

Strategies for the Total Synthesis of C2–C11 Cyclized Cembranoids

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1. Introduction

The C2–C11 cyclized cembranoids, which include the eunicellins (also known as the cladiellins), briarellins, asbestinins, and sarcodictyins, are secondary metabolites isolated from gorgonian octocorals and soft corals.¹ An unusual oxatricyclic ring system containing a hydroisobenzofuran and an oxonene unit with stereogenic centers residing at C1–3, 9, 10, and 14 is common to the eunicellins, briarellins, and asbestinins. However, the location of the cyclohexyl methyl groups (C11 versus C12) and the oxidation level of the six- and nine-membered rings differ among the three classes. Faulkner has proposed that the cyclization of the cembranoid diterpene skeleton initiates a biosynthetic pathway that leads to all four subclasses of these unusual molecules (Figure 1).² Beginning with the cembrane skeleton, C2–C11 cyclization provides the cladiellin framework. An intramolecular etherification of the cladiellin tricycle affords the tetracyclic framework of the briarellin subclass, and a subsequent 1,2-suprafacial methyl shift of the briarellin structure is postulated to deliver the asbestinins as the class that is furthest evolved from the cembrane skeleton. The presence of multiple structural types in a common organism provides circumstantial evidence for Faulkner's proposed biosynthetic pathway. The isolation of a cembrane metabolite with cladiellin metabolites in *Alcyonium molle* and with asbestinin metabolites in *Briareum steckii* are specific

examples.³ The sarcodictyins are also proposed to arise from a C2–C11 cyclization of the cembrane skeleton; however, in these systems, the cyclization results in a fused cyclohexane and oxonane in place of the hydroisobenzofuran of the cladiellins, briarellins, and asbestinins. As a result of this significant structural variation of the sarcodictyins, the synthetic approaches to these molecules are quite different than those for the other three related subclasses.^{4,5} This review will cover efforts toward the eunicellins, briarellins, and asbestinins but will not cover efforts toward the total synthesis of the sarcodictyins.

Eunicellin was the first reported member of the C2–C11 cyclized cembranoid natural products, isolated in 1968 by Djerassi and co-workers from the soft coral *Eunicella stricta* found off the coast of Banyuls-sur-Mer in France.⁶ Since this discovery, over 100 unique secondary metabolites of gorgonian octocorals have been characterized, including the first asbestinin in 1980² and the first briarellin in 1995.⁷ A wide range of structural diversity is displayed by this group of marine natural products. The natural role of these cembranoids is proposed, based upon mollusk and fish lethality assays, to involve predation deterrence.⁷ Upon further investigation, several of the members of these subclasses have demonstrated significant pharmacological potential.^{7–13} Particularly, these diterpenes have been shown to exhibit in vitro cytotoxicity against various cancer cell lines, anti-inflammatory properties, antimicrobial activities, and histamine and acetylcholine antagonism. The fascinating molecular architecture of these cembranoids, as well as their potential as therapeutic agents, has sparked much interest in the synthetic community over the past decade. A variety of approaches toward these challenging structural motifs have been investigated and several total syntheses have been accomplished. Efforts toward the total synthesis of the cladiellins, briarellins, and asbestinins are the subject of this review.

2. Total Syntheses of the Cladiellins, Briarellins, and Asbestinins

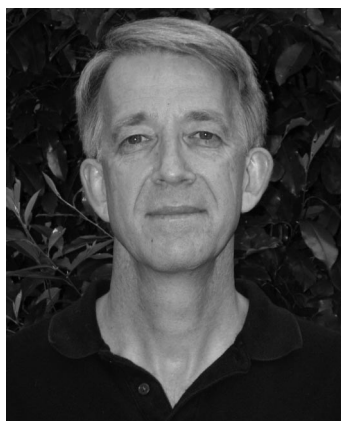
2.1. Prins-Pinacol Condensation-Rearrangement

The first total synthesis of a C2–C11 cyclized cembranoid natural product was completed by Overman and MacMillan, who reported the total synthesis of (–)-7-deacetoxyalcyonin acetate (**1**),¹⁴ a cladiellin, in 1995.¹⁵ The synthesis hinges upon the formation of the hydroisobenzofuran functionality via a Prins-pinacol condensation-rearrangement, which had been previously employed by the Overman laboratory for the stereoselective synthesis of tetrahydrofurans.¹⁶ Dienyl diol **3**, the substrate for the Prins-pinacol rearrangement, was

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Michael Crimmins was born in E. St. Louis, Illinois, on January 3, 1954. He received his B.A. degree from Hendrix College (1976) and his Ph.D. from Duke University (1980), where he worked on synthetic applications of intermolecular photochemical cycloadditions under the direction of Professor Steven W. Baldwin. He was a postdoctoral associate at the California Institute of Technology working with Professor David A. Evans from 1980–1981. He joined the faculty at the University of North Carolina at Chapel Hill in 1981 as Assistant Professor of Chemistry. He was subsequently promoted to Associate Professor (1988) and Professor (1993). In 2001 he was named George and Alice Welsh Distinguished Term Professor and assumed the position of Mary Ann Smith Distinguished Professor in January 2003. He is currently Chair of the Department of Chemistry at UNC–CH. His research interests are in the development of new synthetic methods and their application to the total synthesis of biologically active compounds.

prepared from (*S*)-dihydrocarvone (**2**)¹⁷ (Scheme 1). Formation of the kinetic enol triflate of dihydrocarvone,¹⁸ followed by iodination,¹⁹ provided the dienyl iodide **4**.²⁰ Subsequent halogen–lithium exchange and exposure of the vinyl lithium species to alkynyl aldehyde **5** (prepared in four steps from (*S*)-glycidyl pivalate)²¹ provided diol **3** upon deprotection.²² With the stage set for the key Prins-pinacol condensation-rearrangement, diol **3** was combined with enal **6** in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ to provide the hydroisobenzofuran **7** as a single diastereomer in 79% yield. The stereochemical outcome of this transformation is predicted to arise from transition state **8** (Figure 2). Following formation of the more stable (*E*)-oxocarbenium ion,²³ the molecule adopts the chairlike conformation necessary for the 6-*endo* cyclization process. Transition state **8** orients all substituents in a pseudoequatorial orientation while also allowing the oxo-

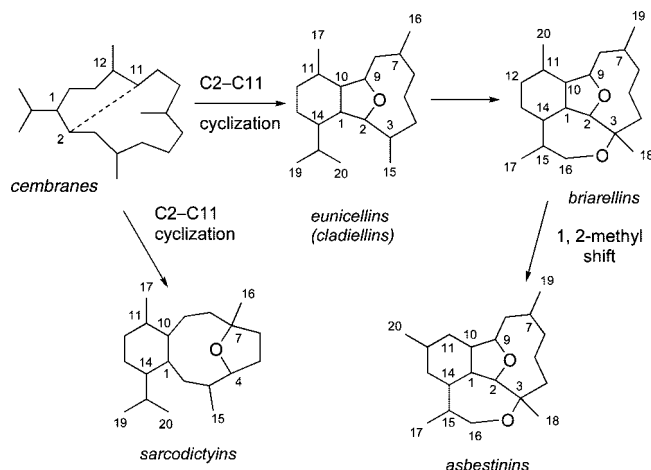
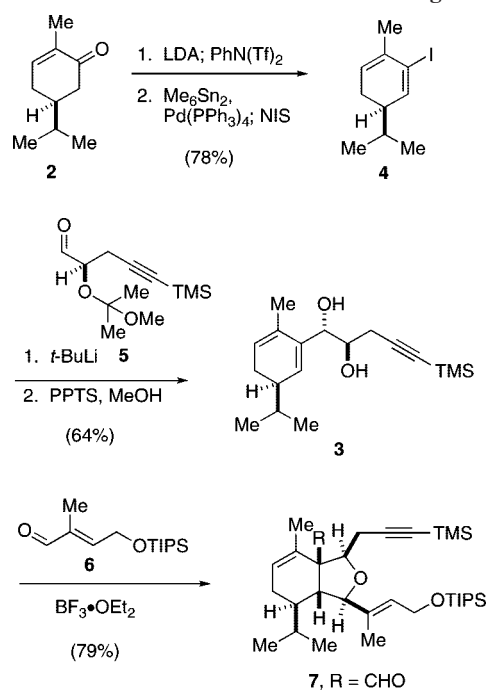


Figure 1. Proposed biosynthesis.

Scheme 1. Prins-Pinacol Condensation-Rearrangement



carbenium ion to approach the diene from the opposite face of the bulky isopropyl substituent.¹⁶ The observed stereochemistry supports this model.

With the cyclohexene and tetrahydrofuran in place, attention was turned toward formation of the oxonane (Scheme 2). Removal of the triisopropylsilyl (TIPS) group from

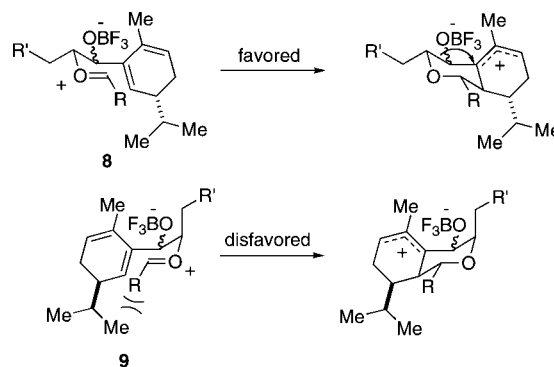
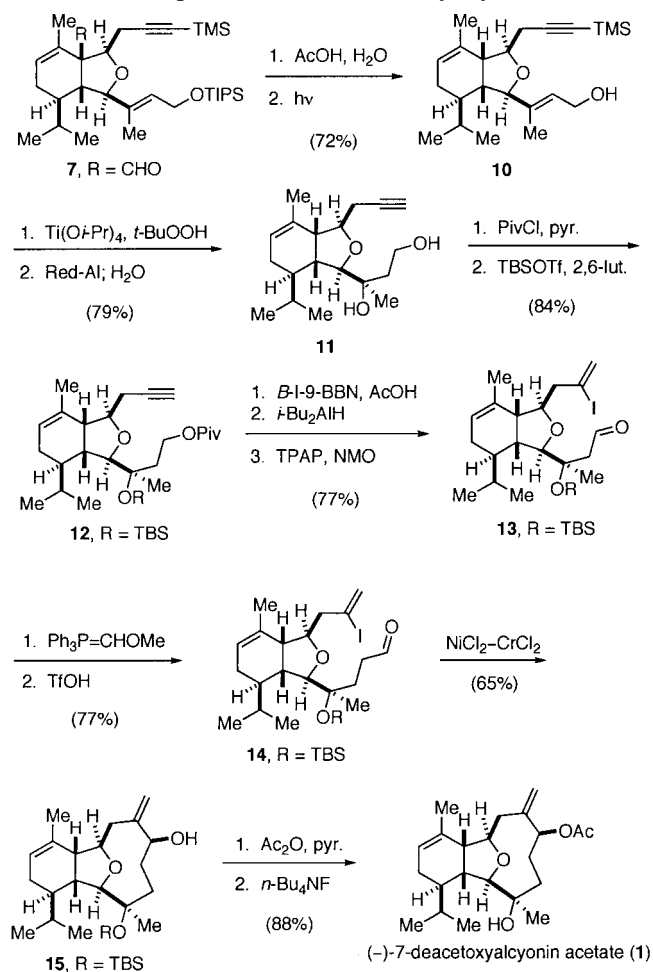


Figure 2. Transition states for Prins-pinacol condensation-rearrangement.

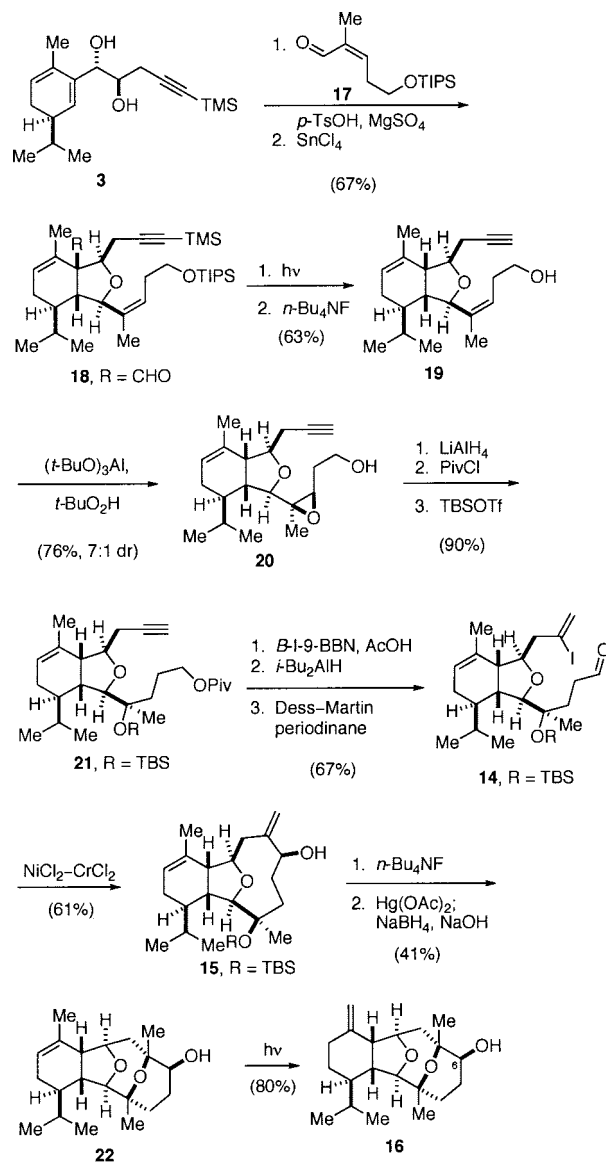
Scheme 2. Completion of (–)-7-Deacetoxyalcyonin Acetate



primary silyl ether **7** and photochemical decarbonylation of the formyl group gave bicycle **10**.²⁴ The allylic alcohol was next exploited to achieve a Sharpless asymmetric epoxidation of the trisubstituted alkene,^{25,26} and the resultant epoxide was reduced regioselectively using bis(2-methoxy)ethoxy-aluminum hydride (Red-Al).^{27–29} Addition of water at the end of the reaction produced NaOH, which also effected deprotection of the terminal acetylene, delivering diol **11** in one pot. A series of five straightforward reactions converted alcohol **11** to the aldehyde **13**,^{30,31} which, following a one-carbon homologation, was utilized in an intramolecular Nozaki–Hiyama–Kishi coupling using NiCl₂–CrCl₂.^{32,33} Notably, the resultant tricycle **15** was formed in 65% yield with high (>20:1 dr) diastereoselectivity. Acetylation of the secondary alcohol **15** followed by desilylation of the tertiary *t*-butyldimethylsilyl (TBS) ether provided (–)-7-deacetoxyalcyonin acetate (**1**), marking the first successful total synthesis of a member of the C2–C11 cyclized cembranoid family.

The Overman laboratory next extended the Prins-pinacol condensation-rearrangement approach to a cladiellin of potential pharmacological utility. Sclerophytin A (**16**) was reported to possess a tetracyclic diether structure and showed promising *in vitro* cytotoxicity against the L1210 leukemia cell line (1 ng/mL).^{9,34,35} The strategy envisioned for sclerophytin A also involved a Prins-pinacol approach, this time using a (*Z*)- α,β -unsaturated aldehyde as the nucleophile. The synthesis would assess the viability of using a (*Z*)- α,β -unsaturated aldehyde without isomerization of the alkene, while accomplishing the first total synthesis of this thera-

Scheme 3. Overman's Completion of the Proposed Structure of Sclerophytin A



peutically intriguing natural product. Utilizing diol **3** from the (–)-7-deacetoxyalcyonin acetate synthesis¹⁵ and aldehyde **17** (prepared in four steps from 3-buten-1-ol),³⁶ a two-step condensation and rearrangement procedure was employed (Scheme 3).^{37,38} Condensation of the two components under acidic conditions provided an acetal that efficiently delivered bicycle **18** upon treatment with tin tetrachloride. The (*Z*)-olefin remained intact throughout the cyclization with no stereomutation observed. Deformylation²⁴ and removal of the silyl protecting groups gave the allylic alcohol **19**, suitably poised for a substrate-controlled epoxidation. Treatment of allyl alcohol **19** with (*t*-BuO)₃Al/*t*-BuO₂H provided a separable 7:1 mixture of epoxides, favoring the desired diastereomer **20**.³⁹ Reductive opening of the epoxide and sequential differential protection of the resultant 1,4-diol provided alkyne **21**. Refunctionalization of alkyne **21** to the Nozaki–Hiyama–Kishi candidate completed a more efficient synthesis of vinyl iodide **14**, which had been utilized in the synthesis of (–)-7-deacetoxyalcyonin acetate.^{15,30} Upon treatment with NiCl₂–CrCl₂, the oxonane was formed, delivering the desired isomer of allylic alcohol **15** in good yield.^{32,33} Cleavage of the tertiary silyl group followed by intramolecular etherification with Hg(OAc)₂ (followed by

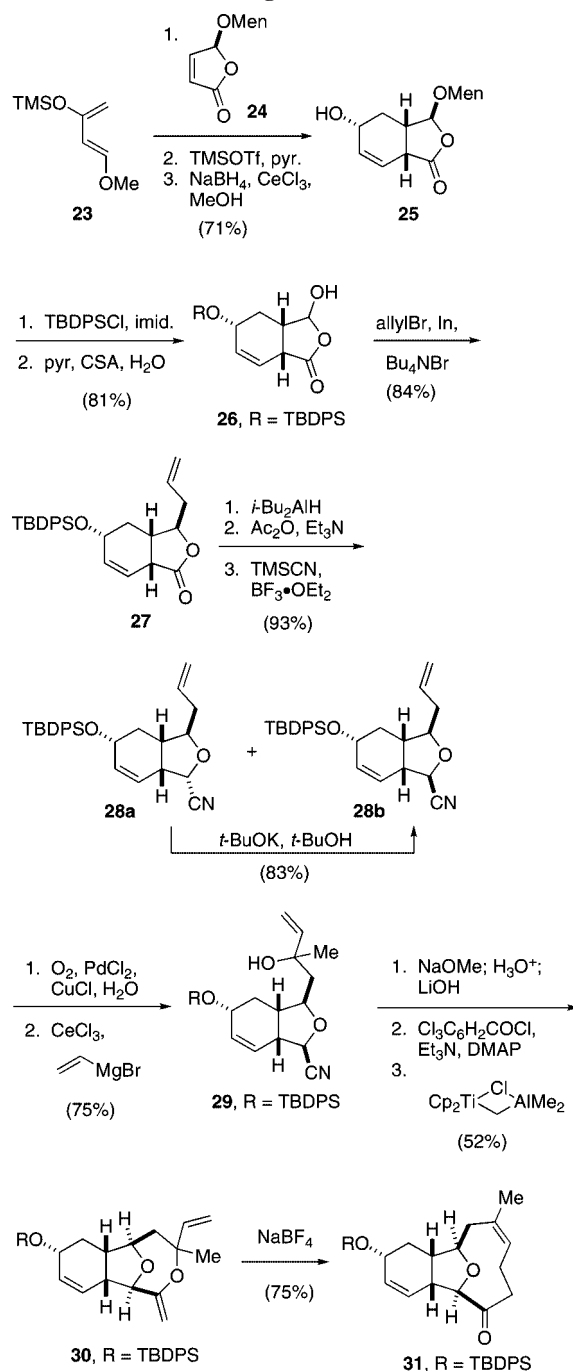
NaBH₄) provided diether **22** in moderate yield.⁴⁰ Photoisomerization of the trisubstituted alkene to the exocyclic olefin gave the proposed structure of sclerophytin A (**16**).^{41,42} However, the data for the synthetic and natural material differed greatly.^{9,37} The C6 epimer of tetracycle **16** was also prepared via oxidation⁴³ and reduction but also failed to correlate with the natural product.

