangement.



(a) KHMDS, $(TMSO)_2$, THF, 46%; (b) CH_3MgBr, THF, 99%.

Scheme 7

A final method studied to introduce the desired carbon would attempt to utilize an intramolecular delivery to the concave face of the tricycle (*Scheme 8*). Dienone **52** was prepared directly by selenation and oxidative elimination. This compound was found to be unstable to air and autooxidation resulted in the formation of the dienedione **53**. Global reduction of **53** to the diol was followed by selective formation of the α-stannyl ether **55**. Fortunately the reduction of the dione provided an α carbinol at C8 such that a [2,3] Wittig rearrangement would install the C6 methyl group with the desired stereochemistry. Surprisingly, this compound proved to be inert towards attempts to affect deprotonation/rearrangement, which may reflect the hindered nature of the olefin, and the desired product could not be formed under a variety of conditions.



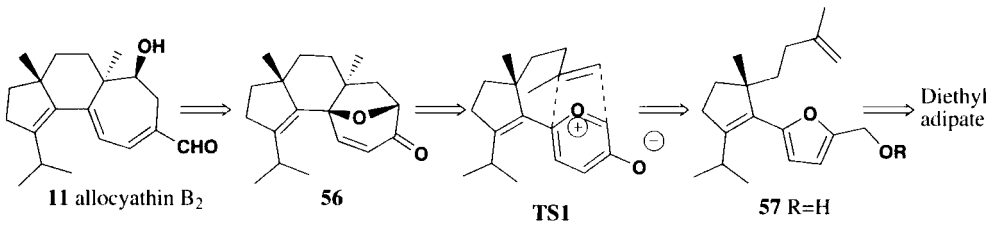
(a) LDA, PhSeCl, 96%; (b) *m*-CPBA, CH_2Cl_2, 45%; (c) air; (d) L-selectride, 88%; (e) KHMDS, TBSOTf, 69%; (f) Bu_3SnCH_2I, KH, 18-crown-6, THF.

Scheme 8

The Paquette approach to the cyathins provides an excellent method to assemble the tricyclic core in rapid fashion. The all *cis* nature of the ring junctions provides high levels of stereocontrol in the introduction of functionality on the ring system. This could be highly advantageous as in the introduction of the C9 methyl group but also makes introduction of groups on the concave face extremely difficult.

3. Magnus' Approach

Magnus and co-workers[31] have recently reported an efficient synthesis of the cyathin skeleton through a key 5C+2C annulation to generate ring C. This approach succeeds in a rapid and stereoselective synthesis of the 5-6-7 carbon skeleton with the requisite 1,4 *anti* methyl groups and a fully elaborated A ring. The synthetic analysis based upon the key cycloaddition targeted the assembly of the cycloaddition partners on an A-ring template (*Scheme 9*).



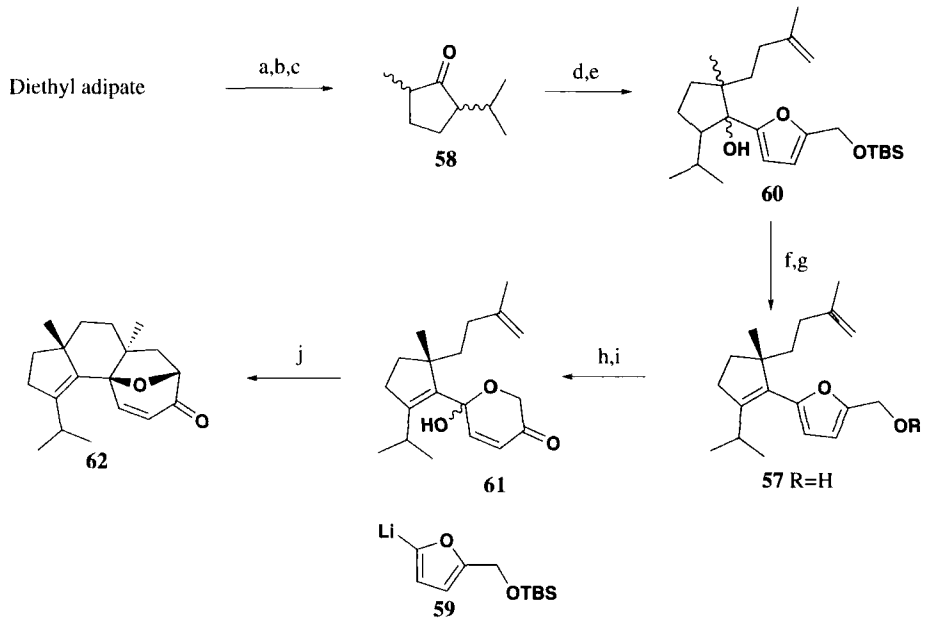
11 allocyathin B_2 **56** **TS1** **57** R=H

Scheme 9

The key step in the synthesis is a pyrylium ylide-alkene [5+2] cyclization. The relative stereochemistry of the C6 methyl group was predicted to be *anti* to the C9 methyl group based upon transition state modeling at the MM2 level. The early portions of the synthesis were dedicated to preparation of the pyrylium ylide precursor **57**. The [5+2] cyclization then simultaneously generates the B and C rings of the cyathane system in a single transformation.

