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Studies on the Synthesis of (−)-Gymnodimine. Subunit Synthesis and Coupling

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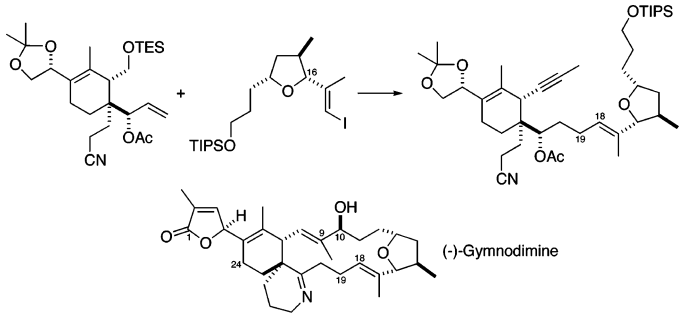

Two principal subunits of the marine algal toxin (−)-gymnodimine were synthesized. A trisubstituted tetrahydrofuran representing C10−C18 of the toxin was prepared via a highly stereoselective iodine-mediated cyclization of an acyclic alkene bearing a bis-2,6-dichlorobenzyl (DCB) ether. The formation of a cis-2,5-disubstituted tetrahydrofuran in this process conforms to a stereodirecting effect by the DCB group proposed by Bartlett and Rychnovsky. A cyclohexene subunit corresponding to the C1−C8, C19−C24 portion of gymnodimine was synthesized via Diels−Alder cycloaddition of a 1,2,3-trisubstituted diene to a symmetrical dienophile obtained from Meldrum's acid. Differentiation of carbonyl groups in the cycloadduct was made by an intramolecular reaction with a neighboring alcohol to form a γ-lactone. Linkage of the two subunits at C18−C19 was accomplished by using a B-alkyl Suzuki coupling in which a borane prepared from the pendent alkenyl chain of the cyclohexene domain was reacted with the (*E*)-iodoalkene attached at C16 of the tetrahydrofuran sector. Subsequent transformations positioned functional groups in the coupled product for a future macrocyclization event that would close the 15-membered ring of gymnodimine.

Introduction

Marine algal toxins are notorious not only for their undesirable effects on the human gastric system but also for the devastation they can cause in the natural environment.[1] In the United States, illnesses associated with seafood consumption account for approximately 20% of all foodborne disease outbreaks, and half of those are caused by naturally occurring algal toxins. Around the world, more than 60 000 incidents of sickness due to ingestion of marine algal toxins are reported each year with 1.5% of those cases resulting in fatality. The major source of marine algal toxins is unicellular algae (phytoplankton), which form the base of the marine food chain. Enormous blooms of these algae are created by aggregation and/or proliferation of the organism under favorable conditions, a phenomenon currently categorized under the broad term Harmful Algal Blooms (HABs) but previously known as "red tides". Although red tides were described as long as 3000 years ago, their occurrence and geographical distribution have increased markedly in recent times, with the result that incidents of human poisoning from marine algal sources have also increased.[2]

Chemical studies of bioactive compounds produced by HABs have led to the identification of several highly potent neurotoxins, including the brevetoxins,[3] prymnesins,[4] and gymnocin-A.[5] Blooms of the dinoflagellate *Gymnodinium sp.* are frequently associated with production of these toxins and it was during

(1) Van Dolah, F. M. *Environ. Health Perspect.* **2000**, *108*, 133.
(2) Luckas, B.; Dahlmann, J.; Erler, K.; Gerdts, G.; Wasmund, N.; Hummert, C.; Hansen, P. D. *Environ. Toxicol.* **2005**, *20*, 1.
(3) Lin, Y.-Y.; Rish, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773.
(4) (a) Igarashi, T.; Satake, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1996**, *118*, 479. (b) Igarashi, T.; Satake, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 8499.

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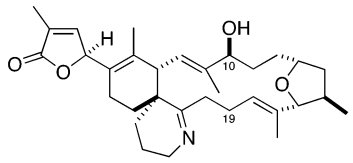
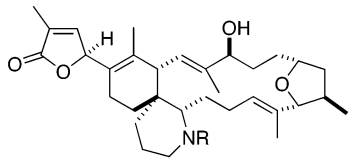
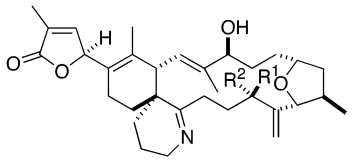
one such bloom in 1994 in Foveaux Strait off the South Island of New Zealand that gymnodimine is believed to have made its appearance. A year later, oysters collected from the same area by Yasumoto yielded sufficient gymnodimine for its planar structure to be determined.[6] Subsequently, the relative and absolute configuration of the toxin was established as **1** by X-ray crystallographic analysis of the *p*-bromobenzamide derivative **3** of the reduction product gymnodamine (**2**).[7] More recently, several analogues of **1**, gymnodimines B (**4**) and C (**5**) as well as deoxygymnodimine B (**6**), have been isolated from *Gymnodinium sp.*,[8] and in 2002 gymnodimine itself was found in clams harvested in Tunisia.[9]



Gymnodimine (**1**)



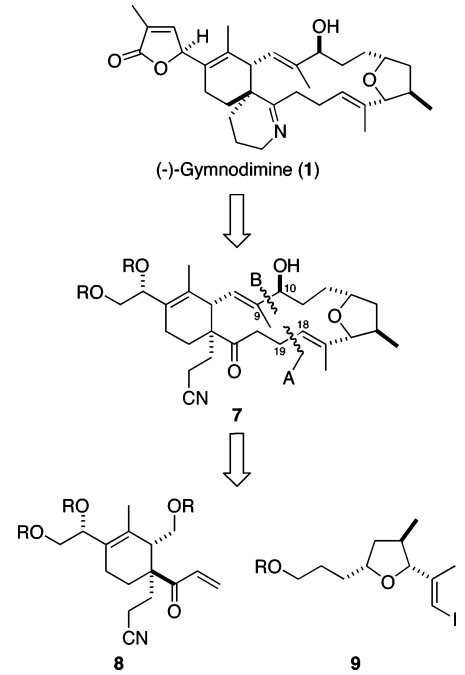
R = H, Gymnodamine (**2**)
R = *p*-BrC_6H_4CO (**3**)



R^1 = H, R^2 = OH, Gymnodimine B (**4**)
R^1 = OH, R^2 = H, Gymnodimine C (**5**)
R^1 = R^2 = H, 18-Deoxygymnodimine B (**6**)

Gymnodimine has been shown to be a potent neurotoxin and is believed to be responsible for several incidents of neurotoxic shellfish poisoning that have occurred in New Zealand.[10] In a mouse bioassay, **1** showed acute toxicity by injection (LD_{50} 96 μg/kg) and oral administration (LD_{50} 755 μg/kg); however, toxicity was diminished when **1** was ingested with food.[11] The toxicity of gymnodamine (**2**) is negligible (MLD > 4040 μg/kg) compared to that of **1**, indicating that the imine moiety of gymnodimine is necessary for activity. Interestingly, the neurotoxic spirolides[12] and pinnatoxins[13] which also contain a spiroimine unit show much reduced activity when the imine function is reduced or hydrolyzed to an amino ketone, suggesting that there is a common pharmacophore bearing the spiroimine signature in marine toxins.

SCHEME 1. Retrosynthetic Analysis of Gymnodimine



(-)-Gymnodimine (**1**)

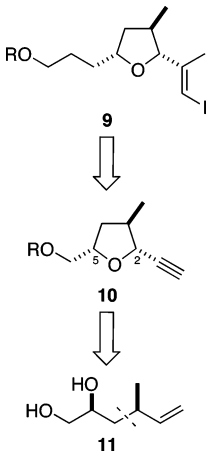
7

8 **9**

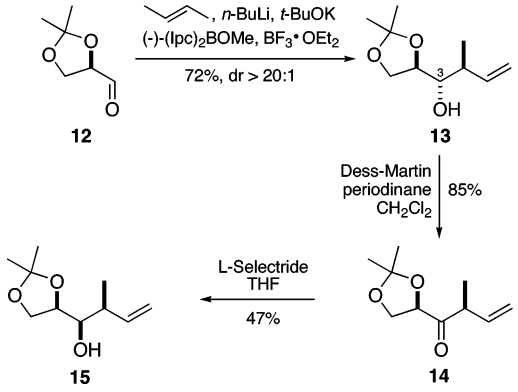
Progress toward the total synthesis of gymnodimine has been disclosed by Murai[14] and Romo,[15] and two reports from this laboratory have outlined independent approaches to the tetrahydrofuran subunit[16] of **1** and to the spiroimine portion.[17] This paper presents further details of our routes to these two domains of gymnodimine and describes their coupling to give a structure that we foresee leading to **1**. Our strategy is outlined in Scheme 1 and envisions construction of the central macrocyclic portion of gymnodimine from two sectors that are connected first at C18−C19 (bond A) followed by ring closure through linkage of C10 and C11 at bond B. Elaboration of the spiroimine and butenolide subunits of **1** would take place after the macrocycle **7** is completed. The two segments that merge into **7** are defined as the pentasubstituted cyclohexene **8** and the trisubstituted tetrahydrofuran **9**, the means for their connection being open to variation. This blueprint mandates the preparation of **8** and **9** in enantiopure form and thus imposes certain restrictions upon the routes chosen for their syntheses.

