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A Unified Strategy for Enantioselective Total Synthesis of Cladiellin and Briarellin Diterpenes: Total Synthesis of Briarellins E and F, and the Putative Structure of Alcyonin and Revision of Its Structure Assignment

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Abstract

Enantioselective total syntheses of briarellin E (**12**) and briarellin F (**13**), as well as the structure originally proposed for the cladiellin diterpene alcyonin (**10**), have been realized. Comparison of the spectral data for synthetic **10**, natural alcyonin, cladiellisin (**33**), and cladiellaperoxide (**34**), as well as chemical transformations of **10** and natural alcyonin, suggest that the structure of this coral metabolite is allylic peroxide **11**. The unified approach detailed herein can be used to access both C4-deoxygenated and C4-oxygenated cladiellins and briarellins. The central step in these syntheses is acid-promoted condensation of (Z)-α,β-unsaturated aldehydes **17** with cyclohexadienyl diols **18**, to form intermediates **16** incorporating the hexahydroisobenzofuran core and five stereocenters of these marine diterpenes (Scheme 1).

Introduction

Corals are among myriad marine invertebrates serving as repositories of bioactive molecules.[1] Several studies suggest that soft corals and gorgonian octocorals produce a number of secondary metabolites to deter predation by mollusks and fishes.[2] With regard to human medicine, many of these molecules show promising cytotoxicity against a variety of cancer cell lines, and some display anti-malarial activity.[2,3] However, coral reef ecosystems are under accelerating decline worldwide as a result of human activity: global warming, pollution, and over-fishing are believed to have led to detrimental increases in ocean acidity and temperature, disease from normally symbiotic bacteria, and adverse competition with macroalgae.[4] The possible loss of this rich source of molecules with potential value in human medicine is one motivation to develop efficient chemical syntheses of coral secondary metabolites. These efforts are further warranted because, despite remarkable advances in spectroscopy and parallel synthesis over the last 20 years, the total synthesis of natural products continues to play an important role in structure elucidation[5] and drug discovery,[6] as well as inspiring the development of new chemical transformations for the expeditious synthesis of molecular complexity.[7]

A striking array of diterpene cyclic ethers has been isolated from soft corals and gorgonian octocorals.[1] In particular, the cladiellins (also known as the eunicellins, e.g., **1**),[8] asbestinins

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(e.g., **2** and **3**),[9] and briarellins (e.g., **4**, and **5**)[10,11] comprise a sizable portion of a large and diverse family of C2– C11-cyclized cembranoid diterpenes (Figure 1).[12] Over the past 40 years, approximately 60 cladiellins, 15 briarellins, and 30 asbestinins have been discovered in corals inhabiting the Caribbean and Mediterranean seas and the Atlantic, Pacific, and Indian oceans.[12,13] The cladiellins, briarellins, and asbestinins have in common an otherwise rare oxatricyclic ring system composed of hexahydroisobenzofuran (2-oxabicyclo[4.3.0]nonane) and oxacyclononane units. With the exception of C14 of the pachyclavulariaenones,[11,13g,h] six stereogenic centers (carbons 1–3, 9, 10, and 14) of these diterpenes are identical.[12,13] Although the structures of several members of this family have been corroborated by X-ray analysis,[14,15] structure elucidation in this area has generally relied upon MS and NMR, IR, and UV spectral analyses, as well as chemical correlations.[12,13] Prior to the synthesis studies carried out in our laboratory[16] and subsequent ones by the groups of Paquette,[16c,17] Molander,[18] Crimmins,[19] Hoppe,[20a] and Kim,[21] absolute configurations had not been unambiguously established for any of these coral metabolites.[22] Additionally, our total synthesis studies[16b–e] and those of Paquette[16c,17,23] led to the structure reassignment of several cladiellins. The challenges these complex molecules pose for structure elucidation are further highlighted by the efforts of natural products researchers: in 1995, Rodríguez and Cóbar disclosed their originally proposed structure of briarellin A and several congeners;[10a] eight years later, after reexamination of its spectral data and comparison with data obtained for newly isolated briarellins, these workers revised their structure assignment for briarellin A to allylic peroxide **4**.[10b] Analysis of new data also led recently to revisions of the structure assignment of four asbestinin diterpenes.[13b]

This group of C2–C11-cyclized cembranoid diterpenes has been the subject of numerous synthetic investigations over many years.[24] The enantioselective total synthesis of 6-acetoxycladiell-7(16),11-dien-3-ol (**6**),[25] reported in 1995 by MacMillan and Overman,[16a] was the first total synthesis accomplishment in this area (Figure 2). Subsequently, independent total syntheses of the originally proposed structure of sclerophytin A (**7**)[26] by Paquette[17a] and our laboratory[16b] prompted revision of the structure assignment of this cladiellin diterpene.[23a] By photochemical isomerization of the endocyclic alkene of cladiell-11-ene-3,6,7-triol (**8**),[14d] another cladiellin diterpene synthesized in our laboratory, we were able to confirm the revised structure assignment for sclerophytin A (**9**)[16c] proposed by Paquette and co-workers;[23a] this group also completed a total synthesis of diterpene **9** by a different approach.[16c] More recently, total syntheses of additional cladiellin diterpenes have been accomplished by the Molander[18], Crimmins,[19a,19c] Clark,[20b] Hoppe,[20a] and Kim[21] groups.

Three cladiellin diterpenes and most briarellin and asbestinin diterpenes contain additional oxygen substitution at C4 of the oxacyclononane ring.[12,13] To address the unmet synthesis challenges posed by this C4 functionalization, and the additional oxepane ring found in the briarellins and asbestinins, we undertook the total synthesis of alcyonin (originally proposed structure **10**)[27] and briarellins E (**12**) and F (**13**).[28] A full description of these studies, which led to a revised structure assignment for alcyonin (**11**)[16e] and the first total syntheses of briarellin diterpenes (**12** and **13**), is the subject of this report.[16f] Subsequent to the completion of these studies, incisive inaugural total syntheses of asbestinin diterpenes,[19b,d] 11-acetoxy-4-deoxyasbestinin D (**2**)[29] and asbestinin-12 (**3**),[9b] were reported by Ellis and Crimmins.

Results and Discussion

In our third-generation synthesis approach to the C2–C11-cyclized cembranoid diterpenes,[16d] we envisioned diterpenes **6–13** arising from a common intermediate, *cis*-3,4-epoxy alcohol **15** (Scheme 1). Elaboration of precursors of this type by regio- and stereoselective opening of the epoxide functionality with either hydride or oxygen nucleophiles should afford **14** (X = H or OR), which would possess the requisite C3–C4 substitution pattern present in **6–13**. If the C14 side chain of intermediate **14** is an isopropyl group (R = H), we could target cladiellins,

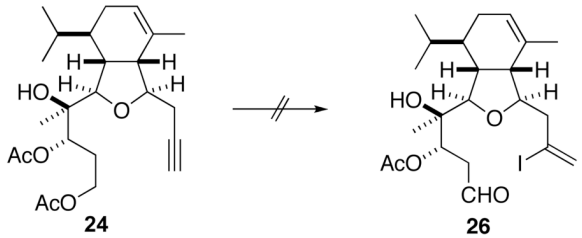
whereas a (*S*)-1-methyl-2-hydroxyethyl side chain (R = OH) would allow access to the briarellins. A logical precursor to *cis*-3,4-epoxy alcohol **15** is Z alkene **16**, which we anticipated could arise from acid-catalyzed Prins-pinacol condensation[7d] of a (Z)-α,β-unsaturated aldehyde **17** and an alkynyl dienyl diol **18**. If successful, this transformation would deliver the hexahydroisobenzofuran core and five stereocenters of these coral metabolites. Alkynyl dienyl diol **18** was expected to arise from (*S*)-(+)-carvone (**19**) and (*S*)-(–)-glycidol (**20**). We have previously described the evolution and successful implementation of this approach for the total synthesis of cladiellins **6–9** that lack substitution at C4.[16d] Herein, we discuss the ultimate fruition of this unified strategy toward C2–C11-cyclized cembranoid diterpenes having an acyloxy substituent at C4, specifically the originally proposed structure **10** of alcyonin and briarellins E (**12**) and F (**13**).[30]

Enantioselective Total Synthesis of the Originally Purported Structure 10 of Alcyonin

To explore the prospects for accessing cladiellins and briarellins bearing oxygenation at C4, we chose alcyonin as our initial total synthesis target.[27] This marine metabolite was reported by Kakisawa and coworkers in 1988 from specimens of the soft coral *Sinularia flexibilis* found in waters off Okinawa. On the basis of spectroscopic data, augmented by some chemical transformations, structure **10** was proposed for alcyonin (Figure 2).[27]

The starting point for our total synthesis effort was the known *cis*-3,4-epoxy alcohol **21**, which is available in 9 steps and 14% overall yield from (*S*)-dihydrocarvone (Scheme 2).[16b,d] After a number of attempts to open the epoxide of intermediate **21** and alcohol-protected congeners with exogenous oxygen nucleophiles failed, we acetylated the hydroxyl group of **21** to afford epoxy ester **22**. Employing the method of Giner,[31] epoxy ester **22** was treated sequentially with trifluoroacetic acid to effect internal opening of the epoxide (**A** → **B**) and H_2O, unraveling intermediate **B** to give a mixture of primary and secondary acetates. Analysis of the unpurified product by ^1H NMR revealed that ring-opening of the epoxide had occurred with high regio- and stereoselectivity, as no trace of other isomers was seen. Reduction of this crude mixture of acetates with $LiAlH_4$ gave triol **23**. Standard acetylation of this intermediate at room temperature afforded diacetate **24**. Alternatively, triol **23** could be elaborated to crystalline carbonate derivative **25** by sequential treatment with pivaloyl chloride and triphosgene. Single-crystal X-ray analysis of 1,3-dioxolan-2-one **25** corroborated its structure,[32] rigorously establishing the relative configuration at C3 and C4, which we had assigned initially on the basis of precedent[31] and the mechanistic considerations depicted in Scheme 2.

As the proposed structure **10** of alcyonin has an acetyl group at C4, we initially tried to advance diacetate **24** to intermediate **26** as a prelude to closing the oxacyclononane ring by Nozaki–Hiyama–Kishi cyclization (eq 1).[16d,33] However, we were never able to elaborate the delicate γ -hydroxy-β-acetoxyaldehyde functionality.



(1)

In an alternative approach, we saw the dioxolanone unit of **25** serving as a late-stage progenitor of the C3 hydroxy and C4 acetoxy substituents of **10**, because the related conversion of a

dioxolane fragment to a hydroxy benzoate had been reported with a derivative of Taxol®.[34] However, the lability of intermediates derived from **25** eventually demanded recourse to a lengthier sequence to arrive at a viable precursor for forming the oxacyclononane ring (Scheme 3). Thus, triol **23** was selectively protected by sequential reaction with pivaloyl chloride and TBDMSOTf to yield protected-triol **28**. Using a sequence introduced by Suzuki,[35] alkyne **28** was iodoborated by reaction with *B*-iodo-9-borabicyclo[3.3.1]nonane (*B*-I-9-BBN) in hexane,[36] and the resulting vinyl borane intermediate was protonolyzed by the addition of acetic acid at −78 °C. Oxidative work-up with sodium perborate[37] then provided vinyl iodide intermediate **29** in 80% yield. Yields of the iodoboration step were higher when hexane, rather than the more commonly used solvent CH_2Cl_2,[35] was employed. The pivaloyl group of **29** was cleaved with *i*-Bu_2AlH, and the resulting primary alcohol was oxidized with Dess–Martin periodinane (DMP)[38] to give vinyl iodide aldehyde **30** in excellent yield for the two-step sequence.

As in our previous syntheses of cladiellins **6–9** lacking oxygen substituents at C4, the oxacyclononane ring of **10** was successfully forged by Nozaki–Hiyama–Kishi cyclization.[16d,33] Using reaction conditions identical to those employed previously,[16d] vinyl iodide aldehyde **30** was converted to oxatricyclic intermediate **31** in good yield (Scheme 3). Analysis of the crude product by ^{1}H NMR revealed that this cyclization occurred with exquisite stereoselection: only one allylic alcohol epimer was detected. Based on our previous modeling studies,[16d] we postulate that the observed product **31** in this instance arises from the plausible four-centered assembly **C**, which minimizes transannular and eclipsing interactions in the incipient nine-membered ring.

To complete the total synthesis of structure **10**, the silyl protecting groups of **31** were discharged by reaction with *n*-Bu_4NF at room temperature, a process that was likely facilitated by 1,2-migration of the TBDMS group of the tertiary siloxy substituent. Finally, selective acetylation of the C4 alcohol of **32** by reaction in pyridine at 0 °C with excess acetic anhydride and a catalytic amount of 4-(N, N-dimethylamino)pyridine (DMAP) delivered **10**, the purported structure of alcyonin in good yield. The selectivity observed in acetylation of the C4 alcohol is consistent with the expected low-energy conformation of triol **32**. Computational modeling[39] of this triol suggests that its nine-membered ring adopts the same conformation as observed for this ring in both the X-ray model and computational models of 6-acetoxycladiell-7(16),11-dien-3-ol (**6**).[16d] This conformation projects the C4 alcohol away from the ring in a sterically unencumbered environment.

Revision of the Structure Assignment for Natural Alcyonin

The structure of **10** was fully supported by NMR and mass spectral data. For example, the position of the acetate substituent of this product was evident from the diagnostic ^{1}H NMR chemical shifts of H4 (δ 4.99) and H6 (δ 4.17). However, the NMR data of synthetic **10** did not match those reported for natural alcyonin.[27] A comparison of the NMR data for **10**, 6-acetoxycladiell-7(16),11-dien-3-ol (**6**),[16a,25] natural alcyonin,[27] and several structurally related cladiellins,[40] showed that the acetate functionality of alcyonin did not reside at C6.