2.2. Claisen Rearrangement Strategy

Concurrently with the Overman laboratory, the Paquette group undertook the synthesis of sclerophytin A (**16**) via a unique route.^{9,13,34,35,37,44} Their strategy relied upon a Claisen rearrangement as the key step to provide the functionalized oxonane core of the natural product.⁴⁵ The synthesis commenced with a Diels–Alder cycloaddition involving the Danishefsky diene (**23**) and the homochiral dienophile **24** (Scheme 4).^{46,47} The Diels–Alder adduct contained a labile silyl enol ether that was hydrolyzed,⁴⁸ and the resultant enone was reduced under Luche conditions⁴⁹ to provide allylic alcohol **25** in good yield. Ensuing silylation of the allylic alcohol and hydrolysis of the menthyl ether delivered the hemiacetal **26**. Allylation of bicycle **26** afforded a 13:1 ratio of adducts, favoring the desired diastereomer **27**.⁵⁰ The lactone was reduced to the hemiacetal, which was acetylated. Treatment of the oxocarbenium ion derived from the acetate with trimethylsilyl cyanide gave a 1:1 mixture of nitriles **28a** and **28b**.^{51,52} Efficient conversion of nitrile **28a** to nitrile **28b** was achieved with *t*-BuOK in *t*-BuOH. Wacker oxidation⁵³ of the terminal alkene with subsequent vinylation of the resultant ketone provided tertiary alcohol **29** in 75% yield for two steps. Mild hydrolysis of the nitrile provided an acid,^{54–56} which was used in a Yamaguchi macrolactonization to give a lactone.^{57,58} A Tebbe methylation of the lactone carbonyl provided the target diene **30** for the key Claisen rearrangement.⁵⁹ Treatment of the mixture of diastereomeric dienes with sodium tetrafluoroborate in refluxing toluene provided the desired oxonene **31**, but the two diastereomers reacted at two distinctly different rates.⁴⁵ The noted variation in reaction rate can be explained by examining the transition states for each rearrangement (Figure 3). The requisite chair conformations to access the desired rearranged product should both be accessible; however, transition state **30a** suffers from enhanced steric interactions over its corresponding epimer **30b**, resulting in slower Claisen rearrangement.

With the formation of the oxonene completed, attention was turned toward properly functionalizing the six- and nine-membered rings. Diastereoselective addition of methyl lithium to the ketone **31**, protection of the resultant tertiary alcohol as a benzoate ester, removal of the silyl protecting group, and oxidation of the derived alcohol provided enone **32** (Scheme 5). Hydroxymethylation of the enone **32**, utilizing ytterbium triflate,⁶⁰ was followed by silyl protection of the resultant alcohol. Diastereoselective conjugate addition of the Gilman reagent derived from isopropylmagnesium chloride provided ketone **33** with the complete diterpene skeleton of sclerophytin A (**16**). Three-step reductive removal of the cyclohexanone carbonyl gave ester **34**.⁴⁹ Reduction of the benzoate ester, followed by oxymercuration and oxidative demercuration, gave a 3:7 mixture of epimeric alcohols **35** in 54% yield, forming the final ring of the natural product.⁶¹ Protection of the secondary alcohol as an acetate ester was followed by cleavage of the silyl ether and ensuing Grieco elimination.⁶² Reduction of the acetate ester provided the

Scheme 4. Claisen Rearrangement



purported structure of sclerophytin A (**16**). However, as also observed by Overman, the spectroscopic data for this material differed significantly from that reported for the natural product.⁹ Oxidation³¹ and reduction of the secondary alcohol provided the C6 epimer **36**, which still did not match the data for the naturally isolated material. Additionally, tetracycle **16** was much less polar than an authentic sample of the natural compound.

Armed with the knowledge that the initially assigned structure of the natural product was likely not correct, and that the true structure was not the C6 epimer, the Paquette group performed extensive NMR studies and a comprehensive literature investigation. As a result, a new structural assignment for sclerophytin A (**37**) was proposed.⁶³ To access the newly proposed structure, in all of its C6 and C7 epimeric forms, alkene **34** was dihydroxylated using osmium

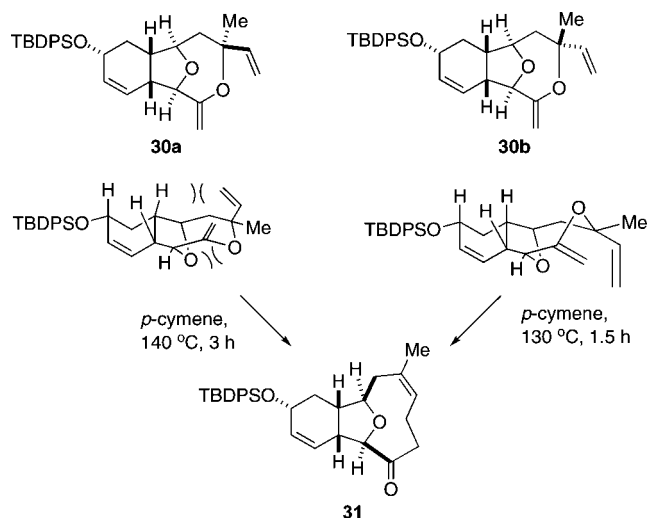


Figure 3. Claisen rearrangement transition states.

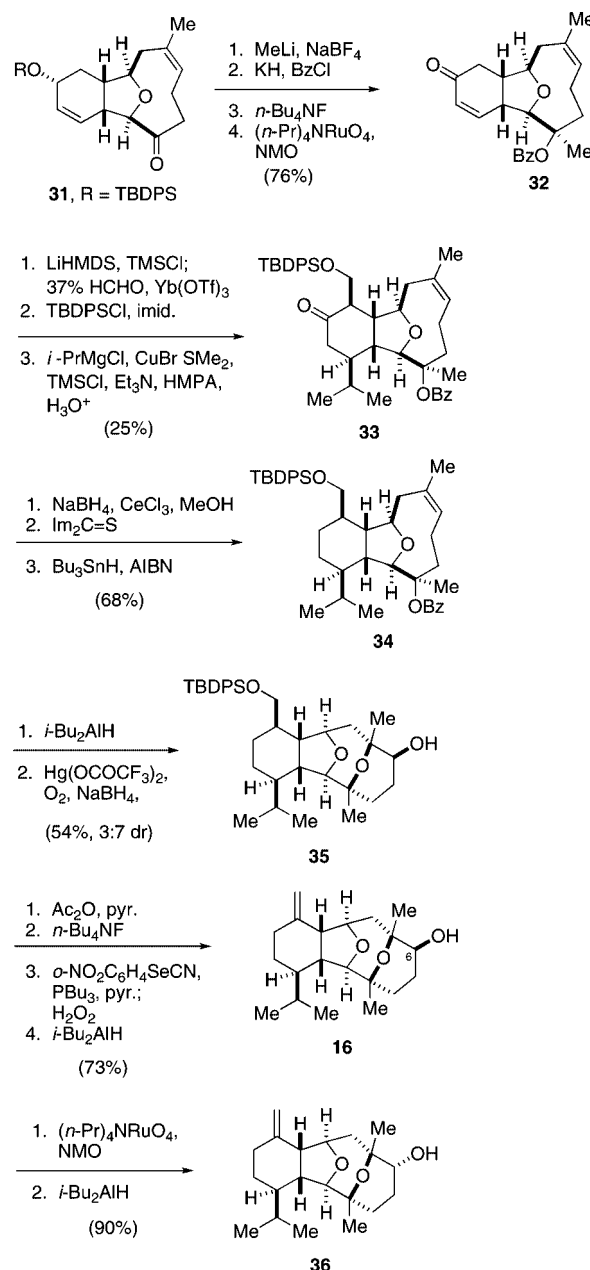
tetraoxide to provide a nearly equal mixture of diastereomers **38** (1.5:1 dr, Scheme 6).^{64,65} Oxidation of the C6 alcohol,⁶⁶ and cleavage of the silyl ether with fluoride, provided the keto-alcohol **39**. Grieco elimination of the primary alcohol followed by concomitant removal of the tertiary benzoate and reduction of the C6 ketone via dissolving metal conditions gave triol **37**.⁶² Using one of three different reductive conditions, each of the four possible C6, C7 diastereomers of sclerophytin A was accessed. Gratifyingly, triol **37** matched the data for the natural product, serving to establish the true structure of sclerophytin A.

2.3. A Return to the Prins-Pinacol Condensation-Rearrangement

With knowledge of the reassignment of the structure by the Paquette group, the Overman laboratory had concurrently targeted authentic sclerophytin A (**37**) using an intermediate from their previous synthesis of the purported structure.^{37,38,64} Hydroxyl-directed epoxidation of tricycle **15** gave 95% of the desired epoxide (Scheme 7),⁶⁷ which upon reductive cleavage with *i*-Bu₂AlH^{27–29} gave the diol **40**. Finally, cleavage of the silyl ether and photochemical isomerization of the endocyclic alkene provided sclerophytin A (**37**), albeit in lower yield than the previous photoisomerization (vide supra, Scheme 3).³⁷

In 2003, Overman applied the Prins-pinacol condensation-rearrangement approach to the synthesis of a C4-oxygenated cladiellin, alcyonin (**41**).⁶⁸ Protection of epoxide **20** (previously prepared in the synthesis of sclerophytin A, Scheme 2)^{15,37,38} as its acetate ester and treatment with aqueous trifluoroacetic acid prompted a 6-*exo* opening of the epoxide to provide diol **42** (Scheme 8).^{69–71} Reductive removal of the acetate, selective protection of the primary alcohol as a pivalate ester, and protection of the remaining hydroxyl groups as silyl ethers provided alkyne **43**. Iodoboration,^{30,72,73} reduction of the ester, and oxidation⁴³ of the resultant alcohol provided the alkenyl iodide **44**. The Nozaki–Hiyama–Kishi protocol was once again used to form the oxonane **45**, again in excellent diastereoselectivity.^{32,33} Fluoride-promoted cleavage of the silyl ethers and careful acetylation of the C4 hydroxyl provided the proposed structure of alcyonin (**41**). However, reminiscent of the sclerophytin A saga, the spectral data for the synthetic and natural material did not match. A C6 peroxide analog **46** was proposed by the Overman group

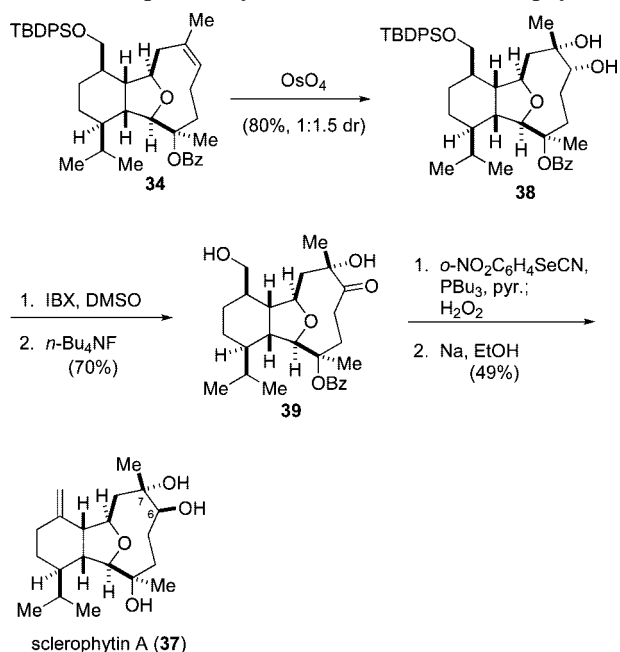
Scheme 5. Paquette's Endgame for the Original Structure of Sclerophytin A



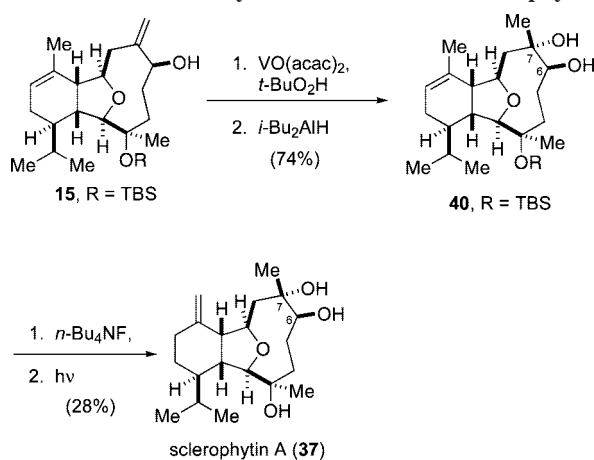
based upon the observed spectral data and reactivity of the synthetic and natural molecules,^{74–77} but no total synthesis of this reassigned compound has been achieved to date.

After the successful foray into the syntheses of cladiellin natural products, the Overman laboratory turned its attention to the briarellin subclass of the C2–C11 cyclized cembrane natural products.^{7,78,79} Again envisioning a Prins-pinacol reaction as the key step in forming the characteristic hydroisobenzofuran portion of the molecule (Scheme 9),¹⁶ the synthesis commenced via protonolysis of the silyl ketene acetal of lactone **47** (prepared in two steps from (*S*)-(+)-carvone).^{80,81} Reduction of the lactone **47** gave diol **48**. The primary alcohol was selectively protected as a silyl ether, and the secondary alcohol was oxidized to deliver the corresponding enone **49**.⁸² The enone **49** was converted to the corresponding enol triflate **50**,^{18,83} which was processed to the dienyl iodide **51**²⁰ via the vinyl stannane.¹⁹ The vinyl iodide was converted to the vinyl lithium species, which was treated with chiral aldehyde **5**, generating the diol **52** in 62%

Scheme 6. Paquette's Synthesis of Authentic Sclerophytin A



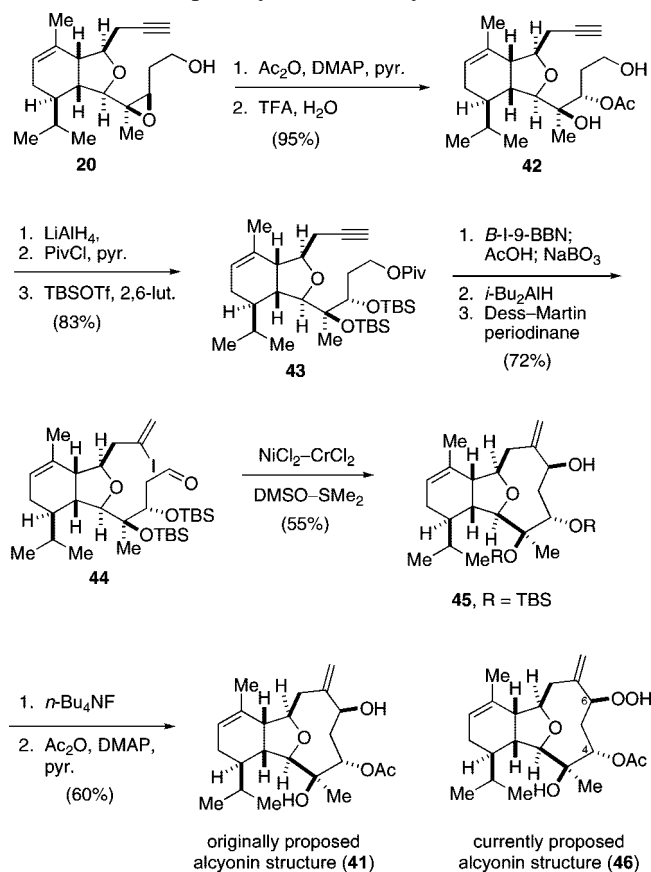
Scheme 7. Overman's Synthesis of Authentic Sclerophytin A



yield (3:1 dr) following methanolysis of the 2-methoxypropyl (MOP) acetal. The stage was set for the key Prins-pinacol condensation-rearrangement. Treatment of diol **52** with acid in the presence of aldehyde **53**, followed by subjection of the condensed product to tin tetrachloride, catalyzed the rearrangement, providing the hydroisobenzofuran **54** in 84% yield as a single detectable diastereomer. Photolytic deformylation²⁴ and selective basic hydrolysis of the *t*-butyldiphenylsilyl and trimethylsilyl protecting groups gave alcohol **55**. Regioselective and stereoselective epoxidation⁸⁴ of the acyclic alkene followed by acetylation of the primary alcohol then facilitated acetate-assisted opening of the epoxide.⁶⁹ Treatment of acetate **56** with aqueous acid, followed by acetylation of the resultant alcohol, efficiently provided alkyne **57**.

