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. An unusual oxatricyclic ring system containing a hydroisobenzofuran and an oxoneone 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). 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. 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. 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. Since this discovery, over 100 unique secondary metabolites of gorgonian octocorals have been characterized, including the first asbestinin in 1980 and the first briarellin in 1995. 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. Upon further investigation, several of the members of these subclasses have demonstrated significant pharmacological potential. 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-deacetoxyalcyomin acetate (1), a cladiellin, in 1995. 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. Diethyl diol 3, the substrate for the Prins-pinacol rearrangement, was
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 vinyllithium 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 BF₃·OEt₂ 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-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...
primary silyl ether 7 and photochemical decarbonylation of the formyl group gave bicycle 10. 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, which, following a one-carbon homologation, was utilized in an intramolecular Nozaki−Hiyama−Kishi coupling using NiCl2−CrCl2. 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). 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 therapeutically intriguing natural product. Utilizing diol 3 from the (-)-7-deacetoxyalcyonin acetate synthesis and aldehyde 17 (prepared in four steps from 3-buten-1-ol), a two-step condensation and rearrangement procedure was employed (Scheme 3). 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 stereoconversion observed. Deformylation 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. 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. Upon treatment with NiCl2−CrCl2, the oxonane was formed, delivering the desired isomer of allylic alcohol 15 in good yield. Cleavage of the tertiary silyl group followed by intramolecular etherification with Hg(OAc)2 (followed by...
NaBH₄) provided diether 22 in moderate yield.⁴⁰ Photosomerization 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. Efficient conversion of nitrile 28a to nitrile 28b was achieved with i-BuOK in i-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 methyllithium 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 cyclohexane 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 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 Oxidation 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
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-Bu2AlH27-29 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)15,57,58 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 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 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%
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 deformylation and selective basic hydrolysis of the t-butyldiphenylsilyl and trimethylsilyl protecting groups gave alcohol 55. Regioselective and stereoselective epoxidation of the acyclic alkene followed by acetylation of the primary alcohol then facilitated acetate-assisted opening of the 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 Stannylalumination-protonolysis and a subsequent iodod-estannylation 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

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 methyllithium 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 via the ring-closing metathesis reaction of dienes generated by glycolate alkylation and glycolate aldol reactions. 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) was first targeted, represent-
ing the first C13, C18 oxygenated cladiellin to be prepared via total synthesis.\textsuperscript{114,115} The synthesis commenced with the reaction of (S)-benzylglycidyl ether (74)\textsuperscript{116} with dimethylsulfonium methyldide 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.\textsuperscript{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.\textsuperscript{109} Reduction of the chiral auxiliary and ring-closing metathesis provided the oxonene 78.\textsuperscript{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 oxidation\textsuperscript{43} of alcohol 78 and stabilized Wittig reaction provided an enoate, which was reduced with \( i \)-Bu\textsubscript{2}AlH. The resultant allylic alcohol was protected as a 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,\textsuperscript{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,\textsuperscript{31} which was treated with benzoxymethyltriethylphosphorane to give tetraene 81 as a 3:1 mixture of \( Z/E \) isomers. Under ambient conditions, tetraene 81 underwent a spontaneous, highly \textit{exo}-selective Diels–Alder cycloaddition. The minor isomer from the Wittig reaction could be recycled to the reactive tetraene 81.
by photochemical isomerization in the presence of diphenyl disulfide, providing an overall 78% yield of tricycle 82. 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.

