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Stereoselective Synthesis of the C1−C9 and C11−C25 Fragments of Amphidinolides C, C2, C3, and F

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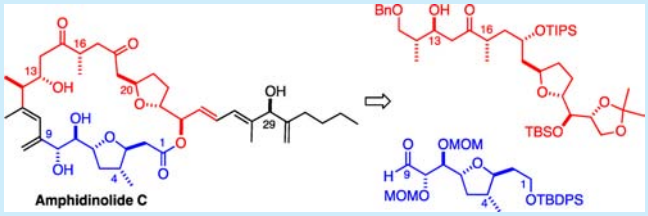
Supporting Information

ABSTRACT: An efficient synthesis of the C1−C9 and the C11−C25 fragments of amphidinolides C, C2, C3, and F from a common intermediate is reported. The construction of the C1−C9 fragment involves an intramolecular hetero-Michael cyclization to form the 3,5-disubstituted *trans*-tetrahydrofuran moiety. The approach to prepare the C11−C25 fragment utilizes a highly stereoselective aerobic cobalt-catalyzed alkenol cyclization and a chelated Mukaiyama aldol reaction to form the C13−C14 bond and to concomitantly install the C13 hydroxyl group.



Amphidinolides are a large family of bioactive secondary metabolites with almost 40 members isolated from symbiotic marine dinoflagellates *Amphidinium spp.* (from the Okinawan flatworm)[1] and Brazilian octocoral *Stragulum bicolor* and its predator, the nudibranch *Marionia limceana*.[2] Among these bioactive natural products are amphidinolides C (**1**), C2 (**1b**), C3 (**1c**), and F (**1d**),[3] which share the same complex 25-membered macrolide core that is decorated with 11 stereogenic centers including an *anti*-vicinal diol and a 1,2-*trans*-disposed methyl hydroxy functionality at C12 and C13, respectively (Figure 1). Engraved in this stereochemically rich common core are two *trans*-2,5-disubstituted tetrahydrofuran ring systems, a trisubstituted 1,3-diene, and a 1,4-diketone moiety.

The only structural differences among these amphidinolides reside in the C29 functionalization within the C25−C34 triene motif. Interestingly, these relatively minor structural discontinuities at C29 directly impact their antineoplastic activities. Alcohol **1** possesses a (*S*)-hydroxyl group at C29 and is the most highly active against murine lymphoma L1210 and human epidermoid carcinoma KB cell lines with IC_{50} of 5.8 and 4.6 ng/mL, respectively (Table 1).[3a,4] Biological activity decreases about 1000-fold simply by acetylating the C29 hydroxyl group to provide acetate **1b**[3b] or oxidation to ketone **1c**,[3c] an indication that the C29 hydroxyl group is essential for potent biological activity.

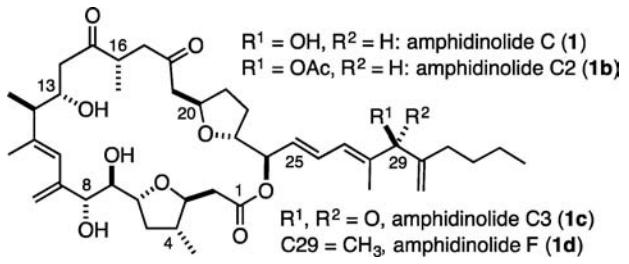


Figure 1. Amphidinolides C, C2, C3, and F.

Table 1. Bioactivity Profile of 1−1d

amphidinolide	IC_{50} (ng/mL): murine lymphoma L1210	IC_{50} (ng/mL): epidermoid carcinoma KB
C (**1**)	5.8	4.6
C2 (**1b**)	800	3000
C3 (**1c**)	7600	10000
F (**1d**)	1500	3200

The unique bioactivity and structural complexities of **1**−**1d** make them attractive and challenging targets in the synthetic community,[5] with Mahapatra and Carter[6] and Fürstner et al.[7] recently reporting the total syntheses of **1** and **1d**.

Our retrosynthetic approach to access **1**−**1d** involves dissecting these molecules into three segments: the southern C1−C9 fragment (**3**), the northern C11−C25 fragment (**2**), and the C27−C34 side chain (**4**, Scheme 1).

