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Strategic Use of Pinacol-Terminated Prins Cyclizations in Target-Oriented Total Synthesis

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An important objective of contemporary synthesis endeavors is the development of new transformations that rapidly evolve molecular complexity in a stereocontrolled fashion. One approach toward this goal is to combine two or more distinct reactions into a single transformation, producing a process often referred to as a sequential, tandem, cascade, or domino reaction. In this Perspective, we discuss the development of one such tandem reaction, the acid-promoted (or catalyzed) Prins–pinacol rearrangement, with particular emphasis on its implementation as the key strategic element in the total synthesis of heterocyclic and carbocyclic natural products.

Introduction

Since the synthesis of organic molecules emerged as a recognizable science 175 years ago, the reasons for pursuing such undertakings have changed considerably. Wöhler's synthesis of urea from ammonium cyanate demonstrated for the first time that naturally occurring organic substances could be produced in the laboratory from simple inorganic starting materials.[1] Early practitioners of organic chemical synthesis engaged in these efforts largely to aid the elucidation of the structures of natural products extracted from terrestrial plant sources. In addition to its continued importance in structure confirmation, particularly for scarce marine natural products,[2] synthesis of organic molecules in the modern era is practiced for a wide variety of reasons: to validate the biological activity of natural products or screening leads, conduct structure–activity investigations, probe the mechanism of biological processes, prepare unnatural substances with unique properties, investigate the conceptual underpinnings of organic chemistry, and produce useful commodities.[3]

While the past 50 years have witnessed extraordinary progress in the discovery of new reagents, reactions, and synthesis strategies,[4] the tools of synthetic organic chemistry are often found lacking when confronted with the challenge of preparing even modestly elaborate molecules in a practical fashion. Better means to orchestrate the rapid evolution of molecular complexity in a stereocontrolled manner are required. One way that molecular complexity can be expeditiously constructed is by combining two or more distinct reactions into a single transformation (Figure 1).[5] A classic example of this approach is the Robinson annulation, which is illustrated by the pyridine-promoted synthesis of the Wieland–Miescher ketone (**3**) from 4-diethylamino-2-butanone (**1**) and 2-methyl-1,3-cyclohexadione (**2**).[6] During this process, four independent reactions occur sequentially: β-elimination of diethylamine from **1** to generate methyl vinyl ketone, 1,4-addition of **2** to this intermediate, intramolecular aldol condensation of the resulting adduct, and β-elimination of H_2O. A striking example of the power of this strategy for the synthesis of complex natural products, particularly when guided by biosynthetic considerations, is found in Heathcock's elegant total syntheses of the *Daphniphyllum* alkaloids.[7] In the remarkable conversion of dihydrosqualene dialdehyde **4** to dihydro-*proto*daphniphylline (**5**), at least eight distinct transformations occur during the formation of seven new σ bonds and five rings.

Our involvement with tandem reactions began in 1979 with the invention of the aza-Cope–Mannich reaction for synthesizing substituted pyrrolidines.[8] In subsequent years, this transformation has been shown to be of exceptional value for the stereocontrolled synthesis of alkaloid natural products.[9] For example, in our enantioselective total synthesis of (−)-strychnine (**8**), exposure of 2-azabicyclooctanol **6** to excess paraformaldehyde initiated a three-step condensation–rearrangement–cyclization cascade delivering azatricycloundecane **7** in 98% yield.[10] Elaboration of **7** in five additional steps provided (−)-strychnine (**8**). Another tandem process that has been of considerable interest in our laboratories is illustrated by the central strategic step of our recent total

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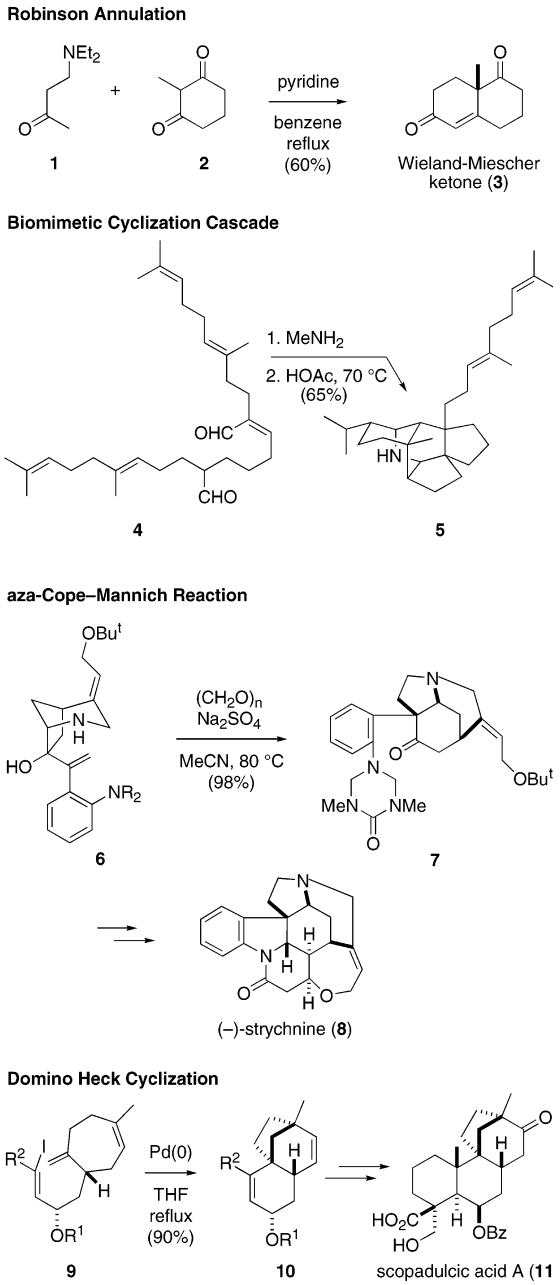
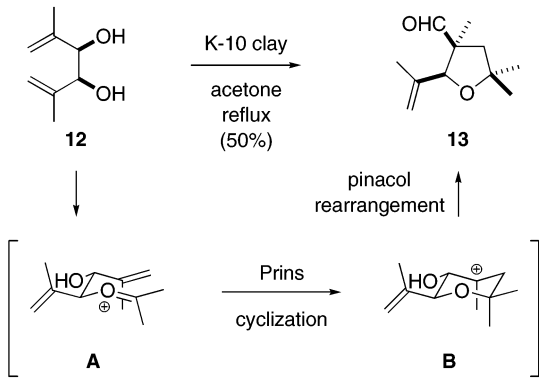


FIGURE 1. Examples of tandem reactions in chemical synthesis.

synthesis of (−)-scopadulcic acid A (**11**).[11] In this pivotal step, exposure of dienyl vinyl iodide **9** to a Pd(0) catalyst generated from $Pd(OAc)_2$, Ph_3P, and $AgCO_3$ triggered a cascade Heck cyclization to generate tricycle **10**, an intermediate possessing three of the four carbocyclic rings and two of the four quaternary carbon stereocenters of **11**.

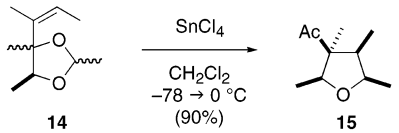
Mousset and co-workers discovered the cascade reaction that is the subject of this account serendipitously in 1969.[12] In an attempt to make the acetonide of meso allylic diol **12** by condensation with acetone in the presence of an acidic clay catalyst, these investigators instead obtained tetrahydrofuran **13** in high yield (Scheme 1). Although the relative configuration of **13** was misassigned originally and an unlikely mechanism proposed,[12] these workers suggested in subsequent studies that this

SCHEME 1. Mousset's Initial Example of a Pinacol-Terminated Prins Cyclization



unexpected transformation proceeded by initial acid-promoted condensation of **12** and acetone to generate an oxocarbenium ion that underwent Prins cyclization via chair conformer **A**, followed by pinacol rearrangement of the resulting hydropyranyl β-hydroxy carbenium ion **B** to ultimately generate the tetrahydrofuran product.[13] In this high-yielding and stereoselective process, two C−C bonds, one C−O bond, and two fully substituted carbon stereocenters are created. Surprisingly, other workers did not explore this novel and efficient synthesis of 3-acyltetrahydrofurans[14] until the mid 1980s, when we were led to this transformation from another direction.

Unaware at the time of Mousset's seminal studies, we originally conceived of the preparation of substituted tetrahydrofurans by acid-promoted rearrangement of allylic acetals as an extension of our laboratory's method for synthesis of substituted pyrrolidines from 5-alkenyloxazolidines (one implementation of the aza-Cope−Mannich reaction).[9] In our initial study, we found that a variety of polysubstituted 3-acyltetrahydrofurans, including ones such as **15** in which each carbon is stereogenic (eq 1), were formed in high yield upon exposure of 4-alkenyl-1,3-dioxolanes (allylic acetals) to a slight excess of $SnCl_4$.[15] These preliminary studies, and later investigations in our laboratory, demonstrated that with proper choice of reaction conditions this uncommon tetrahydrofuran synthesis has extremely broad scope.[16]



(1)

The use of pinacol rearrangements to terminate cationic cyclizations has subsequently been shown to be a powerful strategy for designing stereoselective ring-forming cascade reactions.[17] The evolution of this chemistry in our laboratories is the subject of this Perspective.[18] In particular, we will illustrate how pinacol-terminated Prins cyclizations have been employed as pivotal steps in the stereocontrolled synthesis of oxacyclic and carbocyclic natural products. This discussion will highlight the synergistic relationship between the development of new transformations and total synthesis of structurally complex natural products.

