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An Intramolecular Diels−Alder Approach to the Eunicellins: Enantioselective Total Syntheses of Ophirin B and Astrogorgin

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Abstract: The enantioselective syntheses of the eunicellins ophirin B and astrogorgin have been completed. Ring-closing metatheses provide efficient access to the oxonene rings, and highly diastereoselective intramolecular Diels−Alder reactions resulted in the formation of the hydrobenzofuran portion of the molecules.

Introduction

The eunicellins, briarellins, asbestinins, and sarcodyctins are related subclasses of the C2,C11-cyclized cembranoid diterpenes isolated as secondary metabolites of gorgonian octocoral found in the Caribbean and West Pacific Ocean.[2−4] The presence of all four structural types of natural products in the same organism provides circumstantial evidence for the biosynthetic pathway proposed by Faulkner in which a cembrane skeleton is the precursor to all these metabolites. An unusual oxatricyclic ring system containing a hydroisobenzofuran and an oxacyclononane unit with stereogenic centers at C1−3, 9, 10, and 14 are common to the eunicellins, briarellins, and asbestinins. However, the location of the cyclohexyl methyl groups (C11 vs C12) and the oxidation level of the six- and nine-membered rings differ among the three classes. It has been postulated that upon oxidation at C16, the eunicellins (cladiellins) are converted to the briarellins (Scheme 1). Further, a suprafacial 1,2-methyl shift from C11 to C12 could transform the briarellins to the asbestinins.

Since the original report of the isolation of eunicellin from *Eunicella stricta* appeared in 1968,[5] extensive investigation of gorgonian soft coral has resulted in the isolation of over 50 novel secondary metabolites in the class. Preliminary investigations into the biological activity have shown that a variety of the eunicellin, briarellin, and asbestinin metabolites exhibit insect growth inhibition activity and in vitro cytotoxity against several cancer cell lines. On the basis of mollusk and fish lethality assays, the natural role of C2−C11-cyclized cembranoids has been suggested to be predatory deterrence. Interest in the chemical synthesis of members of these subclasses has piqued in recent years due to their novel structures and diverse biological activities.[6−9]

The first total synthesis of a eunicellin diterpene was the synthesis of (−)-7-deacetoxyalcyonin acetate reported by Overman in 1995 (Figure 1).[10,11] The subsequent synthesis and structural reassignment of sclerophytin A by both the Paquette[12,13] and Overman[11,14,15] laboratories was followed by Molander's[16] disclosure of the second synthesis of (−)-7-deacetoxyalcyonin acetate. Briarellins E and F are the only members of the briarellin class that have been prepared by chemical synthesis.[17,18] Each of the early synthetic approaches to the eunicellins and briarellins employed a strategy where the hydroisobenzofuran unit was incorporated prior to oxonene ring formation.[19]

While these strategies were clearly effective, an alternate approach was envisioned wherein the medium ring ether moiety might be used as a stereochemical control element for stereoselective intramolecular Diels−Alder reaction to construct the

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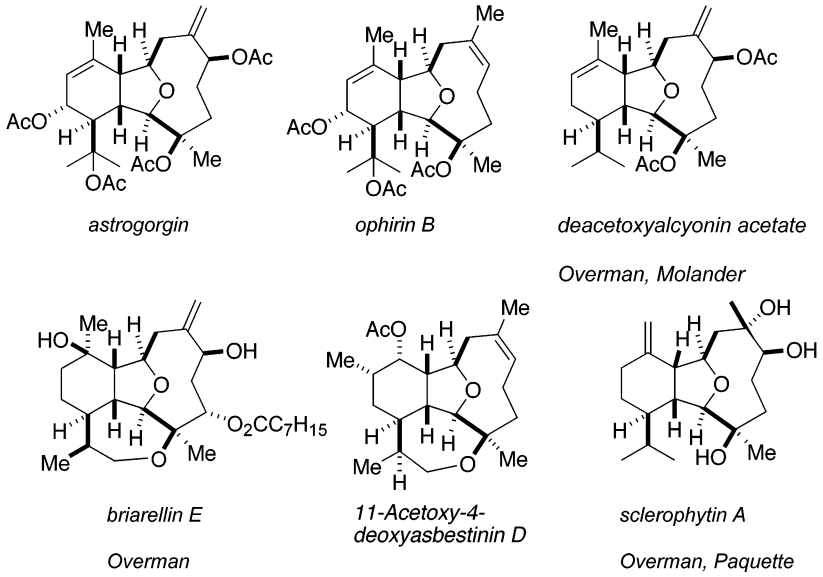
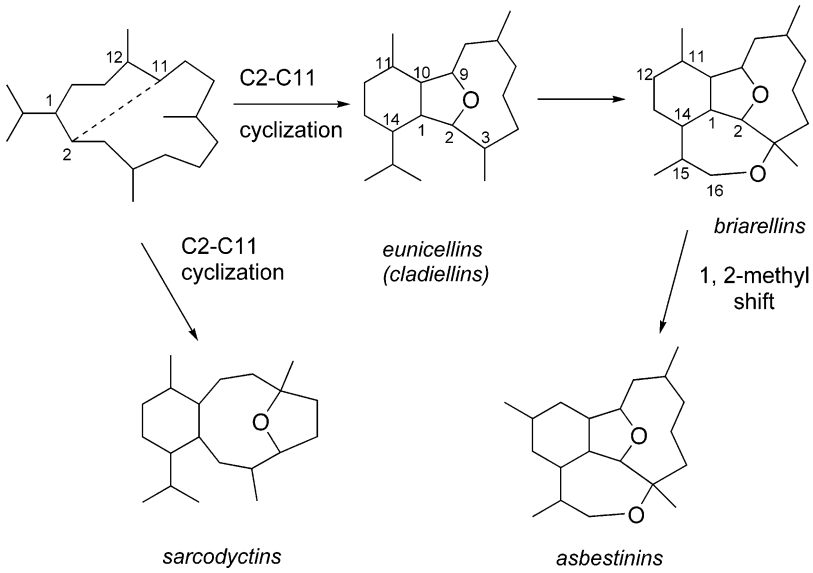


Figure 1. C2−C11 Cyclized Cembranoid Natural Products.

