Natural Product Synthesis

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Total Syntheses of Amphidinolide H and G**

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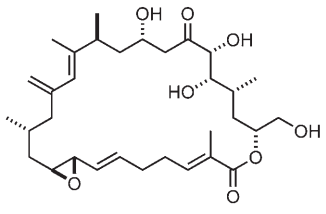
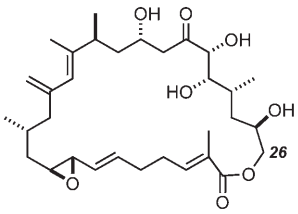
Dinoflagellates of the genus *Amphidinium* are exceptionally rich sources of bioactive secondary metabolites.[1] Generally referred to as "amphidinolides", the ensemble of complex macrolides of mixed polyketide origin derived from these microalgae has evoked considerable interest in the synthetic and bio-organic chemistry communities.[2,3] The many successes notwithstanding, some of the most potent members of the series such as amphidinolide H (**1**)[4] and all of its close relatives (**2**–**4**), remain unconquered, despite numerous attempts.[5,6]



Amphidinolide H (**1**)



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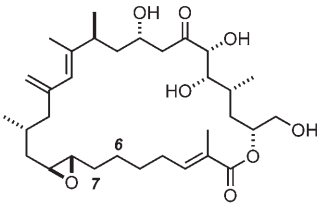
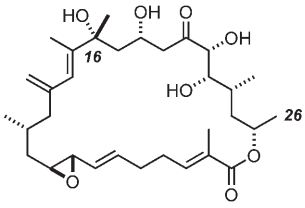


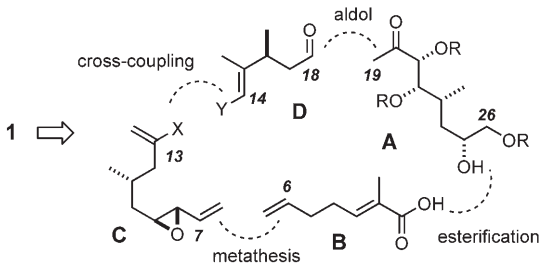
Amphidinolide H4 (**3**)



Amphidinolide B1 (**4**)

The exceptional cytotoxicity of **1** against KB human epidermoid carcinoma cells (IC_{50} value: 0.52 ng mL^{-1}) rivals that of many renowned anticancer agents. Interestingly, **1** seems to target the actin cytoskeleton, to which it forms covalent bonds through opening of the epoxide ring.[7] Herein we report the first total synthesis of this intricate macrolide which arose only after a careful orchestration of the assembly process and a scrupulous optimization of the protecting-group regime.

For the sake of convergence, **1** was dissected into four building blocks which were to be combined by esterification, an aldol reaction, metal-catalyzed cross-coupling, and olefin metathesis (Scheme 1). Although this strategy was a priori



Scheme 1. Retrosynthetic analysis of amphidinolide H (**1**).

flexible, it was by no means obvious in which order these crucial steps should be executed. While related aldol processes were successful in different model studies toward **1** and **4**,[5,6] a late-stage Stille reaction for the formation of the s-*cis*-1,3-diene subunit of **4** had previously met with failure.[6a] Since inter- as well as intramolecular metathesis reactions of vinyl epoxides are also surprisingly rare,[8] the planning for the final assembly process had to evolve with time, on the basis of the knowledge gathering underway.

These uncertainties meant it was imperative to develop routes to the required building blocks that were not only productive and scalable, but also modular, such that they could be adapted to the specific needs of the target. To this end, conversion of Roche ester **5** into enoate **6**[9] followed by reduction and Sharpless epoxidation[10] afforded **7** in high yield and optical purity (93% *de*; Scheme 2). DIBAL-H in toluene[11] cleanly opened the oxirane ring to give diol **8** by selective delivery of the hydride to the carbon atom distal to the alcohol (d.r. > 20:1); it was essential to quench the reaction with *t*BuOH at −60 °C to avoid cleavage of the primary TBS ether and hence secure good yields when working on a large scale. Routine protecting-group interconversions led to the trisilylated derivative **9**, the terminal OTES-group of which underwent a slow but effective Swern oxidation to give multigram amounts of aldehyde **10**.

