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Studies for the synthesis of marine natural products*

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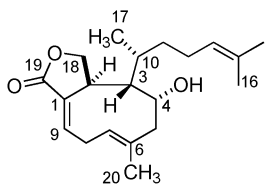
Abstract: The process of allylic transposition in S_E' reactions is a significant construct for synthesis. The flexibility of a variety of allylation strategies provides for the rational design of pathways to a diverse array of complex targets. Our recent studies of S_E' reactions will examine issues of stereoselectivity and efficiency in the context of applications toward the synthesis of marine natural products such as the xenicane diterpenes, which feature the strained *E*-cyclononene ring system, and peloruside A, a 16-membered macrocyclic lactone.

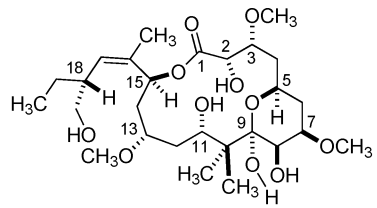
Keywords: natural products; xenicanes; peloruside A; asymmetric allylation reactions; *B*-alkyl Suzuki cross-coupling; Kumada cross-coupling; *E*-cyclononenes.

INTRODUCTION

The isolation and structural elucidation of secondary metabolites from marine sources have provided an array of unique molecular architectures stimulating new opportunities in organic chemistry. While specific substances are deemed to be important largely because they express significant biological properties, it should be widely appreciated that many novel molecular structures have inspired major advancements in the science of organic synthesis. Our studies toward selected marine natural products have examined the efficiency of S_E' substitution reactions for complex constructions pertaining to issues of functionality and stereochemistry [1]. Recent investigations toward 4-hydroxydictyolactone (**1**) and peloruside A (**2**) present distinctly different challenges for synthesis and are illustrative of these developments (Scheme 1).



4-Hydroxydictyolactone (1)



Peloruside A (2)

Scheme 1 Structures of marine metabolites **1** and **2**.

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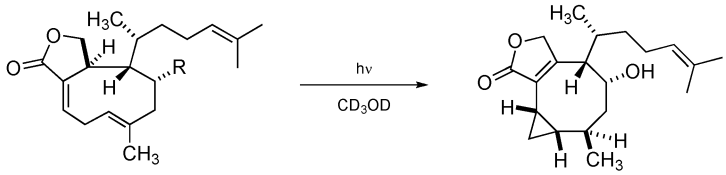
STUDIES TOWARD THE XENICANES

Guella and Pietra first reported the isolation and elucidation of 4-hydroxydictyolactone (**1**) from *Dictyota ciliolate* in 1993 as an example of the xenicane family of marine natural products which notably exhibit the strained nine-membered carbocyclic core containing an *E*-trisubstituted alkene [2,3]. The parent compound, dictyolactone (**3**), had been previously isolated from the sea hare *Aplysia depilans* in 1979 [4], although it was described in the enantiomeric series owing to the initial report of the diterpene, xenicin from *Xenia elongata* [5]. Subsequently, Kakisawa and coworkers showed that xenicane examples originating from *Dictyotaceae* algae possess the antipodal configuration as compared to members of the family which are isolated from soft coral [6]. Thus, it cannot be assumed that these metabolites are distributed through the aquatic environment via a common food chain.



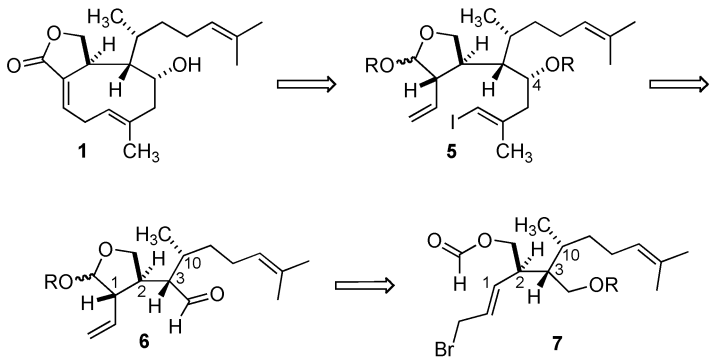
1 (R = OH)
3 (R = H: Dictyolactone)

4 (4-Hydroxycrenulide)

Scheme 2 Photoisomerization of **1** to **4**.

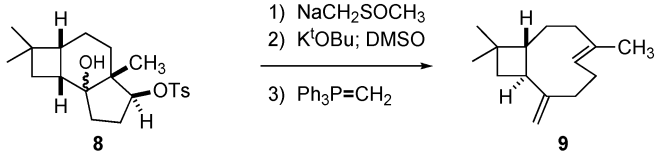
In addition, the UV irradiation of **1** (Scheme 2) produces a photoisomerization to give 4-hydroxycrenulide (**4**), which had been previously isolated from samples of *Dictyota* [2]. While the photochemical conversion formally presents an intramolecular ene process, the prospects of a concerted reaction would anticipate an antarafacial homo[1,5]-hydrogen shift, yielding the C-6 diastereomer. In fact, a free radical mechanism may be operative in the formation of **4**, and may characterize enhanced reactivity in the strained *E*-cyclononene ring system of **1**. Irradiation of the corresponding (*Z*)-6,7-isomer of **1** did not afford cyclopropane products. The reactivity of the (*E*)-cycloalkene system may be an important factor leading to the reports of cytotoxicity, and the antibiotic and antiviral activities generally ascribed to xenicane diterpenes.

Our plans for synthesis of 4-hydroxydictyolactone (**1**) have focused on the deployment of the *B*-alkyl Suzuki reaction [7] as a palladium-catalyzed cross-coupling to incorporate the intact *E*-cycloalkene (Scheme 3).



Scheme 3 Retrosynthetic plan toward 4-hydroxydictyolactone (**1**).