With two of the rings of the tetracycle formed, epoxidation of the trisubstituted olefin proceeded with good stereoselectivity, and attention was turned to the formation of the oxepane of the briarellin core (Scheme 10). Cleavage of the silyl ether and formation of the primary triflate under basic conditions triggered an intramolecular etherification, forming the third ring of the tetracyclic natural product. Next, the C12 carbinol was installed by acid-catalyzed opening of the

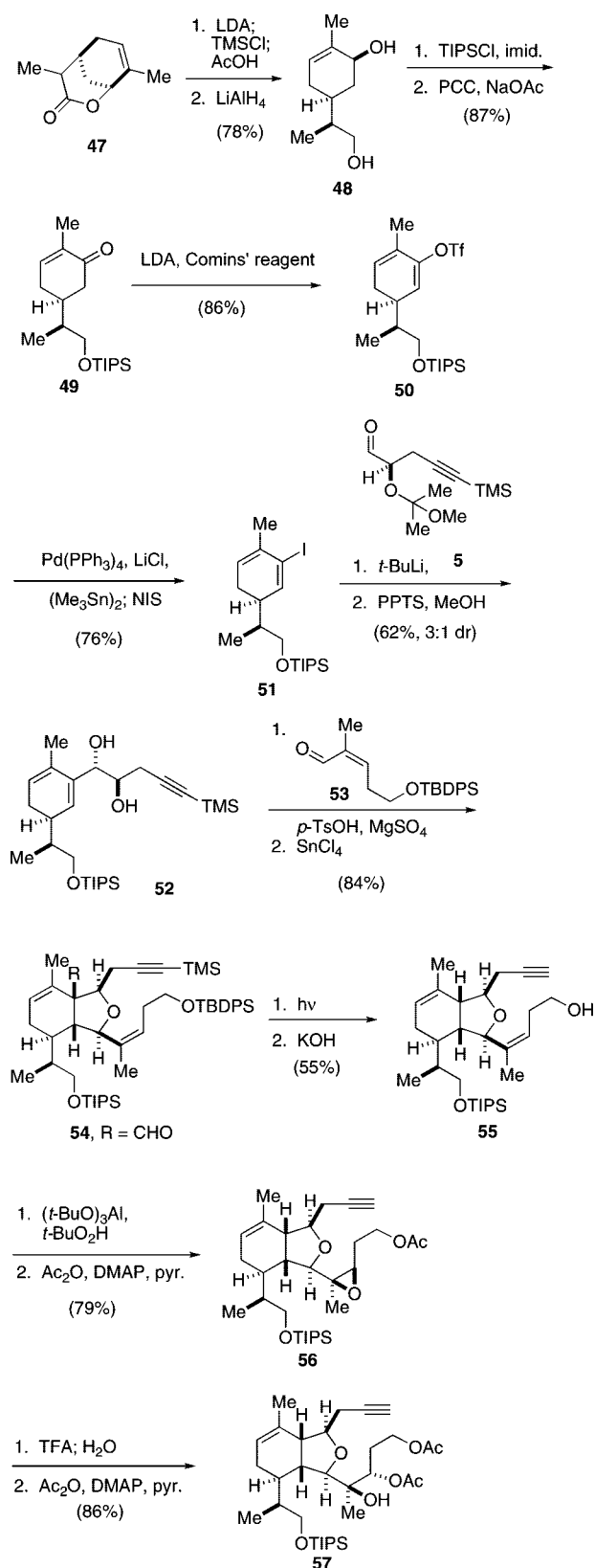
Scheme 8. Attempted Synthesis of Alcyonin



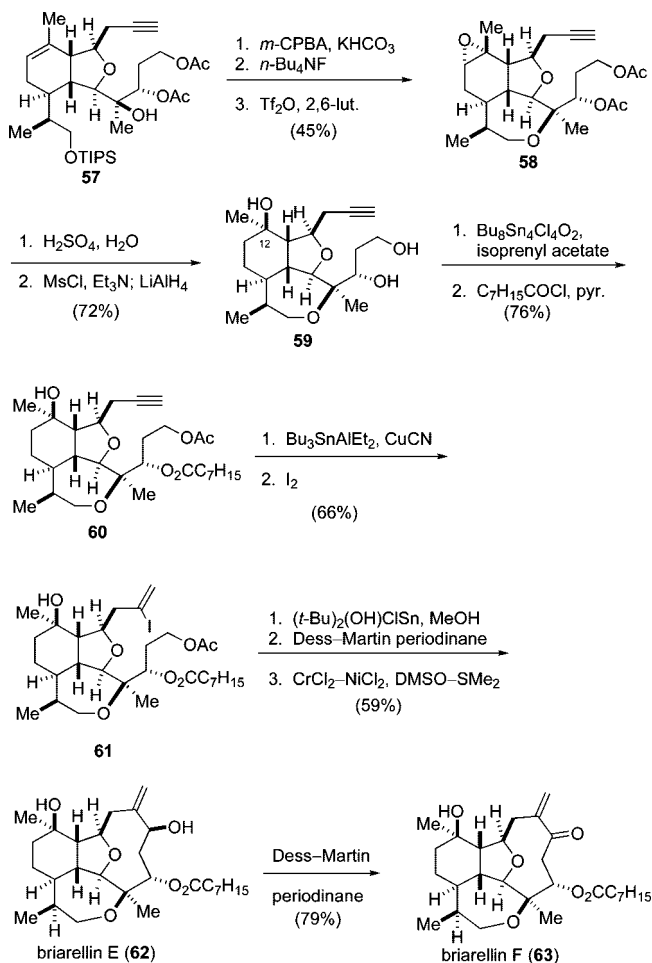
epoxide, followed by removal of the resultant C12 hydroxyl to generate tricycle **59**. A two-step procedure was next used to install the octanoyl side chain and provide ester **60**.⁸⁵ Stannylaluminum-protonolysis and a subsequent iododestannylation incorporated the vinyl iodide for the Nozaki–Hiyama–Kishi reaction.⁸⁶ The acetate group was selectively removed,⁸⁰ and oxidation of the primary alcohol provided the aldehyde.⁴³ The cyclization again proceeded with complete stereoselection in 79% yield to provide briarellin E (**62**).^{32,33} Oxidation of the allylic alcohol provided the enone, briarellin F (**63**).⁴³

2.4. [4 + 3]-Annulation

The Molander laboratory has developed a [4 + 3]-annulation strategy amenable for the construction of the hydroisobenzofuran of the cembranoids.^{87–89} (–)-7-Deacetoxyalcyonin acetate (**1**), previously synthesized by the Overman group, was chosen as the initial target for their investigations.^{14,15} To prepare a dialdehyde surrogate, bis-acetal **64** was constructed via a [2 + 2]-cycloaddition of methoxy ketene and α -phellandrene (**65**),^{90,91} followed by photochemical rearrangement (Scheme 11).^{92,93} Treatment of this bis-acetal **64** with alkoxydiene **66** in the presence of titanium tetrachloride effected the formal [4 + 3]-addition, establishing two of the seven stereocenters of the target molecule in a single step. A diastereoselective methylation was followed by a Krapcho decarboxylation of the methyl ester, which also partially epimerized the newly formed methyl stereocenter.⁹⁴ Since the stereochemistry of the methyl substituent was crucial for the subsequent silyl enol ether formation, the stereocenter of the minor diastereomer was epimerized to the necessary configuration under basic conditions. Formation of the more substituted silyl enol

Scheme 9. Forming the Hydroisobenzofuran of the Briarellins


ether,⁹⁵ selenation, and selenoxide elimination delivered enone **69**.⁹⁶ Conjugate addition of the cuprate derived from 2-ethoxyvinyl lithium^{97,98} and in situ formation of the vinyl triflate provided aldehyde **70** following hydrolysis of the ethyl enol ether.⁸³ A Nozaki–Hiyama–Kishi cyclization gave the cyclopentenol in good yield as a mixture of diastereomers.^{32,33}

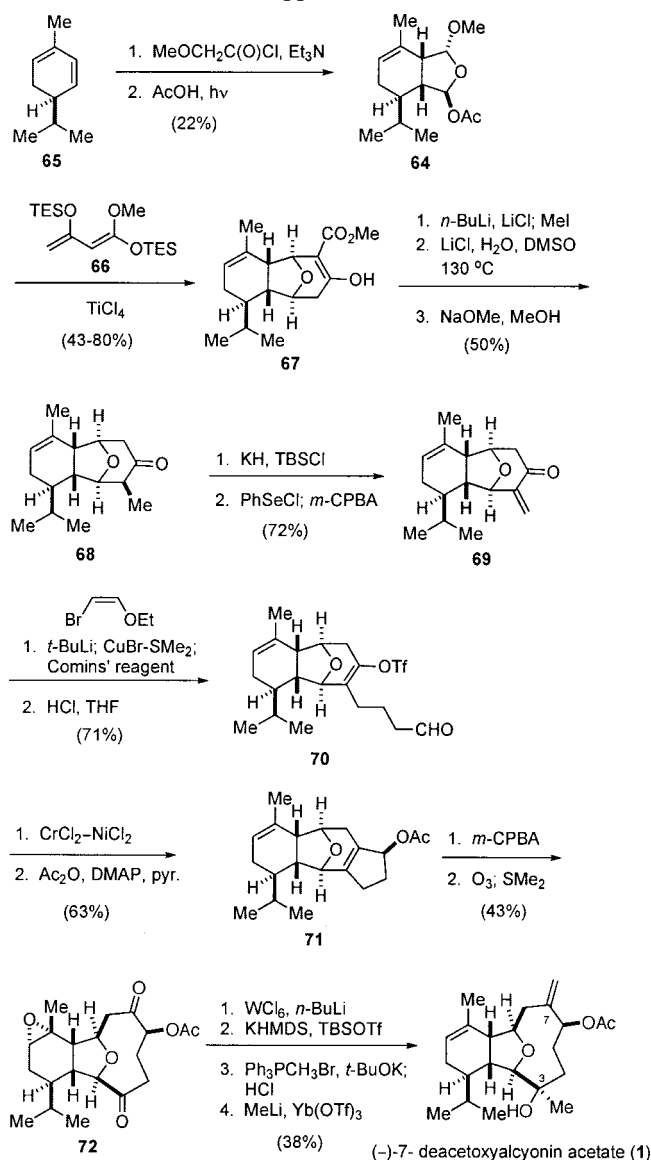
Scheme 10. Total Syntheses of Briarellins E and F


After a Mitsunobu reaction that served to transform the undesired cyclopentanol into the desired,⁹⁹ the merged material was progressed to the acetate ester **71**. The trisubstituted olefin was selectively protected as an epoxide, whereupon ozonolysis of the tetrasubstituted olefin delivered the nine-membered diketone **72**. The Sharpless tungsten reagent was used to restore the epoxide to trisubstituted olefin.¹⁰⁰ Finally, selective protection of the C3 ketone as the enol silane, methylenation of the C7 ketone, and subsequent hydrolysis of the silyl enol ether returned the C3 ketone. Conversion of the C3 ketone to the tertiary carbinol with methyl lithium in the presence of ytterbium triflate provided (–)-7-deacetoxyalcyonin acetate (**1**)⁹ as a single detectable diastereomer.¹⁰¹

2.5. Ring-Closing Metathesis/Intramolecular Diels–Alder Cycloaddition

The Crimmins laboratory has developed a general strategy for the construction of medium ring ethers^{102–106} via the ring-closing metathesis reaction^{107,108} of dienes generated by glycolate alkylation¹⁰⁹ and glycolate aldol reactions.^{105,110–112} As a result of this penchant, a novel strategy was envisioned for the synthesis of cembranoid natural products involving initial formation of the oxonene ring prior to the hydroisobenzofuran moiety. The synthesis of these final two rings hinged upon an intramolecular Diels–Alder approach that would complete the tricycle while concomitantly establishing the C1, C10, C13, and possibly the C14 stereocenters. Ophirin B (**73**)¹¹³ was first targeted, represent-

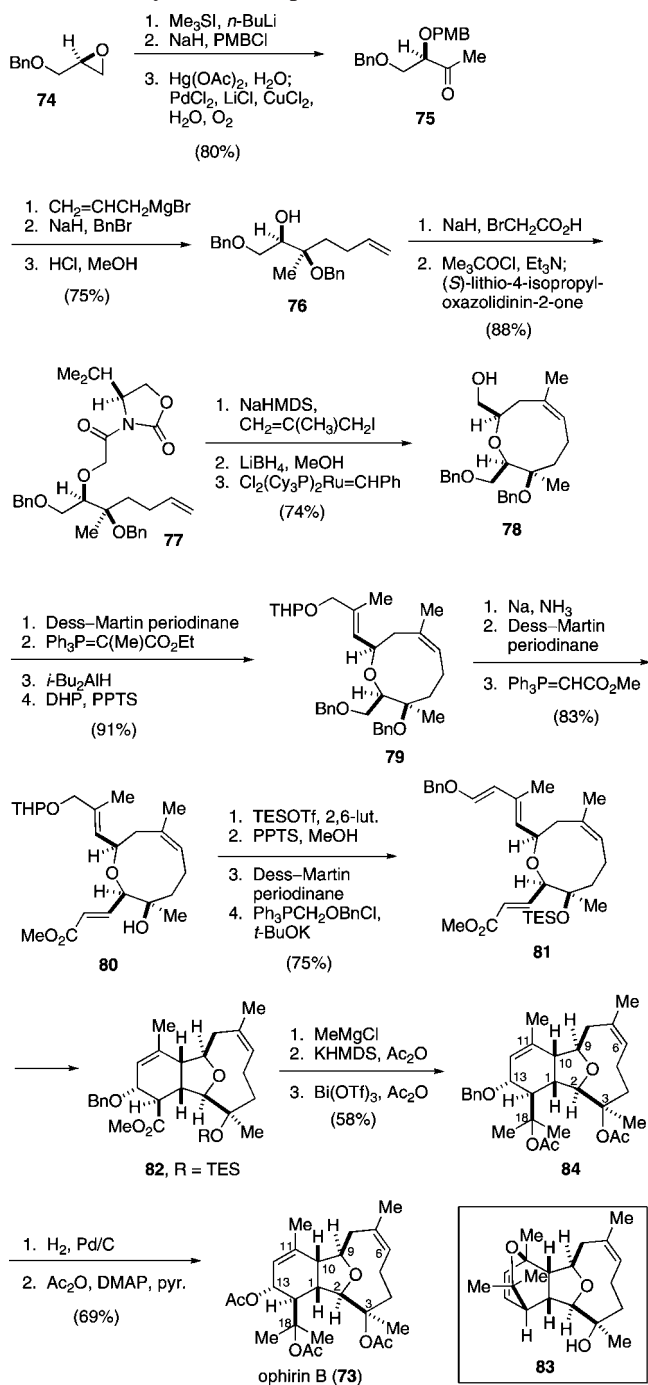
Scheme 11. Molander's Approach to the Cladiellins



ing the first C13, C18 oxygenated cladiellin to be prepared via total synthesis.^{114,115} The synthesis commenced with the reaction of (*S*)-benzylglycidyl ether (**74**)¹¹⁶ with dimethylsulfonium methylide followed by protection of the resulting secondary alcohol as a *p*-methoxybenzyl ether (Scheme 12). Wacker oxidation of the terminal alkene provided ketone **75** in 80% yield over three steps.^{117,118} Chelation-controlled stereoselective addition of vinyl magnesium bromide and protection of the resultant alcohol as a benzyl ether preceded deprotection of the secondary alcohol under acidic conditions to produce the alcohol **76**. Standard formation of the corresponding glycolic acid and glycolate provided imide **77**, prepared for a glycolate alkylation. The sodium enolate of imide **77** was alkylated with methallyl iodide in 93% yield to provide a single detectable diastereomer of the diene.¹⁰⁹ Reduction of the chiral auxiliary and ring-closing metathesis provided the oxonene **78**.¹⁰⁸

With the nine-membered ring **78** in hand, careful ordering of transformations was necessary for the installation of the diene and dienophile for the key Diels–Alder cycloaddition. To this end, an oxidation⁴³ of alcohol **78** and stabilized Wittig reaction provided an enoate, which was reduced with *i*-Bu₂AlH. The resultant allylic alcohol was protected as a

Scheme 12. Synthesis of Ophirin B



tetrahydropyranyl ether to provide oxonene **79**. Dissolving metal reduction of oxonene **79** cleaved the benzyl ethers and provided the corresponding diol. The primary alcohol was oxidized,⁴³ and the resulting aldehyde was treated with a stabilized Wittig reagent to give the enoate **80**, which would serve as the dienophile in the upcoming Diels–Alder reaction. The diene unit was completed by a series of four steps. Protection of the C3 tertiary alcohol as the triethylsilyl ether was followed by removal of the tetrahydropyranyl (THP) ether under acidic conditions. The resultant alcohol was oxidized to the aldehyde,³¹ which was treated with benzyloxymethylenetriphenylphosphorane to give tetraene **81** as a 3:1 mixture of *Z/E* isomers. Under ambient conditions, tetraene **81** underwent a spontaneous, highly *exo*-selective Diels–Alder cycloaddition. The minor isomer from the Wittig reaction could be recycled to the reactive tetraene **81**