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 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 ensuing deprotection of the allylic trisopropylsilyl 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
The Crimmins laboratory had also utilized glycolate aldol reactions as an entry into dienes for ring-closing metathesis.\textsuperscript{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 cembranes 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.\textsuperscript{11} 11-Acetoxy-4-deoxyasbestinin D (95) shows cytotoxicity against CHO-K1 cells (ED\textsubscript{50} = 4.82 µg/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.\textsuperscript{114,115} To begin the synthesis, (R)-benzyl glycidyl ether (96) was opened with 2-propenylmagnesium bromide in the presence of copper iodide.\textsuperscript{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,\textsuperscript{129,130} under the improved conditions developed in the Crimmins laboratory for complex glycolate aldol reactions,\textsuperscript{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.\textsuperscript{108} Reductive removal of the benzyl ether and oxidation\textsuperscript{131} 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.\textsuperscript{132} Careful, selective deprotection of the primary silyl ether in the presence of the labile enol ether provided the primary alcohol,\textsuperscript{133} which was oxidized under Swern conditions.\textsuperscript{131} The resulting aldehyde was treated with a stabilized Wittig reagent to install the dienophile.\textsuperscript{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).\textsuperscript{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\textsubscript{4}NF, and the alcohol was oxidized to the ketone 101.\textsuperscript{43} A diastereoselective addition of methylmagnesium chloride formed the tertiary alcohol in high yield. At this point, hydrosylation 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 diastereoselectively was low. However, treatment of diene 103 with (+)-disopinocamphylborane 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 hydroboring reagent for the functionalization of a 1,1-disubstituted olefin.\textsuperscript{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.\textsuperscript{80} This total synthesis of 11-acetoxy-4-deoxyasbestinin D (95)\textsuperscript{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).\textsuperscript{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.\textsuperscript{139–141} A similar sequence to that utilized for 11-acetoxy-4-deoxyasbestinin D (95) was followed to prepare asbestinin-12 (104).\textsuperscript{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 hydroboring reagent was useful for accessing the desired primary alcohol.\textsuperscript{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-
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 laboratory114,115,120,126 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 ether150 and subsequent alkylation of the alcohol with 2-chlorodimethyl acetamide proceeded efficiently. Selective allylic oxidation151 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 Methylation 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 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 Oxidation13 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-one-3,6,7-triol (116) in 94% yield (Scheme 18).38,64,155 A one-pot procedure was also
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 (IC50 18 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 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 carbeneid of diazoketone 124 was formed; ensuing oxonium ion formation and [2,3]-Wittig rearrangement occurred to deliver the oxone 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 exo/endo mixture of isomers, which was equilibrated to the desired exo-adduct 128 under basic conditions.

With the tricycle elaborated, the ketone 128 was methylated, and the enol ether was hydrolyzed under acidic conditions (Scheme 20). Selective hydrogenation of the 1,1-disubstituted olefin was followed by methylolation 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-chloroperbenzoic acid (m-CPBA) delivered the epoxide, which was opened intramolecularly by the C3 tertiary alcohol to afford (±)-vigulariol (119).160
2.8. Homoaldol/Ring-Closing Metathesis Approach

In 2008, the Hoppe laboratory reported an enantioselective synthesis of vigulariol (119), relying upon a homoaldol reaction to provide a bicycle suitable for ring-closing metathesis. The synthesis commenced with the reduction of cyclohexenone 131, accessible in four synthetic steps or directly via extraction from commercially available eucalyptus oil, and carbamolylation to afford allylic carbamate 132 (Scheme 21). The partner for the homoaldol reaction was synthesized from diol 133 via sequential protections, followed by Swern oxidation. Stereospecific deprotonation of cyclohexene 132 to form metalloenolate 132a, transmetalation to titanium, and addition of the aldehyde 134 to the resultant homoenolate provided 33% of the desired diastereomer 135. Condensation with the appropriate acetate provided ketone 136. Ring-closing metathesis of diene 136 delivered the oxonene, which was epoxidized diastereoselectively to provide tetracycle 137. Hydrogenolysis of the benzyl ether and methylenation expediently afforded vigulariol (119).

