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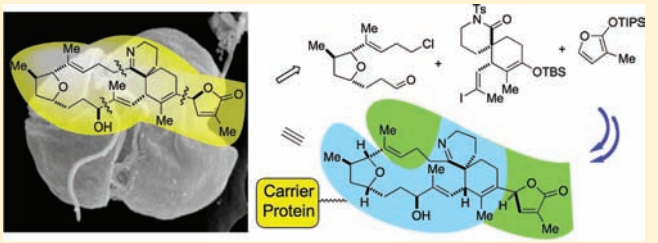
Total Synthesis of the Spirocyclic Imine Marine Toxin (−)-Gymnodimine and an Unnatural C4-Epimer

Ke Kong,[‡] Ziad Moussa,[§] Changsuk Lee,[∥] and Daniel Romo*[,†]

[†]Department of Chemistry, Texas A&M University, P.O. Box 30012, College Station, Texas 77842-3012, United States

Supporting Information

ABSTRACT: The first total synthesis of the marine toxin (−)-gymnodimine (**1**) has been accomplished in a convergent manner. A highly diastereo- and enantioselective *exo*-Diels−Alder reaction catalyzed by a bis-oxazoline Cu(II) catalyst enabled rapid assembly of the spirocyclic core of gymnodimine. The preparation of the tetrahydrofuran fragment utilized a chiral auxiliary based *anti*-aldol reaction. Two major fragments, spirolactam **56** and tetrahydrofuran **55**, were then coupled through an efficient Nozaki−Hiyama−Kishi reaction. An unconventional, ambient temperature *t*-BuLi-initiated intramolecular Barbier reaction of alkyl iodide **64** was employed to form the macrocycle. A late stage vinylogous Mukaiyama aldol addition of a silyloxyfuran to a complex cyclohexanone **83** appended the butenolide, and a few additional steps provided (−)-gymnodimine (**1**). A diastereomer of the natural product was also synthesized, C4-*epi*-gymnodimine (**90**), derived from the vinylogous Mukaiyama aldol addition.



INTRODUCTION

Among the various bioactive marine natural products that have been isolated and studied, marine toxins occupy a very unique, albeit notorious, position. Often produced by microalgae, especially dinoflagellates, marine toxins are the culprits of numerous cases of massive fish kills, marine wildlife death, and even human intoxication due to consumption of contaminated seafood.[1] Despite the negative societal and economical impacts brought by these incidents, many of these naturally occurring toxins, including tetrodotoxin,[2a] domoic acid,[2b] and okadaic acid,[2c,d] have served as extremely valuable tools for probing biological or pharmacological phenomena, primarily in the area of the human nervous system.[2] For this reason, studies of marine toxins continue to be the subject of extensive research worldwide in a number of disciplines, from chemistry to cell biology.

One such emerging class of marine toxins is the spirocyclic imine containing natural products,[3] with representative examples including gymnodimine (**1**, Figure 1), spirolides (**2**),[4] pinnatoxins (**3**),[5] pteriatoxins,[6] and spiro-prorocentrimine.[7] Gymnodimine (**1**) has a special place in this family of spirocyclic imine toxins, as it possesses a 6,6-spirocyclic imine, an elaborate butenolide appendage, and is also one of the first members isolated. Yasumoto and co-workers first isolated gymnodimine in 1995 from oysters *Tiostrea chilensis* collected off the coast of New Zealand, and the gross structure was initially assigned on the basis of extensive NMR studies.[8] Subsequently, Munro, Blunt, and co-workers established the relative and the absolute configurations of gymnodimine through X-ray crystallographic analysis of a *N*-acylated derivative of an imine reduced gymnodimine.[9] More recently, two new analogues, gymnodimines

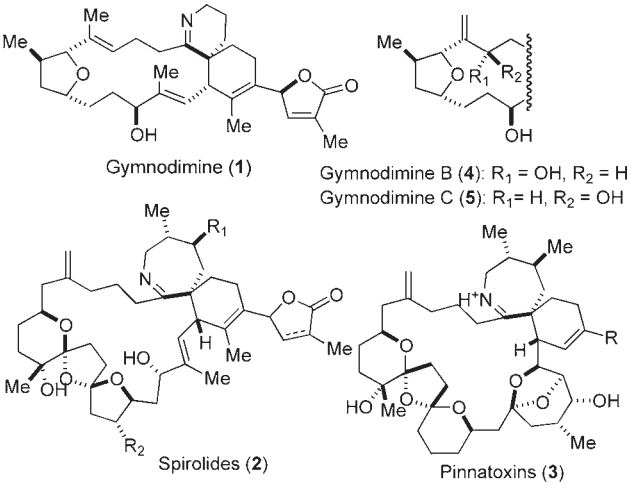


Figure 1. Structures of representative spirocyclic-imine-containing marine natural products.

B (**4**) and C (**5**), were isolated that include an apparent allylic oxidation with olefin transposition.[10]

Following its initial isolation off the coasts of New Zealand, gymnodimine has also been identified in the waters surrounding the Tunisian, South African, European, and North American coasts, likely due in part to transport via ballast water by the shipping industry.[11] The worldwide occurrence of gymnodimine and other marine toxins in ocean waters poses serious concerns

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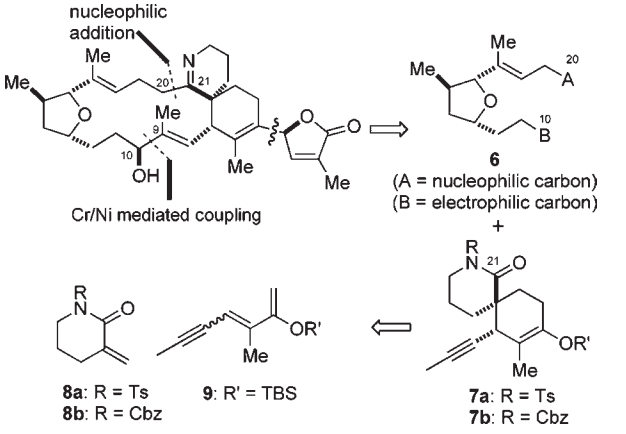
over the potential impact to seafood safety. Indeed, gymnodimine has been associated with several incidents of neurotoxic shellfish poisoning in New Zealand.[12] Gymnodimine exhibited high toxicity (LD_{50}: 96 μg/kg by injection; 755 μg/kg by oral administration); however, the toxicity was significantly reduced when administered with food.[13] More recent studies demonstrated that gymnodimine, along with 13-desmethyl spirolide C and pinnatoxin A, exert their toxic effects via binding to nicotinic acetylcholine receptors with picomolar affinities with no sign of apparent reversibility in short time frames.[14] The toxicity of gymnodimine has been attributed, at least in part, to the imine functionality, as its reduction leads to a nontoxic derivative.[9] This hypothesis was further supported by the loss of toxicity when the imine functionality of the related toxin, spirolide B, was reduced to an amine, or in the case of spirolides E and F, which bear a hydrolyzed imine ring.[4b] On the basis of recent X-ray crystal structures of gymnodimine and 13-desmethyl spirolide C bound to acetylcholine binding proteins, the origin of the pharmacological effect of the spirocyclic imine appears to be a key hydrogen bond between the protonated cyclic imine and a tryptophan residue that positions these natural toxins within the center of the binding pocket.[14]

This family of spirocyclic-imine-containing marine toxins has spurred intense synthetic efforts that have culminated in total or formal syntheses of the pinnatoxins by the groups of Kishi, Hirama, and Zakarian[14b,15] and pteriatoxins by Kishi.[16] Synthetic studies toward the spirolides have also been described.[17] However, the total synthesis of gymnodimine remained elusive prior to our communication in 2009.[18] The challenging structural elements of gymnodimine include a trisubstituted tetrahydrofuran within a 16-membered carbocyclic macrocycle, an azaspiro[5.5]undecadiene moiety, and a labile chiral butenolide. The total synthesis of gymnodimine and analogues will enable more detailed SAR studies of spirocyclic imine marine toxins. In addition, efficient syntheses of various fragments of gymnodimine would facilitate the development of an efficient enzyme-linked immunosorbent assay (ELISA) for detection of gymnodimine and congeners. Herein, we describe the full details of our synthetic endeavors toward this class of marine toxins, which has led to the first total synthesis of (−)-gymnodimine and (+)-C4-*epi*-gymnodimine.[19]