Prins-Pinacol Synthesis of Oxacyclic Ring Systems

Reaction Scope and Mechanism. A large number of natural products and medicinally useful agents contain substituted cyclic ethers; correspondingly a variety of methods have been developed for their stereocontrolled synthesis.[19] In the most common strategy, the oxacyclic ring is constructed by forming a C−O σ bond.[19] An alternative approach effects cyclization by C−C σ bond formation. As previously discussed, our investigations of such a strategy for cyclic ether synthesis began with the construction of 3-acyltetrahydrofurans by acid-promoted rearrangement of allylic acetals or direct condensation−rearrangement of allylic diols with aldehydes or ketones.[15,16]

In the 15 years since we began work in this area, we have employed Prins-pinacol reactions to construct a wide variety of oxacyclic ring systems.[20] Some representative examples are shown in Figure 2. The conversion of acetal **16** to spirocyclic tetrahydrofuran **17** illustrates the use of this cyclic ether synthesis to assemble tetrahydrofurans having additional heteroatom functionality.[20c] Alternatively, when the starting allylic diol is a 1-alkenylcycloalkane-1,2-diol, ring-enlarging tetrahydrofuran annulation results as depicted in the Lewis acid-catalyzed condensation of propenyl cyclobutane diol **18** and cyclohexanone (**19**) to form tricyclic ether **20**.[20a,b] If the alkene is contained within a ring, polycyclic ethers of an alternate topography are produced, exemplified by the synthesis of hexahydroisobenzofuran **23** from allylic diol **21** and *trans*-cinnamaldehyde (**22**).[20e] On the other hand, polysubstituted tetrahydropyrans are formed when the allylic alcohol functionality resides outside the ring generated upon Prins cyclization, for example **24** + **25** → **26**.[20d]

Our current understanding of the mechanism of the Prins-pinacol synthesis of acyltetrahydrofurans derives from several observations. Among these are three distinctive features of this tetrahydrofuran synthesis: incorporation of the alkene unit in a suprafacial fashion, preferential formation of the all-cis stereorelationship of the acyl group and single substituents at C2 and C5, and the observation that in most cases both the syn and anti allylic acetal stereoisomers provide the same tetrahydrofuran product.[15−17] Additionally, tetrahydrofurans of high enantiomeric purity are obtained from rearrangements of enantioenriched acetals (Scheme 2).[15,16c] Although we initially envisaged this tetrahydrofuran synthesis proceeding by oxonia-Cope rearrangement followed by aldol cyclization (**27/29** → **A** → **C** → **30**), the complete retention of configuration observed in the production of enantioenriched tetrahydrofurans **28a** and **28b** from enantioenriched acetals **27** and **29** is in accord with the alternative Prins cyclization−pinacol rearrangement mechanism first proposed by Mousset (**27/29** → **A** → **B** → **28**).[13,15,16c] This conclusion assumes that rotation about the C−C single bonds in oxocarbenium ion **C**, which is devoid of stereocenters, would be faster than intramolecular aldol reaction thus delivering a racemic product by an oxonia-Cope rearrangement−aldol cyclization sequence.[21]

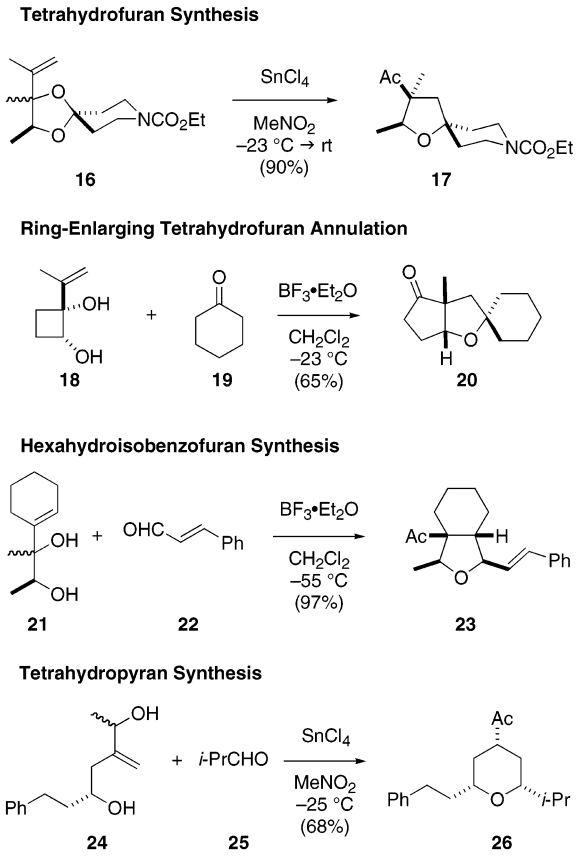
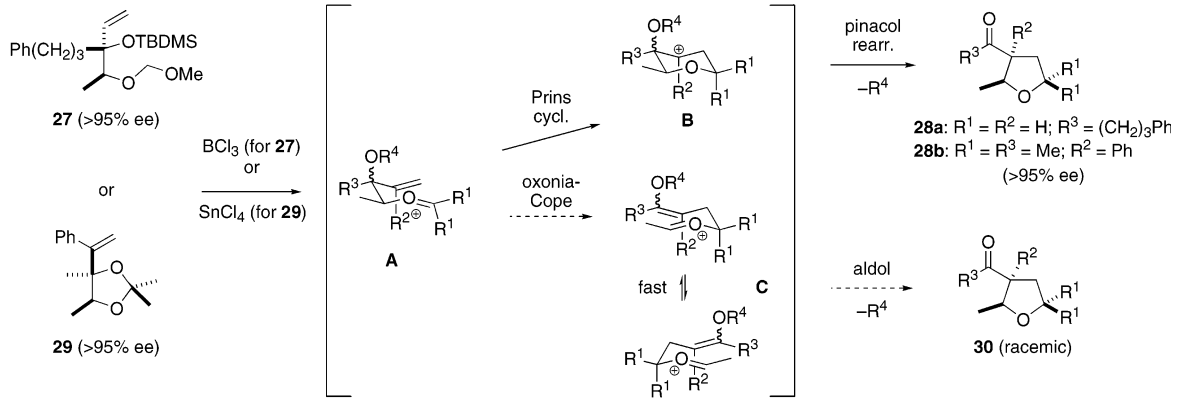


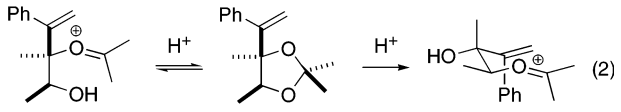
FIGURE 2. Examples of the Prins−pinacol synthesis of oxacyclic ring systems.

SCHEME 2. Evidence for a Prins−Pinacol Mechanism



Studies in our laboratories have shown that the stereochemical outcomes of Prins−pinacol reactions are governed by both steric and stereoelectronic effects. Of particular importance are the nucleophilicity of the alkene,[22] the size and relative stereochemistry of allylic and homoallylic substituents,[23] and the configuration of the oxocarbenium ion.[15−17,20,24] For example, stereoselective formation of **28** in the rearrangement of **29** is ascribed to homoallylic oxocarbenium ion **A** undergoing Prins cyclization[25] by a chair topography in which the homoallylic methyl substituent is pseudoequatorial, with pinacol rearrangement occurring faster than conformational changes of chair hydropyranyl cation **B**.[26] An alternative possibility, also consistent with the observed stereoselection, would involve the cyclization and rearrangement steps occurring with some degree of concert. The origin of stereoselection in the Prins−pinacol synthesis of tetrahydrofurans is discussed in more detail in a recent publication.[16c]

Before turning to applications of this chemistry in target-directed synthesis, an important simplifying feature of the Prins−pinacol synthesis of tetrahydrofurans should be noted. Although acetals such as **29** could open in the presence of acid to form two different oxocarbenium ions (**A** and **D**, eq 2), only homoallylic oxocarbenium ion **A** has sufficient overlap with the alkene π bond to undergo C−C bond formation.[27] Therefore, there is no need to orchestrate selective formation of the homoallylic oxocarbenium ion to trigger Prins−pinacol rearrangement, because allylic oxocarbenium ion **D** when formed is preferentially trapped by the homoallylic OH group to reform acetal **29**.



Target-Directed Total Synthesis of Oxacyclic Natural Products

(±)-*trans*-Kumausyne and (±)-Kumausallene.[28] Our early total synthesis objectives were modest and focused on a family of halogenated tetrahydrofuranoid lipids isolated from red algae of the genus *Laurencia* (Figure 3).[29] The common structural feature of these nonisoprenoid sesquiterpenes, exemplified by *cis*- and *trans*-kumausyne (**31** and **32**)[30] and kumausallene (**33**),[31] is an all-cis, 3-oxygenated-2,5-dialkyltetrahydrofuran unit having one or more bromine atoms incorporated at various positions of the side chains. At the time we initiated our synthesis studies, no total synthesis of a member of this family had been reported.[32]

We set out to develop a strategy for the synthesis of these marine acetogenins in which hydrobenzofuranone **36** would be a common synthetic intermediate (Scheme 3).[20b] Intermediate **36** encodes the three stereocenters of the central tetrahydrofuran rings of these halogenated lipids and provides sites for the elaboration of the remaining six carbon atoms. We anticipated that Prins cyclization of the productive (*E*)-oxocarbenium[24] ion

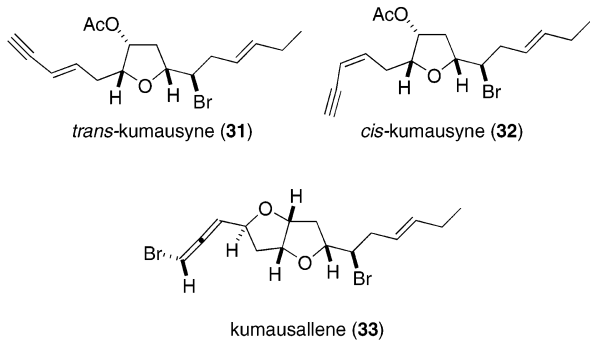
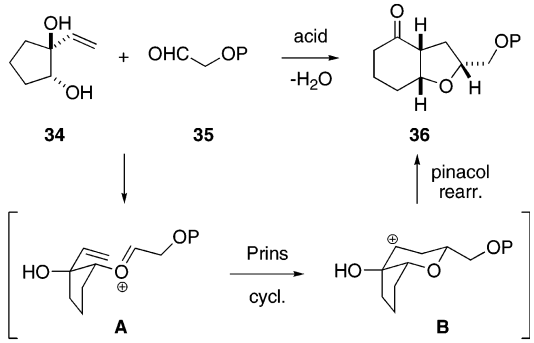


FIGURE 3. Oxacyclic sesquiterpenes from *Laurencia* red algae.