Scheme 1. Proposed Biosynthesis of the C2−C11 Cyclized Cembranoids



hydrobenzofuran unit. Our previous successes in the construction of medium ring ethers encouraged the investigation of this strategy. We have demonstrated the preparation of unsaturated seven-,[20,21] eight-,[22−25] and nine-membered[26−28] cyclic ethers by employing acyclic conformational constraints to facilitate the formation of medium rings by ring-closing metathesis reactions. Ophirin B (**1**)[29] and astrogorgin (**2**)[29,30] were attractive targets because their additional oxidation at C13 and C18 offered the opportunity for the simultaneous installation of the C1, C10, C13, and C14 stereogenic centers by a strategic intramolecular Diels−Alder cycloaddition of the tetraene **3** (Scheme 2). The medium ring of each of the Diels−Alder substrates would be formed through a ring-closing metathesis of the appropriate dienes **4**, which could arise from a common intermediate **5** through an asymmetric glycolate alkylation.[31] Thus, a divergent synthesis of both **1** and **2** could result from *N*-acyloxazolidinone **5**, ultimately derivable from methyl ketone **6**.

The synthesis of the *N*-acyloxazolidinone **5** began by exposure of (*S*)-benzylglycidyl ether to dimethyl-sulfonium methylide as described by Mioskowski[32] to install the desired olefin functionality (Scheme 3). The resulting allylic alcohol **7** was then protected as its *p*-methoxybenzyl ether to afford alkene **8** in excellent yield. Alkene **8** was converted to methyl ketone **6** under modified Wacker conditions.[33,34] Alkene **8** could also be

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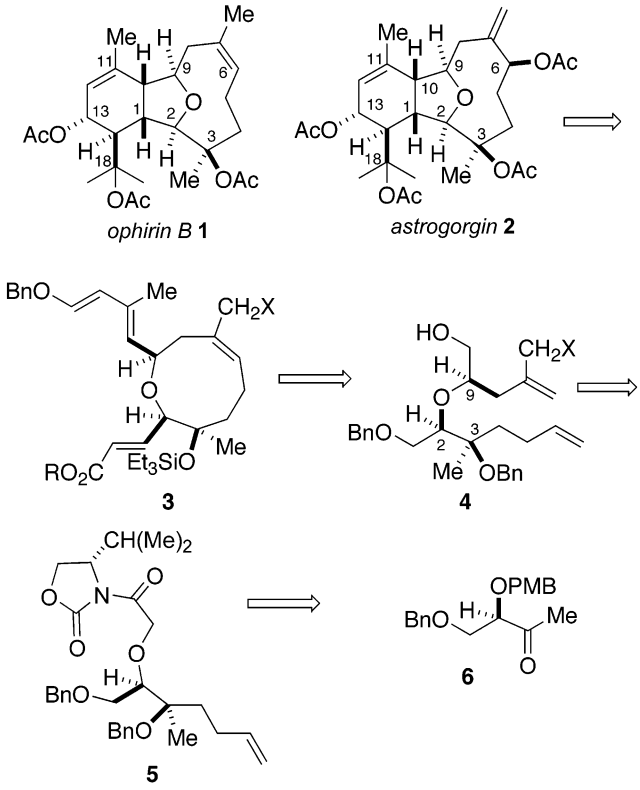
Scheme 2. Retrosynthetic Plan

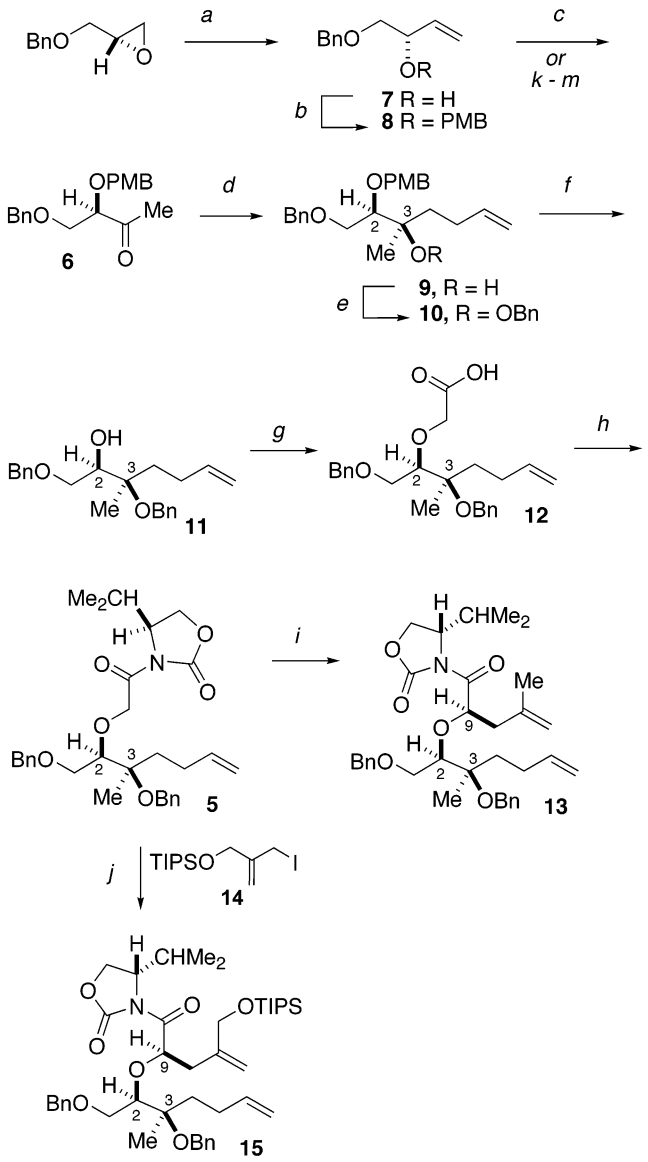


converted to methyl ketone **6** through Lemieux−Johnson cleavage of the alkene followed by addition of methylmagnesium chloride to the aldehyde and subsequent oxidation of the intermediate secondary alcohol to the ketone **6**. The critical C9 stereogenic center was introduced by a chelation-controlled addition of 3-butenylmagnesium bromide to ketone **6**, which supplied the tertiary carbinol in high yield as a single detectable stereoisomer **9** by ^{1}H NMR. The tertiary alcohol was protected as a benzyl ether providing ether **10**, whereupon exposure to acidic methanol at 65 °C, the PMB ether was cleaved to reveal the secondary alcohol **11**. Alkylation of the secondary alcohol (NaH, $BrCH_2CO_2H$) produced the glycolic acid **12** in high yield. *N*-Acyloxazolidinone **5** was then obtained in 89% yield through acylation of lithio-(*S*)-4-isopropyloxazolidinone with the mixed anhydride of acid **12**.

