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# First Enantioselective Total Synthesis of Amphidinolide F

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## Keywords

asymmetric synthesis; macrolide; umpolung; diene; sulfone; silver catalysis

Over 30 members of the diverse amphidinolide family of biologically active macrolides have been isolated from the dinoflagellate *Amphidinium* sp.[1] From this family, amphidinolides C (**1–2**)[2] and F(**3**)[3] stand among the most complex and densely functionalized members (Figure 1).[4] These natural products **1**–**3** contain eleven stereogenic centers embedded within a 25-membered macrolactone including two *trans*-disposed tetrahydrofuran ring systems, a 1,4-diketone motif and a highly substituted diene moiety at $C_9$–$C_{11}$. In addition to the sizable structural challenges present in **1**–**3**, these macrolides have shown significant cytotoxic activity.[2,3] Consequently, compounds **1**–**3** have attracted considerable synthetic attention from numerous laboratories[5] including our own.[6] Despite these sizable endeavors,[5–6] neither amphidinolide C nor amphidinolide F have been successfully synthesized in the 20+ years since their isolation. It should be noted that the stereochemical assignment of compound **3** is based on analogy to compound **1** and isolation from the same organism. Herein, we disclose the first total synthesis of amphidinolide F (**3**), which confirms both the absolute and relative stereochemistry of the natural product.

Our initial disconnection in the retrosynthesis involved cleavage of the $C_1$ macrolactone linkage to provide the ketone **4** (Scheme 1). This ketone **4** should be accessible from sulfone **5** and iodide **6** through an umpolung strategy[7] involving a sulfone alkylation/oxidative desulfurization sequence[6a, 8] which would mask the otherwise challenging 1,4-dicarbonyl functionality. We noticed considerable “hidden” symmetry within the tetrahydrofuran (THF) portions of fragments **5** and **6**. Specifically, the $C_1$–$C_8$ and the $C_{18}$–$C_{25}$ portions contain nearly identical functionalization, oxidation state and stereochemistry. This observation led us to propose that compounds **5** and **6** might be accessible via common intermediate **7**. Ketone **7** should provide access to over half the carbon backbone of the macrocycle as well as the majority of the stereochemistry present in amphidinolide F.

Synthesis of the common intermediate **7** is shown in Scheme 2. Starting from the known alcohol **8**,[9] oxidation and Ohira-Bestmann reaction[10] cleanly provided the alkyne **10**. Removal of the benzylidine acetal under acidic conditions followed by protection and Shonagashira cross coupling provided enyne **13**. Sharpless asymmetric dihydroxylation yielded the diol **14** in excellent yield and diastereoselectivity.[11] Building on the work from Gagosz[12] and Krause,[13] we had hoped to use a gold-catalyzed cyclization to generate the enol ether **16**. The presence of the 1,2-diol moiety complicates any cyclization conditions as both furan and pyran formation might be feasible. Unfortunately, all attempts to facilitate

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this transformation under Au-catalysis failed to generate the desired product. Fortunately, we found that $AgBF_4$[14] nicely provided the desired dihydrofuran **16** in good yield and complete stereoselectivity (>20:1 dr). This transformation was routinely performed on 5-gram scale and provided sufficient quantities of **16** which might serve as a building block for a variety of *trans*-disposed furan-containing natural products. Subsequent silyl protection and removal of the enol benzoate with MeLi•LiBr[15] produced the common intermediate **7**.