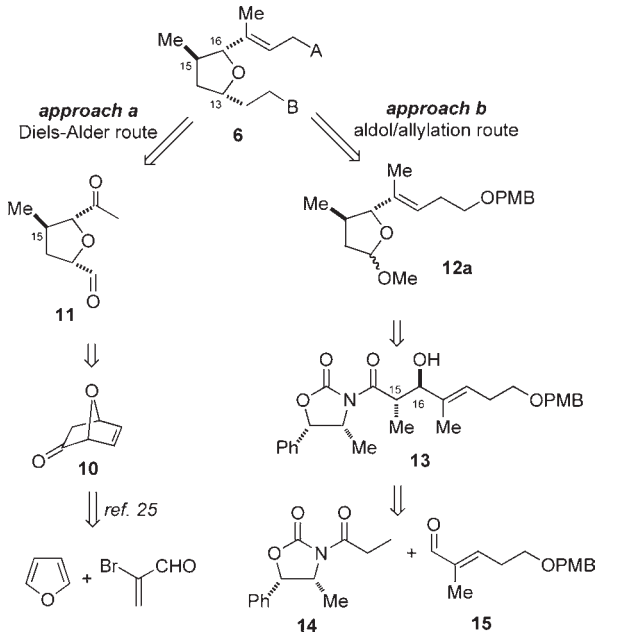
RESULTS AND DISCUSSIONS

Retrosynthetic Analysis. Mindful of the known sensitivity of the butenolide moiety of gymnodimine to both basic and even neutral conditions,[20] we decided to delay the introduction of this functionality until the late stages of the synthesis (Scheme 1). This would have the additional benefit of maximizing convergency and avoiding unnecessary adjustments of the oxidation state of the butenolide. From a retrosynthetic perspective, we initially projected a late-stage coupling to assemble the C9−C10 bond to close the 16-membered macrocycle. Among numerous possibilities considered, we were attracted to the Nozaki−Hiyama−Kishi (NHK) coupling due to its well-established functional group compatibility[21] and its prior use in macrocylizations.[22] While some degree of stereocontrol at the C10 carbinol center might be expected during this intramolecular NHK coupling, due to minimization of eclipsing interactions of the intermediate vinyl chromium species,[22] neither the stereoselectivity nor the relative stereochemical outcome of this macrocyclization reaction could be predicted initially. In the worst-case scenario, an inversion process would be required to correct the

Scheme 1. Initial Synthetic Plan for Gymnodimine



Scheme 2. Strategies for the Synthesis of Tetrahydrofuran 6



stereochemistry of a C10 diastereomer.[23] Further disconnection at the C20−C21 bond would lead to two precursors of similar complexity, namely tetrahydrofuran **6** and spirolactam **7**. In the forward sense, these two fragments would be joined at C20/C21 through a nucleophilic addition of the tetrahydrofuran fragment to the δ-lactam carbonyl, with a number of possible strategies envisioned. At the outset of our studies, we recognized the challenges associated with this strategic bond disconnection given the poorly electrophilic and sterically congested nature of the C21 lactam carbonyl bearing an α-quaternary carbon. As described below, the eventual realization of such a disconnection became a primary hallmark of our synthesis.

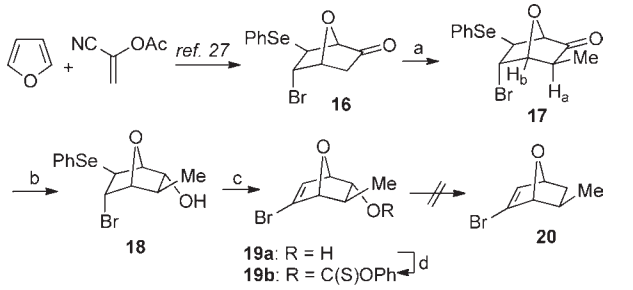
A Diels−Alder reaction appeared well suited for the preparation of spirolactam **7**, leading back to α-methylene lactam **8** and diene **9** as precursors. The utility of a catalytic, enantioselective Diels−Alder process was attractive given that it had rarely been used in natural product total synthesis at the time we initiated our studies.[24]

Synthesis of the Tetrahydrofuran Fragment 6. In contemplating a synthetic plan toward the tetrahydrofuran fragment **6**, two approaches were considered and evaluated (Scheme 2). In the first approach (approach a, Scheme 2), the bicyclic ketone **10**, bearing two of the three stereogenic centers necessary for the formation of fragment **6**, was recognized as a good starting point.[25] Conceivably, the methyl group at C15 could be introduced in a diastereoselective fashion taking advantage of the bicyclic nature of **10**, while the olefin in **10** would serve as a latent ketoaldehyde **11** to ultimately reveal a *cis*-substituted tetrahydrofuran bearing the C13 and C16 stereocenters. Adding to the appeal of this approach was the ease of preparing known ketone **10** and its availability in high enantiomeric excess through an oxazaborolidine-catalyzed enantioselective Diels–Alder reaction of furan with α-bromoacrolein.[26] Alternatively, use of acyclic stereocontrol to access tetrahydrofuran **6** would initially involve an *anti*-aldol reaction between carboximide **14**[27] and aldehyde **15**[28] (approach b, Scheme 2) followed by a diastereoselective allylation of furanose **12a**.

Our initial explorations of the Diels–Alder strategy toward tetrahydrofuran **6** began with the known ketone **16**, readily prepared in racemic form from furan and α-acetoxyacrylonitrile in three steps (Scheme 3).[29] While methylation of the enolate derived from ketone **16** was initially complicated by incomplete conversion and self-condensation, considerable experimentation revealed conditions (LiHMDS, DMPU, MeI) to generate methyl ketone **17** in a reproducible manner with high diastereoselectivity and acceptable yield. The *exo* stereochemistry of the methyl group in ketone **17** was judged from the absence of the vicinal coupling between H_a and H_b (dihedral angle ~80°). Reduction of the ketone **17** with $NaBH_4$ delivered a 4:1 mixture of epimeric alcohols with the *endo* product **18** isolated in 72% yield. Oxidative elimination of the phenylseleno group afforded the vinyl bromide **19a**. However, our extensive efforts to substitute the bromine for a methyl group were unsuccessful in addition to attempted deoxygenation of the thiocarbonate **19b**. Therefore, we abandoned this approach and resorted to the alternative approach involving initial acyclic stereocontrol to set the stereochemistry of the tetrahydrofuran **6**.

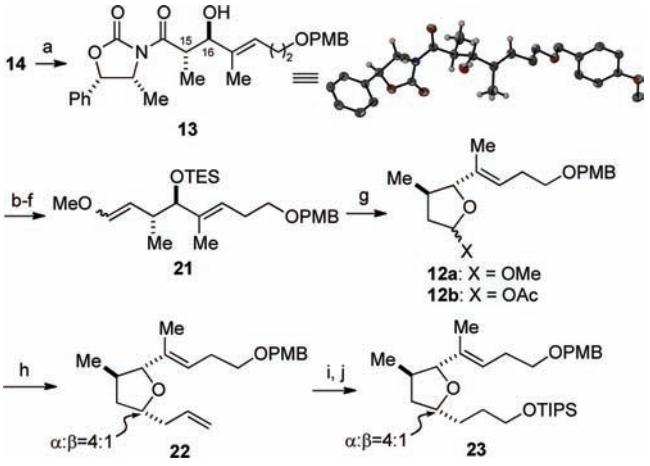
The successful synthesis of tetrahydrofuran **6** commenced with an *anti*-aldol reaction according to the protocol developed by Heathcock,[30] which set the C15/C16 stereogenic centers (Scheme 4). While a mixture of three diastereomers was obtained, the major diastereomer **13** could be isolated in 68% yield and possessed the desired *anti* stereochemistry. The relative stereochemistry was initially deduced from coupling constant analysis (i.e., H_{15} and H_{16}, J = 8.7–9.3 Hz)[28] and was subsequently confirmed by X-ray crystallographic analysis (Scheme 4, inset).[31a] Among various protocols examined to cleave the auxiliary, sodium methoxide proved to be the most efficient in delivering the corresponding methyl ester (80% yield). Following standard transformations, the ester was converted to the methyl enol ether **21** in good overall yield, and cyclization with acidic methanol gave methoxy furanose **12a**. Treatment of the latter with allyl trimethylsilane in the presence of $BF_3 \cdot OEt_2$ provided the allylated furan **22** in moderate diastereoselectivity (dr, 4:1), a result consistent with Woerpel's "inside attack" model.[32] Extensive screening of reaction parameters including Lewis acid, solvent, and silanes failed to provide any noticeable improvement in diastereoselectivity. Treatment of acetoxyfuranose **12b**, derived from hydrolysis followed by acetylation of furanose **12a**, with chiral allylating reagents (e.g., Brown's Ipc_2BAll reagent) in attempts to achieve a double diastereoselective reaction only led to marginal enhancement of the diastereoselectivity (dr, 5:1) and low yield (10%).[33] Thus, the inseparable mixture of allyl diastereomers **22** was carried forward and a site selective hydroboration followed by oxidation and silylation provided the tetrahydrofuran fragment **23**.

Scheme 3. Attempted Synthesis of the Tetrahydrofuran Fragment via a Diels–Alder Approach[a]



[a] Reagents and conditions: (a) LiHMDS, MeI, DMPU, THF, −78 → 22 °C, 63%; (b) $NaBH_4$, MeOH/THF, 0 °C, 72%; (c) H_2O_2, 62%; (d) PhOC(S)Cl, py, CH_2Cl_2, 93%.

