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An Intramolecular Diels−Alder Approach to the Eunicelins: Enantioselective Total Synthesis of Ophirin B

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The eunicellins, briarellins, and asbestinins are related subclasses of the C2,C11-cyclized cembranoid diterpenes produced as secondary metabolites of gorgonian octocoral.[1] An unusual oxatricyclic ring system with stereogenic centers at C1−3, 9, 10, and 14 are common to all three subclasses, while they differ in location of the cyclohexyl methyl group (C11 vs C12) and in oxidation level of the six- and nine-membered rings. The diverse biological activity displayed by members of these classes[2] has piqued interest in the chemical synthesis of these intriguing structures.

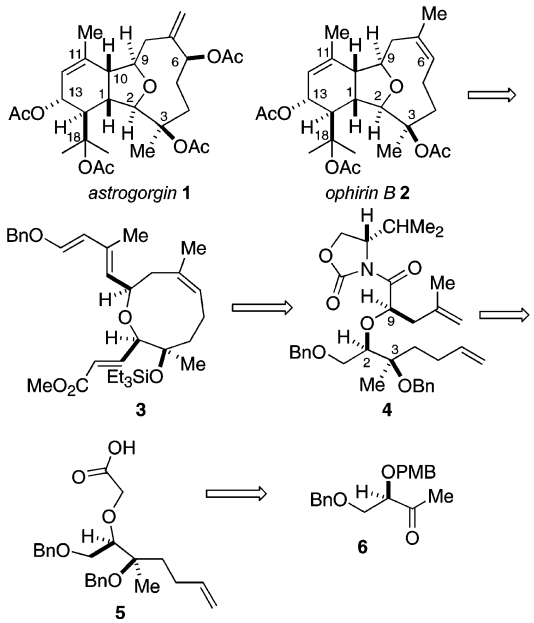
Previous synthetic approaches to the eunicellins and briarellins have relied entirely on strategies wherein the hydroisobenzofuran unit was incorporated prior to the oxonane ring.[3] Astrogorgin **1**[4] and ophirin B **2**[5,6] seemed particularly attractive targets because of the additional oxidation at C13 and C18, which offered an opportunity for the simultaneous installation of the C1, C10, C13, and C14 stereogenic centers by a strategic intramolecular Diels−Alder cycloaddition of tetraene **3**. We report here the successful implementation of this plan in the context of the first total synthesis of a C13, C18 oxygenated eunicellin, specifically ophirin B.

Our strategy (Scheme 1) for the synthesis of the Diels−Alder substrate **3** was predicated on our recent successes in the construction of medium ring ethers. We had previously demonstrated that unsaturated seven-,[7] eight-,[8] and nine-membered[9] cyclic ethers could be prepared by ring-closing metathesis through exploitation of acyclic conformational constraints. Thus, Diels−Alder substrate **3** would be derived from diene **4**, which would be fashioned through an asymmetric glycolate alkylation[10] of the *N*-acyloxazolidinone derived from glycolic acid **5**.

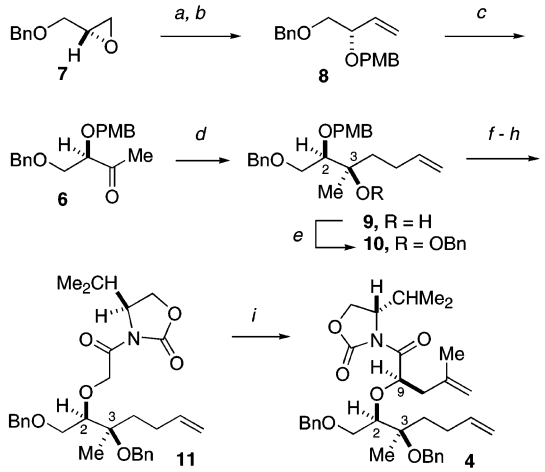
The preparation of diene **4** is illustrated in Scheme 2. The reaction of (*S*)-benzylglycidyl ether with dimethyl-sulfonium methylide[11] was followed by protection of the resulting allylic alcohol as its *p*-methoxybenzyl ether to afford alkene **8** in excellent yield. The alkene **8** was treated under modified Wacker oxidation[12] conditions to deliver the methyl ketone **6**. The chelation-controlled addition of 3-butenylmagnesium bromide to ketone **6** supplied the tertiary carbinol **9** as a single detectable stereoisomer. The tertiary alcohol was protected as a benzyl ether providing ether **10**. The PMB ether was cleaved by exposure of ether **10** to acidic methanol at 65 °C followed by alkylation of the ensuing alcohol with sodium hydride and sodium bromoacetate to produce a high yield of the glycolic acid **5**. Acylation of the glycolic acid **5** through its mixed anhydride delivered the *N*-acyloxazolidinone **11** in 89% yield. The C9 stereogenic center was installed by alkylation of the sodium enolate of oxazolidinone **11** with methallyliodide to stereoselectively provide the diene **4** (93%, >98:2 d.r.).[10]

