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Total Synthesis of Brevenal

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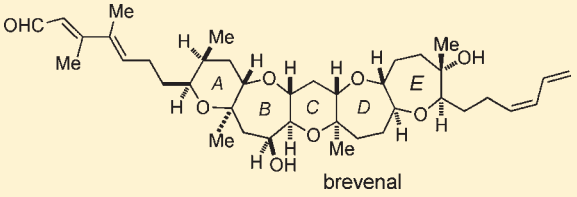
Supporting Information

ABSTRACT: This Article describes the total synthesis of the marine ladder toxin brevenal utilizing a convergent synthetic strategy. Critical to the success of this work was the use of olefinic−ester cyclization reactions and the utilization of glycal epoxides as precursors to C−C and C−H bonds.



brevenal

The dinoflagellate-derived marine ladder toxin family of natural products has presented the scientific community with a number of interesting challenges. Structurally, their fused ether architectures remain a challenge in terms of isolation, structure elucidation, and synthesis.[1] Environmentally, their role in food poisoning and red tide events has long made them a curse on marine life and on the fishing industry.[2] Functionally, their ion channel binding properties have made them useful tools in biology.[3] Thus, the 2005 report from the Bourdelais and Baden laboratories that described the isolation and structure elucidation of brevenal, a ladder toxin from the dinoflagellate *Karenia brevis*, was met with considerable enthusiasm.[4] In addition to its interesting pentacyclic structure, brevenal's impressive biological profile included ion channel activity,[5] a lack of neurotoxicity, along with an ability to increase tracheal mucous velocity in animal models of asthma.[6] These properties have led to brevenal receiving a significant amount of attention including from the synthetic community where two total syntheses and one partial synthesis have been reported.[7] The initial total synthesis by the Sasaki group also included a structural reassignment of the C(26) stereocenter. The synthesis utilized alkyl Suzuki couplings and required 32 steps to the brevenal core, 47 total steps (longest linear sequence), and was completed in 0.2% overall yield. The second synthesis was accomplished by Kadota and Yamamoto and represented an improvement in terms of side-chain construction but not with respect to the number of steps (47 steps to the core, 57 total steps (longest linear sequence), 0.8% overall yield). Finally, Crimmins recently reported a synthesis of the A, B- and E-rings that centered around his asymmetric glycolate alkylation, RCM chemistry.[8]

From a general interest in the synthesis and ion channel binding properties of the ladder toxins, we also became interested in brevenal.[9,10] Influenced a great deal by methodology that enables the cyclizations of olefins having pendant esters,[11−13] we settled upon the strategy illustrated in Scheme 1 that called for the coupling of A−B bicyclic alcohol **4** with E-ring acid **5** and olefinic−ester cyclization (OLEC) to the brevenal C-ring **2**.[14] Incorporation of the C(19) angular methyl group and cyclization to the D-ring would complete the brevenal pentacyclic core as **1**.

With this plan in mind, we initially targeted the generation of the A−B bicycle. As envisioned, the formation of the A-ring required two unprecedented reactions, OLEC to the ring itself where a cyclic template would not be present on the cyclization precursor and a stereoselective epoxidation, C−C bond-forming reaction on an A-ring dihydropyran that lacked an allylic stereocenter. Our attempts to solve these problems began with 4-hydroxybutanal derivative **6** and a Brown crotylboration reaction to give **8** having the C(8) and C(9) brevenal stereocenters in 90% yield and in 95:5 er (Scheme 2).[15] Extension of the olefin and the DCC-mediated esterification using acid **10** gave cyclization precursor **11**. In the conversion of olefinic ester **11** into A-ring substrate **12**, we compared enol ether−olefin RCM with our recently developed OLEC chemistry and found OLEC to be superior with respect to both yield and efficiency (conditions A and B). The OLEC reaction was run on multigram scale and delivered **12** in 88% yield. Also interesting was the comparison of the OLEC conditions using CH_3CHBr_2 (condition B) with those using CH_2Br_2 (condition C) and the Tebbe reagent (condition D).[16,17] The use of CH_2Br_2 gave a 1:1 mixture of cyclic and acyclic enol ether in 70% yield, while the use of the Tebbe reagent resulted in the decomposition of starting material with no noticeable product formation.[18]

We next examined oxidation to the aforementioned C(11) hydroxyl group followed by a directed C−C bond-forming reaction to the C(12) methyl group. We were pleased to find that the reaction of dihydropyran **12** with DMDO and $AlMe_3$ was stereoselective, giving the desired product **16** in 66% yield (Scheme 3).[19] We envision that the C(12) angular methyl group comes from a directed transfer of methyl as indicated by **15**.

In light of the fact that we had previously utilized substrates having pendant acetals in the Me_3Al epoxide opening reactions,[20] the generation of methyl ether **17** was somewhat surprising to us.

