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Stereoselective Allylstannane Addition for a Convergent Synthesis of a Complex Molecule

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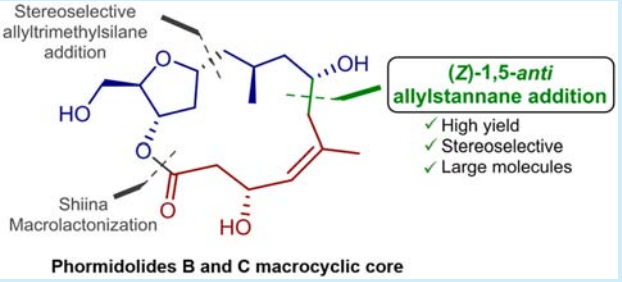
Supporting Information

ABSTRACT: A convergent methodology with 13 lineal steps for the synthesis of phormidolides B and C macrocyclic core is described. Stereoselective formation of the tetrahydrofuran (THF) core was achieved using a stereocontrolled allylation reaction. The key step of the synthesis is a (*Z*)-1,5-*anti* stereoselective allylstannane addition where a new stereocenter and a trisubstituted double bond are formed simultaneously. Finally, Shiina macrolactonization conditions improved the yield of the final cyclization.



Marine natural products have become an important source of drugs for the treatment of different illnesses.[1] Several natural products and their simplified analogs have been approved as drugs for the treatment of various diseases.[2] In particular, compounds with a macrolide motif in their structure are ideal drug candidates because of their interesting biological activities.[3] In this field, phormidolides B and C were isolated from *Petrosiidae* sponge in the coasts of Tanzania.[4] They are cytotoxic in three tumor cell lines in the micromolar range (HT-29, A-549, and MDA-MB-231) with an unknown mechanism of action.

Phormidolides are interesting synthetic targets because of their structural complexity (Figure 1). Their structure can be divided into three smaller fragments to confront their total synthesis: fatty acids, polyhydroxylated chain, and macrolide ring. A suitable strategy to synthesize these fragments separately is vital to complete their total synthesis and confirm all the stereochemical information. Herein, an improved synthetic approach to the synthesis of the macrocyclic core **1** is described.

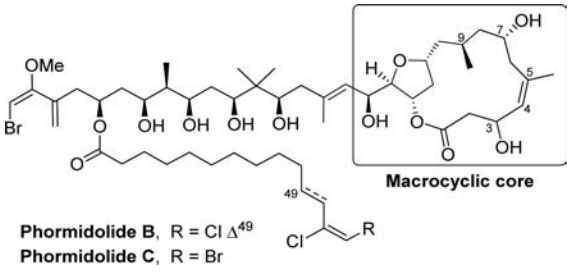
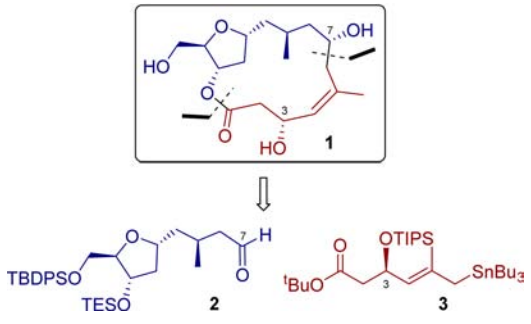


Figure 1. Structures of phormidolides B and C.

The retrosynthetical analysis of **1** is based on a more convergent approach than the previously described by our group.[4] After only two disconnections molecular fragments **2** and **3** were obtained which could be easily synthesized in a few synthetic steps. The formation of the C6−C7 bond was envisioned through a stereoselective allylstannane addition to the aldehyde **2**. The end game of the synthesis will be based on the macrolactonization under Shiina conditions and further removal of the protecting groups (Scheme 1).

