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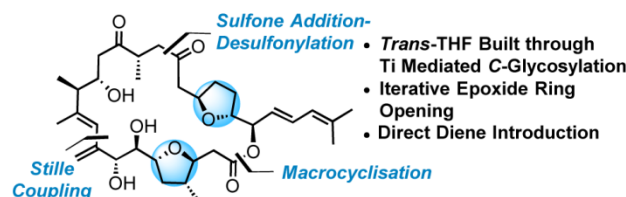


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Total Synthesis of the Marine Macrolide Amphidinolide F.

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ABSTRACT: A new and efficient convergent approach toward the synthesis of amphidinolide F is described through the assembly of three fragments. The two *trans*-tetrahydrofurans were built by a diastereoselective *C*-glycosylation with titanium enolate of bulky *N*-acetyl oxazolidinethiones. The side-chain was inserted by a Liebeskind-Srogl cross coupling reaction. A sulfone condensation/ desulfonylation sequence, a Stille cross-coupling, and a macrolactonisation were applied to connect the fragments.

Amphidinolides are part of a large family of macrolides containing more than 30 members, all being isolated from different strains or species of the dinoflagellate *amphidinium*.¹ Amphidinolides F (**1**),² C (**2**),³ C2 (**3**),⁴ and C3 (**4**) particularly drawn our attention due to the presence of two *trans*-tetrahydrofurans, 11 to 12 stereogenic centers, and two diene-frameworks at C9-C11 and at C25-C28, which make these molecules unique in their family. These marine natural products are very similar in terms of structure, exhibiting the same macrolactone. In consequence, the stereochemical assignment of amphidinolide F (**1**) was originally deduced from its analogy with amphidinolide C (**2**). The differences rely only on the side chain, amphidinolide F (**1**) being six carbons shorter. On the other hand amphidinolide C (**2**) contains one more stereogenic center at C29, and natural derivatives C2 (**3**) and C3 (**4**) show differences only at this position, the hydroxyl group being acylated for **3** while oxidized for **4** (Figure 1).

These amphidinolides show significant cytotoxic activities against some cancer cell lines. Amphidinolide C (**2**) is particularly active on murine lymphoma L1210 and human epidermoid carcinoma KB cells lines (IC₅₀ of 5.8 and 4.6 ng/mL respectively),³ while a reduced cytotoxicity is observed for **1** (1.5 and 3.2 µg/mL),² **3** (0.8 and 3.0 µg/mL),⁴ **4** (7.6 and 10.0 µg/mL).⁵ Amphidinolides F (**1**) and C (**2**) have received a great interest from organic chemists, producing numerous synthetic approaches⁶ to these macrolides and finally culminating to two total syntheses of both amphidinolide F (**1**) and C (**2**).^{7,8} We describe herein our achievement of the total synthesis of amphidinolide F (**1**).

From a retrosynthetic point of view, we initially planned to construct the THF ring using a *C*-glycosylation to form the C19-C20 bond.^{6i,6r} Unfortunately, we found from model experiments that the diene framework was not compatible with the generated oxonium intermediate during this reaction.

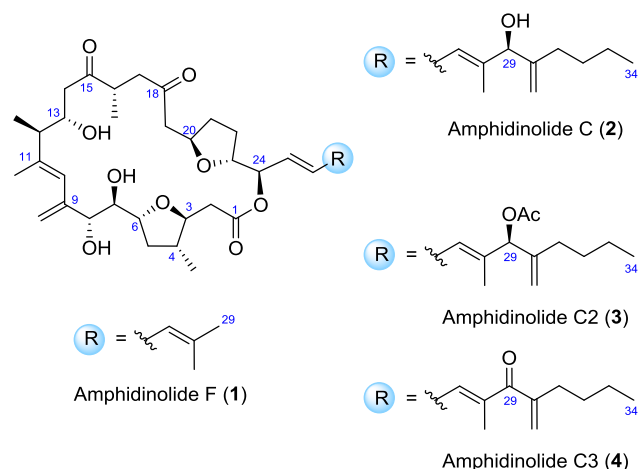
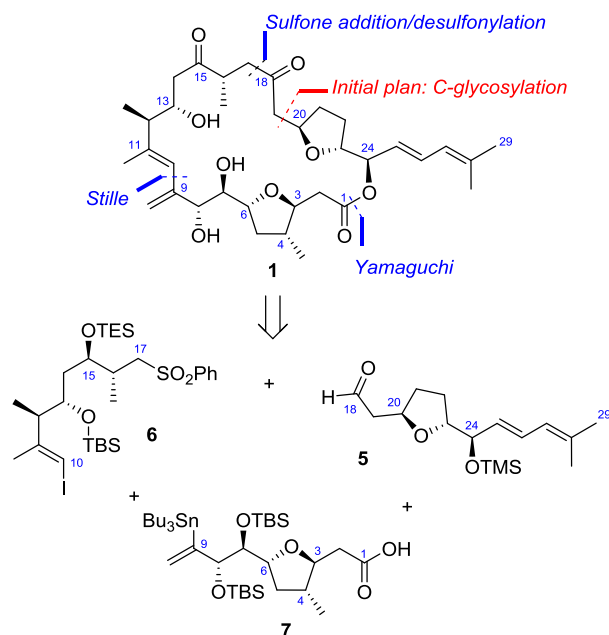