A highly functionalized A-ring building block was assembled through Dieckman cyclization of diethyl adipate followed by methylation and decarboxylation to provide ketone **58**. Alkylation of the kinetic enolate of **58** installed a tethered trisubstituted alkene as a latent dipolarophile. Treatment of the resultant ketone with the 2-lithiofuran derivative **59** resulted in complex mixtures; the use of the derived cerate efficiently generated the tertiary carbinol **60**. Dehydration of the alcohol to place the C3-C4 alkene of **57** occurred upon exposure to thionyl chloride in pyridine. Deprotection of the alcohol was followed by oxidative rearrangement using the Williams procedure[32] to provide the unstable pyrylium ylide precursor **61**.

Initial attempts to form the pyrylium ylide *via* the acetate derivative of **61** failed, but treatment of the hemiacetal with a dilute solution of TFA was sufficient for generation of the transient dipolar intermediate (**TS1**). Intramolecular [3+2] cycloaddition ensued with the unactivated olefin to simultaneously form the C5 -C6 and C13-C14 bonds during ring-closure while correctly placing the C6 angular methyl group in the tricycle **62**.



(a) KOEt, 2-iodopropane; (b) NaOEt, MeI, $PhCH_3$; (c) H_2SO_4, H_2O, reflux; (d) LDA, THF, 4-iodo-2-methyl-1-butene, 53%; (e) $CeCl_3$, **59**, 90%; (f) $SOCl_2$, pyridine, 94%; (g) CsF, 97%; (h) O_2, hυ, rose bengal; (i) $(CH_3)_2S$; (j) TFA, CH_2Cl_2, 62% from **57**.

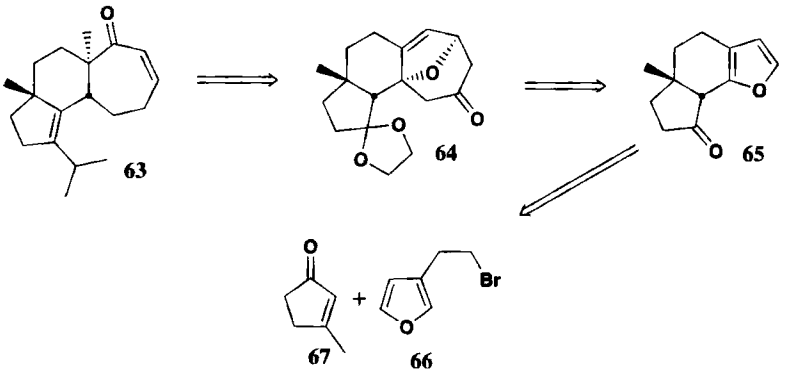
Scheme 10

4. Wright's Approach

Our approach[33] to the synthesis of the cyathane core relies upon a key electrochemical mediated furan annulation and an intermolecular 4C+3C cycloaddition on a highly substituted annulated furan. We have targeted the highly advanced intermediate **63** as a universal precursor for the synthesis of a variety of cyathins and erinacines as well as key analogs to study the NGF inducing properties of these natural products. The oxo-bridged tricycle **64** was envisioned as a key intermediate *en route* to precursor **63** and has been the initial focus of our investigations.

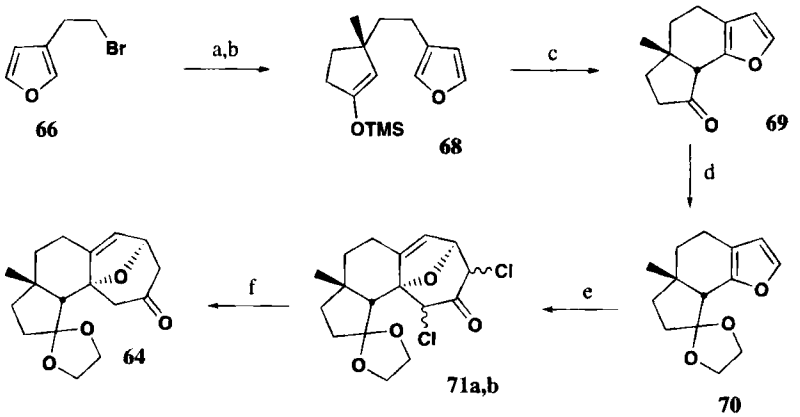
The analysis we used to develop a route to the 5-6-7 core (*Scheme 11*) relies on a key [4+3] cycloaddition for the formation of **64** which necessitates a direct route for the preparation of the annulated furyl ketone **65**. We were intrigued by reports from Moeller[34] and co-workers who had shown that furans could be coupled to electron rich alkenes, including methylenol ethers. We envisioned that coupling this process with cuprate addition chemistry could provide a two-step furan annulation protocol. Towards this end, silylenolether **68** was prepared by TMSCl accelerated cuprate addition of the Grignard reagent derived from **66** to 3-methylcyclopentenone **67**. The second stage of this annulation protocol required the oxidative coupling of two electron-rich olefins to close the six-membered B-ring under electrochemical conditions. This intermediate silylenol ether proved to be somewhat unstable toward hydrolysis and had to be used immediately without the benefit of further purification.