3. Miscellaneous Approaches to the Partial Synthesis of C2–C11 Cyclized Cembranoids

A variety of approaches leading to partial syntheses of cladiellins have been reported. Among these, some unique strategies have been elucidated, adding to the methods for the synthesis of C2–C11 cyclized cembranoid natural products. Though none of the following attempts have yet resulted in a total synthesis, they provide valuable insight into several approaches that have shown promise in the setting of cladiellin, briarellin, and asbestinin syntheses. Some of the earliest reported work involving cladiellins employed an annulation-fragmentation strategy for the formation of the five- and nine-membered rings of these cembranoids. The Hoffmann laboratory began with symmetrical ketone 138 and performed a diastereoselective allylation in high yield (Scheme 22). Hydrobromination provided the alkyl bromide, which was uneventfully converted to the alkyl iodide 139 under Finkelstein conditions. A samarium-mediated Barbier-like cyclization provided the cyclopentanol, which was fragmented using cerium(IV) ammonium nitrate to provide bicycles 140 and 141 in 27% yield and 7% yield, respectively. No further efforts have been reported within the past decade utilizing this strategy.

Several years prior to the successful ring-closing metathesis approaches of Crimmins and Hoppe, the Overman laboratory had explored ring-closing metathesis of the hydroisobenzofuran portion of the eunicellins they had prepared via the Prins-pinacol condensation-rearrangement strategy en route to (-)-7-deacetoxyalcyonin acetate (1) (vide supra). Diol 115 was transformed into oxetane 142 via iodination and cyclization (Scheme 23). The oxetane was then opened with vinyllithium, carboaluminated, and protected to yield triene 143 in 55% yield for three steps. When triene 143 was treated with the Schrock molybdenum...
catalyst 144,180 none of the desired oxonene was observed; instead, the cyclic product was truncated by one carbon to afford oxocene 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 carbeneoid 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 phenylselenyl chloride, which triggered a rearrangement to yield oxabicycloundecane 153 in 78% yield. Additionally, treatment of ketone 151 with phenylselenyl trifluoroacetate gave 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
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 oxidation\(^{195}\) 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.\(^{199}\)

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 underwent oxidative rearrangement when treated with pyridinium chlorochromate (PCC),\(^{197,198}\) and the resultant ketone was treated under Rubottom oxidation conditions to provide alcohol 166.\(^{195}\) Reduction, esterifica-
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 SN2′ displacement of the chloride set the stage for installation of an additional oxygen substituent via SN2′ 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. Dihydroxylation 205 and oxidation of the secondary alcohol 131 gave ketone 174. Rhenium-catalyzed allylic alcohol transposition206,207 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 tetracycle 178 (Scheme 29).210 A second alkylation using a palladium-mediated coupling gave alkene 179 in 83% yield.211,212 Hydroboration—oxidation of the terminal olefin213 protected 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;215 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 acetel was hydrolyzed,220,221 and treatment with a Grignard reagent gave diol 186. Formation of the dioxepane222 preceded oxidation of the selenide, which
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 methylation 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 methylation 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 cycloadition. 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 asbestosin syntheses from the Crimmins laboratory demonstrates the crucial nature of the C3 configuration and 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. 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-phenylpropanol gave the tetrahydrofuran, and reduction of the chiral auxiliary provided alcohol 202. Ozonolysis and base-promoted epimerization accessed lactol 203 in moderate yield. Methylation, oxidation, and a Grignard addition delivered allylic alcohol 204. Ring-closing metathesis107 and
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 fragmentation 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. 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), which could be epimerized to the desired configuration under basic conditions (Scheme 33). Selective hydroboration and oxidation of the terminal olefin was followed by chlorination to give alkyl chloride 209. A three-step sequence installed the tertiary acetate, and the alkyl chloride was transformed into alkyl iodide 210. At this point, a key samarium iodide-mediated cyclization provided tetracycle 211. Dehydration and ozonolysis gave the cladiellin skeleton 212. Chemoselective methylation was followed by addition of methylolithium to the C3 carbonyl. At this point, oxymercuration and reduction gave the 3,7-epimer of polyanthellin A 213.

Finally, in 2007, the Wright laboratory reported studies toward the eunicellins (Scheme 34). Dienone 214 underwent Diels–Alder cycloaddition to provide tricycle 215 in 85% yield. Conjugate addition and Luche reduction accessed allylic alcohol 216. Mitsunobu inversion and protection delivered the desired allylic ether configuration of tricycle 217. Reduction of the ester and Nozaki–Hiyama–Kishi cyclization gave allylic alcohol 218. 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.

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


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