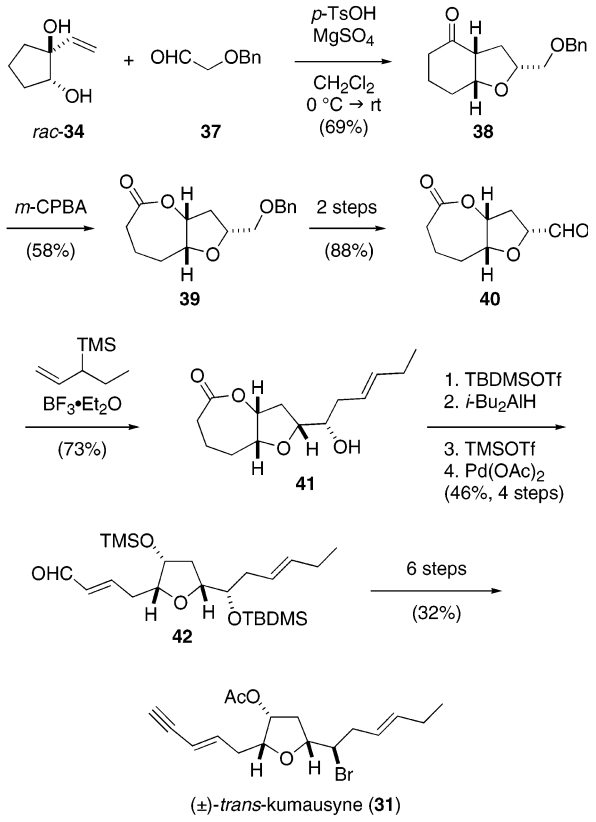
SCHEME 3. Key Step in the Total Synthesis of *Laurencia* Sesquiterpenes



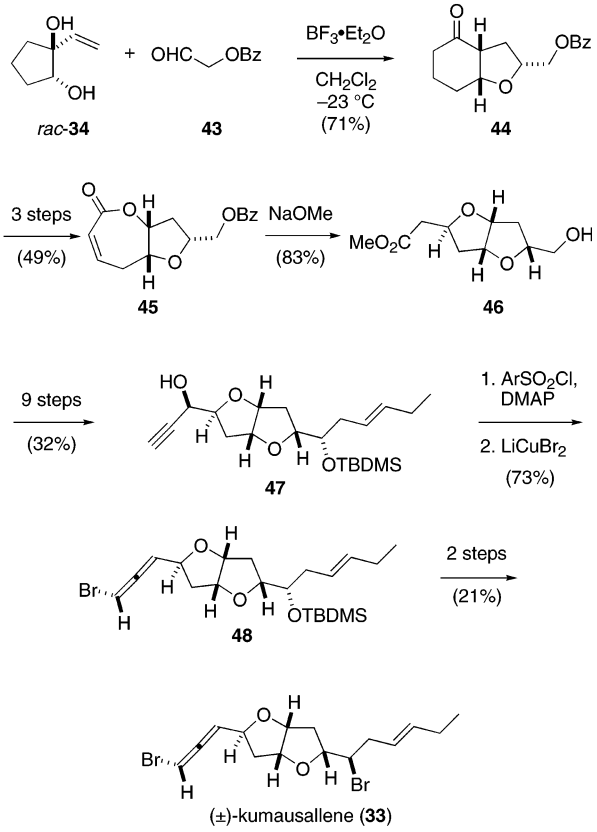
derived from condensation of **34** and **35** would proceed via conformer **A** to position the allylic C−O σ-bond orthogonal to the empty p-orbital of the incipient hydropyranyl carbocation **B**. Selective migration of the ring fusion bond of β-hydroxy carbenium ion **B** during pinacol rearrangement was expected to arise from the higher migratory aptitude of the more substituted, α-alkoxy carbon center.[26]

Our total synthesis of (±)-*trans*-kumausyne (**31**) commenced with the *p*-toluenesulfonic acid promoted condensation of racemic cyclopentane diol **34**, available in two steps and 48% yield from 1,2-cyclopentadione, with α-(benzyloxy)acetaldehyde (**37**) to provide *cis*-hydrobenzofuranone **38** in 69% yield on a multigram scale (Scheme 4).[20b] Regioselective Baeyer−Villiger oxidation[33] of **38** using *m*-chloroperbenzoic acid (*m*-CPBA) gave bicyclic lactone **39** in 58% yield after removal of the minor isomer (∼14%) by chromatography. Debenzylation of **39** and oxidation of the derived primary alcohol provided α-alkoxy aldehyde **40**, to which the *trans*-2-pentenyl moiety was appended by a stereoselective (Felkin−Ahn) Sakurai reaction[34] with 3-(trimethylsilyl)-1-pentene providing **41** in good yield. Protection of the secondary alcohol of **41** as the TBDMS ether, reductive cleavage of the lactone with *i*-Bu_2AlH, and sequential treatment of the resulting aldehyde with TMSOTf/*i*-Pr_2NEt and $Pd(OAc)_2$[35] afforded (*E*)-enal **42** in 46% overall yield. A series of six steps then transformed **42** to (±)-*trans*-kumausyne (**31**). This first total synthesis of a halogenated tetrahydrofuranoid sesquiterpene from a *Laurencia* red algae proceeded in 15 steps and 3.7% yield from *rac*-**34**. Additional investigations in our laboratory demonstrated that by conducting the Prins−pinacol reaction with (1*S*,2*R*)-**34**, which is accessible in three steps and 84% ee from 1,2-cyclopen-

SCHEME 4. Total Synthesis of (±)-Kumausyne



SCHEME 5. Total Synthesis of (±)-Kumausallene



tadione and (*S*)-*O*-methylprolinol, provides (−)-**38** in 57% yield with no measurable loss of enantiomeric purity.

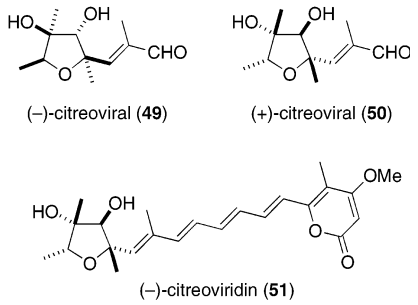


FIGURE 4. Polysubstituted tetrahydrofurans from the *Penicillium citreoviride* rice fungus.

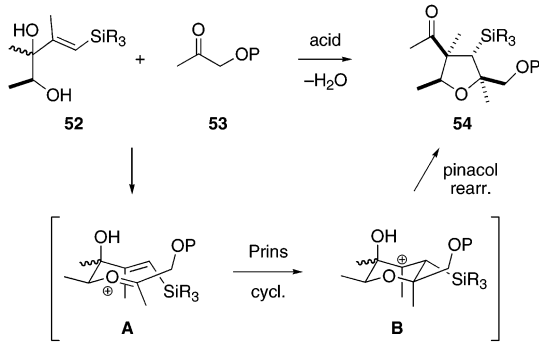
This preparation of (−)-**38** in useful enantiomeric purity defines a convenient asymmetric approach for the synthesis of **31** and structurally related *Laurencia* lipids.

By modifying the manner in which the hydrobenzofuranone intermediate **36** was elaborated, (±)-kumausallene (**33**) was synthesized. In this endeavor, $BF_3{\cdot}OEt_2$-promoted condensation of racemic diol **34** and α-(benzoyloxy)acetaldehyde (**43**) delivered *rac*-hydrobenzofuran **44** in 71% yield (Scheme 5). The choice of benzoyl as the protecting group in this case was predicated upon its expected lability to base-catalyzed cleavage at an opportune time. A three-step sequence of standard reactions transformed **44** to α,*β*-unsaturated lactone **45**. Treatment of **45** with NaOMe effected methanolysis of the lactone, 1,4-addition of the resulting C7 alkoxide to the tethered α,*β*-unsaturated methyl ester, and cleavage of the benzoyl protecting group to provide *cis*-dioxabicyclo[3.3.0]octane **46** with high stereoselectivity (≥10:1). The two side chains were then elaborated to provide **47**. Conversion of **47** to the sterically hindered trisylate derivative permitted regio- and stereoselective transformation to bromoallene **48** (>15:1 dr) upon treatment with $LiCuBr_2$[36] in THF at reflux. Finally, the secondary bromine substituent was installed, albeit in low yield, to give (±)-kumausallene (**33**). This first total synthesis of (±)-kumausallene was accomplished in 18 steps and 1.4% yield from *rac*-**34**.

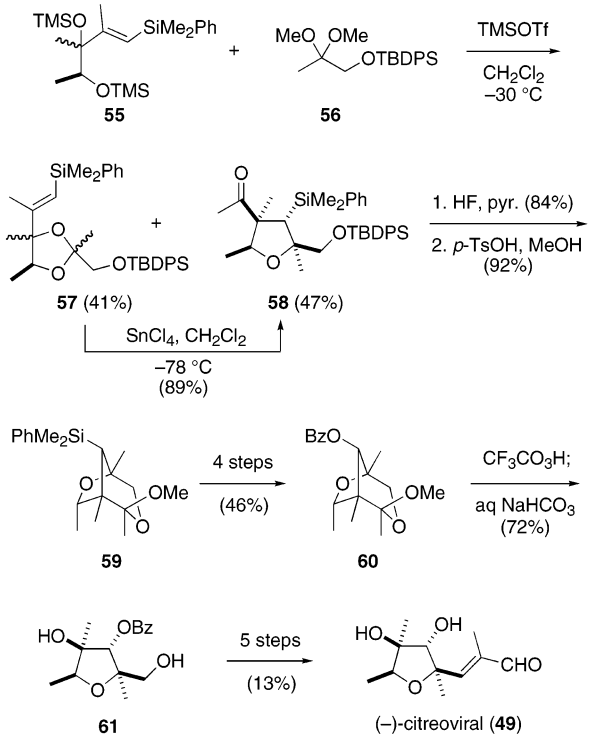
(−)-Citreoviral.[37] The potent neurotoxic mycotoxin (−)-citreoviridin (**51**)[38] and the simpler congener (+)-citreoviral (**50**)[39] co-occur in the rice fungus *Penicillum citreoviride* (Figure 4). The polysubstituted tetrahydrofuran rings that these fungal metabolites have in common has stimulated the development of imaginative methods for their synthesis. Total syntheses of citreoviridin (**51**)[40] and citreoviral (**50**)[41] in both racemic and optically active form have been achieved by several groups. Our interest in targeting citreoviral stemmed largely from the opportunity to investigate stereoselection in the Prins−pinacol condensation of allylic diols with unsymmetrical ketones.