Late-stage Stille coupling[8] to install **4** is proposed to access **1**−**1d** from a common macrocyle and to prepare different analogues for further structure−activity relationship studies. Recognition of hidden structural homology between the *trans*-tetrahydrofurans **2** and **3** allowed for their syntheses from a common readily available D-gluconic acid *δ*-lactone **5**.

The synthesis of **3** began with a one-pot, acid-catalyzed methanolysis and bis-ketalization of **5**, followed by reduction with $NaBH_4$ in refluxing ethanol and $NaIO_4$-mediated oxidative cleavage of the ensuing vicinal diol to afford aldehyde **6** (Scheme 2).[9] Crude **6** was then subjected to stereoselective Ando's Horner−Wadsworth−Emmons reaction with phosphonate **7** to obtain acrylate **8** with greater than 12:1 *Z*/*E* selectivity.[10] Lactone **9** was then prepared from **8** via acidic bis-deketalization and spontaneous lactonization, followed by

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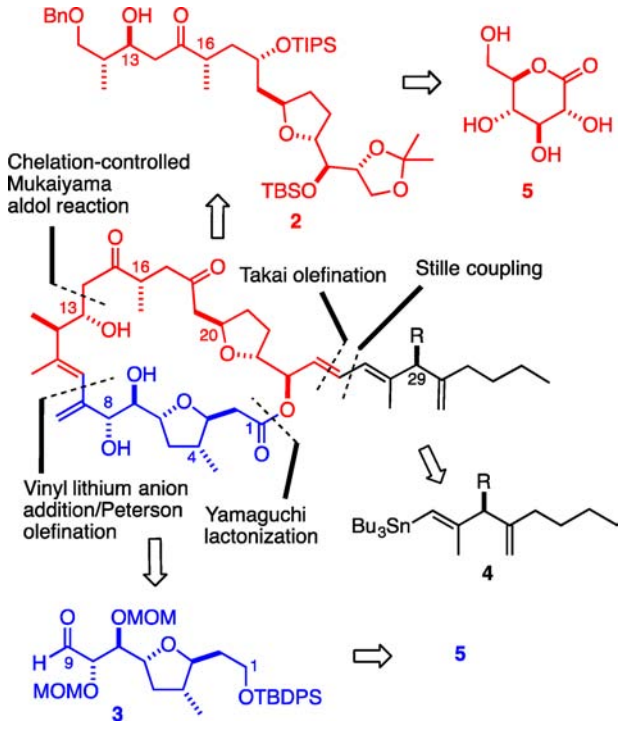
Scheme 1. Retrosynthetic Analysis