(5) Satake, M.; Shoji, M.; Oshima, Y.; Naoki, H.; Fujita, T.; Yasumoto, T. *Tetrahedron Lett.* **2002**, *43*, 5829.
(6) Seki, T.; Satake, M.; Mackenzie, L.; Kaspar, H.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 7093.
(7) Stewart, M.; Blunt, J. W.; Munro, M. H. G.; Robinson, W. T.; Hannah, D. J. *Tetrahedron Lett.* **1997**, *38*, 4889.
(8) (a) Miles, C. O.; Wilkins, A. L.; Stirling, D. J.; Mackenzie, A. L. *J. Agric. Food Chem.* **2000**, *48*, 1373. (b) Miles, C. O.; Wilkins, A. L.; Stirling, D. J.; Mackenzie, A. L. *J. Agric. Food Chem.* **2003**, *51*, 4838.
(9) Bire, R.; Krys, S.; Fremy, J.-M.; Dragacci, S.; Stirling, D.; Kharrat, R. *J. Nat. Toxins* **2002**, *11*, 269.
(10) Stirling, D. J. *N. Z. J. Mar. Freshwater Res.* **2001**, *35*, 851.
(11) Munday, R.; Towers, N. R.; Mackenzie, L.; Beuzenberg, V.; Holland, P. T.; Miles, C. O. *Toxicon* **2004**, *44*, 173.
(12) (a) Hu, T.; Curtis, J. M.; Oshima, Y.; Quilliam, M. A.; Walter, J. A.; Waston-Wright, W. M.; Wright, J. L. C. *Chem. Commun.* **1995**, 2159. (b) Hu, T.; Curtis, J. M.; Walter, J. A.; Wright, J. L. C. *Tetrahedron Lett.* **1996**, *37*, 7671. (c) Hu, T.; Burton, I. W.; Cembella, A. D.; Curtis, J. M.; Quilliam, M. A.; Walter, J. A.; Wright, J. L. C. *J. Nat. Prod.* **2001**, *64*, 308. (d) Cembella, A. D.; Lewis, N. I.; Quilliam, M. A. *Nat. Toxins* **1999**, *7*, 197.
(13) (a) Uemura, D.; Chou, T.; Hanio, T.; Nagatsu, A.; Fukuzawa, S.; Zheng, S.; Chen, H. *J. Am. Chem. Soc.* **1995**, *117*, 1155. (b) Chou, T.; Kamo, O.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 4023. (c) Chou, T.; Haino, T.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 4027.
(14) (a) Ishihara, J.; Miyakawa, J.; Tsujimoto, T.; Murai, A. *Synlett* **1997**, 1417. (b) Tsujimoto, T.; Ishihara, J.; Horie, M.; Murai, A. *Synlett* **2002**, 399.
(15) (a) Yang, J.; Cohn, S.; Romo, D. *Org. Lett.* **2000**, *2*, 763. (b) Ahn, Y.; Cardenas, G. I.; Yang, J.; Romo, D. *Org. Lett.* **2001**, *3*, 751.
(16) White, J. D.; Wang, G.-Q.; Quaranta, L. *Org. Lett.* **2003**, *5*, 4109.
(17) White, J. D.; Wang, G.-Q.; Quaranta, L. *Org. Lett.* **2003**, *5*, 4983.

SCHEME 2. Synthetic Plan for the Tetrahydrofuran Subunit



SCHEME 3. First Generation Synthesis of the Tetrahydrofuran Precursor

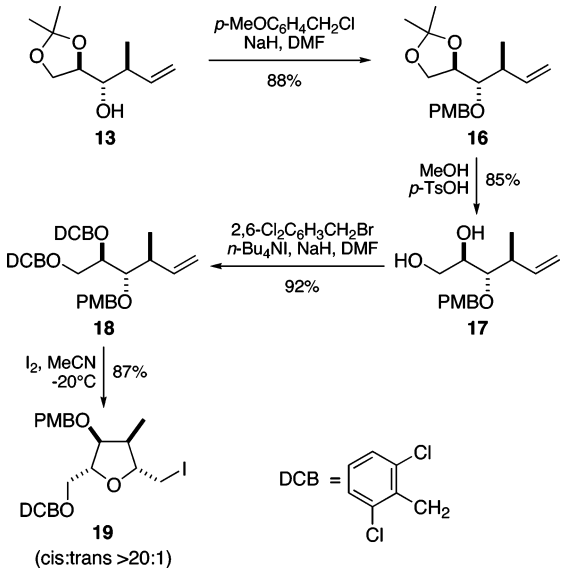


Results and Discussion

Synthesis of the Tetrahydrofuran Subunit. Alkynyl-substituted tetrahydrofuran **10** (Scheme 2) seemed a logical precursor to **9** since reliable methodology exists for transforming a terminal alkyne into the trisubstituted (*E*)-iodoalkene moiety present in **9**. Establishing the 2,3,5-trisubstitution pattern of **10** was more problematic, however. A substituted furan as the point of departure toward **10** seemed untenable, and preference was therefore given to a pathway from an acyclic precursor in the hope that the cis-2,5 orientation of alkynyl and alkoxymethyl groups in **10** could be generated stereoselectively. From this perspective, (2*S*,4*R*)-4-methyl-5-hexen-1,2-diol (**11**) appeared to be an attractive entry to **10**, especially since **11** can be envisioned as the asymmetric crotylation product of (*R*)-glyceraldehyde.

Treatment of the acetonide (**12**)[18] of (*R*)-glyceraldehyde with *trans*-2-butene and (−)-diisopinylcampheylmethoxyborane under conditions described by Brown[19] afforded homoallylic alcohol **13** in good yield and with excellent stereoselectivity (Scheme 3). However, subsequent removal of the unwanted hydroxyl substituent from C3 of **13** proved impossible, steric encumbrance around this site making attempts at derivatization of the alcohol for purposes such as Barton−McCombie deoxygenation[20] completely unproductive. Furthermore, although the mesylate of **13** could be prepared, this unstable substance underwent elimination to a conjugated diene before its displacement by hydride could be effected. This, again, reflects a high degree of steric compression around C3 of **13**. In the hope that inversion at this center would lead to a more compliant substrate for erasure of the C3 hydroxyl group, **13** was oxidized to ketone **14**, which gave predominantly (9:1) the (3*R*) alcohol **15** upon reduction with L-Selectride. This circuitous tactic was to no avail, however, since **15** was as unreactive as **13** toward reagents designed to activate the free alcohol for its removal.

SCHEME 4. The Bartlett−Rychnovsky Cis-2,5-Disubstituted Tetrahydrofuran Synthesis



The difficulty associated with deletion of the superfluous hydroxyl group in **13** and **15** persuaded us to postpone removal of this function to a later stage, and our advance toward **9** was therefore continued from **13** (Scheme 4). After protection of this alcohol as its *p*-methoxybenzyl (PMB) ether **16**, the acetonide was cleaved in acidic methanol to give diol **17** as the putative substrate for cyclization to a tetrahydrofuran. Precedent suggested there would be strong preference for an electrophile initiated cyclization of **17** to yield a tetrahydrofuran rather than a tetrahydropyran, but precedent also indicated that a preponderance of the cis-2,5-disubstituted tetrahydrofuran would prevail only under a narrow set of conditions. One of those protocols, discovered by Bartlett and Rychnovsky,[21] entails iodoetherification of a 2,6-dichlorobenzyl 4-pentenyl ether. Pursuing this line of inquiry, diol **17** was exposed to 2,6-dichlorobenzyl bromide, tetra-*n*-butylammonium iodide, and sodium hydride to afford bis ether **18**. Treatment of **18** with iodine in acetonitrile at low temperature then gave tetrahydrofuran **19** as the sole detectable stereoisomer. The configuration of **19** was initially established by NOE measurements which defined a cis orientation of the C2 hydrogen and C3 methyl group as well as a cis relationship of the C3 proton with the iodomethyl substituent (Figure 1). Subsequently, X-ray crystallographic analysis of **19** fully confirmed this assignment.

The highly stereoselective formation of **19** from **18** is to be contrasted with an alternative pathway (Scheme 5) in which

(18) Schmid, C. R.; Bryant, J. D. *J. Org. Chem.* **1991**, *56*, 4056.
(19) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293.
(20) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin, Trans. 1* **1975**, 1574.
(21) Rychnovsky, S. D.; Bartlett, P. A. *J. Am. Chem. Soc.* **1981**, *103*, 3963. A mechanism accounting for this effect is presented by the authors and its application to **18** has been discussed in ref 16.

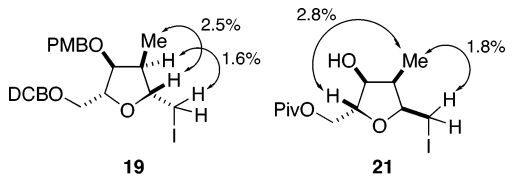
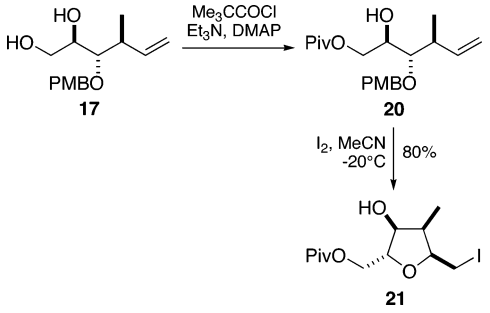


FIGURE 1. Nuclear Overhauser enhancements (NOE) measured from NMR spectra of **19** and **21**.

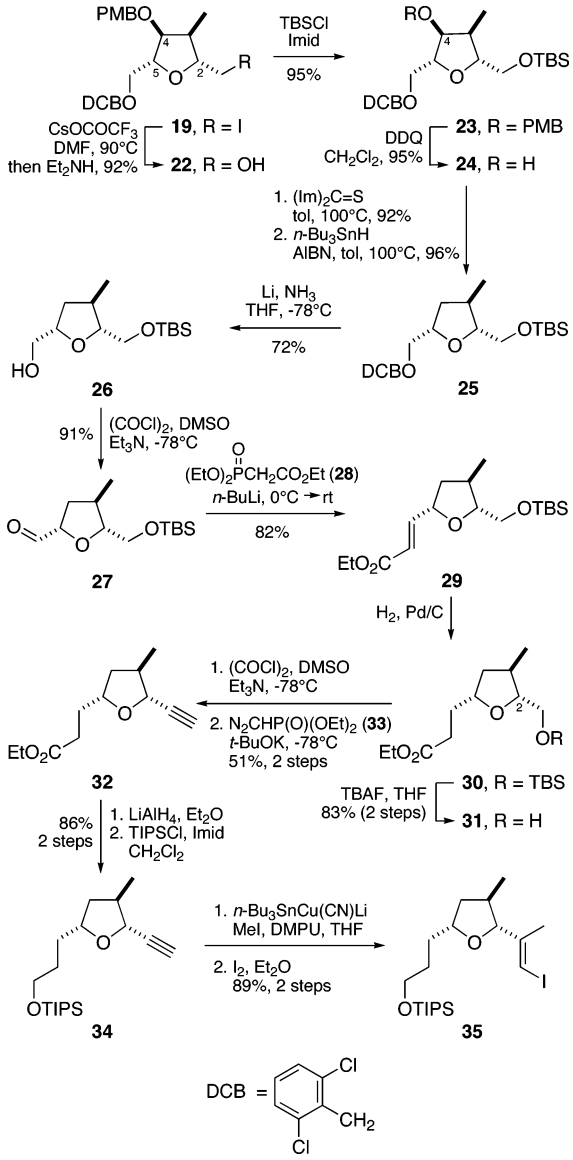
SCHEME 5. Synthesis of a Trans-2,5-Substituted Tetrahydrofuran



diol **17** was converted to pivalate **20** before intramolecular iodoetherification. In that case, tetrahydrofuran **21** in which the *p*-methoxybenzyl ether had been cleaved was formed exclusively, its trans configuration at C2 and C5 again being assigned on the basis of NOE measurements (Figure 1). The divergent results from iodoetherification of **18** and **20** lend credence to the Bartlett−Rychnovsky mechanism for cyclization of acyclic alkenols to tetrahydrofurans which postulates that increasing steric bulk attached to the oxygen incorporated into the tetrahydrofuran favors cis-2,5-disubstitution.[21]