The approach we devised to construct a polysubstituted tetrahydrofuran **54** that contains the functionality required for elaboration to (−)-citreoviral (**49**) is outlined in Scheme 6. We targeted the enantiomer of natural citreoviral (**50**) because this enantiomer had not been prepared previously and enantioenriched allylic diols **52** were foreseen to be readily available from (*S*)-(−)-ethyl lactate.[42] We anticipated that by incorporating a bulky silyl protecting group into ketone **53**, condensation of this

SCHEME 6. Central Step in the Synthesis of (−)-Citreoviral



SCHEME 7. Total Synthesis of (−)-Citreoviral



intermediate with diol **52** would generate a homoallylic (*E*)-oxocarbenium ion.[24] Preferential Prins cyclization of this intermediate by chair topography **A**, which places the bulky siloxymethyl substituent pseudoequatorial and the methyl group pseudoaxial, would deliver hydropyranyl cation **B**. Because the equatorial C−SiR_3 σ bond of β-silyl, β-hydroxy carbenium ion **B** would be nearly orthogonal to the empty p-orbital, pinacol rearrangement was expected to predominate over desilylation to deliver tetrahydrofuran **54**. Conversion of **54** to (−)-citreoviral (**49**) was envisioned to arise from regioselective and stereospecific oxidative scission of the C4−COMe[43] and C3−SiR_3[44] σ bonds.

The starting material for our total synthesis of (−)-citreoviral (**49**) was the enantioenriched disiloxy alkene **55**,[45] which was efficiently produced in three steps and 81% overall yield by tantalum-promoted coupling[46] of 1-(dimethylphenylsilyl)propyne[47] and (*S*)-3-(*tert*-butyldiphenylsiloxy)-2-butanone[42] followed by removal of the TBDPS ether and silylation of the resulting diol with TMSCl (Scheme 7). Condensation of **55** with dimethyl

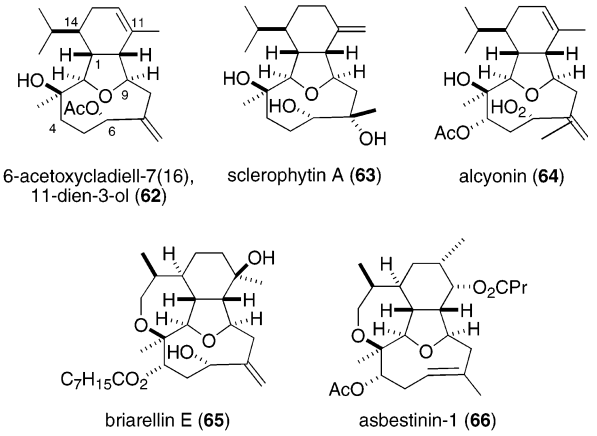


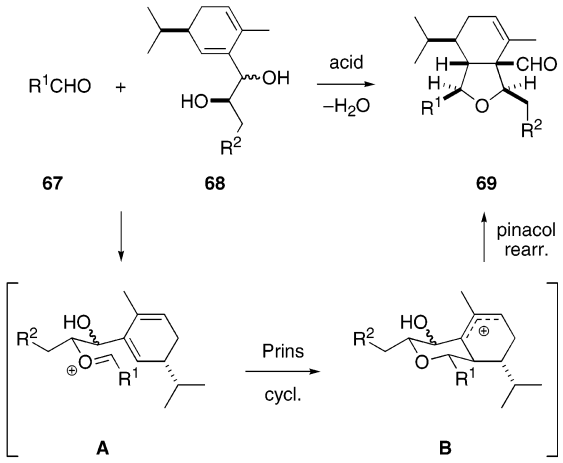
FIGURE 5. Representative cladiellin, briarellin, and asbestinin diterpenes from marine corals.

ketal **56**[48] in the presence of TMSOTf at −30 °C in CH_2Cl_2 led to a separable mixture of acetal **57** and tetrahydrofuran **58** in 88% combined yield. Re-subjection of **57** to the reaction conditions gave only recovered acetal, suggesting that **57** is not an intermediate on the pathway to **58** under these conditions. However, **57** could be converted efficiently to **58** by exposure to 1.2 equiv of $SnCl_4$ at −78 °C in CH_2Cl_2. This sequence takes advantage of Noyori's method for generating acetals (and consequently oxocarbenium ions) under mild conditions by TMSOTf catalyzed condensation of silyl ethers with acetals.[49] Use of this variant was critical, as attempted Lewis acid promoted condensation of the diol precursor of **55** with 1-(*tert*-butyldiphenylsiloxy)-2-propanone led primarily to ionization of the labile tertiary allylic hydroxyl group.

Tetrahydrofuran ketone **58** was converted to (−)-citreoviral in the following manner. To protect the ketone and simplify isolation of subsequent intermediates, **58** was transformed to bicyclic acetal **59** by discharging the TBDPS protecting group and exposing the resulting hydroxy ketone to acidic methanol and trimethyl orthoformate. Using a reported procedure,[50] the $SiMe_2Ph$ group was activated and then oxidatively cleaved to provide acetal **60** in 46% overall yield after benzoylation of the derived secondary alcohol. Baeyer−Villiger oxidation of **60** with CF_3CO_3H[51] followed by basification delivered diol **61**, which was converted by five steps into (−)-citreoviral (**49**). This first total synthesis of the unnatural enantiomer of citreoviral was executed in 16 steps and 2.4% overall yield from (*S*)-3-(*tert*-butyldiphenylsiloxy)-2-butanone. Moreover, this synthesis demonstrated for the first time that two substituents could be introduced at C5 of a 3-acyltetrahydrofuran, with high stereocontrol, by the condensation of allylic diols with unsymmetrical ketones.

Cladiellin and Briarellin Diterpenes.[52] A wide variety of oxacyclic diterpenes has been isolated from soft corals and gorgonian octocorals.[29] The cladiellins (e.g., **62**−**64**),[53] briarellins (e.g., **65**),[54] and asbestinins (e.g., **68**)[55] belong to the C2,C11-cyclized cembranoid diterpene family and have in common a rare oxatricyclic ring system composed of hexahydroisobenzofuran and oxacyclononane units, as well as six stereogenic carbons (C1−3, C9, C10, and C14; Figure 5).[56] Although the proposed

SCHEME 8. Plan for Assembling the Hexahydroisobenzofuran Core of Cladiellin Diterpenes

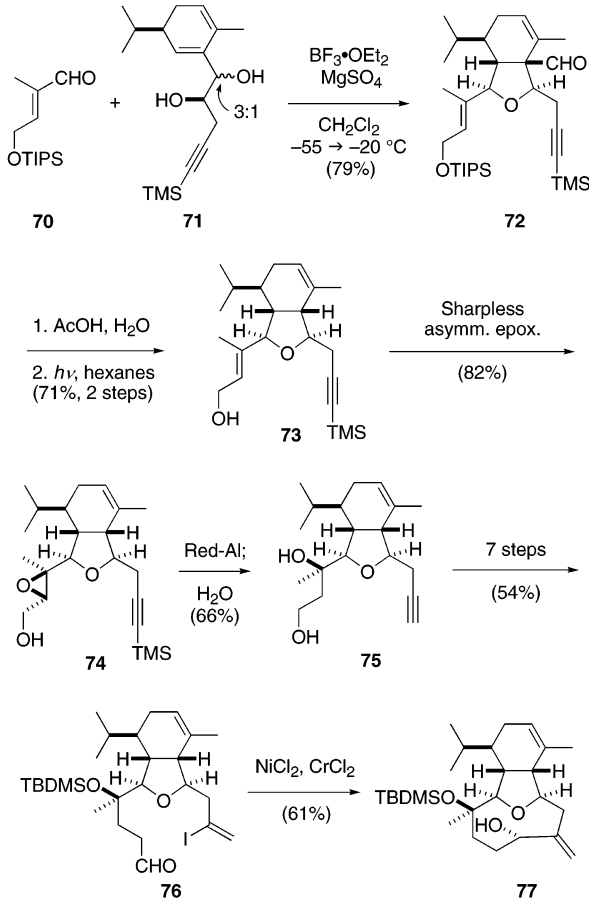


structures of several members of this diverse family have been corroborated by X-ray analysis, structure determination in this area generally has relied upon MS and NMR, IR, and UV spectral analyses.[56] The absolute stereochemistry of several cladiellins has been proposed on the basis of single-crystal X-ray diffraction, CD, or NMR experiments, whereas the absolute configuration of briarellin and asbestinin diterpenes had not been established prior to our total synthesis investigations.[56]

We initially targeted for total synthesis one of the simpler members of this diverse family, 6-acetoxycladiell-7(16),11-dien-3-ol (**62**). We envisioned that Prins-pinacol condensation of an appropriately functionalized aldehyde **67** with the (*S*)-carvone-derived alkynyl dienyl diol **68** could rapidly generate the hexahydroisobenzofuran core of the cladiellin diterpenes (Scheme 8). We anticipated that Prins cyclization of the productive (*E*)-oxocarbenium ion **A**[24] would proceed by attack at the terminus of the 1,3-cyclohexadiene unit to generate allylic cation **B** by a favored 6-endo cyclization.[27] In this putative cyclization pathway, the homoallylic substituent would adopt a pseudoequatorial orientation, and the oxocarbenium ion electrophile would approach the diene from the face opposite the bulky isopropyl group. We foresaw formyl tetrahydroisobenzofuran **69** evolving to 6-acetoxycladiell-7(16),11-dien-3-ol (**62**) by stereoselective deformylation, elaboration of the R^1 and R^2 side chains, and cyclization to form the oxacyclononane ring.