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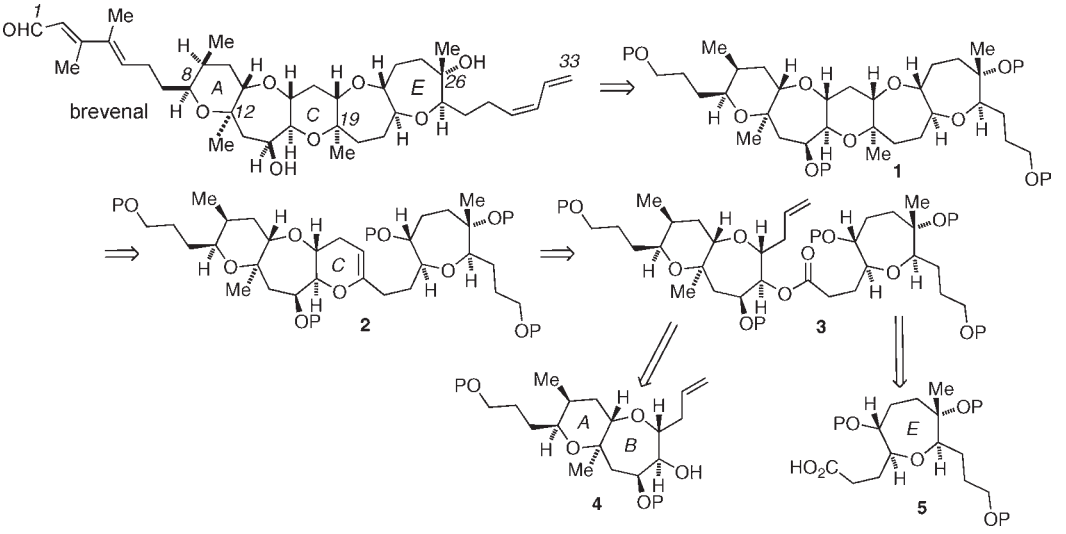
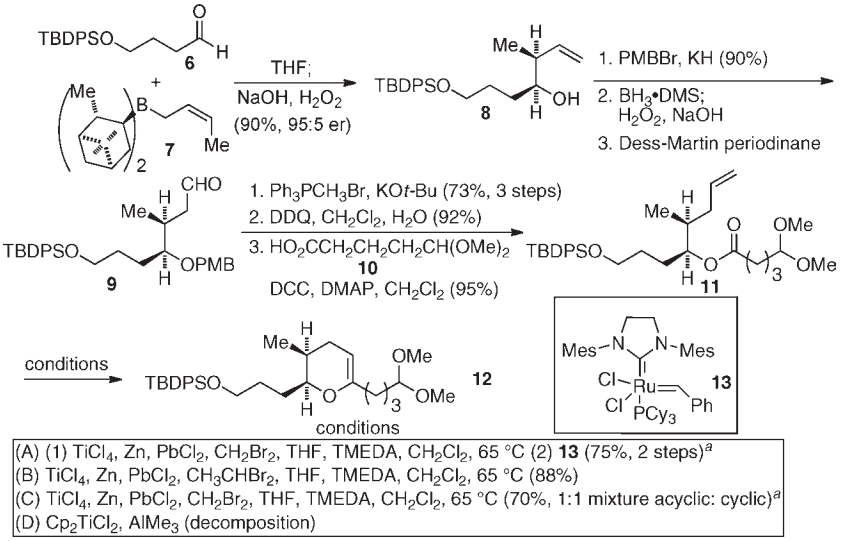
Scheme 1. OLEC Plan to Brevenal



Scheme 2. Brevenal A-Ring[a]



[a] We believe that the lower yield in entry C is due to the instability of the acyclic enol ether to purification.

While the fact that **16** and **17** are readily separable makes this process workable, the generation of **17** is obviously not ideal. Although we have dedicated a considerable amount of time and effort in attempts to overcome the formation of **17**, to date we have not been able to find conditions or substrates that are more effective than those shown.[21]

Having established the brevenal A-ring, we next targeted the B-ring and subjected **16** to a two-step cyclization protocol involving the initial generation of a cyclic mixed acetal and the subsequent elimination of methanol to give **18** (Scheme 4).[22] This sequence was superior to our previously reported one-step reaction using PPTS and pyridine due to the sensitive nature of **18** to PPTS at 130 °C.[23] DMDO epoxidation and in situ coupling with allyl Grignard gave allyl oxepane **19** in 87% yield as a 10:1 mixture of diastereomers.[24,25]

The completion of our synthesis of the brevenal A−B ring system is illustrated in Scheme 5. Oxidation of the C(15) alcohol and Rubottom oxidation introduced the C(14) hydroxyl group as a 6:1 mixture favoring the desired diastereomer **20**.[26] In a fashion similar to Sasaki's findings with a related substrate,[7a] the *i*-Bu_2AlH reduction of **20** delivered the C(14), C(15) diol corresponding to **21** as the major product. It turns out that a free alcohol is required for the synthesis of **21**. When a C(14) TES ether was used in the reduction, the undesired C(15) stereoisomer was isolated as the major product. Treatment of the diol with Bu_2SnO and benzyl bromide gave A,B coupling precursor **21** as the major product.[27] Worthy of mention here is that all of the stereocenters in **21** arose from substrate-controlled diastereoselective reactions once the C(8) and C(9) stereocenters had been established (Scheme 2).