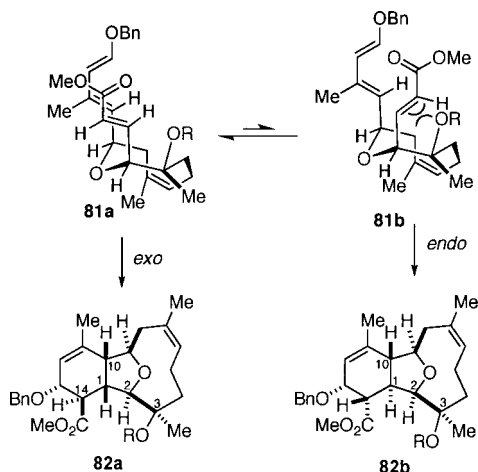


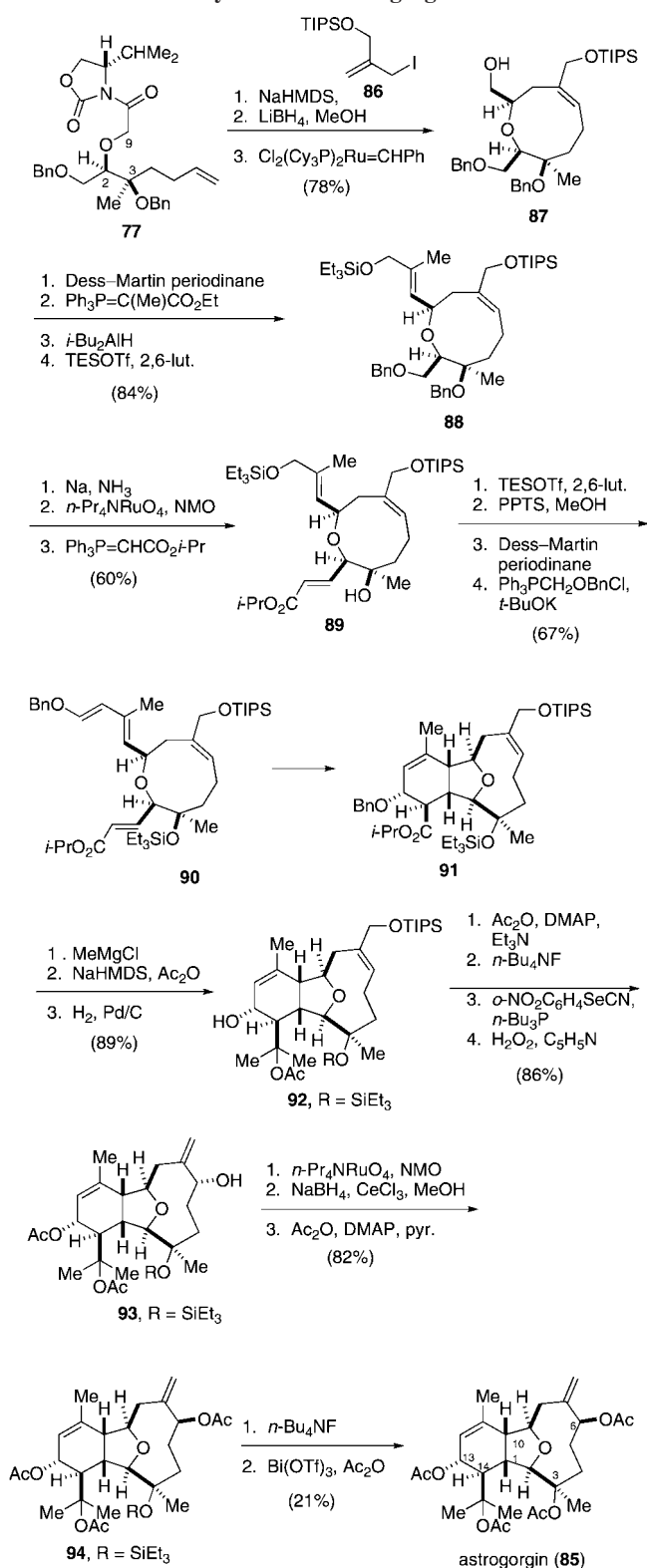
Figure 4. Diels–Alder selectivity models.

by photochemical isomerization in the presence of diphenyldisulfide, providing an overall 78% yield of tricycle **82**.¹¹⁹ The observed stereochemistry from the cycloaddition can be rationalized by inspection of selectivity models **81a** and **81b**, which demonstrate the importance of the C3-protecting group (Figure 4). Specifically, the C3 hydroxyl protecting group has a significant steric interaction with the C14 proton and carbon in the *endo*-model, which is mitigated in the *exo*-case. This hypothesis has been corroborated by varying the size of the C3-protecting group and observing the diastereoselectivity of the cycloaddition. Additionally, the work of Holmes using C3 epimers (vide infra) supports these selectivity models.¹²⁰

With the tricyclic core formed, addition of methylmagnesium chloride to ester **82** delivered the tertiary alcohol. A careful acetylation sequence was required to preclude formation of tetracycle **83**. Removal of the silyl ether provided the diol, and the C18 hydroxyl was selectively acetylated under basic conditions.⁴⁴ The C3 hydroxyl was then converted to its acetate ester **84** in the presence of a Lewis acid.^{121,122} Finally, cleavage of the benzyl ether, and acetylation under basic conditions, provided ophirin B (**73**), which possessed identical spectroscopic properties in all respects to the natural material.

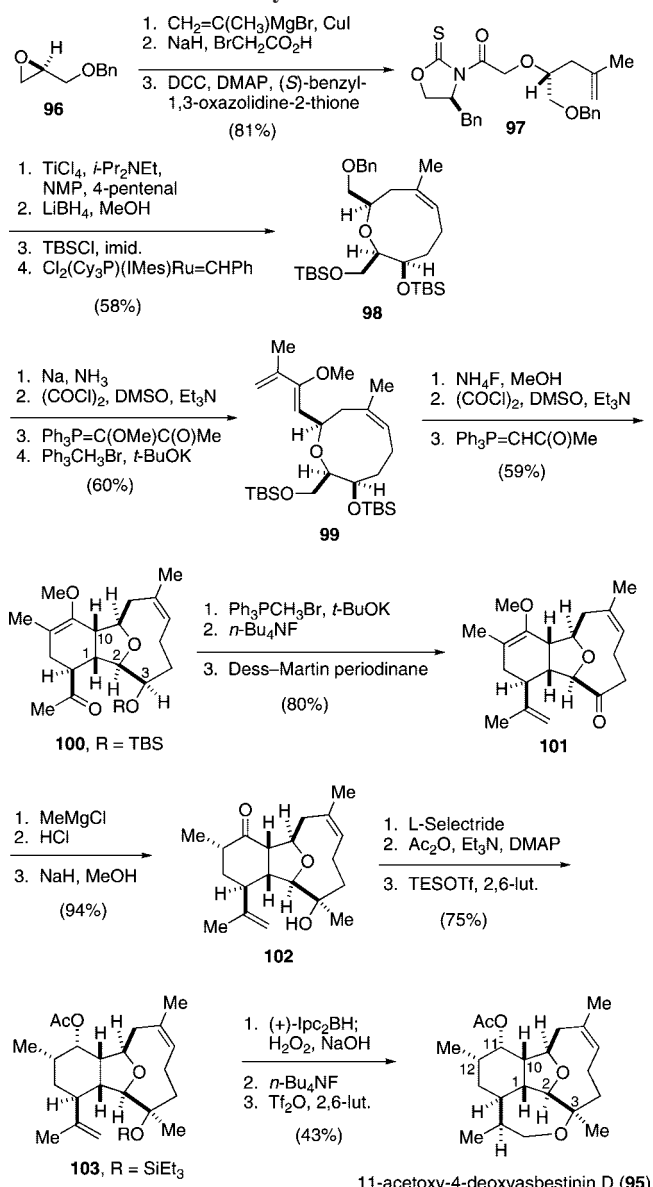
In addition to the synthesis of ophirin B (**73**),^{114,115} the Crimmins group pursued the synthesis of a structurally related, biologically active cladiellin, astrogorgin (**85**).^{113,123} Identical to ophirin B (**73**), except for an additional oxygenated stereocenter at C6 and an exocyclic olefin in place of the endocyclic unsaturation in ophirin B, it was believed that astrogorgin (**85**) could be constructed utilizing a more highly functionalized electrophile for the alkylation of glycolyl oxazolidinone **77**.¹⁰⁹ The allylic iodide would possess a latent synthetic handle that could be used to install the C6 stereocenter following construction of the tetracycle (Scheme 13). Thus, utilizing the glycolate **77**, from the ophirin B synthesis, alkylation of its sodium enolate, followed by reductive removal of the auxiliary and ring-closing metathesis, gave oxonene **87** in 78% overall yield.¹⁰⁸ An identical sequence was utilized to install the diene and dienophile as was applied in the ophirin B (**73**) synthesis,^{114,115} and the key intramolecular Diels–Alder cycloaddition again proceeded under ambient conditions to provide tricycle **91** as a single diastereomer. Addition of methylmagnesium chloride to the ester and acetylation of the C18 tertiary alcohol proceeded uneventfully, followed by careful hydrogenation of the C13 benzyl ether. Acetylation of the C13 alcohol with

Scheme 13. Total Synthesis of Astrogorgin



ensuing deprotection of the allylic triisopropylsilyl protecting group provided an alcohol that was utilized in an allylic transposition to provide the epimeric C6 hydroxyl for astrogorgin (**85**).^{124,125} An oxidation³¹ and Luche reduction⁴⁹ delivered the desired C6 alcohol stereoselectively. Acetylation of the C6 hydroxyl, and exchange of the C3 TES group with the fourth and final acetate group, was accomplished to provide astrogorgin (**85**), which was identical in all regards to the naturally isolated material.^{113,123}

Scheme 14. First Total Synthesis of an Asbestinin



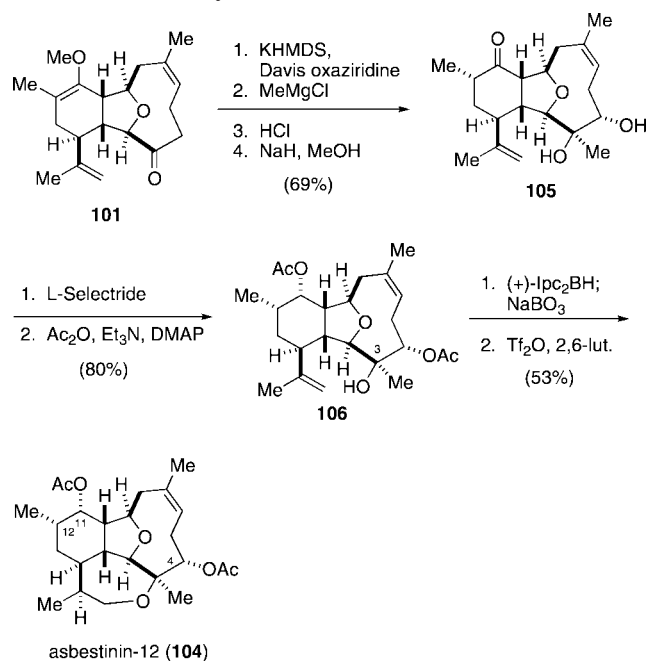
The Crimmins laboratory had also utilized glycolate aldol reactions as an entry into dienes for ring-closing metathesis.^{105,110–112} To explore the viability of this protocol for cembrane natural products, the asbestinin subclass was targeted, as it was the only subclass of the C2–C11 cembranoids yet to be prepared by total synthesis. Specifically, 11-acetoxy-4-deoxyasbestinin D (**95**) was selected because of its interesting molecular topology as well as biological properties.¹¹ 11-Acetoxy-4-deoxyasbestinin D (**95**) shows cytotoxicity against CHO-K1 cells ($\text{ED}_{50} = 4.82 \mu\text{g}/\text{mL}$) and antimicrobial activity against *Klebsiella pneumoniae*. As in the previous cladiellin syntheses, an intramolecular Diels–Alder cycloaddition was envisioned as a key step in the strategy.^{114,115} To begin the synthesis, (*R*)-benzyl glycidyl ether (**96**) was opened with 2-propenylmagnesium bromide in the presence of copper iodide.^{126–128} The alcohol produced was processed to the oxazolidinethione **97** under standard conditions (Scheme 14). Subjection of the titanium enolate of oxazolidinethione **97** to 4-pentenal,^{129,130} under the improved conditions developed in the Crimmins laboratory for complex glycolate aldol reactions,¹¹² gave the aldol adduct in 70% yield as a single detectable diastereomer. Reduction of the chiral auxiliary and protection of the diol

as the bis-TBS ether provided a ring-closing metathesis candidate. Treatment of the diene with the Grubbs second-generation catalyst gave the oxonene **98** in high yield.¹⁰⁸ Reductive removal of the benzyl ether and oxidation¹³¹ of the corresponding alcohol to the aldehyde was followed by two sequential Wittig reactions to complete the diene **99** necessary for the Diels–Alder reaction.¹³² Careful, selective deprotection of the primary silyl ether in the presence of the labile enol ether provided the primary alcohol,¹³³ which was oxidized under Swern conditions.¹³¹ The resulting aldehyde was treated with a stabilized Wittig reagent to install the dienophile.¹³⁴ During the course of the Wittig reaction, a spontaneous Diels–Alder cycloaddition ensued to provide the desired tricycle **100** as a single diastereomer. The *exo*-selectivity of this cyclization can again be explained using the aforementioned models (Figure 4).^{114,115}

Attention was next turned to refunctionalizing the oxonene. After methylenation of the methyl ketone, the C3 silyl ether was removed with *n*- Bu_4NF , and the alcohol was oxidized to the ketone **101**.⁴³ A diastereoselective addition of methylmagnesium chloride formed the tertiary alcohol in high yield. At this point, hydrolysis of the enol ether provided the α -methyl ketone **102** as a mixture of C12 epimers. Chromatographic separation of the diastereomers followed by base-catalyzed equilibration of the undesired isomer allowed all material to be recycled to the desired C12 configuration. Diastereoselective reduction of the ketone was followed by acetylation of the secondary alcohol and protection of the C3 tertiary alcohol as a silyl ether. Although regioselective hydroboration of the 1,1-disubstituted olefin **103** with standard dialkylboranes was chemoselective, the diastereoselectivity was low. However, treatment of diene **103** with (+)-diisopinocampheylborane followed by oxidative workup delivered the desired primary alcohol as a single diastereomer, serving as a rare example of the successful use of a chiral hydroborating reagent for the functionalization of a 1,1-disubstituted olefin.^{135,136} The tertiary protecting group was next cleaved. With the diol in hand, formation of the primary triflate under basic conditions triggered a spontaneous, intramolecular etherification to form the final ring of the tetracycle **95**.⁸⁰ This total synthesis of 11-acetoxy-4-deoxyasbestinin D (**95**)¹¹ represents the first synthesis of a natural product from the asbestinin subclass, serving to confirm the absolute configuration of this group of molecules.

Application of the above route to an asbestinin with substitution at C4, asbestinin-12 (**104**), is presented below. Asbestinin-12 (**104**) was completed through the utilization of a diastereoselective α -hydroxylation of the ketone **101** (Scheme 15).^{137,138} Treatment of the potassium enolate of ketone **101** with the Davis oxaziridine provided a single detectable diastereomer of the alcohol in good yield.^{139–141} A similar sequence to that utilized for 11-acetoxy-4-deoxyasbestinin D (**95**) was followed to prepare asbestinin-12 (**104**).¹²⁶ Addition of methylmagnesium chloride to the C3 ketone and hydrolysis of the enol ether provided the ketone **105** as a mixture of diastereomers, which could again be equilibrated and separated to provide the desired C12 configuration. Reduction of the ketone and selective acetylation of both secondary alcohols gave diene **106** in good yield. Again, the chiral hydroborating reagent was useful for accessing the desired primary alcohol.^{135,136} This time, the hydroboration was carried out on the free C3 hydroxyl, demonstrating that the large protecting group at C3 is not necessary for the diastereoselectivity observed; the stereo-

Scheme 15. Total Synthesis of Asbestinin-12

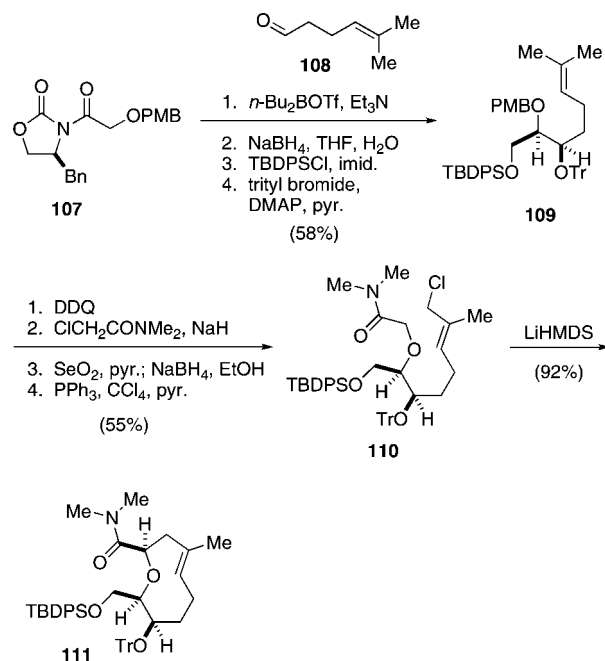
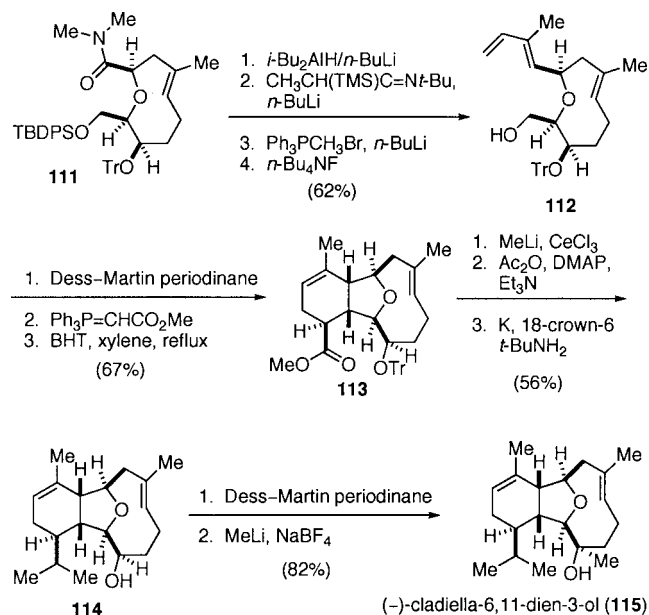


selection is dictated by the chiral reagent. Intramolecular etherification proceeded in good yield to provide asbestinin-12 (**104**),⁸⁰ which was also identical to all spectroscopic data for the natural product.¹³⁷

2.6. Intramolecular Amide Enolate Alkylation

Each of the previously described syntheses have targeted cembranoids containing a (*Z*)-oxonene or lacking an endocyclic olefin within the nine-membered ring of the natural products. In 2006, the Kim laboratory reported a route to the more sensitive (*E*)-olefin containing cladiellins that are also ubiquitous in the isolation literature.¹⁴² The approach involved an intramolecular amide enolate alkylation, which has been well-documented within their group for the efficient formation of medium ring ethers.^{143–145} Upon forming the oxonene via this process, an intramolecular Diels–Alder cycloaddition analogous to that reported by the Crimmins laboratory^{114,115,120,126} was used to form the remaining two rings of several cladiellin natural products. Their synthesis commenced with an asymmetric glycolate aldol reaction under the Evans dibutylboron triflate conditions (Scheme 16).^{146–148} Reduction of the chiral auxiliary and sequential protection of the diol provided alkene **109**. Oxidative removal of the *p*-methoxybenzyl ether¹⁴⁹ and subsequent alkylation of the alcohol with 2-chlorodimethyl acetamide proceeded efficiently. Selective allylic oxidation¹⁵⁰ and chlorination of the resultant alcohol¹⁵¹ afforded amide **110** prepared for the key intramolecular alkylation. Treatment with lithium hexamethyldisilazide led to formation of the desired (*E*)-oxonene **111** in 92% yield as a single detectable diastereomer.^{143–145}