Constant current anodic oxidation of **68** with a carbon electrode in a buffered solution of lithium perchlorate in acetonitrile/*iso*-propanol provided the tricyclic furan **69** exclusively as the more stable *cis* isomer.



Scheme 11

The next key transformation involved cycloaddition across the furan ring to install the seven membered C-ring through formation of the C5-C10 and C12-C13 bonds (*Scheme 12*). We felt it was critical to control the facial selectivity of the cycloaddition since we intended on exploiting the unique



(a) Mg, THF; (b) CuI, TMSCl, Et_3N, **66**, -78°C to r.t; (c) anodic oxidation, MeCN, *i*-PrOH, $LiClO_4$, 2,6 lutidine, 65%; (d) *p*-TsOH, $HO(CH_2)_2OH$, $CH(OEt)_3$, 85%; (e) 1,1,2 trichloroacetone, $NaOCH_2CF_3$, CF_3CH_2OH; (f) Zn-Cu couple, NH_4Cl, MeOH, 75% from **70**.

Scheme 12

conformation of the oxabicyclo[3.2.1]octane to control the introduction of remaining C-ring functionality, most notably the C6 angular methyl group. Examination of models of **69** revealed a cup-shaped nature that suggested that approach of the three-carbon fragment would occur preferentially from the β-face. However, there was also concern that an opposing directing effect from the C9 β-methyl group could also be present. To exacerbate the steric bulk present on the α-face of the tricyclic

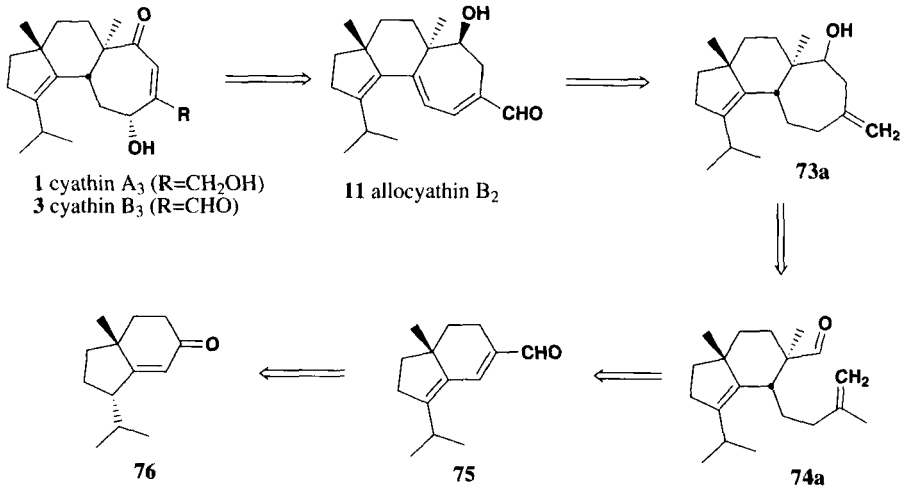
system, the ketone was converted to the corresponding dioxolane. This positions a portion of the ketal directly under the furan ring and helps shield this face from attack. The ensuing [4+3] cycloaddition on furan **70** is one of the few attempts to effect these cycloadditions on an annulated furan. Several of the traditional methods for cycloaddition failed including activation of halo-acetone derivatives with iron nonacarbonyl and zinc-copper couple. After considerable experimentation, it was found that a modification of the Fohlisch procedure[35] could produce the desired cycloadduct in very good yield. The [4+3] cycloaddition between **70** and the oxyallyl cation derived from 1,1,3 trichloroacetone provided a mixture of diastereomers **71a,b**. It was observed that the cycloaddition only proceeded to completion if a dilute solution of 1,1,3 trichloroacetone in trifluorethanol was added slowly to **70** with concurrent addition of a sodium trifluoroethoxide solution in trifluoroethanol. At the time the nature of the diastereomers **71a,b** was not known, but reductive dechlorination provided a single compound **64**, showing that the addition occurred with high facial selectivity.

