Natural Products

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Total Synthesis of Amphidinolide F**

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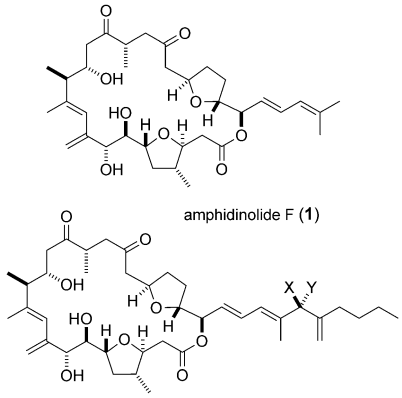
Dedicated to the Bayer company on the occasion of its 150th anniversary

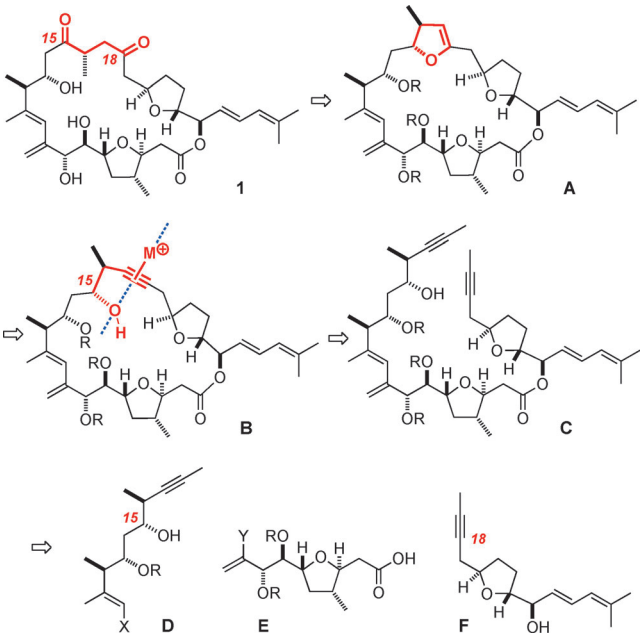
Marine dinoflagellates of the *Amphidinium* genus are a remarkably prolific source of bioactive secondary metabolites. More than thirty macrolides have been isolated from different strains, which are collectively called amphidinolides but can actually be clustered into various subfamilies.[1,2] One such panel comprises amphidinolide C, C2, C3, and F, which exhibit different side chains but share the same odd-numbered frame consisting of a 25-membered macrocycle adorned with 11 (12) stereogenic centers, two 1,3-diene units, and two *trans*-disposed tetrahydrofuran rings (Scheme 1).



Scheme 1. Structures of the amphidinolides C and F.

Despite the obvious structural homology, these compounds exhibit surprisingly different biological activities: whereas amphidinolide C (**2**)[3] is highly cytotoxic for the murine lymphoma L1210 and the human epidermoid carcinoma KB cell lines (IC_{50} of 5.8 and 4.6 ng mL^{-1}, respectively), its close relatives **1**,[4] **3**,[5] and **4**[6] are up to three orders of magnitude less potent. It remains to be seen, however, if this striking bio-profile extends to a larger panel of tumor cell lines. Because of the low isolation yields, the material supply is a serious concern and may be one of the reasons why **1**–**4** attracted considerable attention from the synthetic community.[7] Despite this, more than 20 years passed after the initial isolation report before amphidinolide F (**1**) as the first and, until now, only member of this subfamily succumbed to total synthesis in 2012.[8]

As part of our long-term commitment to the amphidinolide family,[9–12] we now present another successful approach to amphidinolide F (**1**) that is radically different in its conception and considerably shorter in its implementation. In an attempt to reflect the peculiarities of this target in the synthesis blueprint, our plan evolved around the conspicuous 1,4-diketone moiety located at the C15 and C18 atoms (Scheme 2). Such a nonconsonant ("umpoled") pattern is very unusual for a polyketide skeleton and its biosynthesis is certainly not obvious. We envisaged that a directed transannular alkyne hydration would provide access to this



Scheme 2. Retrosynthetic analysis of **1** based on a directed transannular alkyne hydration to be catalyzed by a carbophilic Lewis acid; the dotted blue line in **B** indicates the quasi linear array that the reacting sites must be able to reach.