Figure 1. Structures of amphidinolide F, C, C2 and C3

Therefore, we changed this disconnection in order to perform the *C*-glycosylation reaction prior to the diene installation. Following this idea, we envisioned forging the macrolactone core with a sulfone condensation/desulfonylation sequence to connect **5** (C18-C29) to **6** (C10-C17), and a Stille cross coupling to attach the sub-unit **7** (C1-C9), followed by a macrolactonisation (Scheme 1). Fragments **5**, **6** and **7** could be synthesized through high diastereoselective reactions from chiral synthons easily accessible from the chiral pool or from well-known asymmetric reactions (e.g. Sharpless asymmetric epoxidation of allylic alcohol).

The synthesis of C18-C29 sub-unit **5** started from chiral lactone **8**,⁹ which was protected as a TBDPS (*tert*-butyldiphenylsilyl) ether and compound **9** was then subjected

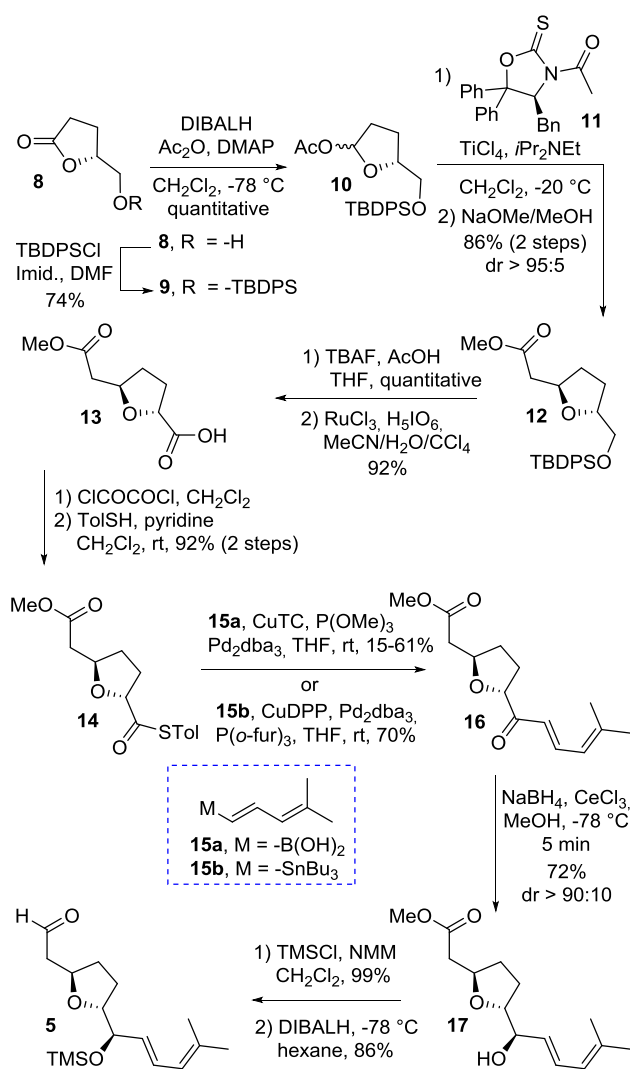
Scheme 1. Retrosynthetic analysis of amphidinolide F (1)