Synthesis of the $C_1$–$C_{14}$ subunit is shown in Scheme 3. We had hoped to directly trap the enolate derived from ketone **7** with methyl iodide to generate the $C_4$ methyl derivative **20**; however, the $C_6$ stereochemistry appeared to be the dominant stereocontrolling element in the alkylation – yielded the undesired $C_4$ methyl stereochemistry. Fortunately, we were able to exploit this directing effect to our advantage through hydrogenation of the *exo*-methylene compound **19** using Wilkinson's catalyst to provide the correct stereochemical combination **20**. Deoxygenation of the $C_5$ carbonyl followed by deprotection and oxidation at $C_8$ generated the aldehyde **22**. Next, we required the stereoselective addition of a 2-metallo-1,3-diene species to the α-silyloxy aldehyde **22**. The prerequisite iodide **27** was prepared in 4 steps from the previously prepared iodide **24**[6a] through a regioselective hydrostannylation of enyne **25**. This regiochemistry is counter to what is typically observed with most Pd-catalyzed hydrostannylations.[16] Treatment of iodide **27** with *n*-BuLi followed by addition to the aldehyde **22** provided the $C_8$–$C_9$ coupled material in good yield and reasonable diastereoselectivity (3:1 dr).[17] We had been concerned that the organolithium species might undergo 1,3-metallotropic shifts[18] to generate allenyl metallo species as well as scramble the $C_{10}$–$C_{11}$ *E/Z* olefin geometry; however, we did not see evidence of this rearrangement occurring under the reaction conditions. Generation of a related vinyllithium species via a hydrazone using Shapiro conditions led to extensive decomposition. After $C_8$ silylation, incorporation of the $C_{14}$ iodide via a two-step sequence provided fragment **6**.

The construction of the second major fragment was also accomplished using common intermediate **7** (Scheme 4). As before, deoxygenation at $C_{22}$ easily provided tetrahydrofuran **28**. Removal of the pivolate at $C_{18}$ followed by oxidation generated aldehyde **29**. Addition of the organolithium species derived from the known iodide **30**[19] provided the 2° alcohols **31** and **32** as an inseparable mixture of stereoisomers. We initially had hoped to convert the $C_{18}$ alcohol into its corresponding dimethyl ketal via oxidation followed by ketalization under Noyori conditions. This approach had proven productive in our prior model system.[6] While the oxidation was effective, we were never able to ketalize the corresponding ketone under a diverse array of conditions. Consequently, we selected protection of alcohol(s) **31** and/or **32** as its ethoxyethyl (EE) ether as a viable alternative. While we believe both $C_{18}$ alcohols **31** and **32** are viable compounds for the synthetic sequence, we proceeded forward with the 18*S* isomer **31**[17] for practicality reasons including simplification of NMR spectra. Oxidation of the mixture **31** and **32** with TPAP, NMO followed by reduction with L-Selectride gave the *18*S isomer **31** in high distereoselectivity [15:1 (**31:32**), 85% yield over two steps]. After EE protection of alcohol **31**, debenzylation and incorporation of the sulfone moiety at $C_{15}$ provided the compound **34**. Selective 1° TBS deprotetion using HF•pyr followed by Swern oxidation revealed the key α-oxy aldehyde **35**. We had initially planned to exploit Julia-Kocienski-Blakemore olefination[20] of this aldehyde with the known PT sulfone;[21] however, this reaction showed a preference for the undesired *cis* alkene. While alternate, multi-step solutions have been developed to circumvent this problem,[5c,5j] we continued to look for a direct solution. Fortunately, use of the Vedejs-type tributyl phosphonium salt **36**[22] cleanly generated the desired *E* alkene **37** in good selectivity (97% yield, 11:1 *E:Z*). Exchange of the $C_{24}$ silyl protecting groups provided the $C_{15}$–$C_{29}$ fragment **5**.

The completion of the total synthesis of amphidinolide F is shown in Scheme 5. The key coupling of the major fragments was accomplished by treatment of sulfone **5** with LHMDS and HMPA followed by the addition of alkyl halide **6** smoothly formed the $C_{14}$–$C_{15}$ coupled material **38**.[6a] The nucleophilicity of sulfone carbanions was instrumental in the success of this challenging coupling between an α-branched alkyl iodide and an α-branched nucleophile.[23] Next, oxidative desulfurization was accomplished using LDA/DMPU followed by treatment with Davis' oxaziridine to provide the desired ketone **4** along with the Piv deprotected ketone **39** in a combined 65% yield (94% BORSM). While this type of oxidation has been known for some time,[24] it is only recently starting to gain attention as a viable method for the incorporation of carbonyl moieties in synthesis.[6,8] Interestingly, the Davis oxaziridine proved superior to our previous TMSOOTMS conditions.[6a,8a] Both compounds **4** and **39** were easily converted to the seco acid **42**. In contrast to our synthesis of amphidinolide B,[25] macrolactonization proved to be an effective way for construction of the cyclized product **43** with Yamaguchi conditions[26] being optimum. Next, careful deprotection at $C_{18}$ under aqueous acidic conditions followed by oxidation yielded the sensitive $C_{15}$, $C_{18}$-diketone. Finally, global desilylation using $Et_3N{\bullet}3HF$[27] provided synthetic amphidindolide F (**3**) which matched with the natural material ($^1H$, $^{13}C$, $[\alpha]_D$).[2]

