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# Stereoselective Synthesis of Amphidinolide T1

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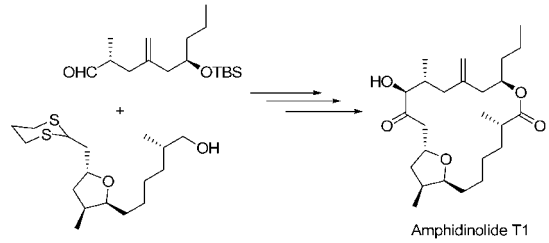
## ABSTRACT




**A highly stereoselective total synthesis of amphidinolide T1 is achieved using Sharpless asymmetric epoxidation, base-induced epoxide opening, radical cyclization, diastereoselective reduction followed by allylation, Evans methylation, base-induced reductive elimination, umpolung reaction, chemoselective oxidation, and regioselective macrolactonization.**

Marine dinoflagellates of the genus *Amphidinium* have been recognized as a source of novel secondary metabolites called amphidinolides, a growing family of macrolides with unique structure and interesting biological activity.[1] Despite their common origin and uniformly high toxicity against various cancer cell lines, the amphidinolides possess a high degree of structural diversity incorporating many variegated molecular scaffolds. Amphidinolide T1 (**1**) isolated from extracts of the strain Y-56 of the dinoflagellate *Amphidinium* sp. is a 19-membered macrolide possessing a trisubstituted tetrahydrofuran moiety, one exomethylene, three branched methyls, one ketone, and one hydroxyl group. It showed potent activity against murine lymphoma L1210 and human epidermoid carcinoma KB cell lines.[2] The structure of **1** was established by detailed NMR studies, and the absolute stereochemistry was established by modified Mosher's method followed by a single crystal X-ray analysis.[3] Because of its potent biological activity, low abundance, and unique molecular architecture, amphidinolide T1 has attracted significant attention from the synthetic community, and as the result three total syntheses have been appeared in the literature. The first total synthesis of amphidinolide T1 was reported by Ghosh and co-workers in 2002,[4] and later Fürstner[5] and Jamison[6] also reported the synthesis of this molecule using very different strategies to effect macrocycle formation. Additionally, Zhao et al.[7] reported the synthesis of amphidinolide T3 (**1a**) (Figure 1) that is structurally related to amphidinolide T1. In continuation of our synthesis of complex natural products, we report herein a new convergent and stereoselective total synthesis of amphidinolide T1.

Our retrosynthetic analysis of amphidinolide T1 is shown in Figure 1. The formation of the macrolactone was envisaged from a seco acid **2**, which was disconnected at the C12−C13 bond into trisubstituted tetrahydrofuran fragment **3** and homoallyl ether fragment **4**. In the forward direction

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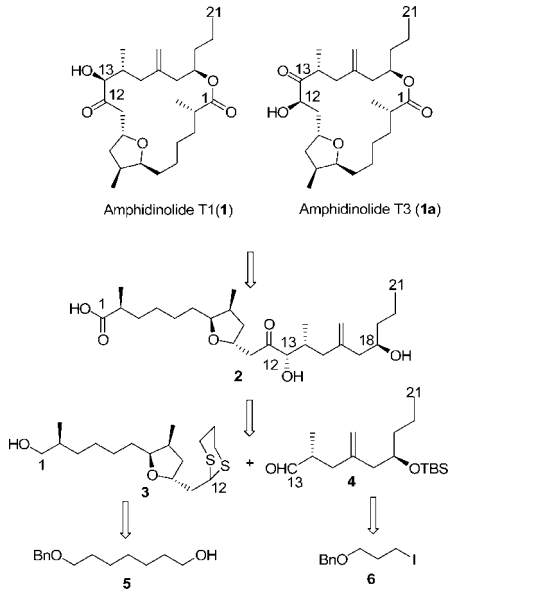