TOTAL SYNTHESES

To date, there have been three approaches to these natural products that have led to the synthesis of one or more of the cyathanes. Allocyathin B_2 (**11**), which does not contain the 6,7 trans ring fusion, has been the primary target of these efforts. Erinacine A (**12**) has also yielded to total synthesis through the intermediacy of fully synthetic **11**.

1. Snider's Synthesis

Because many of the cyathins had been constructed semi-synthetically from allocyathin A_3 (**1**),[3-6,8] Snider selected this natural product as the initial target of their synthesis.[36-37] The retrosynthetic analysis used by Snider and co-workers relied on a key cyclization of the seven-membered C-ring (*Scheme 13*). It was speculated that the cyathins could be synthesized from the alcohol **73a**, which in turn could be produced from the aldehyde **74a** *via* an intramolecular carbonyl-ene reaction.



1 cyathin A_3 (R=CH_2OH)
3 cyathin B_3 (R=CHO)

11 allocyathin B_2

73a

76

75

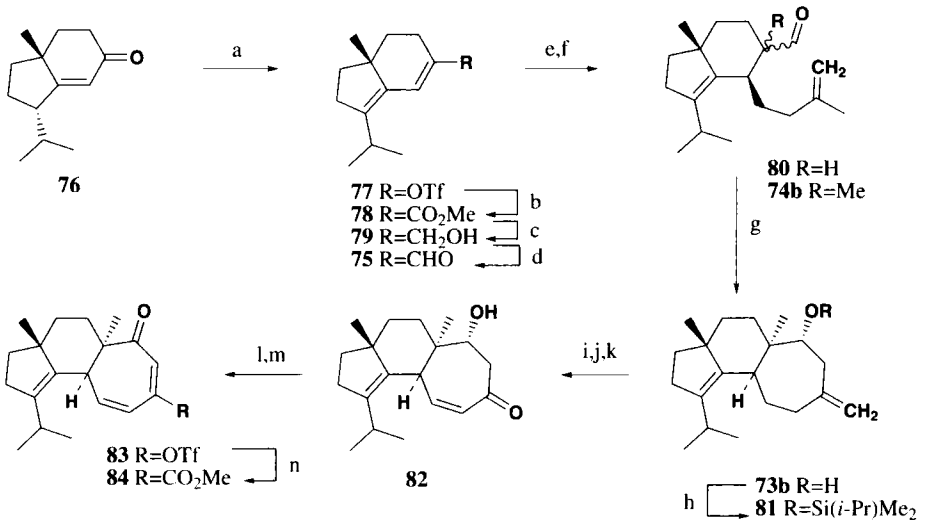
74a

Scheme 13

The ene substrate was envisioned to arise from the enal **75**, which in turn would arise from readily available **76**. The fortuitous discovery of the synthesis of enone **76** provided an excellent AB- ring precursor.

The enol triflate **77** was readily prepared from the previously reported enone **76** (available in 2 steps).[38] Palladium catalyzed carbonylation of **77** gave the dienoate **78**, which was reduced and reoxidized to give the aldehyde **75**. Copper(I) catalyzed conjugate addition of pentenyl magnesium bromide gave **80** as a mixture of epimers at C6. The stereoselectivity of the cuprate addition was unfortunate because the incorrect stereochemistry was generated at C5. However, subsequent methylation of **80** did provide the desired α methylated product **74b** as a prelude to C-ring closure. The intramolecular carbonylene reaction proceeded readily to form the C13-C14 bond and give the alcohol **73b** that contains the entire cyathane skeleton.

Oxidative cleavage of the exocyclic methylene was followed by conversion to the enone by a selenation/elimination sequence to give **82**, after alcohol deprotection. The alcohol **82** was oxidized and the resulting β-diketone was converted selectively to the enol triflate **83** upon treatment with N-phenyltriflimide. Installation of the remaining carbon of the cyathin system was accomplished *via* palladium catalyzed carbonylation to provide the methyl ester **84** in good yield.