With a route to **19** of correct absolute configuration for incorporation into the tetrahydrofuran substructure of gymnodimine now firmly established, two important tasks remained. These were deletion of the oxygen function at C4 and removal of the dichlorobenzyl group from its site in the C5 side chain. The latter was required in order for this substituent to be extended and functionalized in a manner that would facilitate closure of the gymnodimine macrocycle at C9−C10 (linkage B in **7**). According to this scenario, functional group modification at C2 of **19** en route to iodoalkene **9** would be delayed until those two processes were completed. However, it was found necessary to exchange the iodo substituent of **19** for an alcohol before proceeding with our planned sequence and this was accomplished by displacement of iodide from **19** with cesium trifluoroacetate followed by treatment with diethylamine (Scheme 6).[21] Alcohol **22** was converted to its TBS ether **23** and the *p*-methoxybenzyl ether was cleaved with DDQ to afford **24**. Reductive removal of the C4 hydroxyl group from this substrate proved to be straightforward. Alcohol **24** was converted to its imidazoyl thioate and the latter was reduced with tri-*n*-butylstannane in the presence of a radical initiator.[20] The resulting desoxy product **25** now required cleavage of the dichlorobenzyl ether, a transformation that was readily accomplished with lithium-ammonia at low temperature. Primary alcohol **26** was oxidized under Swern conditions to aldehyde **27**, which was reacted with the anion of phosphonate **28** to yield trans-α,*β*-unsaturated ester **29**. Catalytic hydrogenation of **29** yielded **30** from which TBS protection was removed to give **31**.

SCHEME 6. Deoxygenation and Elaboration of a Tetrahydrofuran Subunit for Gymnodimine



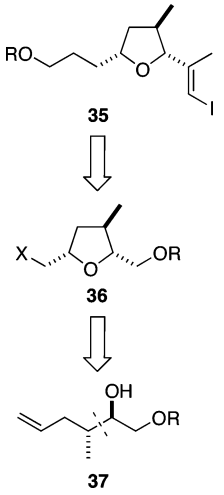
Installation of an (*E*)-iodoalkene chain at C2 of **31** employed the stannylcupration−iodination protocol developed by Lipshutz,[22] an operation that first required conversion of **31** to alkyne **32**. This was achieved by Swern oxidation of **31** to the corresponding aldehyde and reaction of the latter with the anion of Gilbert−Seyferth reagent **33**.[23] Before functionalizing the alkyne, ester **32** was reduced to an alcohol that was protected as TIPS ether **34**. Alkyne **34** was then smoothly transformed to iodoalkene **35**, the species programmed schematically as **9** for coupling with cyclohexene subunit **8**.

Second Generation Synthesis of 9. The lengthy sequence from glyceraldehyde acetonide **12** to tetrahydrofuran **35** portrayed in Schemes 3, 4, and 6 suffers from a strategic flaw arising from the presence of an extraneous oxygen substituent that must be erased before reaching **35**. This defect prompted consideration of a new, shorter route to **35** that avoided this

(22) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Reuterm, D. C. *Tetrahedron Lett.* **1989**, *30*, 2065.

(23) (a) Gibert, J. C.; Weerasooriya, U. J. *Org. Chem.* **1979**, *44*, 4997. (b) Seyferth, D.; Marmor, R. S. *Tetrahedron Lett.* **1970**, *11*, 2493.

SCHEME 7. Second Generation Approach to Tetrahydrofuran Domain of Gymnodimine



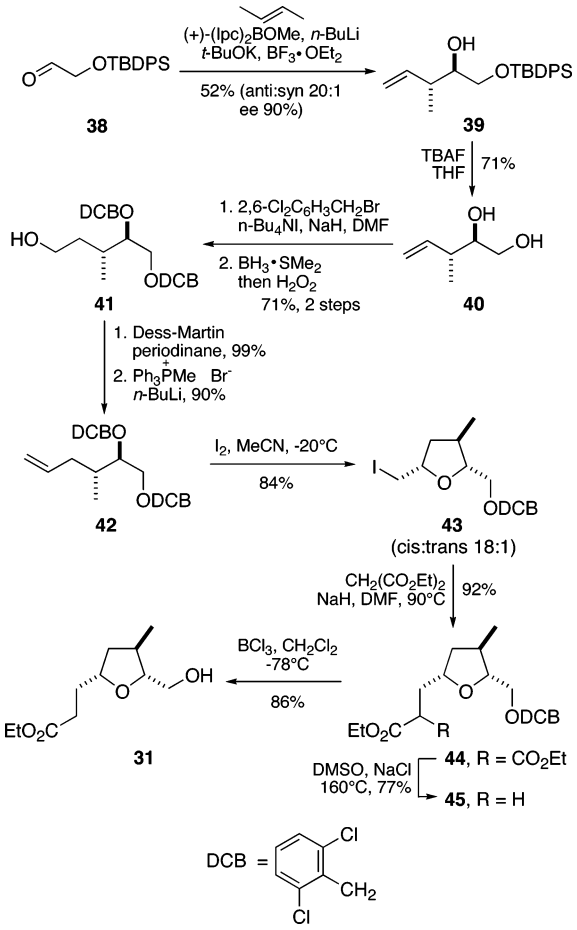
impediment. Specifically, it appeared that closure of the tetrahydrofuran from the opposite direction to that shown in Scheme 4, i.e., from right-to-left instead of left-to-right, could circumvent the deoxygenation problem. The new approach is outlined in Scheme 7 and reverses the tactical moves shown in Scheme 2 by generating tetrahydrofuran **36**, absent the unwanted C4 oxygen but with correct absolute configuration, from acyclic precursor **37**.

Pursuing this plan led to aldehyde **38** as the point of departure, and asymmetric crotylation of this substance under Brown's conditions[19] furnished homoallylic allylic alcohol **39** at an acceptable level of stereochemical purity (Scheme 8). Cleavage of silyl protection from **39** gave diol **40**, which, following precedent established with **17**, was converted to its bis(2,6-dichlorobenzyl) ether. Hydroboration−oxidation of the vinyl group produced alcohol **41**, and Dess-Martin oxidation of this substance to an aldehyde followed by Wittig olefination gave cyclization substrate **42**. As with **18**, iodoetherification of **42** resulted in highly efficient formation of a tetrahydrofuran, in this case **43** with cis substituents at C2 and C5. A barely detectable (by ^{1}H NMR) amount of the trans-2,5 isomer of **43** was present in the reaction product.

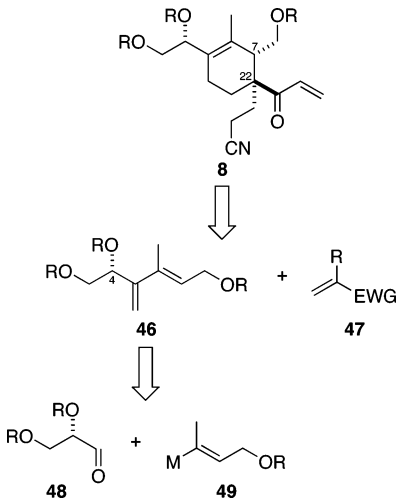
Convergence of **43** with material obtained by the earlier route from glyceraldehyde acetonide was accomplished by displacement of the iodo substituent with the anion of diethyl malonate, decarboxylation of diester **44** to monoester **45**, and final cleavage of the dichlorobenzyl ether to furnish **31**. This substance was identical with the hydroxy ester prepared previously. The final operation in the second generation sequence, cleavage of DCB ether **45**, was incompatible with the lithium-ammonium reduction used previously to cleave the dichlorobenzyl ether from **25** since competing reduction of the ester function of **45** intervened. Fortunately, an efficient cleavage of DCB ether **45** was realized with boron trichloride to yield **31**. The ten-step sequence from **38** to **31** shortens the previous pathway from **12** by five steps and delivers **31** in an overall yield of 15%.

Synthesis of the Cyclohexene Subunit. The second major subunit required in our synthesis plan for gymnodimine was the pentasubstituted cyclohexene **8**. This fragment incorporates three stereocenters, including the extracyclic stereogenic carbon that will become part of the butenolide appendage of **1**, a quaternary carbon bearing functionality from which the spiroimine can be fabricated, and a functional moiety that accommodates

SCHEME 8. Implementation of Second Generation Tetrahydrofuran Synthesis



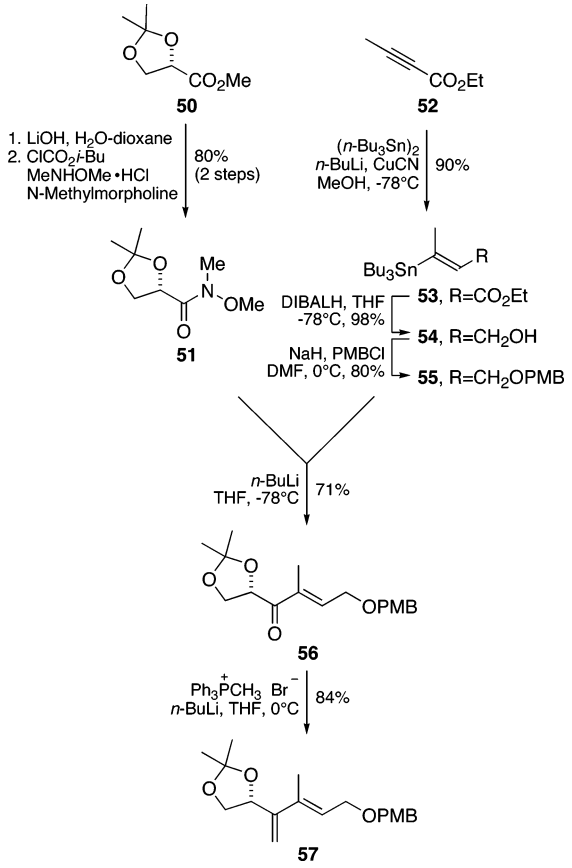
SCHEME 9. Retrosynthetic Analysis of the Cyclohexene Subunit



bond formation with the tetrahydrofuran sector **9**. After considering several routes to **8**, our plan settled on a Diels−Alder approach that would combine diene **46**, already endowed with a stereogenic center corresponding to C4 of **1**, with dienophile **47** (Scheme 9). A pathway to **46** was foreseen from (*S*)-glyceraldehyde derivative **48** in combination with an alkenylmetal reagent **49**.