In summary, the total synthesis of amphidinolide F has been accomplished in 34 steps (longest linear sequence). Highlights to the synthetic sequence include a silver-catalyzed dihydrofuran formation, use of a common intermediate **7** to access both the $C_1$–$C_8$ and $C_{18}$–$C_{25}$ fragments, regioselective hydrostannylation of enyne **25**, diasteroselective addition of a 2-lithio-1,3-diene species to aldehyde **22** and the sulfone alkylation/oxidative desulfurization sequence to couple the major subunits and incorporate the $C_{15}$ carbonyl moiety.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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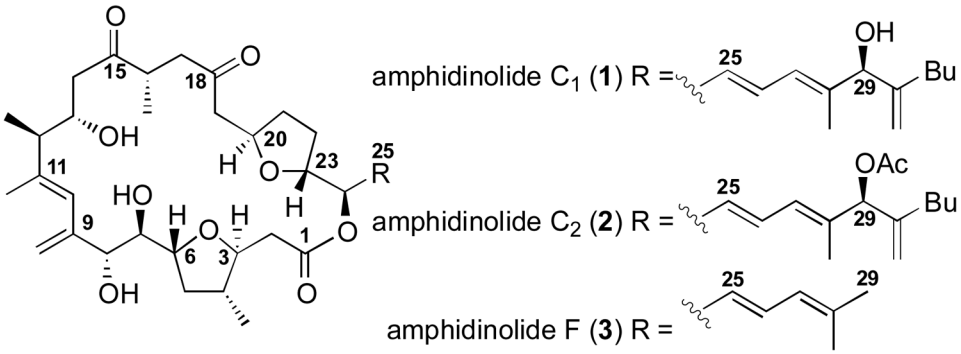
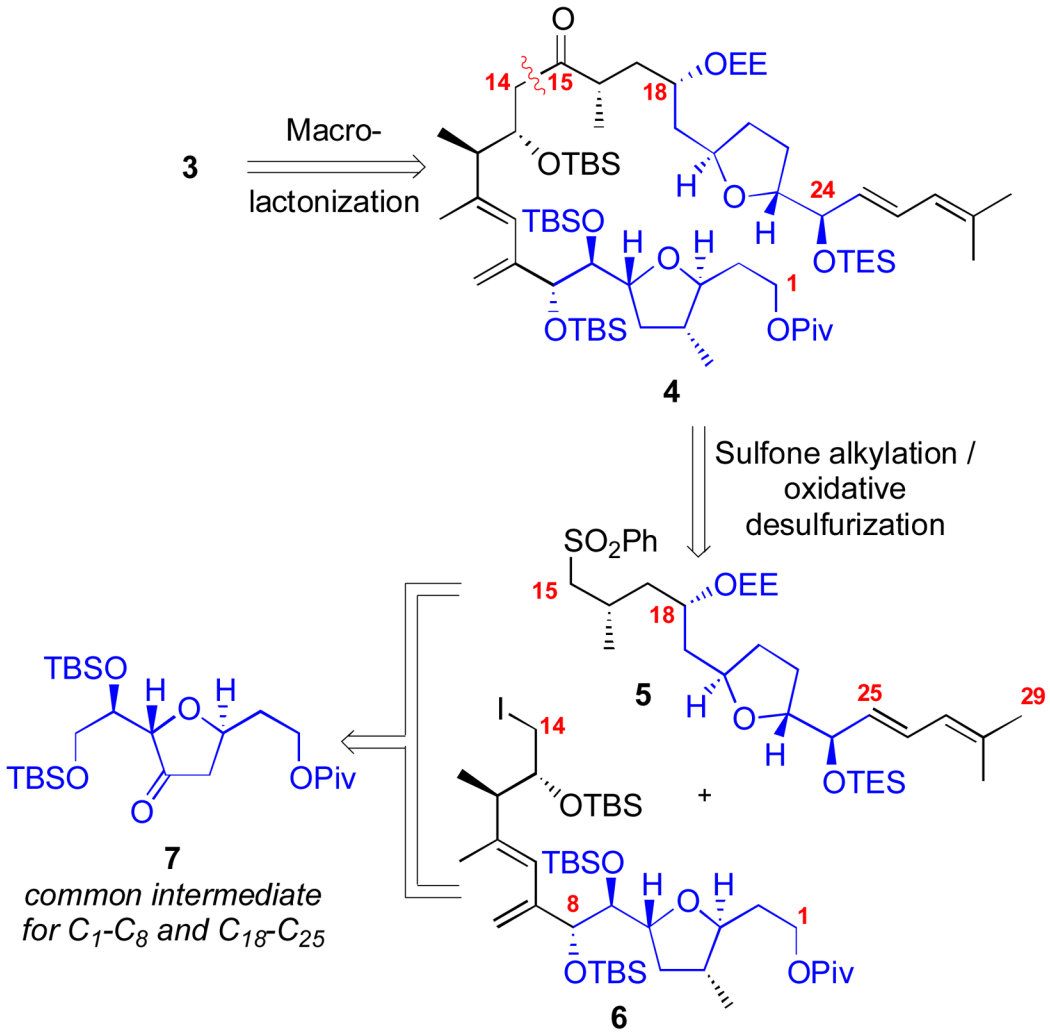
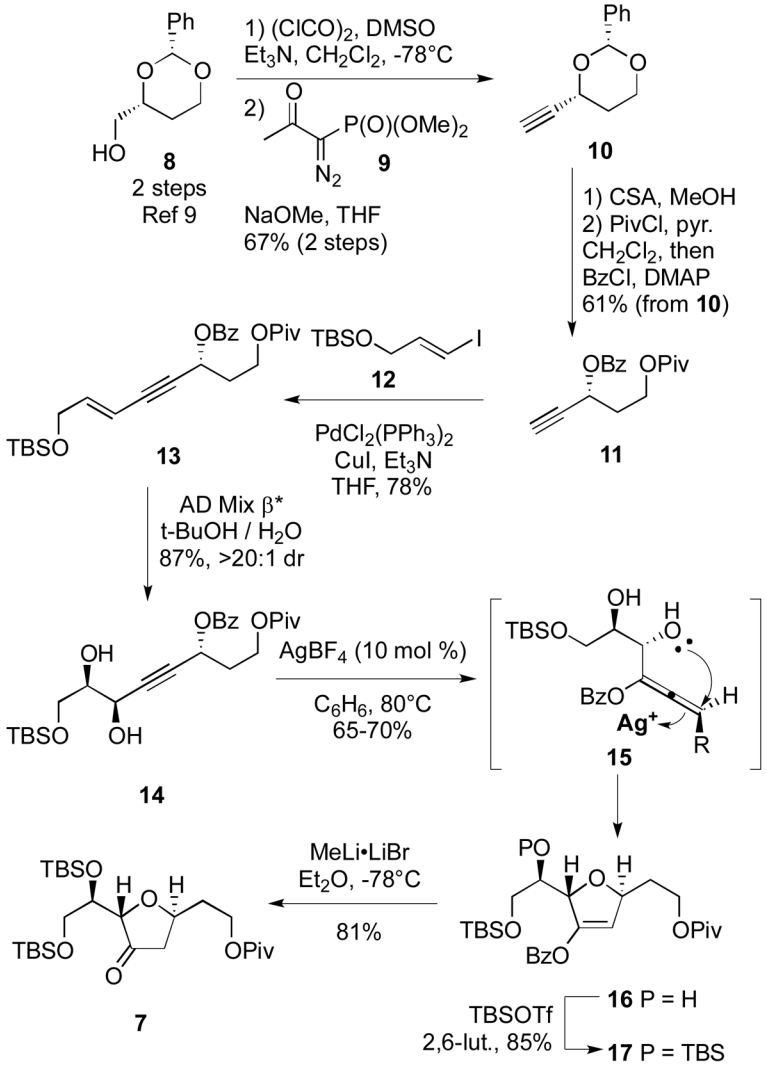