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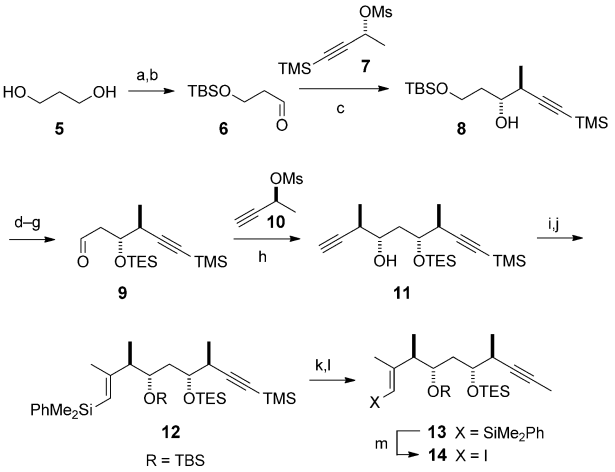
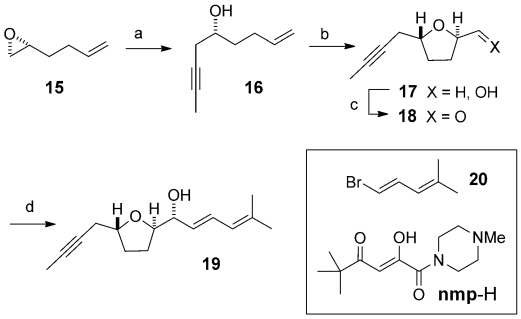
peculiar motif. Amongst the different conceivable incarnations of this strategy, we opted for a hydroxy group (rather than a ketone)[13] at C15 as the steering substituent and set the alkyne site at the C17–C18 position. Activation of a substrate of type **B** by a carbophilic noble-metal catalyst should trigger a 5-*endo-dig* cyclization with formation of a dihydrofuran **A**, which unveils the signature 1,4-oxygenation pattern upon hydrolysis. This transformation is supposed to be highly regioselective, as a 4-*exo-dig* pathway is unlikely to compete. Although research into π-acid catalysis in general has gained considerable momentum,[14] late-stage implementations in the total synthesis of highly complex targets are rare.[15,16] By subjecting an elaborate compound of type **B** to a carbophilic catalyst, we thought to express our confidence in this methodology that has grown considerably since our first forays.[17] This plan is contingent upon the ability to forge the necessary cycloalkyne from an adequate precursor **C** by ring-closing alkyne metathesis (RCAM),[18,19] as well as on the proper choice of protecting groups, thus allowing the C15–OH function to be revealed in due time.

Mechanistically speaking, the projected hydration step is thought to proceed through an outer-sphere attack of the oxygen atom onto the activated alkyne, *trans* to the inducing noble metal template; to this end, the partners must be able to reach a quasi linear array (Scheme 2).[14,15] Handheld models suggested that an *R*-configured secondary alcohol at C15 in **B** might be better predisposed to meet this geometric precondition than the 15*S*-isomer. It was planned to access the required building block **D** by garnering its hidden symmetry through a two-directional approach based on the powerful *anti*-propargylation methodology developed by Marshall.[20] To this end, aldehyde **6** was subjected to a zinc-mediated, palladium-catalyzed reaction with mesylate **7** (98% *ee*) to give product **8** (d.r. = 90:10) in high yield on a multigram scale (Scheme 3).[21] The compound was then elaborated into aldehyde **9**, posed for a second Marshall propargylation. After some experimentation it was found that the indium variant worked better in this particular case,[22] for which the uncapped mesylate **10** was used to ensure proper differentiation of the alkyne termini in the resulting product **11**. Gratifyingly, careful flash chromatography allowed the other diastereomers present at this stage to be largely removed. After TBS protection of the free OH to ascertain the critical orthogonality to the C15 TES ether, the terminal alkyne was subjected to a silylcupration followed by a methyl iodide quench.[23] Under optimized conditions the reaction worked admirably well, affording compound **12** as a single isomer. Basic methanol allowed for removal of the alkynyl TMS group without affecting the three other silyl residues. C-Methylation followed by iodine-for-silicon exchange gave alkenyl iodide **14** as surrogate of synthon **D**. However, this product turned out to be rather light sensitive and was therefore released from its immediate precursor **13** only on demand.