The preparation of diene **46** commenced with saponification of commercially available ester **50**, conversion of the resulting

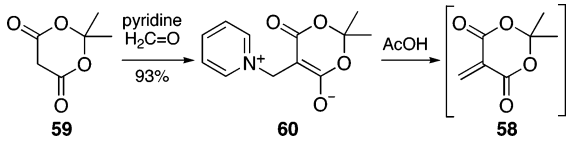
SCHEME 10. Synthesis of a 1,3-Diene for Diels−Alder Cycloaddition



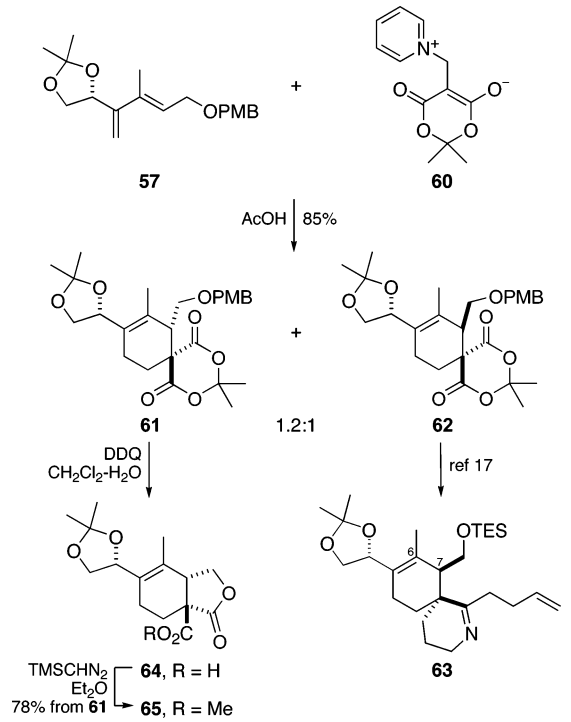
carboxylic acid to a mixed anhydride with isobutyl chloroformate, and then treatment of the anhydride with *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of *N*-methylmorpholine (Scheme 10). Amide **51**[24] was produced in good yield by this sequence. The partner for conjunction with **51** was prepared from ethyl 2-butynoate (**52**) by reaction with hexa-*n*-butyldistannane in the presence of *n*-butyllithium and copper(I) cyanide.[25] The resulting ester **53** was reduced to alcohol **54**, which was protected as its *p*-methoxybenzyl ether **55**. Transmetallation of (*E*)-stannane **55** with *n*-butyllithium followed by addition of **51** afforded α,β-unsaturated ketone **56**,[26] and Wittig olefination of this ketone then furnished diene **57**.

The choice of a dienophilic partner for Diels−Alder reaction with **57** was made with due consideration for the fact that cycloaddition would be required to generate a quaternary stereogenic carbon (C22) adjacent to a hindered stereogenic center at C7. In trial runs, unsymmetrical dienophiles reacted sluggishly with diene **57** and showed regio- or stereoselectivity in the cycloaddition that was too low for a feasible advance on **8**. We therefore chose the highly reactive dienophile **58**,[27] prepared from Meldrum's acid (**59**) via zwitterion **60** (Scheme 11), as the partner for **57**, recognizing that this would not lead to stereogenicity at the new quaternary carbon in the cycloadduct, but that a distinction could probably be made later between the pair of carboxyl substituents through their interaction with

SCHEME 11. Preparation of a Dienophile from Meldrum's Acid



SCHEME 12. Diels−Alder Cycloaddition Leading to a Cyclohexene Subunit for 1



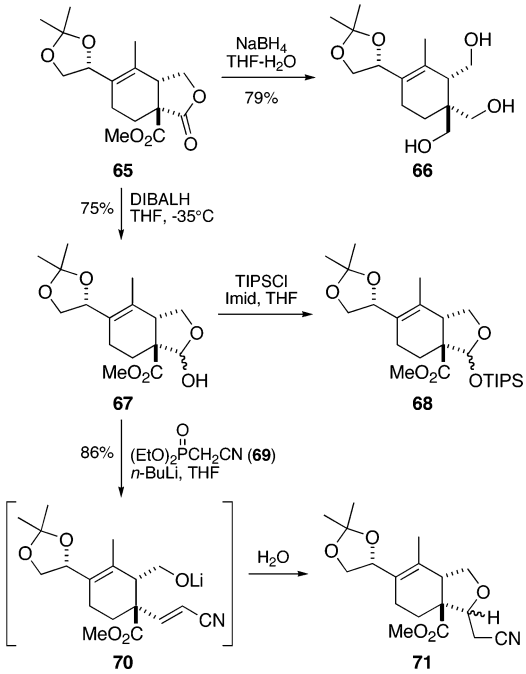
neighboring functionality at C7. There was also the possibility that the single (but remote) stereogenic center in **57** would steer a dienophile toward the face of the diene that would produce the desired (*S*) configuration at C7. In the event, this overly optimistic outcome did not materialize and the reaction of **57** with **60** in acetic acid produced cycloadducts **61** and **62** in nearly equal amounts (Scheme 12). Fortunately, **61** and **62** were easily separable by chromatography and both were crystalline. It was therefore possible to ascertain by X-ray crystallographic analysis the precise stereostructure of each cycloadduct.

A previous study with **62** showed that this cycloadduct could be converted in ten steps to spiroimine **63** having correct configuration at the spiro carbon for gymnodimine.[17] Unfortunately, this left us with the problem of inverting configuration at C7 for which we saw no obvious solution that would avoid a highly likely cyclohexene double bond migration toward C6−C7. We therefore decided to adopt cycloadduct **61** as our platform for departure toward substructure **8**. The *p*-methoxybenzyl ether of **61** was cleaved with 2,3-dichloro-5,6-dicyanobenzoquinone in a reaction that led directly to lactone carboxylic acid **64** and the acid was converted to its more tractable methyl ester **65** with trimethylsilyldiazomethane.

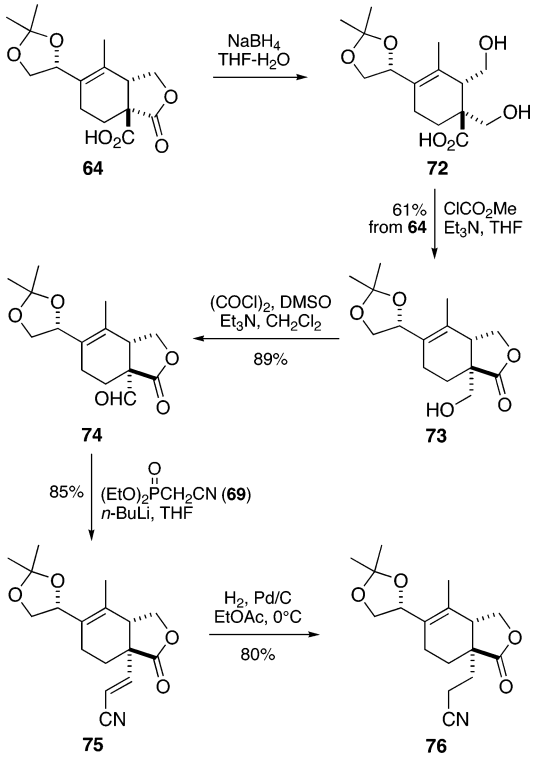
Spontaneous formation of cis-fused lactone **64** upon debenzylation of **61** conveniently differentiated the two carbonyl functions of **61**, and efforts were therefore focused upon reduction of **64** to exploit this felicitous result. Exposure of **65** to sodium borohydride terminated in exhaustive reduction of the lactone ester to the undesired triol **66**, but controlled

(24) Lee, C. E.; Kick, E. K.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 9735.
(25) Piers, E.; Wong, T.; Ellis, K. A. *Can. J. Chem.* **1992**, *70*, 2058.
(26) Gilbson, C. L.; Handa, S. *Tetrahedron*: *Asymmetry* **1996**, 1281.
(27) Zia-Ebrahimi, M.; Huffman, G. W. *Synthesis* **1996**, 215.

SCHEME 13. Elaboration of a Cis-Fused γ-Lactone from Diels−Alder Cycloaddition



SCHEME 14. Preparation of a Trans-Fused γ-Lactone for Advancement of the Cyclohexene Subunit of 1



treatment of **65** with diisobutylaluminum hydride led to the more promising hemiacetal **67** (Scheme 13). It was assumed that **67** would exist in an equilibrium mixture with its open hydroxy aldehyde isomer and that the primary alcohol could be trapped as a silyl ether, but to our disappointment, treatment of **67** with triisopropylsilyl chloride gave only silyl acetal **68**. On the other hand, Horner−Wadsworth−Emmons reaction of **67** with the anion of diethyl cyanomethylphosphonate (**69**)[28] led transiently to α,β-unsaturated nitrile **70**, which closed spontaneously to **71** upon neutralization. Although **71** could, in principle, revert to a ring-opened isomer, e.g., **70**, via β-elimination, no means could be found for accomplishing this transformation. Consequently, further progress from **71** was effectively blocked.

We now realized that spontaneous formation of cis-fused lactone acid **64** upon debenzylation of **61** had ensnared us in a cul-de-sac and that a different route from **61** was needed if we were to gain access to **8**. The possibility of using **61** to reach a trans-fused γ-lactone seemed attractive, since increased strain in that system should offer better prospect for opening the five-membered ring and incorporating the functional substituents needed for **8**. In this context, a return to **64** provided hope, reduction of this substance with sodium borohydride affording diol **72** rather than triol **66** (Scheme 14). Conversion of carboxylic acid **72** to a mixed anhydride with methyl chloroformate followed by treatment with triethylamine resulted in trans-fused lactone **73** and the latter underwent Swern oxidation to furnish crystalline aldehyde **74**. X-ray crystallographic analysis of **74** confirmed that this substance indeed possessed a trans ring fusion. The angular aldehyde of **74** could now be employed in a Horner−Wadsworth−Emmons condensation with phosphonate **69**[28] to give (*E*)-α,β-unsaturated nitrile **75** in which the disubstituted alkene was selectively hydrogenated under carefully controlled conditions to yield nitrile lactone **76**.

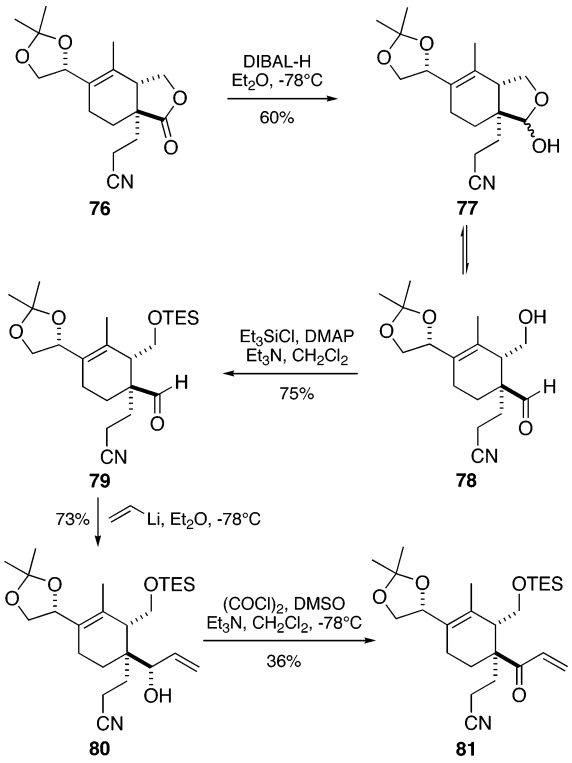
(28) Deschamps, B.; Lefebvre, G.; Seyden-Penne, J. *Tetrahedron* **1972**, *28*, 4209.