With **21** in hand, we next targeted the synthesis of the brevenal E-ring (Scheme 6). From olefinic-ester **22**, which is available in four steps from L-glyceraldehyde acetonide,[28] OLEC successfully gave oxepene **23** in 66% yield along with 22% of the

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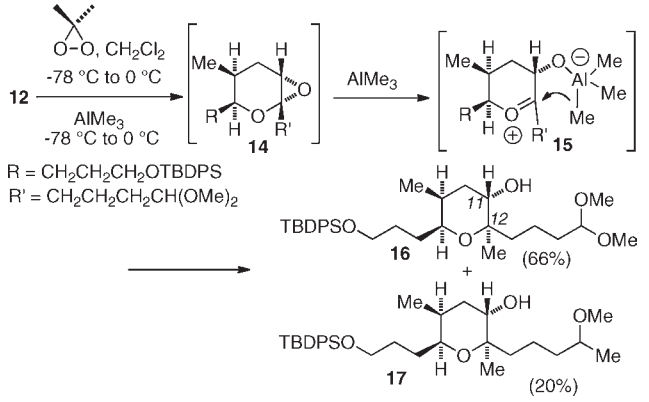
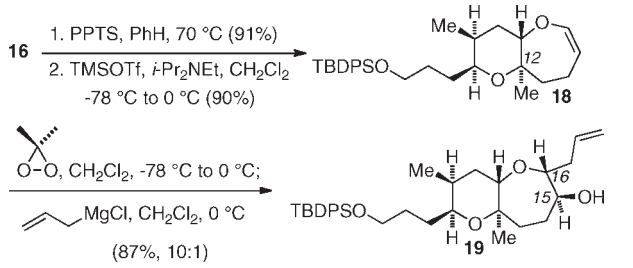
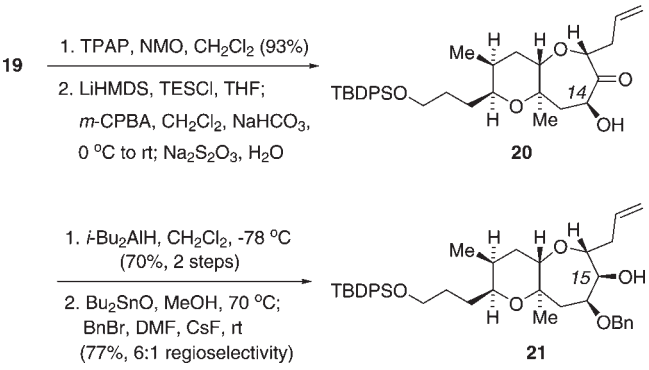
Scheme 3. Epoxidation-Directed Addition to the A-Ring



Scheme 4. Brevenal's B-Ring



Scheme 5. Completion of Brevenal's A−B Ring Precursor



corresponding acyclic enol ether. The acyclic enol ether byproduct could be converted into **23** using the Grubbs second generation catalyst **13**, but the conversion was relatively low, that is, 35%, and included varying quantities of the corresponding dihydropyran from olefin isomerization and cyclization.[29] Oxidation of **23** and in situ reduction using *i*-Bu_2AlH gave **24** as a single diastereomer.[30] Mechanistically, we believe that the epoxide oxygen atom directs the reduction in a fashion similar to the analogous reaction with Me_3Al, for example, **15**, Scheme 3.[19] Oxidation of the C(26) alcohol to the corresponding ketone and addition of MeMgBr in toluene gave a 7:1 mixture of 3° alcohol **25**.[7,31] Silyl ether formation, hydrolysis of the benzylidene acetal, and conversion of the C(21) alcohol into the corresponding homoallyl derivative gave **27**.[32] After switching the C(23) protecting group from TES to PMB, oxidative fragmentation of the alkene afforded the E-ring coupling precursor **29**.

With the synthesis of both of the precursors completed, we were prepared to examine their utility in the generation of the remainder of brevenal. Esterification of E-ring acid **29** using A,B-alcohol **21** and the Yamaguchi acid chloride gave ester **30** (Scheme 7).[33] Despite the presence of a number of potential coordination sites, the Ti OLEC chemistry was impressive here giving C-ring enol ether **31** in 83% yield.

Our initial attempts to incorporate the C(19) angular methyl group are outlined in Schemes 8 and 9. From **31**, our initial plan was to utilize the oxidation, $AlMe_3$ protocol. On the basis of a related reaction that had been successful in our hemibrevetoxin B synthesis, we had hoped that the C(14) ether would control the facial selectivity in the epoxidation reaction and, as a consequence of the mechanism (see Scheme 3), the stereoselective incorporation of the C(19) angular methyl group. In the event, exposure of a CH_2Cl_2 solution of the epoxide from **31** to $AlMe_3$ resulted in the generation of ketone **33**. Presumably **33** comes from a pinacol-type rearrangement of the intermediate epoxide, that is, **32**.[34]

The choice of solvent proved important in overcoming the generation of **33**. When the epoxide opening reaction was carried out in toluene rather than CH_2Cl_2, we isolated **34** having the desired connectivity but as a mixture of C(18) and C(19) diastereomers (Scheme 9).[35] While the observed solvent effect is certainly interesting, that **34** was isolated as an inseparable mixture of diastereomers as a result of the poor selectivity in the epoxidation reaction made this approach untenable and forced us to modify our strategy.