We rationalized that the formation of a palladium metallocycle would overcome the entropic and ring strain features which often dominate processes for direct ring closure in 9- and 10-membered carbocycles, and the subsequent reductive elimination would be sterically feasible to yield the desired *E*-cyclononene. This approach is a departure from the classic work of Prof. E. J. Corey, who devised the use of the Grob fragmentation of **8** (Scheme 4) for the synthesis of ±-caryophyllene (**9**) [8]. This stereocontrolled event established an important precedent for the preparation of medium-ring carbocycles, particularly *E*-cyclononenes via the fragmentation of fused bicyclic systems. Recently, Corey has reported the Grob fragmentation leading to a stable *E*,*Z*-cyclononadienone for the enantioselective synthesis of caryophylloids [9].

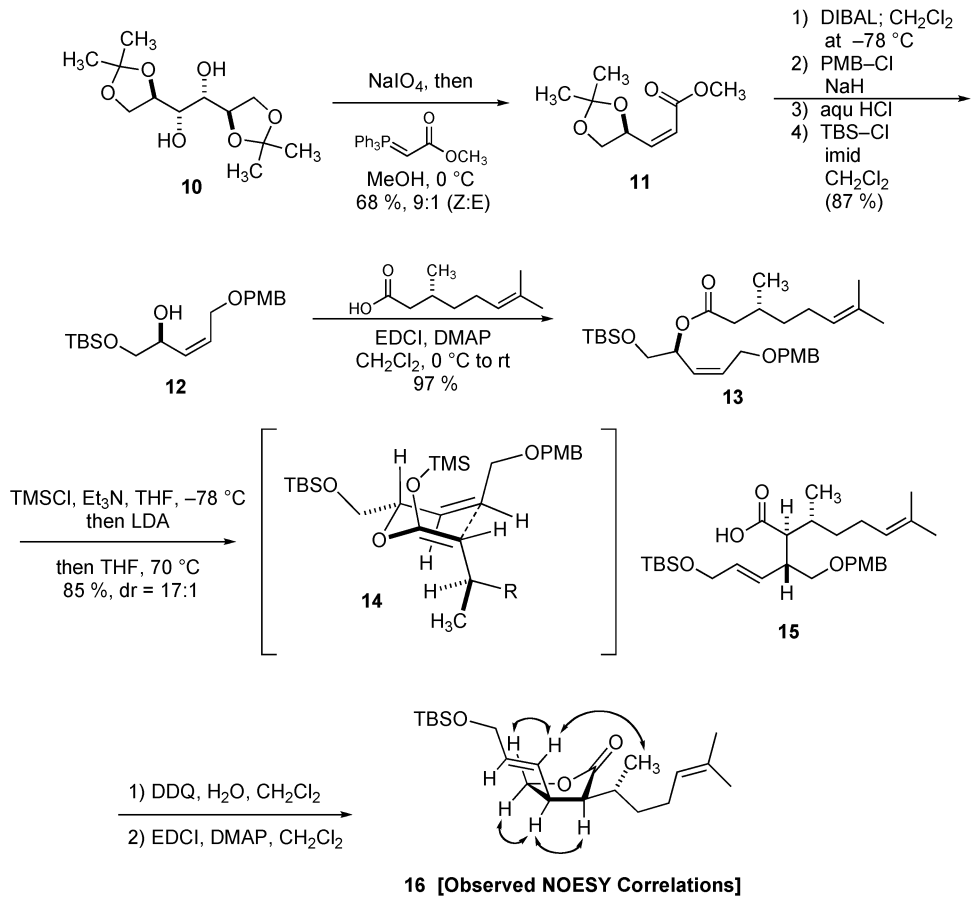


Scheme 4 The Grob fragmentation route to (±)-caryophylene (**9**).

With the advent of ring-closing metathesis (RCM) [9], new opportunities have been explored for the synthesis of medium-ring carbocycles. However, *E*-cyclononenes present obvious problems for RCM strategies [11]. While the alkenyliodide **5** (Scheme 1) serves as the penultimate intermediate for the *B*-alkyl Suzuki ring closure, we envisioned its efficient construction via two sequential S_E' allylation processes. One of these reactions would establish the stereochemistry at C-4 and provide for conversion of aldehyde **6** to the vinylic iodide **5**. The initial allylation was projected as a stereocontrolled intramolecular event as depicted by the reduction of bromide **7** to yield the tetrahydrofuranyl ring as an element of constraint to aid in the subsequent cyclononene ring closure. In fact, the stereogenicity depicted at C-1 in the formation of **6** appeared to be a requirement for the prospects of a successful ring closure.