This compound was used in a subsequent boron glycolate aldol reaction controlled by the reliable Evans auxiliary[12] to afford **12** with excellent *syn* selectivity (d.r. > 20:1). This

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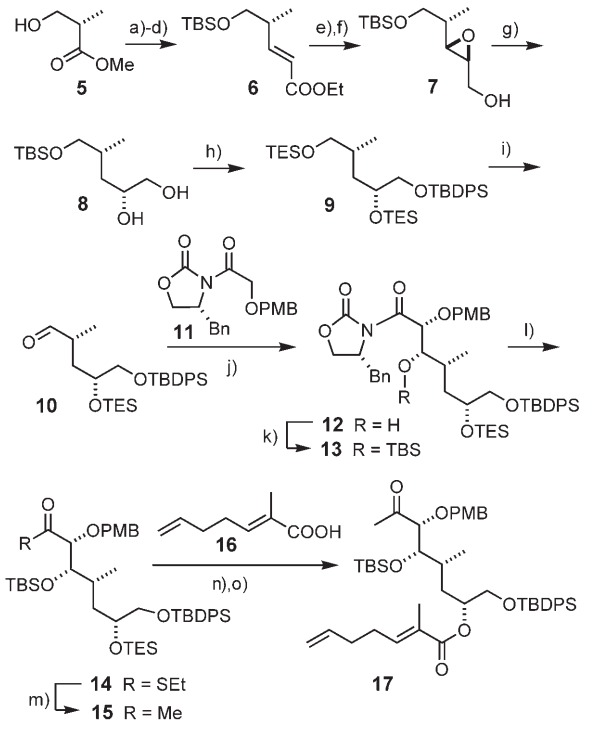
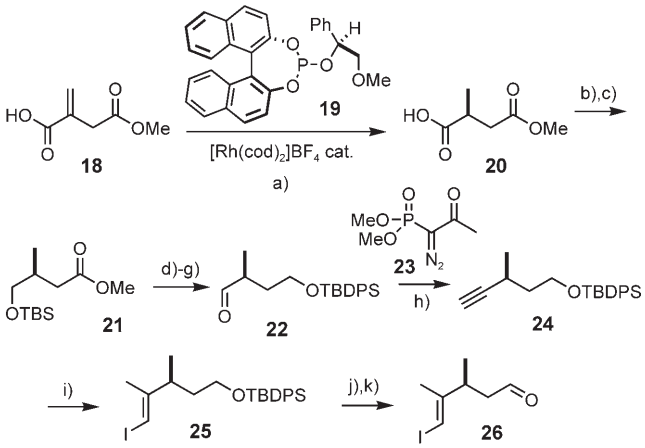
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 2. a) TBSCl, imidazole, DMF; b) DIBAL-H, CH_2Cl_2, −78 °C; c) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C→RT; d) $(iPr)_2NEt$, LiCl, $(EtO)_2P(O)CH_2COOEt$, MeCN, 69% (over 4 steps); e) DIBAL-H, CH_2Cl_2, −78 °C, 86%; f) (+)-DET, $Ti(OiPr)_4$ cat., *t*BuOOH, MS (4 Å), CH_2Cl_2, −20 °C, 68% (93% *de*); g) (1.) DIBAL-H, toluene, −40 °C; (2.) *t*BuOH quench, −60 °C→RT, 78%; h) (1.) TBDPSCl, imidazole, CH_2Cl_2, 97%; (2.) PPTS, EtOH, 55 °C; (3.) TESCl, imidazole, CH_2Cl_2, 85% (over 2 steps); i) DMSO, $(COCl)_2$, $(iPr)_2NEt$, CH_2Cl_2, −78 °C→RT, 82%; j) **11**, Bu_2BOTf, toluene, −50 °C, 82%; k) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; l) EtSH, *n*BuLi, THF, 0 °C, 61% (over 2 steps); m) CuI, MeLi (2 equiv), Et_2O, −78 °C→−10 °C, 89%; n) PPTS, EtOH, 56%; o) **16**, DCC, DMAP, CH_2Cl_2, 75%. Bn = benzyl, DCC = 1,3-dicyclohexylcarbodiimide, DET = diethyl tartrate, DIBAL-H = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, MS = molecular sieves, PMB = *para*-methoxybenzyl, PPTS = pyridinium *para*-toluenesulfonate, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, Tf = triflate.

transformation has precedence in the studies of Chakraborty and Suresh, and later Zhang and Carter,[5f,6p] who had performed related reactions toward the synthesis of amphidinolide H and B1, respectively. Compound **12** was silylated with TBSOTf and 2,6-lutidine[13] and the resulting product **13** was then converted into thioester **14**, which reacted with Me_2CuLi to give the methyl ketone **15** in high yield.[14] Significantly, this building block exhibits a fully orthogonal protecting-group pattern, which does not impose any restrictions on the final stages of the synthesis. However, the ultimately successful route to **1** relied on the early installation of the unsaturated ester, which was readily accomplished by selective cleavage of the TES moiety with PPTS followed by esterification of the released alcohol with acid **16**[15] to give **17** as a fully functional surrogate of the "south-eastern" part of **1**.