The C9 stereogenic centers for both natural products were installed by alkylation of the sodium enolate of oxazolidinone **5**. For ophirin B (**1**) methallyliodide was employed to stereoselectively provide the diene **13** (93%, >98:2 d.r.).[31] Asymmetric alkylation with iodide **14** was used for the route to astrogorgin (**2**) and provided the diene **15** in excellent yield.

With the appropriate dienes in hand, attention was turned toward closure of the oxonene ring. Prior success in the formation of oxonene rings for the synthesis of isolaurallene and obtusenyne using ring-closing metathesis provided confidence for this crucial transformation. Diene **13** was subjected to the Grubbs catalyst ($Cl_2(Cy_3P)_2Ru{=}CHPh$, CH_2Cl_2, 40 °C),[35] but only dimer **17** was obtained (Scheme 4). Even the more reactive ruthenium carbene ($Cl_2(Cy_3P)(sIMes)Ru{=}CHPh$, CH_2Cl_2, 40 °C)[36] led to exclusive formation of **17**. Inspection of models and preliminary molecular modeling calculations led to speculation that the dipole-stabilized conformation of the *N*-acyloxazolidinone portion of **13** was positioning the two alkenes distally. It was reasoned that removal of the auxiliary providing alcohol **18** would not only alleviate the unfavorable conformational bias but might also introduce the possibility for a stabilizing intramolecular hydrogen bond between the primary hydroxy of diene **18** and the incipient ring ether oxygen. Thus, imide **13** was reduced with sodium borohydride to provide the alcohol **18**, which was then exposed to the Grubbs catalyst (Cl_2-

Scheme 3. Synthesis to Divergent Point[a]



[a] (a) Me_3SI, *n*-BuLi, THF, −10 °C to 25 °C, 99%; (b) NaH, THF, DMF, *p*-$MeOC_6H_4CH_2Cl$, 90%; (c) $Hg(OAc)_2$, H_2O; then $PdCl_2$, LiCl, $CuCl_2$, H_2O, O_2, 89%; (d) $CH_2{=}CHCH_2CH_2MgBr$, THF, −78 °C, 94%; (e) NaH, $C_6H_5CH_2Br$, Bu_4NI, THF, 93%; (f) MeOH, HCl, 65 °C, 85%; (g) NaH, $BrCH_2CO_2H$, THF, DMF, 98%; (h) Me_3CCOCl, Et_3N, THF, −78 °C to 0 °C, (*S*)-lithio-4-isopropyl-oxazolidin-2-one, 89%; (i) $NaN(SiMe_3)_2$, THF, $CH_2{=}C(CH_3)CH_2I$, −78 °C to −45 °C, 93%; (j) $NaN(SiMe_3)_2$, THF, −78 °C to −45 °C, 90%; (k) OsO_4, $NaIO_4$, H_2O, THF; (l) MeMgCl, THF; (m) DMSO, $(COCl_2)$, Et_3N, CH_2Cl_2.

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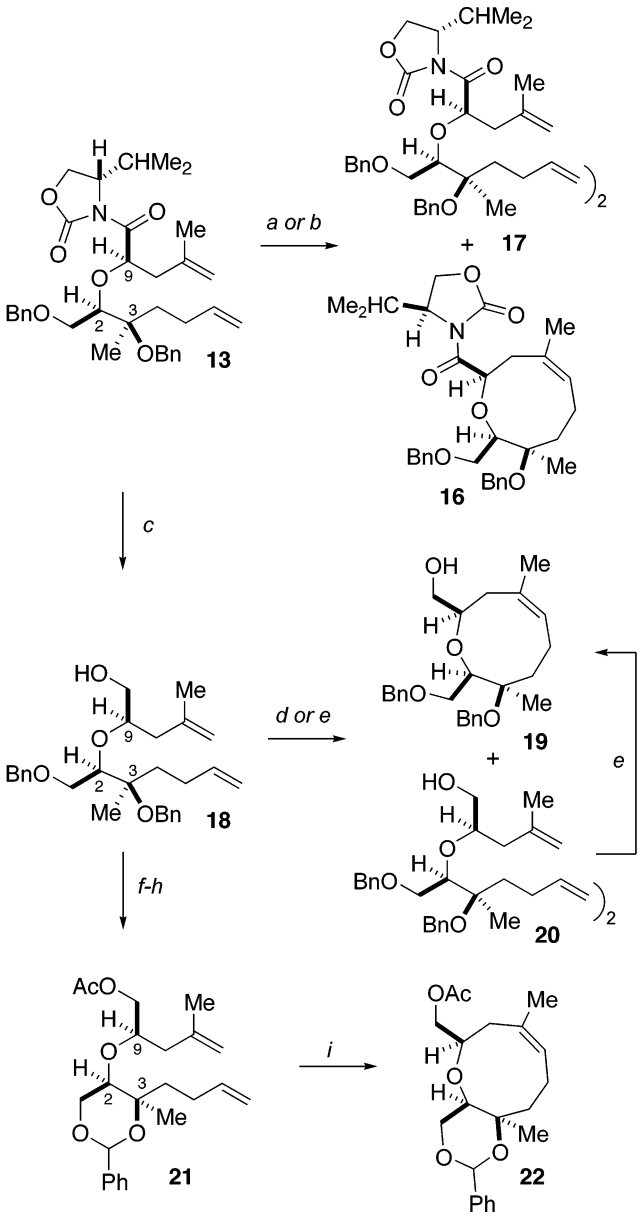
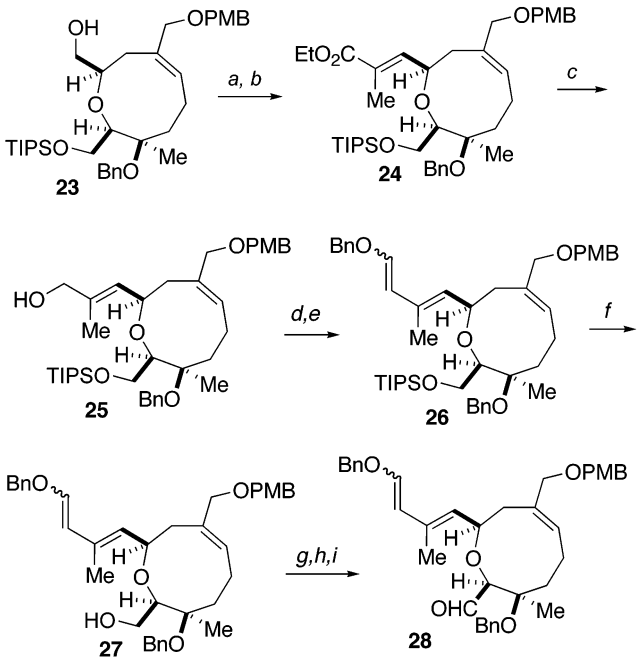
Scheme 4. Ring-Closing Metathesis to Form Oxononene[a]