The synthesis of aldehyde **2** (Scheme 2) starts with commercially available 2-D-deoxyribose. Oxidation at the anomeric position with bromine followed by chemoselective sequential protection afforded lactone **5**. Then lactone **5** was transformed into acetyl acetal **6** as a 6:4 mixture of epimers. The addition of allyltrimethylsilane promoted by $BF_3{\cdot}OEt_2$ to

Scheme 1. Retrosynthesis of Phormidolides Macrocyclic Core



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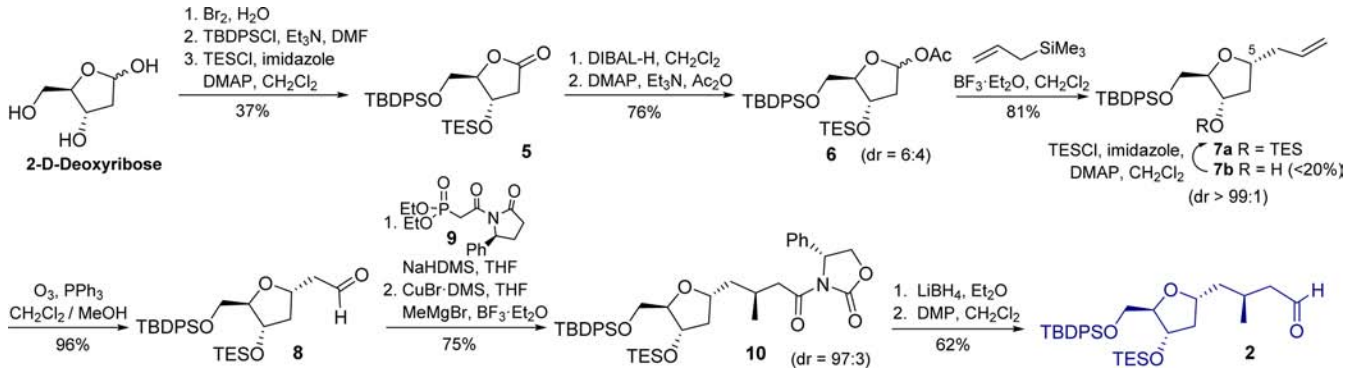
Scheme 2. Synthesis of Aldehyde 2



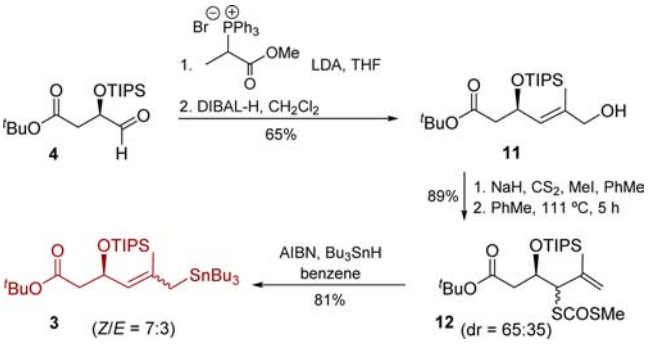
acetylated compound **6**, using the Tran et al. method,[5] gave only the desired 5*R* diastereomer **7a** and its deprotected version **7b**. Alcohol **7b** can be protected in the crude mixture and then purified to obtain **7a** with an 81% yield and excellent diastereoselectivity.[6] One of the advantages of this new synthesis is the diastereoselective formation of the C−C bond in position 5 to furnish the pure enantiomer **7**. This methodology addresses a significant weakness in the previous synthetic route: the unselective installation of the alkyl substituent onto the tetrahydrofuran portion of the core structure.[4]

In order to elongate the chain, allyl derivative **7a** was subjected to an ozonolysis to reach aldehyde **8**. Chiral phosphonate **9**[7,8] was needed at this point to introduce the methyl group by means of a diastereoselective 1,4 addition to afford compound **10** in good yield. Removal of the chiral auxiliary and oxidation with Dess-Martin periodinane (DMP)[9] gave aldehyde **2** in 10 steps with easily scalable procedures.