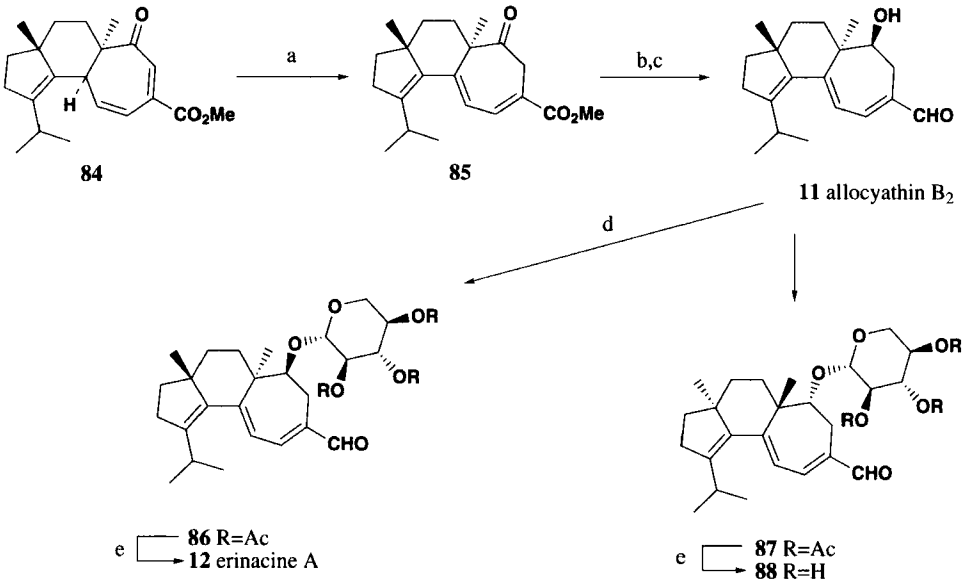


(a) Proton Sponge, Tf_2O, 88%; (b) $Pd(OAc)_2$, Ph_3P, CO, *i*-Pr_2EtN, 85%; (c) DIBAL, 97%; (d) MnO_2, 95%; (e) $H_2CC(CH_3)(CH_2)_2MgBr$, CuBrDMS, TMSCl, 91%; (f) KO-t-Bu, MeI, 75%; (g) Me_2AlCl, 87%; (h) *i*-$Pr(Me)_2SiCl$, imid., 95%; (i) OsO_4, KIO_4, 77%; (j) LHMDS, PhSeCl, H_2O_2, 72%; (k) AcOH, H_2O; (l) Dess-Martin, 72% from **81**; (m) KHMDS, $PhNTf_2$, 75%; (n) $Pd(OAc)_2$, Ph_3P, CO, *i*-Pr_2EtN, 75%.

Scheme 14

With the key intermediate **84** in-hand, the stage was set for the final manipulation of the peripheral functionality to complete the total synthesis (*Scheme 15*). Isomerization of **84** under basic conditions gave the non-conjugated ketone **85** that also removed the undesired stereochemical

arrangement at C5. Global reduction of **85** was followed by selective oxidation of the allylic alcohol to give the racemic allocyathin B_2 (**11**). Glycosylation of racemic **11** with α 1-bromo-2,3,4-tri-*O*-acetyl xylose provided erinacine A triacetate (**86**) and the diastereomer **87**. The two diastereomers were separated and then deprotected to give **12** and **88** respectively. This synthetic approach delivered **11** and **12** in 17 and 19 steps respectively.



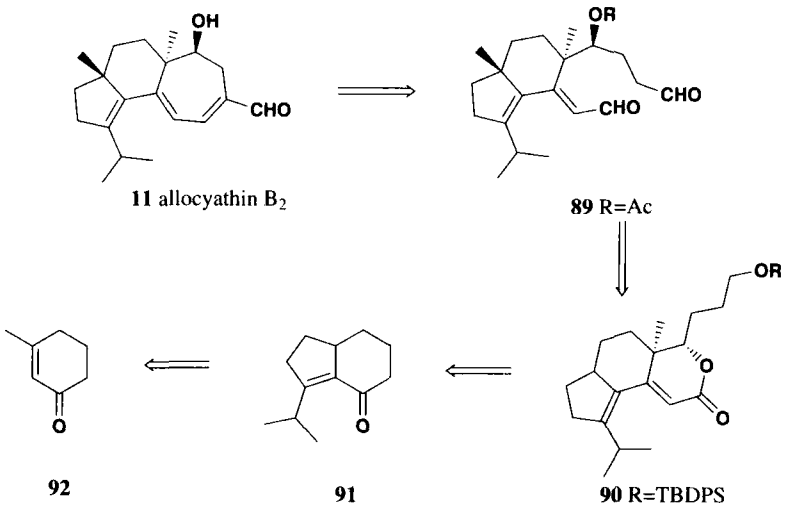
(a) Et_3N, MeOH, 94%; (b) LAH, 89%; (c) MnO_2, 94%; (d) triacetyl-α-D-xylopyranosyl bromide, $Hg(CN)_2$, $HgCl_2$, 34%; (e) K_2CO_3, MeOH, >90%.