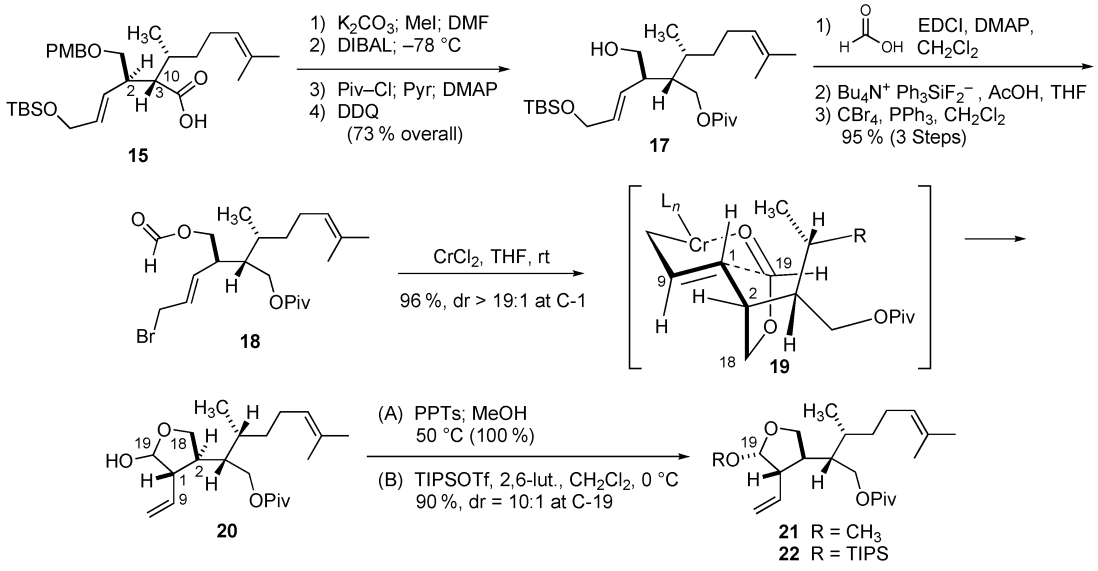
RESULTS AND DISCUSSION

The preparation of nonracemic **7** (Scheme 3) required a high degree of stereocontrol for the assembly of the contiguous stereotriad of C-2, C-3, and C-10. This aspect is often problematic because the tertiary centers of asymmetry possess an "all-carbon" substitution pattern. The Claisen rearrangement is particularly well suited to meet this challenge. As illustrated in Scheme 5, the synthesis of the optically pure Ireland–Claisen precursor **13** utilized the diacetonide of D-mannitol as a chiral pool source. Oxidative cleavage and direct Wittig olefination in methanol gave a 9:1 (*Z*:*E*) ratio of unsaturated methyl esters [12]. Upon flash chromatography and diisobutylaluminum (DIBAL) reduction, the *Z*-allylic alcohol was protected as the *para*-methoxybenzyl ether (PMB), and ketal hydrolysis was followed by protection of the primary alcohol to yield **12**. Esterification of **12** with (*R*)-(+)-citronellic acid produced **13** which provided for kinetic deprotonation at –78 °C. We anticipated the formation of the *E*(O)-TMS enol ether, and subsequent heating of the tetrahydrofuran (THF) solution in a resealable Carius tube at 70 °C resulted in the isolation of carboxylic acid **15** (85 %) as the major product (dr 17:1). The minimization of steric factors in the chair-like transition state **14** account for the formation of diastereomer **15**, which was confirmed by conversion to the *cis*-butyrolactone **16** for NMR studies leading to the observed nuclear Overhauser enhancement spectroscopy (NOESY) correlations.



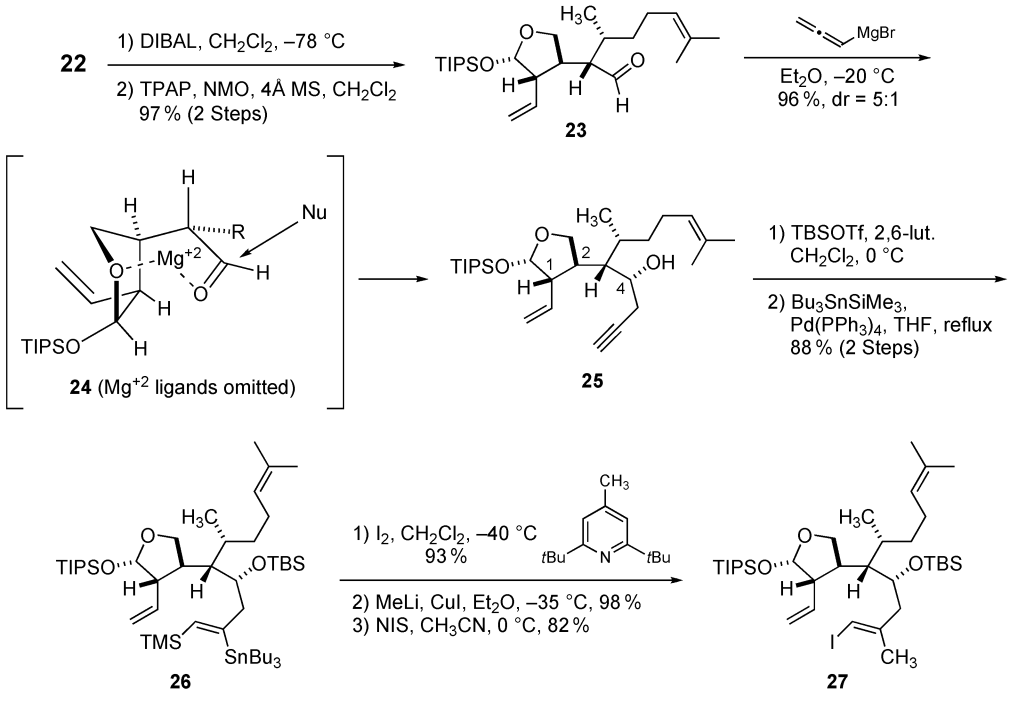
Scheme 5 Formation of acid **15** via the Ireland–Claisen rearrangement.

Carboxylic acid **15** was transformed into the pivaloate (Piv) **17** (Scheme 6) in four straightforward steps (73 % overall from **15**), and esterification with formic acid led to **18** upon introduction of the allylic bromide. Adaptation of the Nozaki–Hiyama conditions [13] provided a facile intramolecular cyclization to the lactol **20**. High stereocontrol at C-1 was observed for the S_E' alkylation via internal coordination of the alkenylchromium species **19**, and the subsequent quantitative conversion to the methyl acetals (reaction A) gave an inseparable mixture of diastereoisomers (dr 1.4:1). On the other hand, the tri-isopropylsilyl ether **22** was formed with excellent stereoselectivity (dr 10:1) (reaction B), and was purified as a single C-19 diastereomer for further reactions.