to DIBALH reduction/acetylation to lead to activated ketal **10**.¹⁰ α -glycosylation of ketals derived from 5-substituted THF is known to usually be a low selective process due to a competition between the lowest energy oxonium conformer, leading to the *cis*-THF and the most reactive oxonium conformer, leading to the *trans*-THF.¹¹ Nevertheless, the use of the titanium enolate of oxazolidinethione **11** showed a good *trans* selectivity because of steric bulk,¹² favoring the reaction on the most reactive oxonium conformer. Thus, when ketal **10** reacted with titanium enolate of oxazolidinethione **11**, *trans*-THF **12** was isolated after methanolysis of the auxiliary, as almost the sole diastereomer (86%, dr \geq 95:5). As we envisioned introducing directly the corresponding dienic side chain using a chemo-selective Liebeskind-Srogl cross coupling,¹³ construction of a thioester moiety was required. Therefore the hydroxyl group was deprotected and oxidized into carboxylic acid **13** with *in situ* generation of ruthenium tetroxide.¹⁴ Carboxylic acid **13** was then transformed into thioester **14**, through activation into an acyl chloride followed by reaction with thiocresol. As we initially carried out the cross coupling with the corresponding boronic acid derivative **15a**^{6r} in presence of CuTC (copper thiophene carboxylate) and Pd₂dba₃/P(OMe)₃, we observed non-reproducible results (15-61%) in the formation of dienone **16**, due to the instability of boronic acid **15a**. However ketone **16** was obtained in a 70% yield when more stable stannane **15b** was used for the cross-coupling in conjunction with the use of CuDPP (copper diphenylphosphinate) and Pd₂dba₃/P(o-fur)₃.¹⁵ Moreover, we also experienced that the synthesis of **15b** is shorter and more practical than that of **15a** (3 steps vs 6). Reduction of dienone **16** using Luche conditions¹⁶ at -78 °C gave us the *syn* product **17** in a polar Felkin-Anh fashion selectivity (dr \geq 90:10).⁶ⁿ Finally, the hydroxyl group was etherified with a fragile TMS protecting group, and the ester was converted into aldehyde **5** by using a selective reduction with DIBALH (Scheme 2).

In parallel, the synthesis of sub-unit C10-C17 (**6**) was conducted. The inherent symmetry of the C12-C16 segment could

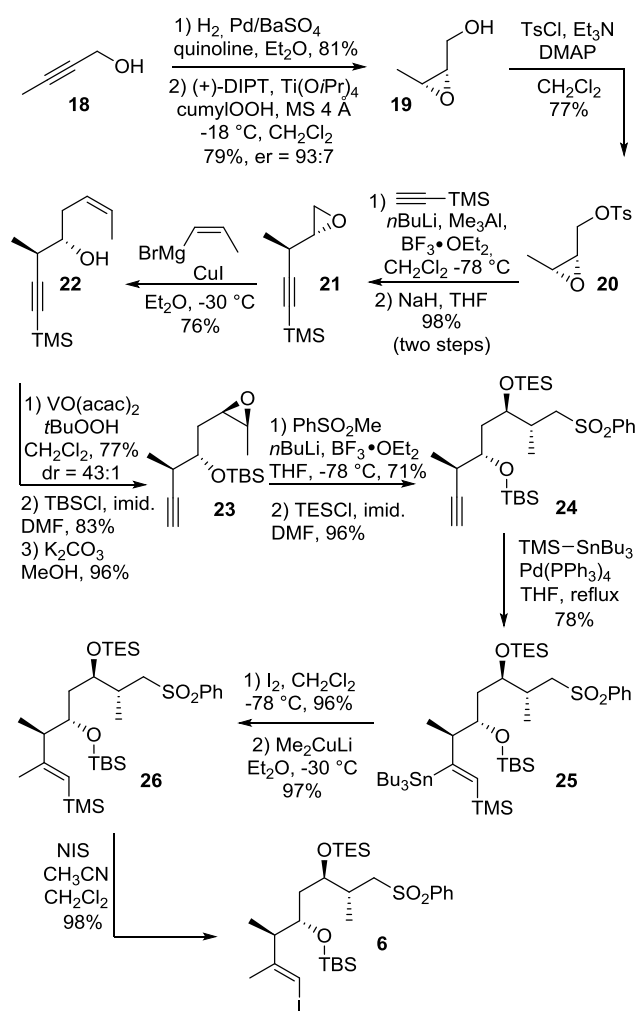
Scheme 2. Synthesis of the C18-C29 fragment (5).



