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Studies directed toward the syntheses of amphidinolides: formal total synthesis of (−)-amphidinolide P

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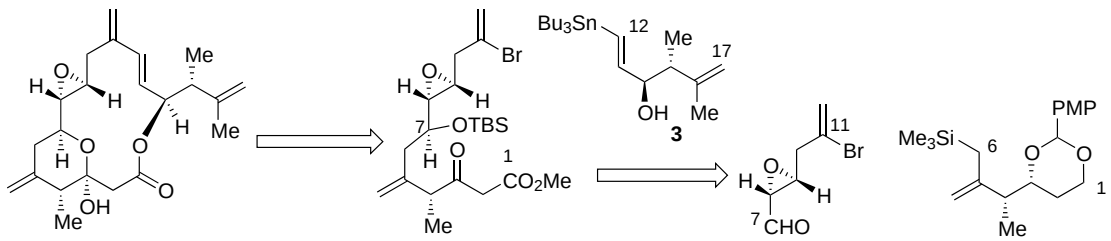
Abstract—A formal total synthesis of (−)-amphidinolide P (**1**) has been achieved via an efficient convergent strategy for the stereoselective construction of the two advanced intermediates **2** and **3**, used recently by Williams et al. in their synthesis of the same molecule.

Amphidinolides represent a family of cytotoxic marine natural products with diverse structural features and pronounced biological activities that include very potent anticancer activities displayed by many of these molecules against various tumour cell lines and an increase in rabbit skeletal muscle actomyosin ATPase activity by one of them.[1–3] Recently, Williams et al. have achieved the total synthesis of (−)-amphidinolide P (**1**),[4] which turned out to be the enantiomer of the natural product isolated by Kobayashi.[5] In continuation of our work on the synthesis of amphidinolides O and P,[6] we now report a formal total synthesis of (−)-amphidinolide P (**1**) via the stereoselective construction of the two advanced intermediates **2** and **3** following a concise strategy. A Stille coupling of **2** and **3** and the conversion of the resulting acyclic precursor to the final macrolide **1** in two steps have already been reported.[4]

We planned the construction of the vinyl bromide **2** from two subunits, the C_7–C_{11} aldehyde **4** and the C_1–C_6 allylsilane component **5**. The actual synthesis of **2** is outlined in Scheme 1. The THP-protected propargyl alcohol **6** was alkylated with 2,3-dibromopropene using ethylmagnesium bromide and a catalytic amount of cuprous bromide,[7] which was followed by acid-catalyzed THP-deprotection to give the enyne **7** in 75% yield. Hydride reduction of the acetylenic moiety of **7** using Red-Al gave a '1,4-diene' intermediate with an allylic alcohol moiety that was subjected to a Sharpless asymmetric epoxidation reaction using natural diisopropyl L-(+)-tartrate to furnish the chiral epoxy alcohol **8** (>98% ee)[8] in 60% yield from **7**.

Oxidation of **8** using SO_3–py complex gave the C_7–C_{11} aldehyde **4** in 70% yield. The two chiral centres in the other component **5** were generated by an Evans aldol reaction between the chiral oxazolidinone **9** and the aldehyde **10**,[9] prepared from monoPMB-protected propane-1,3-diol by oxidation. The *syn* aldol adduct **11** was transformed into the methyl ester intermediate **12** in three steps in 70% overall yield: treatment with DDQ under anhydrous conditions to convert the PMB-ether to the PMP-acetal, oxidative removal of the chiral auxiliary and conversion of the acid to an ester using CH_2N_2. Next, the ester **12** was reacted with trimethylsi-