Scheme 6 Nozaki–Hiyama cyclization in the formation of lactol **20**.

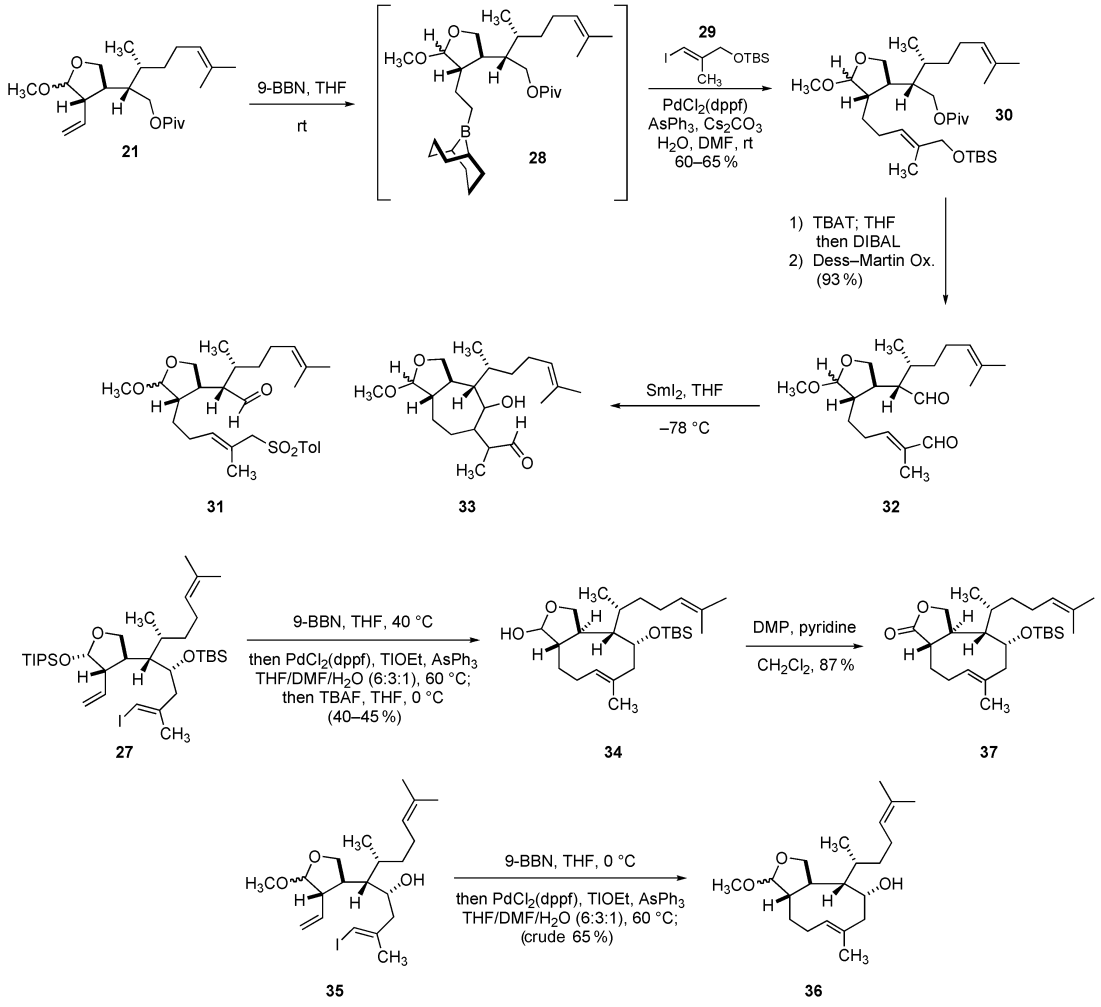
Upon preparation of aldehyde **23** (Scheme 7), we began studies of allylation reactions with Lewis acid activation. The coordination of divalent cations offered improved stereoselectivity at C-4. These findings led to the use of allenylmagnesium bromide [14], which proved to be operationally effective for preparative scale reactions. This S_E' propargylation conveniently gave high yields of alcohol **25** with



Scheme 7 Stereocontrolled preparation of **27**.

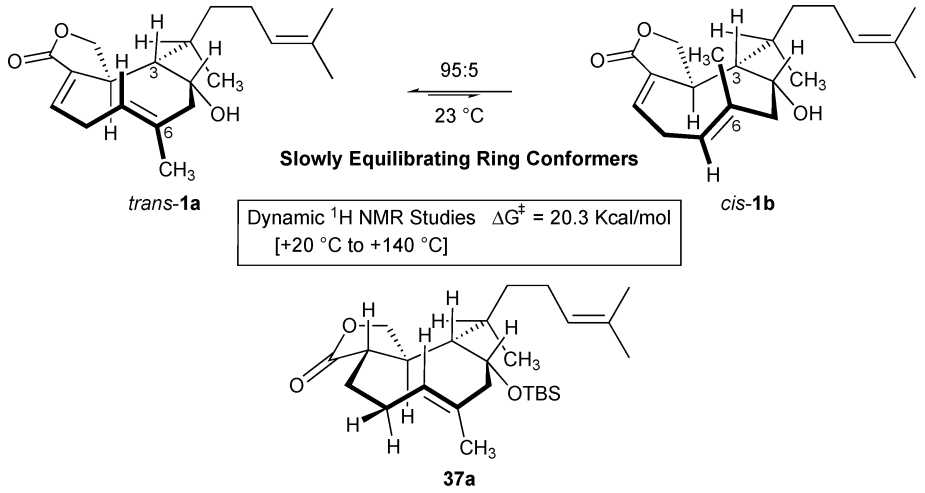
C–C bond formation from the *exo*-face of the coordination complex **24** (dr 5:1). Finally, the synthesis of the desired alkenyl iodide precursor for ring cyclization was obtained by the palladium-catalyzed silylstannylation [15] of the terminal alkyne of **25** followed by three efficient steps for stereocontrolled conversion to the *E*-trisubstituted **27**.

