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Synthetic Studies on Amphidinolide B1

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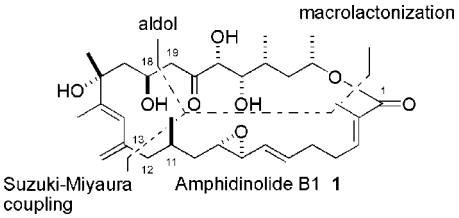
ABSTRACT



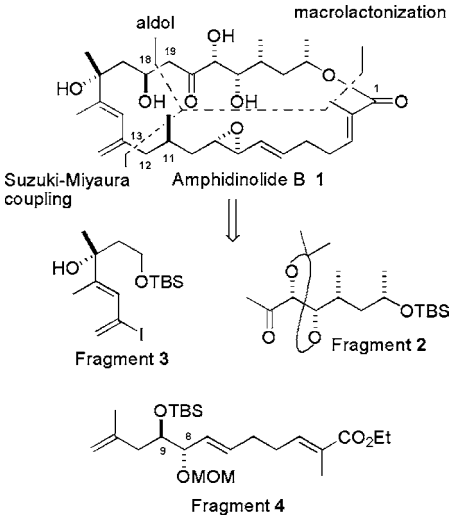
The syntheses of three fragments, 2, 3, and 4, of amphidinolide B1 have been accomplished. The 1,3-isomerization of allylic alcohol 10 was accomplished via rhenium oxo catalysis and has been applied successfully in the synthesis. (–)-MIB-catalyzed asymmetric vinylzinc addition to aldehyde 31 and the 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*)-crotyldiisopinocamphenylborane (prepared from *trans*-butene, *n*-BuLi, *t*-BuOK, and (+)-Ipc$_2$BOMe) in

Scheme 1



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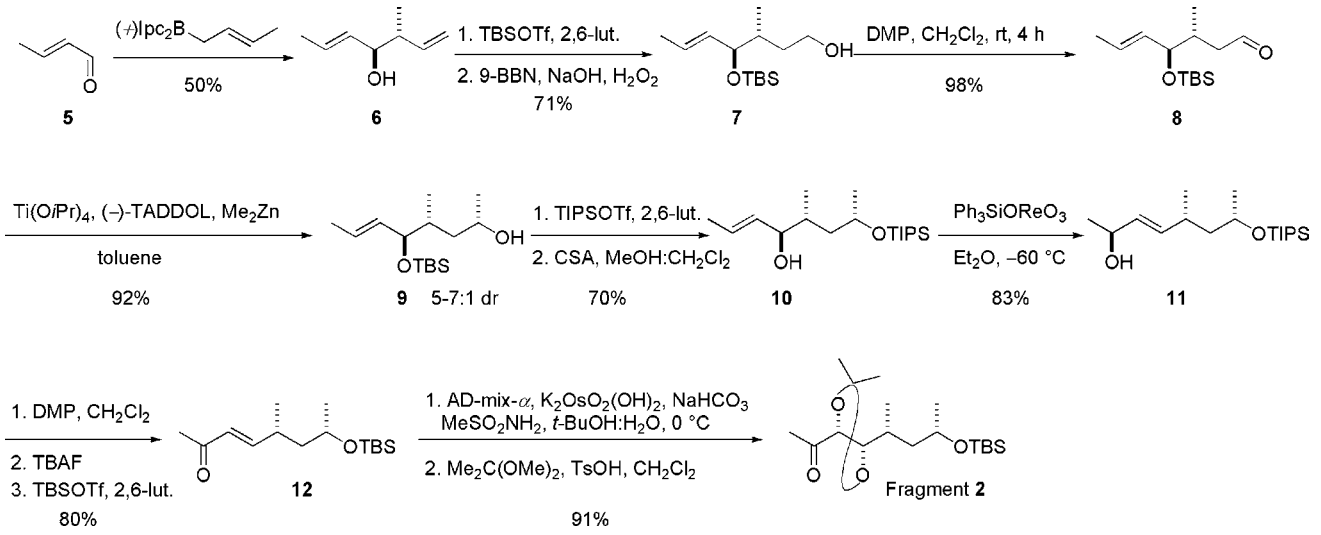
Scheme 2



the presence of $BF_3{\cdot}OEt_2$ in THF−Et_2O 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 $Ti(O^iPr)_4$ was examined with the chiral ligands BINOL and bissulfonamide.[8] Unfortunately, the conversions were unacceptable in both cases (25% and 29%, respectively). However, diastereoselective methylation to obtain **9** was achieved with Seebach's method[9] [Me_2Zn and $Ti(O^iPr)_4$ 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**. $Ph_3SiOReO_3$[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 dihydroxylation[12] followed by acetonide formation completed the synthesis of fragment **2**.

