A General Strategy for the Synthesis of Cladiellin Diterpenes: Enantioselective Total Syntheses of 6-Acetoxycladiell-7(16),11-dien-3-ol (Deacetoxyalcyonin Acetate), Cladiell-11-ene-3,6,7-triol, Sclerophytin A, and the Initially Purported Structure of Sclerophytin A

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Abstract: Enantioselective total syntheses of the cladiellin diterpenes, 6-acetoxycladiell-7(16),11-dien-3-ol (deacetoxyalcyonin acetate, **6**), cladiell-11-ene-3,6,7-triol (**1**), sclerophytin A (**8**), and tetracyclic diether **7**, have been achieved by differential elaboration of tricyclic allylic alcohol **57**. The central step in these syntheses is acid-promoted condensation of α,β-unsaturated aldehydes **45**, **69** or **87**, and cyclohexadienyl diol **44** to form, with complete stereocontrol, the hexahydroisobenzofuran core and five stereocenters of these cladiellin diterpenes. These syntheses also feature stereospecific photolytic deformylation of β,γ-unsaturated aldehydes **46**, **70**, and **71** to remove the extraneous carbon introduced in the Prins−pinacol step; chemo- and stereoselective hydroxyl-directed epoxidation of **49**, **72**, and **90** followed by regioselective reductive opening with hydride to install the C3 tertiary hydroxyl group; and a diastereoselective Nozaki−Hiyama−Kishi cyclization of iodoaldehyde **56** to forge the oxacyclononane ring and the C6 hydroxyl stereocenter. Other key transformations include chemo- and stereoselective hydroxyl-directed epoxidation of tricyclic allylic alcohol **57** followed by regioselective reductive opening with hydride to install the C7 tertiary hydroxyl center of **1** and **8**; chemo-, regio-, and stereoselective intramolecular oxymercuration−reductive demercuration of dienyl diol **62** to form the bridging tetrahydropyran ring of tetracyclic diether **7**; and photochemical isomerization of the endocyclic double bond of **92** and **1** to give exocyclic congeners **7** and **8**. The absolute stereochemistry of the synthetic products originates from two chiral nonracemic starting materials, (*S*)-(+)-carvone and (*S*)-(−)-glycidol. These syntheses define a versatile and concise strategy for the total synthesis of cladiellin diterpenes and provide additional illustrations of the uncommon utility of pinacol-terminated cationic cyclizations for the stereocontrolled synthesis of complex oxacyclic products.

Introduction

Marine invertebrates produce an astounding array of secondary metabolites,[2] including a variety of structurally novel diterpene cyclic ethers.[3] One large family of oxacyclic diterpenes is derived from cembrane precursors by C2−C11 bond formation and includes the cladiellins (also known as eunicellins), the briarellins, the asbestinins, and the sarcodictyins (Figure 1).[3] By oxidation at C16 and oxepane formation, the cladiellins are believed to be biosynthetically converted to the briarellins. A subsequent suprafacial 1,2-methyl shift from C11 to C12 would transform the briarellins to the asbestinins.[3]

The cladiellins, briarellins, and asbestinins have in common a rare oxatricyclic ring system composed of hexahydroisobenzofuran (2-oxabicyclo[4.3.0]nonane) and oxacyclononane units, as well as six stereogenic centers (carbons 1, 2, 3, 9, 10, and 14). Although the structures of several members of this class have been established by X-ray analysis,[4,5] structure elucidation in this area has generally relied upon mass spectrometric and NMR, IR, and UV spectral analyses.[3] The absolute stereochemistry of several cladiellins has been proposed on the basis of single-crystal X-ray diffraction,[4d] CD,[4a,6] or NMR experiments.[7] These studies indicate the *R* absolute configuration (as depicted in **1**) for each of the six common stereogenic centers of cladiellin

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(2) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1−49 and earlier reviews in this series.

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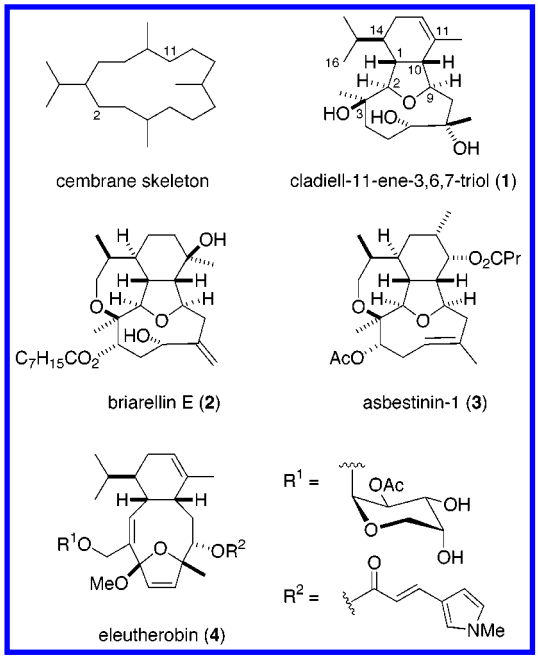

Figure 1. Representative cladiellin, briarellin, asbestinin, and sarcodictyin diterpenes.

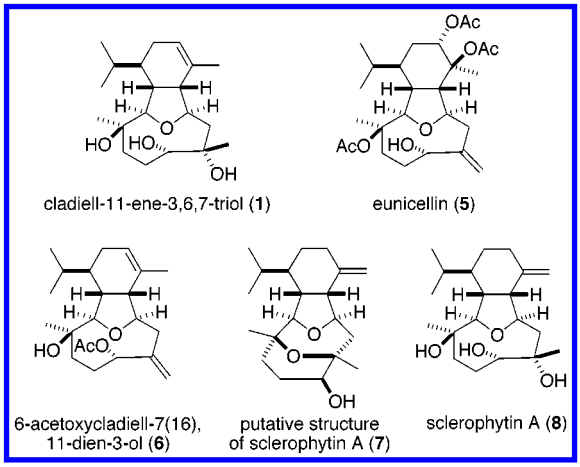

Figure 2. Representative cladiellin diterpenes.

diterpenes.[8] Absolute configurations have not been established for any members of the asbestinin or briarellin diterpene subclasses.

Cladiellin diterpenes have been isolated from several coelenterates found in the Mediterranean Sea and the Atlantic and Pacific Oceans.[3] Djerassi, Kennard, and co-workers isolated the first member of this group, eunicellin (**5**), in 1968 from the soft coral *Eunicella stricta* found off the coast of Banyuls-sur-Mer in France (Figure 2).[4g] Since this initial disclosure, over 50 members of this subclass of 2,11-cyclized cembrane diterpenes have been isolated from gorgonians and soft corals.[3,9] Uchio and co-workers revealed the structures of cladiell-11-ene-3,6,7-triol (**1**)[4c] and 6-acetoxycladiell-7(16),11-dien-3-ol (**6**, also referred to as deacetoxyalcyonin acetate),[10,11] diterpene ethers obtained from a *Cladiella* species of soft coral inhabiting the waters around Ishigaki Island, Okinawa. The isolation of sclerophytin A from the soft coral *Sclerophytum capitalis*, collected from the waters surrounding Enewetak, Micronesia, was reported by Sharma and Alam in 1988.[12] Although depicted in an ambiguous way in the original accounts,[4d,12] the structure of sclerophytin A was most reasonably construed to be **7**.[6a,13] However, contemporaneous synthesis studies in the sclerophytin area by the Paquette group[14] and our group[15] demonstrated that the originally proposed structure of sclerophytin A was incorrect. Reinvestigation of NMR and mass spectra of sclerophytin A by Paquette and co-workers[16a] and total syntheses in our and the Paquette laboratories showed that sclerophytin A was cladiell-11(17)-ene-3,6,7-triol (**8**).[16b]

Biological activity of the cladiellin diterpenes has not been extensively studied, although preliminary investigations have revealed that in addition to insect growth inhibition activity, many members exhibit in vitro cytotoxicity against several cancer cell lines.[3] In particular, sclerophytin A was reported to display notable in vitro toxicity against the L1210 leukemia cell line (1 ng mL^{-1}).[12] On the basis of mollusk and fish lethality assays, the natural role of cladiellin, briarellin, and asbestinin diterpenes is suggested to be predation deterrence.[3,17]

The unique and complex architecture of the cladiellin, briarellin, asbestinin, and sarcodictyin diterpenes, coupled with their largely unexplored potential in medicine or as tools for biological studies, make these compounds attractive targets for total synthesis. Our synthesis of 6-acetoxycladiell-7(16),11-dien-3-ol (deacetoxyalcyonin acetate, **6**), disclosed in 1995,[18] represented the first total synthesis of a member of the 2,11-cyclized cembranoid oxacyclic diterpene family. Total syntheses of the first sarcodictyin diterpene, eleutherobin (**4**),[19] were reported by the Nicolaou[20] and Danishefsky[21] groups in 1997 and 1998, respectively. Most recently, we and the Paquette group disclosed

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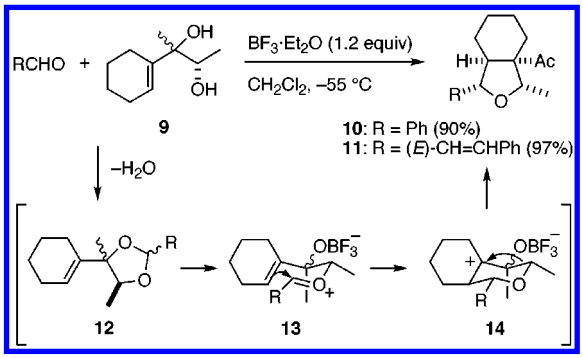
independent total syntheses of sclerophytin A (**8**),[16b] and we described the total synthesis of cladiell-11-ene-3,6,7-triol (**1**).[16b] In this contribution, we discuss the evolution of our strategy for the total synthesis of cladiellin, briarellin, and asbestinin diterpenes and present details of our total syntheses of cladiellin diterpenes **1**, **6**, and **8** as well as the putative structure **7** of sclerophytin A.[22]