With the preparation of lactone **76**, we were in position to move forward using chemistry already developed in Scheme 13 but without the unhappy prospect of encountering a ring-locked species such as **71**. The first task with **76** was selective reduction of the lactone moiety without perturbing the nitrile, a process that was accomplished with diisobutylaluminum hydride in ether at low temperature (Scheme 15). The reduction product was immediately revealed as a mixture of hemiacetal stereoisomers **77** and its opened form **78**. The mobile equilibrium interconnecting **77** and **78** permitted clean silylation of the latter to give primary ether **79**. Although this substance contains an exposed nitrile alongside a sterically hindered aldehyde, reaction of **79** with vinyllithium at low temperature was completely selective, affording a 4:1 mixture of stereoisomeric allylic alcohols in which the Felkin−Anh isomer **80** predominated. Swern oxidation of the mixture of alcohols furnished vinyl ketone **81**, our putative coupling partner for tetrahydrofuran subunit **9**.

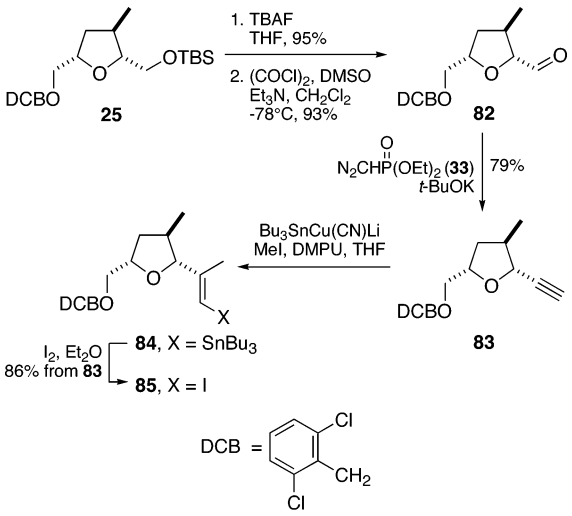
Fragment Coupling. Our initial plan for connecting the tetrahydrofuran domain to the cyclohexene subunit of gymnodimine projected conjugate addition of a vinylcopper species derived from **35** to enone **81**. To preserve our limited quantities of these materials, model coupling experiments were conducted on structurally modified variants of **35** and **81**. First, a truncated version of tetrahydrofuran **35** was prepared from **25** by cleaving the TBS ether and oxidizing the resultant primary alcohol to aldehyde **82** (Scheme 16). This aldehyde was reacted with Gilbert−Seyferth reagent **33**[23] in the presence of a base to yield alkyne **83**. Stannylcupration of **83** and subsequent reaction with methyl iodide furnished stannane **84**, which upon treatment with iodine gave (*E*)-iodoalkene **85**.

A coupling partner for **84** or **85** was conveniently at hand in the form of enone **86**, the C7 epimer of **81**, which had been prepared previously in the course of advancing Diels−Alder

SCHEME 15. Synthesis of a Vinyl Ketone for Coupling with a Tetrahydrofuran

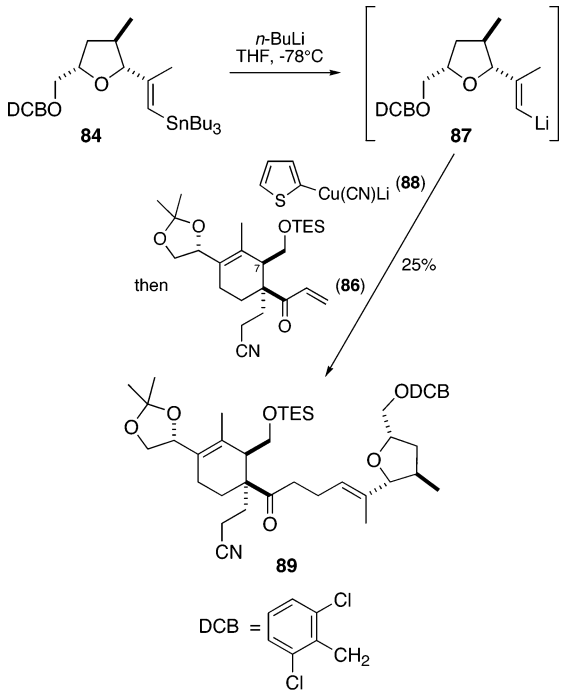


SCHEME 16. Synthesis of a Tetrahydrofuran for Coupling with 81



adduct **62** to spiroimine **63**.[17] However, when **86** was treated with the organocopper reagent obtained by transmetalation of stannane **84** with *n*-butyllithium and then a further transmetalation of lithio species **87** with thienylcopper reagent **88**,[29] the yield of coupled product **89** was a disappointing 25% (Scheme 17). This result was attributed, on the basis of subsequent experiments, to inefficient formation of an organocopper species from **87**. However, replacement of **84** by iodoalkene **85** as a coupling partner for **86** resulted in no improvement to the yield (22%) of **89**.

SCHEME 17. Conjugate Addition of Alkenylstannane 84 to Vinyl Ketone 86



Failure of our conjugate addition strategy for uniting two major subunits of **1** caused us to revise our approach in favor of one that did not hinge upon transmetalation of lithioalkene **87**. A B-alkyl Suzuki−Miyaura coupling[30] came to mind as a possible method for linking iodoalkene **35** with a cyclohexene fragment such as **80**, but to implement this plan it was first necessary to protect the secondary alcohol of **80**. This was accomplished by acetylation, and acetate **90** was reacted with 9-borabicyclo[3.3.1]nonane followed by degassed water to quench excess 9-BBN (Scheme 18). Alkylborane **91** was not isolated from this reaction but was carried forward immediately to the coupling step with iodoalkene **35**. This reaction, which was conducted in the presence of cesium carbonate, triphenylarsine, and a catalytic quantity of palladium bis(diphenylphosphino)ferrocene dichloride, produced **92** in 62% yield. The use of triphenylarsine as an additive in this process was clearly beneficial since the yield of **92** dropped to 36% when this substance was omitted.

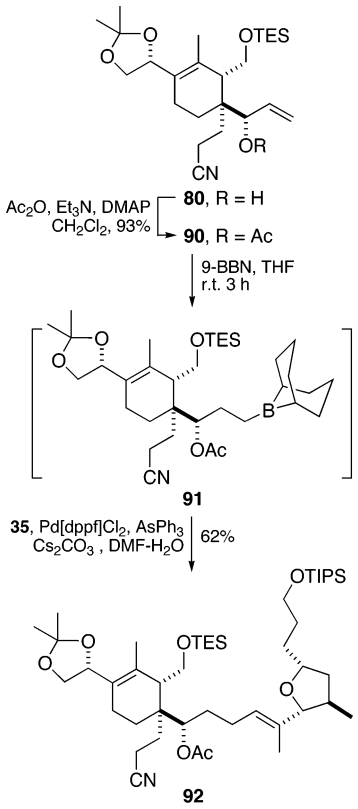
Further progress from **92** toward a precursor from which the macrocycle of gymnodimine could be fashioned now required manipulation of the C7 alkyl substituent that had lain dormant since its incorporation as silyl ether **79**. An end-game for **1** was conceived in which this substituent would be replaced by an alkyne, the alkyne would then be transformed to an (*E*)-iodoalkene, and the latter would be employed in an intramolecular Nozaki−Hiyama−Kishi reaction[31] with an aldehyde at the distal terminus of the tetrahydrofuran side chain. Attempts to realize this plan began with selective cleavage of the TES ether from **92**, which was followed by oxidation of the liberated primary alcohol **93** to aldehyde **94** (Scheme 19). Previous experience with an aldehyde related to **94** had informed us that

(29) Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945.

(30) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.

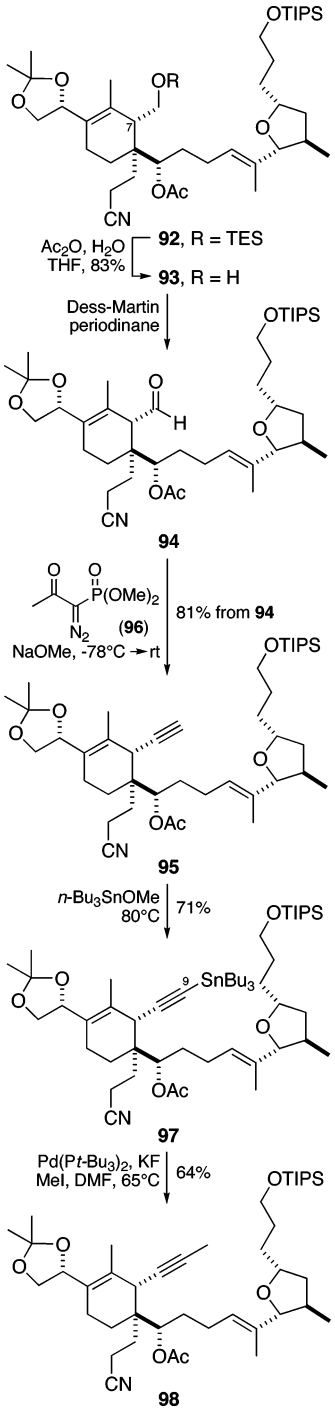
(31) (a) Jin, H.; Uenishi, J.-I.; Christ, W. J.; Kishi. Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (b) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5282.

SCHEME 18. B-Alkyl Suzuki Coupling of Iodoalkene 35 with Acetate 90



the cyclohexene double bond readily migrates into conjugation and therefore **94** was advanced without delay to alkyne **95** with diazophosphonate **96**.[32] The C9 methyl substituent of gymnodimine could now be imported into **95** if methylation of the terminal alkyne could be achieved without impacting either the nitrile or acetate functions, but it was clear that deprotonation of the alkyne under strongly basic conditions could not be used for this purpose. Fortunately, a method due to Suzuki[33] involving methylation of an alkynylstannane appeared to be well suited to our needs. Following Suzuki's protocol, reaction of **95** with neat tri-*n*-butylmethoxystannane[34] at elevated temperature led cleanly to **97** and this afforded methyl-substituted alkyne **98** upon treatment with methyl iodide in the presence of potassium fluoride and a catalytic quantity of bis(tri-*tert*-butylphosphine)-palladium. Subsequent attempts to move **98** toward a substrate suitable for closing the macrocyclic core of **1** met difficulties that stem from the relatively hindered environment of the alkyne. For example, attempted silylcupration−iodination,[35] hydrozirconation−iodination,[36] and palladium-catalyzed hydrostannylation−iodination[37] of **98** all returned unreacted starting material. It is clear from these failures that alkyne **98** is not a viable entity for completing our route to **1** and that a different strategy must be found for creating the macrocyclic portion of gymnodimine.