An oxidative Mukaiyama cyclization reaction[24] opened an expeditious entry into the tetrahydrofuran segment **F** (Scheme 4). While this work was in progress, the group of Pagenkopf reported a model study directed towards amphidinolide C (**2**) following a similar logic.[7e,l] Our approach is



Scheme 3. a) TBSCl, Et_3N, CH_2Cl_2, 0°C→RT, 86%; b) TEMPO (10 mol%), KBr, NaOCl, pH 8.6 buffer, CH_2Cl_2, 0°C, 86%; c) **7**, Pd(OAc)$_2$ (5 mol%), PPh_3 (5 mol%), Et_2Zn, THF, −78°C→−20°C, 87%; d) HCl (1%, *v*/*v*) in EtOH, 91%; e) TESOTf, 2,6-lutidine, CH_2Cl_2, 0°C, quant.; f) PPTS (10 mol%), MeOH, CH_2Cl_2, −50°C, 80%; g) SO_3·pyridine, iPr_2NEt, DMSO, CH_2Cl_2, −30°C, 93%; h) **10**, InI, [$PdCl_2$(dppf)] (5 mol%), THF/HMPA, 73%; i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 91%; j) $PhMe_2SiLi$, CuCN, MeI, THF, 0°C, 90%; k) K_2CO_3, MeOH, 40°C, 88%; l) *n*BuLi, MeI, THF, −78°C → RT, 97%; m) NIS, MeCN, benzene, 0°C, 88%; dppf = 1,1′-bis(diphenylphosphino)ferrocene; Ms = methanesulfonyl; NIS = N-iodosuccinimide; PPTS = pyridinium *p*-toluenesulfonate; TBS = *tert*-butyl-dimethylsilyl; TES = triethylsilyl; TEMPO = 2,2,6,6-tetramethyl-1-piperinyloxy radical; Tf = trifluoromethansulfonyl; TMS = trimethylsilyl.

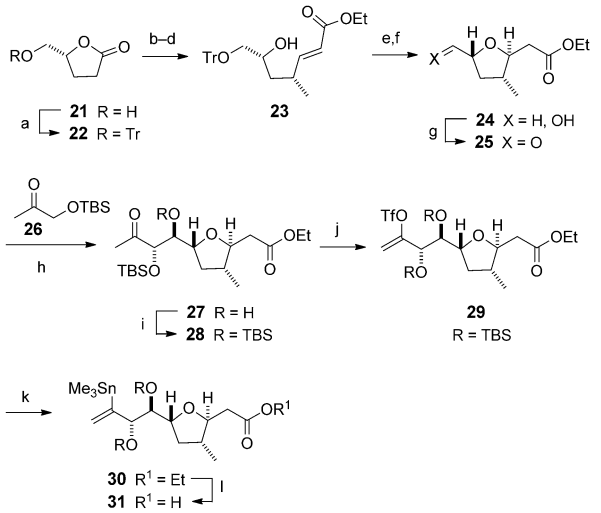


Scheme 4. a) Propyne, *n*BuLi, BF_3·Et_2O, THF, −78°C, 87%; b) (nmp)$_2$Co (10 mol%), *t*BuOOH (10 mol%), O_2 (1 atm), *i*PrOH, 55°C, 84%; c) SO_3·pyridine, iPr_2NEt, DMSO, CH_2Cl_2, 0°C, 86%; d) i) **20**, *t*BuLi, Et_2O, −78°C, then $ZnBr_2$, Et_2O, −35°C→0°C; ii) (−)-*N*-methylephedrine/*n*BuLi, toluene, 0°C; iii) **18**, Et_2O, −20°C, 85%.