Scheme 15

2. Tori's Total Synthesis of Allocyathin B_2

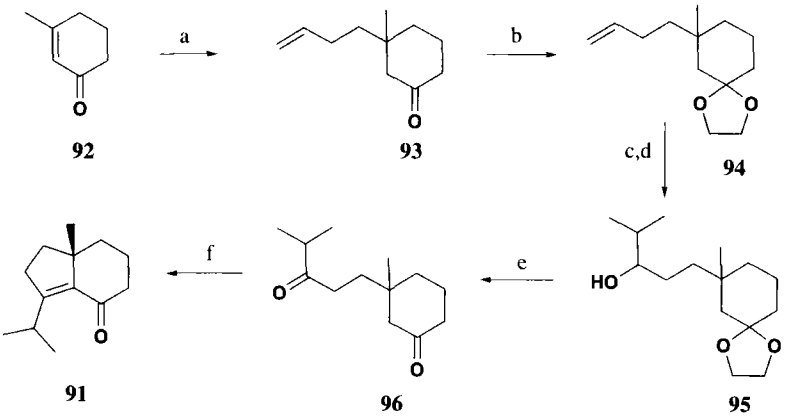
Tori and co-workers[39] have recently disclosed a total synthesis of allocyathin B_2. Their strategy (*Scheme 16*) centered upon the application of two key aldol cyclizations to annulate both rings A and C onto a preformed B-ring. Cyclization of the seven-membered C-ring was targeted late in the synthesis by using an AB-ring template **89** for the last cyclization. The ultimate aldol precursor, dialdehyde **89,** was envisioned to arise from lactone **90**. This tricycle, in turn, was designed to arise from hydrindanone **91** which would be derived from 3-methylcycohexenone. These two key transformations would also be accomplished using aldol cyclo-condensations.

The synthetic approach commenced with conjugate addition of the cuprate derived from 4-bromo-1-butene to enone **92**. Oxidative cleavage of the terminal vinyl group, after ketalization, gave an aldehyde that was converted to the isopropyl ketone **96** through sequential Grignard addition and oxidation. Base catalyzed aldol cyclization followed by dehydration occurred effectively to generate the fused hydrindanone system **91** in six chemical operations. Generation of the C6 quaternary center α-to the enone would require the sequential addition of a methyl group and a side chain for closure of



Scheme 16

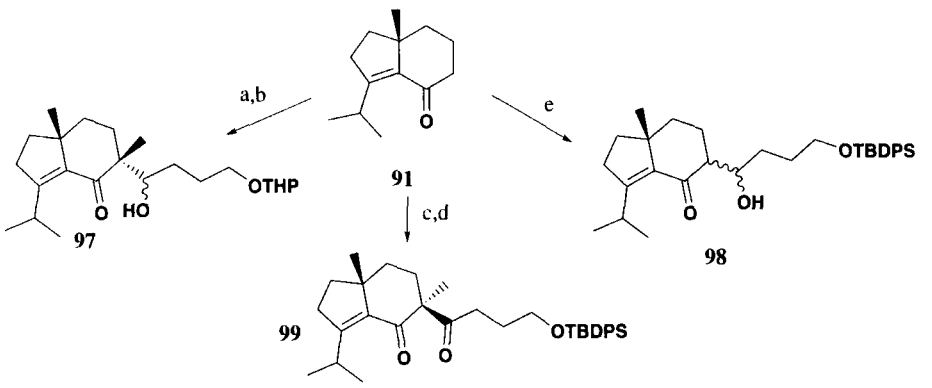
ring C. Tori and co-workers were able to nicely take advantage of the addition order to set the correct stereochemical relationship between C6 and C9. The preference for electrophiles to approach the enolate from the face *syn* to the C9 methyl group allowed these workers to add the methyl group first, followed by the side chain (in the form of an enolate acylation) and set the *anti* disposition between the two methyl groups and give the key diketone **99**.



(a) $CH_2CHCH_2CH_2MgBr$, CuBrDMS, THF; (b) $HOCH_2CH_2OH$, TsOH, PhH, 88% from **92**; (c) O_3, Zn, AcOH; (d) *i*-PrMgBr, 83%; (e) Jones oxidation; (f) 5%-KOH, MeOH, 73% from **95**.