SCHEME 19. Modification of C7 Functionality of Coupled Product 92



This will be the subject of future efforts directed toward the total synthesis of this intriguing structure.

In summary, a convergent approach to an advanced intermediate containing the C3−C32 sector of gymnodimine has been developed. In complementing a previous study that led to the spiroimine nucleus of **1**, the present work lays groundwork upon which the final stages of a completed synthesis of gymnodimine can be based.

Experimental Section

(2*S*,4*R*,5*R*)-2-Iodomethyl-5-(2,6-dichlorobenzyloxymethyl)-4-methyltetrahydrofuran (43). A solution of alkene **42** (1.60 g, 3.59

(32) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561. (b) Muller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521.

(33) Hosoya, T.; Wakao, M.; Kondo, Y.; Doi, H.; Suzuki, M. *Org. Biomol. Chem.* **2004**, *2*, 24.

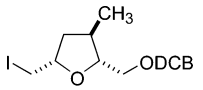
(34) Logue, M. W.; Teng, K. *J. Org. Chem.* **1982**, *47*, 2549.

(35) Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin Trans. I* **1981**, *1*, 2527.

(36) (a) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4912. (b) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 680.

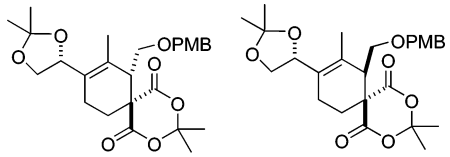
(37) Semmelhack, M. F.; Hooley, R. J. *Tetrhedron Lett.* **2003**, *44*, 5737.

mmol) in dry CH_3CN (300 mL) was cooled to −20 °C and a solution of iodine (1.4 g, 5.38 mmol) in dry CH_3CN (50 mL) was added slowly via syringe. The dark-brown mixture was stirred for



43

3 h at −20 °C and then diluted with Et_2O and saturated $Na_2S_2O_3$ (50 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 200 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (hexane−EtOAc, 10:1) of the residue gave 1.24 g (84%) of **43**: $[\alpha]_D^{23}$ −24.8 (*c* 1.25, $CHCl_3$); IR (neat) 2957, 2927, 2872, 1579, 1564, 1437, 1197, 1101, 994, 778, 767 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (d, J = 7.7 Hz, 3H), 1.77 (ddd, J = 7.7, 12.7, 15.4 Hz, 1H), 2.02 (ddd, J = 5.1, 8.1, 12.8 Hz, 1H), 2.19 (m, 1H), 3.17 (dd, J = 8.0, 10.0 Hz, 1H), 3.28 (dd, 4.8, 10.0 Hz, 1H), 3.64 (m, 2H), 3.71 (m, 1H), 4.16 (m, 1H), 4.78 (d, J = 11.8 Hz, 1H), 4.82 (d, J = 11.8 Hz, 1H), 7.22 (dd, J = 7.6, 8.4 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 Mz, $CDCl_3$) δ 11.3, 17.9, 35.3, 40.1, 68.2, 72.6, 78.4, 86.5, 128.8, 130.3, 133.9, 137.3; HRMS (FAB) *m*/*z* 414.9728 ($[M + H]^+$; calcd for $C_{14}H_{18}O_2Cl_2I$ 414.9729).

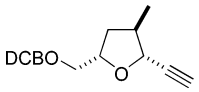


61 **62**

9-(2′,2′-Dimethyl[1′,3′]dioxolan-4′-yl)-7-(4′′-methoxybenzyloxymethyl)-3,3,8-trimethyl-2,4-dioxaspiro[5.5]undec-8-en-1,5-diones (61 and 62). To a solution of **60** (172 mg, 0.54 mmol) in anhydrous EtOH (8 mL) was added glacial acetic acid (37 μL, 0.65 mmol) followed by a solution of diene **57** (153 mg, 0.65 mmol) in EtOH (4 mL). The mixture was stirred for 48 h at room temperature, the solvent was removed under vacuum, and the residue was diluted with cold water and EtOAc. The separated organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. Flash chromatography (hexane−EtOAc, 1:1) of the residue afforded 217 mg (85%) of a mixture (1.2:1) of **61** and **62**. The mixture was separated by spinning rotor chromatography (CH_2Cl_2−EtOAc, 100:5) to provide pure **61** and **62**.

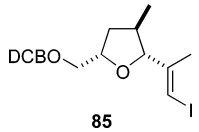
***(4′R,7S)*-61:** $[\alpha]_D^{23}$ +8.6 (*c* 1.05, $CHCl_3$); IR (mixture) (neat) 2986, 2936, 2873, 1770, 1736, 1613, 1514, 1456, 1379, 1304, 1278, 1249, 1209, 1157, 1055, 1033, 860, 822, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.38 (s, 3H), 1.41 (s, 3H), 1.61 (s, 3H), 1.69 (s, 3H), 1.97 (m, 1H), 2.08 − 2.32 (m, 3H), 3.44 (dd, J = 8.0, 11.2 Hz, 1H), 3.45 (t, J = 8.0 Hz, 1H), 3.58 (m, 1H), 3.77 (s, 3H), 3.76 (m, 1H), 4.05 (dd, J = 7.0, 8.0 Hz, 1H), 4.34 (s, 2H), 5.01 (t, J = 7.0 Hz, 1H), 6.83 (m, 2H), 7.18 (m, 2H); ^{13}C NMR (100 Mz, $CDCl_3$) δ 16.7, 21.1, 25.7, 26.8, 28.9, 29.8, 31.8, 45.7, 50.2, 55.6, 67.8, 68.5, 73.4, 75.2, 105.7, 109.5, 114.1, 127.0, 129.6, 129.8, 129.9, 159.6, 165.5, 170.7; HRMS (mixture) (CI) *m*/*z* 474.2249 ($[M]^+$; calcd for $C_{26}H_{34}O_8$ 474.2254).

***(4′R,7R)*-62:** $[\alpha]_D^{23}$ −10.4 (*c* 0.5, $CHCl_3$); IR (mixture) (neat) 2986, 2936, 2873, 1770, 1736, 1613, 1514, 1456, 1379, 1304, 1278, 1249, 1209, 1157, 1055, 1033, 860, 822, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.39 (s, 3H), 1.43 (s, 3H), 1.67 (s, 3H), 1.71 (s, 3H), 1.98−2.27 (m, 3H), 2.39−2.53 (m, 1H), 3.37 (m, 1H), 3.65 (t, J = 8.0 Hz, 1H), 3.79 (s, 3H), 3.70−3.82 (m, 2H), 4.00 (t, J = 8.0 Hz, 1H), 4.37 (m, 2H), 5.04 (t, J = 7.0 Hz, 1H), 6.85 (d, J = 7.9 Hz, 2H), 7.18 (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 Mz, $CDCl_3$) δ 16.4, 20.1, 26.0, 26.7, 28.9, 29.7, 31.8, 45.7, 50.3, 55.7, 67.5, 68.9, 73.5, 74.3, 105.7, 109.4, 114.1, 128.5, 129.2, 129.7, 129.9, 159.7, 165.5, 170.7; HRMS (mixture) (CI) *m*/*z* 474.2249 ($[M]^+$; calcd for $C_{26}H_{34}O_8$ 474.2254).



83

(2*R*,3*R*,5*S*)-5-(2,6-Dichlorobenzyloxymethyl)-2-ethynyl-3-methyltetrahydrofuran (83). To a solution of potassium *tert*-butoxide (1M in *i*-PrOH, 4.3 mL, 4.3 mmol) in THF (10 mL) at −78 °C was added a solution of diethyl (diazomethyl)-phosphonate **33** (0.77 g, 4.3 mmol) in THF (2 mL). The mixture was stirred for 5 min, and aldehyde **82** (0.66 g, 2.2 mmol) was added slowly. The mixture was allowed to slowly warm to room temperature and the reaction was quenched by addition of water (5 mL). The solvent was removed under vacuum and the residue was partitioned between EtOAc and water. The phases were separated, the aqueous phase was extracted with EtOAc (2×), and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. Flash chromatography (hexane−EtOAc, 15:1) of the residue afforded 0.51 g (79%) of **83**: $[\alpha]_D^{23}$ −20.7 (*c* 1.04, $CHCl_3$); IR (neat) 3302, 2961, 2931, 2874, 1735, 1563, 1437, 1197, 1102, 779, 767 cm^{-1}; 1H NMR (300 MHz, $CDCl_3$) δ 1.13 (d, J = 6.7 Hz, 3H), 1.70 (m, 1H), 2.09 (m, 1H), 2.38 (m, 1H), 2.48 (d, J = 1.9 Hz, 1H), 3.55 (dd, J = 5.8, 9.9 Hz, 1H), 3.70 (dd, J = 6.0, 10.0 Hz, 1H), 4.07 (dd, J = 2.2, 7.5 Hz, 1H), 4.25 (m, 1H), 4.85 (d, J = 10.7 Hz, 1H), 4.90 (d, J = 10.7 Hz, 1H), 7.21 (dd, J = 7.7, 8.4 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 Mz, $CDCl_3$) δ 17.1, 36.8, 41.1, 66.3, 68.2, 73.5, 75.5, 83.5, 128.8, 130.3, 135.7, 137.3; HRMS (CI) *m*/*z* 298.0524 ($[M]^+$; calcd for $C_{15}H_{16}O_2Cl_2$ 298.0527).

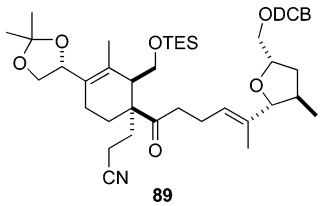


85

(2*R*,3*R*,5S)-5-(2,6-Dichlorobenzyloxymethyl)-2-[(*E*)-2-iodo-1-methylvinyl]-3-methyltetrahydrofuran (85). To flame-dried CuCN (33 mg, 0.37 mmol) was added THF (1.5 mL) under argon, and the mixture was cooled to −78 °C. *n*-BuLi (2.58 M, 0.29 mL, 0.74 mmol) was added slowly, and the resulting mixture was stirred for 10 min at −65 °C. The suspension gradually became a homogeneous, colorless solution that was re-cooled to −78 °C. To this solution was added *n*-Bu_3SnH (0.13 mL, 0.74 mmol), and the resulting mixture was stirred for 10 min, during which time the solution became yellow. A solution of alkyne **83** (32 mg, 0.11 mmol) in THF (0.5 mL) was slowly added to the reaction mixture. After the resulting mixture was stirred for 30 min at −78 °C, MeI (50 μL) and DMPU (80 μL) were added. This mixture was allowed to warm slowly to room temperature. The reaction was quenched by addition of a solution of saturated $NH_4Cl/NH_3 \cdot H_2O$ (9/1), and the mixture was diluted with EtOAc. The phases were separated and the aqueous phase was extracted with EtOAc (2×). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum to give vinyl stannane **84**.