Despite the disappointing result to **34**, we felt that the facility of both epoxide and oxocarbenium ion formation was advantageous. To overcome the lack of selectivity in the C−C bond-forming reaction, we set out to identify conditions where the stereochemical outcome of the C(19) C−C bond formation would be decoupled from the stereochemistry of the C(18), C(19) epoxide. That is, we felt that if we were able to generate an oxocarbenium ion that was analogous to **32** but that had the adjacent alkoxide masked with a nontransferable group, the lack of selectivity in the C(19) bond formation might be overcome. Largely driving these efforts was the overwhelming propensity for axial addition to oxocarbenium ions in six-membered rings.[36] Although precedent for the proposed reaction sequence existed,[37] to the best of our knowledge the precedent was not extensive. Thus, before carrying out the chemistry on our brevenal substrate, we opted to initially explore the proposed chemistry with model bicyclic enol ether **35**. Enol ether **35** was chosen largely because we had previously demonstrated that its DMDO epoxidation chemistry was not selective.[25] In the event, when the epoxide from **35** was exposed to a mixture of TESOTf and $ZnMe_2$,[38] we isolated *C,C*-ketal **38** having the expected mixture of silyl ether diastereomers but as a single stereoisomer at the newly formed 3° ether center (Scheme 10). Through the use of NOE correlation experiments, we subsequently showed that the methyl group was in the desired axial position.

Having established the ability to generate oxocarbenium ions in the model substrate, we were prepared to examine the reaction in brevenal substrate **31** (Scheme 11). Unfortunately, the treatment of the epoxide from **31** with TESOTf and $ZnMe_2$ was capricious, giving trace amounts of the desired product **40** along with other oxidized material that included methanol adduct **39**. As has been proposed by Wei for a related transformation, we

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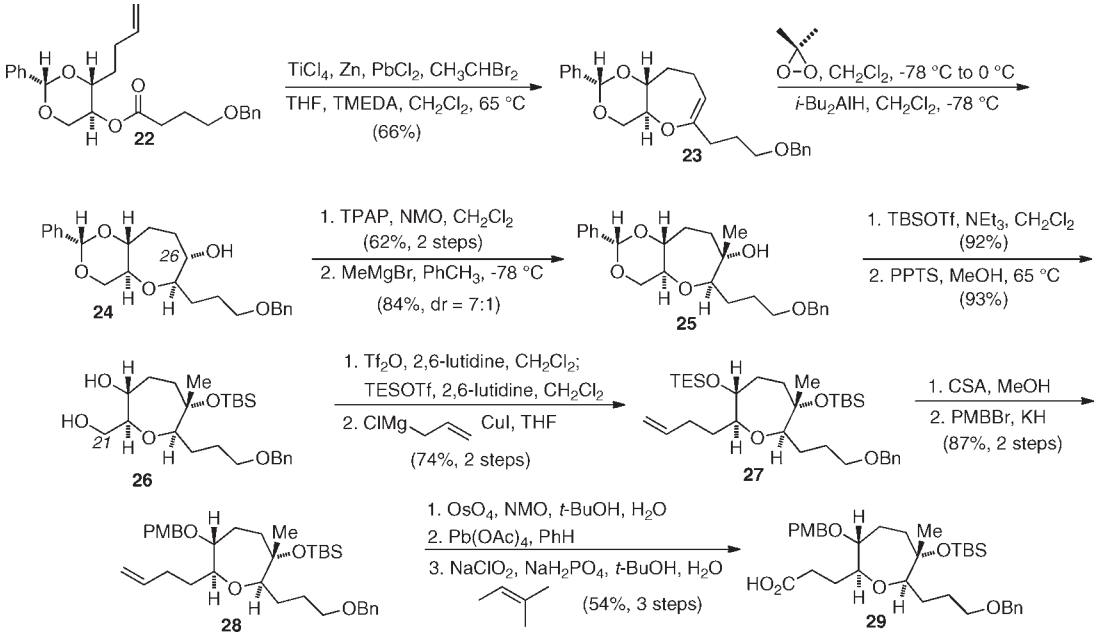
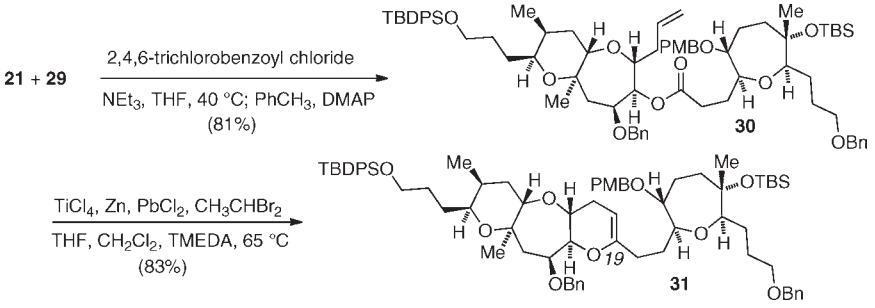
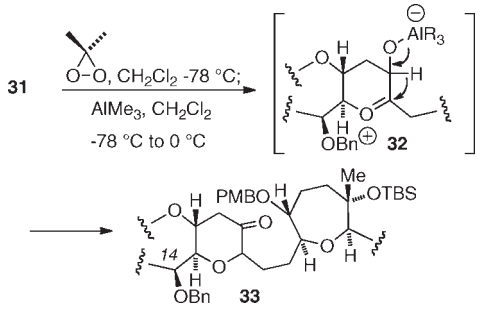
Scheme 6. Synthesis of Brevenal's E-Ring Precursor



