Published in final edited form as:
Org Lett. 2006 February 2; 8(3): 427–430.

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_2BOMe) in 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

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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.

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

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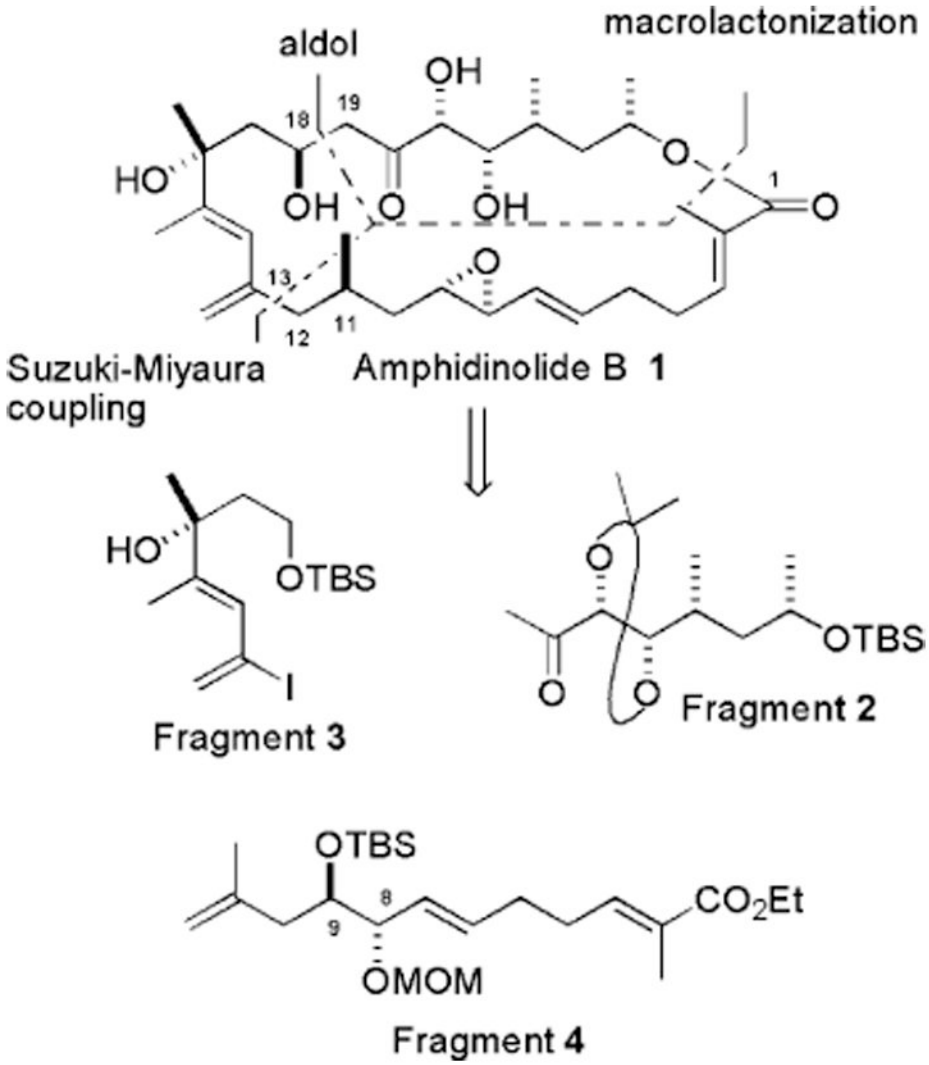
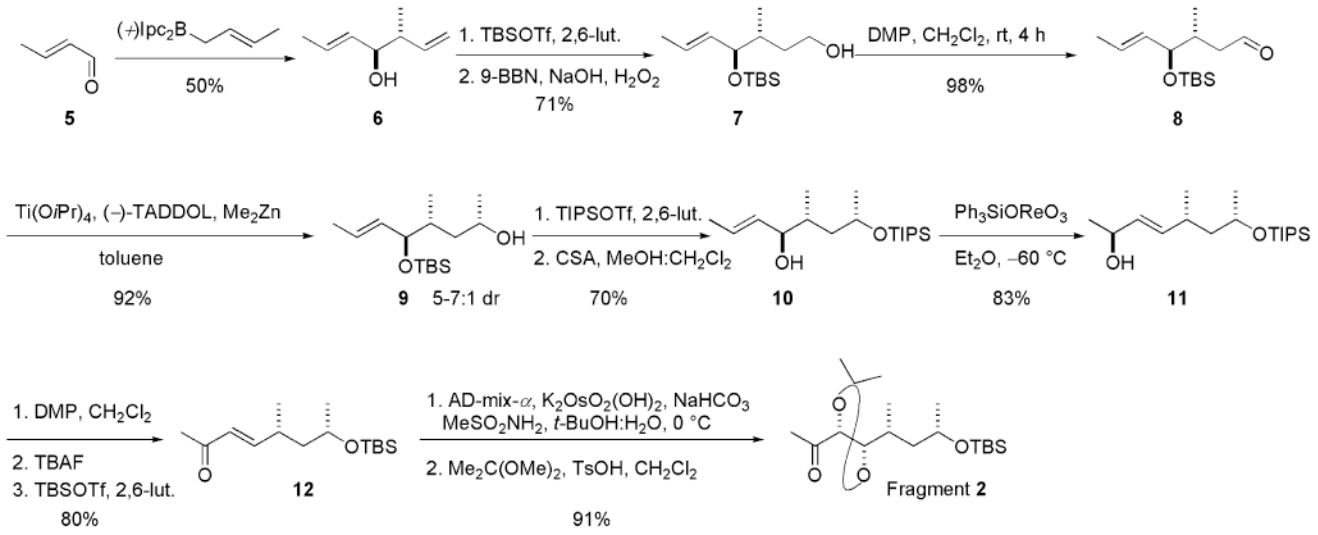
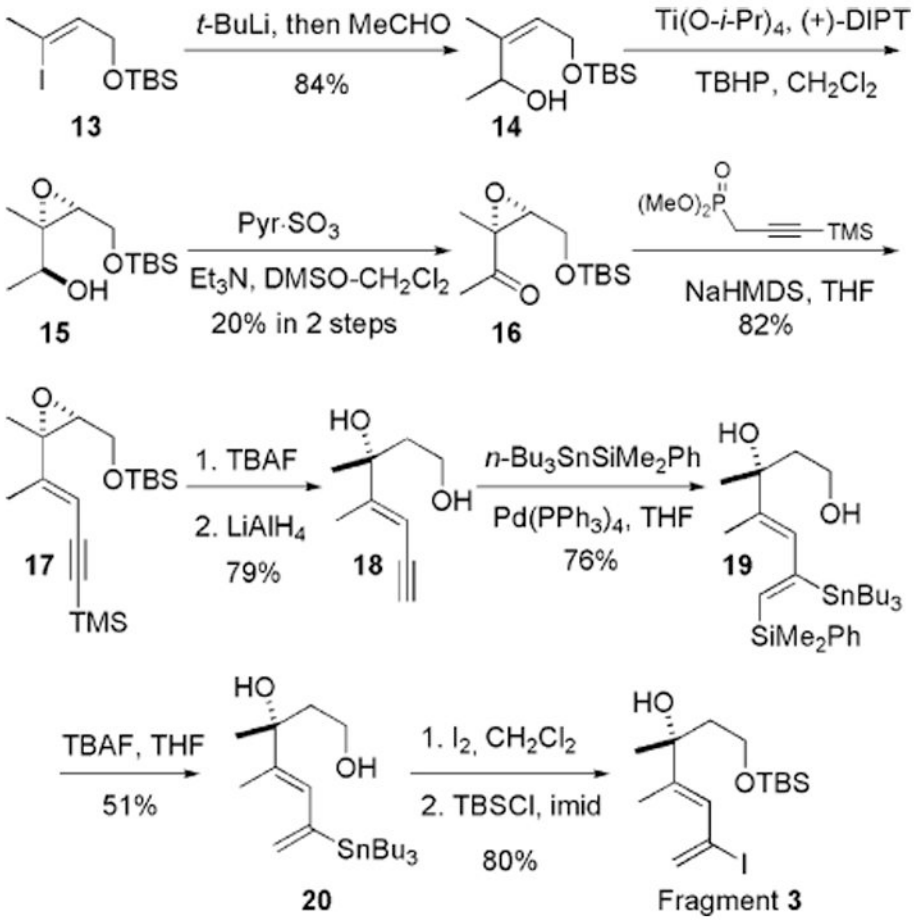


Scheme 1.