Our studies of the *B*-alkyl Suzuki cross-coupling [7] initially explored the reactivity of alkene **21** (Scheme 8) which provided 60–65 % unoptimized yields of **30** using iodide **29**. The protected diol **30** presented clear opportunities for cyclononene formation. However, subsequent preparation of sulfone **31** failed to produce the cyclic β-hydroxysulfones upon treatment with strong bases in spite of evidence of α-sulfonyl carbanion formation (deuterium incorporation) [16]. Alternatively, the reductive pinacol coupling of dialdehyde **32** gave rise to the cycloheptenol isomers **33**. Fortunately, the successful cyclization of **27** occurred upon hydroboration of the terminal alkene to deliver the *E*-cyclononene **34** in 40 % unoptimized yields as an example of an intramolecular *B*-alkyl Suzuki reaction .



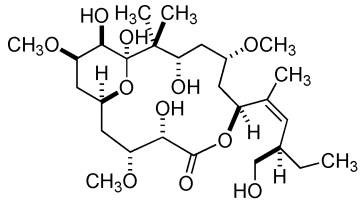
Scheme 8 *B*-Alkyl Suzuki cross-coupling studies.

We recognized that the steric environment imposed by the presence of the silyl ethers in **27** made the monosubstituted alkene surprisingly inaccessible, and competing hydroboration of the trisubstituted olefin diminished production of the desired **34**. To address this problem, the methyl acetals **21** were utilized in the preparation of the diastereomeric mixture of alcohols **35** via the route described in Scheme 8. In the cyclization process, the reaction temperature was reduced to 0 °C, improving chemoselectivity for the initial hydroboration, and improving results in the production of **36**. Subsequently, cyclization products **34** and **36** were independently converted into the lactone **37** for full characterization. In this regard, Pietra and coworkers studied the slow equilibration of ring conformations of 4-hydroxydictyolactone (**1**) [17], and assigned the *trans*-conformer **1a** (Scheme 9) in which the C-3 hydrogen is *trans* to the methyl at C-6, as the major contributor at room temperature. *Cis*-conformer **1b** was detected in small amounts. Our efforts for direct cyclization leading to the *E*-cyclononene systems **34** and **36** were confirmed by the key NOESY correlations of our NMR studies, which established *trans*-**37a** as the observed conformation of this strained xenicane framework.



Scheme 9 Nine-membered ring conformations of 4-hydroxydictyolactone and dihydro-**37**.

STUDIES TOWARD PELORUSIDE A (2)



2 (Peloruside A)

The potent microtubule-stabilizing activity of (+)-peloruside A (**2**), has attracted widespread attention owing to the reports of the cytotoxicity of **2** in multi-drug-resistant cancer cell cultures [18]. Indeed, the unique molecular architecture of **2** may ultimately serve as the primary stimulus for the creation of new therapeutic agents for the treatment of certain cancers. On the other hand, we have also recognized opportunities presented by the arrangement of dense functionality and stereochemical features in structure **2** for advancements of synthetic organic chemistry. Investigations of Northcote and coworkers had de-

scribed the isolation and structure elucidation of the 16-membered macrolactone **2** from the marine sponge *Mycale hentscheli* [19]. These efforts included NMR studies leading to assignments of relative stereochemistry. Subsequently, the initial synthesis of the biologically inactive antipodal of **2** by DeBrabander and coworkers established the absolute configuration [20], and recent NMR studies by Northcote, Diaz, and others [21] have provided a conformational analysis in chloroform and in water (Fig. 1). The primary substitution pattern of **2** reveals a skipped 1,3,5-polyol arrangement of polyketide origins. This pattern is disrupted by the introduction of two oxidations to incorporate the C-2 hydroxy and the C-9 ketone, which is masked as the hemiketal. In this regard, the macrocycle is conformationally restricted in the region from C-1 through C-10 owing to the presence of the bridging tetrahydropyranyl ring.

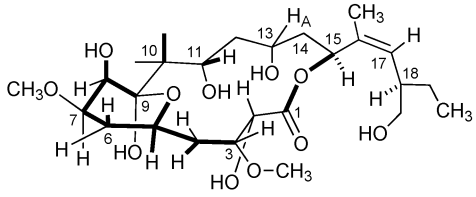
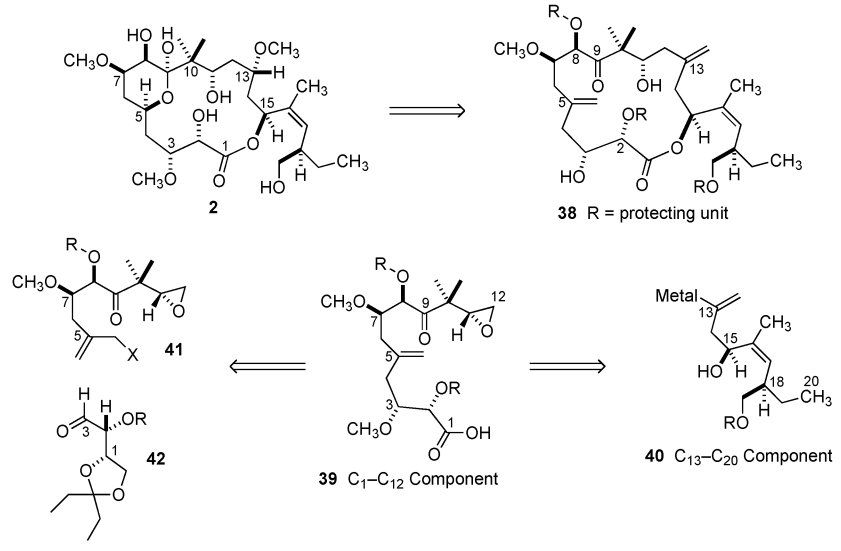


Fig. 1 Conformational illustration of peloruside A in $CHCl_3$.