Scheme 17

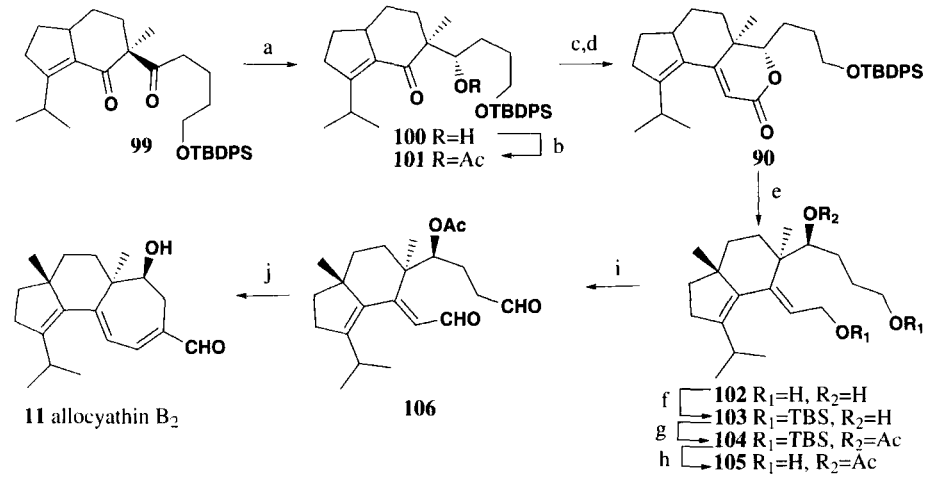
After considerable experimentation, it was discovered that zinc borohydride would effect a highly stereoselective reduction of the exocyclic ketone which was converted to the corresponding acetate **101**. Enolization of the acetate initiated an intramolecular aldol reaction to give the unsaturated lactone **90** after dehydration with thionyl chloride.



(a) LDA, MeI, THF; (b) LDA, THF, $HCO(CH_2)_3OTHP$, 20%; (c) LDA, THF, $ClCO(CH_2)_3OTBDPS$, -78°C, 37%; (d) tBuOK, MeI, 91%; (e) LDA, THF, $HCO(CH_2)_3OTBDPS$, 87%.

Scheme 18

Reduction of the lactone and protecting group adjustments gave a diol which was oxidized to the corresponding dialdehyde **106** as a prelude to the final aldol cyclization. Treatment of the dialdehyde promoted condensation to close ring-C which was followed by dehydrated and deprotection of the C14 alcohol to give allocyathin B_2 in 18 steps.



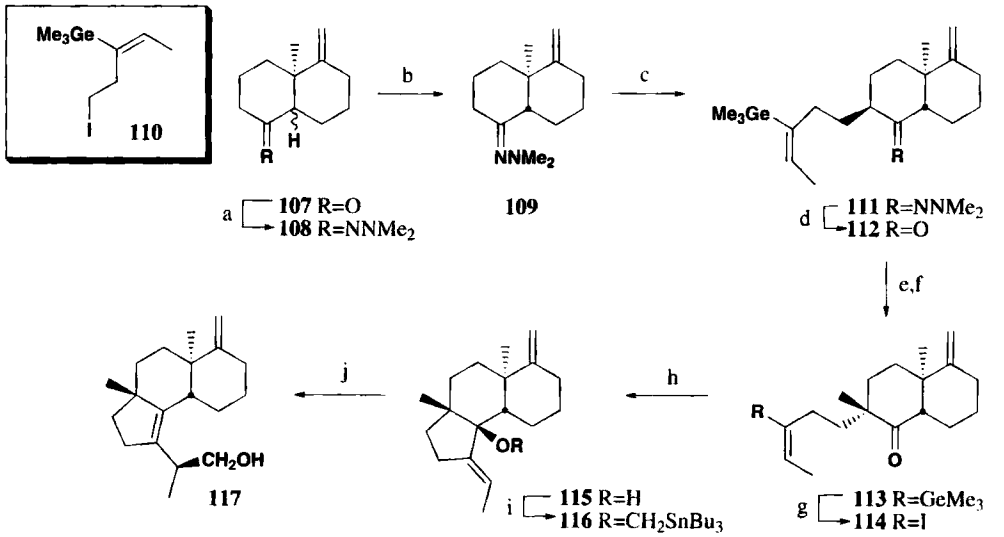
$Zn(BH)_4$, Et_2O, -78°C; (b) Ac_2O, DMAP, pyridine; (c) LHMDS, THF, -78°C; (d) $SOCl_2$, pyridine, CH_2Cl_2; (e) LAH; (f) TBSCl, Et_3N, 37% from **90**; (g) Ac_2O, DMAP, Py; (h) PPTS, MeOH, 52% from **103**; (i) Swern; (j) 5%-KOH MeOH, 74% from **105**.

Scheme 19

3. Piers' Synthesis of Sarcodonin G

Recently, Piers and co-workers have reported the first synthesis of a member of the sarcodonin class of cyathane diterpenoids (*Scheme 20*).[40] Their strategy relied on the use of a *trans*-

fused decalin as a latent BC-ring system which would undergo consecutive cyclopentyl annulations to form ring A and a one-carbon ring expansion to produce the seven membered C-ring.