Unfortunately, a sample of natural alcyonin is no longer available;[41] however, reexamination of the published NMR data of natural alcyonin reveals that the signal at δ 4.76, assigned to H6 of the *S. flexibilis* isolate, is downfield by 0.3–0.4 ppm from signals for this hydrogen in other cladiell-7(16),11-dien-3,6-diols as is the absorption for C6; for example the C6 methine hydrogen of cladiellisin (**33**) is observed at δ 4.40 (Figure 3).[40] Furthermore, no signal for the hydrogen of the putative allylic hydroxyl group was reported,[27] nor is such a signal found in the ^{1}H NMR spectrum of natural alcyonin. However, a distinct signal at δ 8.0, corresponding to one hydrogen, is clearly visible in the ^{1}H NMR obtained in the Kakizawa group (Figure 4).[41]

We conclude that the actual structure of alcyonin is allylic hydroperoxide **11** (Figure 3). Strong support for this proposal comes from the ^{1}H and ^{13}C NMR data reported for cladiellisin (**33**)[40a] and cladiellaperoxide (**34**).[42] The molecular masses of structures **10** (MW = 378) and **11** (MW = 394) are obviously different. Nonetheless, the mass spectral data reported for natural alcyonin (*m/e* 378.2403)[27] could be consistent with the newly proposed structure, as electrospray or FAB ionization is often required to observe the molecular ion of an alkyl hydroperoxide.[43]

Additionally, chemical transformations reported for natural alcyonin coincide better with the revised structure assignment **11**. It was reported that attempted benzoylation of alcyonin afforded tetracyclic hemiacetal **35** rather that the expected C6 benzoate, an outcome that was ascribed to air oxidation of the putative allylic alcohol (Scheme 4).[27] However, numerous reports have documented the successful acylation of 6-hydroxy cladiell-7(16),11-dienes.[16d,44] Furthermore, we have never observed air oxidation of **10** or related structures.[16] However, if alcyonin were indeed hydroperoxide **11**, the formation of **35** upon attempted benzoylation is the anticipated outcome, as the benzoyl peroxide intermediate **D** would be expected to fragment to the C6 keto derivative **E** in the presence of triethylamine. The constitutional relationship of our synthetic product **10** and natural alcyonin was confirmed by oxidation of synthetic **10** with Dess–Martin periodinane (DMP)[38] to form hemiacetal **35**. The NMR and mass spectrometric data of this product were indistinguishable from those of **35** derived from natural alcyonin.[27,41]

Enantioselective Total Synthesis of Briarellin E (12) and Briarellin F (13)

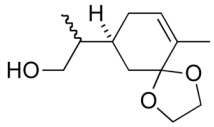
Having established that we could efficiently access cladiellins containing a hydroxyl substituent at C4, we desired to extend our approach to the total synthesis of the more complex briarellin diterpenes.[28] Like most briarellin diterpenes,[45] briarellins E (**12**) and F (**13**) were isolated by Rodríguez and co-workers from Caribbean gorgonian octocorals belonging to the genus *Briareum* (Figure 2).[10,28] The constitution and relative configuration of these coral metabolites were established on the basis of NMR studies and chemical correlations.

The briarellin diterpenes contain a number of structural features that pose additional challenges for synthesis. Besides the hexahydroisobenzofuran core and oxacyclononane ring found in cladiellins **6–11**, briarellins E (**12**) and F (**13**) possess an oxepane ring arising from etherification between C3 and C19, a methyl-substituted stereocenter at C15, and a tertiary hydroxyl group at C11. We envisioned that briarellins **12** and **13** could arise from intermediate **14** depicted in Scheme 1, wherein R and X would be hydroxyl groups or appropriately protected variants. The proper choice of orthogonal protecting groups for the primary alcohol functionality of the precursor aldehyde **17** and cyclohexadienyl diol **18** (R = OP) in Scheme 1 likely would be important for the success and efficiency of this strategy.

These syntheses began by installing the C15 stereocenter starting from (*S*)-(+)-carvone (**19**). Reaction of **19** with 2.2 equiv of 9-borabicyclo[3.3.1]nonane (9-BBN), followed by oxidation of the derived organoborane with basic hydrogen peroxide, afforded diol **36** as a ~1:1 mixture of methyl epimers in 73% yield (Scheme 5).[46] Resolution of diol mixture **36** by medium-pressure liquid chromagraphy (MPLC) on silica gel afforded pure samples of crystalline diols **36a** and **36b**, the relative configurations of which were secured by single-crystal X-ray analysis.[32] Diol **36b** possesses the configuration at C15 found in briarellin diterpenes. Because diol mixture **36** was difficult to resolve chromatographically on a practical scale, we developed a stereoselective process for converting (*S*)-(+)-carvone to diol **36b**. Thus, chemoselective oxidation of the primary alcohol of epimer mixture **36** with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and *N*-chlorosuccinimide (NCS) using a modification of Einhorn's procedure[47] gave bicyclic lactone **37**, a 1:1 mixture of methyl epimers, in 79% yield.[48,49,50] The silyl ketene acetal derivative of lactone **37** was generated by sequential treatment with

lithium diisopropylamide (LDA) and trimethylsilyl chloride (TMSCl). Protonation of this intermediate with acetic acid at 0 °C took place with high stereoselectivity from the less-hindered face.[51] Reduction of the crude lactone product with $LiAlH_4$ then delivered diol **36b** in 78% overall yield after recrystallization.[51]

Several alternate approaches for securing pure samples of diol **36a** from intermediates generated from (*S*)-(+)-carvone were also examined. As methyl epimers of an intermediate generated by hydroboration of limonene had been separated using Amano PS lipase,[52] we examined acetylation of **38** with isopentenyl acetate using this enzyme. However, diastereoselection was found to be low (~2:1) in diisopropyl ether, both with and without added H_2O. In a more speculative approach, hydroboration of diene ketal **39** with 9-borabicyclo [3.3.1]nonane was also examined. Again, diastereoselection was unsatisfactory.



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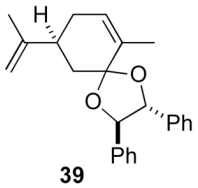

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With the C15 stereocenter of the briarellins in place, we turned to elaborating diol **36b** to an appropriate precursor for the critical the Prins–pinacol reaction. Selective protection of the primary alcohol of **36b** with a triisopropylsilyl group (TIPS), followed by oxidation of the secondary alcohol with pyridinium chlorochromate (PCC) in the presence of sodium acetate (NaOAc)[53] provided enone **40** in high yield (Scheme 6). Transformation of **40** to its derived kinetic enol triflate[54] using LDA and 2-[N,N- bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (Comins' reagent),[55] followed by palladium-catalyzed coupling with $(Me_3Sn)_2$[56] and in situ iodination of the resulting vinylstannane with *N*-iodosuccinimide (NIS) [57] delivered cyclohexadienyl iodide **41**,[58] Coupling of α-alkoxy aldehyde **42**[16d] with the dienyllithium species generated from **41**, followed by removal of the 1-methyl-1-methoxyethyl protecting group gave cyclohexadienyl diol **43** in 62% yield as an inconsequential 3:1 mixture of allylic alcohol epimers.[59]

Our efforts turned to the assembly of the hexahydroisobenzofuran core of briarellins E (**12**) and F (**13**) along the lines we had developed previously in our syntheses of cladiellins **6–11**. [16d] Wittig reaction of 3-(*tert*-butyldiphenylsiloxy)propanal **44**[60] with iodophosphorane **45**[61] afforded *Z* vinyl iodide **46** in 47% yield (Scheme 7).[62] We chose the *tert*-butyldiphenylsilyl (TBDPS) ether[63] as the side-chain protecting group with the expectation that it would tolerate the acidic conditions used in the Prins-pinacol condensation–rearrangement sequence and could be selectively cleaved in the presence of the C19 TIPS ether at a later stage.[64] Lithium–halogen exchange of **46** with *tert*-butyllithium, followed by reaction of the resulting vinyllithium species with *N*,*N*-dimethylformamide (DMF) provided isomerically pure (*Z*)-α,β-unsaturated aldehyde **47** in high yield.[65] Condensation of this aldehyde and cyclohexadienyl diol **43** at −20 °C in the presence of *p*-toluenesulfonic acid (TsOH) and $MgSO_4$ provided the corresponding acetal,[66] which was exposed to 10 mol% of $SnCl_4$ at −78 °C to room temperature to give formyl tetrahydroisobenzofuran **48** as a single stereoisomer in excellent yield for the two-step sequence.[67] The critical Prins-pinacol conversion was readily scaled, with 84% yield being realized in runs that provided up to 3 g of formyl tetrahydroisobenzofuran product **48**. Stereospecific photolytic deformylation of **48**,[68] followed by selective cleavage of the TBDPS and TMS protecting groups with aqueous KOH yielded homoallylic alcohol **49** in moderate yield for the two steps.[69,64] Hydroxyl-mediated epoxidation of this intermediate with $(t\text{-BuO})_3Al/t\text{-BuO}_2H$[70] afforded *cis*-3,4-epoxy alcohol **50** in 79% yield.[71] Stereoselection in this transformation was 10:1, which is readily rationalized

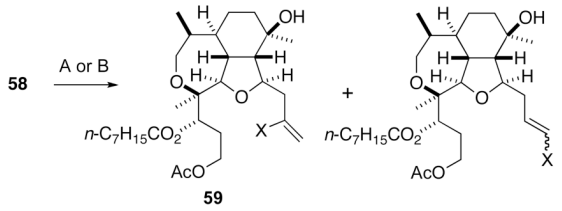
by epoxidation occurring by way of conformer **F**, in which the side chain is oriented to minimize destabilizing $A^{1,3}$ interactions.[16d] Acetylation of alcohol **50**, followed by sequential reaction of epoxy acetate **51** with trifluoroacetic acid (TFA),[31] H_2O, and excess Ac_2O and catalytic DMAP provided hydroxy diacetate **52** in 86% yield for the three-step sequence.

The stage was set to complete the assembly of the dioxatricyclic moiety of briarellins E (**12**) and F (**13**). In early scouting experiments, we attempted to form the oxepane ring by reaction of the diol resulting from cleavage of the TIPS group of intermediate **52** with trifluoromethanesulfonic anhydride (Tf_2O) and 2,6-lutidine.[72] However, attack of the C19 primary triflate π-bond was preferred over displacement by the C3 tertiary hydroxyl group. This result necessitated functionalization of the double bond prior to oxepane formation (Scheme 8). Epoxidation of hexahydroisobenzofuran intermediate **52** with *m*-chloroperoxybenzoic acid (*m*-CPBA) at 0 °C proceeded with 10:1 stereoselectively from the α-face to deliver epoxide **53** in 77% yield.[73] Diagnostic ^{1}H NOE enhancements between the C11 methyl substituent and the C10 and C12 methine hydrogens signaled the relative configuration of this product. Stereoselection in forming epoxide **53** is believed to result from oxidation taking place via *cis*-hexahydroisobenzofuran conformer **G** wherein the 1-methyl-2-siloxyethyl substituent adopts a pseudoaxial orientation to avoid a *syn*-pentane interaction with the C2 side chain, thereby shielding the convex β-face (Scheme 8). Removal of the TIPS protecting group of **53** with *n*-Bu_4NF gave diol **54**. Exposure of this intermediate to Tf_2O and 2,6-lutidine[72] delivered dioxatricycle **55** after 4 days at room temperature in yields ranging from 55–68%. Under these conditions, the ratio of intramolecular etherification to elimination was ~ 6:1 (^{1}H NMR analysis). Attempts to accelerate this process by heating the reaction led to a greater proportion of the propylidene byproduct arising from elimination of the primary triflate intermediate.

With the dioxatricyclic ring system and eight of the nine stereocenters common to **12** and **13** in place, we turned to elaboration of the cyclohexane ring and the side chains of intermediate **55** in preparation to forming the final oxacyclononane ring. Regio- and stereoselective hydration of the epoxide of **55** with dilute aqueous H_2SO_4 gave diol **56** in 80% yield (Scheme 9). Introduction of the C11 tertiary alcohol with the required *R* configuration in this step results from of the tertiary carbenium ion **H** produced by S_N1 opening of the epoxide being trapped by water from the less-congested, convex β-face. Low- temperature mesylation of the secondary alcohol of diol **56**, followed by in situ reduction with $LiAlH_4$ removed the extraneous hydroxyl substituent at C12 and the two acetate protecting groups to generate triol **57** in high yield. The β C11,C12 epoxide was an observable intermediate in this sequence. The relative configuration of the tertiary alcohol stereocenter of **57** was established by ^{1}H NMR NOE experiments, with a strong NOE between the C11 methyl substituent and the C9 methine hydrogen being particularly diagnostic. Selective acetylation of the primary alcohol of triol **57** upon reaction with isopropenyl acetate and $Bu_8Sn_4Cl_4O_2$,[74] followed by appendage of the octanoyl side chain gave tricyclic hydroxy diester intermediate **58**.

One of the more challenging transformations encountered in our efforts to extend our existing chemistry to the preparation of briarellins E (**12**) and F (**13**) was elaboration of the 2-propynyl side chain of intermediate **58** to a 2-iodo-2-propenyl group in preparation for closing the final nine-membered ring. The iodoboration/protonolysis sequence we had employed in our synthesis of the putative structure of alcyonin and in our earlier cladiellin diterpene total syntheses,[16] promoted elimination of the tertiary alcohol functionality of **58**. Palladium-catalyzed hydrostannylation/iodination[75] and stannylcupration/protonolysis[76] proceeded with low regioselectivity (eq 2). Also unsuccessful was hydrostannylation catalyzed by Wilkinson's catalyst,[77] and α -stannylation by reaction with a di-*n*-butyliodotin hydride ate complex.[78] Successful regioselective functionalization of the terminal alkyne functionality of intermediate **58** was finally realized using a stannylalumination/protonolysis sequence reported by

Oehlschlager (Scheme 10).[79] Thus, CuCN-catalyzed addition of $Bu_3SnAlEt_2$ to alkyne **58** at −30 °C, followed by quenching with aqueous NH_4Cl cleanly generated the internal vinylstannane regioisomer, which was directly iodinated to provide vinyl iodide **59** in 66% overall yield.