Scheme 2.



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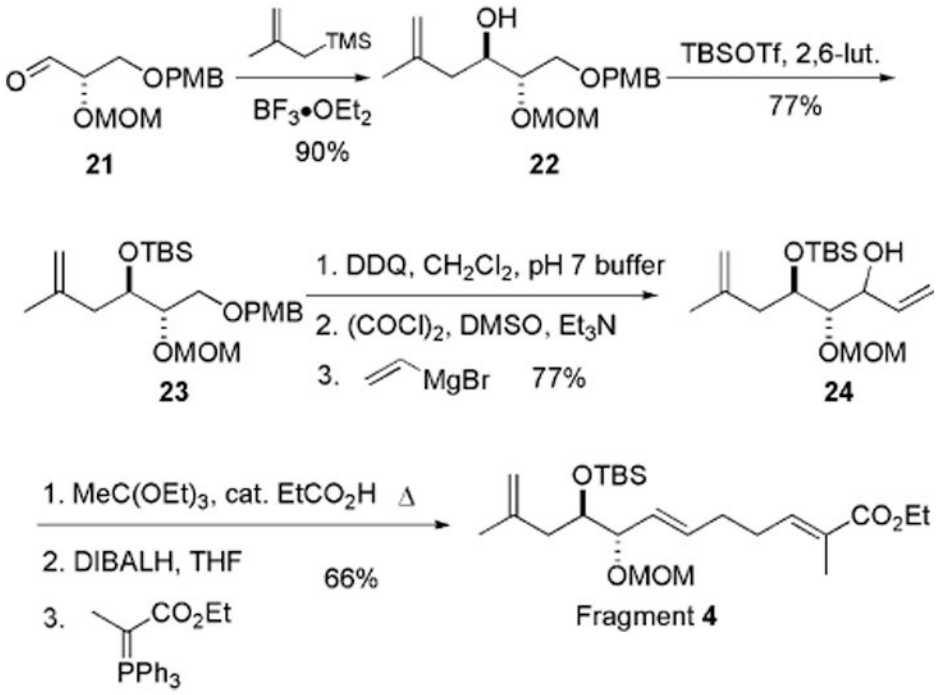