different in that the aerobic cobalt-catalyzed etherification step was conducted with substrate **16**, containing two different π-bonds that might, a priori, be amenable to oxidation. Gratifyingly, the transformation was strictly chemoselective, in that the olefinic site of **16** reacted cleanly, whereas the alkyne entity survived uncompromised. We acknowledge, however, that the "second generation" Pagenkopf catalyst carrying nmp ligands (Scheme 4)[7e] afforded consistently better yields than other cobalt species previously used in the literature.[24] Oxidation of the resulting *trans*-disubstituted tetrahydrofuran derivative **17** to the corresponding aldehyde

18 followed by a chelate-controlled *N*-methylephedrine-assisted addition[25] of the dienylzinc reagent derived from bromide **20**[26] also proceeded smoothly. Thus, the required building block **19** was accessible in appreciable overall yield and good diastereoselectivity (d.r. ≈ 95:5) in only four operations.

Fragment **E** was prepared from the known alcohol **24**,[3c] which in turn was obtained from the commercially available furanone **21** in six readily scalable steps (Scheme 5).[27,28] A



Scheme 5. a) TrCl, pyridine, 91%; b) (i) LDA, MeI, THF, −78°C→ −30°C; (ii) LDA, THF, −78°C, aq. work up, 93% (over both steps); c) Dibal-H, CH_2Cl_2, −78°C; d) $Ph_3P{=}CHCOOEt$, toluene, 80°C, 85% (over both steps); e) TBAF·$3H_2O$, THF, 0°C, 87%; f) TFA, EtOH, CH_2Cl_2, 0°C, 86%; g) SO_3·pyridine, *i*Pr_2NEt, DMSO, CH_2Cl_2, 0°C; h) **26**, L-proline (50 mol%), DMF, 66% (over both steps); i) TBSOTf, pyridine, CH_2Cl_2, 0°C→RT, 91%; j) KHMDS, $PhNTf_2$, THF, −78°C, 73%; k) [$Pd_2(dba)_3$] (15 mol%), P(2-furyl)$_3$ (60 mol%), Me_6Sn_2, LiCl, THF, 81%; l) KOH, THF, EtOH, H_2O, 45°C, 98%; dba = dibenzylideneacetone; Dibal-H = di-isobutylaluminum hydride; KHMDS = potassium hexamethyldisilazide; LDA = lithium di-isopropylamide; TBAF = tetra-*n*-butylammonium fluoride; TFA = trifluoroacetic acid; Tr = trityl.