After several failed attempts to carry out the proposed Prins–pinacol reaction with α-alkoxy aldehydes, which would directly install the tertiary oxygen substituent at C3 of 6-acetoxycladiell-7(16),11-dien-3-ol (**62**), we turned to a condensation–rearrangement sequence employing an α,*β*-unsaturated aldehyde. In a pivotal step in the total synthesis of **62**, condensation of (*E*)-2-methyl-4-(triisopropylsiloxy)-2-butenal (**70**) and alkynyl dienyl diol **71** (available in five steps and ~45% yield from (*S*)-(+)-carvone) with $BF_3{\cdot}OEt_2$ at −55 → −20 °C in CH_2Cl_2 gave formyl tetrahydroisbenzofuran **72** in 79% yield as a single isomer (Scheme 9). Acidic cleavage of the TIPS protecting group of **72**, followed by stereospecific photolytic deformylation,[57] yielded allylic alcohol **73**. Hydroxyl-directed asymmetric epoxidation of **73** using the conditions developed by Sharpless[58] delivered epoxy alcohol

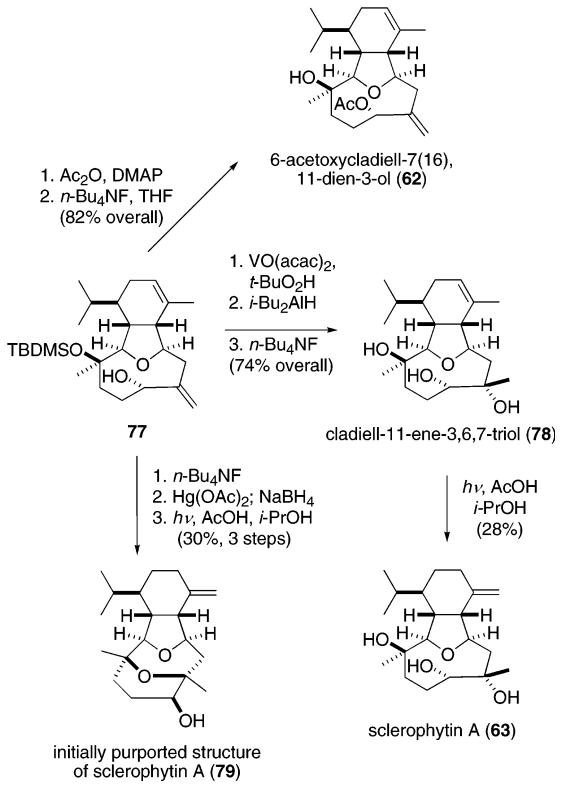
SCHEME 9. Construction of the Tricyclic Core of Cladiellin Diterpenes



74, which was regioselectively opened[59] with sodium bis-(2-methoxyethoxy)aluminum hydride (Red-Al) to furnish diol **75** after cleavage of the trimethylsilyl group. The side chains of **75** were elaborated in a seven-step sequence to provide vinyl iodide aldehyde **76**. The final crucial step, closure of the bridging nine-membered oxacyclic ring, was accomplished by Nozaki–Hiyama–Kishi cyclization[60] to give tricyclic allylic alcohol **77** in 61% yield as a single diastereomer.

Tricyclic allylic alcohol **77** proved to be a versatile intermediate for the synthesis of cladiellin diterpenes lacking oxidation at C4 (Scheme 10). To complete our inaugural total synthesis in this area, **77** was transformed to 6-acetoxycladiell-7(16),11-dien-3-ol (**62**) by acetylation followed by cleavage of the TBDMS protecting group using *n*-Bu_4NF. This first total synthesis of a cladiellin diterpene was accomplished in 20 steps and 4.3% overall yield from (*S*)-(+)-carvone. Alternatively, hydroxyl-directed epoxidation[61] of **77**, regioselective reductive opening of the derived epoxide with *i*-Bu_2AlH,[62] and finally desilylation gave cladiell-11-ene-3,6,7-triol (**78**) in 74% overall yield. Tricyclic intermediate **77** was also employed to prepare the purported structure **79** of sclerophytin A,[53b] a cladiellin diterpene reported to display potent anticancer activity. In this case, the TBDMS protecting group of **77** was first discharged, and the resulting diol was treated with $Hg(OAc)_2$ to effect stereoselective transannular oxymercuration. After reductive cleavage of the organomercurial species,[63] pho-

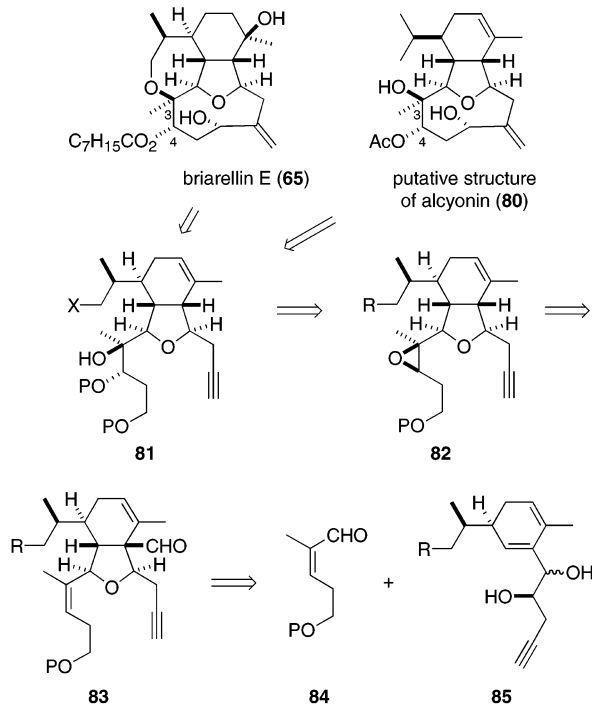
SCHEME 10. Conversion of 77 to Various Cladiellin Diterpenes



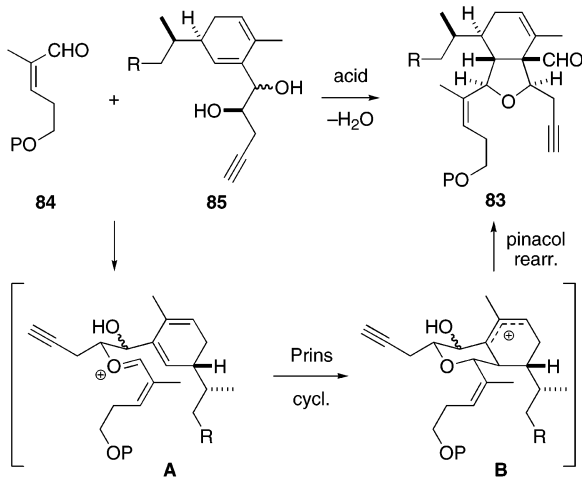
tochemical isomerization[64] of the internal double bond provided **79** as a 4:1 mixture of exo and endo alkene isomers in ~30% yield for the three-step sequence. However, this product showed chromatographic and spectral properties distinct from those reported for the natural product. This conclusion was reached independently in the Paquette group,[65] who proposed an alternative structure for this cladiellin diterpene.[53c] We were able quickly to confirm the validity of this revised structure assignment for sclerophytin A (**63**) by photoisomerization of the double bond of triol **78** to provide a product **63** that was identical in all respects to natural sclerophytin A.[20e,52d]

Several cladiellin diterpenes, exemplified by alcyonin (**64**), and most briarellin and asbestinin diterpenes contain oxygenation at C4 of the oxacyclononane ring (see Figure 5). In all cases, the C3 and C4 oxygen substituents are trans.[56] We envisioned that this functional group array could be established from a Prins−pinacol product having a (*Z*)-4-siloxy-1-methyl-1-butenyl side chain. This analysis is outlined in Scheme 11 in the context of total syntheses of briarellin E (**65**) and the putative structure of alcyonin (**80**). We foresaw the oxepane ring of **65** (as well as that of asbestinin diterpenes) deriving from a protected triol intermediate such as **81** wherein X would be a leaving group. A similar intermediate having X = H should lead directly to **80**. Logical precursors of protected triol **81** are *cis*-3,4-epoxy alcohol **82** and *Z* alkene **83**. We anticipated this latter intermediate coming from Prins−pinacol condensation of a (*Z*)-α,*β*-unsaturated aldehyde **84** and an alkynyl dienyl diol **85**. A central question for the successful implementation of this strategy was whether the homoallylic oxocarbenium ion **A**

SCHEME 11. Unified Plan for Preparing Cladiellin, Briarellin, and Asbestinin Diterpenes