1: (-)-amphidinolide P **2** **4** **5**

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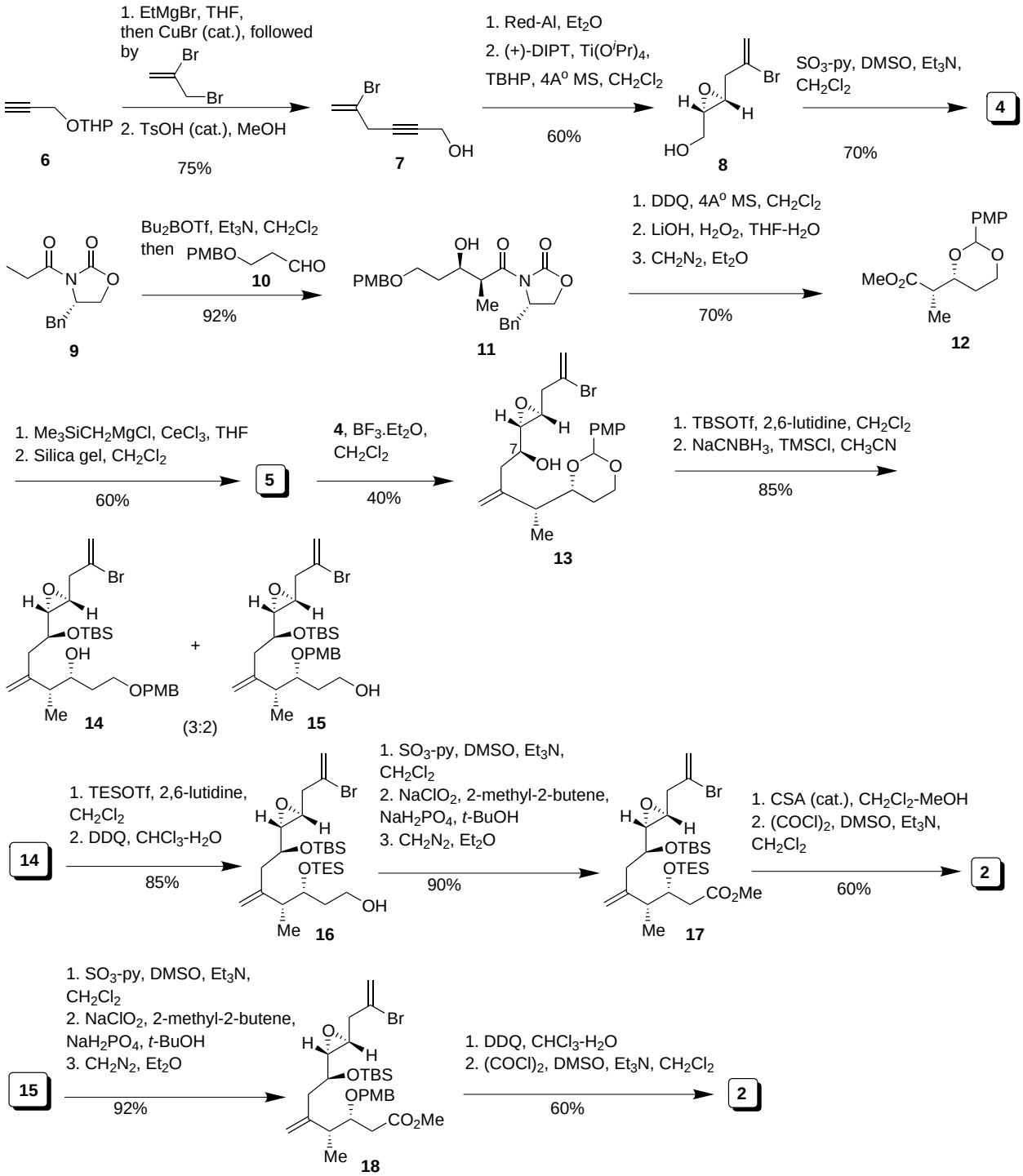
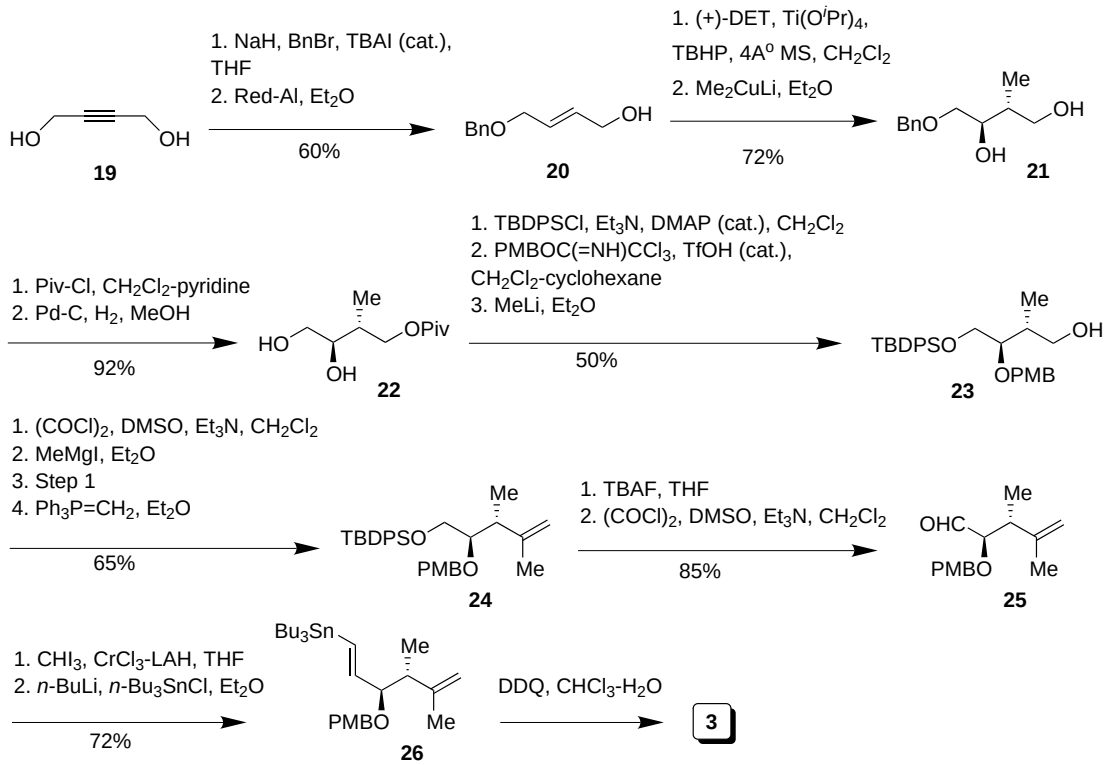