The synthesis of fragment **3** started with known vinyl iodide **13**[13] (Scheme 3). Transmetalation with *t*-BuLi in Et_2O and capture of the resulting vinyllithium species with acetaldehyde yielded (±)-allylic alcohol **14**. Sharpless kinetic resolution[14] 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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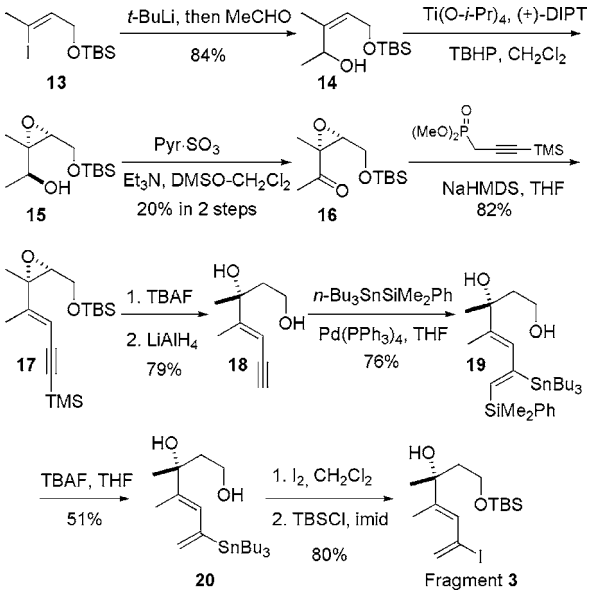
Scheme 3

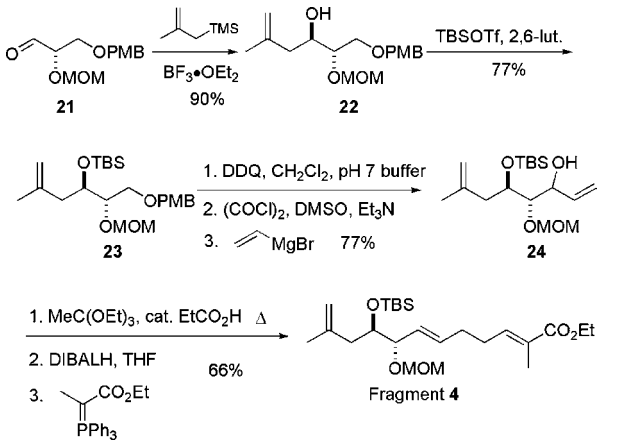


ether and the TMS group by TBAF followed by regioselective opening of the epoxide in the presence of $LiAlH_4$ in Et_2O furnished diol **18**, which was separated from the minor (*Z*) isomer using column chromatography. Functionalization of the enyne **18** to the 1,3-diene iodide was quite problematic. After exploring several possibilities, we found that the triple bond could be silylstannylated regio- and stereoselectively employing *n*-$Bu_3SnSiMe_2Ph$/$Pd(PPh_3)_4$ 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 S_E2' reaction between aldehyde **21** and methallylsilane in the presence of $BF_3{\cdot}OEt_2$ furnished homoallylic alcohol **22** in 90% yield and ≥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 vinylmagnesium 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*-Bu_2AlH 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 reaction[5] 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

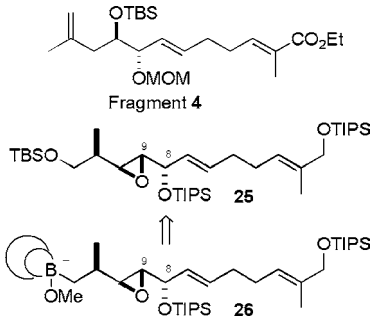
Scheme 4



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 (±)-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., Me = 1.74 kcal/mol) imparts more nonbonding interaction than an $OSiR_3$ group (i.e., $OSiMe_3$ = 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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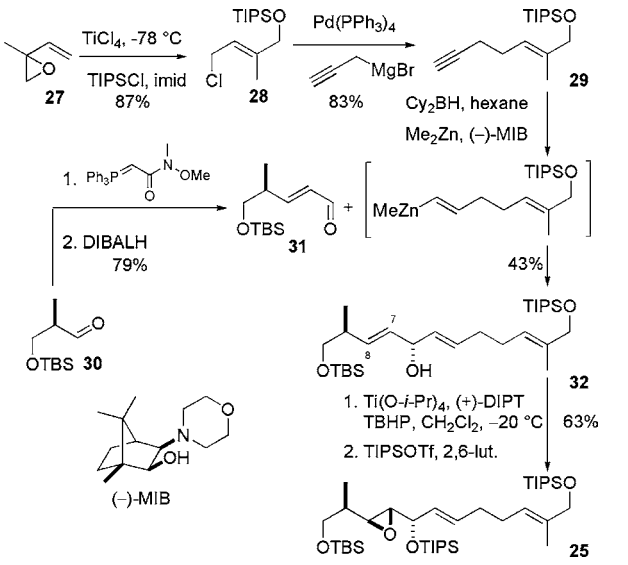
the corresponding iodide easily accessible from compound **25** in two steps.[19] Preliminary studies involving (±)-alkenyliodide fragment **3** and a model alkyl boronate to assemble the 1,3-diene corroborate the feasibility of this strategy.[20]

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

Scheme 6



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 $Pd(PPh_3)_4$ 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*-Bu_2AlH. The key strategy is to employ asymmetric addition of alkenylzinc to aldehyde **31** in the presence of Nugent's[21] isoborneol-based (−)-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 transmetalation 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 (−)-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 ≥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 (±)-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. (−)-MIB-catalyzed asymmetric vinylzinc addition to aldehyde **31**, highly selective late-stage epoxidation of divinyl methanol **32**, and regio- and stereoselective 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.

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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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