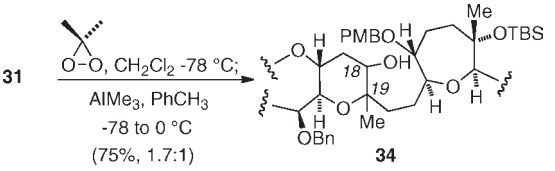
Scheme 7. Coupling to Brevenal's C-Ring



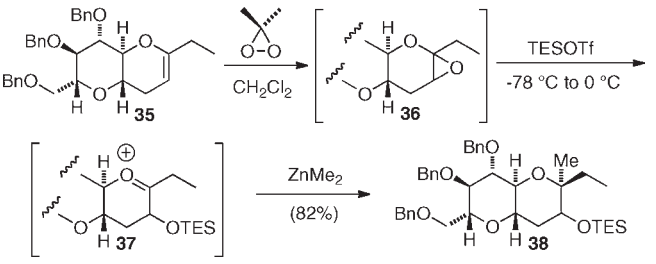
Scheme 8. Pinacol-Type Rearrangement of 31



Scheme 9. Me_3Al Addition to 31



Scheme 10. Oxocarbenium Ions from Glycal Epoxides



believe that **39** comes from the oxidation of $ZnMe_2$ by the epoxide from **31** and the subsequent transfer of methoxide to the epoxide.[39]

Having failed to directly introduce the C(19) angular methyl group into **31**, we decided to examine a stepwise solution to the problem. In contrast to the results from the reaction of $ZnMe_2$, the addition of EtSH to the epoxide from **31** worked well, giving a

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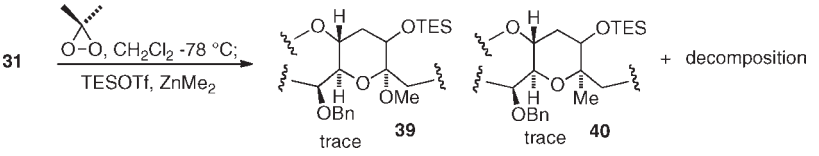
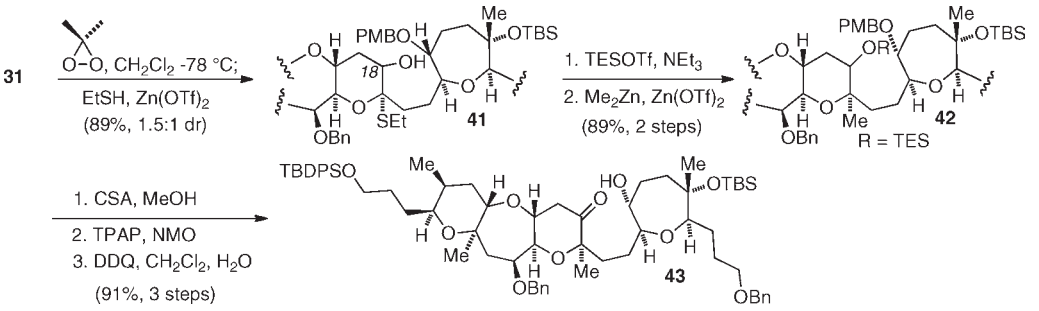
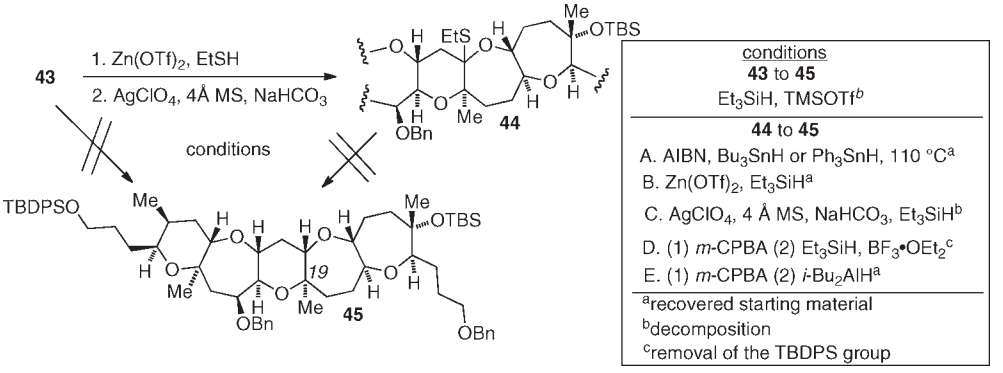
Scheme 11. Attempted Generation of 40



Scheme 12. C(19) Methyl Incorporation



Scheme 13. Attempts at Brevenal's D-Ring



mixture of C(18) alcohol diastereomers **41** in 89% yield (Scheme 12).[40] The stereoselective introduction of the C(19) methyl group was finally accomplished by subjecting the TES ether analogue of **41** to Kadota's recently reported conditions, Me_2Zn and $Zn(OTf)_2$, to give **42**.[41] Removal of the TES group and oxidation gave ketone **43** as a single diastereomer in 81% yield for the five steps following oxidative removal of the PMB ether. A harbinger of future problems with the reductive cyclization of **43** was that it existed exclusively (by ^{1}H NMR) as the hydroxy ketone tautomer and not as the corresponding hemiketal.