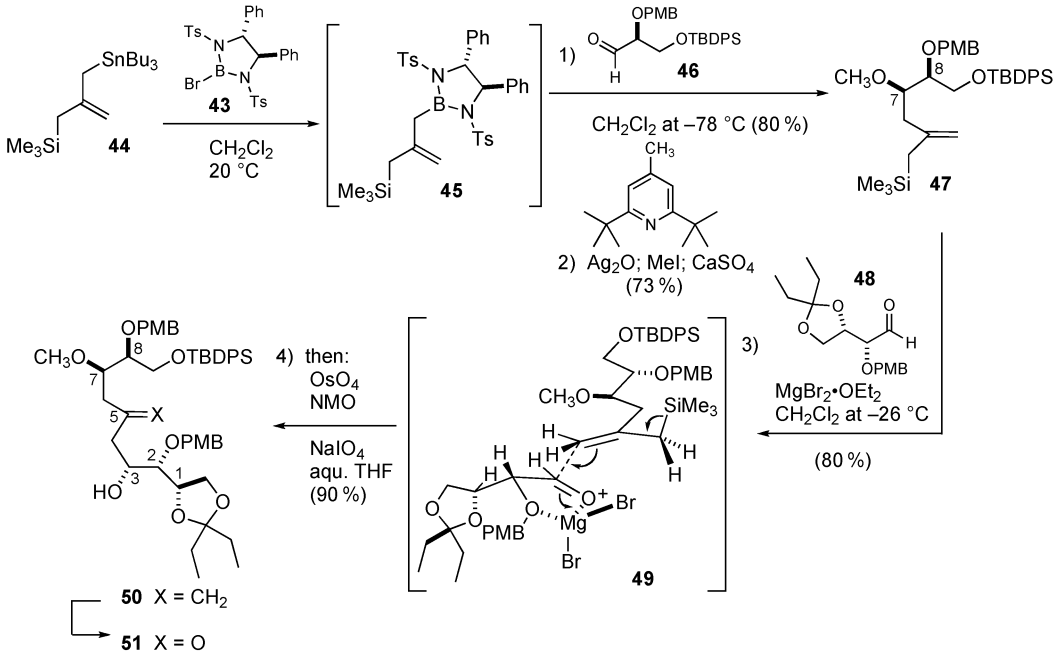
Our retrosynthetic analysis considered a convergent approach (Scheme 10), which would utilize the advantages of S_E' alkylation reactions to design a rationale for addressing the challenging substitution pattern and stereochemical features of **2**. The macrocyclic lactone **38** allows for oxidative introduction of ketones at C-5 and C-13. The stereocontrolled reductions at C-5 and at C-13 would directly lead to the hemiketal, and O-methylations at C-3 and C-13 would complete the synthesis of **2**. Our plans for preparation of **38** chose to incorporate the C-11 stereogenicity in the chiral epoxide of **39**. This plan dictated the deployment of a nucleophilic C-13 to C-20 component **40** as an alkenylorganometallic species which would embody the *Z*-allylic alcohol at C-15. The C-15 alcohol would subsequently undergo intramolecular lactonization upon the unveiling of the C-1 carboxylate. Finally, component **39**



Scheme 10 Convergent retrosynthetic analysis of peloruside A.

was recognized as the product of an ambitious allylation reaction of the activated **41** (X = Br, $SiMe_3$, or $SnBu_3$) and nonracemic aldehyde **42**.

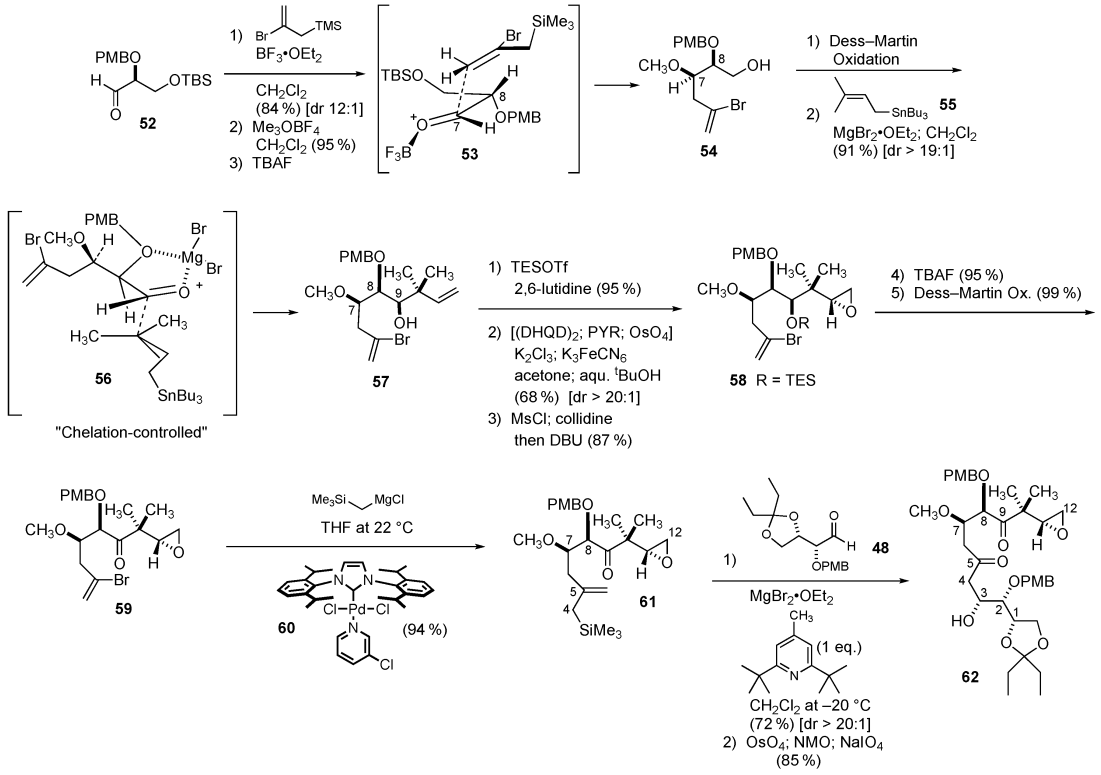
Exploratory studies of our proposed asymmetric allylation were supported by the Corey-Williams protocol [22] using the nonracemic (*R*,*R*)-bromoborane **43** for quantitative transmetalation of stannane **44** for in situ generation of the bifunctional allylic borane **45** (Scheme 4). The chiral auxiliary of **45** provided for a stereoselective condensation with aldehyde **46** at –78 °C to yield (80 %) the *R*-homoallylic alcohol as the major diastereomer (dr 8:1) via a closed, six-membered transition state. O-methylation directly led to the allylsilane **47** for the Sakurai reaction with aldehyde **48** via chelation-controlled conditions through the open, synclinal transition state **49**. This strategy proved highly advantageous for the expedient construction of the C-1 to C-9 ketone **51** in four steps.