[a] (a) $Cl_2(Cy_3P)_2Ru{=}CHPh$, CH_2Cl_2, 40 °C, **17** only; (b) $Cl_2(Cy_3P)(sIMes)Ru{=}CHPh$, CH_2Cl_2, 40 °C, **17** only; (c) $LiBH_4$, MeOH, Et_2O, 0 °C, 92%; (d) $Cl_2(Cy_3P)_2Ru{=}CHPh$, CH_2Cl_2, 40 °C,75%, 3:1 **19**:**20**; (e) $Cl_2(Cy_3P)(sIMes)Ru{=}CHPh$, C_6H_6, 80 °C, 89%, >15:1 **19**:**20**; (f) Ac_2O, pyridine, DMAP, CH_2Cl_2, 95%; (g) $BCl_3{-}SMe_2$, CH_2Cl_2, 0 °C, 71%; (h) $C_6H_5CH(OMe)_2$, CSA, C_6H_6, 93%; (i) $Cl_2(Cy_3P)(sIMes)Ru{=}CHPh$, CH_2Cl_2, 40 °C, <10%.

(Cy_3P)(sIMes)Ru=CHPh, CH_2Cl_2, 40 °C), leading to a 75% yield of a 3:1 mixture of oxonene **19** and dimer **20**. However, when the solvent was changed to benzene and the temperature for the reaction was increased, ($Cl_2(Cy_3P)$(sIMes)Ru=CHPh, C_6H_6, 80 °C) 89% of oxonene **19** and only trace amounts of the dimer **20** were obtained. To determine if the dimer was being reprocessed at a higher temperature, dimer **20** was purified and exposed to the same conditions as before. Once again, a >15:1 mixture of oxonene **19** to dimer **20** was obtained. When oxonene **19** was subjected to the catalyst in the presence of ethylene, no evidence of ring opening was observed. On the basis of the success of closure of diene **18** at 80 °C, diene **13** was also exposed to the Grubbs catalyst at higher temperature ($Cl_2(Cy_3P)$-

Scheme 5 [a]



[a] (a) Dess−Martin periodinane, C_5H_5N, CH_2Cl_2; (b) $Ph_3P{=}C(Me)CO_2Et$, C_6H_6, 80 °C, 100% over two steps; (c) *i*-Bu_2AlH, CH_2Cl_2, −78 °C, 86%; (d) Dess−Martin periodinane, CH_2Cl_2; (e) $Ph_3P^+CH_2OBnCl$, *t*-BuOK, THF, −78 °C, 82% over two steps; (f) *n*-Bu_4NF, THF, 92%; (g) Dess−Martin periodinane, C_5H_5N, CH_2Cl_2; (h) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2; (i) TPAP, NMO, CH_2Cl_2.

(sIMes)Ru=CHPh, C_6H_6, 80 °C). Once again, excellent conversion to the corresponding oxonene **16** was observed. Therefore, it appears that the dimers are kinetic products that are reprocessed to the oxonenes, which are unreactive in the metathesis. To examine the use of a cyclic conformational constraint for the metathesis, benzylidene **21** was prepared. Surprisingly, with the conformational rigidifying element in place, less than 10% of the corresponding oxonene **22** was formed ($Cl_2(Cy_3P)$(sIMes)Ru=CHPh, CH_2Cl_2, 40 °C). The failure of benzylidine **21** to undergo ring-closing metathesis reinforces the importance of the gauche effect and related subtle acyclic conformational constraints in these medium ring metathesis reactions.

With the key oxonene ring in place, attention was turned toward the preparation of the intramolecular Diels−Alder precursor. Initial attempts (on a slightly different substrate **23**) focused on incorporating the diene prior to the enoate with the hope that the formation of the enoate and the Diels−Alder reaction might occur sequentially in the same reaction. To this end, alcohol **23** was converted to the enoate **24** by Dess−Martin oxidation[37−39] and subsequent Wittig olefination to deliver the ester **24** in quantitative yield (Scheme 5). The ester was reduced to alcohol **25**, which was then oxidized to the corresponding aldehyde. Treatment of the aldehyde with benzyloxymethylenetriphenylphosphorane produced a 1.5:1 mixture of the diene diastereomers **26** in good yield. The removal of the TIPS protecting group from **26** proceeded smoothly, but attempts to oxidize the alcohol **27** to the aldehyde **28** led to decomposition. The aldehyde was apparently undergoing rapid reaction with