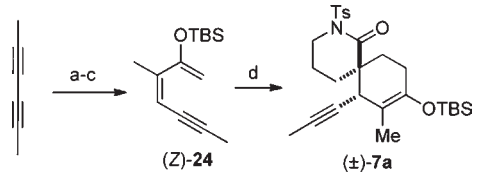
Scheme 4. Synthesis of Tetrahydrofuran Fragment 23 via an anti-Aldol Reaction[a]



[a] Reagents and conditions: (a) *n*-Bu_2BOTf (2.0 equiv), *i*-Pr_2NEt, Et_2O, then **15**, −78 °C, 68%; (b) NaOMe, MeOH, 80%; (c) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 90%; (d) DIBAL, CH_2Cl_2, −78 °C, 93%; (e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 → 22 °C, 99%; (f) Ph_3PCH_2(OMe)Cl, KO*t*Bu, THF, 97%; (g) *p*-TSA, MeOH, 86%; (h) X = OMe, allyl trimethylsilane, $BF_3 \cdot OEt_2$, PhMe/CH_2Cl_2 (1:1), −78 °C, 71%, α/β = 4:1; (i) 9-BBN, THF, then H_2O_2, NaOH, 72%; (j) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 99% (inset: ORTEP representation of the X-ray crystal structure of **13**).

Synthesis of the Spirolactam Fragment 7a. We initially studied the Diels–Alder reaction toward racemic spirolactam to determine the reactivity of the proposed diene and dienophile. Thus, silyloxy diene (*Z*)-**24** was prepared from 2,4-hexadiyne in a highly stereoselective fashion featuring a (*Z*)-selective hydrotelluration reaction (Scheme 5).[19b] Diene (*Z*)-**24** underwent a smooth cycloaddition reaction with *N*-tosyl lactam **8a** in the presence of Et_2AlCl to provide the spirolactam (±)-**7a** in good yield (67%) and excellent diastereoselectivity (dr >95:5). The stereochemical

Scheme 5. Diastereoselective Synthesis of Spirolactam (±)-7a[a]



[a] Reagents and conditions: (a) Bu_2Te_2, $NaBH_4$, EtOH, reflux, 77%; (b) *n*-BuLi, *N*-methyl-*N*-methoxyacetamide, THF, −78 °C, 90%; (c) NaHMDS, TBSOTf, THF, −78 °C, 82%; (d) **8a**, Et_2AlCl, CH_2Cl_2, −30 °C, 67%, dr >95:5.

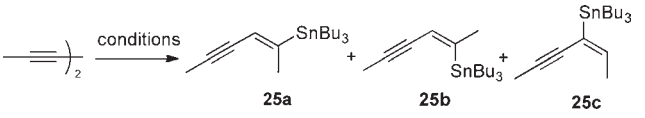
outcome of the Diels−Alder reaction was stereoconvergent with respect to the diene geometry, as the isomeric (*E*)-diene **24** provided the same adduct **7a** in comparable yield under identical conditions (Et_2AlCl, −30 °C), suggestive of a stepwise mechanism for this Diels−Alder process.[19b]

Our initial extrapolation of the asymmetric Diels−Alder variant with lactam **8** and (*Z*)-diene **24** uniformly met with failure, providing no cycloadduct with a variety of chiral catalysts and δ-lactam *N*-activating groups but rather only desilylation of the diene. Reasoning that the olefin geometry may be responsible for the lack of reactivity of the diene under these conditions, due to interactions of the catalyst and (*Z*)-diene **24**, we pursued a diastereoselective synthesis of (*E*)-diene **24**. Use of radical hydrostannylation or Pd-catalyzed hydrostannylation was unsatisfactory, providing the undesired geometrical isomer **25b** and regioisomer **25c** as the major products, respectively (Table 1, entries 1 and 2). Following extensive optimization, we ultimately found that stannylcupration of 2,4-hexadiyne at low temperature gave (*E*)-vinyl stannane **25a** in good regio- and diastereoselectivity (Table 1, entry 3). Adding methanol as a proton source gave a slightly improved yield, but the regio- and diastereoselectivity were diminished (entry 4).[34] The vinyl stannane **25a** was then converted to silyloxy diene (*E*)-**24** following metalation/acylation and silylation (Scheme 6). We were pleased to find that, in the presence of the $[Cu(box)](SbF_6)_2$ Lewis acid developed by Evans,[35] diene (*E*)-**24** participated in a highly efficient Diels−Alder reaction with the bidentate *N*-Cbz lactam **8b**, providing spirolactam **7b** in 85% yield and high diastereoselectivity.[36] After disclosing our initial results,[19i] we found that the efficiency of the Diels−Alder reaction could be further improved by adapting an improved procedure for the preparation of the catalyst[37] and by omitting molecular sieves. Under these conditions, the catalyst loading could be decreased to 10 mol % without detriment to yield or enantioselectivity.

Determination of the enantiomeric excess of the Diels−Alder adduct, *N*-Cbz lactam (+)-**7b**, initially met with some difficulty by chiral HPLC or GC, since neither method fully resolved enantiomers. However, the chiral shift reagent $Eu(hfc)_3$ provided a good initial estimate of the enantiomeric excess following deprotection. Subsequently, Mosher ester analysis of the alcohol derived from reduction of lactam (+)-**7a** with $LiBH_4$ by ^{19}F NMR gave a more accurate measure of enantiopurity (95% ee).

In model studies toward fragment coupling, we found that addition of *n*-BuLi led to clean deprotection of the Cbz group of lactam **7b** with no addition to the lactam carbonyl. Furthermore, activation with a tosyl group proved to be necessary for efficient addition to this hindered δ-lactam. Thus, this two-step process gave a crystalline *N*-Ts lactam **7a** readied for coupling with an appropriate nucleophilic coupling partner (*vide infra*). The *N*-Ts lactam (+)-**7a** enabled determination of absolute configuration through single-crystal X-ray crystallographic analysis (S as heavy atom), confirming correlation to the gymnodimine spirocyclic core (Scheme 6, inset).[31b]

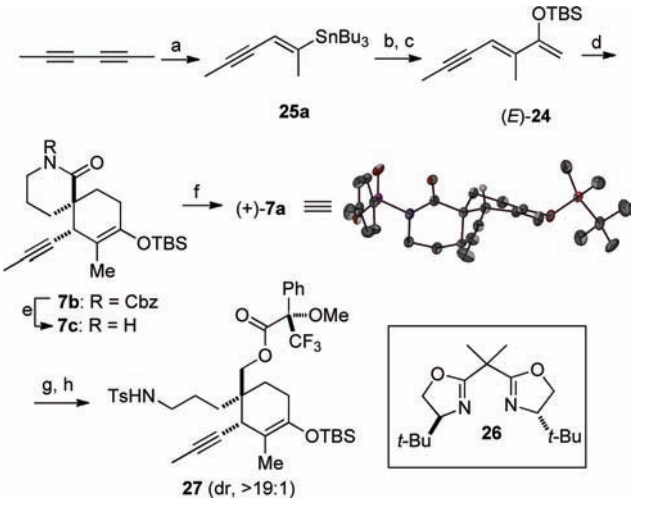
Table 1. Synthesis of (*E*)-Vinyl Stannane 25a from 2,4-Hexadiyne



entry	conditions	% yield[a]	ratio[b] (25a:25b:25c)
1	*n*-Bu_3SnH, AIBN, PhMe, 80 °C	90	1:1.4:0
2	*n*-Bu_3SnH, $PdCl_2(PPh_3)_2$, THF	90	0:0:1
3	$(n\text{-}Bu_3Sn)_2CuCNLi_2$, THF, −78 °C	67[c]	7:0:1
4	$(n\text{-}Bu_3Sn)_2CuCNLi_2$, MeOH, THF, −78 °C	86	5:2:1

[a] Yields refer to isolated, purified yields of the mixture of isomers. [b] Ratios were determined by ^1H NMR (300 MHz) of the crude reaction mixtures. [c] Yield refers to the major isomer **25a**.

Scheme 6. Synthesis of Spirolactam (+)-7a[a]



[a] Reagents and conditions: (a) $(n\text{-}Bu_3Sn)_2CuCNLi_2$, THF, −78 °C, 67%; (b) *n*-BuLi, *N*-methyl-*N*-methoxyacetamide, THF, −78 °C, 77%; (c) Et_3N, TBSOTf, CH_2Cl_2, −78 °C, 90%; (d) **26** (11 mol %), $AgSbF_6$ (20 mol %), $CuCl_2$ (10 mol %), **8b**, CH_2Cl_2, 85%, *exo*/*endo* > 95:5, 95% ee (major diast); (e) *n*-BuLi, THF, −78 °C, 82%; (f) KHMDS, TsCl, THF, 80%; (g) $LiBH_4$, THF, 91%; (h) (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, DCC, DMAP, CH_2Cl_2, 84% (inset: ORTEP representation of X-ray crystal structure of (+)-**7a**).

