

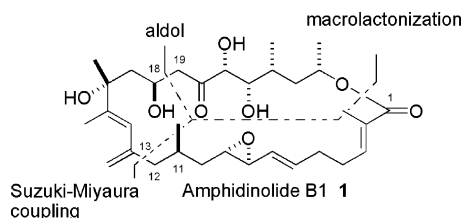
Synthetic Studies on Amphidinolide B1

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Received October 28, 2005

ABSTRACT



The syntheses of three fragments, 2, 3, and 4, of amphidinolide B1 have been accomplished. The 1,3-isomerization of allylic alcohol 10 was accomplished via rhenium oxo catalysis and has been applied successfully in the synthesis. (–)-MIB-catalyzed asymmetric vinylzinc addition to aldehyde 31 and the regio- and stereoselective epoxidation of unsymmetrical divinyl methanol 32 were key steps.

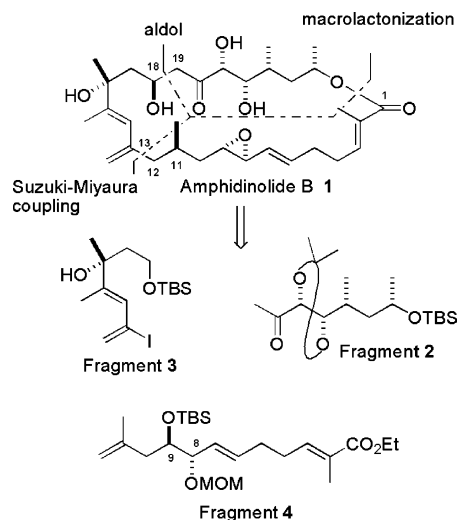
Amphidinolide B1 (1), a polyketide-based 26-membered macrolide, was isolated from a culture of the symbiotic marine dinoflagellate *Amphidinium* sp. (strain Y-5) in 1987 by Kobayashi et al.^{1,2} There have been several reports of partial syntheses toward 1; however, no completed total synthesis has been disclosed yet.³

In our laboratory, we undertook a multipronged approach toward the synthesis of amphidinolide B1 (1) (Scheme 1). One strategy was communicated earlier,⁴ whereas this paper represents an alternative strategy. Our previous strategy involved three major C–C bond-forming reactions and one C–O bond-forming reaction. This new retrosynthetic analysis involves two C–C and one C–O bond-forming coupling reactions: Suzuki–Miyaura coupling,⁵ an aldol reaction,⁶ and macrolactonization using the three fragments 2, 3, and 4. As C–C bond-forming reactions are traditionally more

difficult than C–O bond-forming reactions, we hope that this new strategy will increase the efficiency of the synthesis.

The synthesis of fragment 2 began with Brown's crotylation reaction (Scheme 2).⁷ The reaction of *trans*-crotonaldehyde and (*E*)-crotyldiisopinocampheylborane (prepared from *trans*-butene, *n*-BuLi, *t*-BuOK, and (+)-Ipc₂BOMe) in