Scheme 11 Asymmetric allylation of bifunctional lynchpin **44** for construction of 1,5-stereochemistry in **51**.

Our initial results provided encouragement for an iterative allylation pathway to the fully competent C-1 to C-12 component **39**. As shown in Scheme 12, the Sakurai reaction of chiral aldehyde **52** in the presence of $BF_3{\cdot}OEt_2$ displayed high diastereoselectivity via the Felkin-Anh model **53**, and O-methylation followed by deprotection gave **54**. Oxidation of primary alcohol **54** and S_E' reverse prenylation with the addition of stannane **55** selectively afforded **57** under chelation-controlled conditions with precomplexation of $MgBr_2OEt_2$ as illustrated in **56** to assemble the C-7, C-8, C-9 stereotriad.

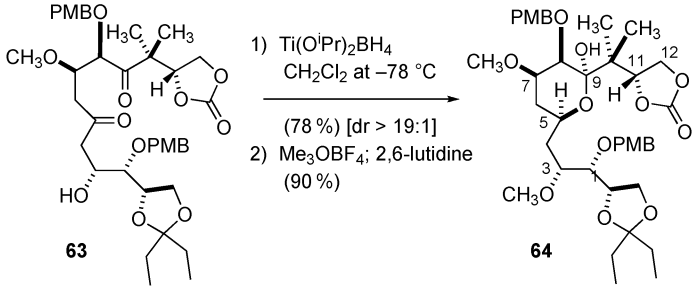
Subsequently, we utilized a chemoselective asymmetric Sharpless dihydroxylation [23] to produce a single diol for mesylation and conversion to the epoxide **58**. Upon straightforward preparation of the C-9 ketone **59**, a Kumada cross-coupling [24] of alkenylbromide **59** occurred with trimethylsilylmethyl magnesium chloride in the presence of the PEPPSI (pyridine-enhanced precatalyst preparation, stabilization, and initiation) palladium catalyst **60** [25]. The reaction installed the nucleophilic allylic silane of **61** under mild conditions in high yield (94 %). Finally, the condensation of **61** with aldehyde **48** was accomplished with high stereoselectivity under the conditions of chelation control as we had previously developed in our model system. This two-step sequence presents a strategic advance



Scheme 12 Iterative allylation strategy for synthesis of **62**.

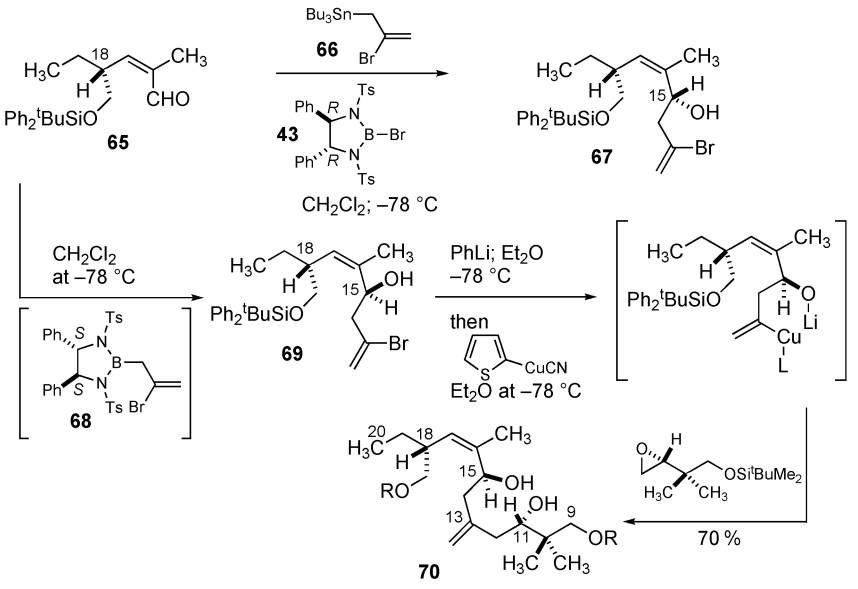
for the utilization of the S_E' construct as a key convergent operation for the preparation of polyfunctional molecules. The subsequent Lemieux oxidation provided the desired C-5 ketone **62** as the product of a formal stereocontrolled acetate aldol reaction leading to C-3–C-4 bond formation.