Fragment Coupling. With both gymnodimine fragments, tetrahydrofuran **23** and spirolactam **7a**, available in multigram quantities and in high enantiopurity, we next focused on identifying appropriate strategies for their coupling. Among the various approaches we attempted, a few selected strategies are described below (Scheme 7).

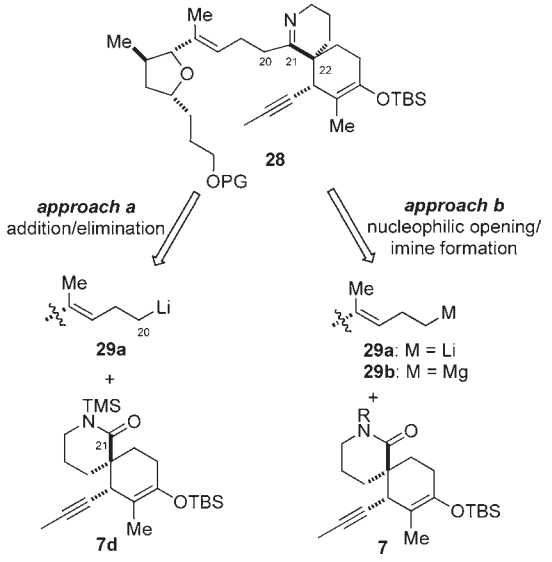
Our initial efforts focused on nucleophilic additions to a *N*-(trimethylsilyl)lactam such as **7d** (Scheme 7, approach a) based on a report by Hua demonstrating that nucleophilic additions of alkyllithium species to *N*-(trimethylsily)lactams **30** selectively provided cyclic ketimines **31** in good to excellent yields through a presumed Peterson-like olefination process (Scheme 8a).[38] We modified Hua's protocol and developed a single-pot variant involving *in situ N*-silylation of the hindered α,α-dimethyl δ-lactam **32a** followed by addition of an alkyllithium. This procedure directly provided the corresponding cyclic ketimines without the need to isolate the labile *N*-trimethylsilyl lactam intermediates (Scheme 8b).[19c] However, all attempts to apply this protocol to the more advanced substrate **7c** met with failure when the *in situ* generated *N*-(trimethylsilyl)lactam **7d** was treated with (4-methyl-3-pentenyl)lithium species (Scheme 8c). Recovery of only starting material **7c** from these attempts underscored the severe steric issues that any successful coupling protocol would have to overcome.

The aforementioned failed strategy led us to focus on a potentially more challenging intermolecular monoaddition of an alkylmetal species to an electrophilic *N*-tosyl lactam to deliver an intermediate amino ketone that could be recyclized to an imine (Scheme 7, approach b). We anticipated that the steric issues, which thwarted our previous attempts of additions to this δ-lactam, would slow double addition to the intermediate ketone. In model studies, treatment of *N*-Ts lactam **32b** with only a slight excess of *n*-BuLi (1.05 equiv) gave only the double addition product, alcohol **38a** (43%, Scheme 9a). However, ketone **37b** became the major product (69%) when the nucleophilicity of the alkylmetal species was attenuated by use of a Grignard reagent. In this case, use of excess Grignard reagent was required, and this would not be ideal with more elaborate alkyl Grignards (i.e., the tetrahydrofuran fragment **29**). This reaction also gave significant quantities of the tertiary alcohol **38b**. An alternative strategy involved monoreduction of *N*-Ts lactam **32b** to an intermediate carbinolamine, which was readily accomplished with diisobutylaluminum hydride, and subsequent NaH/alkyllithium addition to provide the amino alcohol **39** in good overall yield (Scheme 9b). However, the required redox corrections made this route less than ideal.

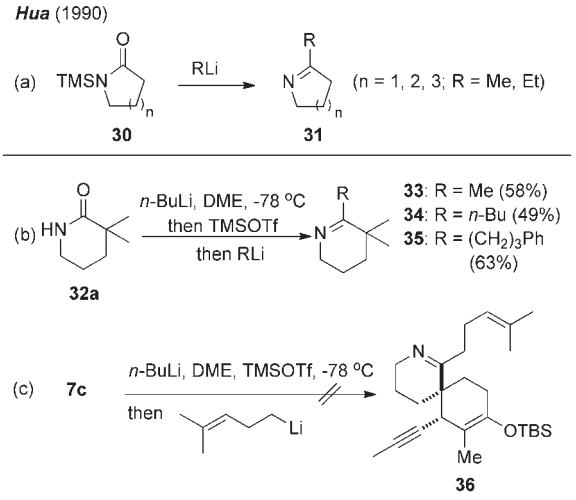
To our surprise, the more functionalized substrate *N*-Ts lactam **7a** underwent efficient nucleophilic opening with MeMgBr to provide the desired amino ketone **40a** in good yield without double addition that plagued our model substrates (Scheme 10). Furthermore, more reactive alkyllithium species such as MeLi, *n*-BuLi, and even 4-methyl-3-pentenyl lithium smoothly added to *N*-Ts lactam **7a** at low temperature (−78 or −20 °C) with no double addition detected. Related examples of controlled ring-opening reactions of *N*-protected lactams have been reported; however, in these cases, an *N*-alkoxycarbonyl group assisted in stabilizing the tetrahedral intermediate in a manner similar to a Weinreb amide.[39] This contrasts to the present case of a *N*-tosyl lactam **7a** bearing an adjacent quaternary carbon where steric effects likely play a key role in preventing double addition.

Extension of these findings to the synthesis of gymnodimine required a suitably functionalized tetrahydrofuran precursor. The PMB group of tetrahydrofuran fragment **23** was cleaved under dissolving metal conditions, and the resulting alcohol **41a** was converted to the homoallylic iodide **42** through the intermediacy of mesylate **41b** (Scheme 11). Initial experimentation under the aforementioned conditions, involving treatment of *N*-Ts lactam **7a** with the alkyllithium derived from alkyl iodide **42** by halogen-metal exchange with *t*-BuLi, provided the desired amino ketone **43**, albeit in low yield. Modifying the order of addition by addition of *t*-BuLi to a mixture of alkyl iodide **42** and *N*-Ts lactam

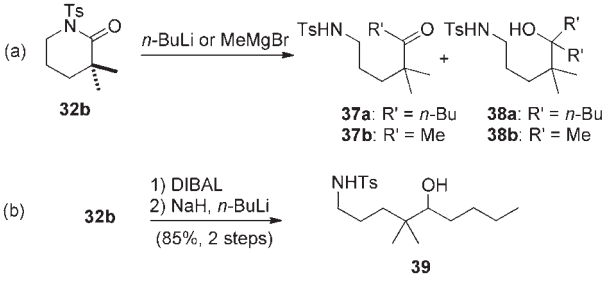
Scheme 7. Strategies Explored for Fragment Coupling



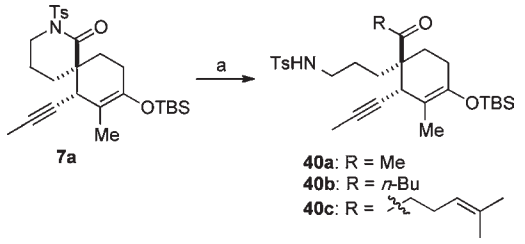
Scheme 8. Attempted Imine Synthesis via a Modified Hua Protocol



Scheme 9. Direct Alkylmetal Addition to Model δ-Lactams

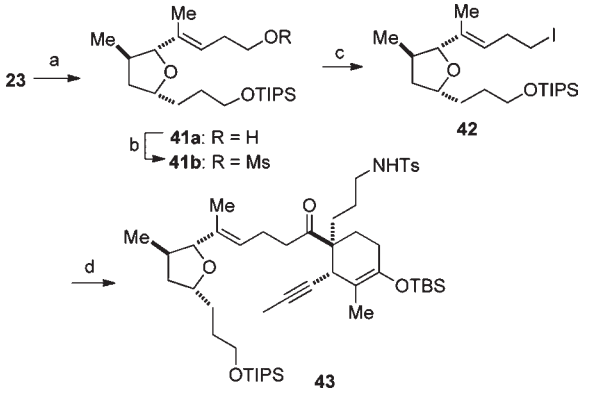


Scheme 10. Addition of Alkyllithium Species to *N*-Ts Lactam 7a[a]



[a] Reagents and conditions: (a) for **40a** and **40b**: RLi, Et_2O, −78 °C, 98% (**40a**), 68% (**40b**); for **40c**: 5-bromo-2-methyl-2-pentene, *t*-BuLi, TMEDA, Et_2O/THF, −20 °C, 63%.