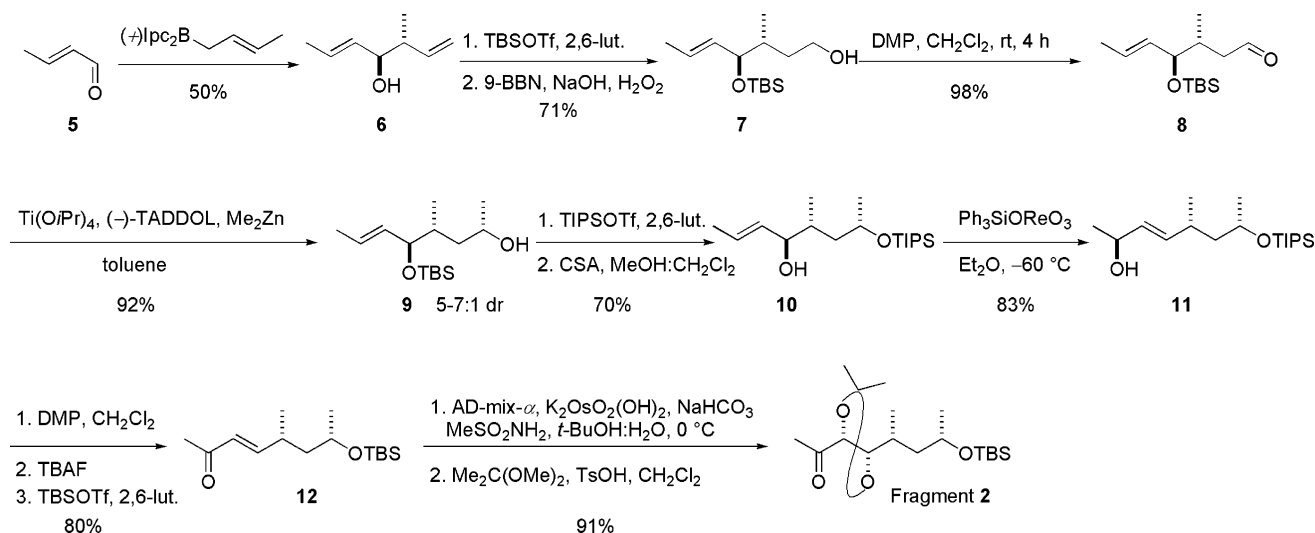
Scheme 1

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Scheme 2



the presence of $\text{BF}_3 \cdot \text{OEt}_2$ in $\text{THF}-\text{Et}_2\text{O}$ at -78°C produced the allyl alcohol **6** in 50% yield and 14:1 anti/syn selectivity. Silyl protection of the hydroxyl group and a regioselective hydroboration–oxidation sequence furnished alcohol **7**, which was oxidized to the corresponding aldehyde **8** using Dess–Martin periodinane. The asymmetric methylation of **8** with Me_2Zn and $\text{Ti}(\text{O}i\text{Pr})_4$ was examined with the chiral ligands BINOL and bisulfonamide.⁸ Unfortunately, the conversions were unacceptable in both cases (25% and 29%, respectively). However, diastereoselective methylation to obtain **9** was achieved with Seebach's method⁹ [Me_2Zn and $\text{Ti}(\text{O}i\text{Pr})_4$ in the presence of (–)-TADDOL] in 92% yield and a 5–7:1 diastereomeric ratio (based on ^1H NMR). Protection of the free alcohol as a TIPS ether (the minor isomer can be separated at this stage) and selective cleavage

of the allylic TBS ether furnished **10** in 70% yield over two steps. At this point, the stage was set to manipulate allylic alcohol **10** to the requisite α,β -unsaturated ketone **12** and to install the remaining stereogenic centers. The 1,3-isomerization of **10** and subsequent oxidation promised to be an atom-efficient method to access ketone **12**. $\text{Ph}_3\text{SiOREO}_3$ ¹⁰ is currently the most effective catalyst for 1,3-isomerization.¹¹ When we treated **10** in the presence of 1 mol % catalyst in ether at -60°C , complete isomerization to regioisomeric allylic alcohol **11** was observed in 5 min. Oxidation of the alcohol **11** under Dess–Martin periodinane conditions furnished the α,β -unsaturated ketone **12**. Swapping TIPS protection with TBS, Sharpless asymmetric dihydroxylation¹² followed by acetone formation completed the synthesis of fragment **2**.

The synthesis of fragment **3** started with known vinyl iodide **13**¹³ (Scheme 3). Transmetalation with $t\text{-BuLi}$ in Et_2O and capture of the resulting vinylolithium species with acetaldehyde yielded (±)-allylic alcohol **14**. Sharpless kinetic resolution¹⁴ of (±)-**14** gave the desired epoxide **15** in 85–90% enantiomeric excess (ee) and unreacted alcohol in 25–30% ee as a mixture that proved difficult to separate. The crude mixture was subjected to a Parikh–Doering oxidation to yield easily separable epoxy ketone **16** and the corresponding α,β -unsaturated ketone (not shown). The α,β -unsaturated ketone was subjected to a Luche reduction to produce (±)-allylic alcohol **14**, which was recycled under Sharpless kinetic resolution conditions. The Horner–Wadsworth–Emmons condensation of epoxy ketone **16** with phosphonate in the presence of NaHMDS produced enyne **17** [82% yield, $E/Z = 6:1$]. Simultaneous cleavage of TBS

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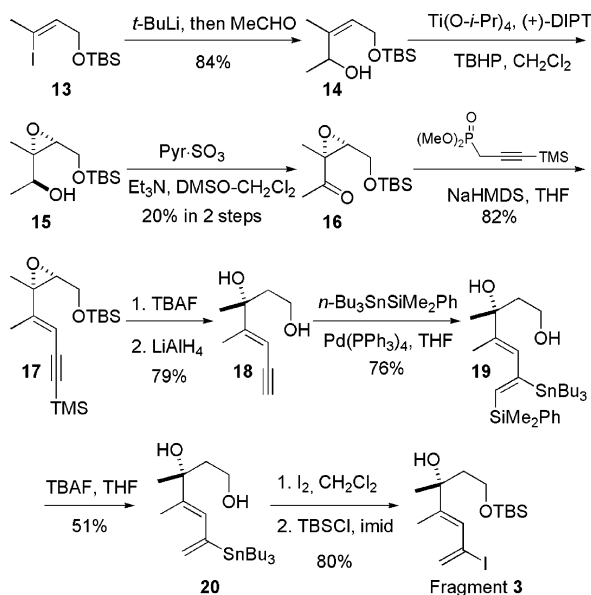
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Scheme 3