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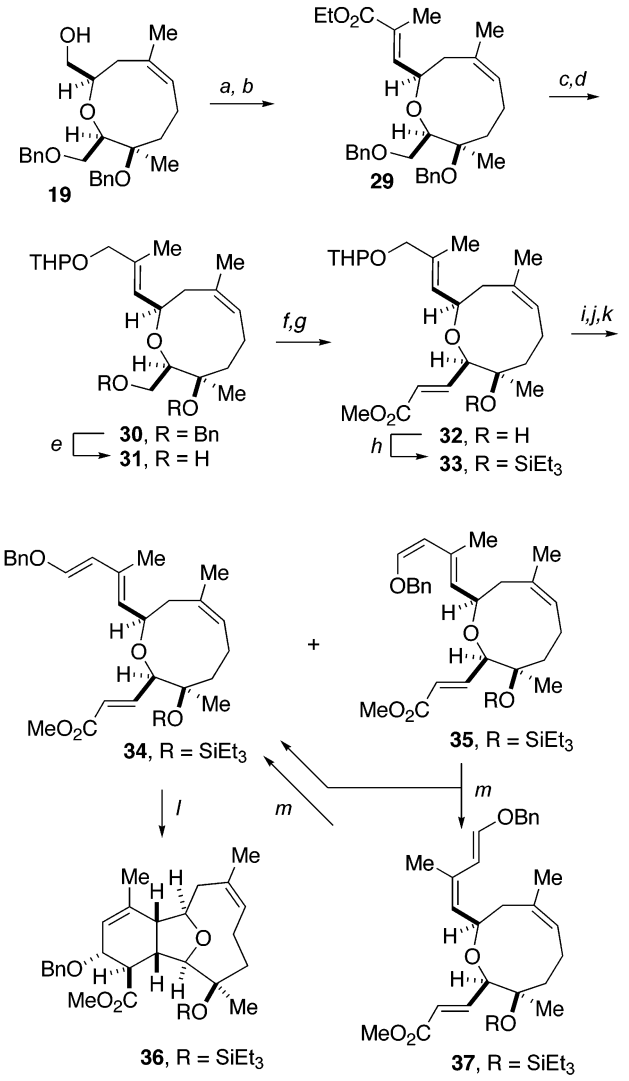
Scheme 6. Intramolecular Diels−Alder to Form Eunicellin Core[a]



[a] (a) Dess−Martin periodinane, C_5H_5N, CH_2Cl_2; (b) $Ph_3P{=}C(Me)CO_2Et$, C_6H_6, 80 °C, 99% over two steps; (c) *i*-Bu_2AlH, CH_2Cl_2, − 78 °C, 93%; (d) DHP, PPTS, CH_2Cl_2 98%; (e) Na, NH_3, THF, 91%; (f) Dess−Martin periodinane, CH_2Cl_2; (g) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 40 °C, 91% over two steps; (h) Et_3SiOTf, CH_2Cl_2, 2,6-lutidine, 95%; (i) PPTS, MeOH; (j) Dess−Martin periodinane, CH_2Cl_2; (k) $Ph_3P^+CH_2OBnCl$, *t*-BuOK, THF, −78 °C; (l) C_6H_6, 25 °C (78% from **33**); (m) *hν*, PhSSPh, C_6H_6.

the diene enol ether. It was therefore decided to introduce the enoate at C2 prior to completion of the diene moiety.

Reordering the sequence allowed for efficient introduction of the diene and the enoate for the intramolecular Diels−Alder reaction. The alcohol **19** was oxidized using Dess−Martin conditions, and the resulting aldehyde underwent a Wittig olefination to afford the (*E*)-enoate **29** (Scheme 6). Reduction of **29** followed by protection of the alcohol as the THP ether provided **30**. The benzyl ethers were then reductively cleaved giving diol **31**. Oxidation of the primary alcohol and conversion of the resultant aldehyde to enoate **32** proceeded in excellent yield. The tertiary alcohol was then protected as the TES ether giving **33**. Next, the THP ether was selectively removed under mild acidic conditions, and the resulting alcohol was oxidized to the aldehyde. Exposure to benzyloxymethylenetriphenylphosphorane resulted in a 3:1 mixture of **34**:**35** dienes. Although the Wittig olefination was not selective, a fortuitous event ensued during the Diels−Alder reaction. When the mixture of dienes **34** and **35** was allowed to stand at room temperature, diene **34** was rapidly and quantitatively converted to the desired oxatricyclic system **36** as a single diastereomer. Next, the possibility of isomerizing diene **35** to diene **34** was explored. Exposure of the diene **35** to iodine in benzene caused hydrolysis of the enol ether, while irradiation in benzene in the presence of Me_6Sn_2 or Bu_6Sn_2 did not effect isomerization. However, when a mixture of cycloadduct **36** and diene **35** was irradiated in the presence of catalytic PhSSPh,[40] adduct **36** was unaffected, but diene **35** was converted to a 1:1 mixture of diene **34** and the *Z*,*E*-diene isomer **37**. Again, after standing, diene **34** was transformed to cycloadduct **36** and the *Z*,*E*-diene **37** was unaltered. This process was repeated on the mixture until essentially all the diene had been consumed, resulting in a 78% overall isolated yield (from the THP ether) of a single exo Diels−Alder adduct **36**. It is interesting to note that when the C3−O was the free OH a 3:1 mixture of exo:endo diastereomers of the cycloaddition was obtained. The Diels−Alder cycloaddition of a similar system, with a benzyl ether at the C3−O position resulted in a 4.5:1 exo:endo ratio of Diels−Alder adducts. Thus, it is suggested that the size of the group at the C3−O position effects the diastereoselectivity of the cycloaddition with hydrogen < benzyl < triethylsilyl increasing exo selectivity. The stereochemical assignments of the two Diels−Alder adducts **36** (exo) and **38** (endo) were made based on two-dimensional NOESY experiments. In the exo adduct **36**, a strong interaction was observed between the hydrogens at C1−C10, at C14−C2, and between the C2 hydrogen and the C3 methyl group. In contrast, in the endo adduct **38**, a strong interaction was observed between the hydrogens at C1−C2, as well as the C3 methyl group with the hydrogens at both C1 and C2 (Scheme 7).

Inspection of the transition states **39** and **40** in Scheme 7 provides a rationale for the observed selectivity based on changing the protecting group of the C3 hydroxyl. In transition-state **40**, which leads to the endo Diels−Alder adduct, a significant nonbonding interaction develops between the OR group and the alpha hydrogen of the enoate, whereas the nonbonded interaction between the beta hydrogen of the enoate and the OR group in transition state **39** appears to be less significant. Thus as R progresses from hydrogen to benzyl to triethylsilyl, the exo selectivity of the intramolecular Diels−Alder increases. This is further supported by a report by Holmes, wherein similar Diels−Alder reactions of substrates with a protected secondary alcohol at C3 (of opposite configuration to **34**, i.e., H instead of OR and OR instead of Me for a substrate similar to **34**) undergo endo selective Diels−Alder cycloadditions.[41] Another interesting point is that even heating diene **35** to 80 °C in benzene did not effect cycloaddition, presumably due to the inability of the diene of **35** to adopt the required s-cis conformation for cycloaddition to occur.