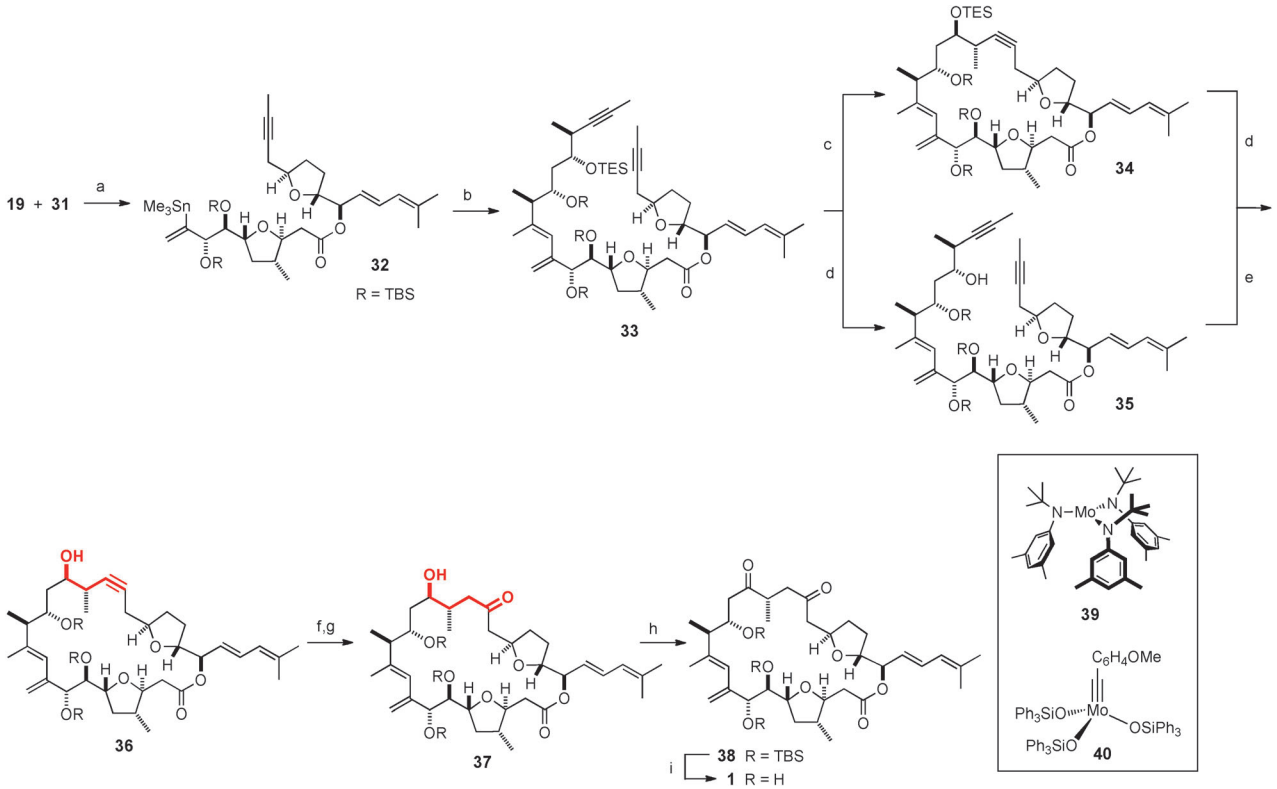
proline-catalyzed aldol reaction of the derived aldehyde **25** with **26** as the prenucleophile[29] furnished the required *anti*-aldol derivative **27** in acceptable yield; its stereostructure was confirmed by Mosher-ester analysis and by NOE studies on the derived isopropylidene acetal. For preparative purposes, however, bis-TBS protection of the diol was preferred, as the isopropylidene acetal turned out to be rather labile. Compound **28** behaved well in the subsequent alkenyl triflate formation, even though it contains two potentially enolizable sites. The kinetic and thermodynamic acidity of the methyl ketone is obviously sufficiently higher than that of the ester group, thus allowing us to secure appreciable amounts of product **29**. For its conversion into stannane **30**, the combination of [$Pd_2(dba)_3$] and tris-2-furylphosphine[30] fared considerably better than the more commonly used [$Pd(PPh_3)_4$] catalyst.[31] Saponification of the ester finally delivered building block **31** and opened the assembly phase of this total synthesis project.

Whereas a Yamaguchi esterification of **19** and **31** gave product **32** without incident,[32] the subsequent Stille coupling proved to be rather challenging (Scheme 6). Only under the very mild conditions, which we had optimized during a previous amphidinolide project,[11,33] could the isomerization-prone 1,3-diene unit of **33** be assembled in a workable 56% yield, although a high catalyst loading was required. With this considerable hurdle overcome, the stage was set for macrocyclization by RCAM, to be followed by transannular alkyne hydration. Two possible scenarios were conceived and explored: the more conservative approach engaged the fully protected diyne into ring closure, followed by selective deprotection of the TES ether at C15; alternatively, one may inverse the order and perform the RCAM step with a substrate already exhibiting the free OH group.