The synthesis of compound **3** started from previously reported aldehyde **4**.[4] Wittig olefination with (1-methoxy-carbonylethyl)triphenylphosphonium bromide[10] and further methyl ester reduction gave alcohol **11** in good yield. Formation of the corresponding xanthate and 3,3-sigmatropic thermal rearrangement furnished compound **12** as an epimeric mixture. Reaction with Bu_3SnH under free radical conditions produced allylstannane **3** as a *Z*/*E* mixture of isomers (7:3 ratio) (Scheme 3).[11] This isomeric mixture was used without separation in the synthetic step described below.

With fragments **2** and **3** in hand, the most important reaction in the synthesis was performed successfully following the procedure described by Thomas et al.[12] The allylstannane addition of **3** to aldehyde **2** resulted not only with a high yield but also with the desired stereoselectivity. In one reaction, a new stereocenter and a trisubstituted double bond were created with complete selectivity for the desired (*Z*)-1,5-*anti* product **13**.[13−15]

Scheme 3. Synthesis of Allylstannane 3



The explanation for this high stereoselectivity is consistent with the mechanism of the reaction depicted in Scheme 4. As reported previously,[11] the stereocenter present in **3** controls the facial selectivity of the transmetalation to give the allyltin trichloride **A** where the prop-1-en-2-yl and OTIPS groups were in a trans relationship on the six-membered oxastannic ring. It is worthy to mention that these kinds of six-membered oxastannic rings have been widely reported[11,16,17] using 6-hydroxystannanes and 6-alkoxystannanes but never using the oxygen of a more oxidated function such as an ester. When aldehyde **2** was added to the reacting mixture it approached this chelated structure to form a new chairlike six-membered transition structure **B** where the group next to tin adopts the preferred axial position to avoid steric hindrance with the apical chloride on the tin. This fact and the preference of the R group of the aldehyde to adopt the equatorial position explain the remote stereocontrol of this reaction to obtain the desired (3*R*,7*S*,*Z*) diastereomer **13**. To the best of our knowledge this has been the first (*Z*)-1,5-*anti* allylstannane stereoselective addition to create a methylated trisubstituted double bond. Furthermore, this addition with multifunctionalized big building blocks such as **2** and **3** shows the utility and robustness of this methodology for the synthesis of natural products.

In the final stage of the synthesis, compound **13** had to be converted to the corresponding seco-acid **14** to perform cyclization. Standard basic conditions were used to protect the homoallylic hydroxyl with TBS. After quantitative conversion, TMSOTf was added to deprotect the *tert*-butyl ester. Then, aqueous workup was necessary and the reaction crude was treated with pyridinium *p*-toluenesulfonate (PPTS) in MeOH obtaining hydroxy-acid **14** in 72% yield for this 2 stage-3 chemical transformation procedure with only one purification (Scheme 5). Following Shiina's methodology,[18] slow addition of **14** to a solution containing 2-methyl-6-nitrobenzoic anhydride (MNBA) and 4-dimethylaminopyridine (DMAP) cleanly afforded macrocycle **15** in 67% yield without formation of dimeric or trimeric species. In our previously described synthesis, Yamaguchi's lactonization conditions afforded the protected macrocycle in 39% yield due to the formation of polymeric species.[4]

Macrocycle **15** was transformed into aldehyde **16** by selective deprotection, followed by oxidation. This aldehyde is an essential fragment for the total synthesis of phormidolides B and C using previously studied methodology.[19] In addition,