With the cycloadduct in hand, attention turned to completion of the synthesis of ophirin B. Addition of methylmagnesium chloride to ester **36** smoothly provided the tertiary alcohol **41** in excellent yield (Scheme 8). Fluoride mediated cleavage of the triethylsilyl ether followed by reductive cleavage of the benzyl ether delivered the triol **43**. Attempts to directly form the triacetate ophirin B (**1**) from triol **43** were thwarted by the formation of the bridged ether **44**. A wide variety of standard

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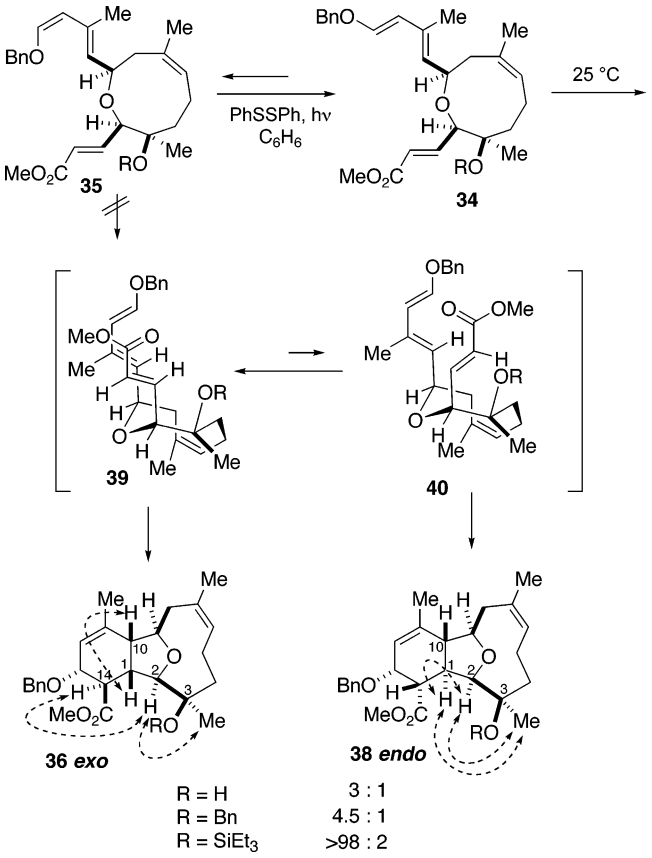
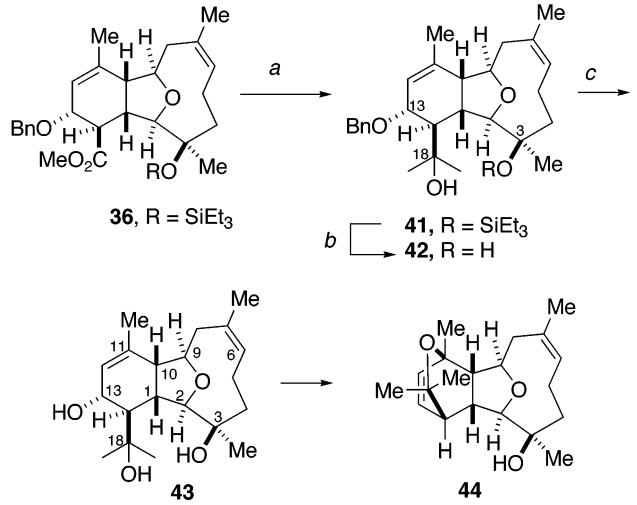
Scheme 7



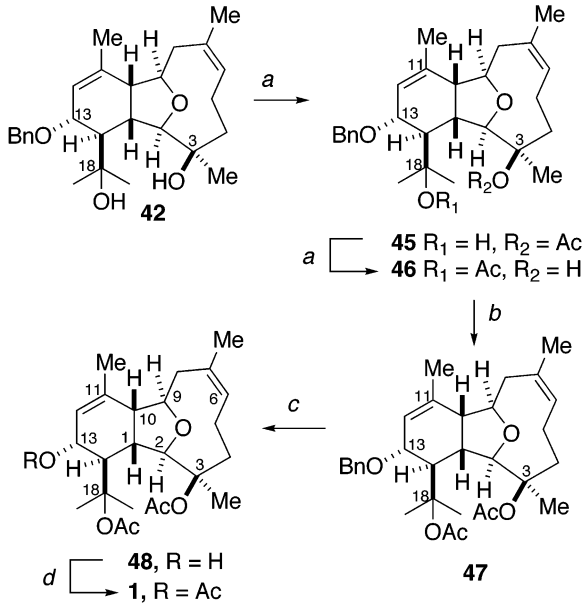
Scheme 8. End Game for Ophirin B[a]



[a] (a) MeMgCl, THF, 0−25 °C, 85% (b) *n*-Bu_4F, THF, 94%; (c) Na, naphthalene, THF −78 °C, 90%.

basic acetylation conditions, such as Et_3N, Ac_2O, DMAP or Ac-(imidazole), imidazole, CH_2Cl_2 or Ac_2O, KH, and THF, resulted in cyclization to the bridged ether **44**. Lewis acid catalyzed acetylations conditions, such as $Sc(OTf)_3$, Ac_2O or $Bi(OTf)_2$, and Ac_2O, produced either the tetracycle **44** or effected decomposition. It was postulated that sterically less hindered C13 allylic alcohol was first to undergo acetylation and that the axial disposition of the C14 hydroxypropyl group suitably positioned the hydroxy for allylic displacement of the C13 allylic acetate. Thus, it seemed reasonable that if the C18 hydroxyl on the hydroxypropyl group could be acetylated first, the formation

Scheme 9. Revised End Game for Ophirin B[a]



[a] (a) KH, THF, Ac_2O, 90%, 1:1 ratio of **45**:**46**; (b) $Bi(OTf)_3$, Ac_2O, THF, 75%; (c) H_2, Pd/C, EtOAc, 70%; (d) Ac_2O, DMAP, C_5H_5N, CH_2Cl_2, 95%.