(2)

The total synthesis of briarellin E (**12**) was completed in three steps from vinyl iodide intermediate **59** as summarized in Scheme 10. Selective removal of the acetate protecting group of **59** using $(t\text{-Bu})_2(OH)ClSn/MeOH$[80] and oxidation of the resulting Dess—Martin periodinane[38] gave vinyl iodide aldehyde **60** in 74% overall yield. Nozaki–Hiyama–Kishi cyclization[33] of this intermediate, using reaction conditions we had employed in our earlier syntheses in this area, provided briarellin E (**12**) in 79% yield. Cyclization proceeded with high stereoselectivity, with none of the allylic alcohol epimer being apparent in ^1H NMR spectra of the crude reaction product. The mildness of this chromium-mediated cyclization is showcased in this transformation, as neither the acyloxy group β to the aldehyde nor the tertiary alcohol was problematic. Finally, Dess–Martin oxidation of **12** afforded briarellin F (**13**) in good yield. Synthetic briarellin E (**12**) was identical in all respects with a natural sample;[81] spectral and optical rotation data for briarellin F (**13**) also compared well with those reported for the natural isolate.[28]

Preliminary Examination of Late-Stage Ring-Closing Methathesis to Form the Oxacyclononane Ring of Briarellin and Asbestinin Diterpenes

The studies summarized herein define a useful sequence for assembling the tricyclic core of briarellin and asbestinin diterpenes. Using these fully functionalized precursors, the nine-membered oxacyclononane ring of briarellins E (**12**) and F (**13**) was readily fashioned by Nozaki–Hiyama–Kishi cyclization. However, this cyclization provides direct access to C2–C11 cyclized cembranoids that contain a C6 alcohol and $\Delta^{7,16}$ unsaturation, and appears less attractive for the construction of briarellin and asbestinin diterpenes possessing an internal trisubstituted $\Delta^{6,7}$ double bond in the oxacyclononane ring.[12,13] As a result, we briefly investigated the possibility of forming of this latter structural motif at a late stage using ring-closing metathesis (RCM). [82] Although one previous attempt to realize this transformation in the cladiellin series was unsuccessful,[83] we hoped that a combination of the conformational constraints imposed by the oxepane ring of briarellin and asbestinin diterpenes and the newer-generation RCM catalysts would enable ring closure.

To rapidly explore the feasibility of such an approach, the $\Delta^{6,7}$ double bond of natural 11-acetoxy-4-deoxyasbestinin D (**2**)[29,84] was cleaved by sequential treatment with O_3 and Me_2S, and the resulting keto aldehyde was exposed to excess methylenetriphenylphosphine to provide diene **61** in good yield for the two-step sequence (Scheme 11). Unfortunately, several attempts[85] to effect ring-closing metathesis of dioxatricyclic diene **61** using either the second-generation Grubbs catalyst (**62**)[86] or the Schrock catalyst (**63**)[87] did not regenerate 11-

acetoxy-4-deoxyasbestinin D (**2**).[88,89] This result, which likely derives from the conformational constraints in tricyclic precursor **61**, contrasts with others' successful efforts to form an oxacyclononane product by ring-closing metathesis. Crimmins and Ellis' realized closure of an acyclic diene with catalyst **62**, which was subsequently elaborated in a multistep sequence to 11-acetoxy-4-deoxyasbestinin D,[19b,d,29] and Hoppe and co-workers' effected cyclization of a bicyclic diene with catalyst **62**, which was later transformed in several steps to a cladiellin diterpene, (+)−vigulariol.[20a]

Conclusions

A unified strategy for the total synthesis of cladiellin and briarellin diterpenes has been realized (Scheme 1). This efficient and flexible approach has been shown to be amenable to accessing both C4-deoxygenated and C4-oxygenated cladiellins and briarellins: cladiellin diterpenes **6–11** were synthesized in 19–21 steps and 1–4% overall yield, and briarellin diterpenes **12** and **13** were prepared in 30–31 steps and 0.3–0.4% overall yield, starting from (*S*)-(+)-carvone (**19**). The defining transformation in this unified approach is acid-promoted condensation of an (Z)-α,β-unsaturated aldehyde with a cyclohexadienyl diol and Prins—pinacol rearrangement of the derived (Z)-α,β-unsaturated oxocarbenium ion, forming with complete stereocontrol the hexahydroisobenzofuran core of these coral metabolites (Scheme 1). The oxacyclononane ring of these natural products was forged by diastereoselective Nozaki–Hiyama–Kishi cyclization, and the oxepane ring of **12** and **13** was formed by dehydrative cyclization of diol **54**.

The viability of this unified strategy was initially verified by total synthesis of the simpler C4-deoxygenated cladiellins **6–9**,[16d] and in this report we have documented the extension of this approach to the putative C4-oxygenated cladiellin **10** and briarellins E (**12**) and F (**13**). The enantioselective total synthesis of the originally proposed structure of alcyonin (**10**) and the discrepancy of its spectral data with those reported for the natural isolate demanded that the structure assignment for this marine diterpene be revised. Reexamination of NMR spectra, MS data, and chemical transformations of natural alcyonin suggest that the structure of this coral metabolite is allylic peroxide **11**. These first total syntheses of briarellin diterpenes, briarellin E (**12**) and briarellin F (**13**), verified their structure assignments and established their absolute configurations. The efficient total syntheses detailed in this account further highlight the power of pinacol-terminated cationic cyclizations for assembling complex oxacyclic natural products [7d]

Experimental Section[90]

(3*R*,4*R*)-dihydroxy-4-(1*R*,3*R*,3a*R*,7*R*,7a*R*)-(7-isopropyl-4-methyl-3-prop-2-ynyl-1,3,3a,6,7,7a-hexahydroisobenzofuran-1-yl)pentyl alcohol (23)

4-(*N*,*N*-Dimethylamino)pyridine (12 mg, 0.11 mmol) was added to a solution of epoxy alcohol **21** (340 mg, 1.1 mmol), pyridine (11 mL), and Ac_2O (0.12 mL, 1.3 mmol) and the solution was maintained at room temperature. After 30 min, the reaction mixture was added to saturated aqueous NH_4Cl (120 mL), the resulting mixture was extracted with ethyl acetate (120 mL), the organic extract was washed sequentially with saturated aqueous $CuSO_4$ (2 × 100 mL) and brine (2 × 100 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (80:20 hexane–ethyl acetate) to afford 370 mg (95%) of acetate **22** as a clear yellow oil: $[\alpha]^{23}_{D}$ +15.7, $[\alpha]^{23}_{577}$ +16.4, $[\alpha]^{23}_{546}$ +18.4, $[\alpha]^{23}_{435}$ +30.0, $[\alpha]^{23}_{405}$ +35.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.40-5.39 (m, 1 H), 4.29-4.19 (m, 2H), 3.89 (ddd, *J* = 4.9, 4.9, 4.9 Hz, 1 H), 3.64 (d,*J* = 8.9 Hz, 1 H), 2.91 (dd, *J* = 9.2, 2.9 Hz, 1 H), 2.62 (ddd, *J* = 16.9, 5.5, 2.6 Hz, 1 H), 2.59-2.54 (m, 1 H), 2.54 (ddd, *J* = 16.9, 4.5, 2.6 Hz, 1 H), 2.46-2.40 (m, 1 H), 2.13-2.02 (m, 1 H), 2.06 (s, 3 H), 2.05-1.98 (m, 1H), 2.00 (dd, *J* = 2.6 Hz, 1H), 1.97-1.89 (m, 1 H), 1.86-1.77 (m, 1 H), 1.67 (d, *J* = 1.1 Hz, 3 H), 1.66-1.58

(m, 1 H), 1.37 (s, 3 H), 1.28-1.21 (m, 1 H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 132.4, 120.9, 81.8, 81.4, 80.3, 70.4, 62.4, 61.4, 61.1, 45.7, 42.7, 37.5, 29.2, 28.6, 26.2, 24.1, 22.1, 21.4, 21.2, 20.5, 18.2; IR (film) 1740 cm^{-1}; HRMS (CI) *m/z* 361.2377 (M+H, 361.2380 calcd for $C_{22}H_{32}O_4$).

Following the general method of Giner,[31] trifluoroacetic acid (0.08 mL, 1.0 mmol) was added dropwise to a solution of the epoxy ester (370 mg, 1.0 mmol) and PhMe (20 mL) at 0 °C. After 2 h, H_2O (20 mL, 1.1 mol) was added, and the resulting mixture was stirred for 1.5 h and then quenched with saturated aqueous $NaHCO_3$ (15 mL). Ethyl acetate (50 mL) was added, the layers were separated, the aqueous layer was washed with ethyl acetate (2 ×50 mL), and the combined organic extracts were dried ($Na2SO_4$), filtered, and concentrated. A THF solution of $LiAlH_4$ (3.4 ml of a 1.0M solution, 3.4 mmol) was added dropwise to a solution of this mixture of crude acetoxy diols and THF (10 mL) at rt. After 45 min, the reaction mixture was cooled to 0 °C and treated dropwise with Rochelles's salt (30 mL), stirred for 1h at rt, and extracted with ethyl acetate (100 mL). The organic extract was washed brine (100 mL), dried (Na_2SO_4), filtered, and concentrated to afford pure **23**, 330 mg (95%, 2 steps) as a clear yellow oil: $[\alpha]^{23}_{D}$ +7.7, $[\alpha]^{23}_{577}$ +7.9, $[\alpha]^{23}_{546}$ +8.5, $[\alpha]^{23}_{435}$ +13.1, $[\alpha]^{23}_{405}$ +14.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ5.53-5.49 (m, 1 H), 4.03-4.00 (m, 1 H), 3.92 (d, *J* = 3.5 Hz, 1H), 3.89-3.85 (m, 3 H), 3.68 (s, 1 H), 3.08 (s, 1 H), 2.99-2.97 (m, 1 H), 2.78 (ddd, *J* = 17.3, 3.9, 2.6 Hz, 1 H), 2.72-2.66 (m, 1 H), 2.56 (ddd, *J* = 17.3, 4.2, 2.6 Hz, 1 H), 2.41 (ddd, *J* = 10.7, 7.6, 3.5, Hz, 1 H), 2.02-1.93 (m, 1 H), 1.92-1.83 (m, 1 H), 1.80-1.67 (m, 3H), 1.69 (d, *J* = 1.5 Hz, 3 H), 1.47-1.33 (m, 1 H), 1.25 (dd, *J* = 7.0, 1 H), 1.04 (s, 3 H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.79 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.3, 123.6, 87.4, 81.0, 80.5, 76.6, 75.7, 72.0, 61.8, 46.7, 41.7, 39.4, 32.9, 27.6, 25.1, 23.6, 22.6, 22.2, 18.6, 17.1; IR (film) 3420, 3310 cm^{-1}; HRMS (CI) *m/z* 337.2367 (M+H, 337.2380 calcd for $C_20H_{32}O_4$).

Acetic acid (6*R*,7*R*,8*R*,9*R*,12*S*,14*S*,15*R*,16*R*)-9,12-dihydroxy-6-isopropyl-3,9-dimethyl-13-methylene-15-oxa-tricyclo[6.6.1.$0^{0,0}$]pentadec-3-en-10-yl ester (10)

A solution of the triol **32** (8.0 mg, 0.024 mmol), dry pyridine (0.3 mL) and 4-(*N*,*N*-Dimethylamino)pyridine (1.0 mg, 0.01 mmol) at 0 °C was treated with acetic anhydride until TLC analysis (70:30 hexane-ethyl acetate) showed complete consumption of the starting material. Saturated aqueous NH_4Cl (5.0 mL) was then added, the aqueous layer was extracted with ethyl acetate (3 × 5.0 mL), and the combined organic extracts were washed sequentially with saturated aqueous $CuSO_4$ (2 × 10 mL) and brine (2 × 10 mL), dried ($Na2SO_4$), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (70:30 hexane–ethyl acetate) to give 6.0 mg (68%) of **10** as a clear colorless oil: $[\alpha]^{23}_{D}$ −64.5, $[\alpha]^{23}_{577}$ −68.7, $[\alpha]^{23}_{546}$ −78.5, $[\alpha]^{23}_{435}$ −147.1, $[\alpha]^{23}_{405}$ −182.5 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63-5.61 (m, 1H, H16), 5.43-5.41 (m, 1H, H12), 5.23-5.21 (m, 1 H, H16), 4.99 (app t, *J* = 4.0 Hz, 1H, H4), 4.21-4.19 (m, 2H, H6 and H9), 3.84 (d, *J* = 8.4 Hz, 1 H, H2), 3.53-3.47 (m, 1 H), 3.02-2.98 (m, 1H), 2.77-2.71 (m, 1 H), 2.67-2.61 (m, 1H), 2.34 (app d, *J* = 3.5 Hz, 2 H), 2.15 (s, 3 H), 2.00-1.91 (m, 1 H), 1.88-1.83 (m, 1H), 1.80 (ddd, *J* = 16.1, 4.35, 4.3 Hz, 1 H), 1.68 (s, 3 H), 1.56-1.52 (m, 2H), 1.39 (s, 3H), 1.30-1.21 (m, 1H), 0.91 (d, *J* = 6.2 Hz, 3H), 0.83 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 147.8, 132.2, 122.0 (C12), 115.1 (C6), 86.9 (C2), 81.1 (C9), 74.7, 73.8 (C4), 72.8 (C6), 44.6, 40.0, 39.6, 39.0, 37.5, 28.7, 22.9, 22.5, 22.0, 21.5, 21.3, 20.8; IR (film) 3443, 1714, 1640 cm^{-1}; HRMS (ESI) *m/z* 401.2310 (M+Na, 401.2304 calcd for $C_{22}H_{34}O_5$).