With diene **4** in hand, the stage was set for the closure of the oxonene ring as illustrated in Scheme 3. Confident because of our prior success in the formation of oxonene rings by ring closing metathesis,[9] we subjected diene **4** to the Grubbs catalyst [$Cl_2(Cy_3P)_2$-Ru=CHPh, CH_2Cl_2, 40 °C],[13] but only dimer **12** was obtained from the reaction. Even the more reactive ruthenium carbene [$Cl_2(Cy_3P)$-(sIMes)Ru=CHPh,[14] CH_2Cl_2, 40 °C] led to exclusive formation of the dimer **12**. Inspection of models and preliminary molecular

Scheme 1. Retrosynthesis Plan for Ophirin B



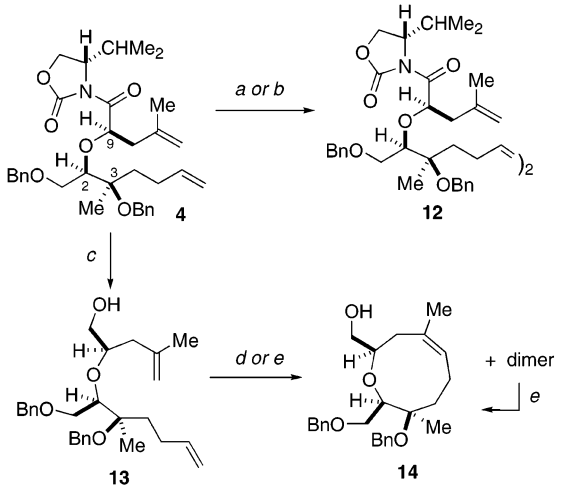
Scheme 2. Synthesis of Diene **4**[a]



[a] (a) Me_3SI, *n*-BuLi, THF, −10 °C to 25 °C, 99%; (b) NaH, THF, *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 to −45 °C, 93%.

10.1021/ja046574b CCC: $27.50

Scheme 3. Formation of the Oxonene Ring[a]



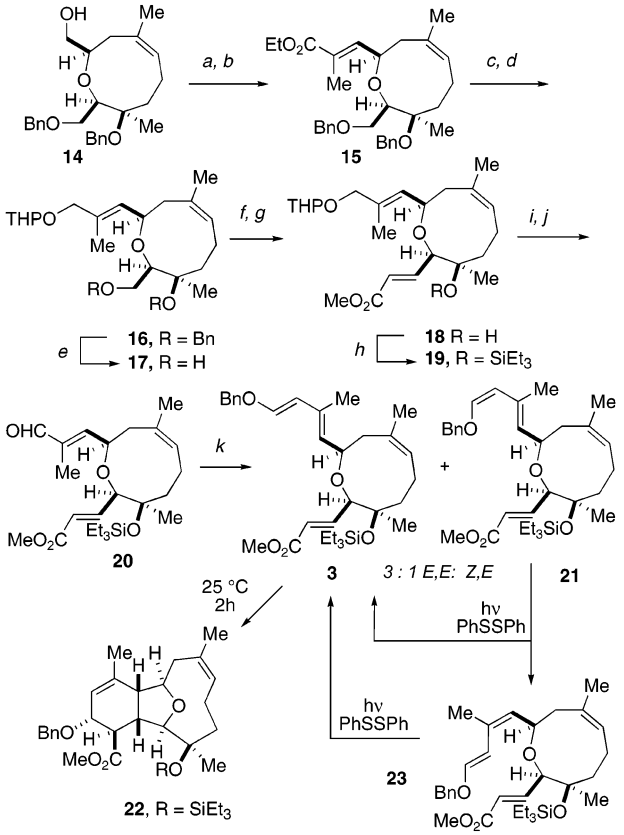
[a] (a) $Cl_2(Cy_3P)_2Ru{=}CHPh$, CH_2Cl_2, 40 °C, dimer only; (b) $Cl_2(Cy_3P)$-(sIMes)Ru=CHPh, CH_2Cl_2, 40 °C, dimer only; (c) $LiBH_4$, MeOH, Et_2O, 0 °C, 92%; (d) $Cl_2(Cy_3P)(sIMes)Ru{=}CHPh$, CH_2Cl_2, 40 °C; 75%, 3:1 RCM/dimer (e) $Cl_2(Cy_3P)(sIMes)Ru{=}CHPh$, C_6H_6, 80 °C, 89%, >15:1 oxonene **14**/dimer.