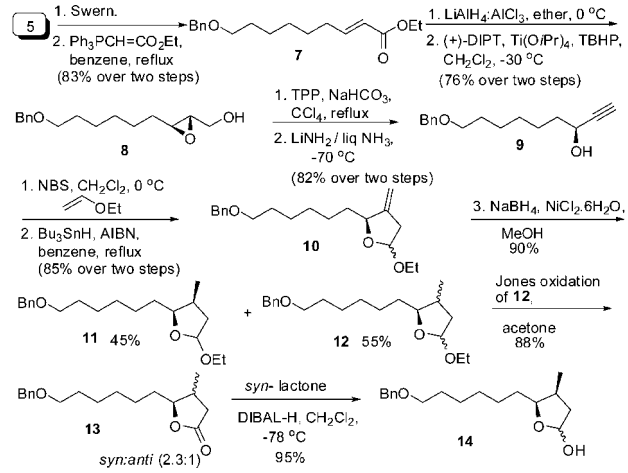

**Figure 1.** Retrosynthetic analysis of amphidinolide T1.

fragment **2** was envisaged to be obtained by an umpolung reaction between **3** and **4**;[8] retrons **3** and **4** can be obtained from **5** and **6**, respectively.

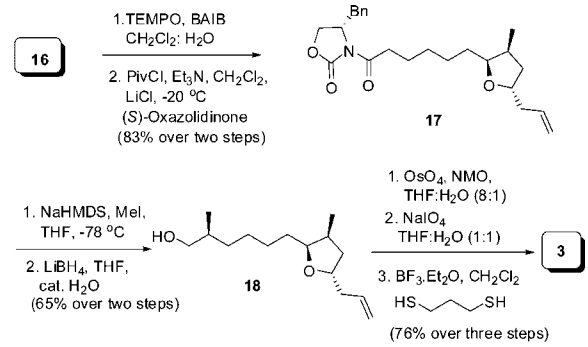
The synthesis of compound **3** started from the known mono benzylether **5**, which was oxidized to the corresponding aldehyde and further homologated by a two-carbon Wittig olefination to afford α,β-unsaturated ester **7** (*E*-isomer) as the sole product (83% over two steps). Compound **7** on reduction with $LiAlH_4/AlCl_3$ afforded an allylic alcohol in 80% yield. Sharpless asymmetric epoxidation[9] of the allyl alcohol using (+)-DIPT, $Ti(^iPrO)_4$ and TBHP at −20 °C furnished epoxy alcohol **8** in 91% yield and in 94% ee. Subsequent reaction of **8** with $PPh_3$ in $CCl_4$ in the presence of $NaHCO_3$ (cat.) at reflux, followed by base-induced dehydrohalogenation using the methodology developed by us,[10] gave alkynol **9** in 82% overall yield.

The alkynol **9** was reacted with ethyl vinyl ether and NBS to afford bromo acetal, which on being subjected to radical cyclization[11] by treatment with *n*-$Bu_3SnH$ and AIBN in refluxing benzene afforded lactolether **10** in 85% overall yield for two steps. The lactolether **10** underwent diastereoselective reduction using $NaBH_4$ and $NiCl_2{\cdot}6H_2O$[12] in methanol to provide four diastereomers, which were separated by column chromatography to afford the required

**Scheme 1.** Synthesis of Segment **3**




**Scheme 2.** Synthesis of Compound **3**




ethoxy tetrahydrofuran **11** and a stereoisomeric mixture of ethoxy tetrahydrofuran **12** in a 1:1.1 ratio in 88% yield.

The mixture of isomers **12** were subjected to Jones oxidation[13] to furnish the *syn*- and *anti*-lactones **13** (2.3:1, 88% yield), which were separated readily by silica gel column chromatography. The *syn*-lactone was reduced with DIBAL-H to give lactol **14** (95% yield), which was subsequently treated with allyltrimethylsilane using a known procedure[14] to furnish allylated product **15.** Although the yields were encouraging with lactol **14** as well as lactol ether **11**, the *anti*:*syn* ration was not attractive. This prompted us to explore a strategy recently developed by us[15] to allylate allyl/benzyl alcohols using allyl trimethyl silane in the presence of a catalytic amount of iodine. Surprisingly,