Scheme 11. Fragment Coupling of 42 and 7a via a Barbier Reaction[a]



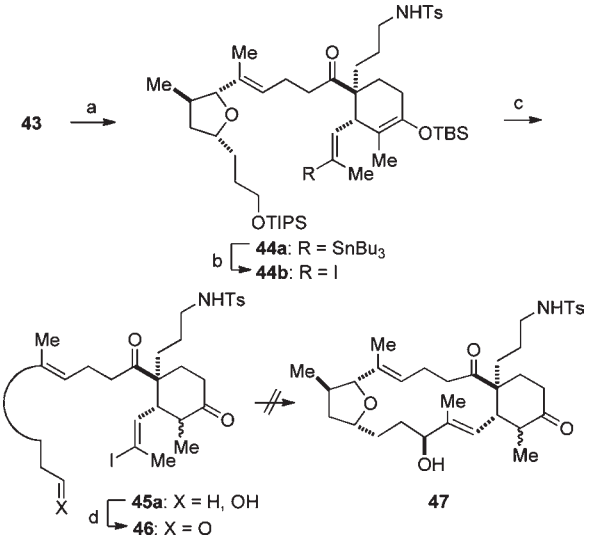
[a] Reagents and conditions: (a) Na°, NH_3(l), THF, −78 °C, 90%; (b) MsCl, Et_3N, CH_2Cl_2, 92%; (c) *n*-Bu_4NI, THF, 66 °C, 91%; (d) **42** + **7a**, Et_2O, −78 °C, then *t*-BuLi, 92%.

7a at low temperature dramatically improved the yield of this intermolecular addition to 92%. The success of this Barbier-type addition laid the foundation for subsequent development of the intramolecular Barbier macrocyclization protocol that proved to be the key for our successful total synthesis of gymnodimine (*vide infra*).

Attempted Macrocyclization *via* a NHK Coupling. In preparation for the projected Cr/Ni mediated macrocyclization, acetylene **43** was subjected to a Pd-catalyzed hydrostannylation reaction under Guibé's conditions to provide **44a** in 39% yield (81% yield, based on recovered starting material) (Scheme 12).[40] After tin−iodine exchange, the two silyl groups were removed with HF·pyridine to provide hydroxy ketone **45a**. Oxidation with Dess−Martin periodinane provided aldehyde **46**, setting the stage for the crucial intramolecular NHK macrocyclization. We were disappointed to find that aldehyde **46** failed to undergo the planned macrocyclization under a variety of conditions. The major adduct isolated from these reactions following aqueous workup was the corresponding deiodinated substrate. Macrocyclization was also studied following treatment of vinyl iodide **46** with SmI_2 or *t*-BuLi; however, this only led to reduction of the aldehyde and deiodination, respectively.

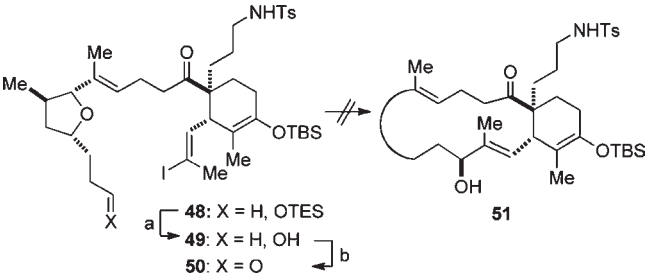
Even though successful NHK couplings of aldehydes in the presence of ketones have been documented,[21] we nevertheless considered whether the failure of **46** to undergo a NHK

Scheme 12. Attempted Macrocyclization of Aldehyde 46 via a Nozaki−Hiyama−Kishi Process[a]



[a] Reagents and conditions: (a) *n*-Bu_3SnH, $(Ph_3P)_2PdCl_2$, THF, 25 °C, 39%, 52% recovered **43**; (b) I_2, CH_2Cl_2, −78 °C; cyclohexene, 64%; (c) HF·Py, CH_3CN, 83%; (d) Dess−Martin periodinane, CH_2Cl_2, 90%.

Scheme 13. Attempted NHK Macrocyclization of Iodoaldehyde 50[a]

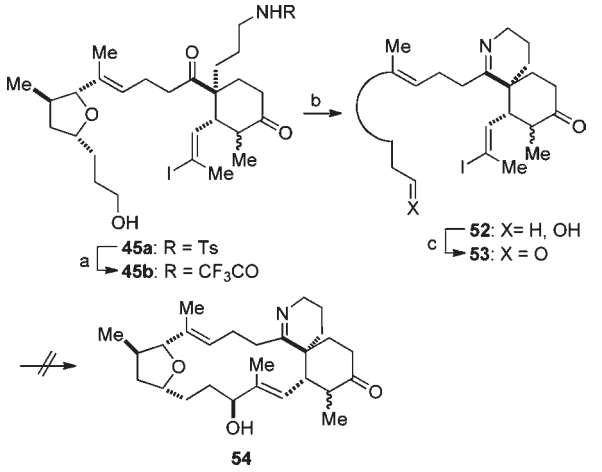


[a] Reagents and conditions: (a) PPTS, MeOH/CH_2Cl_2, 85%; (b) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, 90%.

macrocyclization was due to the acidity of the sulfonamide or ketone functionality.[41] To test this hypothesis, the triethylsilyl ether **48** was prepared in a similar fashion to TIPS ether **44b**, allowing for a selective removal of the triethylsilyl group with PPTS without cleavage of the sensitive silyl enol ether moiety (Scheme 13). The alcohol **49** was then oxidized to aldehyde **50**; however, this substrate also proved to be unsuitable for macrocyclization and only deiodination was again observed (not shown).

We postulated that the reluctance of substrates **46** and **50** to undergo an intramolecular NHK process might be due to unfavorable conformations that preclude macrocyclization. Therefore, we set out to ascertain the effect a preinstalled spirocyclic imine moiety, which we expected would dramatically alter conformational preferences, might have on macrocyclization. Following our previously developed protocol,[42] *N*-Ts spirolactam **45a** was deprotected by conversion to the trifluoroacetamide **45b** upon treatment with $(CF_3CO)_2O$ in the presence of Et_3N, which also led to trifluoroacetylation of the primary alcohol, and then direct reduction with SmI_2 (Scheme 14).[43] The trifluoroacetate ester

Scheme 14. Attempted NHK Macrocyclization of Imine Substrate 53[a]



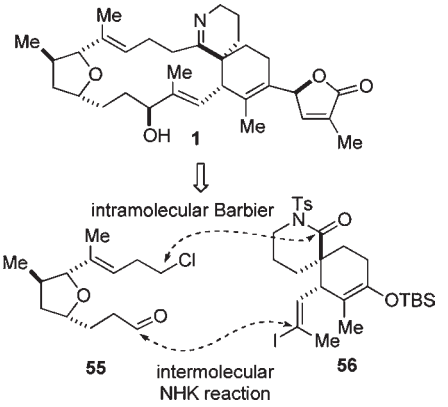
[a] Reagents and conditions: (a) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2; SmI_2, 87%; (b) NH_4OH, MeOH, 80 °C, 81%; (c) Dess–Martin periodinane, CH_2Cl_2, 83%.

underwent hydrolysis during workup of the latter reaction to give alcohol **45b**, and cleavage of the trifluoroacetamide with concomitant cyclization to the imine **52** was realized upon treatment with ammonium hydroxide in warm methanol. Dess–Martin oxidation provided aldehyde **53** for the proposed macrocyclization reaction. Disappointingly, aldehyde **53** was once again resistant to macrocyclization under several NHK reaction conditions.

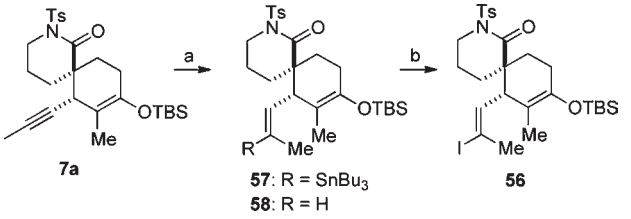
Macrocyclization *via* an Intramolecular Barbier Reaction. The inability to form the gymnodimine macrocycle through various NHK macrocyclization strategies led us to consider reversing the order of coupling to an intermolecular NHK coupling followed by an intramolecular Barbier macrocyclization (Scheme 15). In this plan, the two fragments, chloroaldehyde **55** and spirolactam **56**, would be coupled through an intermolecular NHK coupling. While low diastereoselectivity would be expected in this latter process due to the absence of nearby stereocontrol elements, the novelty of the approach involving a Barbier-type macrocyclization coupled with our success of an intermolecular Barbier reaction to couple fragments **42** and **7a** (*vide supra*) spurred our interest in this strategy. While low diastereoselectivity of the NHK process could be overcome through an oxidation/reduction sequence, a more serious challenge was the proposed late stage intramolecular Barbier reaction on a highly functionalized intermediate. To the best of our knowledge, such a Barbier-type macrocyclization had not been previously documented.[44]