modeling calculations led to speculation that the dipole-stabilized conformation of the *N*-acyloxazolidinone portion of **4** was positioning the two alkenes distally. We reasoned that reductive removal of the auxiliary to provide alcohol **13** would not only alleviate the unfavorable conformational bias, but might also introduce the possibility for a stabilizing intramolecular hydrogen bond between the primary hydroxyl of diene **13** and the incipient ring ether oxygen. Thus, imide **4** was reduced to the alcohol **13**, which was then exposed to the Grubbs catalyst [$Cl_2(Cy_3P)(sIMes)Ru{=}CHPh$, CH_2Cl_2, 40 °C], leading to a 75% yield of a 3:1 mixture of oxonene **14** and the dimer of **13**. However, when the temperature for the reaction was increased, [$Cl_2(Cy_3P)(sIMes)Ru{=}CHPh$, C_6H_6, 80 °C] 89% of oxonene **14** and only trace amounts of the dimer were obtained. To determine if the dimer was being reprocessed at higher temperature, the dimer was separated and exposed to the same conditions as before. Once again, a >15:1 mixture of oxonene **14**/dimer was obtained. When oxonene **14** was resubjected 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 **13** at 80 °C, diene **4** was also exposed to the Grubbs catalyst at higher temperature [$Cl_2(Cy_3P)(sIMes)Ru{=}CHPh$, C_6H_6, 80 °C], which effected closure to the corresponding oxonene. This leads to the conclusion that the dimers are kinetic products that are reprocessed to the oxonenes, which are unreactive in this metathesis.

The oxonene **14** was converted to the Diels−Alder substrate **3**, as shown in Scheme 4. Dess−Martin[15] oxidation of alcohol **14** and subsequent Wittig reaction led to the (*E*)-enoate **15**. Reduction of the ester **15** followed by protection of the alcohol as its THP ether provided ether **16**, and the benzyl ethers were reductively removed to afford diol **17**. Oxidation of the primary alcohol and conversion of the resultant aldehyde to enoate **18** proceeded in 91% yield. The tertiary alcohol was then protected as its TES ether **19**. The THP ether was selectively removed under mild acidic conditions, and the alcohol was oxidized to the aldehyde **20**. Upon exposure of aldehyde **20** to benzyloxymethylenetriphenylphosphorane, a 3:1 mixture of dienes **3**:**21** was obtained.

While the Wittig olefination to form the diene **3** was not highly selective, a fortuitous event ensued during the Diels−Alder reaction. When the mixture of dienes **3** and **21** was allowed to stand at room temperature, diene **3** was rapidly and quantitatively converted to the desired oxatricyclic system **22** (Scheme 4) as a single dia-

Scheme 4. Synthesis of Tetraene **3**[a]