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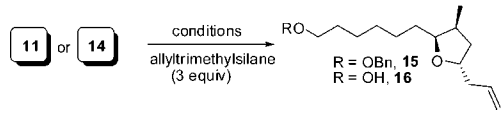
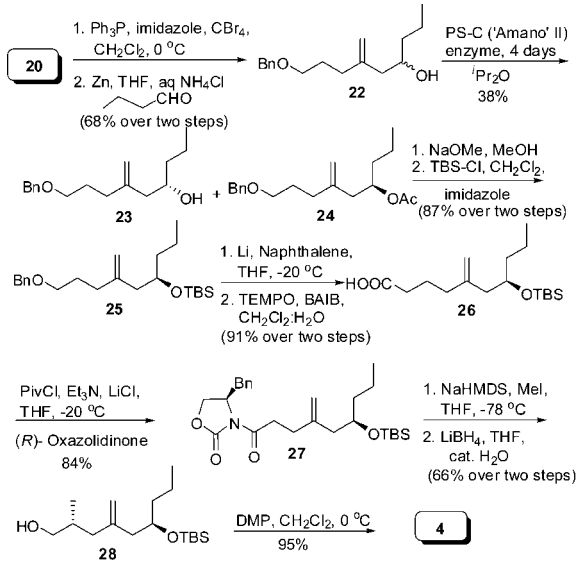
**Table 1.** Improvement of Diastereoselectivity

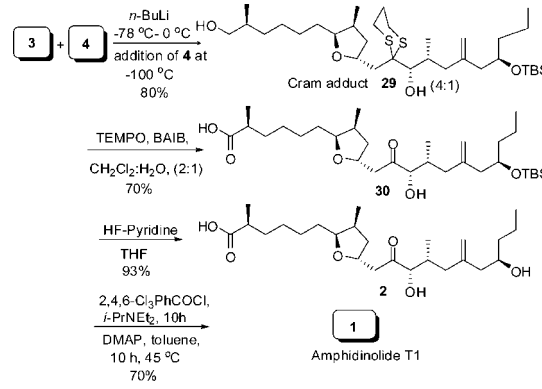



| conditions | substrate | time | yield % | *anti*:*syn* | product |
|---|---|---|---|---|---|
| (1) $BF_3Et_2O$ (3 equiv), $CH_2Cl_2$, −78 °C | **11** | 5 min | 95 | 93:7 | **15** |
| (2) $BF_3Et_2O$ (3 equiv), $CH_2Cl_2$, −78 °C | **14** | 30 min | 92 | 95:5 | **15** |
| (3) $SnBr_4$ (2 equiv), $CH_2Cl_2$, rt | **11** | 1 h | 93 | 94:6 | **15** |
| (4) $I_2$ (1 mol %), $CH_2Cl_2$, rt | **11** | 24 h | 97 | 96:4 | **15** |
| (5) $I_2$ (5 mol %), $CH_2Cl_2$, −78 to 0 °C | **11** | 2 h | 94 | >99:1 | **15** |
| (6) $I_2$ (1.2 equiv), $CH_2Cl_2$, −78 to 0 °C | **11** | 4 h | 90 | >99:1 | **16** |
| (7) $I_2$ (1.2 equiv), $CH_2Cl_2$, −78 to 0°C | **14** | 6 h | 87 | 96:4 | **16** |
| (8) $l_2$ (5 mol %), $CH_2Cl_2$, −78 to 0 °C | **14** | 3 h | 92 | 96:4 | **15** |

**Scheme 3.** Synthesis of Segment **4**




**Scheme 4.** Synthesis of Amphidinolide T1 (**1**)




treatment of lactol ether **11** with allyltrimethyl silane in the presence of iodine (5 mol%) gave the desired product **15** in 94% yield with complete antiselectivity. It is noteworthy to mention here that the presence of 1.2 equiv of iodine led to allylation with concommitant debenzylation to afford **16** in 90% yield. Similarly, allylation of lactol **14** afforded the required product **16** in a ratio of 96:4. Optimized condtions of allylation and/or debenzylation are presented in Table 1.

The primary hydroxyl group in **16** was converted to the carboxy group by oxidation with TEMPO and BAIB in $CH_3CN$ and $H_2O$.[16] N-Acylation of the chiral (*S*)-oxazolidin-2-one using the mixed anhydride conditions furnished **17** in 85% yield over two steps.[17]Diastereoselective alkylation of the Na-enolate of **17** with MeI followed by reductive cleavage of the chiral auxiliary afforded alcohol **18** as the only isomer in 65% overall yield (Scheme 2). The resulting alcohol was treated with catalytic $OsO_4$ and stoichiometric 4-methylmorpholine N-oxide (NMO) to afford the diol which on oxidative cleavage using $NaIO_4$ gave aldehyde.[18] Protection with 1,3-propanedithiol in presence of $BF_3{\cdot}Et_2O$ furnished the dithiane **3** in 76% overall yield.