As mentioned above, the generation of the brevenal D-ring from **43** required a reductive cyclization reaction. To this goal, attempts to convert **43** directly into **45** using TMSOTf and Et_3SiH resulted in decomposition with no discernible product formation (Scheme 13).[42] A more conservative approach involving the generation of mixed ketal **44** was more successful but still required the initial conversion of the ketone into the corresponding dithioketal followed by a $AgClO_4$ catalyzed cyclization to give **44**.[43] Unfortunately, attempts to reduce the thioketal or the corresponding sulfone using either homolytic or heterolytic reaction conditions failed miserably. These reactions led to either the recovery of **44** or its conversion into intractable mixtures. From all of these studies, it became clear that the presence of the C(19) angular methyl group was significantly inhibiting our efforts to the brevenal C-ring.

We also examined the reductive cyclization of ketone **46** where the reduction would take place at the D,E-ring junction and C(23).[44] In contrast to the related reaction with **44**, the homolytic reduction of thioketal **47**, while sluggish, was successful, resulting in oxepane **48** as a single diastereomer (Scheme 14). Removal of the benzyl groups and conversion of the resulting alcohols into the corresponding TBS ethers gave pentacycle **49**, a compound that had been reported previously by Sasaki during his brevenal work.[7] Unfortunately, our spectroscopic data for **49** did not match that previously reported. While not definitively established, we presume that pentacycle **49** differs from the brevenal core at C(23).

The effectiveness of the OLEC approach to the ladder toxins is at least partly due to the fact that the coupling involves an

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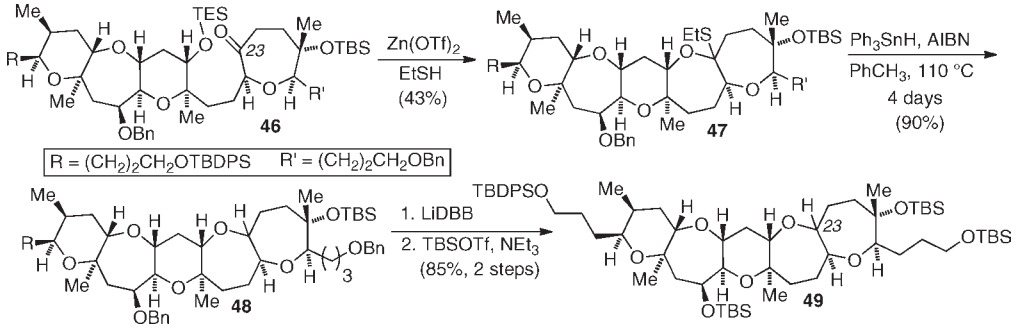
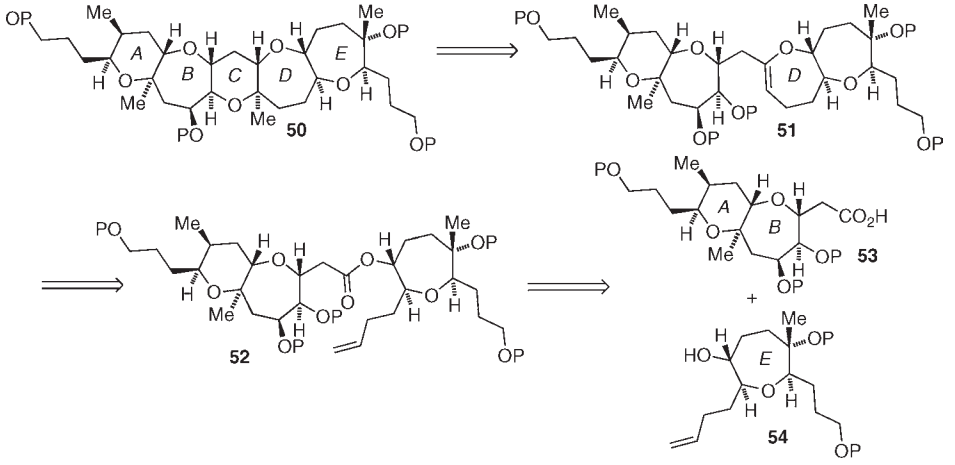
Scheme 14. C(23)-Epi-brevenal Core



Scheme 15. Brevenal Retrosynthesis-2



esterification reaction and, as a result, the ease with which coupling partners can be swapped out. Thus, while our lack of success in converting C-ring precursors **43** and **46** into the brevenal core was disappointing, we realized that we could easily modify the strategy by coupling an A,B-acid with an E-ring alcohol as represented by the coupling of **53** with **54** to give **52** (Scheme 15). Obviously, this new strategy required OLEC to the D-ring oxepene, that is, **51**.