(1*R*,3*R*,3a*R*,7*R*,7a*R*)-4-{4-Methyl-7-[1(*S*)-methyl-2-(triisopropylsilyloxy)ethyl]-3-prop-2-ynyl-1,3,3a,6,7,7a-hexahydroisobenzofuran-1-yl}-(*Z*)-pent-3-en-1-ol (49)

A solution of formyl tetrahydroisobenzofuran **48** (5.0 g, 6.1 mmol) and degassed dioxane (1.2 L) in a Pyrex™ reaction vessel was irradiated at room temperature with a Canrad-Hanovia medium-pressure mercury lamp (100 W) for 36 h, and then the reaction mixture was

concentrated. A solution of this residue, THF (120 mL), and MeOH (60 mL) at room temperature was treated with 1.0 M aqueous KOH (25 mL, 25 mmol), and then heated to reflux. After 15 h, the reaction mixture was allowed to cool to room temperature and then poured into saturated aqueous NH_4Cl (500 mL), the aqueous layer was extracted with CH_2Cl_2 (3 × 500 mL), and the combined organic extracts were dried ($NaSO_4$), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (5:1 hexane–ethyl acetate) to afford 1.6 g (55%, 2 steps) of **49** as a clear colorless oil: $[\alpha]^{23}_{D}$ +15.5, $[\alpha]^{23}_{577}$ +16.5, $[\alpha]^{23}_{546}$ +18.3, $[\alpha]^{23}_{435}$ +33.5, $[\alpha]^{23}_{405}$ +41.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.44 (t, *J* = 7.1 Hz, 1 H), 5.41–5.39 (m, 1 H), 4.55 (d, *J* = 9.9 Hz, 1 H), 3.91–3.87 (m, 1 H), 3.61 (dd, *J* = 9.7, 4.0 Hz, 1 H), 3.63–3.53 (m, 2 H), 3.48 (dd, *J* = 9.7, 6.1 Hz, 1 H), 2.59–2.38 (m, 5 H), 2.27–2.20 (m, 1 H), 2.09–1.98 (m, 2 H), 1.99 (t, *J* = 2.6 Hz, 1 H), 1.95–1.92 (m, 1 H), 1.76 (d, *J* = 0.9 Hz, 3 H), 1.68 (br s, 3 H), 1.62–1.54 (m, 1 H), 1.49–1.44 (m, 1 H), 1.05–1.01 (m, 21 H), 0.97 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.0, 132.7, 127.1, 120.9, 81.1, 79.6, 78.6, 69.9, 66.7, 62.2, 45.4, 41.6, 37.5, 31.9, 31.1, 26.3, 24.4, 21.8, 18.1, 18.0, 15.8, 11.9; IR (film) 3418, 3313, 2121, 1654 cm^{-1}; HRMS (CI) *m/z* 474.3526 (M, 474.3529 calcd for $C_{29}H_{50}O_3Si$).

Acetic Acid (3*S*,4*S*)-3-Acetoxy-4-hydroxy-4-{(1*R*,3*R*,3a*S*,4*R*,5*S*,7*R*,7a*R*)-4,5-epoxy-4-methyl-7-[1(*S*)-methyl-2-(triisopropylsilyloxy)ethyl]-3-prop-2-ynyl-1,3,3a,6,7,7a-hexahydroisobenzofuran-1-yl}pentyl Ester (53) and Acetic Acid (3*S*,4*S*)-3-Acetoxy-4-hydroxy-4-{(1 *R*,3*R*,3a*S*,4*S*,5*R*,7*R*,7a*R*)-4,5-epoxy-4-methyl-7-[1(*S*)-methyl-2-(triisopropylsilyloxy)ethyl]-3-prop-2-ynyl-1,3,3a,6,7,7a-hexahydroisobenzofuran-1-yl}pentyl Ester

m-Chloroperoxybenzoic acid (0.32 g, 1.8 mmol) was added to a stirring mixture of **52** (0.91 g, 1.5 mmol), $KHCO_3$ (1.5 g, 15 mmol), and CH_2Cl_2 (31 mL) at 0 °C. After 4 h, the reaction mixture was poured into 1:1 (vol/vol) saturated aqueous Na_2CO_3–brine (100 mL) and the aqueous layer was washed with CH_2Cl_2 (3 × 100 mL), the combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (6:1 hexane–ethyl acetate) to provide 0.72 g (77%) of **53** and 0.094 g (10%) of the β-epoxide epimer as a clear pale yellow oil. Major isomer **53**: $[\alpha]^{23}_{D}$ −2.5, $[\alpha]^{23}_{577}$ −1.7, $[\alpha]^{23}_{546}$ −2.6, $[\alpha]^{23}_{435}$ −4.6, $[\alpha]^{23}_{405}$ −5.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 (dd, *J* = 11.1, 2.1 Hz, 1 H), 4.11–4.00 (m, 3 H), 3.78 (d, *J* = 2.1 Hz, 1 H), 3.68 (dd, *J* = 9.4, 3.7 Hz, 1 H), 3.38 (t, *J* = 8.7 Hz, 1 H), 3.04 (br s, 1 H), 2.91 (ddd, *J* = 16.3, 3.3, 3.3 Hz, 1 H), 2.79 (br s, 1 H), 2.62–2.55 (m, 2 H), 2.16–1.98 (m, 3 H), 2.14 (t, *J* = 2.5 Hz, 1 H), 2.06 (s, 3 H), 2.03 (s, 3 H), 1.80–1.66 (m, 2 H), 1.47–1.36 (m, 2 H), 1.34 (s, 3 H), 1.07–0.99 (m, 27 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 170.9, 84.7, 80.5, 77.0, 76.9, 74.0, 71.8, 64.6, 61.2, 60.2, 54.8, 43.7, 40.7, 35.2, 34.3, 29.1, 24.5, 23.6, 23.5, 21.0, 20.8, 18.0, 17.8, 17.3, 11.9; IR (film) 3520, 3309, 3287, 1743 cm^{-1}; HRMS (ES) *m/z* 631.3658 (M + Na, 631.3642 calcd for $C_{33}H_{56}NaO_8Si$).

Minor β-epoxide epimer:[91] $[\alpha]^{23}_{D}$ +2.0, $[\alpha]^{23}_{577}$ +2.0, $[\alpha]^{23}_{546}$ +1.3, $[\alpha]^{23}_{435}$ +2.6, $[\alpha]^{23}_{405}$ +2.4 (*c* 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.33 (dd, *J* = 11.0, 2.1 Hz, 1 H), 4.11–4.05 (m, 2 H), 3.98 (ddd, *J* = 9.6, 3.8, 3.8 Hz, 1 H), 3.78 (d, *J* = 2.6 Hz, 1 H), 3.66 (dd, *J* = 9.6, 3.6 Hz, 1 H), 3.44 (dd, *J* = 9.5, 7.8 Hz, 1 H), 3.01 (d, *J* = 4.7 Hz, 1 H), 2.93 (dd, *J* = 9.5, 7.3 Hz, 1 H), 2.82 (ddd, *J* = 17.4, 3.2, 3.2 Hz, 1 H), 2.77 (br s, 1 H), 2.58 (ddd, *J* = 17.4, 3.2, 3.2 Hz, 1 H), 2.46–2.39 (m, 1 H), 2.18 (t, *J* = 2.5 Hz, 1 H), 2.10–2.00 (m, 2 H), 2.07 (s, 3 H), 2.03 (s, 3 H), 1.81–1.66 (m, 3 H), 1.41–1.32 (m, 1 H), 1.29 (s, 3 H), 1.07-1.00 (m, 27 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 170.9, 84.4, 80.4, 76.7, 76.6, 74.2, 72.3, 64.5, 61.2, 59.4, 56.7, 45.4, 40.8, 36.2, 35.8, 29.1, 24.5, 23.6, 22.6, 21.0, 20.9, 18.1, 18.0, 17.4, 11.9; IR (film) 3519, 3309, 3284, 1742 cm^{-1}; HRMS (ES) m/z 631.3632 (M + Na, 631.3642 calcd for $C_{33}H_{56}NaO_8Si$).

Acetic Acid 3-Acetoxy-1(*S*)-[(2*R*,2a*S*,3*S*,*4*S,5a*R*,6*S*,9*R*,9a*R*,9b*R*)-3,4-dihydroxy-3,6,9-trimethyl-2-prop-2-ynyl-2a,5,5a,6,7,9,9a,9b-octahydro-2H-1,8-dioxabenzo[*cd*]azulen-9-yl] propyl Ester (56)

Sulfuric acid (0.61 mL) was added dropwise to a solution of epoxide **55** (930 mg, 2.1 mmol), THF (40 mL) and H_2O (40 mL) at room temperature. After 6 h, saturated aqueous $NaHCO_3$ (80 mL) was added, the mixture was stirred vigorously for 20 min, the aqueous layer was extracted with ethyl acetate (2 × 50 mL), the organic extract was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (50:50 hexane–ethyl acetate) to give 770 mg (80%) of **56** as a waxy colorless solid: $[\alpha]^{23}_{D}$ −14.1, $[\alpha]^{23}_{577}$ −14.0, $[\alpha]^{23}_{546}$ −15.8, $[\alpha]^{23}_{435}$ −26.1, $[\alpha]^{23}_{405}$ −30.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) ^{5} 5.13 (dd, *J* = 9.6, 2.3 Hz, 1 H), 4.10–3.96 (m, 3 H), 3.64-3.57 (m, 2 H), 3.48 (dd, *J* = 13.0, 3.2 Hz, 1 H), 3.47 (d, *J* = 8.8 Hz, 1 H), 2.77 (ddd, *J* = 12.3, 12.3, 8.9 Hz, 1 H), 2.70–2.40 (m, 1 H), 2.64 (ddd, *J* = 17.0, 4.6, 2.7 Hz, 1 H), 2.52 (ddd, *J* = 17.0, 6.2, 2.7 Hz, 1 H), 2.21 (ddd, *J* = 14.6, 7.2, 2.4 Hz, 1 H), 2.11 (t, *J* = 2.7 Hz, 1 H), 2.02 (s, 3 H), 2.01 (s, 3H), 2.04–1.80 (m, 5 H), 1.63–1.56 (m, 1 H), 1.46 (ddd, *J* = 18.3, 9.2, 9.2 Hz, 1 H), 1.26 (s, 3 H), 1.24 (s, 3H), 0.98 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) d 171.1, 170.1, 92.5, 81.5, 78.6, 76.2, 74.4, 73.3, 72.6, 71.0, 67.6, 61.9, 53.4, 39.1, 38.4, 36.4, 30.5, 29.7, 24.6, 21.2, 21.0, 20.5, 19.6, 10.6; IR (film) 3455, 3289, 1733 cm^{-1}; HRMS (CI) *m/z* 453.2491 (M + H, 453.2488 calcd for $C_{24}H_{37}O_8$).

Briarellin E (12)

A mixture of vinyl iodide aldehyde **60** (51 mg, 0.080 mmol), a 100:1 mixture of $CrCl_2$ and $NiCl_2$ (1.1 g), and a dry, degassed 100:1 mixture of DMSO-Me_2S (91 mL) was stirred at room temperature. After 20 h, the resulting dark green mixture was transfered to a stirring mixture of sodium serinate (91 mL of a 1.0 M aqueous solution) and ethyl acetate (60 mL) at 0 °C, and then the cooling bath was removed. After 1 h, the layers were separated, the aqueous layer was extracted with ethyl acetate (2 × 30 mL), and the combined organic extracts were washed with brine (2 × 20 mL), dried (Na2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (1:1 hexane–ethyl acetate) to afford 31 mg (79%) of **12** as a clear yellow oil: $[\alpha]^{23}_{D}$ −8.3, $[\alpha]^{23}_{577}$ −8.7, $[\alpha]^{23}_{546}$ −10.1, $[\alpha]^{23}_{435}$ −21.6, $[\alpha]^{23}_{405}$ −28.7 (*c* 0.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.47 (s, 1 H), 5.18 (s, 1 H), 5.17 (s, 1 H), 4.50 (s, 1 H), 4.19–4.17 (m, 1 H), 3.82 (d, *J* = 9.2 Hz, 1 H), 3.60 (d, *J* = 12.9 Hz, 1 H), 3.38 (dd, , *J* = 13.2, 2.6 Hz, 1 H), 2.97 (s, 1 H), 2.59 (s, 1 H), 2.39–2.25 (m, 5 H), 1.94–1.86 (m, 1 H), 1.83–1.76 (m, 1 H), 1.70–1.53 (m, 6 H), 1.52–1.41 (m, 2 H), 1.33 (s, 3 H), 1.32 (s, 3 H), 1.34–1.20 (m, 9 H), 0.89–0.85 (m, 3 H), 0.81 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 148.1, 115.1, 92.0, 81.9, 76.7, 73.9, 71.6, 67.3, 51.6, 39.7, 39.3, 38.8, 36.3, 35.8, 34.8, 31.6, 29.0, 28.9, 28.7, 25.2, 24.9, 22.6, 17.8, 14.0, 10.4; IR (film) 3432, 1706, 1640 cm^{-1}; HRMS (ES) *m/z* 501.3202 (M + Na, 501.3192 calcd for $C_{28}H_{46}NaO_6$).