We are pleased to report that either way was ultimately successful. Specifically, diyne **33** was cyclized in good yield with the aid of complex **39,** activated in situ with CH_2Cl_2, as previously described by our group,[34] whereas complex **40**[35] carrying somewhat bulkier silanolate ligands gave an acyclic dimer as a by-product.[36] Gratifyingly though, catalyst **40** excelled after reducing the bulk about one of the alkyne units in the cyclization precursor by cleavage of the flanking TES group: the relieved compound **35** was cleanly transformed into product **36** upon warming. This result is remarkable as acidic protons were hardly manageable by earlier generations of alkyne metathesis catalysts; moreover, one has to note that alkylidyne **40** owes its excellent application profile to the silanolate ligands, which might partly exchange with substrates containing free OH groups. Although the compatibility of **40** with protic substituents needs further scrutiny, this encouraging example illustrates the exquisite tolerance of the latest generation of alkyne metathesis catalysts.[35]

The NMR spectra of the cycloalkynes **34** and, in particular, **36** feature massive line broadening in the entire temperature range that was surveyed, with (at least) two slowly equilibrating conformers being detectable at −20°C. This conformational intricacy, however, did not obstruct transannular alkyne hydration from occurring. Excellent results were obtained under platinum catalysis:[37,38] treatment of compound **36** with only 0.2 mol% of [{$(C_2H_4)_2PtCl_2$}$_2$] in Et_2O afforded hydroxyketone **37** (in equilibrium with the corresponding hemiketals) within minutes in essentially quantitative yield after a brief hydrolytic work-up.[39] As expected, the regioisomeric ketone derived from a 4-*exo*-dig pathway could not be detected and both 1,3-diene subunits remained untouched, illustrating the exquisite "alkynophilicity" of the catalyst.[14] Subsequent oxidation of **37** with TPAP[40] furnished diketone **38** that was identical in all regards with the material previously prepared by a different route.[8] Amongst the conceivable conditions for the final deprotection, the use of HF·NEt_3 at slightly elevated temperature gave the best result. The analytical and spectral data of amphidinolide F (**1**) thus formed were in excellent agreement with those described in the literature.[4,8]

Our total synthesis of this exigent marine natural product comprises a longest linear sequence of no more than 21 steps and therefore compares favorably with the only other completed approach known in the literature.[8] A late-stage



Scheme 6. a) 2,4,6-Trichlorobenzoyl chloride, Et_3N, DMAP, toluene, 80%; b) **14**, [$Pd(PPh_3)_4$] (30 mol%), $Ph_2PO_2NBu_4$, CuTC, DMF, 56%; c) **39** (30 mol%), toluene, CH_2Cl_2, 60°C, 73%; d) PPTS (30 mol%), MeOH, CH_2Cl_2, 0°C, 87% (**36**), 95% (**35**); e) **40** (20 mol%), toluene, 100°C, 70%; f) [{$(C_2H_4)PtCl_2$}$_2$] (0.2 mol%), Et_2O, 97%; g) PPTS, benzene, 98%; h) TPAP, CH_2Cl_2, 70%; i) HF·NEt_3, Et_3N, MeCN, 40°C, 60%; CuTC = copper thiophene-2-carboxylate; DMAP = 4-dimethylaminopyridine; TPAP = tetra-*n*-propylammonium perruthenate

interplay of RCAM and π-acid catalysis nicely solved the selectivity issue arising from the unusual 1,4-dioxygenation pattern decorating the target's polyfunctional backbone.[41] The success of this strategy showcases the maturity of these methods and augurs well for future applications.

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