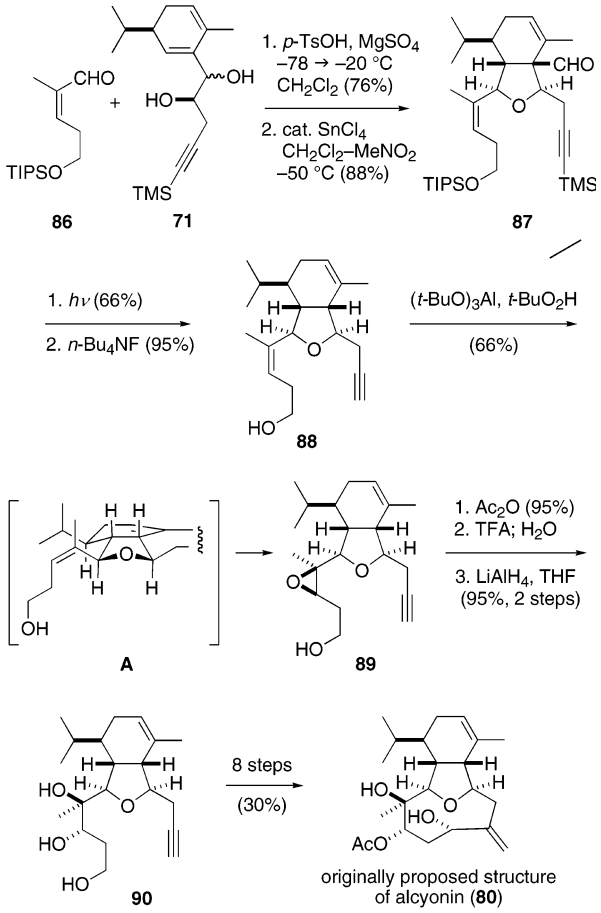
SCHEME 12. Projected Prins−Pinacol Rearrangement Step



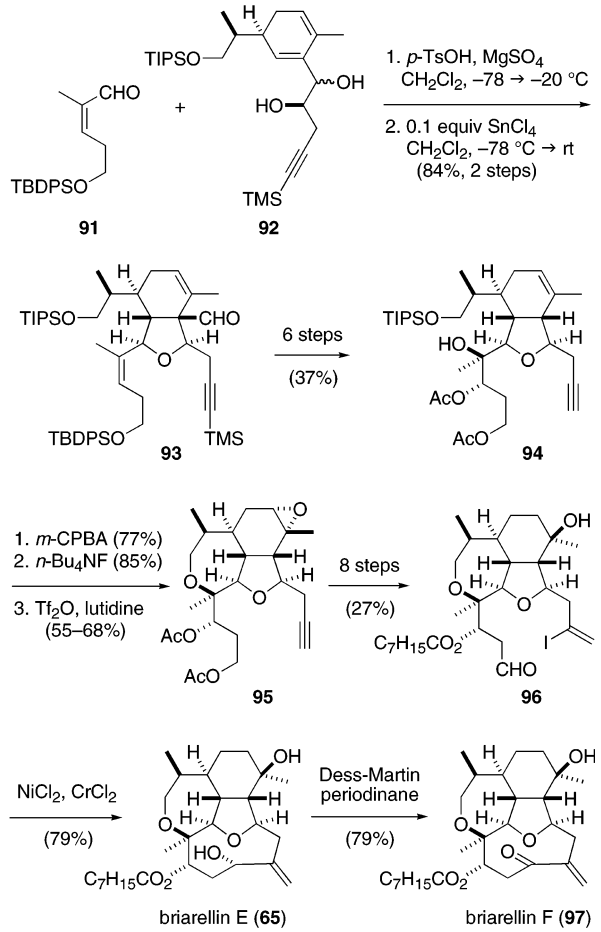
initially generated from condensation of **84** and **85** would undergo Prins cyclization more rapidly than isomerization of the conjugated trisubstituted double bond to the more stable *E* configuration (Scheme 12). That the double bond geometry of **A** might be preserved during the projected condensation-rearrangement sequence was suggested by Child's extensive studies of the stereomutation of oxygen-substituted allyl carbenium ions.[66]

This more general strategy was implemented first to prepare **80**, an exercise that resulted in our revising the structure assignment for the cladiellin diterpene alcyonin. The key steps in this synthesis are summarized in Scheme 13. After a number of attempts to effect direct condensation of **86** and **71** resulted in the formation of a mixture of **87** and its *E* side chain stereoisomer, a two-step alternative was developed. In this procedure, **86** and

SCHEME 13. Total Synthesis of the Structure Initially Proposed for Alcyonin



SCHEME 14. Enantioselective Total Synthesis of Briarellins E and F



71 were condensed at low temperature in the presence of *p*-TsOH and $MgSO_4$ to give the corresponding acetal, which when exposed to 0.1 equiv of $SnCl_4$ in 1:1 $MeNO_2$–CH_2Cl_2 at −50 °C provided formyl tetrahydroisobenzofuran **87** in high yield as a single stereoisomer. Photolytic deformylation[57] of **87**, followed by cleavage of the TIPS and TMS protecting groups with *n*-Bu_4NF delivered homoallylic alcohol **88**. Hydroxyl-directed epoxidation of **88** using (*t*-BuO)$_3$Al/*t*-BuO_2H[67] yielded *cis*-3,4-epoxy alcohol **89**. The high stereoselection of this latter transformation undoubtedly derives from epoxidation occurring by way of conformer **A** in which the side chain is oriented to minimize destabilizing $A^{1,3}$ interactions.[68] Following the method of Giner,[69] the acetate derivative of **89** was exposed to trifluoroacetic acid to effect internal opening of the epoxide. After hydrolytic workup and reduction of the resulting mixture of primary and secondary acetates with $LiAlH_4$, triol **90** was produced in 90% yield. Using a sequence of transformations similar to that employed in our earlier syntheses of the C4-deoxygenated cladiellin diterpenes, this intermediate was converted to **80**. However, spectroscopic data for **80** were not in accord with those reported for the natural product. Reexamination of NMR and MS data, as well as chemical transformations reported for natural alcyonin, led us eventually to propose that alcyonin is **64** (Figure 5), the allylic peroxide analogue of **80**. This enantioselective total synthesis of the initially purported structure **80** of alcyonin was accomplished in 21 steps and 1.5% overall yield from (*S*)-(+)-carvone.

Earlier this year, we reported the use of a similar strategy to complete the first total syntheses of briarellin diterpenes (Scheme 14). In the first pivotal step of these syntheses, formyl tetrahydroisobenzofuran **93** was formed in 84% yield by condensation of (*Z*)-α,*β*-unsaturated aldehyde **91** and alkynyl dienyl diol **92**, followed by Prins–pinacol rearrangement. Intermediate **92** was available in high enantiomeric purity in 10 steps from (*S*)-(+)-carvone. Tetrahydroisobenzofuran **93** was processed as in our earlier synthesis of **80** to provide **94**. The cyclohexene double bond of **94** was then epoxidized with *m*-CPBA, a functionalization that took place from the concave α face of the hexahydroisobenzofuran because the convex *β* face is shielded by the axial 1-methyl-2-(trisopropylsiloxy)ethyl substituent. After discharge of the TIPS protecting group, the oxepane ring was formed by intramolecular displacement of the derived primary triflate. Elaboration of **95** in eight steps provided vinyl iodide aldehyde **96**, an intermediate that once again underwent efficient and stereoselective Nozaki–Hiyama–Kishi cyclization[60] to form in this case briarellin E (**65**). Oxidation[70] of the allylic alcohol of **65** furnished briarellin F (**97**). These enantioselective total syntheses provided the first verification of the structure assignments of the briarellin diterpenes, which had been proposed largely on the basis of NMR data. They also established for the

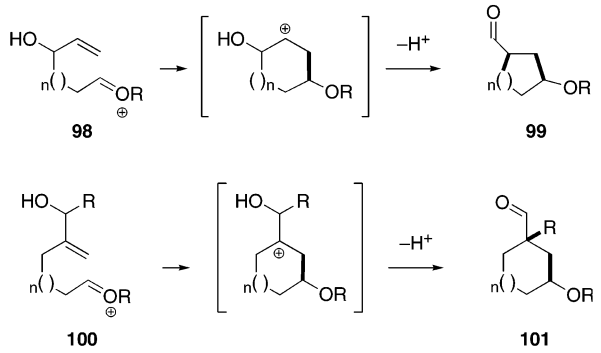


FIGURE 6. Prins−pinacol construction of carbocyclic rings.

first time the absolute configurations of members of the briarellin diterpene family. In these inaugural total syntheses, briarellins E (**65**) and F (**97**) were prepared in 30−31 steps (longest linear sequence) and ~0.4% overall yield from (*S*)-(+)-carvone.

Prins−Pinacol Synthesis of Carbocyclic Ring Systems

Reaction Scope and Mechanism. This approach to ring formation is not limited to forming oxacyclic ring systems. If the oxocarbenium ion intermediate is external to the ring formed upon Prins cyclization, Prins−pinacol reactions can assemble carbocyclic rings.[71] Such transformations are outlined in a general way in Figure 6, wherein the new C−C σ bonds that are formed are depicted in bold font.

Examples illustrating the variety of carbocyclic ring systems we have assembled by Prins−pinacol reactions are shown in Figure 7.[72] For example, propanyl cyclopentanone **103** is the exclusive product of $SnCl_4$ promoted cyclization of 5-alkenyl acetal **102**, followed by oxidative cleavage of the resulting mixture of epimeric methyl ethers.[72f] A particularly valuable expression of this chemistry couples formation of a cyclopentane ring with one-carbon ring expansion of a starting cycloalkane ring. Thus, the angularly fused tricycle **105** containing five-, six-, and eight-membered rings is assembled in one step from precursor **104**, which in turn is available in four straightforward steps from cycloheptanone and cyclohexenyl bromide.[72f] Terminal alkynes also participate in Prins-pinacol reactions as exemplified by the ring-enlarging cyclopentene annulation employed to fashion **107**.[72b] Rings joined by a single bond can also be prepared in this way, illustrated by the conversion of alkylidenecyclohexane acetal **108** to aldehyde **109**.[72e] In this last instance, Prins cyclization is coupled with a ring-contracting pinacol rearrangement.

This strategy for ring construction is not restricted to using a Prins cyclization to initiate the cationic reaction cascade. Exploiting an allyl carbenium ion or a keteniminium ion to commence pinacol-terminated cyclization sequences is illustrated by the transformations summarized in Figure 8.[72g] By using these initiators for cationic cyclization, functionality is installed in the cyclopentane ring that can be employed to readily elaborate the carbocyclic products.