Briarellin F (13)

Dess–Martin periodinane[38] (28 mg, 0.05 mmol) was added to a solution of briarellin E (**12**) (14 mg, 0.03 mmol) and CH_2Cl_2 (3.5 mL), and the resulting mixture was stirred at room temperature. After 45 min, 1.5 M aqueous $Na_2S_2O_3$ (5.0 mL) was added and the mixture was stirred vigorously. After 1 h, CH_2Cl_2 (10 mL) was added, the organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 15 mL), brine (15 mL), dried (Na2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (70:30 hexane–ethyl acetate) to afford 11 mg (79%) of **13** as a waxy colorless solid: $[\alpha]^{23}_{D}$ −63.2, $[\alpha]^{23}_{577}$ −66.0, $[\alpha]^{23}_{546}$ −73.8, $[\alpha]^{23}_{435}$ −125.5, $[\alpha]^{23}_{405}$ −148.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (dd, *J* = 9.6, 5.4 Hz, 1 H), 5.43 (s, 1 H), 5.35 (s, 1 H), 4.45 (dt, *J* = 3.6, 3.3, 1 H), 3.81 (d, *J* = 9.3 Hz, 1 H), 3.62 (d, *J* = 13.1 Hz, 1 H), 3.40 (dd, , *J* = 12.9, 3.3 Hz, 1 H), 3.32 (ddd, *J* = 13.2, 6.6, 0.7 Hz, 1 H), 2.84–2.73 (m, 2 H), 2.70–2.62 (m, 1 H), 2.38 (dd, *J* = 13.2,

3.0 Hz, 1 H), 2.34–2.29 (m, 2 H), 2.16 (dd, *J* = 11.7, 3.9 Hz, 1 H), 1.91–1.83 (m, 1 H), 1.75-1.47 (m, 7 H), 1.33 (s, 3 H), 1.30 (s, 3 H), 1.34–1.20 (m, 9 H), 0.90–0.85 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.7, 173.2, 146.4, 116.1, 92.1, 80.0, 77.2, 72.0, 71.1, 67.6, 53.8, 45.7, 42.7, 40.1, 38.6, 36.3, 34.5, 31.7, 29.0, 28.9, 28.6, 25.1, 24.1, 22.6, 18.4, 14.1, 10.6; IR (film) 3462, 1733, 1691 cm^{-1}; HRMS (ES) *m/z* 499.3033 (M + Na, 499.3036 calcd for $C_{28}H_{44}NaO_6$).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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58. A trace of cyclohexadienyl side product was removed by flash chromatography on $AgNO_3$-impregnated silica gel.
59. The major epimer is assigned the anti configuration (resulting from Felkin-Ahn addition) by analogy to similar couplings in our syntheses of cladiellins: see ref. 16d.
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61. Chen J, Wang T, Zhao K. Tetrahedron Lett 1994;35:2827–2828.
62. (a) For a discussion of the Z selectivity of Wittig reactions with α-iodophosphoranes, see: Arimoto H, Kaufman MD, Kobayashi K, Qiu Y, Smith AB III. Synlett 1998:765–767.767 (b) The minor E vinyl iodide isomer (~5%) formed in this instance was removed by flash chromatography on $AgNO_3$-impregnated silica gel prior to the next step of the reaction sequence.
63. Hanessian S, Lavallee PCanJ. Chem 1975;53:2975–2977.
64. For useful reviews of silyl ether protecting groups, see: (a)Crouch RD. Tetrahedron 2004;60:5833–5871.5871 (b)Nelson TD, Crouch RD. Synthesis 1996:1031–1069.1069
65. The Z configuration of enal **47** was established by NOE difference experiments, see also ref. 16d.
66. This acetal was an inconsequential mixture of four diastereomers.
67. The Z configuration of the TBDPS-protected 1-methyl-4-hydroxy-1-butenyl side chain of **48** was confirmed by NOE difference experiments, see also ref. 16d.
68. Baggiolini E, Hamlow HP, Schaffner K. J. Am. Chem. Soc 1970;92:4906–4921.
69. The tetrasubstituted alkene regioisomer (~10%) formed in the deformylation step was removed by flash chromatography on silica gel.
70. Takai K, Oshima K, Nozaki H. Bull. Chem. Soc. Jpn 1983;56:3791–3795.
71. The minor epoxide stereoisomer (~10%) was removed by flash chromatography on silica gel.
72. Trost BM, Greenspan PD, Geissler H, Kim JH, Greeves N. Angew. Chem., Int. Ed 1994;33:2182–2184.

73. The minor epoxide stereoisomer (~10% yield) was removed by flash chromatography on silica gel and fully characterized (see the Supporting Information).
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81. We thank Prof. A. Rodríguez of the University of Puerto Rico, Río Piedras, for providing a sample of natural briarellin E.
82. For reviews, see: (a)Gradillas A, Pérez-Castells J. Angew. Chem., Int. Ed 2006;45:6086–6101.6101 (b)Nicolaou KC, Bulger PG, Sarlah D. Angew. Chem., Int. Ed 2005;44:4490–4527.4527 (c)Deiters A, Martin SF. Chem. Rev 2004;104:2199–2238.2238 [PubMed: 15137789]
83. Joe D, Overman LE. Tetrahedron Lett 1997;38:8635–8638.
84. We thank Prof. A. Rodríguez of the University of Puerto Rico, Río Piedras, for providing a sample of natural 11-acetoxy-4-deoxyasbestinin D.
85. The limited amount of diene **62** available (~ 8 mg) precluded an extensive investigation of RCM conditions.
86. Scholl M, Ding S, Lee CW, Grubbs RH. Org. Lett 1999;1:953–956. [PubMed: 10823227]
87. Schrock RR, Murdzek JS, Bazan GC, Robbins J, DiMare M, O'Regan M. J. Am. Chem. Soc 1990;112:3875–3886.
88. The only recognized, although not fully characterized, product using catalyst **62** contained one methylene unit less than anticipated, suggesting that, as in our earlier study,83 isomerization of the terminal alkene to its internal isomer89 had preceded ring closure.
89. Hanessian S, Giroux S, Larsson AOrg. Lett 2006;8:5481–5484.5484 and references therein.
90. Experimental procedures for key steps in the total syntheses of the purported structure of alcyonin and briarellins E and F. General experimental details and experimental procedures for other steps can be found in the Supporting Information for this article, or the Supporting Information deposited with the preliminary communications.16e,16f
91. The structure for this compound (**S4**) can be found in Supporting Information.

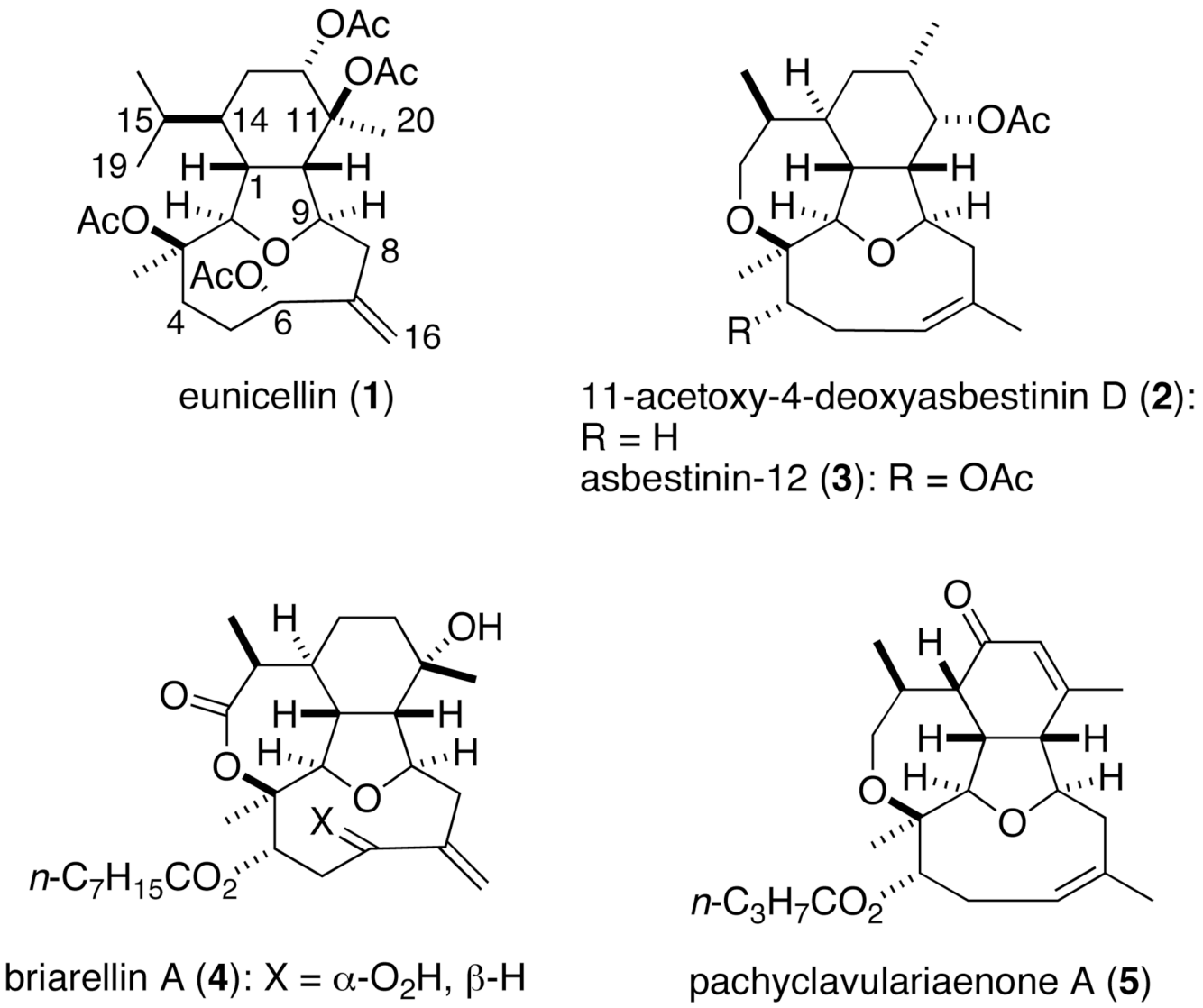
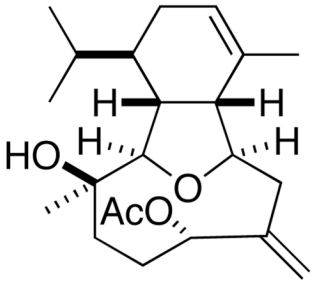
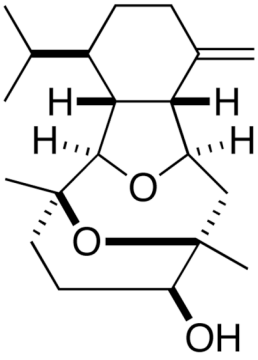


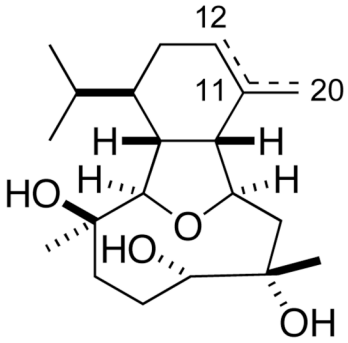
Figure 1.
Representative cladiellin (eunicellin), briarellin, and asbestinin diterpenes.



6-acetoxycladiell-7(16),11-dien-3-ol (**6**)

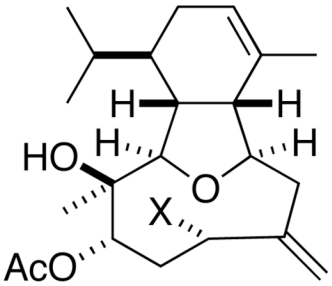


sclerophytin A–original (**7**)



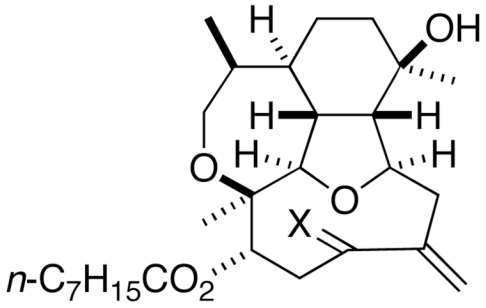
cladiell-11-ene-3,6,7-triol (**8**): $\Delta^{11,12}$

sclerophytin A–revised (**9**): $\Delta^{11,20}$



alcyonin–original (**10**): X = OH

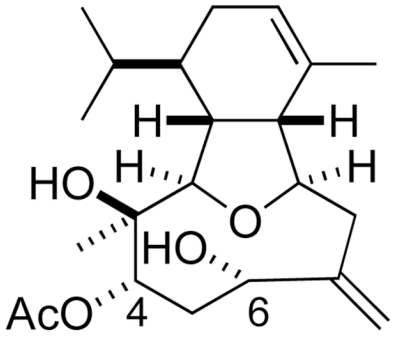
alcyonin–revised (**11**): X = O_2H



briarellin E (**12**): X = α-OH, β-H

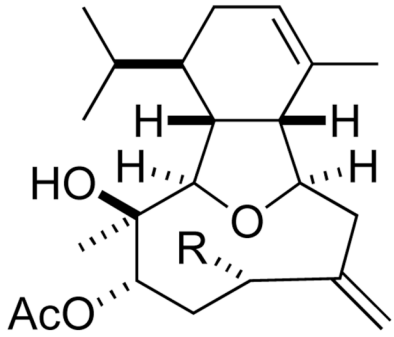
briarellin F (**13**): X = O

Figure 2.
Cladiellin and briarellin diterpene total synthesis targets of the Overman group.



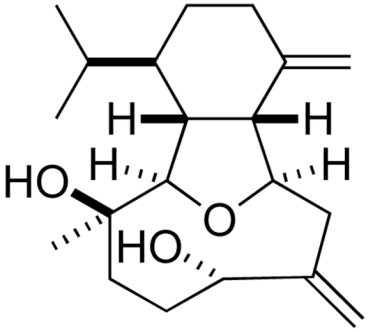
synthetic **10**

H4: δ 4.99 (C4: 73.8 ppm)
H6: δ 4.17 (C6: 72.8 ppm)



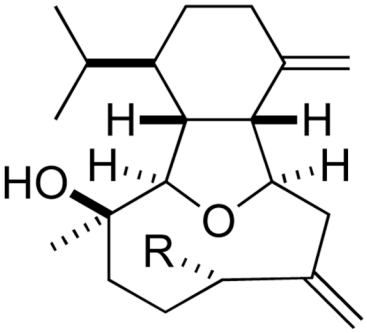
alcyonin (**11**): R = O_2H
(revised structure)

H4: δ 5.06 (C4: 73.1 ppm)
H6: δ 4.76 (C6: 83.7 ppm)
O_2H: δ 8.0



cladiellisin (**33**)

H6: δ 4.40 (C6: 72.9 ppm)



cladiellaperoxide (**34**): R = O_2H

H6: δ 4.74 (C6: 86.3 ppm)
O_2H: δ 7.86

Figure 3.
Diagonostic NMR data for synthetic **10**, natural alcyonin **(11)**, cladiellisin **(33)**, and cladiellaperoxide (**34**).