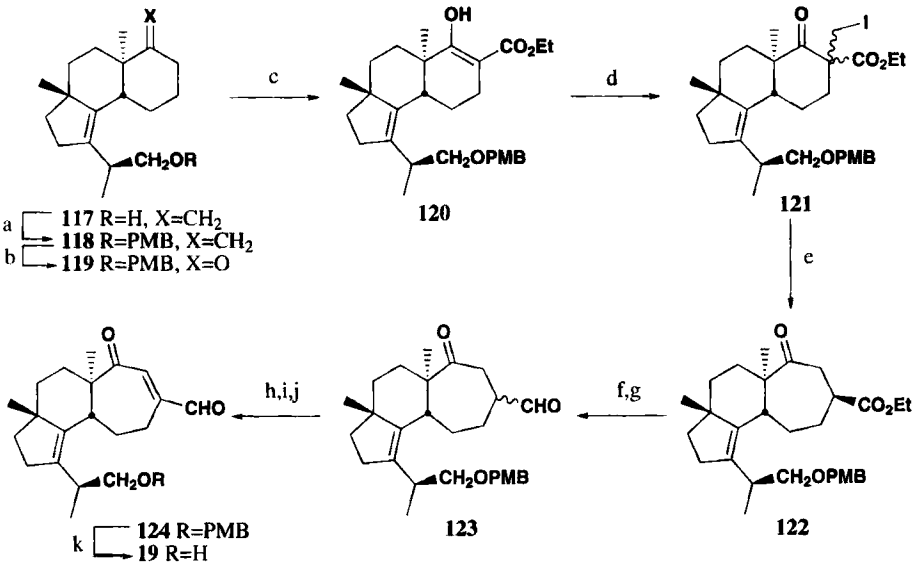
(a) Me_2NNH_2, CSA, 82%; (b) CSA, PhH, reflux; (c) KDA, DMPU, **110**; (d) HOAc, NaOAc, 69% from **108**; (e) NaOMe, MeOH, 82%; (f) $LiNEt_2$, CH_3I, 85%; (g) NIS, CH_2Cl_2, 90%; (h) BuLi, 86%; (i) KH, 18-C-6, Bu_3SnCH_2I; (j) BuLi, 88% from **115**.

Scheme 20

Their approach commenced with the decalone building block **107**[41] that was converted to the corresponding dimethylhydrazone **108** to promote efficient alkylation. The formation of the hydrazone permitted application of an acid catalyzed equilibration to ultimately give the *trans*-fused compound **109**. Alkylation of the hydrazone anion with the bifunctional building block **110** (available in six steps from ethyl pent-2-ynoate) occurs selectively to give ketone **112** after hydrolysis of the hydrazone. Installation of the C9 methyl group occurs stereoselectively to establish the *anti* relationship with the angular methyl group at C6. Conversion of the vinyl germanium moiety to a vinyl iodide was accomplished by subjecting **112** to N-iodosuccinimide. Metal-halogen exchange (n-BuLi) promoted intramolecular addition to the B-ring ketone to yield tricyclic alcohol **115**. This angular hydroxyl function was nicely used to introduce oxygen functionality on the C3-isopropyl group while placing the C3-C4 olefin. Conversion of the alcohol to the α-stannyl ether followed by lithiation gave an anion that underwent a smooth [2,3] Wittig rearrangement to alcohol **117**.

With annulation of ring A complete, efforts were focused on expansion of ring C and installation of the required peripheral functionality (*Scheme 21*). Protection of the primary alcohol as a PMB ether and oxidative cleavage of the exocyclic methylene group gave ketone **119**. Acylation of the ketone with diethylcarbonate was followed by alkylation with methylene iodide to give the iodomethyl keto-ester **121**. Treatment of the iodide with samarium (II) iodide triggered a one carbon ring expansion, probably through an intermediate cyclopropane, to furnish the cycloheptanone **122** in

good yield. With the complete cyathin skeleton intact, final manipulation of ring C remained. Global reduction of **122** and oxidation of the resultant diol gave the keto-aldehyde **123** which was oxidized to a mixture of enals through selenation/elimination. The mixture of positional isomers was converted to enal **124** under basic conditions. Removal of the PMB group with DDQ provided sarcodonin G (**19**) in 21 steps from decalin **107**.



(a) KH, PMBCl, TBAI, 96%; (b) OsO_4, KIO_4, 85%; (c) KH, NaH, $(EtO)_2CO$, 74% (d) TBAF, CH_2I_2, 78%; (e) SmI_2, 71%; (f) Dibal-H; (g) Dess-Martin periodinane, 86% for two steps; (h) piperidine, PhH then PhSeCl; (i) KIO_4, 78% for two steps; (j) DBN, PhH, 95%; (k) DDQ, H_2O, 91%.

Scheme 21

IV. CONCLUSIONS

The cyathane diterpenes have emerged as popular targets for total synthesis owing to a combination of the unique structure and the novel modes of biological activity. A variety of novel and interesting approaches have been studied and three have culminated in total syntheses. There will certainly be more exciting work in this area in the future.

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