Results and Discussion

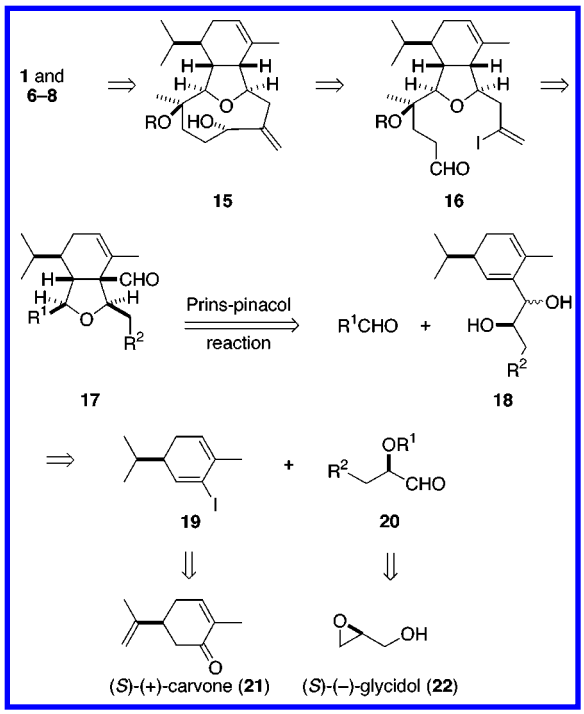
Synthesis Planning and Initial Model Studies. We have previously shown that a variety of stereochemically complex tetrahydrofurans,[23] including oxacyclic natural products,[24] can be constructed efficiently by Lewis acid-promoted condensation-rearrangement of allylic diols and aldehydes or ketones.[25,26] We envisaged that such a sequence having the alkene contained within a six-membered ring might provide convenient entry to the hexahydroisobenzofuran core of the cladiellin, briarellin, and asbestinin diterpenes. This possibility was initially verified through the assembly of hexahydroisobenzofurans **10** and **11** by the BF_3·Et_2O-promoted reaction of cyclohexenyl diol **9** (a 7:1 mixture of *anti* and *syn* stereoisomers) and benzaldehyde or cinnamaldehyde (Scheme 1). ^{1}H NMR NOE experiments clearly revealed the relative configurations of **10** and **11**.[27]

The high stereoselection observed in the formation of **10** and **11** can be rationalized by the intervention of intermediates **12**, **13**, and **14** (see Scheme 1). Because the oxocarbenium ion **13** in each case is resonance-stabilized and the cyclohexene double bond is a relatively weak π nucleophile,[28] the stereochemistry-determining Prins cyclization, **13** → **14**, is proposed to take place by a late transition state.[23a,d] The nature of the stereochemistry-defining step of the Prins−pinacol synthesis of 3-acyltetrahydrofurans is discussed in more detail in a recent publication.[23a]

Scheme 1



Scheme 2



This model study suggested the general strategy for total synthesis of cladiellin diterpenes that is outlined retrosynthetically in Scheme 2. We reasoned that **1**, **6**, **7**, and **8** could be accessed from a common intermediate, tricyclic allylic alcohol **15**. The demanding construction of the nine-membered oxacyclic ring of **15** was envisaged to arise by chromium-promoted (Nozaki−Hiyama−Kishi) coupling of the vinyl iodide and aldehyde functional groups of **16**.[29,30] This tactic was indicated by the pioneering studies of Kishi in using chromium-mediated cyclizations to access synthetically challenging medium-ring

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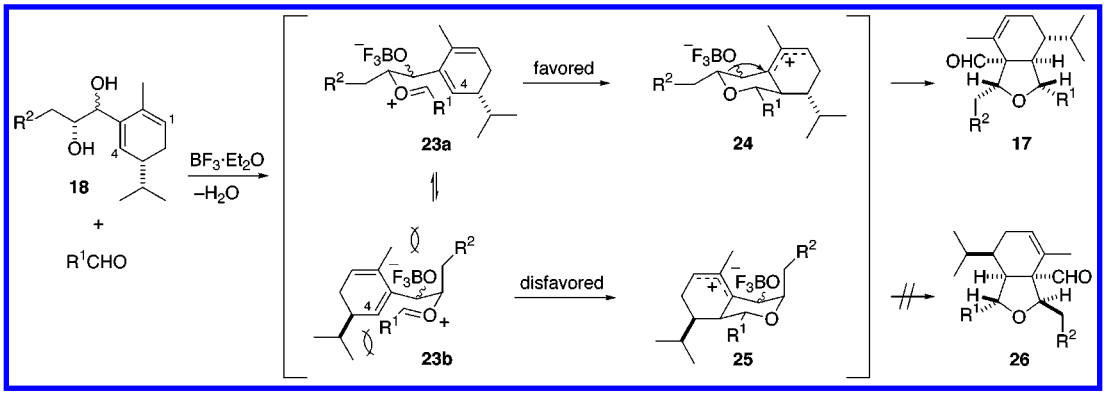


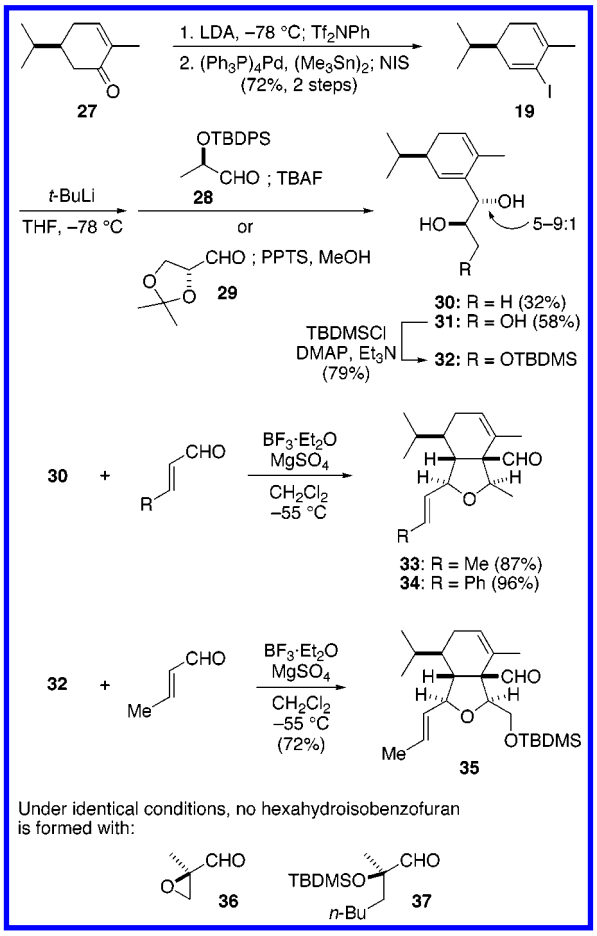
Figure 3. Stereochemical analysis of the pivotal condensation−rearrangement sequence to form **17**.

carbocyclic structures.[31] Iodoaldehyde **16** was projected to arise from formyl hexahydroisobenzofuran **17** by a multistep sequence, the key step of which would be stereospecific deformylation of the β,γ-unsaturated aldehyde functionality.[32] The central strategic step of our plan was to form hexahydroisobenzofuran **17**, an intermediate that contains five of the six invariant stereocenters of the cladiellin diterpenes, from the reaction of cyclohexadienyl diol **18** with an appropriately functionalized aldehyde. We envisioned that enantiopure **18** would be available by coupling of the dienyl iodide **19** derived from (*S*)-(+)-carvone (**21**) and an α-alkoxyaldehyde **20** obtained from (*S*)-(−)-glycidol (**22**).

A number of considerations were involved in our expectation that condensation of **18** and an aldehyde would deliver hexahydroisobenzofuran **17** (Figure 3). First, although the productive[23d] (*E*)-oxocarbenium ion **23** arising from the condensation of **18** and an aldehyde could cyclize in several ways, only cyclization at C4 of the 1,3-cyclohexadiene moiety would generate an allylic cation by a preferred 6-endo cyclization process. Second, face selection in such a Prins cyclization should be rigorously controlled by steric interactions. In the favored cyclization pathway, **23a** → **24**, the homoallylic substituent would adopt a pseudoequatorial orientation, and the oxocarbenium ion electrophile would approach the diene from the face opposite the bulky isopropyl substituent. In contrast, the alternate chair cyclization pathway, **23b** → **25**, would suffer severe steric interactions between the pseudoaxial homoallylic substituent and the methyl substituent of the diene, and between the isopropyl group and the R^1 substituent of the oxocarbenium ion.

We initially examined formation of a functionalized hexahydroisobenzofuran moiety in the model studies summarized in Scheme 3. Cyclohexadienyl diols **30** and **32** (i.e., **18**, R^2 = H or OTBDMS, respectively) were assembled from (*S*)-(+)-carvone by first converting (*S*)-dihydrocarvone (**27**)[33] to its kinetic enol triflate.[34] This intermediate then was coupled with hexamethylditin,[35] and the resulting vinylstannane product was iodinated in situ with *N*-iodosuccinimide (NIS)[36] to provide

Scheme 3



dienyl iodide **19**.[37] Metalation of **19** with *tert*-butyllithium and coupling of the resulting dienyllithium species with (*R*)-α-silyloxy aldehyde **28**,[38] followed by desilylation, provided diol **30** as a 9:1 mixture of epimers; the major isomer is assigned the *anti* configuration on the basis of strong literature precedent.[39] Similar condensation of the lithium species derived from **19** with (*R*)-isopropylidene glyceraldehyde (**29**) and subsequent

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(34) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979−982.

(35) Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277−279.

(36) Seyferth, D. *J. Am. Chem. Soc.* **1957**, *79*, 2133-2136.

(37) This product could be stored indefinitely at 0 °C in base-washed glassware over a piece of copper wire.

(38) Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5180−5182.

(39) (a) Braun, M.; Mahler, H. *Liebigs Ann.* **1995**, 29−40. For early examples of the use of bulky silyl groups to favor Felkin−Ahn stereoselection, see: (b) McCready, R. J.; Overman, L. E. *Tetrahedron Lett.* **1982**, *23*, 2355−2358. (c) Nakata, T.; Oishi, T.; Tanaka, T. *Tetrahedron Lett.* **1983**, *24*, 2653−2656. (d) Keck, G.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265−268.