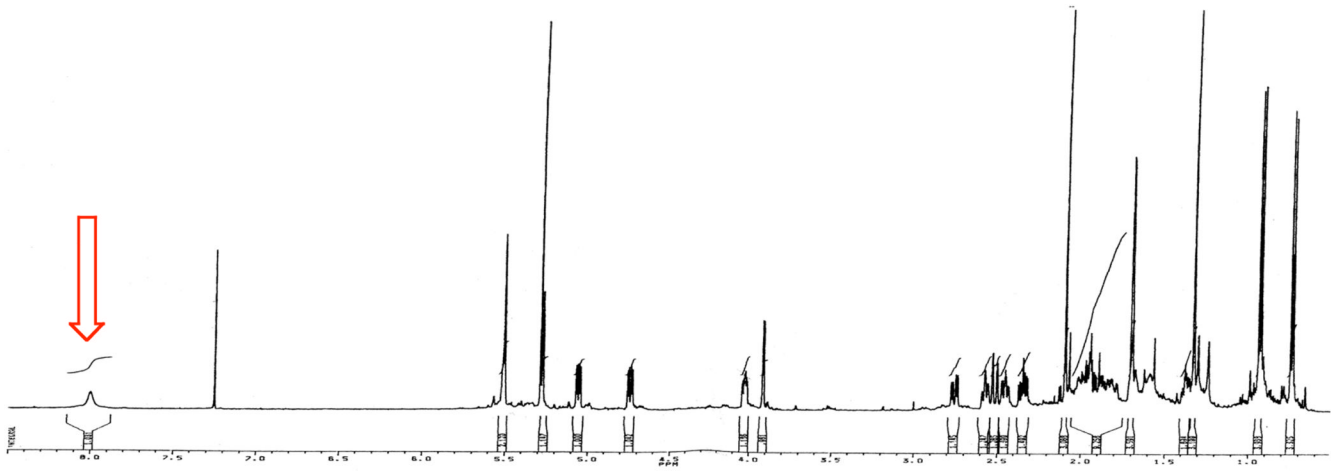
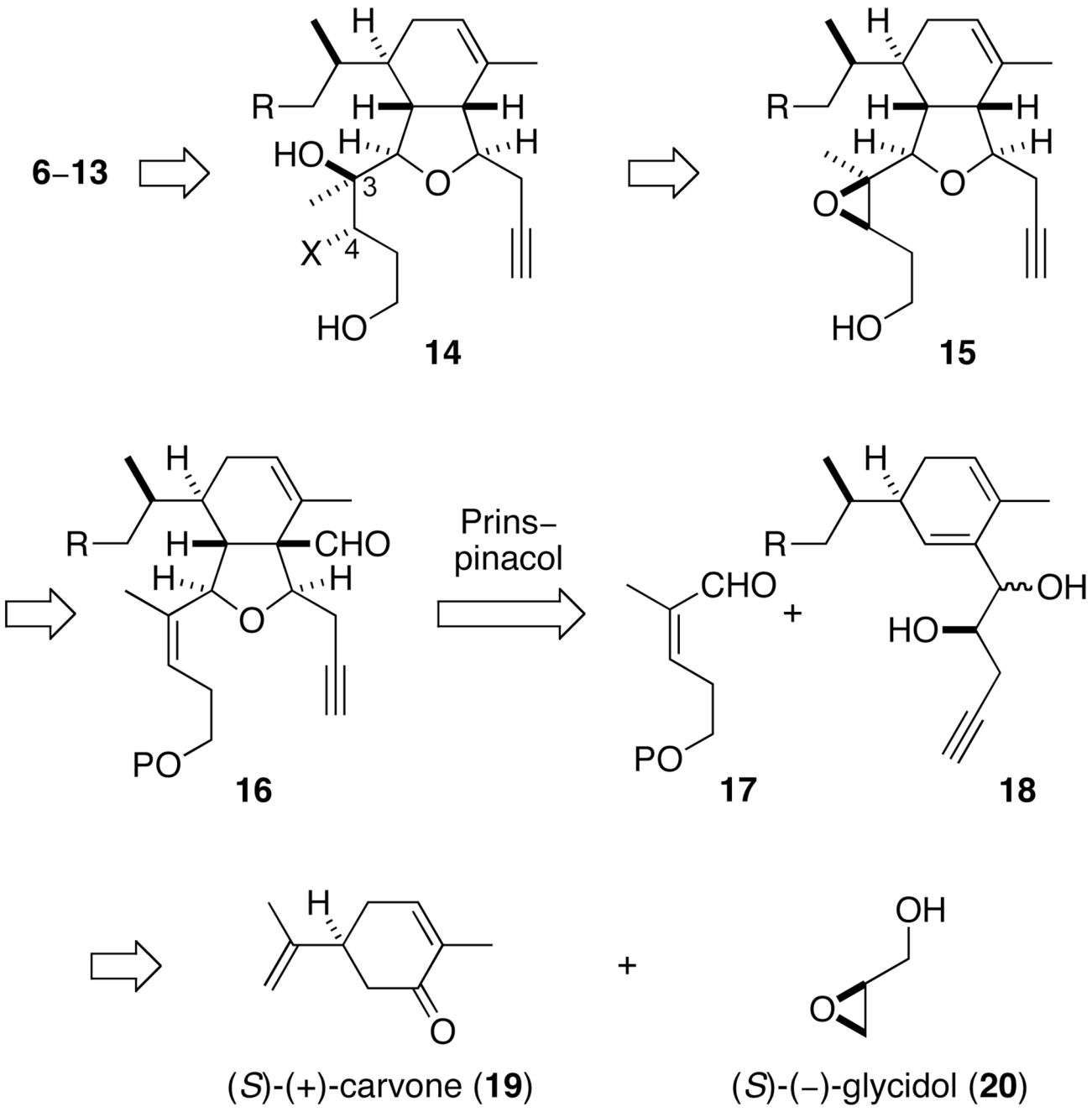
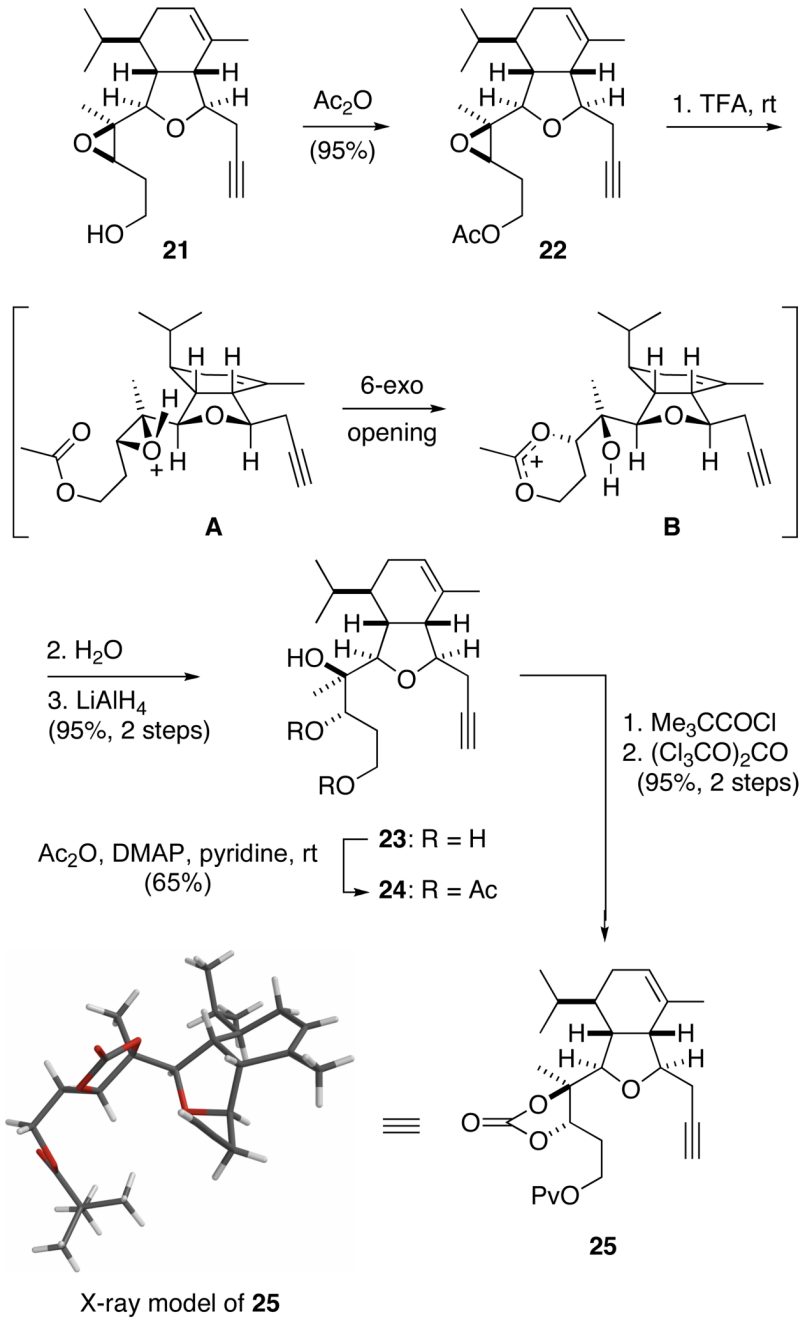


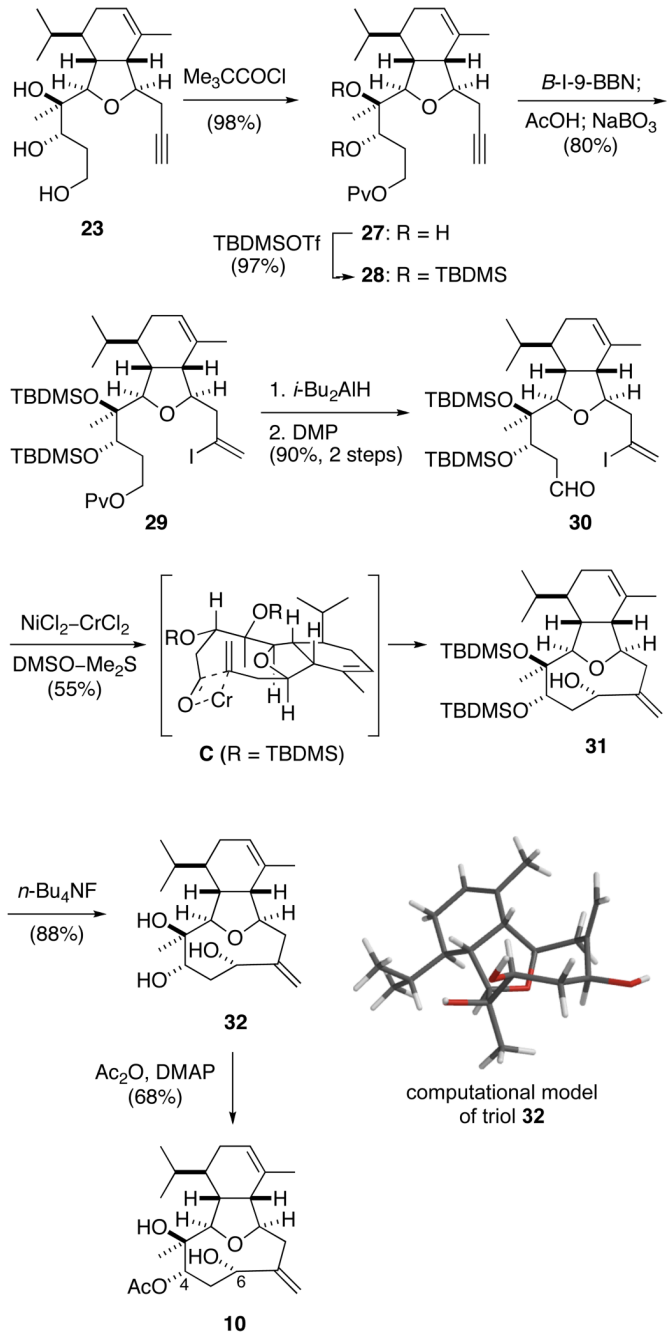
Figure 4.
^{1}H NMR spectrum of natural alcyonin.



Scheme 1.
Unified Plan for Synthesis of Cladiellin and Briarellin Diterpenes

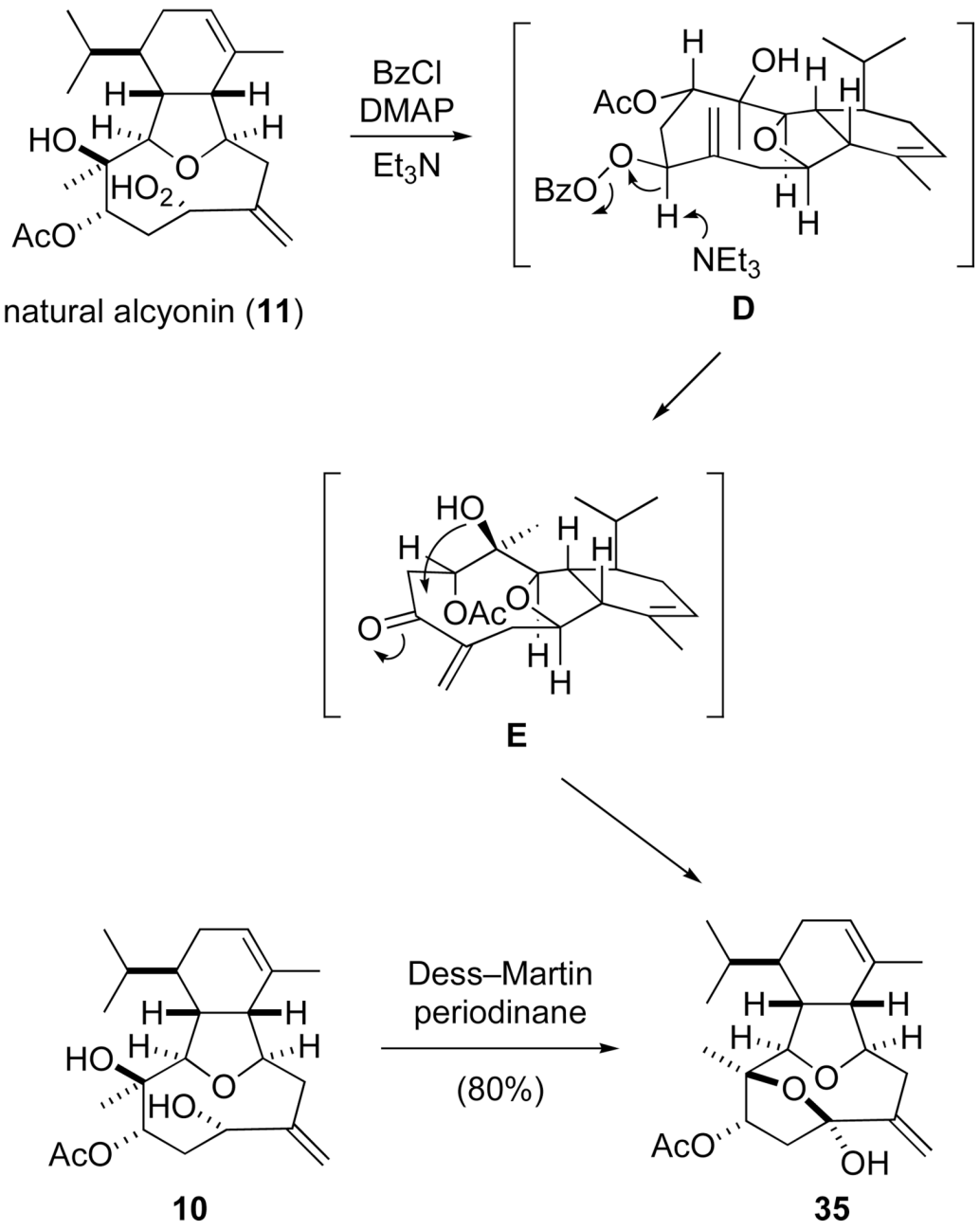


Scheme 2.
Epoxy Ester Rearrangement and Confirmation of the Relative Configuration at C3 and C4