While OLEC to the D-ring would certainly be more challenging than the analogous reaction to the C-ring, other aspects of the new strategy were considered to be advantageous. The late stage introduction of the C(19) angular methyl group and the late stage acid-mediated cyclization to the C-ring would help us to overcome some of the more problematic transformations in our previous efforts.

With the preceding line of thought as background, we utilized Shiina's esterification conditions and anhydride **57** to couple olefinic-alcohol **56** with acid **55** to give **58** (Scheme 16).[45] Yamaguchi conditions were not as effective here. After optimization of the cyclization conditions, we were pleased to be able to generate oxepene **59** in 30% yield from the OLEC reaction of **58**. Acyclic enol ether **60** was the major product here, and we were pleased to find that it could be recycled using the Grubbs second generation catalyst, that is, **13** (Scheme 2), and ethylene at elevated temperatures. This gave an additional 35% of cyclic material that consisted of a 5:1 mixture of **59** and the corresponding dihydropyran (65% overall yield of **59**).[46] Because they proved to be important, the OLEC cyclization conditions are worthy of mention here. As currently employed, these reactions require the generation of Ti(III) prior to the addition of substrate and CH_3CHBr_2.[47] Interestingly, when dibromoethane and **58** were added to the reduced Ti reagent at room temperature and subsequently slowly warmed to reflux over 15 min, only acyclic enol ether was observed. When dibromoethane and **58** were added to reagent at room temperature and warmed to reflux over 2 min, a 30% yield of **59** was isolated. While we do not understand the importance of the temperature on the reaction, it appears to point to the presence of multiple Ti species and their differential reactivity with **58**.

With the D-ring in hand, we targeted the generation of the C-ring. To this goal, the oxidation−reduction reaction of **59** gave ketone **61** in 65% overall yield following oxidation of the 2° alcohol (Scheme 17). In contrast to the oxidation of **31** (Scheme 9), the DMDO oxidation of **59** gave the corresponding epoxide as a single diastereomer. On the basis of DFT calculations in a model oxepene, we believe that the high diastereoselectivity in the generation of the C(18) stereocenter is a result of unfavorable torsional interactions between the C(20) pseudoaxial hydrogen atom and DMDO during the transition state that would lead to the C(18) epimer of **61**.[48] The synthesis of **61** intercepts the same intermediate in Sasaki's synthesis of brevenal.

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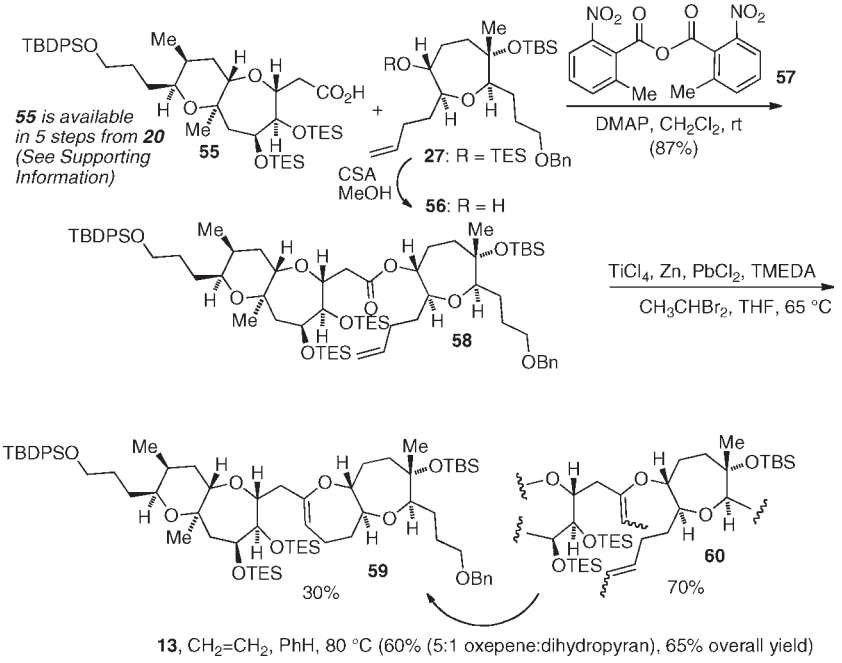
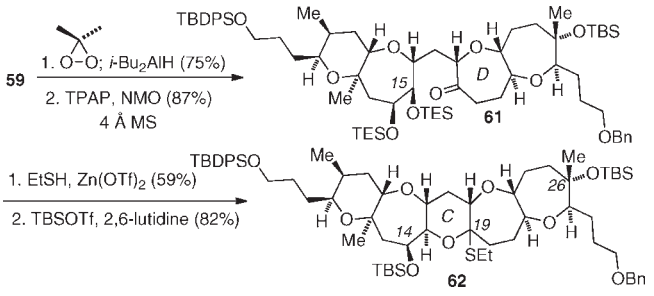
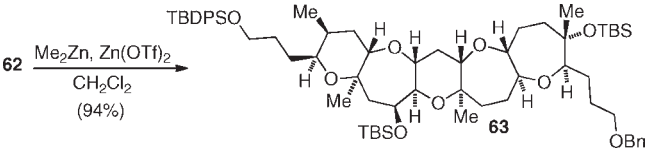
Scheme 16. Subunit Coupling Part 2