The success of Scheme 12 has also facilitated our studies of tetrahydropyranyl ring formation. In this case, the diol derived from the Sharpless asymmetric dihydroxylation of **57** (Scheme 12) was transformed to its corresponding carbonate and advanced in analogous fashion to afford the diketone **63** (Scheme 13). A directed reduction of **63** has been achieved utilizing the C-3 alcohol and $Ti(O^iPr)_2BH_4$ which undergoes in situ oxidation to the titanium(IV) species for Lewis acid coordination to the C-5 carbonyl [26]. The reagent generally provides for 1,3-*syn*-diol formation via the six-membered chelate. In our example, product isolation gave the expected hemiketal, and O-methylation yielded **64** (Scheme 13).



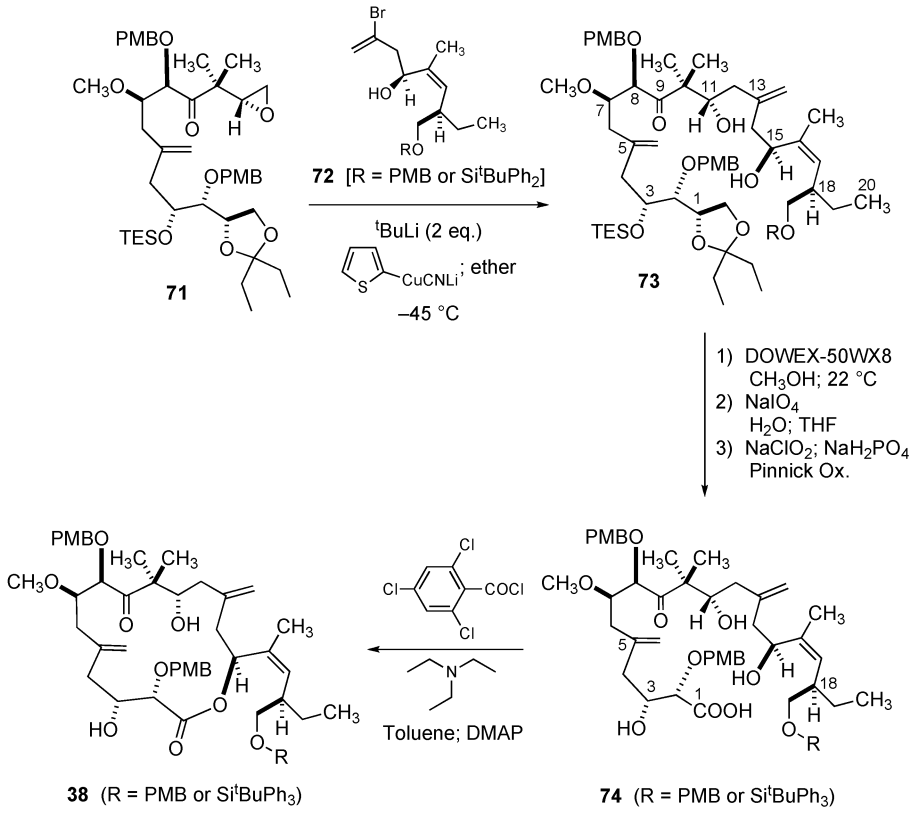
Scheme 13 Reductive formation of the tetrahydropyranyl system.

Allylation reactions have also proven to be useful for the stereocontrolled synthesis of an appropriately functionalized C-13–C-20 precursor for the organometallic species **40** of Scheme 10. Our efforts are summarized by the results of asymmetric allylation in Scheme 14. The preparation of the nonracemic (*Z*)-aldehyde **65** was accomplished by use of the Still–Gennari–Wittig protocol [27] and the subsequent asymmetric allylation was undertaken by quantitative transmetalation of stannane **66** with the chiral (*R*,*R*)-bromoborane **43** to afford a single allylic alcohol diastereomer **67**. In this case, the auxiliary provides for a matched reaction supporting the intrinsic bias for production of the unnatural (*S*)-C_{15} stereochemistry in **67**. With the incorporation of the *tert*-butyldiphenylsilyl ether in the *Z*-aldehyde **65**, we predominantly observed auxiliary control in the mismatched reaction with (*S*,*S*)-borane **68** to yield the natural C_{15} alcohol **69** (dr 19:1). In principle, either C_{15} isomer **67** or **69** may ultimately lead to an efficient macrocyclization. However, our initial studies with **69** have provided an active cuprate reagent following deprotonation and halogen exchange with PhLi at –78 °C, which has yielded the diol **70**.



Scheme 14 Synthesis of the C_{13}–C_{20} components **67** and **69**.

Our ongoing studies (Scheme 15) have demonstrated the reaction of cuprates derived from **72** (R = PMB or Si^{t}BuPh$_2$) with the oxirane **71** at low temperature to provide modest, unoptimized results (30–45 % yields) of the desired adduct **73**. Preliminary efforts have produced small quantities of the *seco*-acid **74** for our lactonization studies leading to the penultimate lactone intermediate **38**, and further efforts toward the natural product are underway.



Scheme 15 Formation of *seco*-acid **74**.

In summary, efficient pathways for enantiocontrolled syntheses of marine natural products exhibiting novel molecular architectures have been devised. Suzuki cross-coupling methodology has been utilized for a direct intramolecular cyclization to form the strained *E*-cyclononene skeleton as featured in 4-hydroxydictyolactone, a prominent example of the xenicane diterpenes. Key elements of stereogenicity were addressed by the incorporation of S_E' allylation reactions. As illustrated in the studies of the 16-membered macrolactone, peloruside A, the versatility of allylation processes has provided an effective strategy for stereoselective transformations in a demanding context. Allylation reactions have been demonstrated as key convergent operations for the preparation of target molecules bearing significant stereochemical complexity and functionality.

ACKNOWLEDGMENTS

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