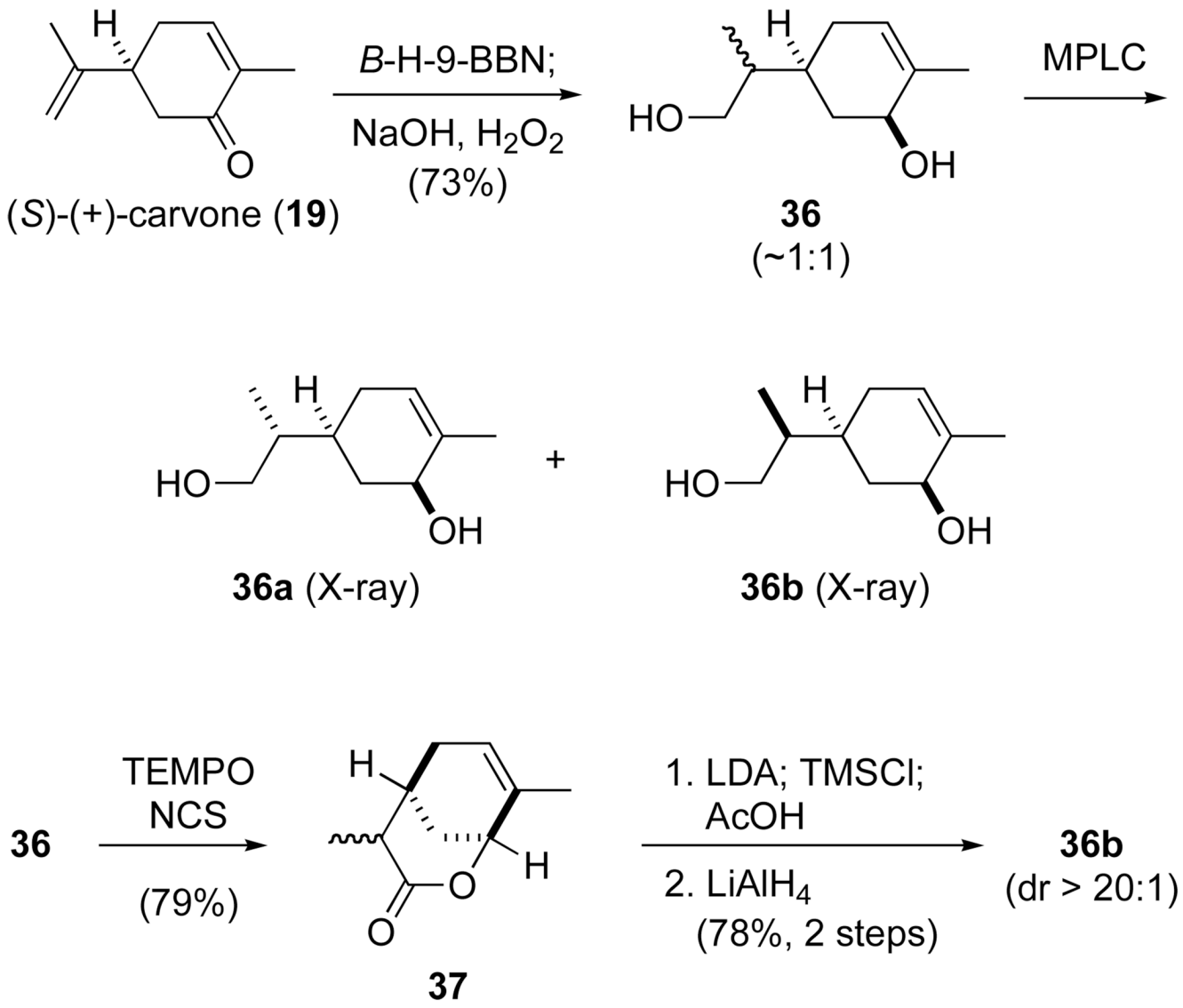


Scheme 3.

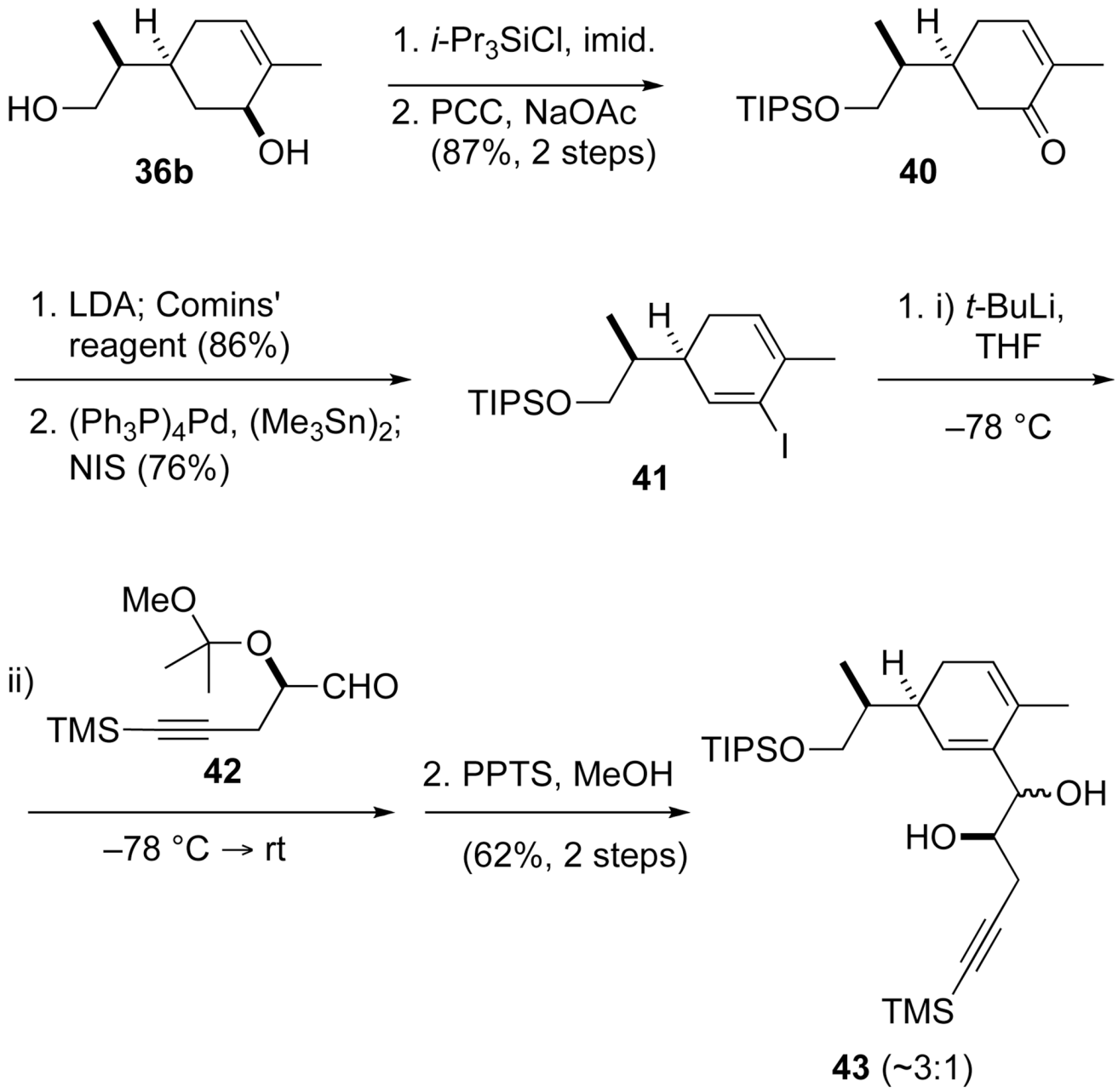
Completion of the Total Synthesis of the Originally Proposed Structure **10** of Alcyonin



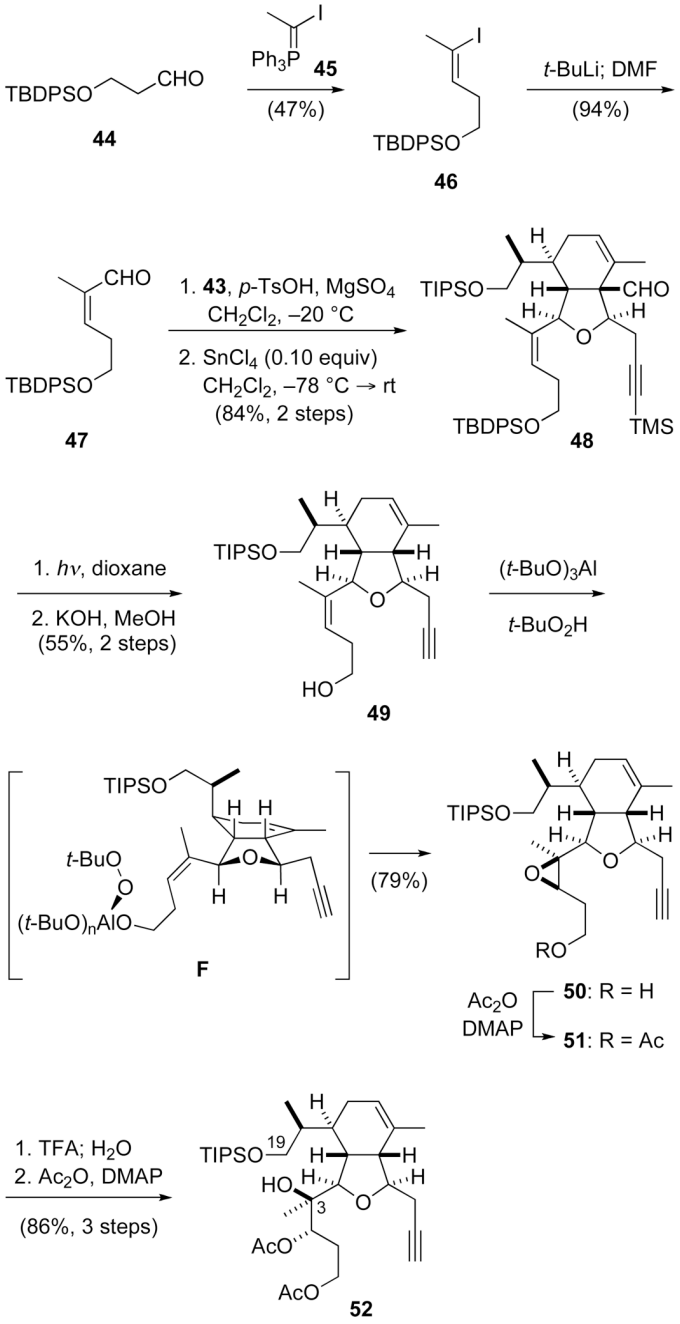
Scheme 4.
Conversion of **10** and **11** to Hemiacetal **35**