Additional insight into the mechanism of Prins−pinacol reactions was gleaned from an investigation of

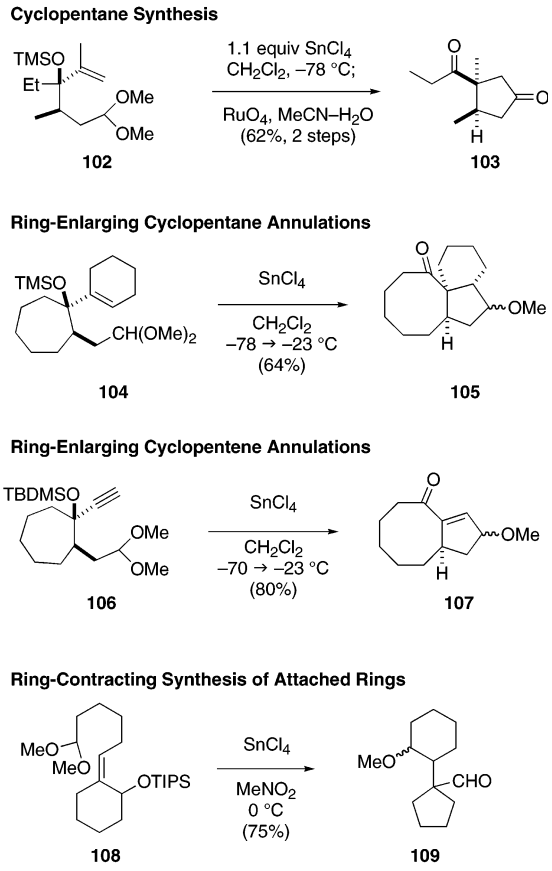


FIGURE 7. Examples of the Prins−pinacol synthesis of carbocyclic ring systems.

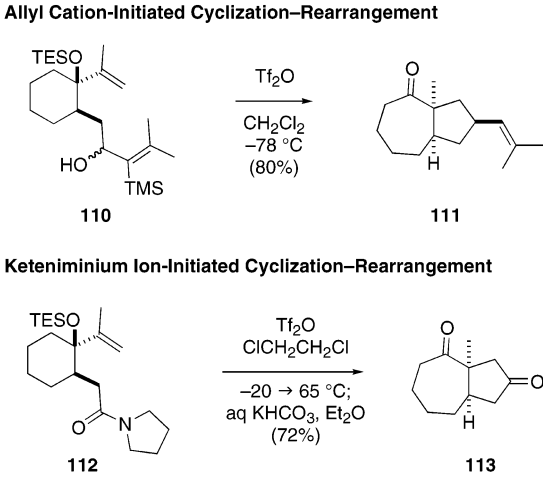
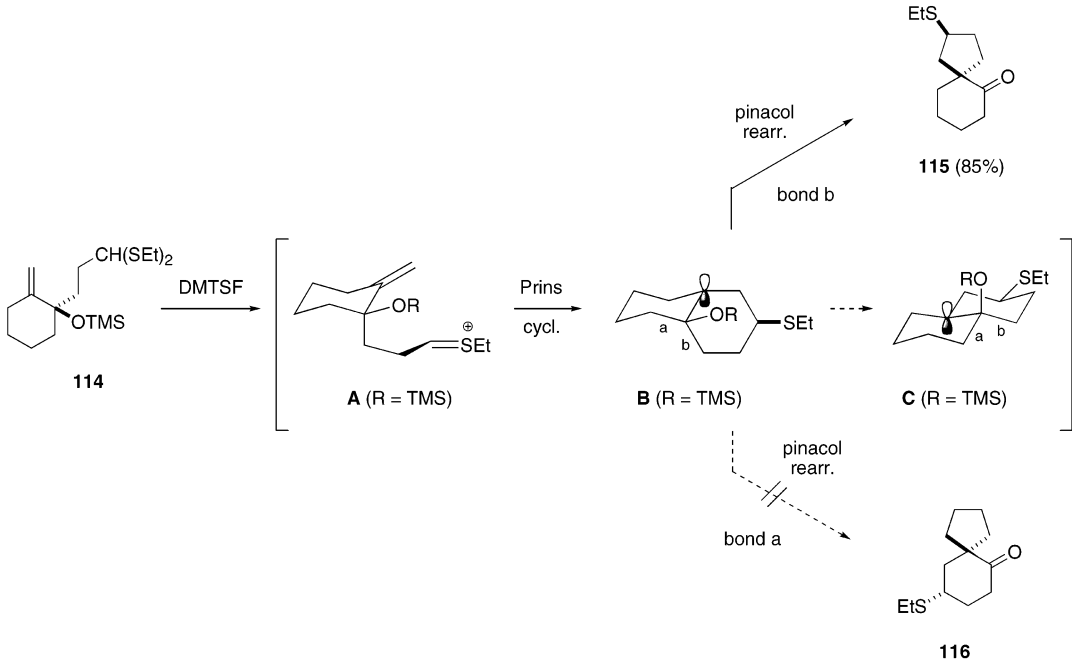


FIGURE 8. Allyl carbenium and keteniminium ions as cyclization initiators.

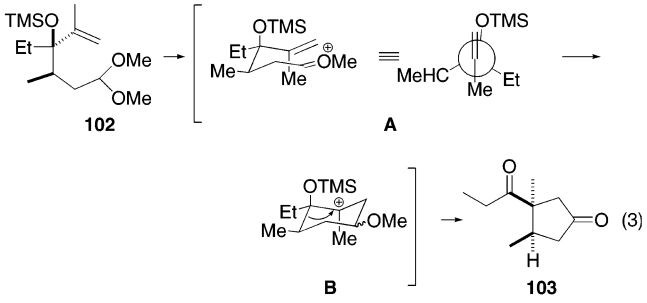
the use of this chemistry to prepare spirocarbocycles. In a revealing example, dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF)[73] promoted cyclization of dithioacetal **114** yielded exclusively spiro[4.5]decan-6-one **115**; the other possible spirocyclic product **116** was not observed (Scheme 15).[72d] In this conversion, the 9-decalyl cation produced upon thio-Prins cyclization underwent pinacol rearrangement exclusively by migration of bond b to generate **115**. As bonds a and b would have nearly identical overlap with the vacant p-orbital in the lowest

SCHEME 15. A Prins−Pinacol Spiroannulation



energy (*trans*-decalin-like) conformation of 9-decalyl cation **C**, pinacol rearrangement of the initially produced cation **B** must occur more rapidly than facile conformational relaxation of this intermediate to **C**.[26]

The stereochemical outcome of Prins−pinacol reactions will generally be dictated by the topography of the Prins cyclization step, a conclusion enforced by the results of the study summarized in Scheme 15. For example, the exclusive formation of propanyl cyclopentanone **103** from **102** is rationalized by the sequence outlined in eq 3. In this transformation, cyclization of this nucleophilic alkene is presumed to occur by an early[74] chairlike transition state **A** in which hyperconjugative interactions between $\pi^*_{C=C}$ and the allylic σ_{C-R} are maximized, whereas interactions between the allylic σ^*_{C-O} and the alkene $\pi_{C=C}$ are minimized.[23]



Target-Directed Total Synthesis of Carbocycle-Containing Natural Products

(−)-Magellanine and (+)-Magellaninone.[75] Our initial targets were polycyclic alkaloids that had been isolated from club moss belonging to the genus *Lycopodium*.[76] In the mid 1970s, Castillo and co-workers revealed the structures of magellanine (**117**), magellaninone (**118**), and paniculatine (**119**), which had been separated from extracts of *Lycopodium magellanicum* and *Lycopodium paniculatum* (Figure 9).[77] These alkaloids have in common a unique tetracyclic skeleton that includes a stereogenic quaternary carbon at the site of angular ring fusion.

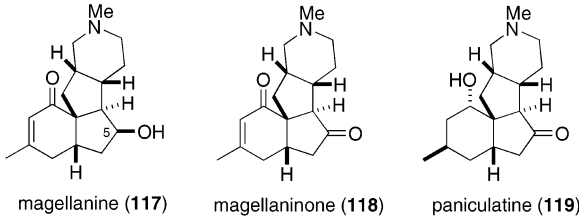
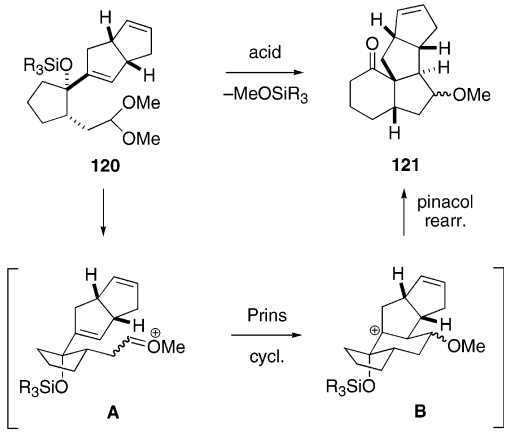


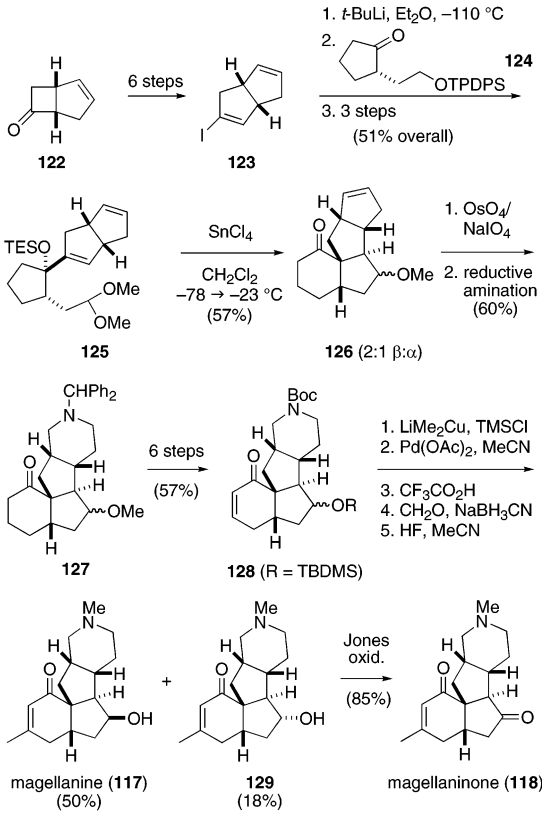
FIGURE 9. Tetracyclic alkaloids from *Lycopodium* club moss.