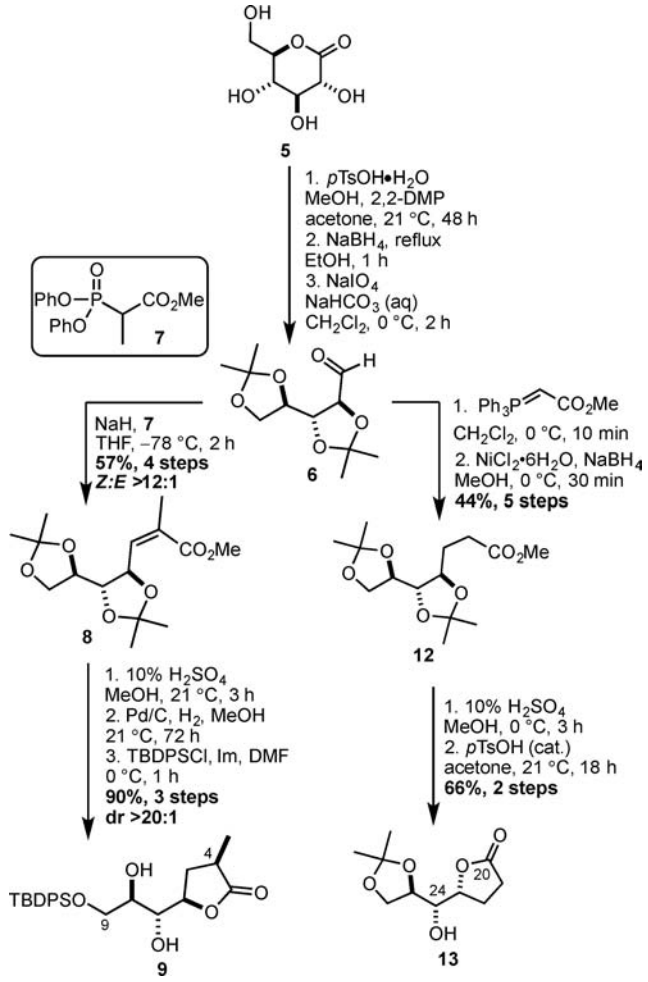


substrate-controlled diastereoselective hydrogenation and selective silylation of the primary alcohol. Lactone **9** was further converted into acrylate **10** in a three-step sequence that involved protection of the diols as MOM acetals using P_2O_5 and $CH_2(OCH_3)_2$ in chloroform,[11] DIBAL-H reduction, and Wittig olefination (Scheme 3). Next, **10** was treated with TBAF to induce a diastereoselective intramolecular hetero-Michael cyclization to form the *trans*-2,5-disubstituted tetrahydrofuran ring with desilylation to reveal the C9 primary alcohol. A similar Michael cyclization was reported by Kobayashi et al. in their structural determination work and by Roush et al.[4,5c] Reprotection of the C9 alcohol as a TES ether and reduction of the C1 methyl ester with $LiAlH_4$ provided primary alcohol **11**.

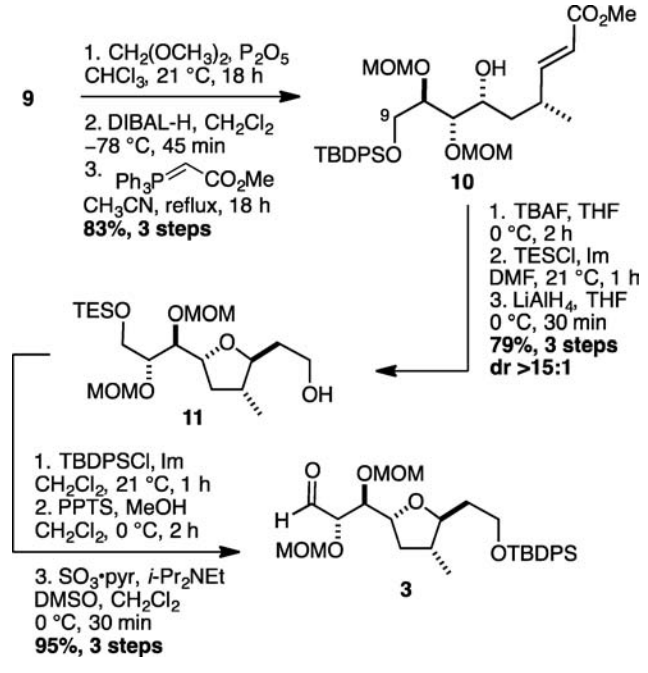
The origin of the high diastereoselectivity of the kinetically controlled hetero-Michael cyclization can be attributed to unfavorable allylic 1,3-strain destabilization of the transition state that leads to minor product **B** (Figure 2). This destabilization effect is absent from the transition state that leads to the major product **A**. Further differential terminal functionalization of **11** was accomplished by silylation of the C1 alcohol and chemoselective cleavage of the C9 silyl ether under mildly acidic conditions (PPTS in MeOH), followed by Parikh–Doering oxidation[12] to obtain the C1–C9 fragment of **1**–**1d** (**3**).