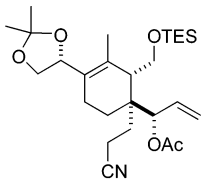
To a solution of stannane **84** in THF (1 mL) at 0 °C was added I_2 (28 mg, 0.11 mmol), and the mixture was stirred for 30 min at room temperature. The mixture was diluted with water and extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under vacuum. Flash chromatography (hexane−EtOAc, 40:1) of the residue yielded 40 mg (86%) of **85**: $[\alpha]_D^{23}$ −13.8 (*c* 0.16, $CHCl_3$); IR (neat) 2957, 2928, 1563, 1437, 1197, 1102, 1044, 777, 768 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (d, J = 6.4 Hz, 3H), 1.66 (m, 1H), 1.82 (s, 3H),

2.05 (m, 2H), 3.60 (m, 2H), 3.90 (d, J = 8.7 Hz, 1H), 4.25 (m, 1H), 4.81 (d, J = 10.8 Hz, 1H), 4.87 (d, J = 10.8 Hz, 1H), 6.29 (s, 1H), 7.21 (m, 1H), 7.36 (d, J = 8.1 Hz, 2H); ^{13}C NMR (100 Mz, $CDCl_3$) δ 17.4, 20.1, 36.9, 37.2, 68.0, 73.7, 77.8, 79.1, 91.1, 128.8, 130.3, 133.8, 137.3, 147.6; HRMS (CI) *m*/*z* 439.9811 ([M − H]$^+$; calcd for $C_{16}H_{19}Cl_2IO_2$ 439.9807).



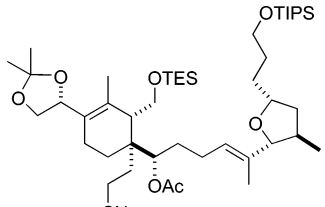
89

3-((1*R*,2*R*)-1-((*E*)-5-((2*R*,3*R*,5*S*)-Tetrahydro-5-(2,6-dichlorobenzyloxylmethyl)-3-methyfuran-2-yl)hex-4-enoyl)-2-(triethylsilanyloxymethyl)-3-methyl-4-((*R*)-2,2-dimethyl-1,3-dixolan-4-yl)-cyclohex-3-enyl)propanenitrile (89). To a solution of vinylstannane **84** (10.5 mg, 17.4 μmol) in THF (0.1 mL) at −78 °C was added *n*-BuLi (7 μL of a 2.5 M solution in hexane, 17.5 μmol). The mixture was stirred for 1 h and a solution of 2-thienyl(cyano)copper lithium (**88**, 70 μL of a 0.25 M solution in THF, 17.4 μmol) was added. The mixture was stirred for 10 min at −78 °C and a solution of **86** (6.5 mg, 14.5 μmol) in THF (0.1 mL) was added. After 2 h at −78 °C, the reaction was quenched by addition of aqueous saturated $NaHCO_3$. The mixture was diluted with EtOAc, the phases were separated, and the aqueous layer was extracted with EtOAc (2×). The combined organic extract was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated under vacuum. Flash chromatography (hexane−EtOAc, 4:1) of the residue afforded 2.8 mg (25%) of **89**: IR (neat) 2954, 2930, 2875, 2248, 1700, 1582, 1564, 1456, 1437, 1378, 1260, 1210, 1156, 1101, 1061, 1017, 863, 813, 767, 746 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.54 (q, J = 7.9 Hz, 6H), 0.92 (t, J = 7.9 Hz, 9H), 1.28 (s, 3H), 1.31 (m, 2H), 1.43 (s, 3H), 1.48 (s, 3H), 1.64, (s, 3H), 1.66 (m, 1H), 1.77 (m 1H), 1.79 (s, 3H), 1.95−2.4 (m, 10H), 2.6 (m, 1H), 3.44−3.55 (m, 4H), 3.62 (dd, J = 5.2, 9.7 Hz, 1H), 3.68 (d, J = 8.0 Hz, 1H), 4.05 (t, J = 7.6 Hz, 1H), 4.20 (m, 1H), 4.81 (d, J = 10.6 Hz, 1H), 4.85 (d, J = 10.6, 1H), 5.04 (t, J = 7.2 Hz, 1H), 5.39 (t, J = 6.5 Hz, 1H), 7.21 (t, J = 8.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H); HRMS (FAB) *m*/*z* 760.3576 ([M − H]$^+$; calcd for $C_{41}H_{60}O_6N^{35}Cl_2Si$ 760.3567).



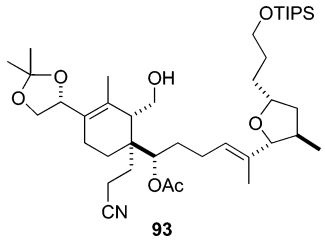
90

1-((1*R*,2*S*)-1-(2-Cyanoethyl)-2-(triethylsilanyloxymethyl)-3-methyl-4-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)cyclohex-3-enyl)-allyl Acetate (90). To a solution of **80** (18.5 mg, 0.044 mmol) in CH_2Cl_2 (0.3 mL) at 0 °C was added Et_3N (0.1 mL, 0.71 mmol), DMAP (2.5 mg), and Ac_2O (2 mL, 0.21 mmol). The mixture was stirred for 2 h at room temperature and the reaction was quenched by addition of a saturated solution of NH_4Cl. The mixture was diluted with CH_2Cl_2, the two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×). The combined organic extract was washed with water and brine, dried over Na_2SO_4, and concentrated. Flash chromatography (hexane−EtOAc, 4:1) of the residue furnished 18.6 mg (93%) of **90**: $[\alpha]_D^{23}$ +15.7 (*c* 0.81, $CHCl_3$); IR (neat) 2954, 2924, 2875, 2248, 1724, 1456, 1370, 1233, 1157, 1056, 1081, 970, 861, 808, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.65 (q, J = 7.9 Hz, 6H), 0.99 (t, J = 8.0 Hz, 9H), 1.41 (s, 3H), 1.44 (s, 3H), 1.59 (m, 1H), 1.78 (s, 3H), 1.79 (m, 2H), 1.91−2.07 (m, 3H), 2.14 (s, 3H), 2.29 (dd, J = 7.2, 16.1 Hz, 1H), 2.58 (m, 2H), 3.58 (dd, J = 2.1, 11.4 Hz, 1H), 3.62−3.68 (m, 2H), 4.06 (dd, J = 6.8, 8.1 Hz, 1H), 5.01 (t, J = 7.5 Hz, 1H), 5.15 (d, J = 17.0 Hz, 1H), 5.26 (d, J = 6.6 Hz, 1H), 5.31 (d, J = 10.5 Hz, 1H), 5.80 (ddd, J = 6.6, 10.5, 17.1 Hz, 1H); ^{13}C NMR (100 Mz, $CDCl_3$) δ 4.7, 7.3, 13.5, 19.3, 19.9, 21.6, 24.2, 26.0, 26.7, 31.2, 41.0, 50.2, 62.3, 67.1, 75.0, 76.3, 109.4, 119.6, 121.2, 128.7, 130.0, 133.2, 170.3; HRMS (ES) *m*/*z* ([M]$^+$ 491.3058; calcd for $C_{27}H_{45}NO_5Si$ 491.3067).



92

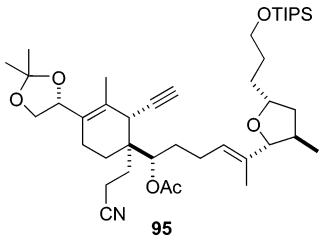
(4*E*)-1-((1*R*,2*S*)-1-(2-Cyanoethyl)-2-(triethylsilanyloxymethyl)-3-methyl-4-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)cyclohex-3-enyl)-5-((2*R*,3*R*,5*R*)-tetrahydro-5-(3-triisopropylsilanyloxypropyl)-3-methyfuran-2-yl)hex-4-enyl Acetate (92). To alkene **90** (27 mg, 55 μmol) was added 9-borabicyclo[3.3.1]nonane (0.44 mL of a 0.5 M solution in THF, 220 μmol) and the mixture was stirred at room temperature for 3 h. Degassed water (16 μL) was carefully added and the mixture was stirred at room temperature for 1 h. In a separate flask, a solution of Cs_2CO_3 (35 mg, 108 μmol), $PdCl_2$-(dppf) (8.3 mg, 11 μmol), $AsPh_3$ (3.3 mg, 11 μmol), and iodide **35** (31 mg, 66 μmol) in DMF (0.2 mL) was prepared and the THF solution of borane **91** was added. The mixture was stirred at room temperature for 10 h and then was diluted with EtOAc. The mixture was washed with water and brine, dried over Na_2SO_4, and concentrated. Flash chromatography (hexane−EtOAc, 4:1) of the residue gave 28.1 mg (62%) of **92**: $[\alpha]_D^{23}$ −14.7 (*c* 0.30, $CHCl_3$); IR (neat) 2954, 2918, 2867, 2849, 2245, 1737, 1590, 1461, 1375, 1236, 1159, 1059, 1016, 857, 810, 752 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.59 (q, J = 7.6 Hz, 6H), 0.94 (d, J = 6.4 Hz, 3H), 0.96 (t, J = 7.7 Hz, 9H), 0.91−1.00 (m, 3H), 1.05 (s, 18H), 1.38 (s, 3H), 1.40 (s, 3H), 1.54 (s, 3H), 1.75 (s, 3H), 2.08 (s, 3H), 1.50−2.25 (m, 18H), 2.56 (m, 2H), 3.55−3.80 (m, 6H), 3.97 (m, 1H), 4.05 (t, J = 7.7 Hz, 1H), 4.98 (d, J = 10.2 Hz, 1H), 5.00 (t, J = 7.7 Hz, 1H), 5.36 (t, J = 8.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.7, 7.3, 11.6, 12.4, 13.7, 14.5, 14.5, 17.6, 18.4, 19.4, 21.5, 22.7, 23.1, 26.1, 26.7, 29.9, 32.0, 33.2, 36.4, 40.3, 41.2, 50.8, 63.8, 67.0, 75.2, 75.3, 78.1, 92.6, 109.3, 121.2, 126.6, 128.5, 130.0, 135.8, 171.0; HRMS (ES) *m*/*z* ([M + Na]$^+$ 854.5772; calcd for $C_{47}H_{85}NO_7NaSi_2$ 854.5762).