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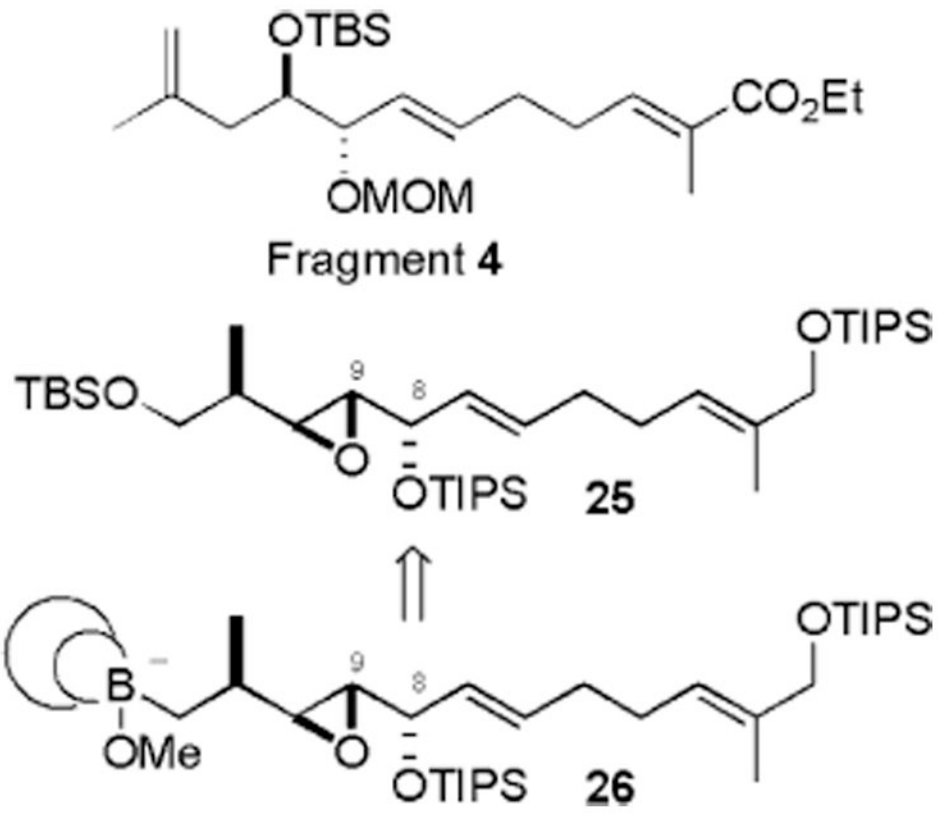
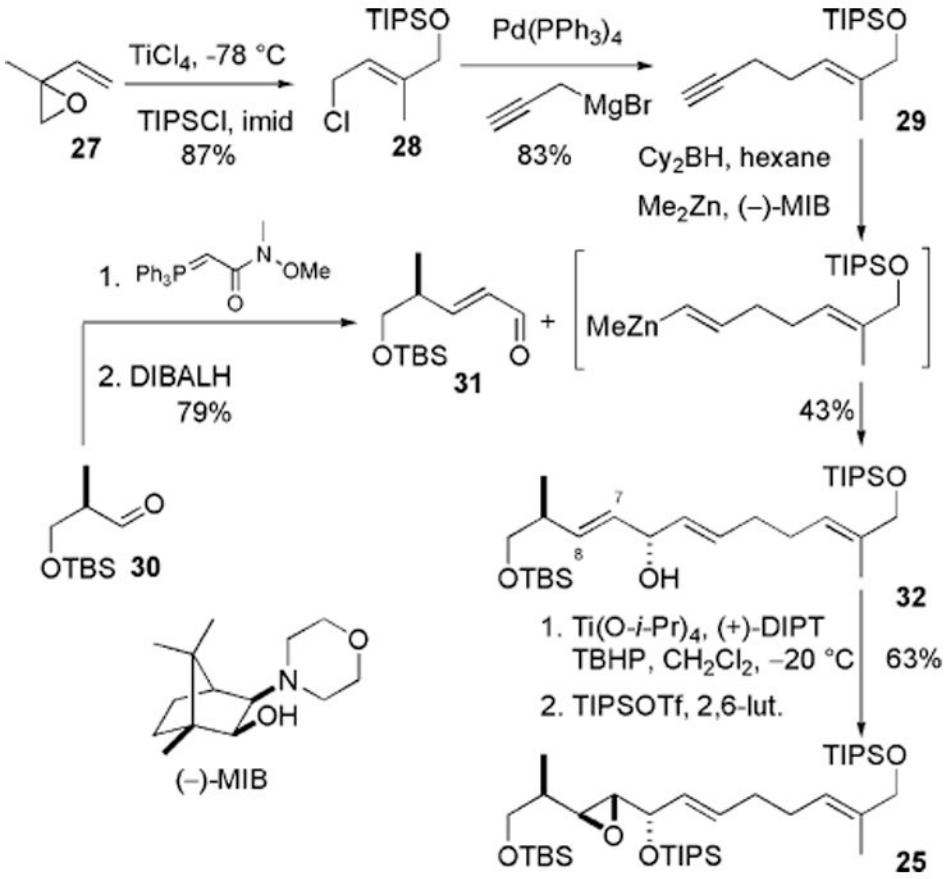


Scheme 5.



Scheme 6.