be advantageously exploited by using ring-openings of epoxides with different nucleophiles. The use of an orthogonally protected hydroxyl group at C15 would selectively generate the ketone function in a later stage.. Thus, commercial alkyne **18** was selectively reduced to the corresponding (Z)-olefin with Pd/BaSO₄-quinoline and a Sharpless asymmetric epoxidation was performed using cumyl hydroperoxide to obtain epoxy alcohol **19** (er = 93:7) (Scheme 3).¹⁷ The protection/activation of the hydroxyl group as tosylate **20** allowed us to accomplish the ring-opening of the epoxide exclusively on its less hindered side with the help of a trimethylaluminium “ate” complex derived from TMS-acetylene in combination with BF₃·OEt₂.¹⁸ The tosylate was then internally displaced by the generation of sodium alkoxide to give terminal epoxide **21**. A second epoxide ring-opening was carried out with (Z)-propenyl Grignard in presence of CuI giving (Z)-homo allyl alcohol **22**. The two new stereogenic centers were installed by a VO(acac)₃ directed-epoxidation and gave almost exclusively a single diastereomer (dr = 43:1).¹⁹ The protection of the hydroxyl as a TBS ether and methanalysis of TMS alkyne protecting group afforded compound **23**. The last epoxide ring opening was performed with lithiated methylphenylsulfone in

synergy with $\text{BF}_3 \cdot \text{OEt}_2$.²⁰ The transformation was quantitative, but a mixture of regioisomers, in a separable 71:29 ratio, was obtained. Fortunately the lithium anion added preferentially on the less hindered face of the epoxide, and after an orthogonal protection with TES ether, compound **24** was obtained. Functionalization of the terminal alkyne present in compound **24** was troublesome. Negishi's zirconium catalyzed carboalumination²¹ or stannylcupration followed by iodolysis²² did not allow us to set up the required functionalities. Thus, a reported four-step approach²³ was successfully applied to our substrate giving rise to the accomplishment of the synthesis of fragment C10-C17 (**6**). A palladium mediated regio- and stereo-selective trimethylsilyl-stannylation of alkyne **24** gave product **25**.²⁴ Then iodolysis of the stannane, followed by a substitution of iodide by dimethylcuprate, afforded compound **26**. Final iodolysis of TMS with NIS²⁵ in $\text{MeCN}/\text{CH}_2\text{Cl}_2$ ended the sequence towards sub-unit **6** (Scheme 3).

Scheme 3. Synthesis of the C10-C17 fragment (6).



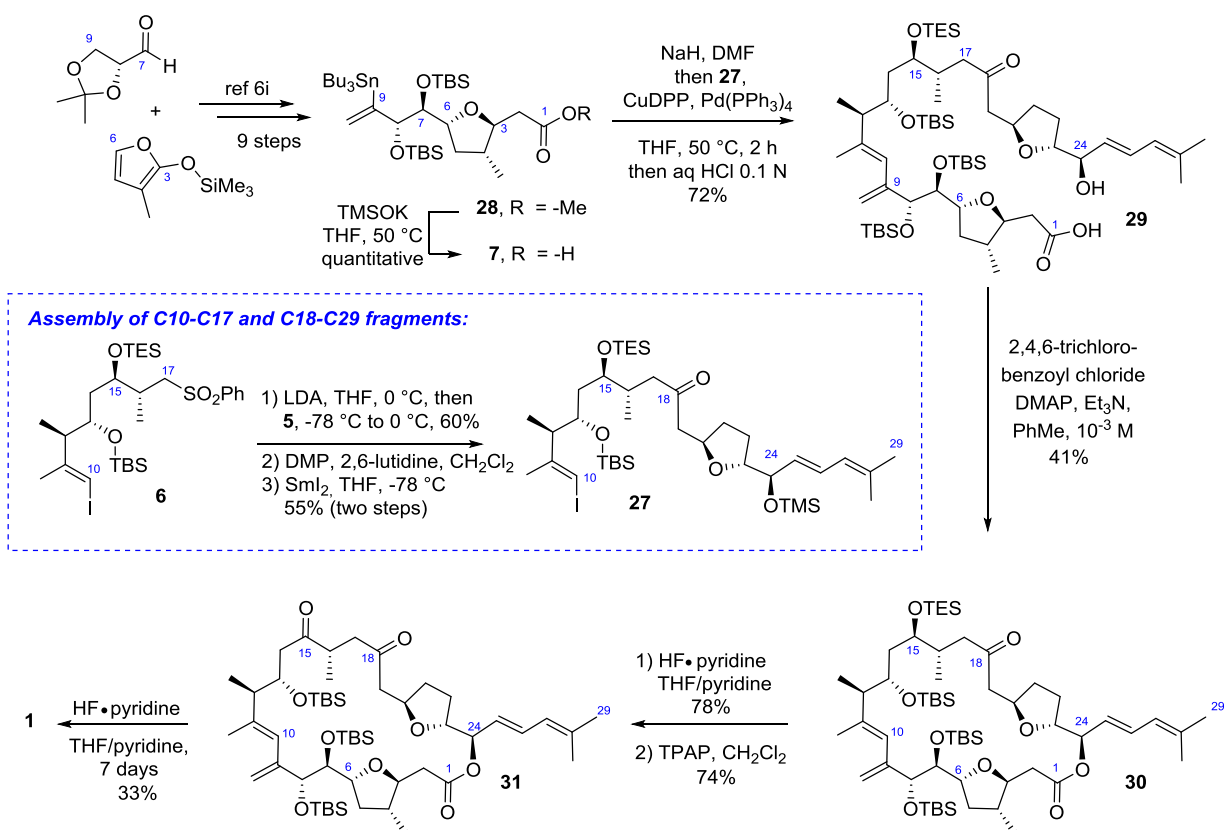
The linkage of subunits **5** and **6** was briefly studied. It was found that base, concentration and temperature were important parameters for the success of the sulfone condensation. Therefore, sulfone **6** was best deprotonated at 0 °C²⁶ with LDA and