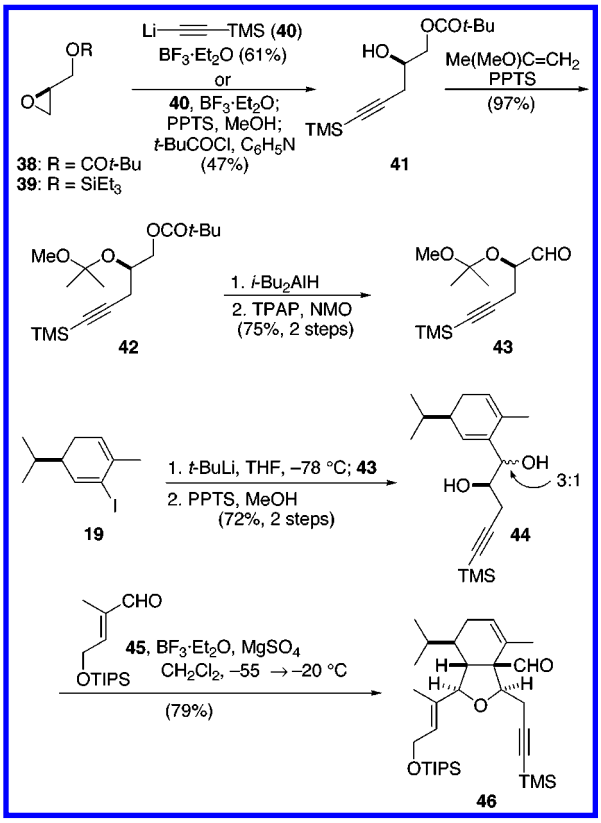
discharge of the acetonide provided **31** as a 5:1 mixture of epimeric triols; literature precedent, weaker in this case, again suggests that the major isomer has the *anti* configuration.[40] Selective silylation of the primary hydroxyl group of **31** gave rise to silyloxy diol **32**.

Condensation of cyclohexadienyl diol **30** or **32** with *trans*-crotonaldehyde in the presence of 1.1 equiv of $BF_3{\cdot}Et_2O$ and excess $MgSO_4$ provided hexahydroisobenzofurans **33** or **35**, respectively, in good yield. Analogous condensation of **30** with *trans*-cinnamaldehyde delivered hexahydroisobenzofuran **34** in nearly quantitative yield. The relative configuration of these products was established by ^{1}H NMR NOE experiments.[27]

The tertiary alcohol stereocenter C3 in all cladiellin diterpenes likely has the *R* absolute configuration.[4−8] Thus, we examined the possibility of both constructing the hexahydroisobenzofuran moiety and installing this stereocenter in a Prins−pinacol reaction. Unfortunately, all attempts to realize such a construction were unsuccessful. For example, attempted condensations of **32** with α,*β*-epoxy aldehyde **36** or α-silyloxy aldehyde **37** under the conditions used to generate **33**−**35** did not produce detectable amounts of formyl hexahydroisobenzofuran products.[27] That the nonsuccess of the Prins−pinacol reactions in these cases is the result of steric congestion at the α-position of the aldehyde is suggested by the failure of the related Prins−pinacol reaction of **30** and pivaldehyde. Our inability to carry out Prins−pinacol condensation-rearrangement with α-oxygenated aldehydes **36** and **37**, as well as related failures with other aldehydes bearing α-methyl and α-oxygen substituents (vide infra), established that the C3 stereocenter would have to be installed after assembly of the hexahydroisobenzofuran ring.

First Generation Total Synthesis of 6-Acetoxycladiell-7(16),11-dien-3-ol (Deacetoxyalcyonin Acetate, 6). We turned to implement the strategy for total synthesis of cladiellin diterpenes depicted in Scheme 2, with 6-acetoxycladiell-7(16),-11-dien-3-ol (**6**) as our initial synthesis target. In this inaugural endeavor, we chose (*E*)-2-methyl-4-silyloxy-2-butenal as the aldehyde component of the central Prins−pinacol reaction with the aim of ultimately setting the C3 stereocenter by Sharpless asymmetric epoxidation of an (*E*)-allylic alcohol intermediate.[41] Furthermore, we selected a 3-(trimethylsilyl)-2-propynyl side chain to be the precursor of the 2-iodo-2-propenyl unit that was to be employed at a late stage to forge the oxacyclononane ring (i.e., $R^2 = C_2TMS$ in Scheme 2). The synthesis of cyclohexadienyl diol **44** began with regioselective opening[42] of (*S*)-glycidyl pivalate (**38**)[43] with lithium (trimethylsilyl)acetylide (**40**) in the presence of $BF_3{\cdot}Et_2O$ to furnish alcohol **41** (Scheme 4). On a multigram scale, it was preferable to perform the epoxide opening with triethylsilyl (TES)-protected (*S*)-(−)-glycidol **39**.[44] In this latter case, the crude product was first treated with pyridinium *p*-toluenesulfonate (PPTS) in MeOH to remove the TES group; the resulting primary alcohol was then selectively acylated with pivaloyl chloride in pyridine to provide **41**. Protection of the hydroxyl group of **41** as a 1-methyl-1-methoxyethyl ether, removal of the pivalate protecting group from **42** with *i*-Bu_2AlH, and finally oxidation of the

Scheme 4



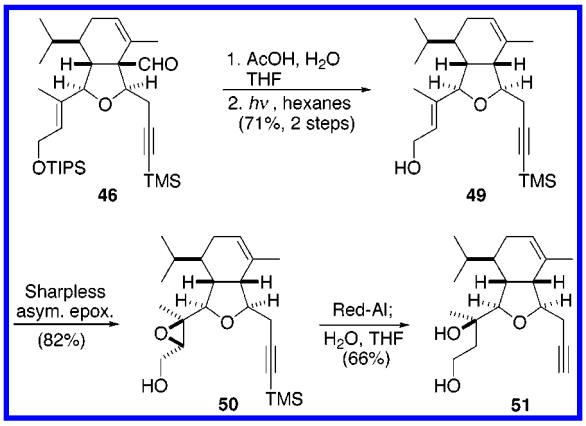
derived primary alcohol with catalytic tetra-*n*-propylammonium perruthenate (TPAP)[45] and *N*-methylmorpholine *N*-oxide (NMO) gave (*R*)-α-alkoxy aldehyde **43** in 75% overall yield. Coupling of the dienyllithium species derived from cyclohexadienyl iodide **19** with **43** and subsequent treatment of the resulting adduct with PPTS in MeOH gave cyclohexadienyl diol **44** as a 3:1 mixture of *anti* (Felkin−Ahn) and *syn* allylic alcohol epimers. The relative configuration of these epimers followed unambiguously from ^{1}H NMR NOE analysis of the corresponding acetonide derivatives.

Cyclohexadienyl diol **44** forms aromatic degradation products in air or in the presence of acids. It was thus necessary to handle this intermediate under an inert atmosphere in base-washed glassware, though it could be stored indefinitely at −78 °C in a degassed benzene matrix. The choice of the fragile 1-methyl-1-methoxyethyl group to protect the homopropargylic hydroxyl functionality of **43** was dictated by the instability of **44** under acidic conditions, even though the propensity of the 1-methyl-1-methoxyethyl group to be cleaved by traces of acid required that intermediates **42** and **43** be employed in subsequent transformations immediately upon their formation.[46]

For the second component of the Prins−pinacol reaction we chose (*E*)-2-methyl-4-(triisopropylsilyloxy)-2-butenal (**45**), an intermediate that could be accessed in high yield by allylic oxidation[47] of the triisopropylsilyl (TIPS) derivative of 3-methyl-2-buten-1-ol.[48] In the first pivotal step of the synthesis,

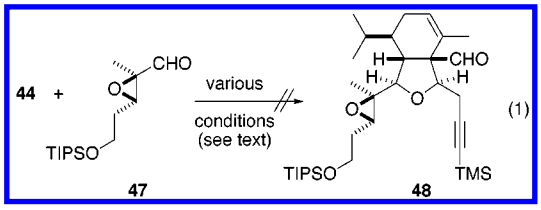
(40) Jurczak, J.; Pikul, S. Bauer, T. *Tetrahedron* **1986**, *42*, 447−488.
(41) (a) Katsuki, T.; Martin, V. S. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1996; Vol. 48, pp 1−299. (b) Hanson, R.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922−1925. (c) Rossiter, B. E.; Sharpless, K. B. *J. Org. Chem.* **1984**, *49*, 3707−3711. (d) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974−5976.
(42) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391−394.
(43) Molander, G. A.; Bobbitt, K. L. *J. Org. Chem.* **1992**, *57*, 5031−5034.
(44) Mori, Y.; Asai, M.; Okumura, A.; Furukawa, H. *Tetrahedron* **1995**, *51*, 5299−5314.
(45) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639−666.
(46) Attempts to improve the efficiency of the dienyl iodide−aldehyde coupling step by using α-silyloxy analogues of aldehyde **43** were unsuccessful: removal of a TBDMS-protecting group from the coupling adduct resulted in the formation of uncharacterized products, whereas dienyllithium addition to the TES-protected analogue of aldehyde **43** provided the desired coupling adduct in low yield because of competing enolization of the aldehyde.
(47) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526−5528.

Scheme 5



cyclohexadienyl diol **44** was condensed with an excess of (*E*)-enal **45** in the presence of 1.1 equiv of $BF_3{\cdot}Et_2O$ to deliver a single (^{1}H NMR analysis) hexahydroisobenzofuran **46** in 79% yield.

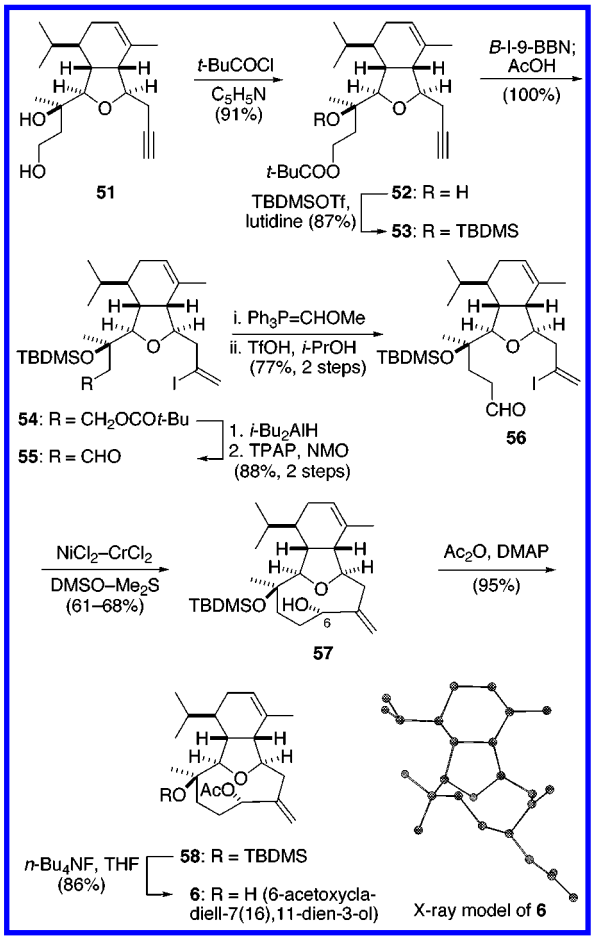
Because the synthesis of cladiellin diterpenes would be simplified considerably if the C3 stereocenter could be introduced in the Prins−pinacol step, we also examined the reaction of cyclohexadienyl diol **44** with aldehyde **47** (eq 1). Not only did the conditions that delivered **46** in high yield not lead to the formation of **48**, but other reaction conditions surveyed[49] also failed to deliver this product. In all cases, only decomposition of **44** was observed.