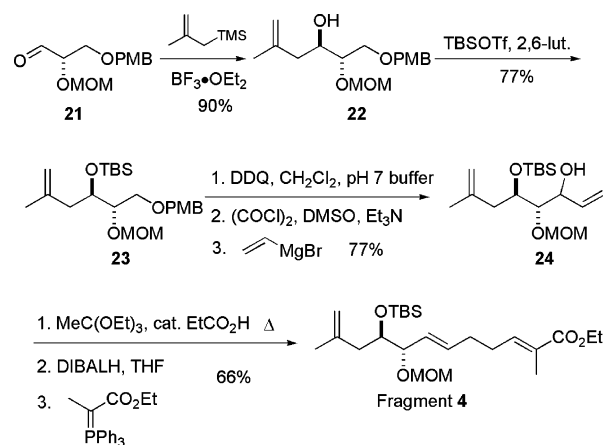


ether and the TMS group by TBAF followed by regioselective opening of the epoxide in the presence of LiAlH_4 in Et_2O furnished diol **18**, which was separated from the minor (*Z*) isomer using column chromatography. Functionalization of the enyne **18** to the 1,3-diene iodide was quite problematic. After exploring several possibilities, we found that the triple bond could be silylstannylated regio- and stereoselectively employing $n\text{-Bu}_3\text{SnSiMe}_2\text{Ph}/\text{Pd}(\text{PPh}_3)_4$ to produce functionalized diene **19**.¹⁵ TBAF-mediated removal of the PhMe_2Si group produced stannane **20**. Reaction with I_2 and selective TBS protection completed the synthesis of fragment **3**.

The synthesis of fragment **4** began with aldehyde **21** (Scheme 4). A nonchelation-controlled $\text{S}_{\text{E}}2'$ reaction between aldehyde **21** and methallylsilane in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ furnished homoallylic alcohol **22** in 90% yield and $\geq 95:5$ diastereomeric ratio (dr).¹⁶ Hydroxyl group protection as a TBS ether **23**, followed by oxidative deprotection of the PMB ether, revealed the primary alcohol. The alcohol was then converted to the aldehyde, which was subjected to vinyl-magnesium bromide addition to provide allyl alcohol **24** as a 1.5:1 diastereomeric mixture (based on ^1H NMR). The allylic alcohol **24** underwent Johnson ortho ester Claisen rearrangement to provide the homologated ethyl ester exclusively as the (*E*) isomer. Reduction to the aldehyde using $i\text{-Bu}_2\text{AlH}$ in THF and the Wittig reaction furnished fragment **4** with exclusive (*E*) selectivity.

With all three fragments securely in hand, we sought to explore the possibility of setting up the C11 stereogenic centers by hydroboration and a subsequent (*B*)-alkyl Suzuki–Miyaura coupling reaction⁵ to assemble the 1,3-diene. We hoped to induce 1,3-stereocontrol on the basis of Evans' alkyl-directed hydroboration model.¹⁷ We have been able to

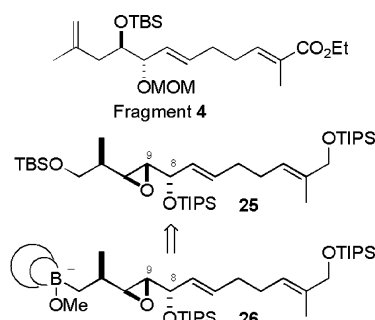
Scheme 4



form the C12–C13 bond successfully using the (*B*)-alkyl Suzuki–Miyaura coupling reaction between (*B*)-alkylborane (derived from regioselective hydroboration of fragment **4**) and (\pm)-1,3-vinyl iodide fragment **3** (synthesis not shown) to put together the C1–C18 portion of the molecule. However, investigations revealed that 1,3-stereocontrol cannot be achieved with this substrate, as hydroboration of fragment **4** with 9-BBN provided a 1:1 inseparable mixture of diastereoisomers at C11 (amphidinolide B1 numbering).