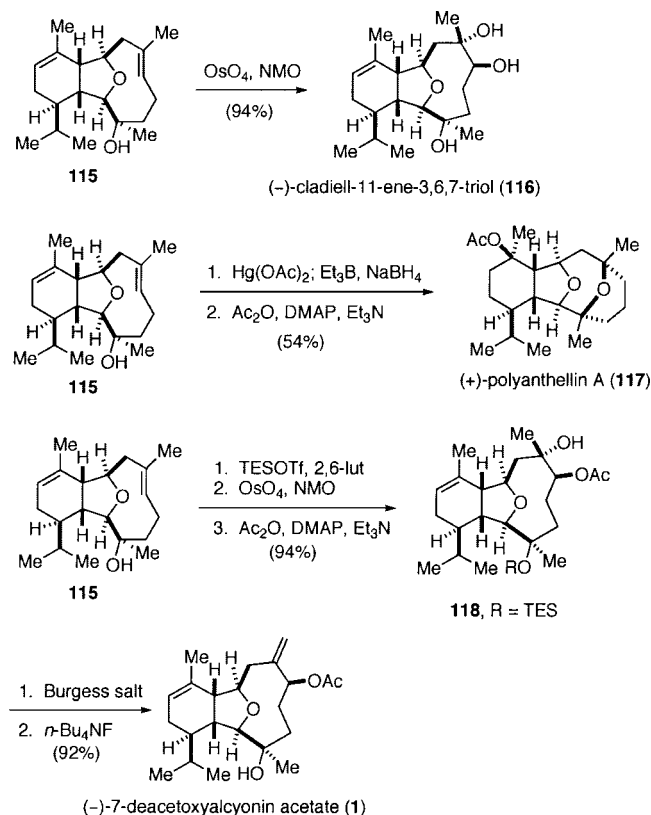
Following formation of the medium ring ether **111**, the functionalization to an appropriate Diels–Alder candidate commenced (Scheme 17). Reduction of the amide to the aldehyde¹⁵² and ensuing olefination by the Corey protocol gave an enal.¹⁵³ Methylenation of the aldehyde and fluoride-promoted removal of the silyl ether gave alcohol **112**. Oxidation⁴³ of alcohol **112** to the aldehyde followed by Wittig olefination gave the intramolecular Diels–Alder substrate, which was treated with 2,6-di-*t*-butyl-4-methylphenol (BHT) in refluxing xylene to afford the desired tricycle

Scheme 16. Formation of (*E*)-OxoneneScheme 17. Completion of First (*E*)-Olefin Containing Cladiellin

113 as a single detectable diastereomer via an *exo*-cycloaddition. Addition of methylmagnesium chloride to the ester and protection of the tertiary alcohol as an acetate ester set the stage for a dissolving metal reduction to deoxygenate the ester and remove the trityl protecting group.¹⁵⁴ Oxidation⁴³ of the C3 alcohol to the ketone and nucleophilic addition with methyllithium provided a single diastereomer of the tertiary alcohol in 82% yield over two steps, completing the total synthesis of (–)-cladiella-6,11-dien-3-ol (**115**),^{35,113} which represents the first total synthesis of an (*E*)-olefin containing C2–C11 cyclized cembrane natural product.

Seeking to further illustrate the versatility of their synthetic approach, three other cembranoid natural products were targeted. Stereoselective dihydroxylation of tricycle **115** allowed access to (–)-cladiell-11-ene-3,6,7-triol (**116**) in 94% yield (Scheme 18).^{38,64,155} A one-pot procedure was also

Scheme 18. Versatile Syntheses of Several Natural Cladiellins

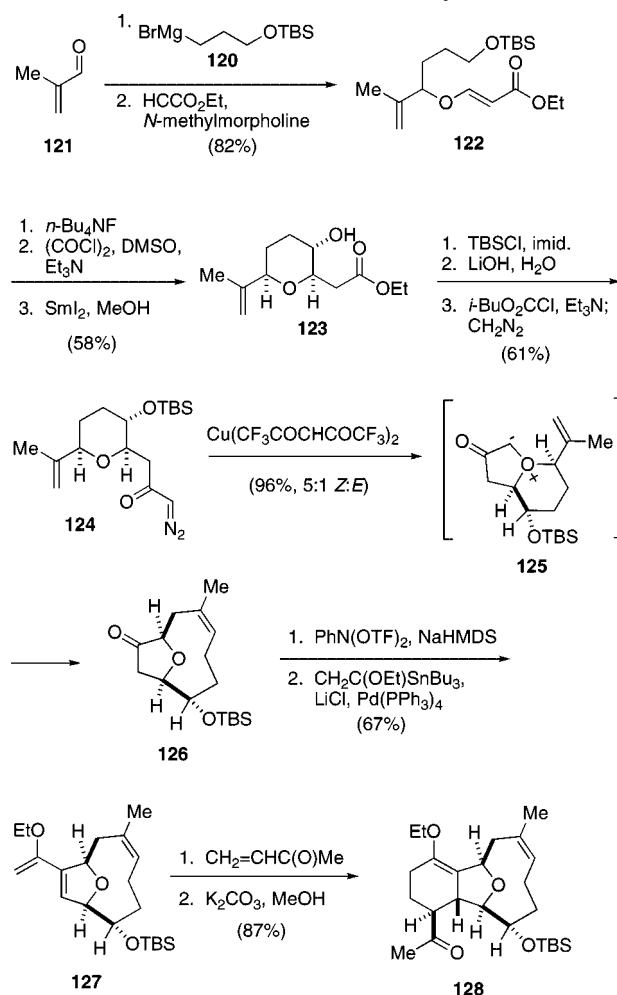


developed involving oxymercuration of both olefins of (-)-cladiella-6,11-dien-3-ol (**115**) and demercuration to provide the tetracycle in 69% yield.¹⁵⁶ Acetylation of the resultant tertiary alcohol provided (+)-polyanthellin A (**117**),^{78,157} marking the first total synthesis of this natural product. Finally, following protection of the tertiary alcohol of (-)-cladiella-6,11-dien-3-ol (**115**), stereoselective dihydroxylation and acetylation of the secondary alcohol gave tertiary alcohol **118**. Dehydration using the Burgess salt provided the exocyclic olefin,¹⁵⁸ and removal of the silyl protecting group afforded (-)-7-deacetoxyalcyonin acetate (**1**),^{14,15,87} representing the third total synthesis of this natural product.

2.7. Wittig Rearrangement/Intermolecular Diels–Alder Strategy

In 2007, the Clark laboratory divulged another unique approach to cladiellin diterpenes, hinging upon a [2,3]-sigmatropic rearrangement used to form the five- and nine-membered rings of the tricycle. Following bicycle formation, an intermolecular Diels–Alder cycloaddition was used to install the cyclohexyl moiety.¹⁵⁹ Vigulariol (**119**), a molecule possessing in vitro cytotoxicity against human-lung adenocarcinoma ($\text{IC}_{50} = 18 \text{ nM}$),¹⁶⁰ was chosen as the initial target. To begin, a Grignard reagent **120** was added to methacrolein (**121**) to give a secondary alcohol (Scheme 19). The reported synthesis of vigulariol (**119**) is racemic due to the employment of a racemic preparation of the secondary alcohol, but it could be rendered enantioselective if a suitable method of preparing the single enantiomer of this alcohol was employed.¹⁶¹ *O*-Alkylation with ethyl propiolate gave enoate **122**.^{162,163} Cleavage of the TBS ether and Swern oxidation¹³¹ of the alcohol gave the aldehyde. A stereoselective samarium-mediated reductive cyclization delivered the tetrahydropyran

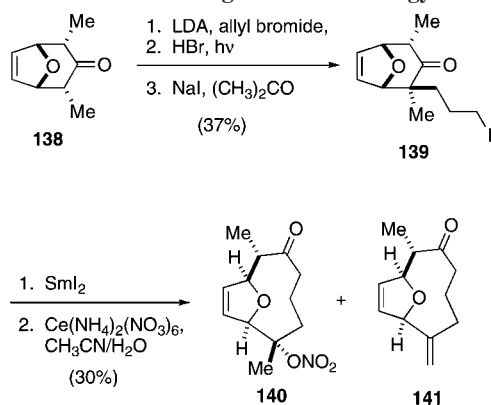
Scheme 19. Intermolecular Diels–Alder Cycloaddition



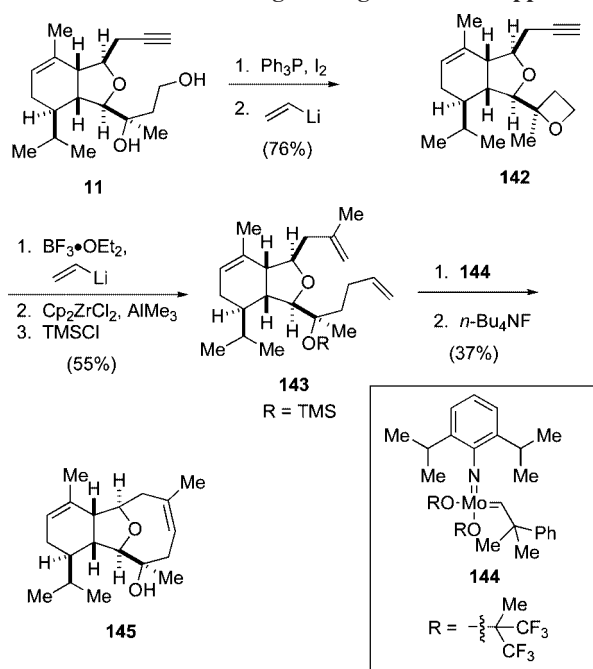
123.¹⁶⁴ Protection of the alcohol, followed by hydrolysis of the ester, provided a carboxylic acid, which was converted to the corresponding anhydride and treated with diazomethane to give diazoketone **124**. At this point, the copper carbenoid of diazoketone **124** was formed; ensuing oxonium ion formation and [2,3]-Wittig rearrangement occurred to deliver the oxonene **126** of the cladiellins.^{165,166} A 5:1 *Z/E* mixture of alkenes was obtained, but the material possessing the (*E*)-oxonene could be converted to the desired isomer using azobisisobutyronitrile (AIBN) and ethanethiol.^{167,168} The tetrahydrofuranone was converted to a vinyl triflate, and a Stille coupling was used to form the diene **127**.¹⁶⁹ Intermolecular Diels–Alder cycloaddition with methyl vinyl ketone gave a 2:1 *exolendo* mixture of isomers, which was equilibrated to the desired *exo*-adduct **128** under basic conditions.

With the tricycle elaborated, the ketone **128** was methyl-enated, and the enol ether was hydrolyzed under acidic conditions (Scheme 20). Selective hydrogenation of the 1,1-disubstituted olefin was followed by methylenation of the ketone to give diene **129**. Cleavage of the silyl ether, oxidation of the alcohol to the ketone,⁴³ and addition of methylmagnesium chloride efficiently provided alcohol **130**. Finally, an epoxidation with *meta*-chloroperoxybenzoic acid (*m*-CPBA) delivered the epoxide, which was opened intramolecularly by the C3 tertiary alcohol to afford (\pm)-vigulariol (**119**).¹⁶⁰

Scheme 22. Annulation-Fragmentation Strategy



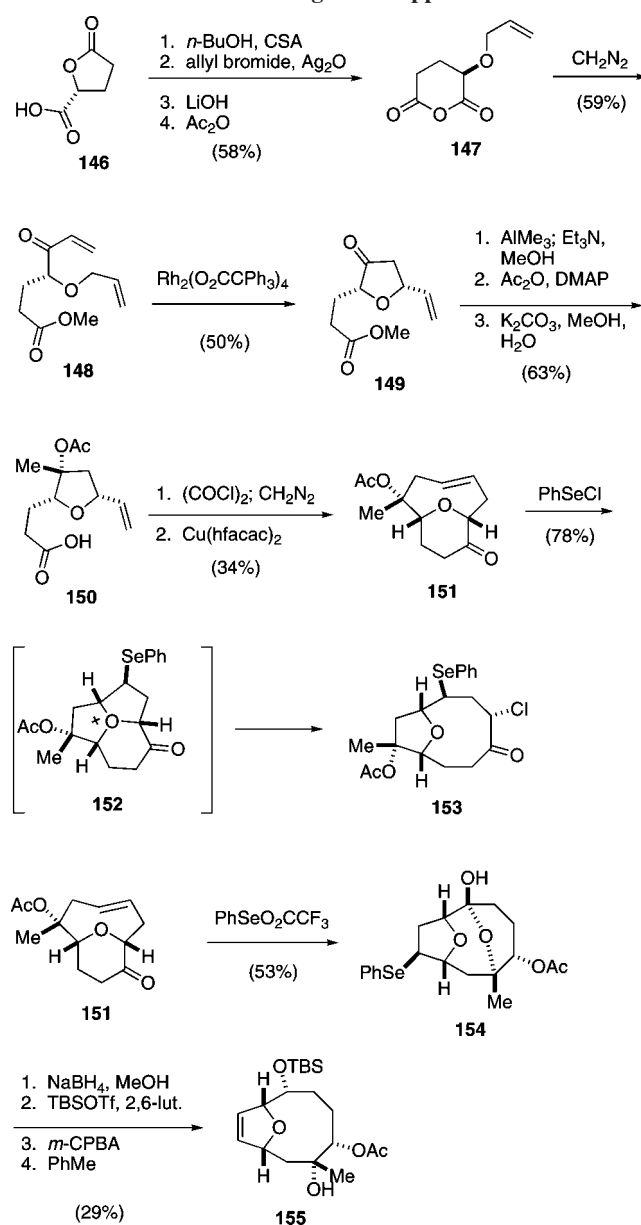
Scheme 23. Overman's Ring-Closing Metathesis Approach



catalyst **144**,¹⁸⁰ none of the desired oxonene was observed; instead, the cyclic product was truncated by one carbon to afford oxocene **145** following deprotection. These seminal studies set the stage for future explorations into ring-closing metathesis of the medium ring ether of the cembranoids using alternative catalysts.

The Clark group reported an approach to the oxabicyclo-[6.2.1]undecane core of the cladiellins in 2000.¹⁸¹ Their strategy featured a novel rearrangement to form the five- and nine-membered rings of these natural products. Beginning with (*R*)- γ -butyrolactone- γ -carboxylic acid (**146**),¹⁸² acid-catalyzed ring opening of the lactone¹⁸³ was followed by allylation of the resultant secondary alcohol (Scheme 24).¹⁸⁴ Hydrolysis and acetylation afforded anhydride **147**. Treatment with diazomethane regioselectively opened the ring, and formation of the rhodium carbenoid provided furanone **149** in 50% yield.^{167,168,185} A diastereoselective methylation¹⁸⁶ preceded acetylation and hydrolysis to give acid **150**. Again, treatment with diazomethane followed by formation of the copper carbenoid set the stage for a spontaneous [2,3]-Wittig rearrangement to give bicycle **151**.^{165,166} As the key step of the synthesis, bicycle **151** was treated with phenylselenenyl chloride, which triggered a rearrangement to yield oxabicycloundecane **153** in 78% yield. Additionally, treatment of ketone **151** with phenylselenenyl trifluoroacetate gave

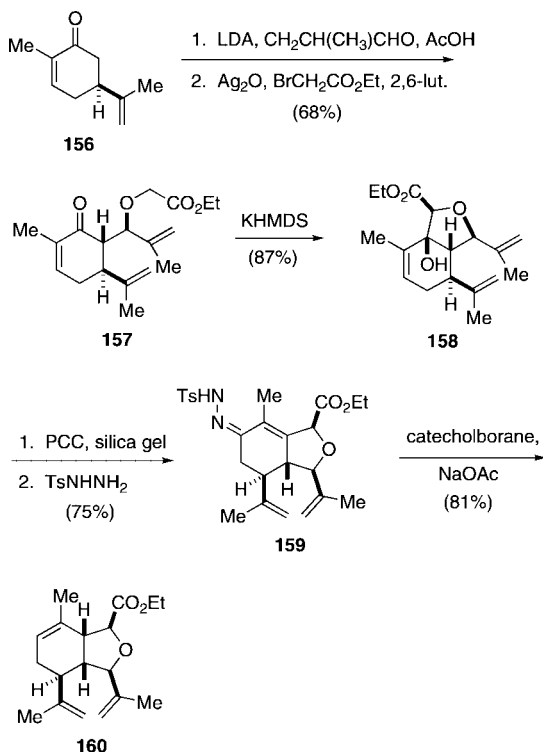
Scheme 24. Clark's Rearrangement Approach



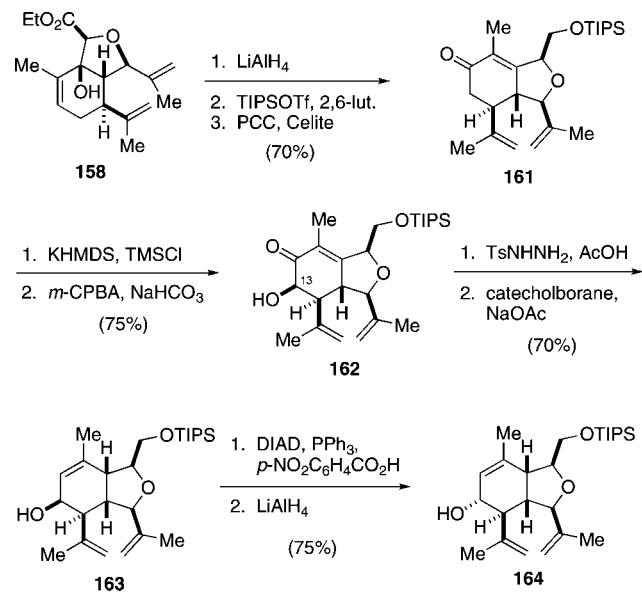
tricycle **154**, albeit in lower yield. Recently, in a separate publication, Clark reported that reduction of tricycle **154**, followed by protection of the resulting alcohol, and oxidative elimination of the selenide gave bicycle **155**, which represents a framework that could potentially be used to complete a cladiellin natural product.¹⁸⁷