Returning to the synthesis of **6**, the next objective was to remove the formyl group of hexahydroisobenzofuran **46** without loss of stereochemistry at the allylic ring junction (Scheme 5). That such an outcome might be realized by photochemical activation was suggested by early studies of Schaffner and coworkers on photochemical deformylation of cyclic β,γ-unsaturated aldehydes.[32] In the event, irradiation of a hexane solution of hexahydroisobenzofuran **46** in a Pyrex reaction vessel with a medium-pressure mercury lamp (100 W) effected deformylation in moderate yield (∼50%). However, if the TIPS group was removed by first exposing **46** to dilute acetic acid, photolytic deformylation proceeded more cleanly and hexahydroisobenzofuran **49** was isolated in 71% overall yield from **46**. Although the deformylation step was not examined in detail until a second generation synthesis, approximately 10% of an isomer (undoubtedly the tetrasubstituted alkene regioisomer) was detected; this isomer could be removed from **49** by careful silica gel chromatography.

We next attended to introduction of the C3 tertiary hydroxyl group. Sharpless asymmetric epoxidation[41] of (*E*)-allylic alcohol **49** provided *trans*-2,3-epoxy alcohol **50** as a 19:1 mixture (by ^{1}H NMR analysis) of diastereomers. Exclusion of water by adding powdered 4 Å molecular sieves to the reaction mixture as well as to the solution of *t*-BuO_2H was critical for obtaining

Scheme 6



reproducibly high yield and high stereoselectivity in this epoxidation reaction.[41] Finally, hydroxyl-directed reductive opening[50] of **50** with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) and cleavage of the trimethylsilyl group with aqueous NaOH (generated in situ by addition of H_2O to the aluminum-alkoxide solution) delivered diol **51** in 54% overall yield from **49**.

With the six stereocenters common to cladiellin diterpenes now in place, we turned to elaboration of the side chains in preparation for forming the oxacyclononane ring (Scheme 6). Sequential protection of **51** by reaction with pivaloyl chloride and TBDMSOTf yielded **53**. Regioselective iodoboration of the alkyne group of **53** using *B*-iodo-9-borabicyclo[3.3.1]nonane (*B*-I-9-BBN) and subsequent in situ protonolysis of the resulting vinyl borane provided vinyl iodide **54**.[51] The use of freshly prepared *B*-I-9-BBN[52] (which could be stored over a piece of copper wire in a sealed tube away from light) was essential to the efficiency of this process, because employment of commercially available *B*-I-9-BBN resulted in partial hydroboration of the trisubstituted cyclic alkene due to contamination of this reagent with 9-BBN. Discharge of the pivalate group from **54** using *i*-Bu_2AlH and oxidation of the resulting primary alcohol using TPAP/NMO[45] furnished aldehyde **55**. Finally, this inter-

(48) Betzemeier, B.; Lhermitte, F.; Knochel, P. *Synlett* **1999**, 489−491.

(49) These included: 0.5 equiv of $SnCl_4$ in $MeNO_2$ (0 °C → 23 °C), 1.0 equiv of CF_3SO_3H in $MeNO_2$ (0 °C), and 1.0 equiv of *p*-TsOH·H_2O and $MgSO_4$ in $MeNO_2$ or CH_2Cl_2 (23 °C).

(50) (a) Viti, S. M. *Tetrahedron Lett.* **1982**, *23*, 4541−4544. (b) Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719−2722. (c) Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1378−1380.

(51) (a) Suzuki, A. In *Reviews on Heteroatom Chemistry*; Oae, S., Ed.; MYU: Tokyo, 1997; Vol. 17, pp 271−314. (b) Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731−734.

(52) Brown, H. C.; Kulkarni, S. U. *J. Organomet. Chem.* **1979**, *168*, 281−293.

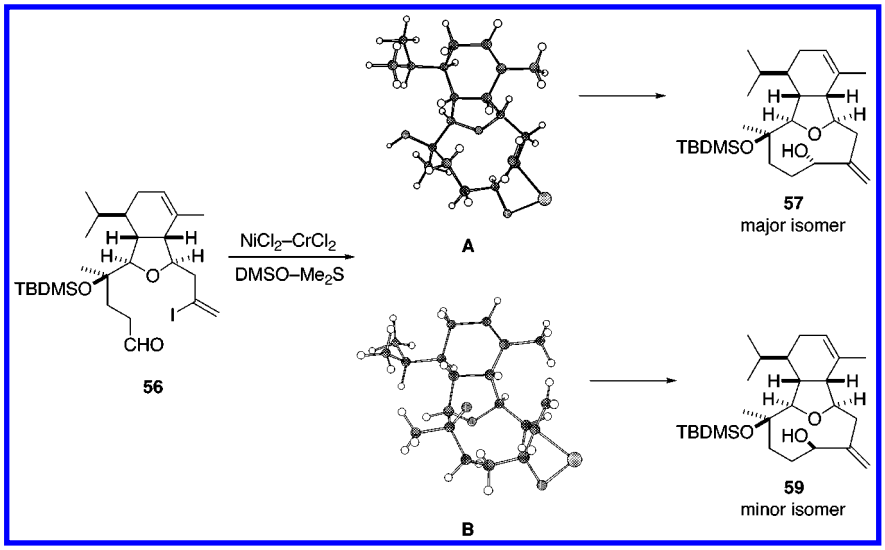


Figure 4. Stereochemical analysis of the intramolecular Nozaki−Hiyama−Kishi coupling to form **57**.

mediate was homologated by sequential treatment with (methoxymethylene)triphenylphosphorane[53] and triflic acid to give rise to **56**.

Having developed a viable route to vinyl iodide aldehyde **56**, we focused on closure of the oxacyclononane ring. Using conditions reported by Kishi,[29b] **56** was treated at room temperature with excess $CrCl_2$ and catalytic $NiCl_2$ in dry, degassed DMSO containing 1 vol % Me_2S to provide **57** in 61−68% yield. This tricyclic ether, which is the intermediate of divergence in our syntheses of various cladiellin diterpenes, was produced as a >20:1 mixture of C6 epimers with the desired *S*-epimer predominating. Acetylation of **57** with acetic anhydride and DMAP in pyridine furnished **58,** which upon exposure to *n*-Bu_4NF gave 6-acetoxycladiell-7(16),11-dien-3-ol (deacetoxyalcyonin acetate, **6**), mp 140−142 °C, in 82% yield. Synthetic **6** exhibited 500 MHz ^{1}H NMR, 125 MHz ^{13}C NMR, IR, and HRMS properties consistent with those reported for the natural product.[10] Moreover, single-crystal X-ray analysis rigorously verified the structure of synthetic **6**.[27] The optical rotation of synthetic **6** was found to be $[\alpha]^{25}_D$ −34.6 (*c* 1.0, $CHCl_3$), whereas natural **6**, which was described as an oil, was reported to have a rotation of $[\alpha]^{25}_D$ −131 (*c* 0.13, $CHCl_3$).[10]

The >20:1 stereoselection seen in the intramolecular vinylchromium−aldehyde coupling of **56** is striking.[30,31] Although vinylchromium(III) dihalide intermediates are commonly viewed as the nucleophilic species in reactions of this general type, to the best of our knowledge the nature (or even the stoichiometry) of the carbon−carbon bond-forming step has not been delineated.[30] Possibilities for this step include a four-centered process involving one molecule of the vinylchrominium species or a six-centered process involving two molecules of the chromium reagent. As a result of this uncertainty, any rationale for the observed stereoselection seen in forming **57** is highly speculative. Although we stress this important proviso, we note that a four-centered process rationalizes the observed stereoselectivity. As depicted in Figure 4, a plausible four-centered assembly **A** leading to the observed product **57** does not suffer from transannular or eclipsing interactions in the incipient nine-membered ring. In contrast, the best conformation we have found for the diastereomeric four-centered assembly **B** is destabilized by both transannular and eclipsing interactions.

(53) (a) Wittig, G.; Schlosser, M. *Chem. Ber*. **1961**, *94*, 1373−1383. (b) Levine, S. G. *J. Am. Chem. Soc.* **1958**, *80*, 6150−6151.

Total Synthesis of Cladiell-11-ene-3,6,7-triol (1). Because a sample of natural 6-acetoxycladiell-7(16),11-dien-3-ol (**6**) is no longer available,[54] we decided to pursue the discrepancy in optical rotations of synthetic and natural **6** by converting **57** to cladiell-11-ene-3,6,7-triol (**1**). Triol **1** had been isolated as a crystalline solid from the same coral species as **6**, and a sample was available for direct comparison.[54] Conformational analysis of the oxacyclononane ring of **57**, as well as examination of the X-ray model of **6** (see Scheme 6), suggested that hydroxyl-directed epoxidation of the exocyclic methylene group of **57** would take place from the peripheral α-face. In the event, epoxidation of **57** with $VO(acac)_2$/*t*-BuO_2H[55] occurred with exquisite facial selectivity to deliver a single epoxy alcohol **60** in excellent yield (Scheme 7). Regioselective opening of this product with *i*-Bu_2AlH[56] provided diol **61**, which upon treatment with *n*-Bu_4NF gave rise to cladiell-11-ene-3,6,7-triol (**1**), mp 205−206 °C. Synthetic **1** exhibited 500 MHz ^{1}H NMR, 125 MHz ^{13}C NMR, IR, HRMS, melting point, and chromatographic properties that were indistinguishable from those of the coral extract.[4c,54] The measured optical rotations of synthetic **1** and natural **1** also were identical: $[\alpha]^{25}_D$ −12.3 (*c* 1.0 or *c* 0.4, $CHCl_3$).[57]

If the TBDMS group of tricyclic allylic alcohol **57** was removed to generate diol **62** prior to hydroxyl-directed epoxidation, a tetracyclic diol product was formed in nearly quantitative yield during the epoxidation event (Scheme 7). This product is assigned structure **64** on the basis of its NMR properties and the expectation that the C3 hydroxyl group of putative epoxy diol intermediate **63** would be well positioned to participate in metal-promoted transannular epoxide ring opening.[6a,13] It did not escape our attention that the ready formation of **64** from cladiellin diol **62** suggested a direct approach for synthesizing **7**.