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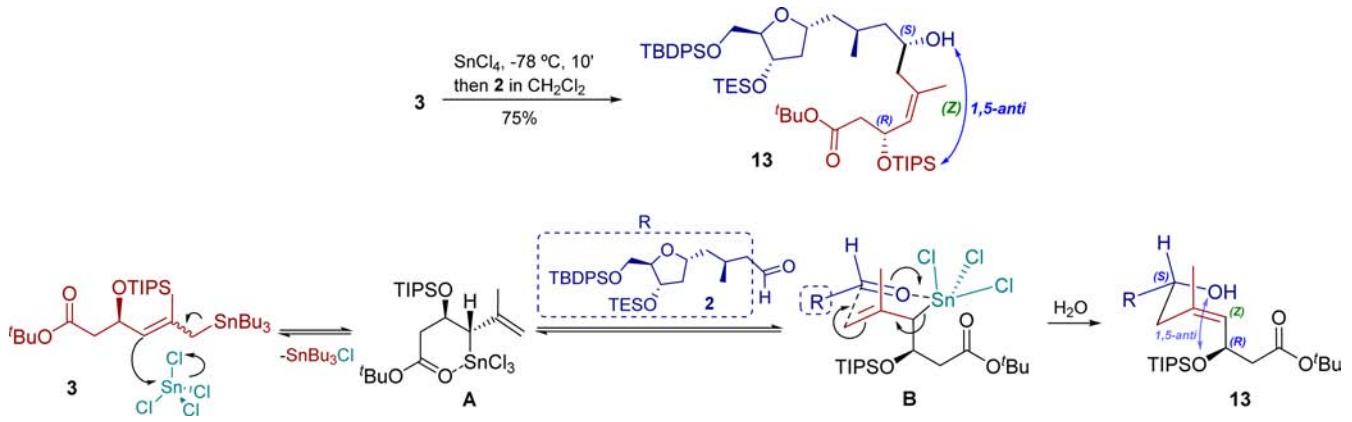
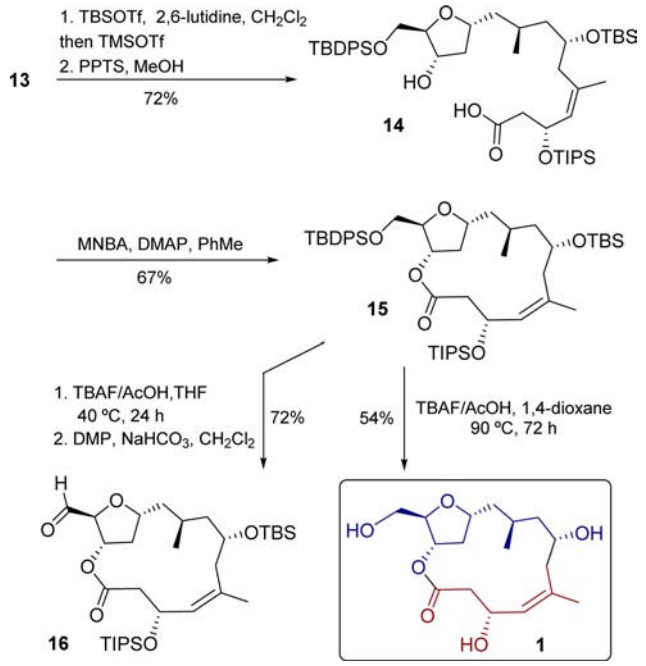
Scheme 4. (*Z*)-1,5-*anti* Allylstannane Addition: Mechanistic Explanation of Its Excellent Stereoselectivity



Scheme 5. Cyclization and Deprotecting Procedures To Obtain 16 or the Desired Macrolide 1



total deprotection gave macrocycle **1** to perform spectral characterization to compare with the natural product and biological tests (IC_{50} tests).[20] Key aspects to control the deprotection included solvent, temperature, and reaction time. An excess of a buffered solution of TBAF/AcOH in THF at 40 °C during 24 h produced selective monodeprotection of **15**. At this temperature di- and trideprotected species were not detected. The obtained alcohol was oxidized with DMP to give aldehyde **16** with high yield. On the other hand, **1** can be obtained by raising the temperature in 1,4-dioxane to 90 °C with a longer reaction time in moderate yield.

In summary, this paper describes a convergent methodology to synthesize **15**, the protected macrocyclic core of phormidolides B and C, with an important improvement in the total yield relative to our previous methodology. The number of linear steps has been reduced from 17 to 13, and the overall yield has been increased 10 times. Three factors contributed to this increase in the overall yield. First, the diastereoselective formation of **7a** by addition of allyltrimethylsilane to the THF core avoided diastereomer separation at the beginning of the synthesis at a multigram scale. Furthermore, this procedure does not produce the nondesired diastereomer that has to be eliminated. Second, the stereoselective link of the two big molecular fragments by the Thomas et al. methodology[12] gave excellent synthetic results in terms of yield and desired stereoselectivity. (*Z*)-1,5-*anti* remote stereocontrol has been achieved through a six-membered oxastannic ring where the coordinating oxygen atom belongs to an ester functionality. This fact broadens the scope for this type of remote stereocontrolled addition with 6-alkyloxycarbonylstannanes. The mild conditions used to perform this reaction and the synthesis of a complex allylstannane opens the possibility to use this methodology in the late stages of a synthesis to link large polyfunctionalized molecular entities with complete stereocontrol.