The two fragments **42** and **7a** were easily modified to incorporate the functional groups required for the proposed intramolecular Barbier strategy. Functionalization of the internal acetylene of **7a** was realized through standard Pd-catalyzed hydrostannylation conditions to initially provide vinyl stannane **57** in only 25% yield along with recovered starting material (Scheme 16). Screening of other hydrometalation protocols, including hydrozirconation,[45] hydroboration,[46] and hydroalumination,[47] either resulted in recovery of starting material or reduction of the *N*-Ts lactam moiety. The steric congestion around this internal alkyne due to the cyclohexyl ring and adjacent quaternary carbon posed a considerable challenge to

Scheme 15. Revised Strategy Based on a Barbier-type Macrocyclization



Scheme 16. Synthesis of Vinyl Iodide 56[a]

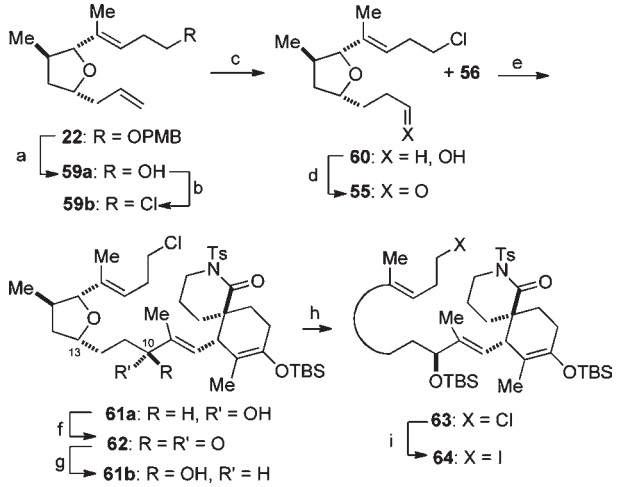


[a] Reagents and conditions: (a) $PdCl_2(PPh_3)_2$, *n*-BuSnH (syringe pump addition), THF/hexanes (1:6), 85%; (b) I_2, CH_2Cl_2, −78 °C, then cyclohexene, 76% (8% recovered starting material).

this otherwise standard transformation. Extensive studies were undertaken to improve the efficiency of the hydrostannylation reaction of alkyne **7a**. While reaction temperature did not have a notable effect on the conversion (23% conversion at 70 °C), a significant solvent effect was observed, with a mixed solvent of THF/hexanes being optimal, as described by Semmelhack and Lee.[48] Careful analysis of the reaction mixture identified significant amounts of alkene **58**, a byproduct that was not derived from protodestannylation of vinyl stannane **57** during stannylation or purification.[49] It is known that in Pd-catalyzed hydrostannylation of acetylenes, a principal competitive pathway is the dimerization of tributyltin hydride to provide bis(tributyltin) and molecular hydrogen.[40a] We suspected alkene **58** was formed from hydrogenation of alkyne **7a** in the presence of minute amounts of precipitated Pd(0). Therefore, we postulated that, by keeping the concentration of *n*-Bu_3SnH low throughout the reaction, the competing hydrogenation pathway could be suppressed. Indeed, when tributyltin hydride was added slowly to the reaction via syringe pump, the vinyl stannane **57** could be obtained reproducibly in 85% yield with minimal amounts of alkene **58**. The subsequent iodine–tin exchange was executed at low temperature in order to minimize competing α-iodination of the reactive silyl enol ether. A neutral workup and use of cyclohexene to quench excess iodine allowed the sensitive vinyl iodide **56** to be isolated in good yield, which was immediately used in the subsequent intermolecular NHK process.

The other required fragment for the proposed NHK coupling was prepared from PMB ether **22** (Scheme 17). Cleavage of the PMB group under dissolving metal conditions afforded the primary alcohol **59a**, which was then converted to alkyl chloride

Scheme 17. Fragment Coupling through a NHK Reaction[a]

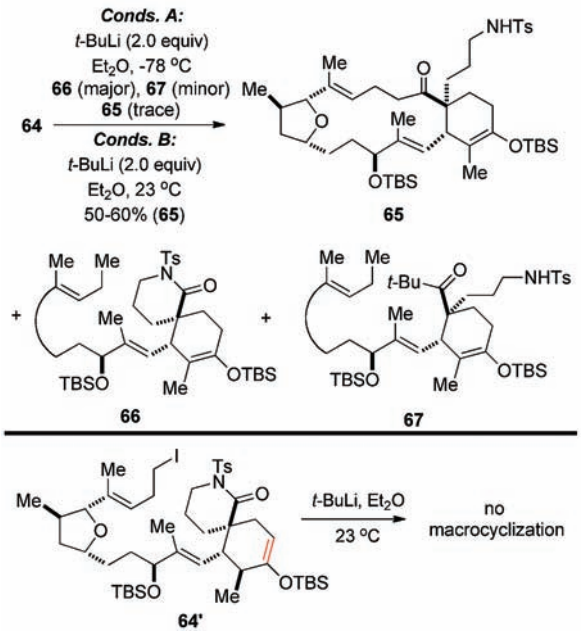


[a] Reagents and conditions: (a) Na, NH_3(l), THF, −78 °C, 92%; (b) PPh_3, CCl_4, DMF, 65 °C, 85%; (c) 9-BBN, THF, then NaOH, H_2O_2, 98%; (d) Dess−Martin periodinane, CH_2Cl_2, $NaHCO_3$, 71%; (e) $CrCl_2$/$NiCl_2$, DMF/THF (1:1), 97% (β-OH/α-OH, 1.3:1); (f) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, 88%; (g) (*R*)-Me-CBS, catecholborane, CH_2Cl_2, 0 °C, 81% (dr, 6:1); (h) TBSOTf, Et_3N, CH_2Cl_2, −78 °C, 86%; (i) NaI, acetone, 65 °C, 99%.

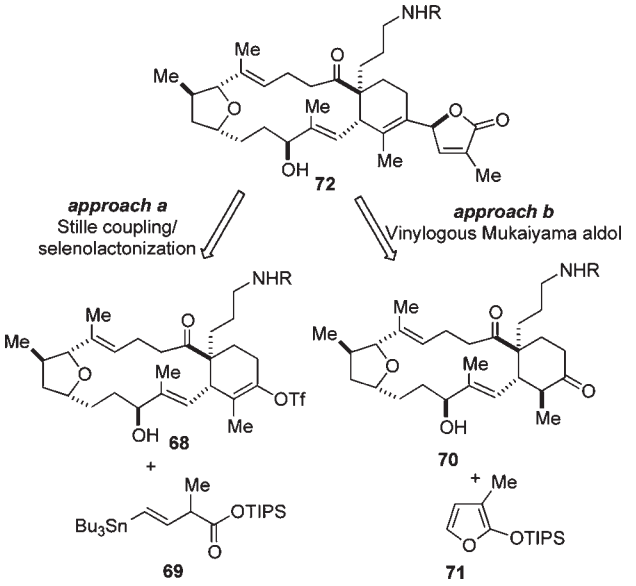
59b in 85% yield. A site selective hydroboration followed by Dess−Martin oxidation yielded aldehyde **55** for the projected NHK reaction. A smooth coupling took place between aldehyde **55** and iodide **56** in the presence of excess $CrCl_2$ doped with catalytic amounts of $NiCl_2$, providing readily separable diastereomeric allylic alcohols **61a** and **61b** in excellent yield but with essentially no diastereoselectivity, as anticipated (dr, 1:1.3; 500 MHz ^{1}H NMR). The minor diastereomer **61a** was readily converted to the desired diastereomer **61b** through an oxidation/asymmetric reduction sequence using the Corey−Itsuno protocol.[50] While modified Mosher ester analysis[51] did not provide unambiguous assignment of the absolute stereochemistry of the C10 stereocenter of these alcohols, the mechanistic model proposed for the Corey−Itsuno reduction[50b] was employed to initially assign relative stereochemistry. The stereochemistry of the major diastereomer **61b** was subsequently confirmed by X-ray crystallographic analysis of an advanced intermediate (*vide infra*). The allylic alcohol **61b** was then protected as a silyl ether, and the minor C13 diastereomer, resulting from previous allylation of the furanose (cf. Scheme 4), could be separated at this stage. A Finkelstein reaction provided the alkyl iodide **64** in high yield, thus setting the stage for the key Barbier-type macrocyclization.