The C11–C25 fragment **2** of the target amphidinolides (**1**–**1d**) was designed by recognizing the hidden structural homology within the macrolide core. It was noted that the stereochemical information within the *trans*-tetrahydrofuran fragments **13** and **9** was essentially identical, except for the C4 methyl substituent (Scheme 2). It was envisioned, therefore, that **17** (and consequently, **2**) and **3** could be prepared from the common source **5**. Indeed, Carter and Mahapatra also reported exploiting this hidden structural homology to construct the two *trans*-tetrahydrofurans from a common intermediate.[6] Thus, aldehyde **6** was converted to its homologated α,β-unsaturated methyl ester, which was then

Scheme 2. Taking Advantage of Structural Homology: Synthesis of Diol 9 and Acetonide 13 from 5



Scheme 3. Construction of the C1–C9 Fragment of 1–1d



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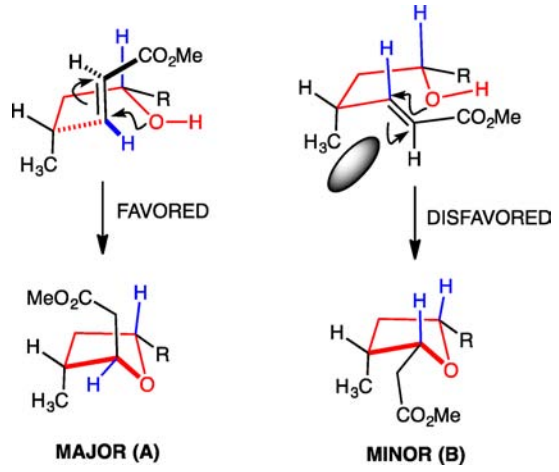
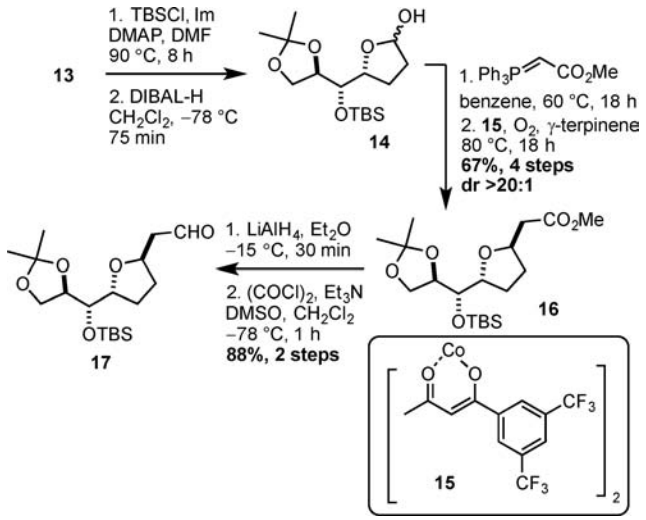


Figure 2. Possible origin of selectivity for Michael cyclization.