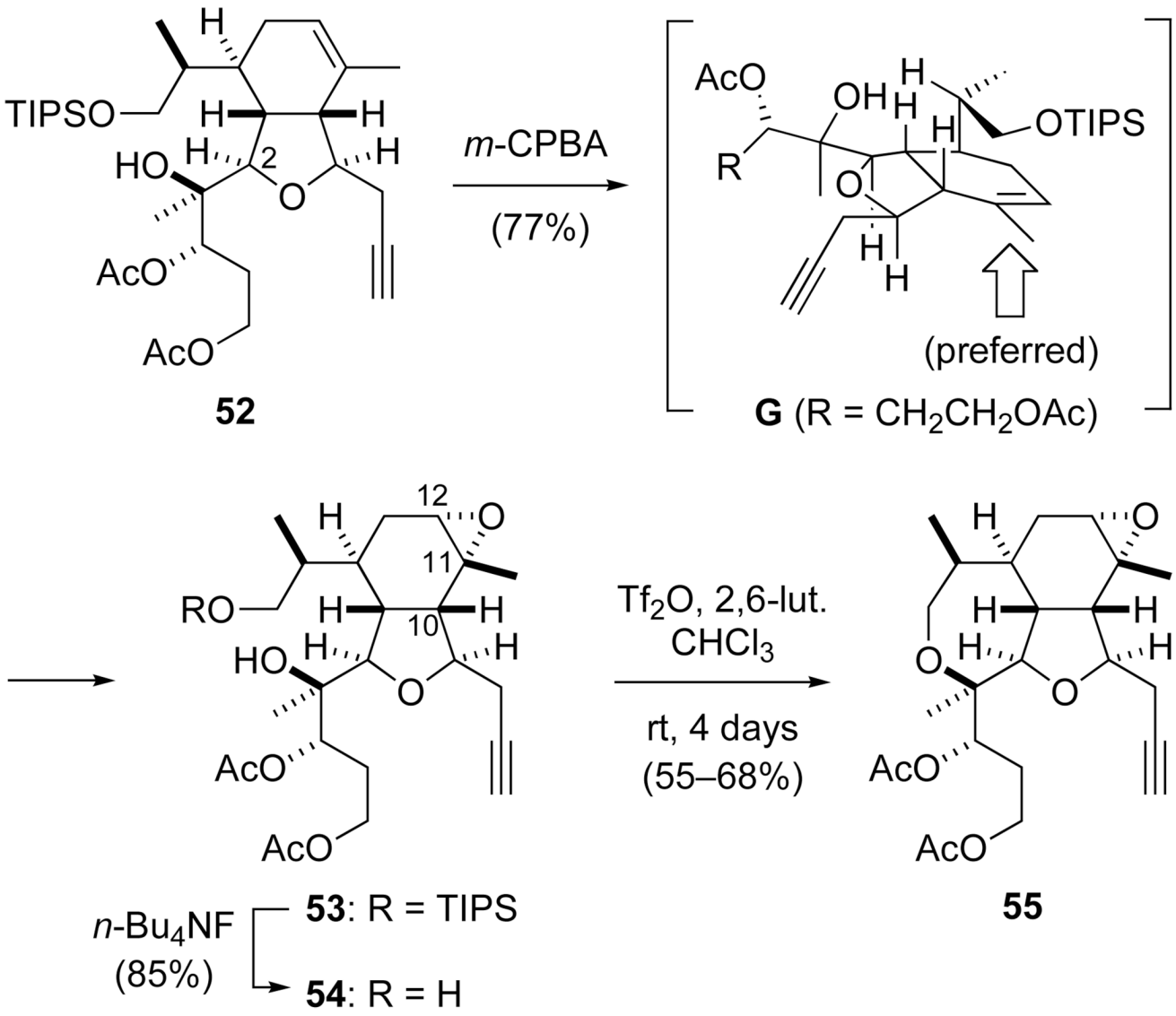
Scheme 5.
Installation of the C15 Stereocenter from (*S*)-(+)-carvone (**19**)



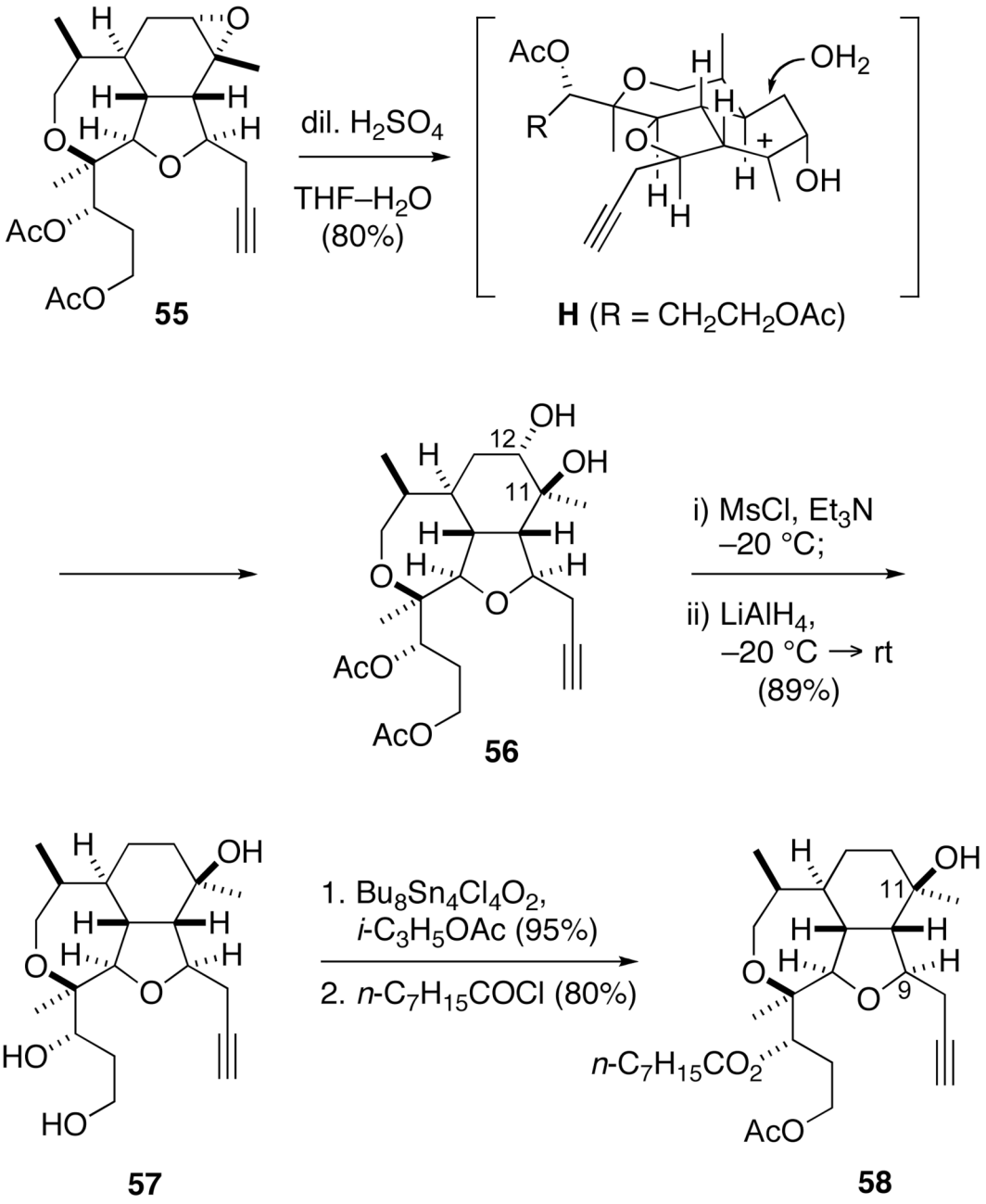
Scheme 6.
Preparation of Cyclohexadienyl Diol **43**



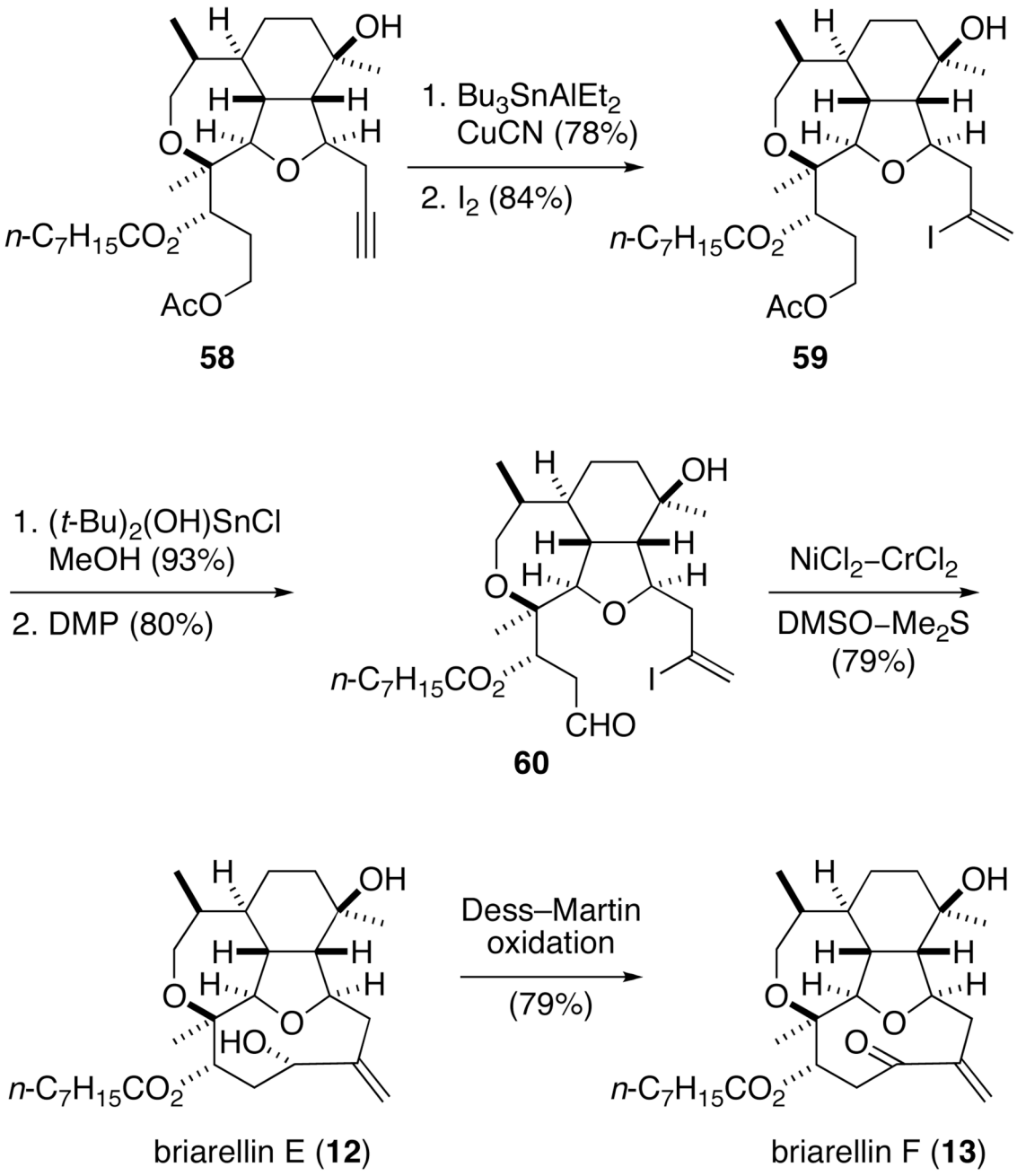
Scheme 7.
Preparation of Hexahydroisobenzofuran Intermediate **52**.



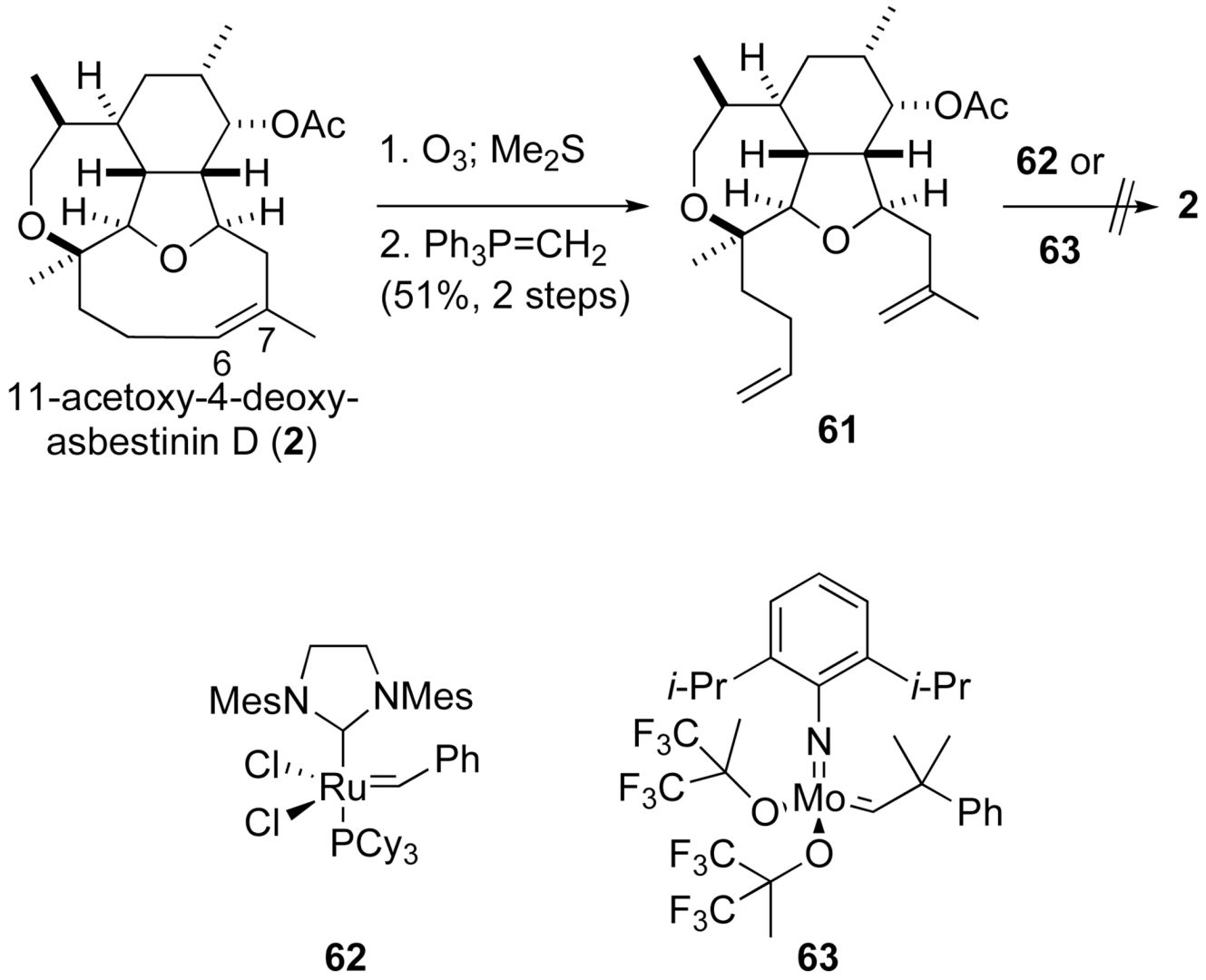
Scheme 8.
Stereoselective Epoxidation and Formation of the Oxepane Ring



Scheme 9.
Synthesis of Tricyclic Hydroxy Diester **58**



Scheme 10.
Completion of the Synthesis of Briarellins E (**12**) and F (**13**)



Scheme 11.
Attempted Late-Stage RCM for Re-forming 11-acetoxy-4-deoxyasbestinin D