93

(4*E*)-1-((1*R*,2*S*)-1-(2-Cyanoethyl)-2-(hydroxymethyl)-3-methyl-4-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)cyclohex-3-enyl)-5-((2*R*,3*R*,5*R*)-tetrahydro-5-(3-triisopropylsilanyloxypropyl)-3-methyfuran-2-yl)hex-4-enyl Acetate (93). A solution of **92** (28.1 mg, 33 μmol) in a mixture of H_2O/HOAc/THF (3/5/11, 1.5 mL) at 0 °C was stirred for 7 h. The reaction was quenched by addition of saturated $NaHCO_3$ and the mixture was diluted with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc (2×). The combined organic extract was washed with brine,

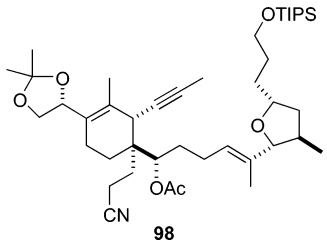
dried over Na_2SO_4, and concentrated. Flash chromatography (hexane−EtOAc, 2:1) of the residue gave 20.1 mg (83%) of **93**: $[\alpha]_D^{23}$ −21.8 (*c* 0.28, $CHCl_3$); IR (neat) 3393, 2928, 2865, 2248, 1734, 1451, 1434, 1383, 1236, 1158, 1097, 1056, 1032, 882, 858, 794 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (d, J = 6.6 Hz, 3H), 1.07 (m, 3H), 1.09 (s, 18H), 1.42 (s, 3H), 1.45 (s, 3H), 1.52−1.78 (m, 12H), 1.58 (s, 3H), 1.80 (s, 3H), 1.85−2.10 (m, 6H), 2.12 (s, 3H), 2.26 (m, 1H), 2.57 (m, 2H), 3.63 (d, J = 8.1 Hz, 1H), 3.70−3.82 (m, 5H), 3.98 (m, 1H), 4.09 (dd, J = 6.7, 8.2 Hz, 1H), 4.98 (d, J = 8.7 Hz, 1H), 5.05 (t, J = 7.3 Hz, 1H), 5.34 (t, J = 6.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.3, 12.0, 13.1, 17.2, 18.1, 18.6, 19.5, 21.1, 24.2, 24.5, 25.7, 26.3, 29.5, 30.3, 30.5, 32.8, 36.1, 39.9, 40.6, 49.7, 61.0, 63.4, 66.7, 74.8, 77.7, 92.2, 109.0, 120.7, 126.1, 127.5, 131.2, 135.6, 170.6; HRMS (ES) *m*/*z* ($[M + Na]^+$ 740.4905; calcd for $C_{41}H_{71}NO_7NaSi$ 740.4898).



95

(4*E*)-1-((1*R*,2*S*)-1-(2-Cyanoethyl)-2-ethynyl-3-methyl-4-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)cyclohex-3-enyl)-5-((2*R*,3*R*,5*R*)-tetrahydro-5-(3-triisopropylsilanyloxypropyl)-3-methyfuran-2-yl)hex-4-enyl Acetate (95). To a solution of alcohol **93** (22.4 mg, 31 μmol) in CH_2Cl_2 (1.0 mL) at 0 °C was added Dess−Martin periodinane (27 mg, 62 μmol). After removal of the cooling bath, the mixture was stirred for 1 h and then diluted with Et_2O. Most of the solvent was removed under vacuum, and the residue was taken up in Et_2O. A mixture of 10% $Na_2S_2O_3$/saturated $NaHCO_3$ (1/1) was added and the mixture was stirred at room temperature for 30 min. The two phases were separated and the organic layer was washed with water and brine. The aqueous washings were back-extracted with Et_2O, and the organic extract was washed with water and brine. The combined Et_2O extract was dried over Na_2SO_4, and concentrated to give 20.5 mg (92%) of aldehyde **94**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (d, J = 6.6 Hz, 3H), 1.04 (m, 3H), 1.05 (s, 18H), 1.39 (s, 3H), 1.44 (s, 3H), 1.50−1.82 (m, 10 H), 1.54 (s, 3H), 1.61 (s, 3H), 1.83−2.09 (m, 6H), 2.10 (s, 3H), 2.36−2.62 (m, 3H), 2.66 (d, J = 4.3 Hz, 1H), 3.61 (d, J = 8.1 Hz, 1H), 3.63−3.72 (m, 3H), 3.95 (m, 1H), 4.08 (dd, J = 6.7, 8.2 Hz, 1H), 4.94 (dd, J = 3.4, 8.8 Hz, 1H), 5.05 (t, J = 7.1 Hz, 1H), 5.30 (t, J = 6.7 Hz, 1H), 9.47 (d, J = 4.9 Hz, 1H).

To a solution of (1-diazo-2-oxopropyl)phosphonic acid dimethyl ester (**96**, 23 mg, 120 μmol) in THF (0.5 mL) at −78 °C was added a solution of sodium methoxide (40 μL of a 0.26 M solution in THF, 10.4 μmol), followed by slow addition of a solution of aldehyde **94** (20.5 mg, 29 μmol) in THF (0.3 mL). After the cooling bath was removed, the mixture was stirred at room temperature for 30 min. A saturated NH_4Cl solution was added and the mixture was stirred vigorously for 20 min and then diluted with EtOAc. The phases were separated and the aqueous layer was extracted with EtOAc (2×). The combined organic extract was washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (hexane−EtOAc, 4:1) of the residue afforded 16.8 mg (83%) of **95**: $[\alpha]_D^{23}$ +14.1 (*c* 0.17, $CHCl_3$); IR (neat) 3308, 2931, 2865, 2352, 2246, 1733, 1699, 1652, 1471, 1452, 1436, 1419, 1394, 1372, 1233, 1153, 1095, 1057, 1032, 881, 854, 787 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, J = 6.7 Hz, 3H), 1.06−1.10 (m, 3H), 1.09 (s, 18H), 1.42 (s, 3H), 1.45 (s, 3H), 1.60 (s, 3H), 1.55−1.71 (m, 7H), 1.75−1.86 (m, 2H), 1.85 (s, 3H), 1.89−2.16 (m, 7H), 2.11 (s, 3H), 2.21 (d, J = 2.5 Hz, 1H), 2.25 (m, 1H), 2.50 (m, 1H), 2.62 (m, 1H), 2.81 (s, 1H), 2.62 (d, J = 5.8 Hz, 1H), 3.64 (dd, J = 2.3, 8.1 Hz, 1H), 3.73 (t, J = 5.7 Hz, 2H), 4.06 (dd, J = 6.7, 8.1 Hz, 1H), 4.39 (m, 1H), 5.96−5.05 (m, 2H), 5.35 (t, J = 7.1 Hz, 1H); ^{13}C NMR (100 Mz, $CDCl_3$) δ 11.7, 12.4, 13.3, 17.6, 18.1, 18.5, 20.2, 21.4, 24.8, 25.6, 26.0, 26.7, 29.9, 30.3, 30.5, 33.2, 36.5, 40.2, 41.0, 41.1, 63.8, 67.4, 73.2, 75.0, 75.1, 78.1, 82.8, 92.6, 109.6, 120.7, 126.4, 127.6, 129.4, 136.1, 170.9; HRMS (ES) *m*/*z* ($[M + H]^+$ 712.4984; calcd for $C_{42}H_{70}NO_6Si$ 712.4972).



98

(4*E*)-1-((1*R*,2*S*)-1-(2-Cyanoethyl)-3-methyl-4-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(prop-1-ynyl)cyclohex-3-enyl)-5-((2*R*,3*R*,5*R*)-tetrahydro-5-(3-triisopropylsilanyloxypropyl)-3-methyfuran-2-yl)hex-4-enyl Acetate (98). A solution of **95** (16.8 mg, 0.024 mmol) in Bu_3SnOMe (0.05 mL) was stirred for 36 h at 85 °C. After the solution had cooled to room temperature, flash chromatography (hexane−EtOAc, 4:1) of the mixture gave 16.0 mg (68%) of stannane **97**.

A mixture of Pd(*t*-$Bu_3P)_2$ (0.1 mg) and KF (0.5 mg) in 0.1 mL of DMF was stirred for 5 min at room temperature, after which MeI (4.5 μL of a 1 M solution in DMF, 4.5 μmol) and a solution of stannane **97** (3.0 mg, 3.0 μmol) in DMF (0.1 mL) were added. The mixture was stirred for 5 min at 60 °C, then was cooled to room temperature and diluted with EtOAc. The solution was washed with water and brine, dried over Na_2SO_4, and concentrated. Flash chromatography (hexane−EtOAc, 4:1) of the residue furnished 1.4 mg (64%) of **98**: $[\alpha]_D^{23}$ +22.7 (*c* 0.41, $CHCl_3$); IR (neat) 2951, 2853, 2242, 1740, 1462, 13777, 1234, 1110, 1060, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (d, J = 6.6 Hz, 3H), 1.08 (m, 3H), 1.09 (s, 18H), 1.42 (s, 3H), 1.46 (s, 3H), 1.60 (s, 3H), 1.56−1.72 (m, 11H), 1.82 (s, 3H), 1.83 (s, 3H), 1.87−2.07 (m, 6H), 2.11 (s, 3H), 2.23 (m, 1H), 2.52 (m, 1H), 2.63 (m, 1H), 2.71 (s, 1H), 3.61−3.67 (m, 2H), 3.74 (t, J = 5.7 Hz, 2H), 3.99 (m, 1H), 4.04 (d, J = 6.7, 8.0 Hz, 1H), 4.98 (dd, J = 2.2, 9.7 Hz, 1H), 5.03 (t, J = 7.4 Hz, 1H), 5.35 (t, J = 7.0 Hz, 1H); ^{13}C NMR (100 Mz, $CDCl_3$) δ 3.7, 11.3, 12.0, 12.9, 17.2, 18.1, 18.2, 19.8, 21.1, 24.5, 25.1, 25.7, 26.3, 29.5, 30.2, 32.8, 36.0, 39.8, 40.8, 41.0, 63.4, 67.0, 74.7, 74.8, 78.0, 92.2, 109.0, 120.6, 126.2, 127.9, 128.5, 135.6, 170.5; HRMS (ES) *m*/*z* ($[M + H]^+$ 726.5110; calcd for $C_{43}H_{72}NO_6Si$ 726.5129).

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Supporting Information Available: Experimental procedures and characterization data for compounds not included in the paper, and ^1H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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