The journey for the synthesis of segment **4** began with alkylation of diethylmalonate **19** with the known iodo compound **6**[19] followed by base-induced reductive elimination. Three different conditions were examined: (i) NaH as base and LAH as reducing agent to afford a mixture of **20** and **21** in 4:1 ratio in 55% yield;[20] (ii) *n*-BuLi as base and DIBAL-H as reducing agent, which did not give the desired product; and (iii) *n*-BuLi as base and $AlH_3$ (alane) as reducing agent to afford **20** exclusively in 60% yield (Table 2). After obtaining compound **20** as a single product, conversion of the hydroxyl group to the corresponding bromo functionality using TPP/$CBr_4$ followed by allylation under Barbier conditions[21] gave a racemic homoallyl alcohol **22**

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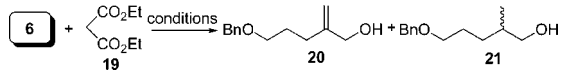
**Table 2.** Optimization of Reductive Elimination




| conditions | product ratio **20**:**21** | yield % |
|---|---|---|
| (1) NaH, **19**, 5 h, NaH, 6 h, $LiAlH_4$, THF, reflux, 6 h | 80:20 | 55 |
| (2) *n*-BuLi, **19**, 2 h, *n*-BuLi, 15 min, DIBAL-H, THF, 0 °C to rt, 5 h | no desired product | |
| (3) *n*-BuLi, **19**, 2 h, *n*-BuLi, 15 min, $LiAlH_4/AlCl_3$, THF, reflux, 5 h | >98 | 60 |

in 68% yield over two steps. Enzymatic kinetic resolution of **22** using lipase PS-C 'Amano' II afforded (*R*)-homoallylic acetate **24** (35% with 98% ee).[22] The unrequired isomer **23** was converted to the required isomer following an oxidation, reduction, and enzymatic resolution sequence. Deacetylation of **24** was achieved by treatment with NaOMe, and protection of the resulting hydroxyl group as its TBS ether gave **25** in 87% yield over two steps.

Treatment of compound **25** with Li/naphthalene[23] afforded the primary hydroxyl compound, which on subsequent oxidation with TEMPO/BAIB gave **26** in 91% yield (two steps). Similar to compound **16a**, compound **26** was converted to alcohol **28** in three steps.[17] Oxidation of **28** with Dess−Martin periodinane in $CH_2Cl_2$ afforded aldehyde **4** in 95% yield.

With the successful synthesis of the two fragments **3** and **4**, we proceeded to assemble both the segments. Dithiane **3** was treated with *n*-BuLi in THF (under Sih's conditions)[8] at −100 °C, and to it was added dropwise the precooled solution of aldehyde (− 100 °C) **4** to afford a stereoisomeric mixture (4:1) mainly consisting of Cram adduct (*syn*) **29** in 80% yield.[8] The required major *syn* isomer was separated easily by silica gel column chromatography. Selective oxidation of the primary hydroxy group in **29** in presence of a secondary hydroxyl with TEMPO/BAIB afforded keto acid **30** in 70% yield by in situ deprotection of thio ketal.[24]

The exposure of the resulting acid **30** to HF•Py complex gave the seco acid **2** in 93% yield. Now, the stage was set to carry out the most crucial macrocyclization reaction under modified Yamaguchi conditions.[25,7] As expected, the seco acid **2** following modified Yamaguchi conditions afforded amphidinolide T1 (**1**) in 70% yield. The spectral ($^1H$ and $^{13}C$ NMR) and analytical data were in good agreement with the data reported for natural product.[3a]

In summary, we have accomplished a highly convergent and stereoselective synthesis of amphidinolide T1. The stereocenters of substituted tetrahydrofuran moiety were obtained by Sharpless asymmetric epoxidation, diastereoselective reduction of the exocyclic double bond, and allylation on the five-membered ring oxa-carbenium ion using our own developed methodology. The C13 and C18 stereocenters were obtained by enzymatic kinetic resolution and umpolung reaction.

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**Supporting Information Available:** Spectroscopic and analytical data and expeimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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