The McIntosh laboratory has developed two strategies for the synthesis of the hydroisobenzofuran of the C2–C11 cyclized cembranoids. The first report relied upon an intramolecular approach to form the furan portion of these molecules.¹⁸⁸ Beginning with (*S*)-carvone (**156**), an aldol reaction¹⁸⁹ with methacrolein and subsequent Williamson etherification of the resultant alcohol provided ester **157** (Scheme 25).^{82,190} An intramolecular aldol reaction delivered bicycle **158** in 87% yield. Oxidation of the tertiary allylic alcohol gave the transposed enone,¹⁹¹ which was converted to the tosylhydrazone **159**. Reduction of tosylhydrazone **159** with catecholborane followed by heating the reaction gave the *cis*-fused isobenzofuran **160**.^{192–194} A similar route was also developed to access natural products containing oxygenation at C13, such as astrogorgin (**85**).^{113–115,123} To this

Scheme 25. Cycloaldol Route to the Isobenzofuran



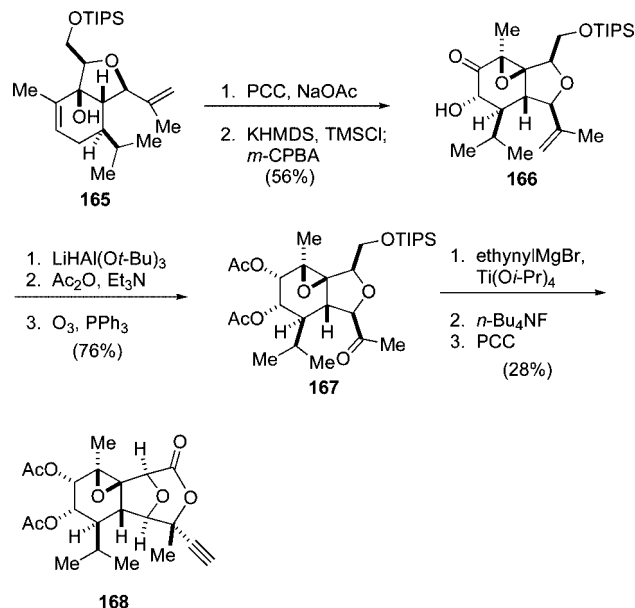
Scheme 26. C13-Oxidized Isobenzofuran



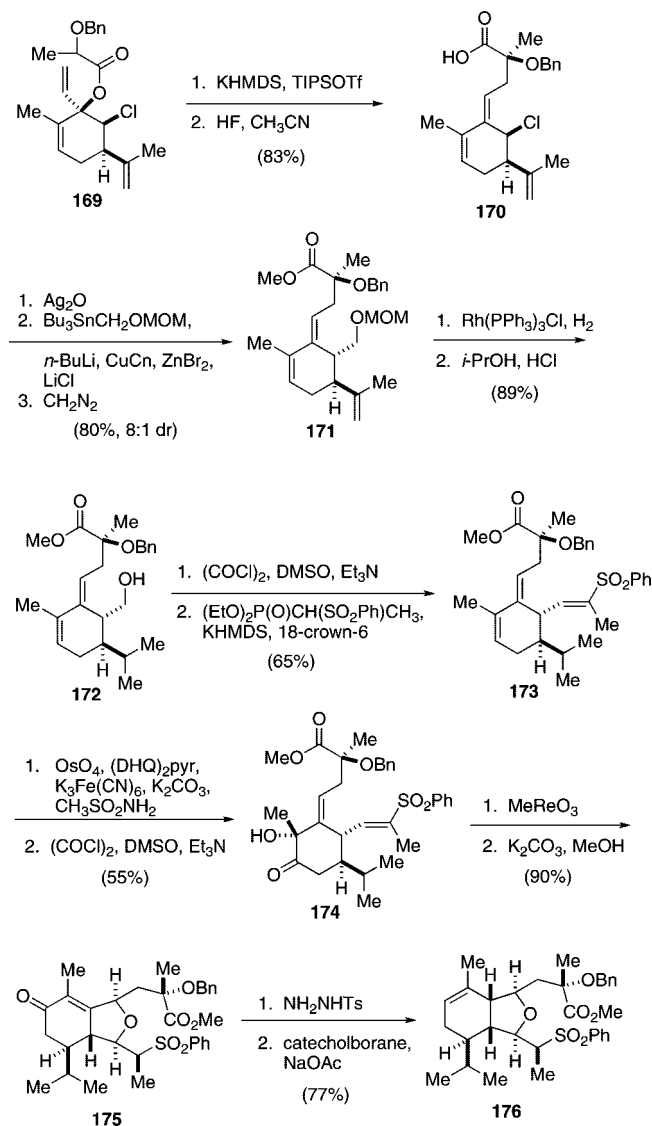
end, ester **158** was reduced to the primary alcohol, the alcohol was protected as a silyl ether, and the secondary allylic alcohol was oxidized to the enone **161** (Scheme 26). Rubottom oxidation¹⁹⁵ of enone **161** gave predominantly the undesired configuration of the C13 alcohol **162** (7:1 dr), and formation of the tosylhydrazone proceeded smoothly. Reduction with catecholborane and in situ allylic diazene rearrangement gave the trisubstituted olefin **163**.^{192–194} A Mitsunobu reaction gave the desired C13 configuration for bicycle **164**.⁹⁹

In 2004, the McIntosh laboratory published further efforts using an intermediate from their cycloaldol approach toward the massileunicellins (Scheme 27).¹⁹⁶ Previously accessed bicycle **165**¹⁸⁸ underwent oxidative rearrangement when treated with pyridinium chlorochromate (PCC),^{197,198} and the

Scheme 27. Further Efforts by McIntosh

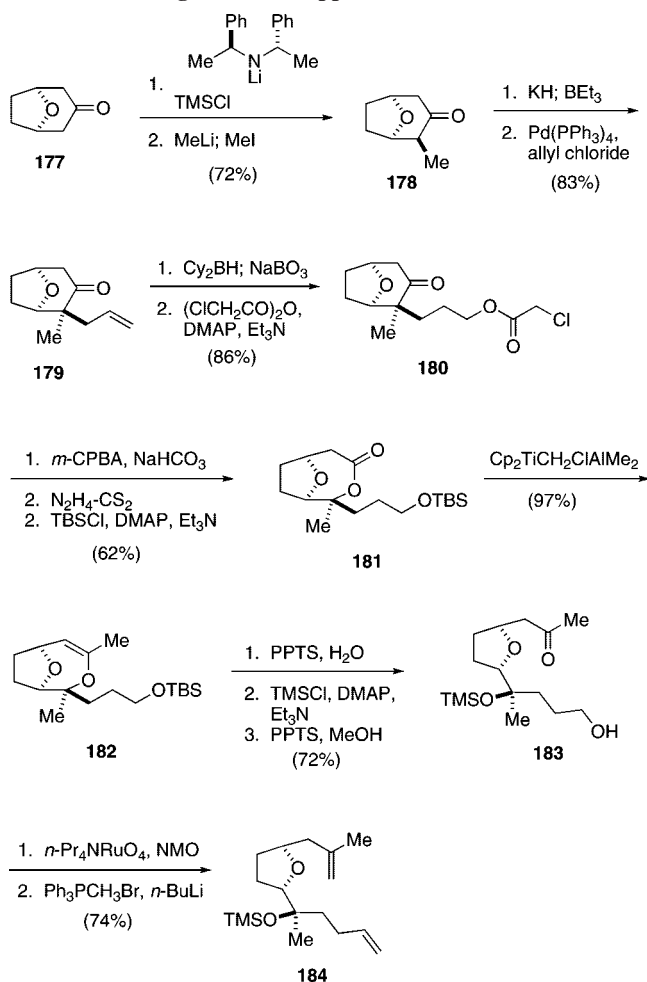


Scheme 28. Rearrangement Approach to the Cladiellins



resultant ketone was treated under Rubottom oxidation conditions to provide alcohol **166**.¹⁹⁵ Reduction, esterifica-

Scheme 29. Fragmentation Approach to the Furan

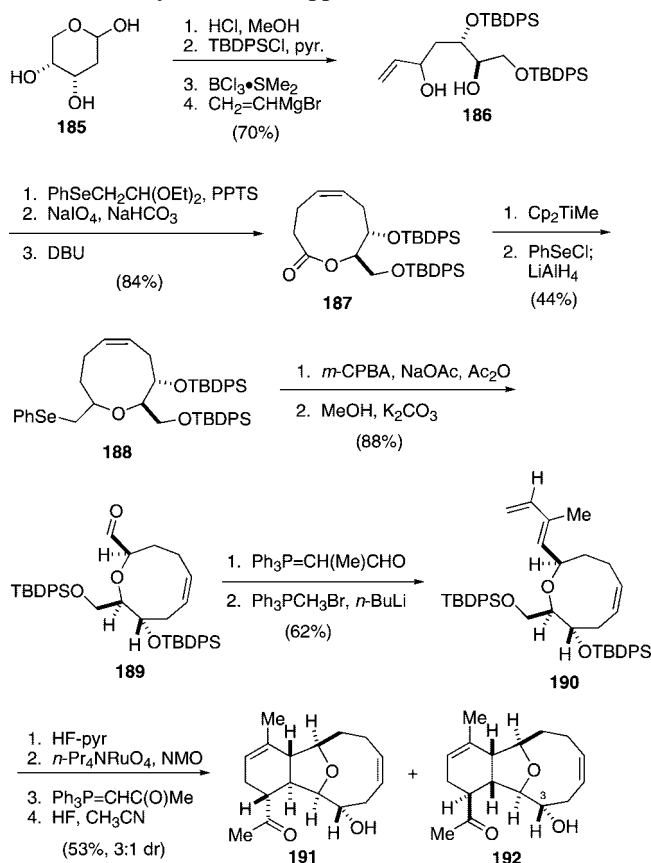


tion, and ozonolysis delivered ketone **167**. Alkynylation,¹⁹⁹ deprotection, and lactonization gave tetracycle **168**. No further efforts involving this route have been reported since 2004.

The second route recently reported by McIntosh involves an Ireland–Claisen rearrangement (Scheme 28). The approach commenced with ester **169** (available in three steps from (*S*)-carvone).^{200,201} Treatment with base in the presence of triisopropylsilyl triflate triggered the sigmatropic rearrangement to give acid **170** after cleavage of the silyl ester.²⁰² Lactonization²⁰³ of acid **170** via S_N2' displacement of the chloride set the stage for installation of an additional oxygen substituent via S_N2' addition of an alkoxy methyl copper nucleophile,²⁰⁴ delivering **171** after formation of the methyl ester. Selective hydrogenation of the 1,1-disubstituted alkene and cleavage of the methoxymethyl ether gave alcohol **172**. A Swern oxidation¹³¹ and a Horner–Wadsworth–Emmons reaction provided sulfone **173**. Dihydroxylation²⁰⁵ and oxidation of the secondary alcohol¹³¹ gave ketone **174**. Rhenium-catalyzed allylic alcohol transposition^{206,207} preceded formation of the tetrahydrofuran **175** via subjection to alkaline conditions. Formation of the tosylhydrazone and reduction triggered an allylic diazene rearrangement to give bicycle **176**,^{192–194} characteristic of the cladiellin subclass.

In 2003, Jung reported efforts toward the initially reported structure of sclerophytin A (**16**).^{9,34,35,208} Formation of the silyl enol ether of ketone **177** using a chiral base²⁰⁹ and subsequent alkylation gave bicycle **178** (Scheme 29).²¹⁰ A second alkylation using a palladium-mediated coupling gave

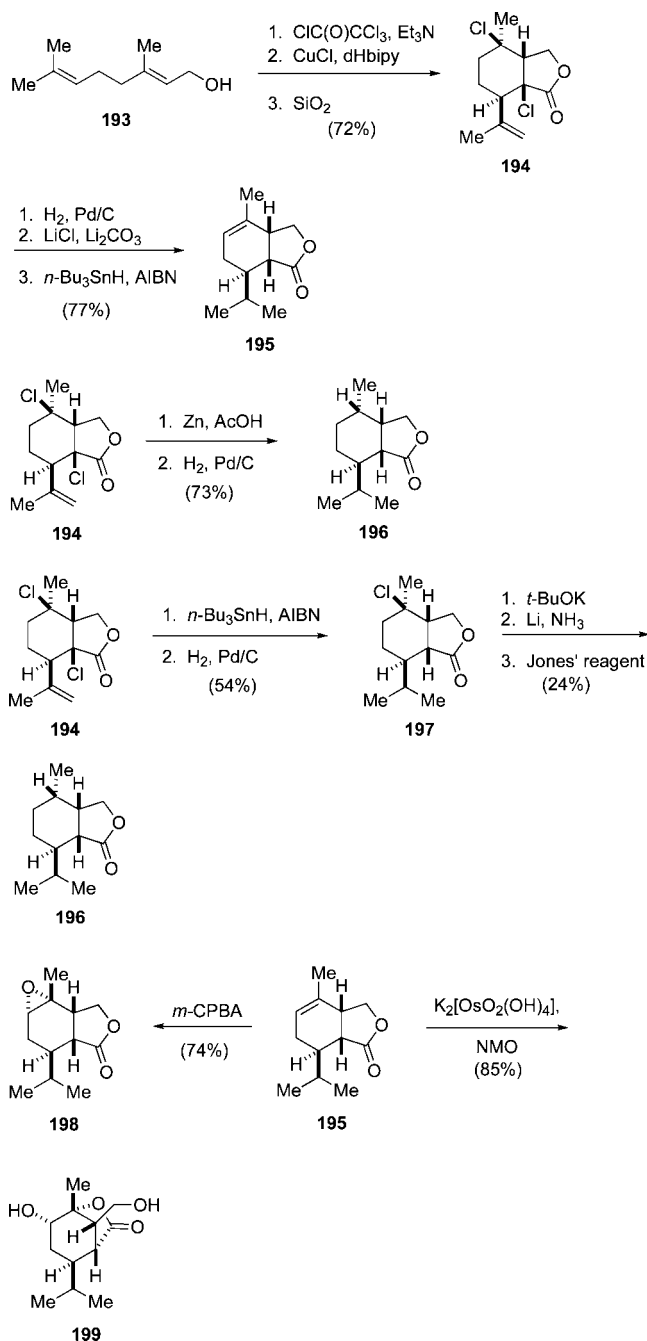
Scheme 30. Cycloaddition Approach of Holmes



alkene **179** in 83% yield.^{211,212} Hydroboration–oxidation of the terminal olefin²¹³ preceded protection of the resultant alcohol as an ester functionality. A Baeyer–Villiger oxidation provided the lactone,²¹⁴ whereupon the chloroacetate was exchanged for a TBS ether to give lactone **181**.²¹⁵ A Tebbe olefination proceeded in good yield,⁵⁹ however, the trisubstituted olefin **182** was isolated rather than the desired exocyclic olefin. The original synthetic plan involved a [3 + 2]-cycloaddition reaction, but the inability to access the exocyclic olefin in good yield precluded this prospect, so the strategy was redirected to take advantage of the alkene **182**. Hydrolysis of the enol ether provided the ketone, and the diol was protected as the bis-silyl ether. Selective removal of the primary silyl protecting group gave ketone **183**. Oxidation of the primary alcohol to the aldehyde³¹ provided a substrate that was proposed to be suitable for a pinacol coupling.²¹⁶ However, no productive reaction could be achieved with the dicarbonyl. In an attempt to overcome this inactivity and form the nine-membered ring, methylenation of both carbonyls gave a diene **184** that was treated to the Grubbs second-generation catalyst to attempt a ring-closing metathesis,¹⁰⁸ but again this was met with no success.

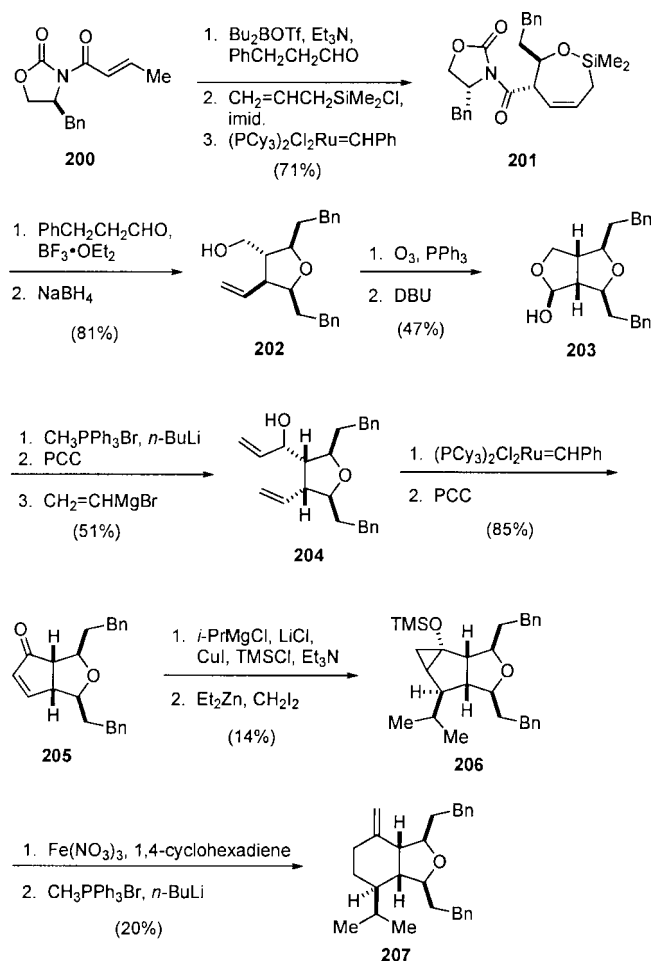
As alluded to earlier, the Holmes laboratory reported a route to cladiellin natural products that employed an intramolecular Diels–Alder cycloaddition (Scheme 30).¹²⁰ The Holmes group has developed a Claisen rearrangement for accessing medium-ring lactones, which has been applied to the synthesis of cladiellin-like structures.^{217,218} Their synthesis commenced with the acid-catalyzed glycosidation of 2-deoxy-D-ribose (**185**),²¹⁹ followed by protection of the diol as silyl ethers. The acetal was hydrolyzed,^{220,221} and treatment with a Grignard reagent gave diol **186**. Formation of the dioxepane²²² preceded oxidation of the selenide, which

Scheme 31. Atom Transfer Radical Cyclization Strategy



triggered a Claisen rearrangement to give lactone **187**.²²³ With an efficient route to lactone **187**, attention was turned toward preparing an appropriate Diels–Alder candidate. Tebbe methylenation of the lactone carbonyl²²⁴ and selenation gave selenide **188**. Oxidation of selenide **188**, Pummerer rearrangement, and loss of methoxide gave aldehyde **189** as a single diastereomer.²²⁵ A stabilized Wittig reaction gave the enal, and methylenation delivered triene **190**. Selective removal of the primary protecting group and oxidation gave the aldehyde,³¹ which upon treatment with a stabilized Wittig reagent¹³⁴ formed the enone, which underwent spontaneous cycloaddition. Upon deprotection, tricycles **191** and **192** were isolated. However, the *endo*-adduct **191** was the major product of this cyclization (3:1 dr). This reversal of selectivity relative to the Diels–Alder reactions in the cladiellin and asbestinin syntheses from the Crimmins laboratory demonstrates the crucial nature of the C3 configuration and