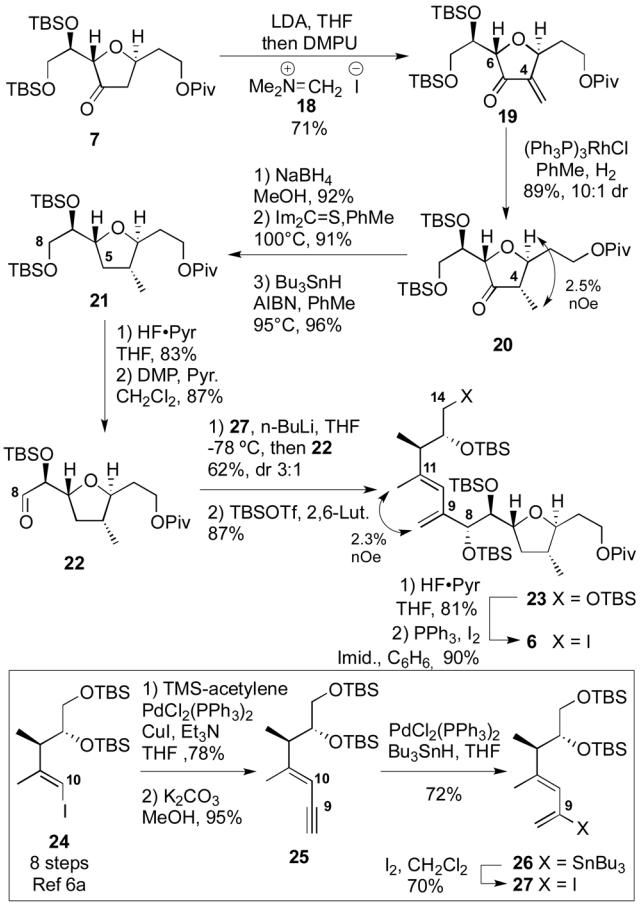

**Figure 1.**
Structurally Complex Amphidinolide Natural Products.



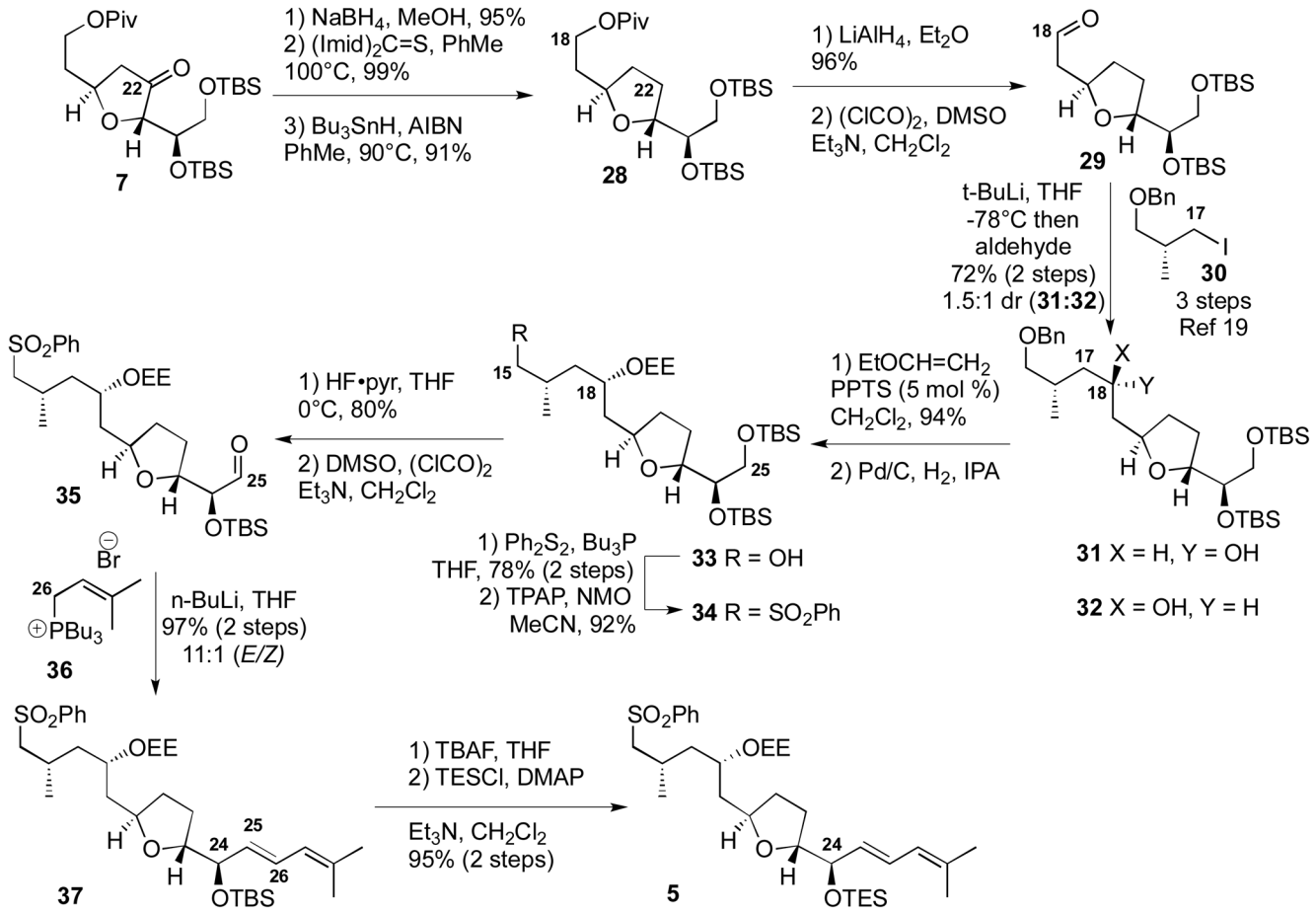

**Scheme 1.**
Retrosynthesis.



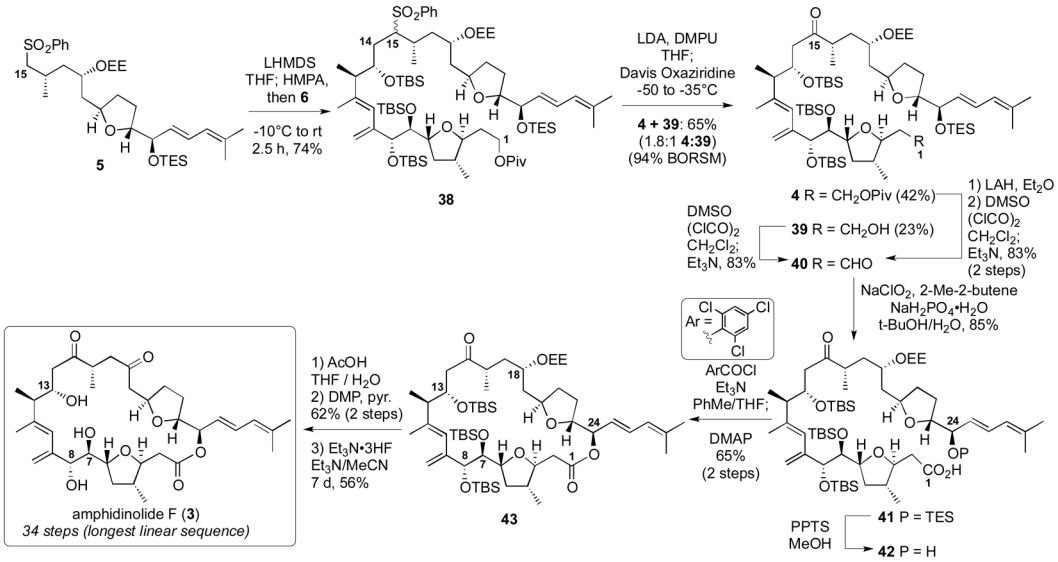

**Scheme 2.**
Synthesis of Common Intermediate.




**Scheme 3.**
Synthesis of $C_1$–$C_{14}$ Subunit.




**Scheme 4.**
Synthesis of $C_{15}$–$C_{29}$ Subunit




**Scheme 5.**
Total Synthesis of Amphidinolide F.