Second-Generation Formal Total Syntheses of Cladiell-11-ene-3,6,7-triol (1) and 6-Acetoxycladiell-7(16),11-dien-3-ol (6). Exploiting Substrate Control to Set the C3 Stereo-

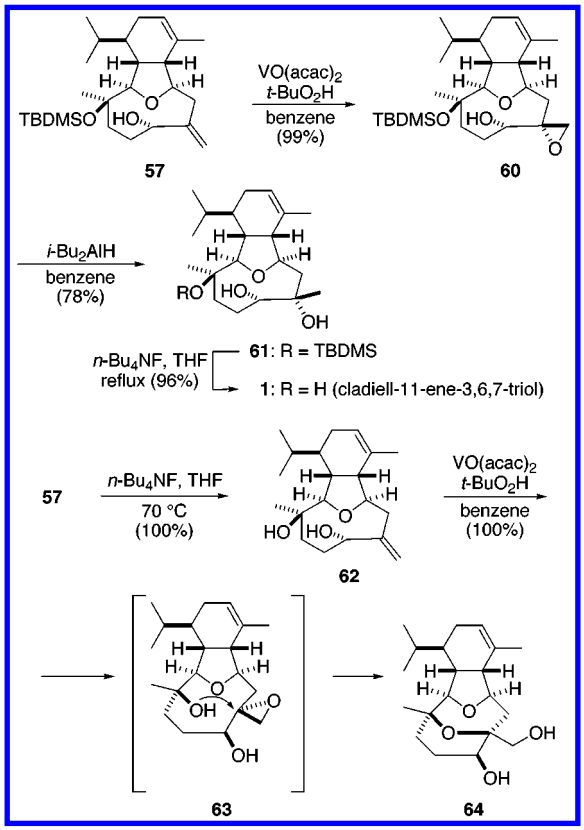
(54) We thank Professor Y. Uchio for exchange of information and for providing a comparison sample of **1**.

(55) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136−6137.

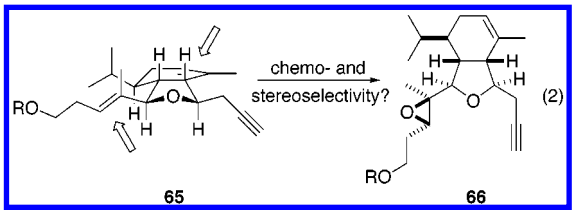
(56) Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597−3600.

(57) (a) A rotation of $[\alpha]^{25}_D$ −16.1 (*c* 0.75, $CHCl_3$) was reported for natural **1**.[4c] (b) The identity of the rotations we measure for crystalline synthetic and natural **1** strongly suggests that natural **6**[10] was contaminated with an impurity having a large negative rotation at the sodium D line.

Scheme 7

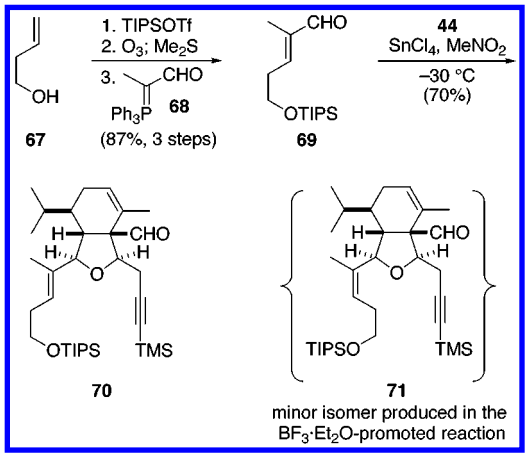


center. In our first-generation synthesis of 6-acetoxycladiell-7(16),11-dien-3-ol (**6**), the hexahydroisobenzofuran moiety was assembled with the alkene side chain being "one-carbon short" to allow reagent control to be employed to introduce oxidation at C3. A more appealing strategy would be to introduce the required five carbons of the left-hand side chain directly in the Prins−pinacol step. Such an approach would be possible if the topography of the hexahydroisobenzofuran and the homoallylic oxygen functionality of a 1-methyl-1-butenyl side chain would regulate chemoselectivity and face selection in the epoxidation event. Because it appeared that epoxidation of the side chain from the face of the hexahydroisobenzofuran oxygen would be favored in conformations of intermediates such as **65** that minimized destabilizing $A^{1,2}$ and $A^{1,3}$ interactions (eq 2),[58] we developed a second entry to cladiellin diterpenes.

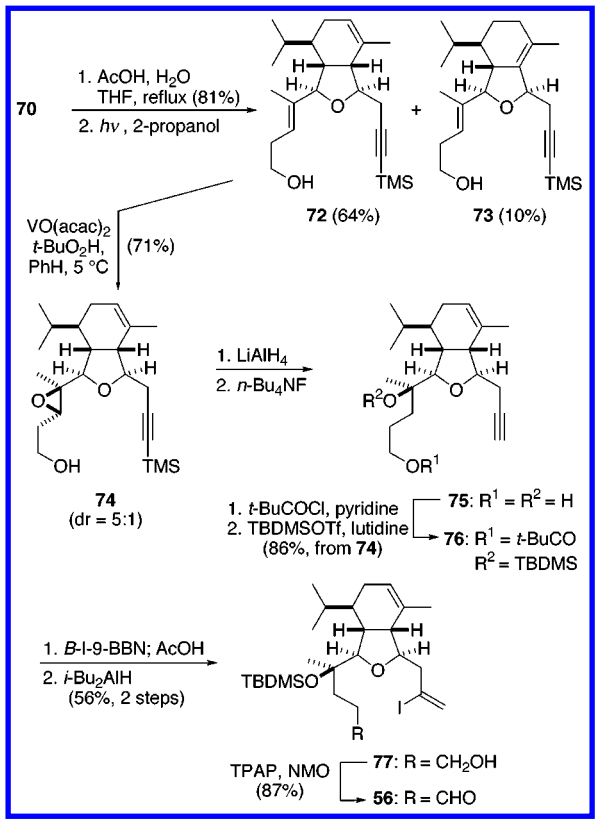


This second generation synthesis began with the preparation of (*E*)-2-methyl-5-(triisopropylsilyloxy)-2-pentenal **69** from commercially available 3-butene-1-ol (Scheme 8). Conventional silylation of **67** followed by ozonolysis provided 3-(triisopropylsilyloxy)propanal,[59] which upon reaction with commercially available ylide **68** furnished isomerically pure **69** in 87% overall yield. Reaction of excess **69** with cyclohexadienyl diol **44** was best realized in the presence of 0.5 equiv of $SnCl_4$ in $MeNO_2$

Scheme 8



Scheme 9



at −30 °C. Under these conditions, hexahydroisobenzofuran **70** was produced in 70% yield. It is of interest that attempts to execute the condensation-rearrangement of **44** and **69** using 1.1 equiv of $BF_3{\cdot}Et_2O$ (in CH_2Cl_2 at −55 → −20 °C) provided an inseparable 9:1 mixture of **70** and another hexahydroisobenzofuran product, later identified as **71** (vide infra). The configuration of the 1-methyl-1-butenyl side chains of **70** and **71** was established easily by ^1H NMR NOE experiments. The reason for partial isomerization of the double bond of the (*E*)-α-methyl-α,*β*-unsaturated aldehyde during the Prins−pinacol reaction in this instance, but not in the formation of **46** under identical conditions, is not fully understood.

The homoallylic ether and propargyl side chains of **70** were then elaborated as summarized in Scheme 9. The TIPS-protecting group was first removed by heating **70** with aqueous acetic acid. The yield of **72** arising from photolytic deformylation[32] of this intermediate was found to be solvent-dependent: deformylation of **70** in 2-propanol provided **72** in 64%

(58) (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370. (b) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860.

(59) Frye, S. V.; Eliel, E. L. *J. Am. Chem. Soc.* **1988**, *110*, 484−489.

yield, whereas the yield of **72** was ~45% when hexane or pentane was used as the solvent. Also isolated from this photodeformylation and fully characterized was tetrasubstituted alkene regioisomer **73**, which was separated easily from **72** by medium-pressure liquid chromatography (MPLC) on silica gel. Homoallylic alcohol-directed epoxidation of **72** with $VO(acac)_2$/*t*-BuO_2H[60] provided an inseparable 5:1 mixture of *trans*-3,4-epoxy alcohols, with the desired *β*-diastereomer **74** predominating.[61] Reductive opening of **74** necessitated more forcing conditions ($LiAlH_4$) than those employed in the similar opening of *trans*-2,3-epoxy alcohol **50**; for example, attempts to reductively cleave epoxide **74** using Red-Al failed, either at room temperature or in refluxing THF. Desilylation of the alkyne group of the diol product with *n*-Bu_4NF yielded **75**, whose hydroxyl groups were differentially protected to provide **76**. Iodoboration-protonolysis[51] of the alkyne of **76** and subsequent cleavage of the pivaloyl-protecting group then generated iodo alcohol **77**. The minor C3 epimer, which had been carried forward since the epoxidation step, could be removed by silica gel chromatography at this stage. Oxidation of **77** with TPAP/NMO[45] yielded iodoaldehyde **56**, thus completing formal total syntheses of **1** and **6**. This second-generation route to intermediate **56** is one step shorter than our original synthesis and proceeds in similar overall yield.