of the bridged ether **44** might be suppressed. On the basis of this rationale, a stepwise approach was undertaken. After the triethylsilyl ether was cleaved providing the diol **42**, several conditions were explored to afford the diacetylated product **47** (Scheme 9). Ultimately, it was determined that diol **42** could be converted to a 1:1 mixture of monoacetates **45** and **46** by exposure to KH and acetic anhydride.[12] While conditions were never found to selectively form either of the monoacetates or to directly produce the diacetate, a plausible solution was identified. The two monoacetates **45** and **46** were separated by chromatography and the C3 acetate **45** could be converted to a 1:1 mixture of monoacetates **45** and **46** by treatment with KH and acetic anhydride in THF through an acetyl migration. Recycling the undesired acetate eventually produced the monoacetate **46** in 90% yield. The C3 acetate was finally installed by treatment of the monoacetate **46** with $Bi(OTf)_3$[42,43] and acetic anhydride at −40 °C (warming resulted in elimination of both acetates) to deliver the desired diacetate **47** in 75% yield. Careful hydrogenolysis of the C13 benzyl ether led to the allylic alcohol **48**, which was transformed to ophirin B (**1**) under standard conditions (Ac_2O, C_5H_5N, DMAP). Synthetic ophirin B displayed identical spectral characteristics (^1H, ^{13}C NMR, IR) and optical rotation to those reported for the isolated natural product.

With the completion of ophirin B, an application of the same synthetic strategy to the synthesis of the more complex natural product astrogorgin (**2**) was investigated. The auxiliary was reductively removed from the alkylation product **15** providing the alcohol **49** (Scheme 10). The oxonene **50** was formed in excellent yield utilizing ring-closing metathesis with Grubbs catalyst ($Cl_2(Cy_3P)(sIMes)R{=}CHPh$, C_6H_6, 80 °C). Dess−Martin oxidation of the alcohol **50** followed by Wittig reaction

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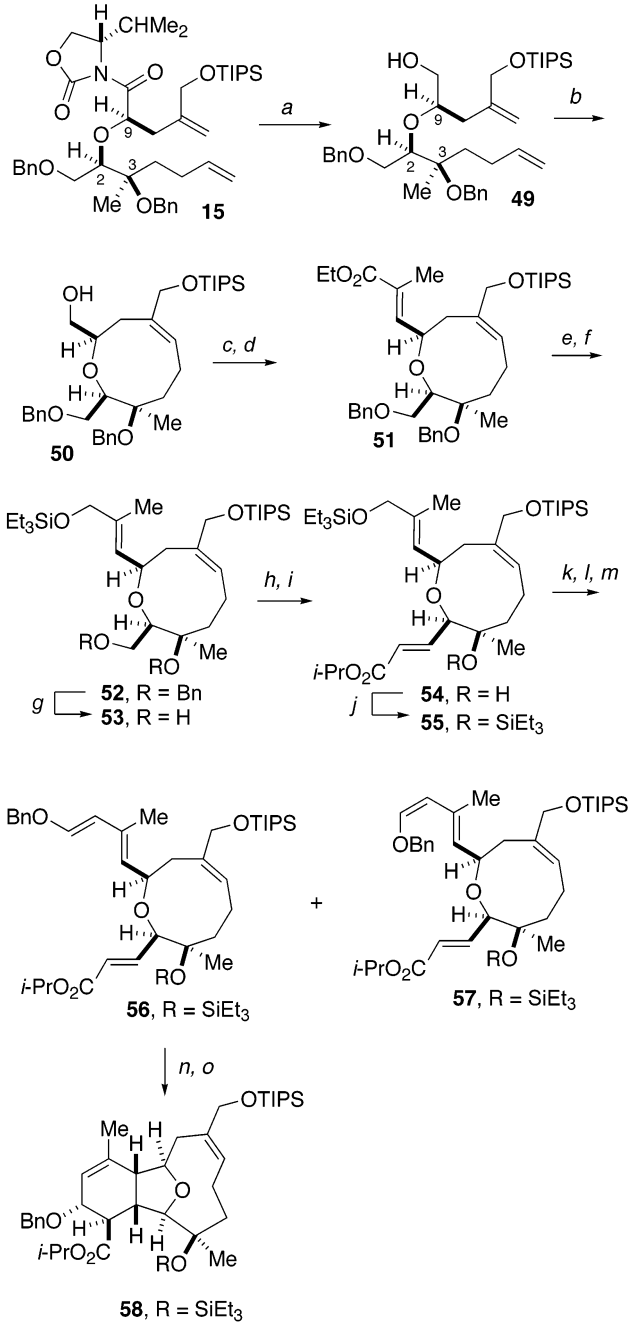
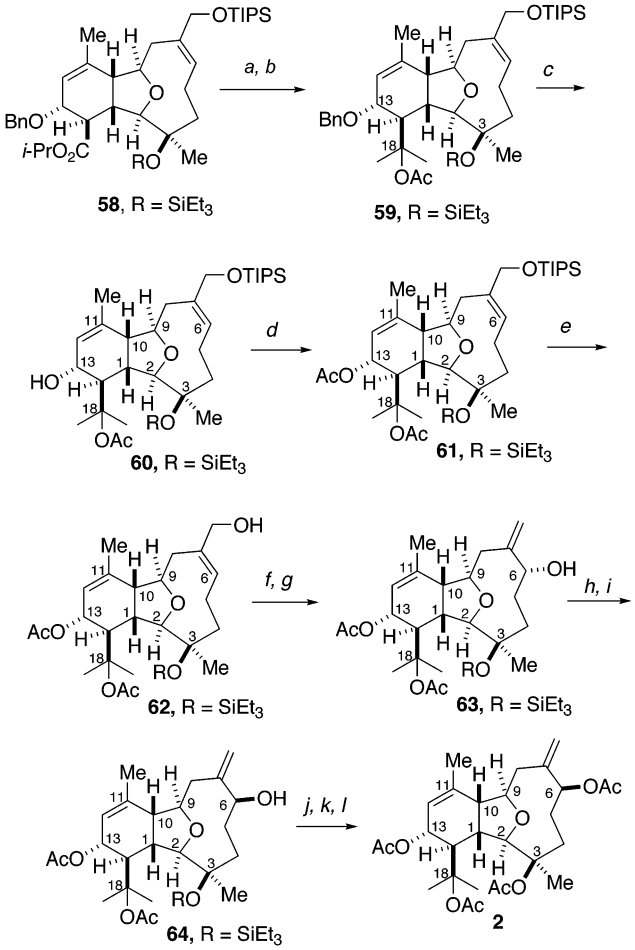
Scheme 10. Synthesis of Astrogorgin Core[a]