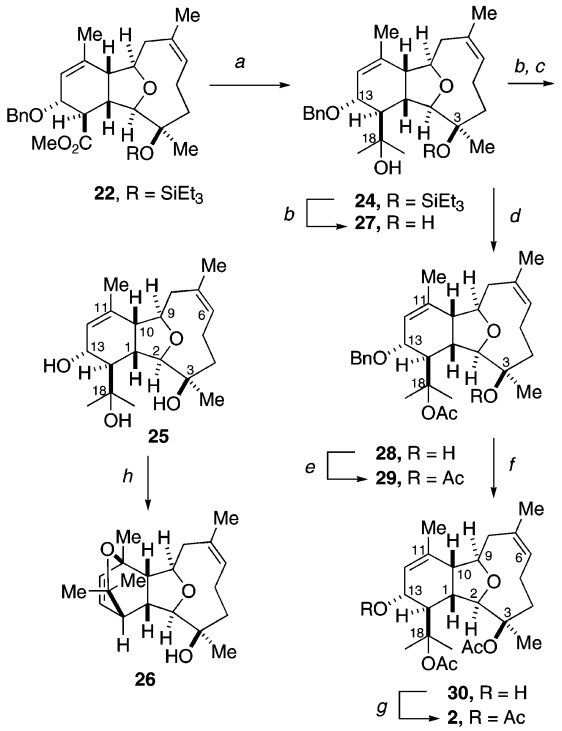
[a] (a) Dess−Martin periodinane, CH_2Cl_2; (b) $Ph_3P{=}C(Me)CO_2Et$, C_6H_6, 80 °C, 99%, two steps; (c) *i*-Bu_2AlH, CH_2Cl_2, −78 °C, 93%; (d) DHP, PPTS CH_2Cl_2, 98%. (e) Na, NH_3, THF, 91%; f) Dess−Martin periodinane, CH_2Cl_2; (g) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 40 °C, 91%, two steps; (h) Et_3SiOTf, CH_2Cl_2, lutidine, 95%; (i) PPTS, MeOH, 97%; (j) Dess−Martin periodinane, CH_2Cl_2; (k) $Ph_3P^+CH_2OBnCl$, *t*-BuOK, THF, −78 °C.

stereomer in about 2h.[17] The diene **21**, however, was unchanged. When the mixture of cycloadduct **22** and diene **21** was irradiated in the presence of catalytic PhSSPh,[16] adduct **22** was unaffected, but diene **21** was converted to a 1:1 mixture of diene **3** and the *Z*,*E* diene isomer **23**. Again, after standing, diene **3** was transformed to cycloadduct **22** and the *Z*,*E* diene **23** was unaltered. This process was repeated on the mixture until all the diene had been consumed, resulting in an 80% overall isolated yield (from the alcohol prior to the Wittig olefination) of a single exo Diels−Alder adduct **22**. With the cycloadduct **22** available, the completion of the synthesis seemed imminent.

Addition of methylmagnesium chloride to ester **22** smoothly led to the tertiary alcohol **24** (Scheme 5). The benzyl and triethylsilyl ethers were easily cleaved to access the triol **25**. Unfortunately, attempts to directly form the triacetate ophirin B (**2**) from the triol under a wide variety of acetylation conditions resulted in the formation of the bridged ether **26**. The axial disposition of the C14 hydroxypropyl group suitably positions the hydroxyl for an allylic displacement of the C13 allylic acetate. Accordingly, the failure of the direct acetylation necessitated a more circuitous solution. The problem was eventually circumvented by a stepwise acetylation of the three hydroxyl groups. The triethylsilyl ether was cleaved with

n-Bu_4NF to give the diol **27**. Diol **27** could be converted to the monoacetate **28** (but not the diacetate) by exposure to KHMDS and acetic anhydride.[3c] The C3 acetate was then installed by treatment of monoacetate **28** with $Bi(OTf)_3$[18] and acetic anhydride to deliver the diacetate **29**. Careful hydrogenolysis of the C13 benzyl

Scheme 5. Completion of the Synthesis of Ophirin B (**2**)[a]



[a] (a) MeMgCl, THF, 85%; (b) *n*-Bu_4NF, THF, 94%; (c) Na, naphthalene, THF, −78 °C, 90%; (d) KHMDS, THF, Ac_2O, 90% BRSM; (e) $Bi(OTf)_3$, Ac_2O, 75%; (f) H_2, Pd/C, EtOAc, 70%; (g) Ac_2O, DMAP, C_5H_5N, CH_2Cl_2, 95%; (h) Ac_2O or AcCl, with a variety of bases and Lewis acid conditions.

ether led to the allylic alcohol **30**, which was transformed to ophirin B (**2**) by the action of acetic anhydride and pyridine. Synthetic ophirin B displayed identical spectral characteristics (^1H, ^{13}C NMR, IR) and optical rotation to those reported for the natural product.[5,6] In summary, a highly stereoselective synthesis of ophirin B has been completed. The highlights of the synthesis are a diastereoselective glycolate alkylation to establish the absolute configuration of C9, a ring-closing metathesis to construct the oxonene ring, an intramolecular Diels−Alder reaction to simultaneously install the C1, C10, C13, and C14 stereocenters, and a stepwise triacetate formation.

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

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