A Third Approach to Cladiellin Diterpenes that Defines a Potential Route for Total Synthesis of Briarellin and Asbestinin Diterpenes. Total Syntheses of Sclerophytin A, the Putative Tetracyclic Structure 7 of Sclerophytin A, and Formal Total Syntheses of Cladiell-11-ene-3,6,7-triol (1) and 6-Acetoxycladiell-7(16),11-dien-3-ol (6). A third approach to cladiellin diterpenes was developed in part to explore the possibility of preparing asbestinin and briarellin diterpenes in the future by related Prins−pinacol strategies. As specifically outlined for briarellin E (**2**) in Figure 5, the cis relationship of the C3 methyl and C4 oxygen functionalities of asbestinin and briarellin diterpenes suggests that the oxepane rings of these tetracyclic diterpenes might be constructed from hexahydroisobenzofurans such as **78** or **79** (R = leaving group) that contain *cis*-3,4-epoxy alcohol side chains. An obvious precursor of such intermediates would be hexahydroisobenzofuran **80** having a protected (*Z*)-1-methyl-4-hydroxy-1-butenyl side chain.

An important issue raised by the prospect of employing **80** would be the configurational stability of a conjugated *Z* double bond during the Prins−pinacol assembly of the hexahydroisobenzofuran nucleus. Because isomerization of a (*Z*)-α,*β*-unsaturated oxonium ion to its more stable *E* stereoisomer could be quite facile, success of the desired construction would depend on the facility of the Prins cyclization step (e.g., **83** → **84**, eq 3). Since this issue had not been investigated previously in any Prins−pinacol reaction,[23−26] we chose to examine it in the context of a projected total synthesis of tetracyclic diether **7**. At the time, we viewed **7** as the most likely structure of sclerophytin A.[6a,13] We envisaged tetracyclic diether **7** as arising from transannular oxymercuration of cladiellin diol **62** directed by the allylic alcohol,[62] followed by reductive demercuration and photoinduced isomerization of the endocyclic double bond.[63]

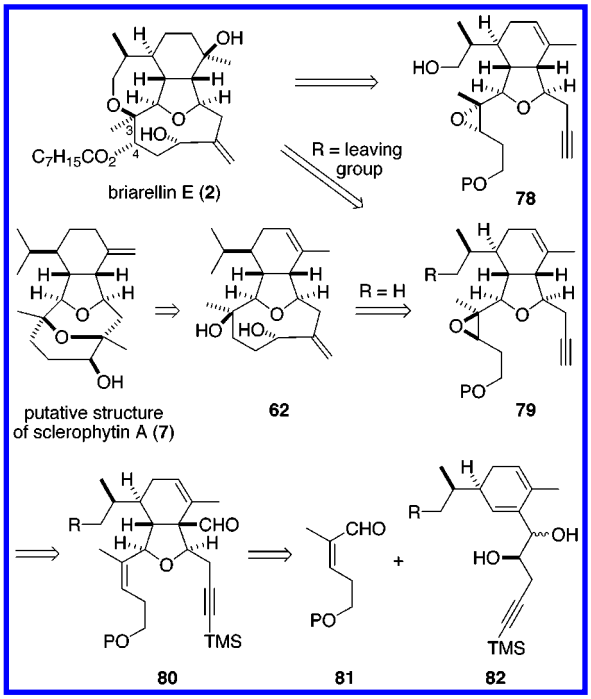
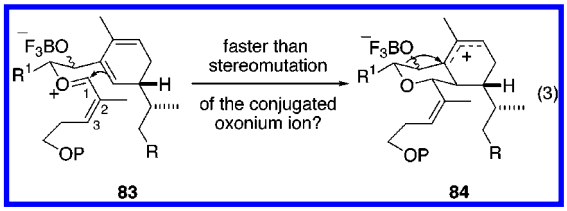


Figure 5. Plan for the synthesis of cladiellin, briarellin, and asbestinin diterpenes from Prins−pinacol reaction of a (*Z*)-α,*β*-unsaturated aldehyde and a cyclohexadienyl diol.

We planned to obtain **62** from *cis*-3,4-epoxy ether **79** (R = H) along the lines developed in our earlier syntheses of cladiellin diterpenes.



That the geometry of the alkene double bond of (*Z*)-α,*β*-unsaturated aldehyde **81** might well be preserved during the projected condensation-rearrangement sequence was suggested by extensive studies of oxygen-substituted allylcarbenium ions.[64] Childs has generated a variety of hydroxy- and methoxyallylcarbenium ions in acidic media and investigated photochemical and thermal isomerization about the C1−O and C2−C3 bonds of these species. For example, treatment of the dimethylacetal of *trans*-2-methyl-2-butenal with FSO_3H at −78 °C produced the corresponding methoxyallylcarbenium ion having exclusively the *E* configuration about the C1−O bond.[64c,g] Irradia-

(60) Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7690−7692.

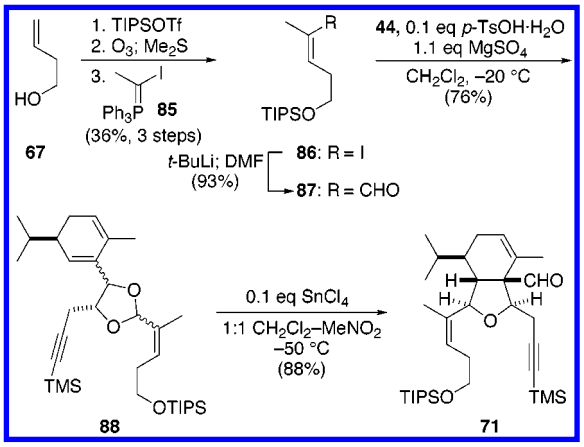
(61) Epoxidation using methyl(trifluromethyl)dioxirane in MeCN−H_2O at 0 °C resulted exclusively in nonstereoselective epoxidation of the cyclic double bond, while epoxidation with (*i*-$PrO)_4Ti$/*t*-BuO_2H and (+)- or (−)-diethyl tartrate in CH_2Cl_2 was too sluggish to be practical.

(62) (a) Henbest, H. B.; McElhinney, R. S. *J. Chem. Soc.* **1959**, 1834−1873. (b) Henbest, H. B.; Nicholls, B. *J. Chem. Soc.* **1959**, 227−236.

(63) (a) Kropp, P. J. In *Organic Photochemistry;* Padwa, A., Ed.; Marcel Dekker: New York, 1979; Vol. 4, pp 1−142. (b) Marshall, J. A.; Hochstetler, A. R. *J. Am. Chem. Soc.* **1969**, *91*, 648−657.

(64) For discussions concerning the stereomutation of alkoxycarbenium ions and oxygen-substituted allylcarbenium ions, see: (a) Childs, R. F.; Shaw, G. B. In *Organic Photochemistry*; Padwa, A., Ed.; Marcel Dekker: New York, 1991; Vol. 11, pp 111−225. (b) Broeker, J. L.; Hoffmann, R. W.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5006−5017. (c) Blackburn, C.; Childs, R. F.; Cremer, D.; Gauss, J. *J. Am. Chem. Soc.* **1985**, *107*, 2442−2448. (d) Cremer, D.; Gauss, J.; Childs, R. F.; Blackburn, C. *J. Am. Chem. Soc.* **1985**, *107*, 2435−2441. (e) Forsyth, D. A.; Osterman, V. M.; DeMember, J. R. *J. Am. Chem. Soc.* **1985**, *107*, 818−822. (f) Childs, R. F.; Blackburn, C. *J. Chem. Soc., Chem. Comm.* **1984**, 812−813. (g) Childs, R. F.; Hagar, M. E. *Can. J. Chem.* **1980**, *58*, 1788−1794. (h) Childs, R. F.; Hagar, M. E. *J. Am. Chem. Soc.* **1979**, *101*, 1052−1053. (i) Childs, R. F.; Lund, E. F.; Marshall, A. G.; Morrisey, W. J.; Rogerson, C. V. *J. Am. Chem. Soc.* **1976**, *98*, 5924−5931. (j) Olah, G. A.; Halpern, Y.; Mo, Y. K.; Liang, G. *J. Am. Chem. Soc.* **1972**, *94*, 3554−3561. (k) Brouwer, D. M. *Tetrahedron Lett.* **1968**, 453−457.

Scheme 10

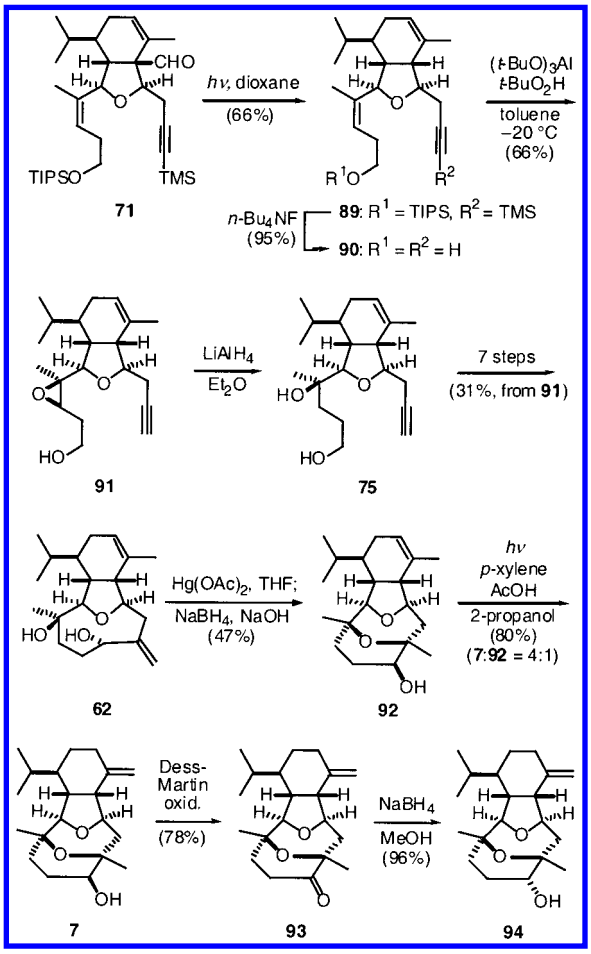


tion of this species at −70 °C induced isomerization about the C2−C3 bond to give the *Z* isomer. This isomer was stable at room temperature, although it underwent *Z* → *E* isomerization upon prolonged heating at 50 °C. Stereomutation about the C1−O bond was concluded to occur by rotation,[64c] whereas stereomutation about the C2−C3 bond was proposed to take place by an addition−rotation−elimination process.[64g] It appeared from these studies that finding reaction conditions that minimized conjugate addition of nucleophiles to C3 of oxonium ion **83** (eq 3), or related precursors, would be essential to the success of our endeavors.