Scheme 32. Marsden's Efforts

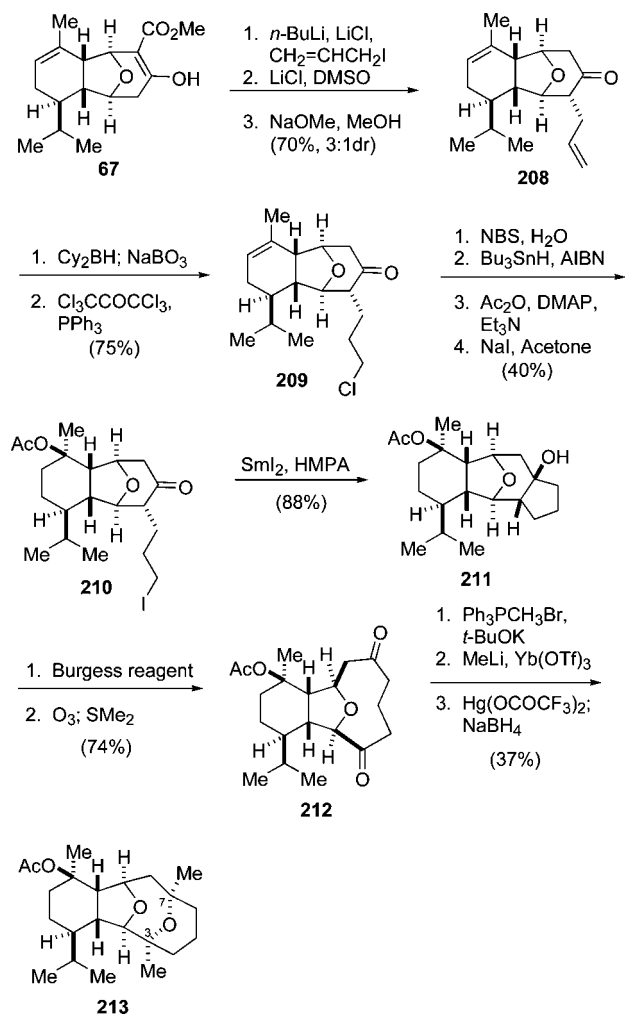


protecting group (Figure 4, Scheme 12).^{114,115,126} When the opposite configuration at C3 is employed, the *endo*-adduct is the dominant product, whereas the *exo*-adduct is favored when using the C3 epimer.

The Quayle group employed an atom transfer radical cyclization to approach the eunicellin core.²²⁶ Preparation of the trichloroacetate of geraniol (**193**) and treatment with a copper catalyst induced cyclization to yield lactone **194** in 72% yield (Scheme 31).^{227–229} Hydrogenation, elimination, and reduction removed all of the halogen substituents to access bicycle **195**. Alternatively, treatment of bicycle **194** with zinc in acetic acid and hydrogenation afforded lactone **196** in good yield. In another sequence, bicycle **194** was reduced and hydrogenated to provide lactone **197**.²³⁰ Finally, elimination, Birch reduction of the resultant cyclopropane, and oxidation of the lactol to the lactone again delivered lactone **196**.²³¹ Additionally, epoxidation of alkene **195** was demonstrated to provide tricycle **198** in good yield, while dihydroxylation of **195** afforded bicycle **199** in 85% yield.

In 2005, Marsden reported an approach to the hydroisobenzofuran core that began with a deconjugative aldol reaction of oxazolidinone **200** with 3-phenylpropanal,²³² followed by silylation and ring-closing metathesis to give allylsiloxane **201** (Scheme 32).¹⁰⁷ Lewis acid-promoted rearrangement of allylsiloxane **201** in the presence of 3-phenylpropanal gave the tetrahydrofuran, and reduction of the chiral auxiliary provided alcohol **202**. Ozonolysis and base-promoted epimerization accessed lactol **203** in moderate yield. Methylenation, oxidation, and a Grignard addition delivered allylic alcohol **204**. Ring-closing metathesis¹⁰⁷ and

Scheme 33. Samarium-Mediated Cyclization to Polyanthellin A Diastereomer

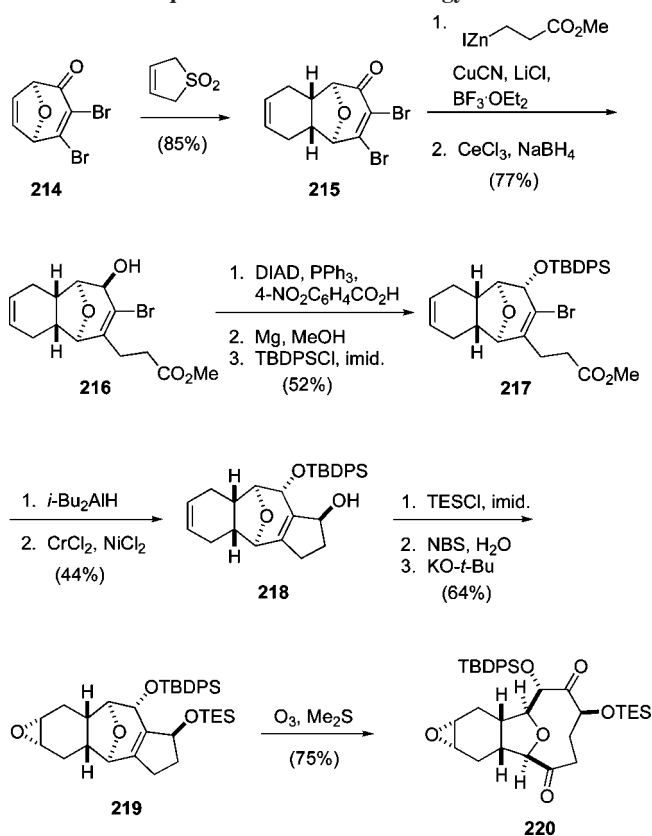


oxidation yielded the lactone **205**, which was used in a conjugate addition and trapped as the enol silane. Cyclopropanation resulted in the formation of tricycle **206**. Radical fragmentation²³³ and methylenation provided the hydroisobenzofuran **207**.

The Molander group has reported a second route to the cladiellins that extends the [4 + 3]-annulation strategy discussed earlier.^{87–89,234} Using tricycle **67** from their earlier synthesis (vide supra, Scheme 11), an alkylation and Krapcho decarboxylation gave the ketone **208** as a mixture of epimers (3:1 dr),⁹⁴ which could be epimerized to the desired configuration under basic conditions (Scheme 33). Selective hydroboration and oxidation of the terminal olefin²¹³ was followed by chomization to give alkyl chloride **210**.²³⁵ A three-step sequence installed the tertiary acetate,^{236–239} and the alkyl chloride was transformed into alkyl iodide **210**.²⁴⁰ At this point, a key samarium iodide-mediated cyclization provided tetracycle **211**.²⁴¹ Dehydration¹⁵⁸ and ozonolysis gave the cladiellin skeleton **212**. Chemoselective methylation was followed by addition of methyl lithium to the C3 carbonyl.¹⁰¹ At this point, oxymercuration and reduction²⁴² gave the 3,7-epimer of polyanthellin A **213**.⁷⁸

Finally, in 2007, the Wright laboratory reported studies toward the eunicellins (Scheme 34).²⁴³ Dienone **214**²⁴⁴ underwent Diels–Alder cycloaddition to provide tricycle **215** in 85% yield.²⁴⁵ Conjugate addition²⁴⁶ and Luche reduction accessed allylic alcohol **216**.⁴⁹ Mitsunobu inversion and

Scheme 34. Sequential Annulation Strategy



protection delivered the desired allylic ether configuration of tricycle **217**.²⁴⁷ Reduction of the ester and Nozaki–Hiyama–Kishi cyclization gave allylic alcohol **218**.^{32,33} The allylic alcohol was protected, and the bromohydrin was formed and cyclized to give epoxide **219**. Ultimately, ozonolysis of the tetrasubstituted olefin delivered the desired tetracycle **220** in good yield.²¹⁷

4. Conclusion

A variety of efforts over the past decade involving the synthesis of C2–C11 cyclized cembranoid natural products have been illustrated. Diverse strategies can be found within the literature that approach these molecular skeletons. It is likely that continued work in this area will produce new, more efficient methods to access these structurally interesting, and biologically important, natural products.

5. References

- Bernardelli, P.; Paquette, L. A. *Heterocycles* **1998**, *49*, 531.
- Stierle, D. B.; Carte, B.; Faulkner, D. J.; Tagle, B.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *102*, 5088.
- Bowden, B. F.; Coll, J. C.; Dai, M. C. *Aust. J. Chem.* **1989**, *42*, 665.
- Nicolaou, K. C.; Xu, J. Y.; Kim, S.; Ohshima, T.; Hosokawa, S.; Pfefferkorn, J. *J. Am. Chem. Soc.* **1997**, *119*, 11353.
- Nicolaou, K. C.; van Delft, F.; Ohshima, T.; Vourloumis, D.; Xu, J.; Hosokawa, S.; Pfefferkorn, J.; Kim, S.; Li, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2520.
- Kennard, O.; Watson, D. G.; Riva di Sanseverino, L.; Tursch, B.; Bosmans, R.; Djerassi, C. *Tetrahedron Lett.* **1968**, 2879.
- Rodriguez, A. D.; Cobar, O. M. *Tetrahedron* **1995**, *51*, 6869.
- Ortega, M. J.; Zubia, E.; Salva, J. *J. Nat. Prod.* **1994**, *57*, 1584.
- Sharma, P.; Alam, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2537.
- Rodriguez, A. D.; Cobar, O. M. *Tetrahedron* **1992**, *49*, 319.
- Morales, J. J.; Lorenzo, D.; Rodriguez, A. D. *J. Nat. Prod.* **1991**, *54*, 1368.
- Selover, S. J.; Crews, P.; Tagle, B.; Clardy, J. *J. Org. Chem.* **1981**, *46*, 964.

- (13) Park, Y.-H.; Chang, S.-K.; Kim, I.-K.; Seo, Y.-W.; Shin, J.-H. *Yakhak Hoechi* **1997**, *41*, 345.
- (14) Uchio, Y.; Kodama, M.; Usui, S.; Fukazawa, Y. *Tetrahedron Lett.* **1992**, *33*, 1317.
- (15) MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391.
- (16) Hopkins, M. H.; Overman, L. E.; Rishton, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 5354.
- (17) Ireland, R. E.; Bey, P. *Org. Synth.* **1973**, *53*, 63.
- (18) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.
- (19) Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277.
- (20) Seyferth, D. *J. Am. Chem. Soc.* **1957**, *79*, 2133.
- (21) Molander, G. A.; Bobbitt, K. L. *J. Org. Chem.* **1992**, *57*, 5031.
- (22) Reetz, M. T. *Angew. Chem.* **1984**, *96*, 542.
- (23) Cremer, D.; Gauss, J.; Childs, R. F.; Blackburn, C. *J. Am. Chem. Soc.* **1985**, *107*, 2435.
- (24) Baggiolini, E.; Hamlow, H. P.; Schaffner, K. *J. Am. Chem. Soc.* **1970**, *92*, 4906.
- (25) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
- (26) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.
- (27) Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719.
- (28) Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1378.
- (29) Viti, S. M. *Tetrahedron Lett.* **1982**, *23*, 4541.
- (30) Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731.
- (31) Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13.
- (32) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644.
- (33) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281.
- (34) Alam, M.; Sharma, P.; Zektzer, A. S.; Martin, G. E.; Ji, X.; Van der Helm, D. *J. Org. Chem.* **1989**, *54*, 1896.
- (35) Hochlowski, J. E.; Faulkner, D. J. *Tetrahedron Lett.* **1980**, *21*, 4055.
- (36) Chen, J.; Wang, T.; Zhao, K. *Tetrahedron Lett.* **1994**, *35*, 2827.
- (37) Overman, L. E.; Pennington, L. D. *Org. Lett.* **2000**, *2*, 2683.
- (38) MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2001**, *123*, 9033.
- (39) Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 1657.
- (40) Bordwell, F. G.; Douglass, M. L. *J. Am. Chem. Soc.* **1966**, *88*, 993.
- (41) Marshall, J. A.; Hochstetler, A. R. *J. Am. Chem. Soc.* **1969**, *91*, 648.
- (42) Kropp, P. J. In *Organic Photochemistry*; Padwa, A. Ed.; Marcel Dekker: New York, 1979; Vol. 4, pp 1–142.
- (43) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
- (44) Paquette, L. A.; Moradei, O. M.; Bernardelli, P.; Lange, T. *Org. Lett.* **2000**, *2*, 1875.
- (45) Kinney, W. A.; Coghlan, M. J.; Paquette, L. A. *J. Am. Chem. Soc.* **1985**, *107*, 7352.
- (46) De Jong, J. C.; Van Bolhuis, F.; Feringa, B. L. *Tetrahedron: Asymmetry* **1991**, *2*, 1247.
- (47) De Jong, J. C.; Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron Lett.* **1990**, *31*, 3047.
- (48) Vorndam, P. E. *J. Org. Chem.* **1990**, *55*, 3693.
- (49) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
- (50) Bernardelli, P.; Paquette, L. A. *J. Org. Chem.* **1997**, *62*, 8284.
- (51) Brueckner, C.; Holzinger, H.; Reissig, H. U. *J. Org. Chem.* **1988**, *53*, 2450.
- (52) Brueckner, C.; Lorey, H.; Reissig, H. U. *Angew. Chem.* **1986**, *98*, 559.
- (53) Tsuji, J. *Synthesis* **1984**, 369.
- (54) Koert, U. *Tetrahedron Lett.* **1994**, *35*, 2517.
- (55) Le Borgne, J. F.; Cuvigny, T.; Larcheveque, M.; Normant, H. *Synthesis* **1976**, 238.
- (56) Koert, U.; Stein, M.; Harms, K. *Tetrahedron Lett.* **1993**, *34*, 2299.
- (57) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367.
- (58) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *Tetrahedron* **1990**, *46*, 4613.
- (59) Pine, S. H. *Org. React.* **1993**, *43*, 1.
- (60) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590.
- (61) Harding, K. E.; Marman, T. H.; Nam, D.-H. *Tetrahedron Lett.* **1988**, *29*, 1627.
- (62) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.
- (63) Friedrich, D.; Doskotch, R. W.; Paquette, L. A. *Org. Lett.* **2000**, *2*, 1879.
- (64) Gallou, F.; MacMillan, D. W. C.; Overman, L. E.; Paquette, L. A.; Pennington, L. D.; Yang, J. *Org. Lett.* **2001**, *3*, 135.
- (65) Bernardelli, P.; Moradei, O. M.; Friedrich, D.; Yang, J.; Gallou, F.; Dyck, B. P.; Doskotch, R. W.; Lange, T.; Paquette, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 9021.
- (66) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019.
- (67) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.
- (68) Kusumi, T.; Uchida, H.; Ishitsuka, M. O.; Yamamoto, H.; Kakisawa, H. *Chem. Lett.* **1988**, 1077.
- (69) Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *Org. Lett.* **2003**, *5*, 1543.
- (70) Giner, J.-L.; Faraldos, J. A. *J. Org. Chem.* **2002**, *67*, 2717.
- (71) Faraldos, J. A.; Giner, J.-L. *J. Org. Chem.* **2002**, *67*, 4659.
- (72) Brown, H. C.; Kulkarni, S. U. *J. Organomet. Chem.* **1979**, *168*, 281.
- (73) Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930.
- (74) Schwarz, H.; Schiebel, H. M. In *The Chemistry of Peroxides*; Patai, S. Ed.; Wiley: New York, 1983; p 279.
- (75) Liu, J.; Zeng, L.; Wu, D. *Chin. Sci. Bull.* **1992**, *37*, 1627.
- (76) Yamada, K.; Ogata, N.; Ryu, K.; Miyamoto, T.; Komori, T.; Higuchi, R. *J. Nat. Prod.* **1997**, *60*, 393.
- (77) He, Y. F.; Wang, R. M.; Liu, Y. Y.; Chang, Y.; Wang, Y. P.; Xia, C. G.; Suo, J. S. *J. Mol. Catal., A* **2000**, *159*, 109.
- (78) Ospina, C. A.; Rodriguez, A. D.; Ortega-Barria, E.; Capson, T. L. *J. Nat. Prod.* **2003**, *66*, 357.
- (79) Rodriguez, A. D.; Cobar, O. M. *Chem. Pharm. Bull.* **1995**, *43*, 1853.
- (80) Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2003**, *125*, 6650.
- (81) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 641.
- (82) Patel, D. V.; VanMiddlesworth, F.; Donaubaer, J.; Gannett, P.; Sih, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 4603.
- (83) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.
- (84) Takai, K.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3791.
- (85) Orita, A.; Sakamoto, K.; Hamada, Y.; Mitsutome, A.; Otera, J. *Tetrahedron* **1999**, *55*, 2899.
- (86) Sharma, S.; Oehlschlager, A. C. *J. Org. Chem.* **1989**, *54*, 5064.
- (87) Molander, G. A.; St. Jean, D. J., Jr.; Haas, J. *J. Am. Chem. Soc.* **2004**, *126*, 1642.
- (88) Molander, G. A.; Jeffrey, S. C. *Tetrahedron Lett.* **2002**, *43*, 359.
- (89) Molander, G. A.; Cameron, K. O. *J. Am. Chem. Soc.* **1993**, *115*, 830.
- (90) Snider, B. B.; Hui, R. A. H. F. *J. Org. Chem.* **1985**, *50*, 5167.
- (91) Chen, X.-T.; Zhou, B.; Bhattacharya, S. K.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 789.
- (92) Umbrecht, G.; Hellman, M. D.; Hegedus, L. S. *J. Org. Chem.* **1998**, *63*, 5173.
- (93) Pirrung, M. C.; Chang, V. K.; DeAmicis, C. V. *J. Am. Chem. Soc.* **1989**, *111*, 5824.
- (94) Krapcho, A. P. *Synthesis* **1982**, 805.
- (95) Urban, J.; Turner, J. V.; Twitchin, B. *Tetrahedron Lett.* **1984**, *25*, 5099.
- (96) Hernandez, A.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 1058.
- (97) Wollenberg, R. H.; Albizati, K. F.; Peries, R. *J. Am. Chem. Soc.* **1977**, *99*, 7365.
- (98) Schlosser, M.; Wei, H.-x. *Tetrahedron* **1997**, *53*, 1735.
- (99) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380.
- (100) Sharpless, K. B.; Umbreit, M. A.; Nieh, M. T.; Flood, T. C. *J. Am. Chem. Soc.* **1972**, *94*, 6538.
- (101) Molander, G. A.; Burkhardt, E. R.; Weinig, P. *J. Org. Chem.* **1990**, *55*, 4990.
- (102) Crimmins, M. T.; DeBaillie, A. C. *Org. Lett.* **2003**, *5*, 3009.
- (103) Crimmins, M. T.; Emmitte, K. A. *Synthesis* **2000**, 899.
- (104) Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029.
- (105) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653.
- (106) Crimmins, M. T.; McDougall, P. J.; Ellis, J. M. *Org. Lett.* **2006**, *8*, 4079.
- (107) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.
- (108) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.
- (109) Crimmins, M. T.; Emmitte, K. A.; Katz, J. D. *Org. Lett.* **2000**, *2*, 2165.
- (110) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894.
- (111) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883.
- (112) Crimmins, M. T.; She, J. *Synlett* **2004**, 1371.
- (113) Seo, Y.; Rho, J.-R.; Cho, K. W.; Shin, J. *J. Nat. Prod.* **1997**, *60*, 171.
- (114) Crimmins, M. T.; Brown, B. H.; Plake, H. R. *J. Am. Chem. Soc.* **2006**, *128*, 1371.
- (115) Crimmins, M. T.; Brown, B. H. *J. Am. Chem. Soc.* **2004**, *126*, 10264.
- (116) Alcaraz, L.; Harnett, J. J.; Mioskowski, C.; Martel, J. P.; Le Gall, T.; Shin, D.-S.; Falck, J. R. *Tetrahedron Lett.* **1994**, *35*, 5449.
- (117) Nicolaou, K. C.; Xu, J. Y.; Kim, S.; Pfefferkorn, J.; Ohshima, T.; Vourloumis, D.; Hosokawa, S. *J. Am. Chem. Soc.* **1998**, *120*, 8661.