Finally, the Shiina methodology for macrolactonization instead of Yamaguchi's conditions led to an increase of the yield from 39% to 67% for this important transformation. All of these changes have allowed us to isolate and characterize aldehyde **16** and triol **1**. NMR chemical shifts of macrocycle **1** are in accordance with the described phormidolides B and C. The small differences in chemical shift are caused by the presence of the polyhydroxylated chain in the natural products. Moreover, the lack of this chain would explain the inactivity of macrolide **1**. Further studies to link the polyhydroxylated chain to the macrolactone are under development.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03252.

Experimental procedures and characterization of the described compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Blunt, J. W.; Copp, B. R.; Keyzers, R. A.; Munro, M. H. G.; Prinsep, M. R. *Nat. Prod. Rep.* **2015**, *32*, 116−211.
(2) Molinski, T. F.; Dalisay, D. S.; Lievens, S. L.; Saludes, J. P. *Nat. Rev. Drug Discovery* **2009**, *8*, 69−85.
(3) Lorente, A.; Makowski, K.; Albericio, F. *Ann. Mar. Biol. Res.* **2014**, *1*, 1003−1013.
(4) Lorente, A.; Gil, A.; Fernández, R.; Cuevas, C.; Albericio, F.; Álvarez, M. *Chem. - Eur. J.* **2015**, *21*, 150−156.
(5) Tran, V. T.; Woerpel, K. A. *J. Org. Chem.* **2013**, *78*, 6609−6621.
(6) The stereochemistry of the new stereocenter in C5 was confirmed by NOE 1D experiments (see Supporting Information).
(7) Yokokawa, F.; Asano, T. *Tetrahedron* **2004**, *60*, 6859−6880.
(8) Ishizaki, M.; Hara, Y.; Kojima, S.; Hoshino, O.; Funagawara-machi, I. *Heterocycles* **1999**, *50*, 779−790.
(9) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.
(10) Boisse, T.; Rigo, B.; Millet, R.; Hénichart, J.-P. *Tetrahedron* **2007**, *63*, 10511−10520.
(11) Carey, J. S.; MacCormick, S.; Stanway, S. J.; Teerawutgulrag, A.; Thomas, E. J. *Org. Biomol. Chem.* **2011**, *9*, 3896−3919.
(12) McNeill, A. H.; Thomas, E. J. *Synthesis* **1994**, *1994*, 322.
(13) The stereochemistry of the new stereocenter was determined using Mosher's derivatization (see Supporting Information).
(14) The configuration of the double bond was confirmed based on the ^{13}C chemical shift of the olefinic methyl group. Previous published work confirms that if this chemical shift is above 20 ppm the configuration is Z (see ref 15).
(15) Lorente, A.; Albericio, F.; Álvarez, M. *J. Org. Chem.* **2014**, *79*, 10648−10654.
(16) MacCormick, S.; Thomas, E. J. *J. Organomet. Chem.* **2006**, *691*, 1437−1440.
(17) Carey, J. S.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1994**, 283−284.
(18) Shiina, I.; Fukui, H.; Sasaki, A. *Nat. Protoc.* **2007**, *2*, 2312−2317.
(19) Lamariano-Merketegi, J.; Lorente, A.; Gil, A.; Albericio, F.; Álvarez, M. *Eur. J. Org. Chem.* **2015**, *2015*, 235−241.
(20) Compound **1** was inactive. It was tested in HT-29, A-549, and MDA-MB-231 cell lines under the same conditions as natural compounds (see ref 4).

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