The synthesis of **7** began with the preparation of (*Z*)-vinyl iodide **86** by Wittig reaction of 3-(triisopropylsilyloxy)propanal[59] with iodophosphorane **85**[65] (Scheme 10). After removal of a trace of the (*E*)-vinyl iodide stereoisomer by flash chromatography on $AgNO_3$-impregnated silica gel, **86** was converted to the corresponding vinyllithium species and then formylated with DMF to provide isomerically pure (*Z*)-enal **87**. Initial attempts to accomplish the direct condensation-rearrangement of **87** and cyclohexadienyl diol **44** delivered a hexahydroisobenzofuran product in which the (*Z*)-alkene side chain had been partially isomerized.[66] As a result, a two-step procedure was developed whereby **44** and **87** were first condensed (catalytic *p*-TsOH·H_2O and $MgSO_4$ in CH_2Cl_2 at −78 → −20 °C) to provide acetal **88**. Prins−pinacol rearrangement of this mixture of diastereomers proceeded efficiently in the presence of 0.1 equiv of $SnCl_4$ in a 1:1 mixture of CH_2Cl_2-$MeNO_2$ at −50 °C to deliver hexahydroisobenzofuran **71** in 88% yield. Under these conditions, the (*E*)-alkene stereoisomer of **71** (**70**, which was available from our earlier studies) could not be detected by ^{1}H NMR analysis of the crude reaction product.

The putative tetracyclic structure **7** of sclerophytin A was then assembled from hexahydroisobenzofuran **71** as summarized in Scheme 11. Photolytic deformylation[32] of **71** proceeded slightly more cleanly in 1,4-dioxane than in 2-propanol to furnish hexahydroisobenzofuran **89** in 66% yield, after removal of ∼10% of the tetrasubstituted alkene regioisomer by MPLC on silica gel. Discharge of both silyl groups of **89** gave **90**, which then underwent homoallylic alcohol-directed epoxidation with (*t*-BuO)$_3$Al/*t*-BuO_2H[67] to provide **91** in 66% yield after removal of the minor epoxide stereoisomer (dr = 6.6:1).[68] Stereoselection in this reaction was highest when (*t*-BuO)$_3$Al/*t*-BuO_2H[67] was employed as the oxidant. Surprisingly, when

Scheme 11



$VO(acac)_2$/*t*-BuO_2H[60] was employed as the oxidant, stereoselection in the formation of **91** was lower than that realized in the corresponding oxidation of the (*E*)-homoallylic alcohol congener **72** (dr = 1.5:1 vs dr = 5:1). This trend is contrary to the expected[58] higher preference for oxidation to take place by way of eclipsed alkene conformation **65** (eq 2) in the *Z* series. Regioselective reductive opening of *cis*-3,4-epoxy alcohol **91** with $LiAlH_4$ provided diol **75**, an intermediate that we had accessed earlier by reductive ring opening of the corresponding *trans*-3,4-epoxy alcohol **74**.

Conversion of **75** to diol **62** using chemistry similar to that developed during our first and second generation cladiellin diterpene total syntheses set the stage for final elaboration to tetracyclic diether **7** (Scheme 11). Sequential treatment of **62** with a slurry of $Hg(OAc)_2$ in THF, followed by reduction of the resulting organomercurial with basic aqueous $NaBH_4$,[69] furnished a single tetracyclic diether **92** in 47% yield (66% based upon consumed **62**). At short irradiation times using a medium-pressure mercury lamp (450 W) fitted with a Vycor filter, and in the presence of acetic acid, light-induced isomerization[63] of the endocyclic double bond of **92** was realized in high yield to give **7** and **92** in a 4:1 ratio. Carrying this reaction to greater conversion led to some photodegradation and did not increase

(65) Wang, J. C. T.; Zhao, K. *Tetrahedron Lett.* **1994**, *35*, 2827−2828.

(66) Two conditions were examined: exposing the reaction partners to 0.5 equiv of $SnCl_4$ and excess $MgSO_4$ in 1:1 $MeNO_2$−CH_2Cl_2 at −50 °C or to 0.1 equiv of *p*-TsOH·H_2O and excess $MgSO_4$ in 1:1 $MeNO_2$−CH_2Cl_2 at 0 °C.

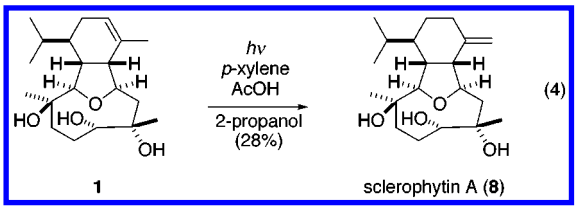
(67) (a) Takai, K.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3791−3795. (b) Hiyama, T.; Kimura, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1037−1040. (c) Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 1657−1660.

(68) The minor epoxide isomer (10% yield) was removed by flash column chromatography on silica gel and fully characterized; see Supporting Information.

(69) Bordwell, F. G.; Douglass, M. L. *J. Am. Chem. Soc.* **1966**, *88*, 993−999.

the amount of **7** produced. Spectral data for **7**, however, did not match those reported for sclerophytin A.[12] At this stage we considered the possibility that sclerophytin A was the alcohol epimer of **7** and consequently oxidized **7** to give ketone **93**; the minor endocyclic alkene isomer could be easily removed at this point by flash chromatography on silica gel. Reduction of **93** with $NaBH_4$ proceeded with high selectivity from the less-hindered β-face to generate **94** in high yield. NMR data for this product were again distinctly different from those reported for sclerophytin A.[12]

The obvious differences between **7** and **94** and sclerophytin A prompted us to look for a sample of natural sclerophytin A, at which point we learned of independent investigations in the Paquette group where **7**, **93**, and **94** had also been prepared.[14] These workers had reinvestigated the natural isolate and proposed that sclerophytin A was cladiell-11(17)-ene-3,6,7-triol (**8**).[16a] Since this structure was simply the double bond regioisomer of cladiellin triol **1**, we were able to quickly confirm this conclusion by photochemically isomerizing **1** to **8** (eq 4).[70]



Conclusions

A versatile and concise strategy for the total synthesis of cladiellin diterpenes has been developed (Scheme 2). The defining step in this approach is an efficient pinacol-terminated Prins cyclization[23−26] that assembles the hexahydroisobenzofuran core and five of the six invariant stereocenters of these marine diterpenes with complete stereocontrol from two simple precursors: enantiopure cyclohexadienyl diol **44** and an α,β-unsaturated aldehyde. The final oxacyclononane ring of these natural products is formed by a highly diastereoselective intramolecular Nozaki−Hiyama−Kishi reaction.[30] The viability of this total synthesis strategy was first verified by a total synthesis of 6-acetoxycladiell-7(16),11-dien-3-ol (deacetoxyalcyonin acetate, **6**) which, when originally disclosed in 1995,[18] constituted the first total synthesis of a 2,11-cyclized cembranoid oxacyclic diterpene. This inaugural total synthesis was achieved in 20 steps and 4.3% overall yield from (*S*)-(+)-carvone and 21 steps and 3% yield from (*S*)-glycidyl pivalate. A second-generation total synthesis of **6** in which the C3 stereocenter was established using substrate, rather than catalyst, control was one step shorter and proceeded in nearly identical overall yield. The first total synthesis of cladiell-11-ene-3,6,7-triol (**1**) was realized in similar overall efficiency from advanced tricyclic intermediate **57**.

As a prelude to future efforts to synthesize members of the more complex briarellin and asbestinin diterpene families, we developed a variant of this strategy where the α,β-unsaturated aldehyde component of the pivotal Prins−pinacol reaction had the *Z*, rather than the more stable *E*, configuration (Figure 5). This approach was employed to prepare the most likely stereoisomer of the purported structure[12] of sclerophytin A, tetracyclic ether **7**. Neither **7** nor its secondary alcohol epimer **94** was identical with sclerophytin A, thus requiring that the structural assignment for this diterpene be revised. A similar conclusion was arrived at contemporaneously by the Paquette group, who after reexamining a sample of natural sclerophytin A proposed structure **8** for this natural product.[16a] We were able to confirm the correctness of this proposal by photoisomerization of the endocyclic double bond of **1** (whose structure had been rigorously established by single-crystal X-ray analysis) to complete a total synthesis of sclerophytin A (**8**).

The concise total syntheses detailed in this account further highlight the power of pinacol-terminated cationic cyclizations for assembling complex oxacyclic natural products. These studies also established for the first time that relatively unstable (*Z*)-α,β-unsaturated aldehydes could take part in Prins−pinacol constructions without erosion of double bond stereochemistry.

Experimental Section[71]

Prins−Pinacol Condensation Using $BF_3{\cdot}OEt_2$. Preparation of (1*R*,3*R*,3a*S*,7*R*,7a*R*)-7-Isopropyl-4-methyl-1-[(*E*)-1-methyl-3-(triisopropylsilyloxy)propenyl]-3-[3-(trimethylsilyl)prop-2-ynyl]-1,6,7,7a-tetrahydroisobenzofuran-3a-carbaldehyde (46). A mixture of dienyl diol **44** (350 mg, 1.1 mmol), (*E*)-enal **45** (2.9 g, 11 mmol), $MgSO_4$ (200 mg), and CH_2Cl_2 (42 mL) was cooled to −55 °C and treated dropwise with $BF_3{\cdot}Et_2O$ (0.15 mL, 1.2 mmol). The mixture was stirred at −55 °C for 3 h, allowed to warm to −20 °C, stirred for 15 min, and added to saturated aqueous NH_4Cl (40 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. Excess aldehyde **45** was removed by bulb-to-bulb distillation (150 °C, 1.0 mm), and the residue was purified by flash chromatography on silica gel (19:1 hexanes−ethyl acetate) to provide 0.45 g (79%) of **46** as a clear colorless oil: $[\alpha]^{25}_D$ +23.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.82 (s, 1 H), 5.70 (s, 1 H), 5.63 (bt, J = 5.2 Hz, 1 H), 4.24 (d, J = 4.8 Hz, 2 H), 4.07 (t, J = 6.6 Hz, 1 H), 4.01 (d, J = 9.9 Hz, 1 H), 2.73 (dd, J = 9.9, 4.0 Hz, 1 H), 2.69 (d, J = 6.6 Hz, 1 H), 2.12−1.92 (m, 3 H), 1.93 (s, 3 H), 1.66 (s, 3 H), 1.37 (m, 1 H), 1.14−0.82 (m, 22 H), 0.79 (app d, J = 7.6 Hz, 6 H), 0.14 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.2, 133.5, 132.2, 131.3, 126.4, 103.4, 89.1, 88.3, 83.8, 62.2, 60.9, 46.0, 38.8, 28.3, 24.4, 23.7, 21.7, 21.2, 21.0, 18.6, 12.6, 11.7, 0.4; IR (film) 2953, 2178, 1718, 1462, 1114 cm^{-1}; HRMS (CI) *m*/*z* 544.3775 (M, 544.3768 calcd for $C_{32}H_{56}O_3Si_2$).