[a] (a) $LiBH_4$, MeOH, Et_2O, 0 °C, 90%; (b) $Cl_2(Cy_3P)$(sIMes)Ru=CHPh, C_6H_6, 80 °C, 96%; (c) Dess−Martin periodinane, C_5H_5N, CH_2Cl_2; (d) $Ph_3P{=}C(Me)CO_2Et$, C_6H_6, 80 °C, 85% over two steps; (e) *i*-Bu_2AlH, CH_2Cl_2, −78 °C, 98%; (f) Et_3SiOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, quant.; (g) Na, NH_3, THF, 70%; (h) TPAP, NMO, CH_2Cl_2; (i) $Ph_3P{=}CHCO_2i$-Pr, CH_2Cl_2, 40 °C, 14:1 (*E*:*Z*), 85% over two steps; (j) Et_3SiOTf, CH_2Cl_2, 2,6-lutidine, quant.; (k) PPTS, MeOH, 85%; (l) Dess−Martin periodinane, C_5H_5N, CH_2Cl_2; (m) $Ph_3P^+CH_2OBnCl$, *t*-BuOK, THF, −78 °C; (n) C_6H_6, 25 °C, 78% over four steps; (o) *hν*, PhSSPh, C_6H_6.

provided the (*E*)-enoate **51**. Reduction of the ester and subsequent protection of the resulting alcohol gave the triethylsilyl ether **52**. The benzyl ethers were cleaved under reductive conditions (Na, NH_3, THF) to afford the diol **53** without cleavage of the triethylsilyl group. Mild oxidation of the primary alcohol with nPr_4NRuO_4 and NMO (Dess−Martin conditions resulted in the cleavage of the triethylsilyl ether) and olefination of the resulting aldehyde led to the enoate **54**. The (*E*)-

Scheme 11. End Game for Astrogorgin[a]



[a] (a) MeMgCl, THF, 0−25 °C, 89%; (b) NaHMDS, THF, Ac_2O, 0 °C, 54%, quant. BRSM; (c) H_2, Pd/C, THF, 85%, quant. BRSM; (d) Ac_2O, DMAP, C_5H_5N, CH_2Cl_2, 91%; (e) *n*-Bu_4F, THF, quant.; (f) *o*-$NO_2C_6H_4SeCN$, *n*-Bu_3P, THF; (g) H_2O_2, C_5H_5N, CH_2Cl_2, 0 °C, 94% for two steps; (h) TPAP, NMO, CH_2Cl_2, quant.; (i) $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 89% (j) Ac_2O, DMAP, C_5H_5N, CH_2Cl_2, 92%; (k) *n*-Bu_4F, THF, 80%; (l) $Bi(OTf)_3$, Ac_2O, THF, −78 °C to − 31 °C, 26%.

stereoselectivity of this olefination was improved by employing the ^{i}Pr ester rather than the methyl ester in the Wittig reagent (14:1 with ^{i}Pr vs 4:1 with Me). The tertiary alcohol **54** was then protected as its triethylsilyl ether **55**. The primary allylic triethylsilyl ether was selectively cleaved under mild acidic conditions to give the allylic alcohol in excellent yield. Oxidation of the alcohol to the aldehyde followed by exposure to benzyloxymethylenetriphenylphosphorane resulted in a 1.4:1 mixture of dienes **56**:**57**. As before, with the ophirin B intermediate, when the mixture of dienes was allowed to stand at room temperature, diene **56** was quantitatively converted to the desired oxatricycle **58** as a single diastereomer within 13 h. Once again, the diene **57** was unchanged. By irradiation of the mixture of cycloadduct **58** and diene **57** with PhSSPh, only the diene **57** was affected and converted to a mixture of diene **56** and the *Z*,*E*-diene isomer. After standing for 13 h, diene **56** was completely transformed to the tricycle **58** and the *Z*,*E*-diene was unaltered. This sequence was repeated until all the diene had been consumed to provide an overall 78% yield (from the allylic alcohol) of a single exo Diels−Alder adduct **58**.

The ester **58** was treated with methylmagnesium chloride, and the resulting alcohol was immediately acetylated to give

59 (Scheme 11). Careful hydrogenolysis of the C13 benzyl ether led to the allylic alcohol **60**, which was further transformed into the diacetate **61**. Next, the triisopropylsilyl ether was selectively cleaved without affecting the hindered C3 triethylsilyl ether to provide the allylic alcohol **62**.

Allylic transposition using the Grieco reagent smoothly provided the exo cyclic olefin **63** as a single diastereomer.[44,45] Unfortunately, the stereochemistry of the C6 allylic alcohol was opposite that required for astrogorgin. Thus, mild oxidation to the enone and selective reduction under Luche conditions[46] afforded the desired allylic alcohol **64** as a single diastereomer in good yield. The allylic alcohol was then acetylated under standard conditions, and the C3 oxygen was unmasked. Treatment with $Bi(OTf)_3$ and Ac_2O provided astrogorgin in 26% yield (the bis elimination product and recovered starting material were the other major components of the reaction). Synthetic astrogorgin displayed identical spectral characteristics (^1H, ^{13}C NMR, IR) and optical rotation to those reported for the isolated natural product.

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In summary, highly stereoselective synthesis of ophirin B and astrogorgin has been completed. The highlights of the syntheses include a diastereoselective glycolate alkylation to establish the absolute configuration of C9, ring-closing metathesis to construct the oxonene ring, and intramolecular Diels−Alder reactions to simultaneously install C1, C10, C13, and C14 stereocenters.

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Supporting Information Available: Experimental procedures as well as ^1H and ^{13}C NMR spectra for all new compounds and synthetic (−)-ophirin B and (−)-astrogorgin. This material is available free of charge via the Internet at http://pubs.acs.org.

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