Scheme 4. Synthesis of Aldehyde 17

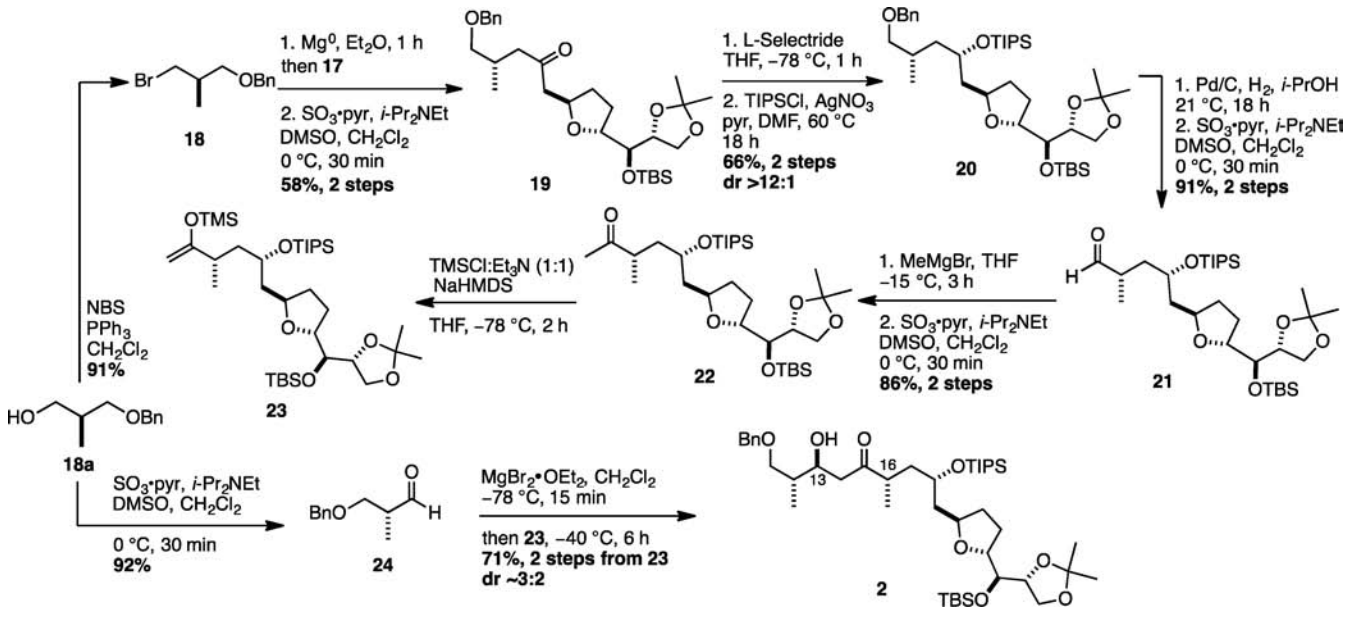


hydrogenated with in situ generation of nickel boride[13] to afford α,β-saturated methyl ester **12** (Scheme 2). Acidic deketalization−lactonization followed by recapture of the resultant vicinal diol as an acetonide yielded **13**. Cyclic hemiacetal **14** was prepared from **13** via silylation and DIBAL-H reduction (Scheme 4). Wittig olefination converted **14** into the corresponding α,β-unsaturated methyl ester to set the stage for the *trans*-tetrahydrofuran formation.

Initial attempts to induce a base-catalyzed *trans*-tetrahydrofuran cyclization using Triton B in CH_2Cl_2 resulted in a high yield, albeit with moderate *trans:cis* selectivity (3:1). It was noted, however, that Hartung's modified Mukaiyama aerobic alkenol intramolecular cyclization[5i,14] proceeded with high stereoselectivity to afford **16** (*trans:cis* >20:1). Ester reduction ($LiAlH_4$) and alcohol oxidation[15] completed the production of aldehyde **17**.

Completion of the synthesis of the C11−C25 fragment **2** of the target amphidinolides (**1**−**1d**) is outlined in Scheme 5. Thus, the Grignard reagent derived from bromide **18** was added to aldehyde **17**, followed by Parikh−Doering oxidation[12] to generate ketone **19**. Attempts to reduce the C18 ketone with $Zn(BH_4)_2$ and K-Selectride resulted in poor stereoselection. Stereoselective reduction was achieved, however, using L-Selectride, and the C18 (*S*)-hydroxyl stereochemical assignment stems from an analogous transformation reported by Carter and Mahapatra.[6] The C18 hydroxyl group was then masked via silylation to give benzyl ether **20**. Palladium-catalyzed debenzylation to reveal the C15 alcohol was followed by oxidation, MeMgBr addition, and another oxidation to produce methyl ketone **22**. TMS enol ether **23** was obtained from **22** using NaHMDS and a TMSCl−Et_3N mixture. The construction of the C11−C25 fragment of **1**−**1d** was completed by a chelated Mukaiyama aldol reaction between **24** and **23** in the presence of $MgBr_2{\cdot}OEt_2$[16] to form the C13−C14 bond and install the C13-hydroxyl group. The diastereoselectivity of this process was lower than anticipated, based upon literature precedent,[16] which prompts future optimization of this process.

Scheme 5. Construction of the C11−C25 Fragment of 1−1d



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In conclusion, stereoselective syntheses of the C1−C9 southern and the C11−C25 northern fragments of amphidinolides C, C2, C3, and F have been accomplished. The two fragments were prepared from a common intermediate by capitalizing on the latent structural homology within the macrocycle. The C1−C9 fragment synthesis involved a diastereoselective TBAF-mediated intramolecular hetero-Michael cyclization. Also employed was Hartung's modified Mukaiyama alkenol cyclization to construct the *trans*-tetrahydrofuran ring in the C11−C25 northern fragment. Another key transformation that was applied to complete the C11−C25 northern fragment was the use of a chelated Mukaiyama aldol reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00217.

Detailed experimental procedures and full spectroscopic data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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