- (118) Hunt, D. F.; Rodeheaver, G. T. *J. Chem. Soc., Chem. Commun.* **1971**, 818.
- (119) Moussebois, C.; Dale, J. *J. Chem. Soc., Org.* **1966**, 260.
- (120) Davidson, J. E. P.; Gilmour, R.; Ducki, S.; Davies, J. E.; Green, R.; Burton, J. W.; Holmes, A. B. *Synlett* **2004**, 1434.
- (121) Orita, A.; Tanahashi, C.; Kakuda, A.; Otera, J. *J. Org. Chem.* **2001**, 66, 8926.
- (122) Orita, A.; Tanahashi, C.; Kakuda, A.; Otera, J. *Angew. Chem., Int. Ed.* **2000**, 39, 2877.
- (123) Fusetani, N.; Nagata, H.; Hirota, H.; Tsuyuki, T. *Tetrahedron Lett.* **1989**, 30, 7079.
- (124) Kato, N.; Wu, X.; Tanaka, S.; Takeshita, H. *Bull. Chem. Soc. Jpn.* **1990**, 63, 1729.
- (125) Clive, D. L. J.; Chittattu, G.; Curtis, N. J.; Menchen, S. M. *J. Chem. Soc., Chem. Commun.* **1978**, 770.
- (126) Crimmins, M. T.; Ellis, J. M. *J. Am. Chem. Soc.* **2005**, 127, 17200.
- (127) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, 125, 10160.
- (128) Hubbs, J. L.; Heathcock, C. H. *J. Am. Chem. Soc.* **2003**, 125, 12836.
- (129) Farquhar, D.; Cherif, A.; Bakina, E.; Nelson, J. A. *J. Med. Chem.* **1998**, 41, 965.
- (130) McNeill, A. H.; Thomas, E. J. *Tetrahedron Lett.* **1993**, 34, 1669.
- (131) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, 43, 2480.
- (132) Guiney, D.; Gibson, C. L.; Suckling, C. J. *Org. Biomol. Chem.* **2003**, 1, 664.
- (133) Schinzer, D.; Boehm, O. M.; Altmann, K.-H.; Wartmann, M. *Synlett* **2004**, 1375.
- (134) Kuroda, H.; Hanaki, E.; Izawa, H.; Kano, M.; Itahashi, H. *Tetrahedron* **2004**, 60, 1913.
- (135) Brown, H. C.; Desai, M. C.; Jadhav, P. K. *J. Org. Chem.* **1982**, 47, 5065.
- (136) Masamune, S.; Lu, L. D. L.; Jackson, W. P.; Kaiho, T.; Toyoda, T. *J. Am. Chem. Soc.* **1982**, 104, 5523.
- (137) Rodriguez, A. D.; Cobar, O. M.; Martinez, N. *J. Nat. Prod.* **1994**, 57, 1638.
- (138) Crimmins, M. T.; Ellis, J. M. *J. Org. Chem.* **2008**, 73, 1649.
- (139) Davis, F. A.; Chattopadhyay, S.; Towson, J. C.; Lal, S.; Reddy, T. *J. Org. Chem.* **1988**, 53, 2087.
- (140) Di Grandi, M. J.; Coburn, C. A.; Isaacs, R. C. A.; Danishefsky, S. J. *J. Org. Chem.* **1993**, 58, 7728.
- (141) Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth.* **1988**, 66, 203.
- (142) Kim, H.; Lee, H.; Kim, J.; Kim, S.; Kim, D. *J. Am. Chem. Soc.* **2006**, 128, 15851.
- (143) Kim, H.; Choi, W. J.; Jung, J.; Kim, S.; Kim, D. *J. Am. Chem. Soc.* **2003**, 125, 10238.
- (144) Lee, H.; Kim, H.; Baek, S.; Kim, S.; Kim, D. *Tetrahedron Lett.* **2003**, 44, 6609.
- (145) Baek, S.; Jo, H.; Kim, H.; Kim, H.; Kim, S.; Kim, D. *Org. Lett.* **2005**, 7, 75.
- (146) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, 103, 2127.
- (147) Jones, T. K.; Mills, S. G.; Reamer, R. A.; Askin, D.; Desmond, R.; Volante, R. P.; Shinkai, I. *J. Am. Chem. Soc.* **1989**, 111, 1157.
- (148) Kraus, G. A.; Kim, J. *Org. Lett.* **2004**, 6, 3115.
- (149) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, 23, 885.
- (150) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, 99, 5526.
- (151) Hooz, J.; Gilani, S. S. H. *Can. J. Chem.* **1968**, 46, 86.
- (152) Kim, S.; Ahn, K. H. *J. Org. Chem.* **1984**, 49, 1717.
- (153) Corey, E. J.; Enders, D.; Bock, M. G. *Tetrahedron Lett.* **1976**, 7.
- (154) Barrett, A. G. M.; Godfrey, C. R. A.; Hollinshead, D. M.; Prokopiou, P. A.; Barton, D. H. R.; Boar, R. B.; Joukhadar, L.; McGhie, J. F.; Misra, S. C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1501.
- (155) Uchio, Y.; Nakatani, M.; Hase, T.; Kodama, M.; Usui, S.; Fukazawa, Y. *Tetrahedron Lett.* **1989**, 30, 3331.
- (156) Kang, S. H.; Lee, J. H.; Lee, S. B. *Tetrahedron Lett.* **1998**, 39, 59.
- (157) Bowden, B. F.; Coll, J. C.; Vasilescu, I. M. *Aust. J. Chem.* **1989**, 42, 1705.
- (158) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, 38, 26.
- (159) Clark, J. S.; Hayes, S. T.; Wilson, C.; Gobbi, L. *Angew. Chem., Int. Ed.* **2007**, 46, 437.
- (160) Su, J.-H.; Huang, H.-C.; Chao, C.-H.; Yan, L.-Y.; Wu, Y.-C.; Wu, C.-C.; Sheu, J.-H. *Bull. Chem. Soc. Jpn.* **2005**, 78, 877.
- (161) Williams, D. R.; Meyer, K. G.; Shamim, K.; Patnaik, S. *Can. J. Chem.* **2004**, 82, 120.
- (162) Winterfeldt, E. *Chem. Ber.* **1964**, 97, 1952.
- (163) Winterfeldt, E.; Preuss, H. *Chem. Ber.* **1966**, 99, 450.
- (164) Matsuo, G.; Kadohama, H.; Nakata, T. *Chem. Lett.* **2002**, 148.
- (165) Pirrung, M. C.; Werner, J. A. *J. Am. Chem. Soc.* **1986**, 108, 6060.
- (166) Roskamp, E. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1986**, 108, 6062.
- (167) Clark, J. S.; Dossetter, A. G.; Whittingham, W. G. *Tetrahedron Lett.* **1996**, 37, 5605.
- (168) Clark, S. J.; Dossetter, A. G.; Blake, A. J.; Li, W.-S.; Whittingham, W. G. *Chem. Commun.* **1999**, 749.
- (169) Kwon, H. B.; McKee, B. H.; Stille, J. K. *J. Org. Chem.* **1990**, 55, 3114.
- (170) Becker, J.; Bergander, K.; Froehlich, R.; Hoppe, D. *Angew. Chem., Int. Ed.* **2008**, 47, 1654.
- (171) Everts, J.; Torres, E.; Fuchs, P. L. *J. Am. Chem. Soc.* **2002**, 124, 11093.
- (172) King, D. J.; Gleadow, R. M.; Woodrow, I. E. *New Phytol.* **2006**, 172, 440.
- (173) Nowakowski, M.; Hoffmann, H. M. R. *Tetrahedron* **1997**, 53, 4331.
- (174) Stohrer, I.; Hoffmann, H. M. R. *Helv. Chim. Acta* **1993**, 76, 2194.
- (175) Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1986**, 51, 1778.
- (176) Balasubramanian, V.; Robinson, C. H. *Tetrahedron Lett.* **1981**, 22, 501.
- (177) Joe, D.; Overman, L. E. *Tetrahedron Lett.* **1997**, 38, 8635.
- (178) Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, 106, 3693.
- (179) Rand, C. L.; Van Horn, D. E.; Moore, M. W.; Negishi, E. *J. Org. Chem.* **1981**, 46, 4093.
- (180) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, 112, 3875.
- (181) Clark, J. S.; Wong, Y. S. *Chem. Commun.* **2000**, 1079.
- (182) Gringore, O. H.; Rouessac, F. P. *Org. Synth.* **1985**, 63, 121.
- (183) Ravid, U.; Silverstein, R. M.; Smith, L. R. *Tetrahedron* **1978**, 34, 1449.
- (184) Aurich, H. G.; Biesemeier, F. *Synthesis* **1995**, 1171.
- (185) Adams, J.; Poupart, M. A.; Grenier, L.; Schaller, C.; Ouimet, N.; Frenette, R. *Tetrahedron Lett.* **1989**, 30, 1749.
- (186) Nicolaou, K. C.; Duggan, M. E.; Hwang, C. K. *J. Am. Chem. Soc.* **1989**, 111, 6666.
- (187) Clark, J. S.; Winfield, L. J.; Wilson, C.; Blake, A. J. *Synlett* **2006**, 2191.
- (188) Chai, Y.; Vicic, D. A.; McIntosh, M. C. *Org. Lett.* **2003**, 5, 1039.
- (189) Martin, S. F.; White, J. B. *Tetrahedron Lett.* **1982**, 23, 23.
- (190) Burk, R. M.; Gac, T. S.; Roof, M. B. *Tetrahedron Lett.* **1994**, 35, 8111.
- (191) Majetich, G.; Condon, S.; Hull, K.; Ahmad, S. *Tetrahedron Lett.* **1989**, 30, 1033.
- (192) Harapanhalli, R. S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3149.
- (193) Greco, M. N.; Maryanoff, B. E. *Tetrahedron Lett.* **1992**, 33, 5009.
- (194) Chu, M.; Coates, R. M. *J. Org. Chem.* **1992**, 57, 4590.
- (195) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, 43, 1599.
- (196) Chai, Y.; McIntosh, M. C. *Tetrahedron Lett.* **2004**, 45, 3269.
- (197) Sundararaman, P.; Herz, W. *J. Org. Chem.* **1977**, 42, 813.
- (198) Ishihara, M.; Masatsuga, Y.; Uneyama, K. *Tetrahedron* **1992**, 48, 10265.
- (199) Kobayashi, S.; Das, P.; Wang, G. X.; Mita, T.; Lear, M. J.; Hiram, M. *Chem. Lett.* **2002**, 300.
- (200) Hutchison, J. M.; Lindsay, H. A.; Dormi, S. S.; Jones, G. D.; Vicic, D. A.; McIntosh, M. C. *Org. Lett.* **2006**, 8, 3663.
- (201) Lindsay, H. A.; Salisbury, C. L.; Cordes, W.; McIntosh, M. C. *Org. Lett.* **2001**, 3, 4007.
- (202) Hong, S.-P.; Lindsay, H. A.; Yaramasu, T.; Zhang, X.; McIntosh, M. C. *J. Org. Chem.* **2002**, 67, 2042.
- (203) Paquette, L. A.; Stirling, C. J. M. *Tetrahedron* **1992**, 48, 7383.
- (204) Trost, B. M.; Klun, T. P. *J. Org. Chem.* **1980**, 45, 4256.
- (205) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, 94, 2483.
- (206) Jacob, J.; Espenson, J. H.; Jensen, J. H.; Gordon, M. S. *Organometallics* **1998**, 17, 1835.
- (207) Morrill, C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, 127, 2842.
- (208) Jung, M. E.; Pontillo, J. *Tetrahedron* **2003**, 59, 2729.
- (209) Bunn, B. J.; Cox, P. J.; Simpkins, N. S. *Tetrahedron* **1993**, 49, 207.
- (210) Valls, J.; Toromanoff, E. *Bull. Soc. Chim. Fr.* **1961**, 758.
- (211) Negishi, E.; Luo, F. T.; Pecora, A. J.; Silveira, A., Jr. *J. Org. Chem.* **1983**, 48, 2427.
- (212) Negishi, E.; Chatterjee, S. *Tetrahedron Lett.* **1983**, 24, 1341.
- (213) Kabalka, G. W.; Yu, S.; Li, N.-S. *Can. J. Chem.* **1998**, 76, 800.
- (214) Cooper, M. S.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Synlett* **1990**, 533.
- (215) Van Boeckel, C. A. A.; Beetz, T. *Tetrahedron Lett.* **1983**, 24, 3775.
- (216) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, 96, 307.
- (217) Anderson, E. A.; Davidson, J. E. P.; Harrison, J. R.; O'Sullivan, P. T.; Burton, J. W.; Collins, I.; Holmes, A. B. *Tetrahedron* **2002**, 58, 1943.
- (218) Congreve, M. S.; Holmes, A. B.; Hughes, A. B.; Looney, M. G. *J. Am. Chem. Soc.* **1993**, 115, 5815.
- (219) Recondo, E. F.; Rinderknecht, H. *Helv. Chim. Acta* **1959**, 42, 1171.
- (220) Goff, D. A.; Harris, R. N., III; Bottaro, J. C.; Bedford, C. D. *J. Org. Chem.* **1986**, 51, 4711.

- (221) Castaneda, A.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5695.
- (222) Baudat, R.; Petrzilka, M. *Helv. Chim. Acta* **1979**, *62*, 1406.
- (223) Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 3075.
- (224) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.
- (225) Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483.
- (226) Helliwell, M.; Fengas, D.; Knight, C. K.; Parker, J.; Quayle, P.; Raftery, J.; Richards, S. N. *Tetrahedron Lett.* **2005**, *46*, 7129.
- (227) Patten, T. E.; Xia, J.; Abernathy, T.; Matyjaszewski, K. *Science* **1996**, *272*, 866.
- (228) Nagashima, H.; Wakamatsu, H.; Ozaki, N.; Ishii, T.; Watanabe, M.; Tajima, T.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 1682.
- (229) Iwamatsu, S.-I.; Kondo, H.; Matsubara, K.; Nagashima, H. *Tetrahedron* **1999**, *55*, 1687.
- (230) Takano, S.; Nishizawa, S.; Akiyama, M.; Ogasawara, K. *Synthesis* **1984**, 949.
- (231) Carter, R.; Hodgetts, K.; McKenna, J.; Magnus, P.; Wren, S. *Tetrahedron* **2000**, *56*, 4367.
- (232) Akindele, T.; Marsden, S. P.; Cumming, J. G. *Tetrahedron Lett.* **2005**, *46*, 7235.
- (233) Booker-Milburn, K. I.; Thompson, D. F. *Tetrahedron* **1995**, *51*, 12955.
- (234) Molander, G. A.; Czako, B.; St Jean, D. J., Jr. *J. Org. Chem.* **2006**, *71*, 1172.
- (235) Magid, R. M.; Fruchey, O. S.; Johnson, W. L. *Tetrahedron Lett.* **1977**, 2999.
- (236) Guss, C. O.; Rosenthal, R. *J. Am. Chem. Soc.* **1955**, *77*, 2549.
- (237) Kupchik, E. J.; Connolly, R. E. *J. Org. Chem.* **1961**, *26*, 4747.
- (238) Noltes, J. G.; van der Kerk, G. J. M. *Chem. Ind.* **1959**, 294.
- (239) Hoeffle, G.; Steglich, W.; Vorbrueggen, H. *Angew. Chem.* **1978**, *90*, 602.
- (240) Finkelstein, H. *Ber.* **1910**, *43*, 1528.
- (241) Molander, G. A.; Etter, J. B. *Tetrahedron Lett.* **1984**, *25*, 3281.
- (242) Broka, C. A.; Lin, Y. T. *J. Org. Chem.* **1988**, *53*, 5876.
- (243) Pelphrey, P. M.; Bolstad, D. B.; Wright, D. L. *Synlett* **2007**, 2647.
- (244) Orugunty, R. S.; Wright, D. L.; Battiste, M. A.; Abboud, K. A. *Org. Lett.* **2002**, *4*, 1997.
- (245) Pelphrey, P.; Jasinski, J.; Butcher, R. J.; Wright, D. L. *Org. Lett.* **2005**, *7*, 423.
- (246) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117.
- (247) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.

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