SCHEME 16. Central Step in the Synthesis of Magellanane Alkaloids



The centerpiece of our strategy for constructing these moss-derived alkaloids is developed in Scheme 16, wherein acid-promoted Prins-pinacol reaction of dienyl acetal **120** was predicted to deliver angularly fused carbotetracycle **121**. This desired stereoisomer would be generated provided that Prins cyclization of the intermediate oxo-

SCHEME 17. Enantioselective Total Syntheses of Magellanine and Magellaninone



carbenium ion **A** took place from the less hindered convex face of the *cis*-bicyclooctadiene moiety. Pinacol rearrangement of β-siloxy carbenium ion **B** would then simultaneously install the crucial quaternary carbon stereocenter and form the core of the magellanane alkaloids. Notably, intermediate **121** possesses the carbotricyclic unit and five stereocenters common to the magellanane alkaloids (Figure 9), as well as sufficient functionality to allow its straightforward elaboration to these target molecules.

The successful implementation of this plan for the synthesis of these *Lycopodium* alkaloids is summarized in Scheme 17. The syntheses began with (1*R*,5*S*)-bicyclo[3.2.0]heptenone (**122**),[78] an intermediate produced on a large scale by Glaxo. This bicyclic ketone served as the starting material for the preparation of both the enantioenriched iodide **123** and cyclopentanone **124**. These two fragments were combined by stereoselective addition of the lithium species generated from **123** to **124**. Treatment of dienyl acetal **125**, available in three additional steps from this adduct, with 1.1 equiv of $SnCl_4$ at $-78 \rightarrow -23$ °C in CH_2Cl_2 provided carbotetracycle **126** in 57% yield as a 2:1 mixture of β and α methoxy epimers. Oxidative cleavage of the cyclopentene ring of **126** with $OsO_4/NaIO_4$[79] gave the corresponding dialdehyde, which was subjected to double reductive amination[80] to furnish azatetracycle **127** in 60% yield. In a six-step sequence of conventional transformations, **127** was elaborated to enone **128**. Chlorotrimethylsilane-promoted 1,4-addition of lithium dimethylcuprate to **128**, followed by oxidation of the resulting silyl enol ether with $Pd(OAc)_2$,[35] cleavage of the Boc protecting group, reductive methylation of the resulting secondary amine, and removal of the TBDMS protecting group then gave magellanine (**117**) and its C5 epimer **129** in 50% and 18% overall yields, respectively. Oxidation of **129** using Jones reagent yielded magellaninone (**118**). These first total syntheses of members of the magellanane family of *Lycopodium* alkaloids were accomplished in ~25 steps and 1.4% yield from (1*R*,5*S*)-bicycloheptenone **122**.

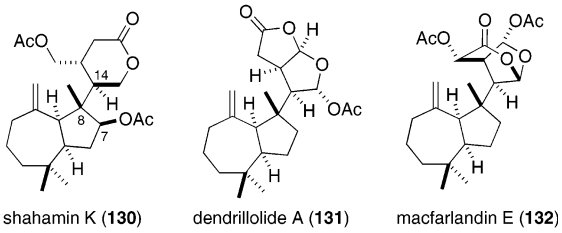
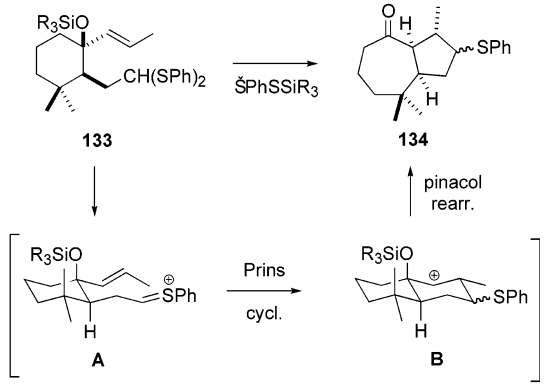


FIGURE 10. Rearranged spongian diterpenes from dorid nudibranches.

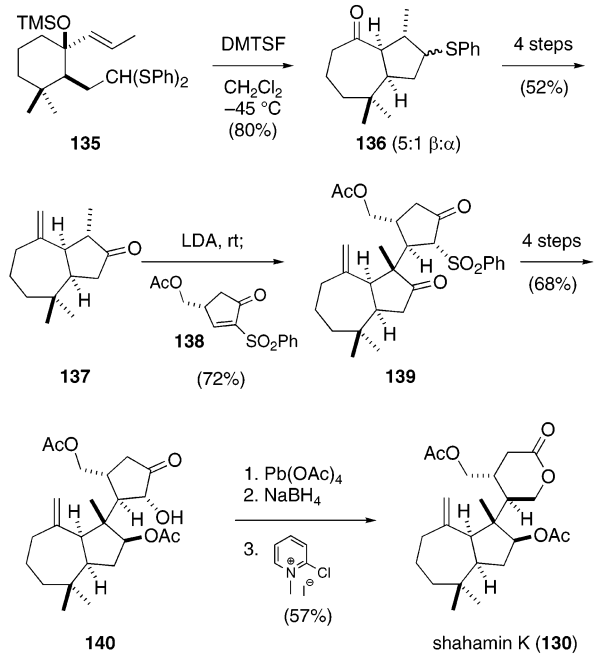
SCHEME 18. Plan for Preparing the *cis*-Hydroazulene Core of (+)-Shahamin K



(+)-Shahamin K.[81] Dorid nudibranches and the marine sponges on which they feed are rich sources of highly oxidized diterpenes possessing a rearranged spongian diterpene skeleton (e.g., **130**−**132**, Figure 10).[29] The common structural motif of these diterpenes is a *cis*-hydroazulene ring attached at C8 to a highly oxidized six-carbon fragment. Anderson and co-workers reported in 1991 the isolation and structure elucidation of shahamin K (**130**), which was acquired from skin extracts of the shell-less mollusk *Chromodoriz gleniei* inhabiting the coastal waters of Sri Lanka.[82] The constitution and relative stereochemistry of **130** were proposed on the basis of NMR studies, whereas the absolute configuration was not determined.

Our plan for fashioning the *cis*-hydroazulene moiety of shahamin K (**130**) is outlined in Scheme 18. We envisioned that ring-enlarging cyclopentane annulation of cyclohexyl precursor **133** would produce *cis*-hydroazulene **134**, an intermediate possessing functionality strategically located for direct introduction of the δ-lactone at C8, the exocyclic methylene group, and the C7 acetoxy substituent. Although not anticipated at the outset of these studies, initial investigations indicated that to preclude competitive ionization of the allylic silyl ether unit of intermediates such as **133**, use of a dithio acetal and dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF)[73] as the cyclization promoter would be critical. Another issue these studies sought to address was whether efficient Prins cyclization (i.e., **A** → **B**) could be

SCHEME 19. Enantioselective Total Synthesis of (+)-Shahamin K



achieved in a substrate in which the alkene is not biased toward the addition of an electrophile to the terminal vinylic carbon.

The realization of this strategy for preparing shahamin K (**130**) is summarized in Scheme 19. Exposure of enantioenriched dithio acetal **135**, available in seven steps from 3-methyl-2-cyclohexenone, to 2 equiv of DMTSF at −45 → 0 °C in CH_2Cl_2 initiated a thio-Prins−pinacol cascade to give *cis*-hydroazulene **136** in 80% yield as a mixture of sulfide epimers. Methylenation of **136**, followed by a two-step sequence to effect oxidative desulfonylation,[83] provided ketone **137**. Addition of enantiopure α-sulfonyl ketone **138**[84] to the thermodynamic enolate derived from **137** at −78 °C delivered diketone **139**. As expected, this coupling occurred exclusively on the convex face of **137** and opposite to the acetoxymethyl substituent of **138** to establish the desired relative configuration between C8 and C14. A four-step sequence of reactions converted *β*-keto sulfone **139** to α-hydroxy cyclopentanone **140**. Finally, oxidative scission of the α-hydroxycyclopentanone unit using $Pb(OAc)_4$ followed by reduction of the product with $NaBH_4$ and lactonization of the resulting seco acid with the Mukaiyama reagent[85] provided shahamin K (**130**) in 57% yield from **140**. This first total synthesis of a rearranged spongian diterpene, which established the absolute configuration of shahamin K, proceeded in 20 steps (longest linear sequence) and 2.9% yield from 3-methyl-2-cyclohexenone. These studies also demonstrated that if a α-thiocarbenium ion is used as the cyclization initiator, the alkene participant in a Prins−pinacol construction of a cis-fused carbocycle does not need to be biased electronically to favor endocyclization.

Conclusion

The need for efficient chemical syntheses of progressively more complicated target structures requires the development of new methods to direct the rapid evolution of molecular complexity in a stereocontrolled manner. Our ability to realize this goal relies heavily upon the design and implementation of new chemical transformations. Using as an example our investigations of pinacol-terminated Prins cyclizations, we have sought to demonstrate how the synergistic interplay of reaction engineering and natural products total synthesis can lead to previously unforeseen possibilities in bond construction.

Acknowledgment. We extend our appreciation to the many Overman group co-workers, cited in the references, whose creativity, dedication, and experimental skill have been critical to the development of this program. We would also like to thank the National Institutes of Health and the National Science Foundation for providing the majority of financial support for these investigations; L.D.P. was supported in part by a Pharmacia & Upjohn Graduate Fellowship in Synthetic Organic Chemistry. The artwork was provided by Jo-Lin Foster.

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