Our initial macrocyclization attempts involving halogen−metal exchange with iodide **64** and *t*-BuLi, under conditions previously developed for the intermolecular process (−78 °C, Et_2O), only provided trace amounts of the desired product **65** (Scheme 18). At least two competitive reaction pathways could be discerned after careful analysis of the reaction mixture. One was the unproductive quenching of the formed alkyllithium species either during the reaction or following quenching, providing deiodinated adduct **66**. Surprisingly, *tert*-butyl ketone **67** derived from *t*-BuLi addition to the highly hindered *N*-Ts lactam was isolated, and this material had also undergone deiodination. To enable macrocyclization, we reasoned that the rate of intermolecular opening by *t*-BuLi had to be suppressed by

Scheme 18. Successful and Unsucessful Barbier-Type Macrocyclizations



Scheme 19. Strategies for Introduction of the Butenolide Moiety



rapid consumption of this reagent while at the same time enabling the intramolecular process. Screening of solvents (Et_2O, THF, and Trapp solvent[52]) and additives (TMEDA, HMPA) failed to provide any improvement. We briefly explored the possibility of forming a different alkylmetal species by varying metalation reagents. Attempted formation of a Grignard reagent by treating iodide **64** with *i*-PrMgCl only led to addition to the *N*-Ts lactam, whereas SmI_2 cleaved the *N*-Ts group.

Ultimately, we varied reaction temperature, reasoning that conformational effects were again preventing macrocyclization, and this proved to be the defining parameter for successful macrocyclization.

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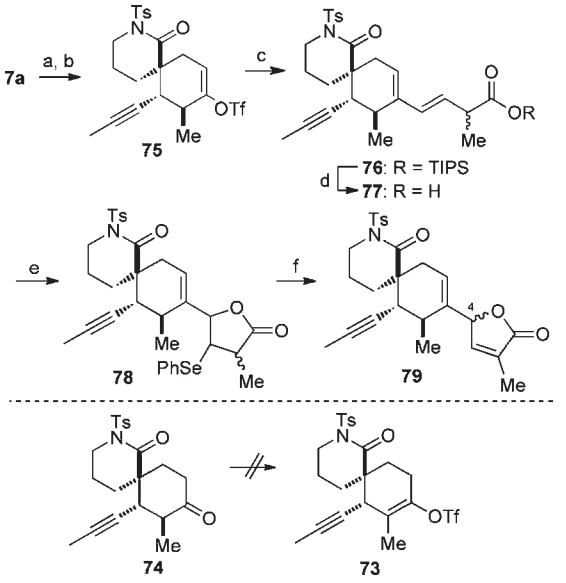
By conducting the reaction at 0 °C, the desired product **65** was obtained in 25% yield. *Further optimization provided macrocycle* ***65*** *in 50−60% yield when t-BuLi was added to the iodide in* Et_2O *at ambient temperature (23 °C), with* ***66*** *and* ***67*** *constituting the minor components of the reaction mixture!* The exact reason for the dramatic effect of temperature on the outcome of this reaction is not clear; however, one possibility is that a dramatic change in conformational equilibria occurs at higher temperatures, which may facilitate the desired macrocyclization by enabling access to a productive conformer. The iodine−lithium exchange is likely the fastest step;[53] however, the fact that the desired macrocyclization is faster than both intermolecular addition of the second equivalent of *t*-BuLi to the *N*-Ts lactam and elimination of *t*-BuI by *t*-BuLi is intriguing and may be partially rationalized by virtue of the fact that each of these processes has a different temperature profile. Similarly, the observation that a closely related substrate, olefin regioisomer **64′**, failed to undergo macrocyclization under similar conditions might reflect the importance of substrate conformation in this Barbier cyclization reaction.

Introduction of the Butenolide and Completion of the Synthesis of (−)-Gymnodimine. Having prepared the macrocyclic structure of gymnodimine, the remaining challenge was to introduce the butenolide moiety. Due to the fragile nature of this fragment,[20] we planned to keep manipulations following introduction of this moiety to a minimum. Toward this goal, we considered various strategies, among which two approaches were of particular interest. One utilized a Stille coupling between the triflate **68** and vinyl stannane **69** (Scheme 19, approach a).[54] A selenolactonization of the derived alkene followed by oxidation and elimination would provide the butenolide.[55] The other option involved use of a rarely studied vinylogous Mukaiyama aldol reaction with a ketone, which rapidly assembles the butenolide in a single operation (Scheme 19, approach b).[56] A subsequent dehydration reaction would then provide the penultimate intermediate **72**.

Our initial effort to execute the proposed cross-coupling strategy was conducted on the model substrate spirolactam **7a** (Scheme 20). Attempted preparation of vinyl triflate **73**, directly from the silyl enol ether precursor **7a** under modified conditions reported by Corey, was unsuccessful.[57] We then resorted to a two-step procedure involving ketone **74** prepared from acidic deprotection of silyl enol ether **7a**. Standard triflation conditions only provided the undesired regioisomer, vinyl triflate **75**. In parallel with extensive studies to obtain the required regioisomeric triflate, the subsequent proposed coupling was explored to incorporate the butenolide. A Stille coupling reaction between triflate **75** and vinyl stannane **69**[58] under Farina's conditions provided the diene **76** in good yield.[59] After cleavage of the silyl group, the carboxylic acid **77** underwent a smooth diastereoselective selenolactonization reaction in the presence of *in situ* generated phenylselenyl chloride (PhSeSePh, SO_2Cl_2) to provide the selenide **78** as a mixture of two diastereomers. Treatment of **78** with H_2O_2 initiated an oxidation/elimination sequence providing butenolide **79** as a mixture of two epimers (epimeric at C4). While this approach was eventually abandoned due to the inability to identify an efficient protocol for the formation of the requisite vinyl triflate **73**, this efficient sequence nevertheless provides a concise strategy for butenolide incorporation onto highly functionalized substrates that may find use in other contexts.

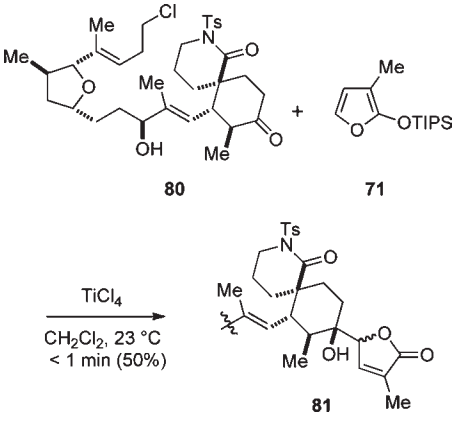
A vinylogous Mukaiyama aldol reaction of a cyclic ketone was next explored for butenolide incorporation, further motivated by

Scheme 20. Appending the Butenolide through a Stille Coupling Reaction[a]



[a] Reagents and conditions: (a) *p*-TsOH, CH_2Cl_2/MeOH, 88%; (b) LiHMDS, $PhNTf_2$, THF, 52%; (c) **69**, $Pd_2(dba)_3 \cdot CHCl_3$, Ph_3As, THF, 84%; (d) TBAF, THF, −78 °C, 84%; (e) PhSeSePh, SO_2Cl_2, CH_2Cl_2, 60%; (f) H_2O_2, CH_2Cl_2, 90%.

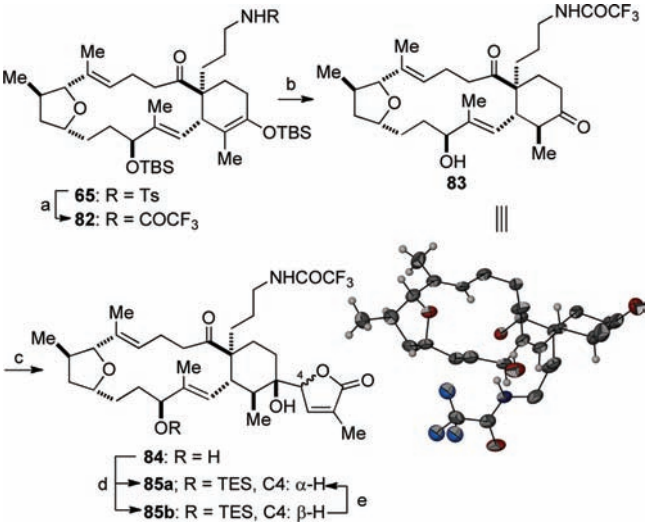
Scheme 21. Butenolide Addition via a Vinylogous Mukaiyama Aldol Reaction: Advanced Model Substrate



the fact that only a few examples of this process have been reported.[60] This strategy was not without risks, given the potential functional group incompatibility issues, since the expected low reactivity of ketone substrates in a Mukaiyama aldol reaction would necessitate the use of strong Lewis or Brönsted acids. Furthermore, the stereochemical outcome of the reaction was unclear. Preliminary studies of the vinylogous Mukaiyama aldol reaction between simple α-alkyl cyclohexanones and several silyloxy furans demonstrated that these reactions could effectively be promoted by $TiCl_4$ to provide the desired adducts in good yield and moderate to high diastereoselectivities.[61] More importantly, studies with the advanced model substrate **80** revealed some key factors for success of this reaction, including: (1) use of the more robust triisopropylsilyl version of the silyloxy furan **71** as the

dx.doi.org/10.1021/ja207385y |*J. Am. Chem. Soc.* 2011, 133, 19844–19856

Scheme 22. Vinylogous Mukaiyama Aldol Addition to Append Butenolide[a]



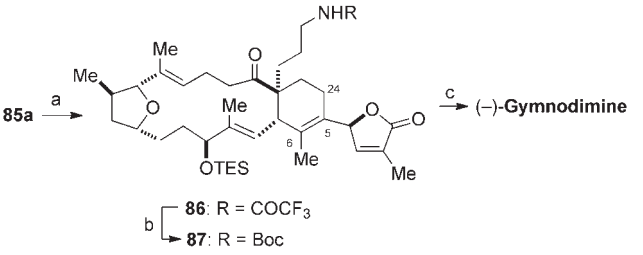
[a] Reagents and conditions: (a) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, SmI_2, 73%; (b) *p*-TsOH, THF/CH_2Cl_2/MeOH, 84%; (c) **71**, $TiCl_4$, CH_2Cl_2, 23 °C, 1 min, dr = 1.1:1, 61%; (d) TESCl, imidazole, DMAP, CH_2Cl_2, 76%; (e) DBU, CH_2Cl_2, **83**.

butenolide precursor, (2) the requirement of having the allylic hydroxyl group *unprotected* in order to prevent elimination to a conjugated diene, and (3) the requirement of very short reaction times following brief exposure of a mixture of the silyloxy furan and ketone to excess $TiCl_4$ (Scheme 21).