aldehyde **5** was then added at -78 °C, followed by a slow warming to 0 °C delivering a complex mixture of four diastereomers. A two-step sequence including 2,6-lutidine buffered Dess-Martin oxidation of C18 alcohol and SmI_2 mediated desulfonylation at -78 °C, afford compound **27** (Scheme 4, boxed).

The next step was the introduction of the last C1-C9 fragment. Sub-unit C1-C9 was synthesized using a strategy reported by us based on a vinylogous Mukaiyama aldol reaction followed by a C-glycosylation with an oxazolidinethione.⁶ⁱ Early studies indicated that the Stille cross-coupling with methyl ester **28** was effective using the copper mediated Liebeskind's protocol²⁷ with a 45-55% yield range depending on the coupling partners. However, we later experienced some difficulties to cleanly saponify the corresponding methyl ester of such complex molecules. Thus, we decided to perform the Stille coupling between the free acid **7**, obtained by reaction of **28** with TMSOK,²⁸ and vinyl iodide **27** (Scheme 4). As we anticipated proto-demetalation issues between the free acid and the *in situ* generated vinyl copper species, we decided to treat first free acid **7** with NaH in DMF followed by addition of vinyl iodide **27** and other reagents needed. We were pleased to note that the cross-coupling was very effective, albeit that it resulted in a partial TMS deprotection. Therefore, treatment of the crude reaction mixture with dilute HCl selectively removed TMS ether and afforded, after purification, compound **29** (72% yield). The macrolactonization took place using Yamaguchi reagent,²⁹ affording compound **30** as a 3:1 mixture of at least two major conformers detectable by NMR.^{7,8} The TES group at C15 was selectively cleaved employing $\text{HF} \cdot \text{pyridine}$ in THF/pyridine³⁰ giving a complex mixture of hydroxyketone and ketals in equilibrium. The probable presence of conformers makes this intermediate very difficult to characterize. Nevertheless, we can establish that the ketal form seems predominant due to the absence of the ketone absorption band ($\nu_{\text{C=O}}$) at 1715 cm^{-1} in the infrared spectrum. The oxidation of hydroxyl at C15 was problematic, and Fürstner's conditions using TPAP (tetrapropylammonium perruthenate)⁸ proved to be the most successful, giving compound **31** in good yield. Final deprotection of the three TBS groups was performed using $\text{HF} \cdot \text{pyridine}$ in THF/pyridine. We noticed that $\text{Et}_3\text{N} \cdot \text{HF}$ reagent system, which was used in the previous total syntheses,^{7,8} produced significant degradation products in our hands (Scheme 4).

In conclusion, we synthesized amphidinolide F (**1**) in 23 steps from the longest linear sequence and 47 total steps, which is a close result to Fürstner's total synthesis (21 steps, longest linear sequence; 39 total steps) and more favorable towards Carter's total synthesis (34 steps, longest linear sequence; 62 total steps). Characterization of our synthetic sample **1** was in accordance with previously reported total syntheses and natural product.³¹ Highlights of this synthesis include the stereoselective synthesis of both *trans*-THF rings using C-glycosylation reactions with the titanium enolate of bulky oxazolidinethiones, the exploitation of an inherent symmetry to build the C10-C19 fragment through iterative ring epoxide openings and a direct and versatile introduction of the dienic side chain *via* a Liebeskind-Srogl cross coupling.

Scheme 4. Synthesis of amphidinolide F (1).



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Notes

The authors declare no competing financial interest.

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- (31) See Supplementary Information for ¹H and ¹³C comparison table between natural and synthetic sample of **1**: (ESI Tables 1 and 2).