Scheme 1. Stereoselective synthesis of **2**.

lylmethylmagnesium chloride in the presence of anhydrous cerium(III) chloride.[10,11] The resulting β-hydroxysilane underwent Peterson-type elimination in the presence of silica gel to furnish the allylsilane **5** in 60% yield.

The Sakurai reaction[12,13] between **4** and **5** provided the required adduct **13** in 40% yield, the major product being an acid-catalyzed rearranged product from **5**. The only isomer that could be detected was the expected product **13**. The stereochemistry of the newly generated C_7 centre was assigned based on the known diastereofacial selectivity found in the nucleophilic additions to chiral epoxy aldehydes.[14] Silylation of **13** was followed by acetal deprotection. Most of the acid-catalyzed deprotection procedures resulted in the decomposition of the starting material. Finally, a silyl-promoted acetal ring opening was successfully carried out using sodium cyanoborohydride in the presence of TMSCl.[15] Two PMB-ethers **14** and **15** were formed in ~3:2 ratio in 85% total yield. Although the acetal opening failed to give any selectivity, both **14** and **15** were useful and



Scheme 2. Stereoselective synthesis of **3**.

could be converted easily to the desired β-ketoester **2** by routine functional group manipulations. In the case of **14**, TES-protection of the secondary hydroxyl group was followed by deprotection of the C_1-hydroxyl group. A two-step oxidation protocol was followed to oxidize the primary hydroxyl group of **16** to a carboxylic acid that was esterified with CH_2N_2 to give **17**. Selective removal of the TES-group was followed by Swern oxidation of the resulting C_3-hydroxyl group to furnish **2**. On the other hand, the primary hydroxyl group of **15** was first transformed into the ester **18** and was subsequently subjected to PMB-deprotection and Swern oxidation to reach the target **2**.

The starting material for the synthesis of **3** was 2-butyne-1,4-diol (**19**, Scheme 2). A slight modification of a reported procedure[16] was followed to prepare the allylic alcohol **20** from **19**, in 60% yield, by monobenzylation and Red-Al reduction. Sharpless asymmetric epoxidation of **20** using natural diethyl L-(+)-tartrate and $Ti(O^iPr)_4$ in stoichiometric amounts (>98% ee)[17] was followed by epoxide ring opening using dimethylcopper lithium to give the 1,3-diol **21** in 72% overall yield in two steps. The minor 1,2-diol was removed from the crude product by oxidative cleavage using $NaIO_4$. Selective protection of the primary hydroxyl group of **21** as a pivalate was followed by the Bn-deprotection to give the 1,2-diol **22** in 92% yield. Routine functional group manipulations transformed **22** into **23** (50% yield in three steps), which was subsequently converted to the olefin **24** in four steps of which the first three were to prepare a methylketo intermediate that was subjected to a Wittig olefination reaction in the fourth step giving an overall yield of 65% from **23**. Desilylation of **24** was followed by Swern oxidation to furnish the aldehyde **25** in 85% yield. The aldehyde **25** was reacted with CHI_3 in the presence of anhydrous $CrCl_2$, generated in situ from $CrCl_3$ and LAH, following the Takai protocol[18] to introduce an *E*-vinyl iodide moiety that was next subjected to an iodine–tin exchange to give the *E*-vinyl stannane **26** in 72% yield. Finally, deprotection of the PMB-ether furnished the desired intermediate **3**. The spectroscopic data and specific rotations of **2** and **3** prepared by us were identical with the reported values.[4]

In conclusion, the convergent synthetic protocol reported herein for the stereoselective construction of the two advanced intermediates **2** and **3** that were used by Williams et al. in their synthesis of (–)-amphidinolide P (**1**) demonstrates a formal total synthesis of the molecule.

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