Scheme 17. Completion of the D-ring and Thioketal Formation



Scheme 18. Brevenal's Pentacyclic Core



In contrast to pentacycle **54**, the spectral data (^{1}H, ^{13}C, IR, MS, $[\alpha]^{20}_D$) matched that reported previously.[7]

Having succeeded in synthesizing **61**, we were finally prepared to complete the synthesis of the C-ring and thus the brevenal pentacyclic core. In contrast to our attempts with **48**, the cyclization of **61** to give the C-ring was uneventful. Impressively, when **61** was subjected to $Zn(OTf)_2$ and EtSH, we were able to remove both TES groups and effect cyclization to generate the desired C(19) thioketal **62** after the generation of the C(14) TBS ether.

The completion of the brevenal core required the incorporation of the C(19) angular methyl group. This task was accomplished using the Kadota methodology and resulted in the brevenal core structure as **63** in 94% yield (Scheme 18).

Our total synthesis of brevenal was completed using a modification of Yamamoto and Kadota's end game protocol for the incorporation of the side chains.[7c] These efforts began with the E-ring side chain (Scheme 19). Yamamoto and Kadota had utilized hydrogenolysis to remove the C(30) benzyl ether. In our hands, reductive conditions were higher yielding giving the corresponding 1° alcohol. Parikh–Doering oxidation and Wittig coupling using phosphonium salt **64** gave the corresponding *Z*-alkene and **65** following oxidative elimination of the phenyl selenide.[49] As has been reported previously,[50] the selective removal of the 1° TBDPS group in the presence of the 2° and 3° TBS groups was accomplished using buffered TBAF. Oxidation of the resulting 1° alcohol and Horner–Emmons reaction with the lithium salt of phosphonate **66** gave **67** in 85% yield for the two steps. Completion of brevenal was accomplished through HF·pyridine removal of the TBS ethers, *i*-Bu_2AlH reduction of the ester, and selective oxidation of the resulting allylic alcohol. Yamamoto and Kadota had carried out the reduction of the ester prior to the removal of the TBS groups using TBAF. In our hands, the allylic alcohol reduction product was unstable to the chromatography that was required after the TBAF deprotection step. Our spectral data for brevenal matched that reported previously.

In conclusion, we have carried out the total synthesis of brevenal utilizing OLEC chemistry to both build the A,B- and E-rings and carry out their convergent coupling. From our perspective, our synthesis compares favorably with other efforts toward this molecule: it required 28 steps to the core from 1,4-butanediol and 38 steps to brevenal (longest linear sequence, 0.99% overall yield). The synthesis has not only enabled us to further explore and optimize the OLEC reactions, but it has also led to a better understanding of the use of glycal epoxides in a

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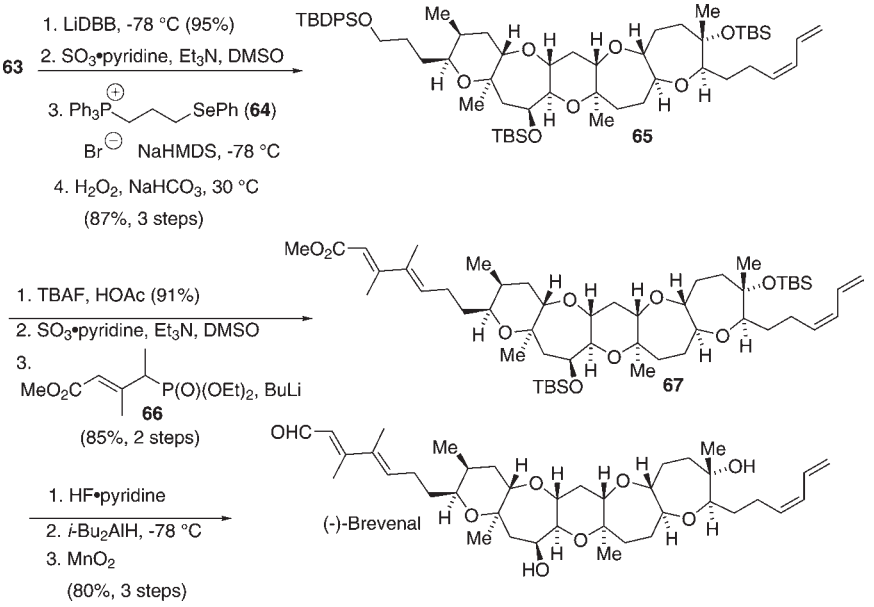
Scheme 19. Brevenal Completion



complex setting. We believe that this work will lead to a better understanding of brevenal's impressive biological properties including its ion channel activity. These latter studies will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectroscopic data for **8**, **9**, **11**, **12**, **16**−**19**, **21**−**31**, **55**, **56**, **58**, **59**, **61**, **63**, **65**, **67**, and brevenal. This material is available free of charge via the Internet at http://pubs.acs.org.

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