Considering A values, an alkyl group (i.e., $\text{Me} = 1.74$ kcal/mol) imparts more nonbonding interaction than an OSiR_3 group (i.e., $\text{OSiMe}_3 = 0.74$ kcal/mol), presumably because the SiR_3 group can be turned away to avoid the steric interaction.¹⁸ This explains the loss of π -facial selectivity in our substrate. As separation of the diastereoisomers was not easy, we revised our strategy and decided to use compound **25** as a new fragment for the C1–C12 segment in which the C11 methyl stereogenic center is preinstalled (Scheme 5). Instead of coupling the 1,3-diene iodide fragment **3** to

Scheme 5



(*B*)-alkylborane (derived by hydroboration from fragment **4**), we decided to couple it to the ate complex **26** derived from

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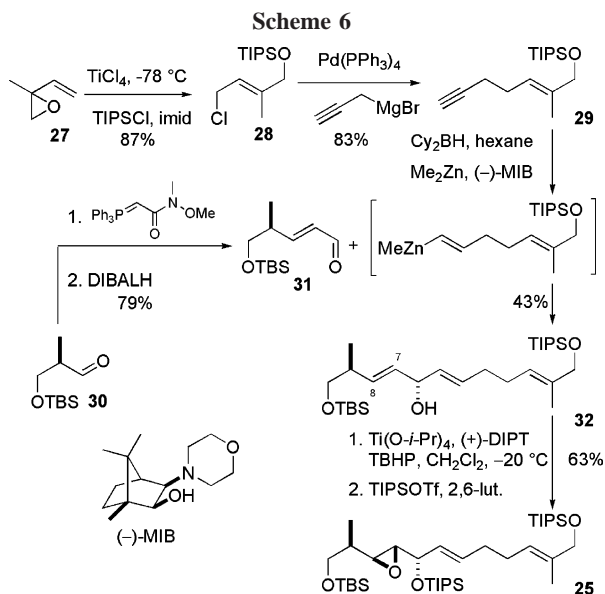
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the corresponding iodide easily accessible from compound **25** in two steps.¹⁹ Preliminary studies involving (\pm)-alkenyl iodide fragment **3** and a model alkyl boronate to assemble the 1,3-diene corroborate the feasibility of this strategy.²⁰

The synthesis of compound **25** commenced with isoprene monoxide (Scheme 6). TiCl_4 -mediated regioselective and



stereoselective opening of the epoxide provided the alcohol, which was protected as a TIPS ether **28**. It was then coupled with propargylmagnesium bromide in the presence of $\text{Pd}(\text{PPh}_3)_4$ to give acetylene **29** in 83% yield. In parallel, aldehyde **31** was synthesized in two steps via the Wittig reaction, followed by reduction with $i\text{-Bu}_2\text{AlH}$. The key strategy is to employ asymmetric addition of alkenylzinc to aldehyde **31** in the presence of Nugent's²¹ isoborneol-based $(-)\text{-MIB}$ ligand.²² Hydroboration of the terminal acetylene **29** with freshly prepared dicyclohexylborane proceeds regioselectively to afford the alkenylborane. Transmetalation of this alkenylborane with Me_2Zn generates the reactive alkenylzinc reagent in situ. Attempts to carry out the trans-

metalation at 0°C , as described in the literature,²³ led to decomposition of the substrate. After extensive experimentation, we found that the reaction could be performed successfully by adding Me_2Zn followed by $(-)\text{-MIB}$ at -78°C to alkenylborane. The mixture was then warmed to -20°C over 10 min. The aldehyde **31** in hexane was added via syringe pump over 20 min while warming the mixture to 0°C to furnish divinyl methanol **32** in 43% yield and $\geq 95\%$ diastereomeric excess (de). This assembled the full carbon backbone of compound **25**. The next challenge was to functionalize stereoselectively the C7–C8 double bond of this unsymmetrical divinyl methanol **32**.

It is documented that the simple (\pm)-unsymmetrical divinyl methanols can be subjected to the Sharpless kinetic resolution conditions to synthesize the optically active monoepoxide.²⁴ However, to the best of our knowledge, Sharpless asymmetric epoxidation has not been applied to desymmetrize a complex unsymmetrical divinyl methanol such as ours in the context of natural product synthesis. We were pleased to find that Sharpless' asymmetric epoxidation provided the C7–C8 monoepoxide in 71% yield (6:1 dr). TIPS protection went uneventfully to furnish **25** in 90% yield.

In conclusion, we have accomplished the synthesis of three fragments, **2**, **3** and, **4**. Compound **25** will be used as the new fragment for the C1–C12 segment. 1,3-Isomerization of allylic alcohol via rhenium oxo catalysis has been applied successfully in our synthesis. $(-)\text{-MIB}$ -catalyzed asymmetric vinylzinc addition to aldehyde **31**, highly selective late-stage epoxidation of divinyl methanol **32**, and regio- and stereo-selective silylstannylation to synthesize stannane **20** have been used as key steps. Continued advancement of these intermediates toward the eventual total synthesis of **1** are currently ongoing in our laboratory.

Acknowledgment. We gratefully acknowledge financial support from NIH (GM062120). J.S.S. acknowledges the American Chemical Society, Division of Medicinal Chemistry, and Aventis Pharmaceuticals for a pre-doctoral fellowship.

Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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