The substrate for the vinylogous Mukaiyama aldol reaction, ketone **83**, was prepared in a few straightforward transformations from silyl enol ether **65** (Scheme 22). First, the robust *N*-tosyl group was replaced with a more readily cleaved trifluoroacetamide, employing our previously reported conditions.[42] Both silyl groups in **82** were then removed under acidic conditions, furnishing a crystalline hydroxy ketone **83**, which enabled determination of the relative stereochemistry of this advanced intermediate by X-ray crystallographic analysis,[31c] confirming the earlier assignment of the C10 allylic alcohol **61b** (Scheme 22, inset). Brief exposure (ca. 1 min) of a mixture of ketone **83** and silyloxy furan **71** to $TiCl_4$ led to a smooth addition reaction to provide lactones **84** as a 1.1:1 mixture of two diastereomers (epimeric at C4) in 61% yield. After silyl protection of the C10 allylic hydroxyl group, the two epimeric alcohols **85a** and **85b** were readily separated. Comparison of ^{13}C NMR data for hydroxyl ketones **85a** and **85b** with that of related adducts from our previous model studies, whose structures were secured through X-ray crystallographic analysis,[61] enabled preliminary assignment of the relative stereochemistry of butenolides **85a**/**85b**.[58] It was found that the undesired silyl ether **85b** could be equilibrated to a 1:2 mixture of **85a** and **85b** upon treatment with DBU at ambient temperature, improving material throughput.[62] Definitive confirmation that hydroxy ketone **85a** possessed the correct C4 relative stereochemistry would ultimately come from subsequent conversion to gymnodimine (*vide infra*).

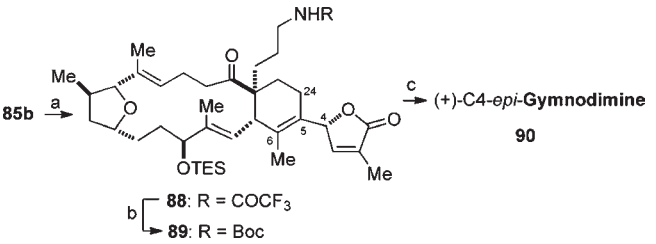
The tertiary alcohol **85a** underwent dehydration under standard conditions (Et_3N, $SOCl_2$) to deliver olefin **86** as the major regioisomer (3:1, Scheme 23). Conditions for cleavage of the trifluoroacetamide group required mild basic conditions to avoid

Scheme 23. Synthesis of Gymnodimine[a]



[a] Reagents and conditions: (a) Et_3N, $SOCl_2$, CH_2Cl_2, −78 °C, 82%, $\Delta^{5,6}$:$\Delta^{5,24}$ = 3:1; (b) Et_3N, $(Boc)_2O$, DMAP, CH_2Cl_2, then hydrazine, 99%; (c) TFA, CH_2Cl_2, high vacuum overnight, 68%.

Scheme 24. Synthesis of C4-*epi*-Gymnodimine[a]



[a] Reagents and conditions: (a) Et_3N, $SOCl_2$, CH_2Cl_2, 0 °C, 50%, $\Delta^{5,6}$:$\Delta^{5,24}$ = 1:1.3; (b) Et_3N, $(Boc)_2O$, DMAP, CH_2Cl_2, then hydrazine, 87%; (c) TFA, CH_2Cl_2, high vacuum overnight, 58%.

cleavage of the butenolide moiety. Unfortunately, attempts to cleave the trifluoroacetamide under a variety of basic conditions (LiOH/THF/H_2O, $NaHCO_3$/MeOH, K_2CO_3/MeOH, $NH_3 \cdot H_2O$/MeOH) only led to decomposition of this sensitive substrate, in good agreement with Miles' finding.[20] Acidic hydrolysis (2 M HCl/MeOH, 44 °C)[63] also proved too harsh for this highly functionalized substrate. An undesirable but required activation of the trifluoroacetamide group was required, and a *tert*-butoxycarbonyl group was chosen, given that this could then be removed by mild acidic conditions. Hence, treatment of the trifluoroacetamide **86** with $(Boc)_2O$ and brief exposure to hydrazine cleaved the trifluoroacetamide and provided *N*-Boc amine **87**.[64] Acid hydrolysis of *N*-Boc amine **87** with CF_3CO_2H cleaved the *N*-Boc group and gave concomitant desilylation of the triethylsilyl group to provide the corresponding primary amine salt. Upon standing at ambient temperature (23 °C) under high vacuum overnight, the free amine underwent a smooth cyclocondensation to provide gymnodimine as a white solid. The spectral data of synthetic gymnodimine was in full agreement with that reported previously for the natural product.[8,9] Furthermore, the trifluoroacetate salt of gymnodimine was prepared and its optical rotation ($[\alpha]_D^{22}$ −14.1 (*c* 0.06, MeOH)) was in good agreement with that reported ($[\alpha]_D^{25}$ −10.4 (*c* 0.13, MeOH)).

Synthesis of C4-*epi*-Gymnodimine. In an analogous fashion to the natural product, C4-*epi*-gymnodimine (**90**) was prepared starting from the C4-epimer **85b** (Scheme 24). For this diastereomer, the elimination step leading to **88** was nonregioselective and provided an approximately equal mixture of two regioisomers. After separation of the regioisomers, C4-*epi*-gymnodimine (**90**)

was isolated as a white solid in two additional steps. Comparison of the ^{1}H and ^{13}C NMR spectra of C4-*epi*-gymnodimine with those of gymnodimine provided evidence that they are epimeric at C4, further supporting the previous stereochemical assignment of alcohols **85a** and **85b**.

CONCLUSIONS

The first total synthesis of the marine toxin (−)-gymnodimine was achieved featuring a convergent coupling between two principal fragments, tetrahydrofuran **55** and spirolactam **56**, prepared in multigram quantity and high enantiomeric excess through an *anti*-aldol reaction and a catalytic, asymmetric Diels−Alder reaction, respectively. Several strategies were studied for fragment coupling, macrocyclization, formation of the cyclic imine, and butenolide incorporation. Ultimately, a successful macrocyclization was achieved employing an unprecedented intramolecular Barbier reaction proceeding at ambient temperature (23 °C) with *t*-BuLi and a highly advanced alkyl iodide intermediate. To the best of our knowledge, this represents the first application of a Barbier-type reaction to form a macrocycle. A late stage vinylogous Mukaiyama aldol reaction of an α-alkyl ketone is also noteworthy, as it constitutes a highly efficient route to attach the labile butenolide moiety of gymnodimine. The application of this vinylogous Mukaiyama aldol reaction may prove useful for the synthesis of other butenolide-containing natural products such as the spirolides, which are of topical interest.[17] The synthetic approach toward gymnodimine described herein is robust and has provided valuable analogues (e.g., C4-*epi*-gymnodimine) to enable more detailed SAR studies of these marine toxins, known to interact with nicotinic acetylcholine receptors. The described synthesis has allowed preparation of potential gymnodimine immunogens as promising candidates for the development of a congener-independent ELISA that could prove useful for monitoring gymnodimine and congeners in the oceans. Collaborative efforts in both these directions are underway, and results emanating from these studies will be reported in due course.

ASSOCIATED CONTENT

Supporting Information. Complete experimental and characterization details for all new compounds reported. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*romo@tamu.edu

Present Addresses

[‡]Department of Chemistry, Colorado State University, Fort Collins, CO 80523.

[§]Department of Chemistry, Faculty of Science, Taibah University, P.O. Box 30002, Almadinah Almunawarrah, Saudi Arabia.

[∥]Department of Chemistry, Texas Christian University, TCU Box 298860, Fort Worth, TX 76129.

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