Prins−Pinacol Condensation Using $SnCl_4$. Preparation of (1*R*,3*R*,-3a*S*,7*R*,7a*R*)-7-Isopropyl-4-methyl-1-[(*E*)-1-methyl-4-(triisopropylsilyloxy)but-1-enyl]-3-[3-(trimethylsilyl)prop-2-ynyl]-1,6,7,7a-tetrahydroisobenzofuran-3a-carbaldehyde (70). A mixture of cyclohexadienyl diol **44** (0.82 g, 2.7 mmol), (*E*)-enal **69** (7.2 g, 27 mmol) and $MeNO_2$ (27 mL) was cooled to −29 °C and then treated dropwise with $SnCl_4$ (0.16 mL, 1.3 mmol), and the solution was maintained at −29 °C for 12 h. The reaction mixture then was added to saturated aqueous NH_4Cl (100 mL), the aqueous layer was extracted with hexanes (3 × 100 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. Excess **69** was removed by bulb-to-bulb distillation (150 °C, 0.10 mm), and the remaining residue was purified by medium-pressure liquid chromatography (MPLC) (Lobar pre-packed column, LiChroprep Si 60 silica gel; 19:1 hexanes−ethyl acetate) to provide 1.0 g (70%) of **70** as a clear pale yellow oil: $[\alpha]^{23}_D$ +32.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6) δ 9.77 (s, 1 H), 5.55 (t, J = 6.6 Hz, 1 H), 5.45 (br s, 1 H), 4.02−3.98 (m, 2 H), 3.62−3.59 (m, 2 H), 2.83 (dd, J = 9.6, 4.2 Hz, 1 H), 2.73 (d, J = 6.4 Hz, 2 H), 2.28 (q, J = 6.8 Hz, 2 H), 1.85−1.81 (m, 5 H), 1.74 (s, 3 H), 1.53−1.49 (m, 1 H), 1.13−1.02 (m, 22 H), 0.84 (d, J = 6.6 Hz, 3 H), 0.75 (d, J = 6.6 Hz, 3 H), 0.17 (s, 9 H); ^{13}C NMR (125 MHz, C_6D_6) δ 199.6, 135.2, 131.4, 127.1, 125.8, 104.0, 88.5, 87.8, 83.7, 63.1, 62.0, 45.8, 38.9, 32.0, 27.9, 24.2, 23.4, 21.3, 20.7, 20.1, 18.3, 12.3, 11.2, −0.1; IR (neat) 2958, 2866, 2726, 2179, 1716, 1462 cm^{-1}; HRMS (FAB) *m*/*z* 557.3864 (M − H, 557.3846 calcd for $C_{33}H_{57}O_3Si_2$). Anal. Calcd for $C_{33}H_{58}O_3Si_2$: C, 70.91; H, 10.46. Found: C, 70.85; H, 10.42.

(70) This conversion was carried out only once on a small scale. It is likely that the efficiency of this conversion could be optimized to be similar to that realized in the closely related photoisomerization of **92** → **7** (64% yield).

(71) General experimental details have been described: Minor, K. P.; Overman, L. E. *J. Org. Chem.* **1997**, *62*, 6379−6387. For standard abbreviations employed in this article, see: *J. Org. Chem.* **2001**, *66*, 24A.

Prins−Pinacol Condensation of a (Z)-Enal. Preparation of (1*R*,3*R*,3a*S*,7*R*,7a*R*)-7-Isopropyl-4-methyl-1-[(*Z*)-1-methyl-4-(triisopropylsilyloxy)but-1-enyl]-3-[3-(trimethylsilyl)prop-2-ynyl]-1,6,7,-7a-tetrahydroisobenzofuran-3a-carbaldehyde (71). *p*-Toluenesulfonic acid monohydrate (0.057 g, 0.30 mmol) was added to a stirring mixture of dienyl diol **44** (0.91 g, 3.0 mmol), (*Z*)-enal **87** (0.98 g, 3.6 mmol), $MgSO_4$ (0.40 g, 3.3 mmol), and CH_2Cl_2 (6.0 mL) at −78 °C. After 30 min, the mixture was warmed to −20 °C and stirred for 2 h before being quenched with saturated aqueous $NaHCO_3$ (20 mL) and warmed to room temperature. The aqueous layer was diluted with saturated aqueous $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (3 × 40 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (98:2 hexanes−ethyl acetate) to give 1.2 g (75%) of **88** (a mixture of four diastereomers) as a clear colorless oil: diagnostic signals: ^{13}C NMR (125 MHz, $CDCl_3$) δ 98.8, 98.9, 99.3, 100.0; HRMS (ES) *m*/*z* 581.3829 (M + Na, 581.3822 calcd for $C_{33}H_{58}NaO_3Si_2$).

A stirring mixture of acetal **88** (1.2 g, 2.1 mmol), $MeNO_2$ (11 mL), and CH_2Cl_2 (11 mL) at −50 °C was treated dropwise with $SnCl_4$ (25 μL, 0.21 mmol). The resulting solution was maintained at −50 °C for 1.5 h before being quenched with saturated aqueous $NaHCO_3$ (20 mL) and warmed to room temperature. The aqueous layer was diluted with saturated aqueous $NaHCO_3$ (20 mL) and extracted with CH_2Cl_2 (5 × 40 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by medium-pressure liquid chromatography (Lobar pre-packed column, LiChroprep Si 60 silica gel; 98:2 hexanes−ethyl acetate) to give 1.0 g (88%) of **71** as a clear colorless oil: $[\alpha]^{25}_D$ +42.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.82 (s, 1 H), 5.72 (br s, 1 H), 5.54 (t, *J* = 7.2 Hz, 1 H), 4.52 (d, *J* = 10.0 Hz, 1 H), 4.07 (t, *J* = 6.5 Hz, 1 H), 3.66 (t, *J* = 7.1 Hz, 2 H), 2.82 (dd, *J* = 10.0, 3.7 Hz, 1 H), 2.70 (d, *J* = 6.4 Hz, 2 H), 2.38−2.42 (m, 1 H), 2.26−2.30 (m, 1 H), 2.01 (br s, 2 H), 1.95 (s, 3 H), 1.77 (s, 3 H), 1.34−1.39 (m, 1 H), 1.02−1.12 (m, 22 H), 0.81 (t, *J* = 6.8 Hz, 6 H), 0.12 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 133.5, 130.8, 128.3, 125.6, 102.7, 88.4, 83.0, 79.3, 63.3, 61.6, 45.3, 38.1, 31.6, 27.8, 23.7, 23.5, 21.1, 20.6, 20.4, 18.0, 17.7, 11.9, −0.2; IR (film) 2957, 2865, 2726, 2179, 1716, 1463 cm^{-1}; HRMS (FAB) *m*/*z* 559.4001 (M + H, 559.4003 calcd for $C_{33}H_{59}O_3Si_2$). Anal. Calcd for $C_{33}H_{58}O_3Si_2$: C, 70.91; H, 10.46. Found: C, 70.91; H, 10.55.

Cyclization to Form (3*R*,7*R*,8*R*,11*S*,14*R*,15*R*,16*R*)-14-(*tert*-Butyldimethylsilyloxy)-3-isopropyl-6,14-dimethyl-10-methylene-15-oxatricyclo[6.6.1.0^{0,0}]pentadec-5-en-11-ol (57). A mixture of alkenyl iodide **56** (60 mg, 0.11 mmol), chromium(II) chloride (570 mg, 6.2 mmol), $NiCl_2$ (5.0 mg, 0.040 mmol), dry and degassed DMSO (25 mL), and Me_2S (0.25 mL) was stirred at room temperature for 36 h, and then saturated aqueous NH_4Cl (25 mL) was added. The resulting mixture was stirred for 20 min, the layers were separated, the aqueous layer was extracted with ether (3 × 20 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (4:1 hexanes−ethyl acetate) to provide 31 mg (68%) of **57** as a clear colorless oil: $[\alpha]^{25}_D$ -45.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.44 (s, 1 H), 5.43 (s, 1 H), 5.21 (s, 1 H), 4.31 (m, 1 H), 4.16 (q, *J* = 3.2 Hz, 1 H), 3.73 (d, *J* = 8.1 Hz, 1 H), 2.73 (dt, *J* = 4.4, 7.7 Hz, 1 H), 2.65 (d, *J* = 8.0 Hz, 1 H), 2.42 (dd, *J* = 9.1, 4.0 Hz, 1 H), 2.38 (m, 1 H), 2.33 (dd, *J* = 14.3, 2.9 Hz, 1 H), 2.14 (m, 1 H), 2.09−1.93 (m, 2 H), 1.85 (m, 1 H), 1.72 (s, 3 H), 1.67 (m, 1 H), 1.57 (m, 2 H), 1.44 (s, 3 H), 1.34 (m, 1 H), 0.96 (d, *J* = 6.6 Hz, 3 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 0.86 (s, 9 H), 0.15 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.7, 132.3, 122.1, 113.7, 88.3, 80.2, 77.4, 74.7, 45.1, 40.4, 39.3, 38.3, 30.2, 28.4, 28.3, 27.3, 26.2, 23.1, 22.0, 21.4, 21.1, 18.3, −1.4, −1.6; IR (film) 3423, 2954, 1464, 1254, 1079 cm^{-1}; HRMS (CI) *m*/*z* 435.3287 (M + H, 435.3294 calcd for $C_{26}H_{47}O_3Si$).

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Supporting Information Available: Experimental procedures for the preparation of compounds **1**, **6**, **8**, **19**, **41**−**45**, **49**, **51**, **53**, **55**, **56**, **93**, and **94**; experimental procedures and characterization data for compounds **9**−**11**, **47**, **50**, **52**, **54**, **58**, **60**, **61**, **64**, **69**, **72**−**74**, **76**, **77**, **86**, **87**, **89**, and **90** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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