The route to building block **D** commenced with an asymmetric hydrogenation of the itaconic acid monoester **18** by using the methodology pioneered by Reetz et al. (Scheme 3).[16] Provided that the catalyst was freshly prepared from $[Rh(cod)_2]BF_4$ and monodentate phosphite **19**,[17] optically active **20** (98% *ee*) could be secured in batches of 25 g by

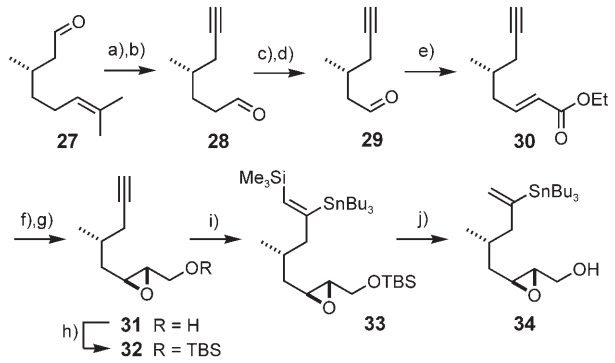


Scheme 3. a) $[Rh(cod)_2]BF_4$ (0.2 mol%), **19** (0.4 mol%), H_2 (1 atm), 1,2-dichloroethane, 95% (98% *ee*); b) BH_3·THF, THF, −10 °C→RT; c) TBSCl, imidazole, DMF, 74% (over 2 steps); d) DIBAL-H, CH_2Cl_2, −78 °C→−10 °C; e) TBDPSCl, imidazole, CH_2Cl_2, 87% (over 2 steps); f) PPTS, EtOH, 50 °C, 75%; g) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C→RT; h) **23**, NaOMe, THF, 84% (over 2 steps); i) (1.) Me_3Al, Cp_2ZrCl_2, 1,2-dichloroethane; (2.) I_2, THF, −20 °C, 71–95%; j) TBAF, THF, 80%; k) DMP, $NaHCO_3$, aq CH_2Cl_2, 0 °C→RT, 78%. cod = cycloocta-1,5-diene, Cp = cyclopentadienyl, TBAF = tetra-*n*-butylammonium fluoride, DMP = Dess–Martin periodinane.

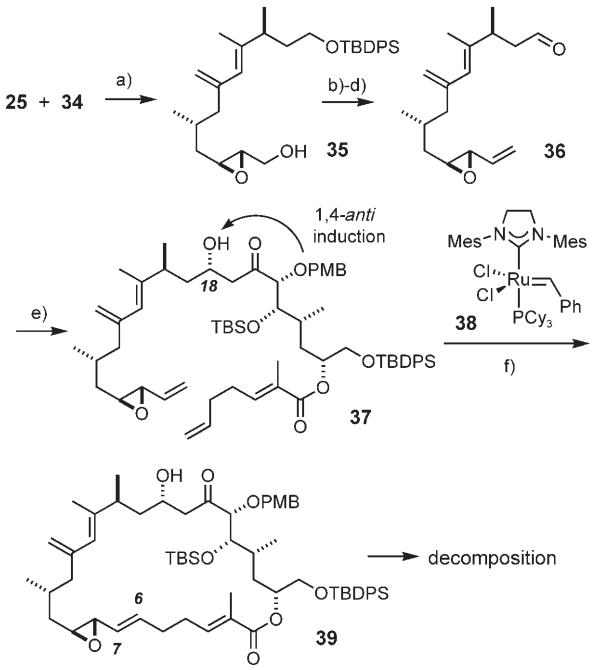
using very low catalyst loadings. Routine oxidation-state and protecting-group management afforded aldehyde **22**, which was converted into alkyne **24** with the aid of the Ohira–Bestmann reagent **23**.[18] A subsequent zirconium-induced carboalumination followed by an iodine quench readily installed the required alkenyl iodide functionality.[6f,19] The resulting product **25** was converted into the somewhat volatile aldehyde **26** as a prelude to the coupling with fragment **17** through aldol chemistry.

The only missing building block **C** was prepared from (*S*)-citronellal (**27**, > 99% *ee*) as shown in Scheme 4. Conversion of the carbonyl group into an alkyne followed by chemoselective ozonolysis of the trisubstituted olefin afforded aldehyde **28** which was transformed into its shorter homologue **29** by selective ozonolysis of the corresponding silyl enol ether; a subsequent Horner–Emmons reaction gave **30** in respectable yield over the entire sequence, even though some intermediates were highly volatile and therefore needed to be handled with care. Reduction of the ester in **30** followed by Sharpless epoxidation[10] allowed installation of the missing oxirane to afford **31** with high stereochemical control (98% *de*).

Next, we faced the problem of converting the alkyne terminus of **31** into a suitable donor that was amenable to a cross-coupling reaction with alkenyl iodides **25** or **26**. Even though the literature indicated that a Stille reaction[20] might be problematic,[6a] we were confident of accomplishing such a transformation by recourse to the powerful procedure



Scheme 4. a) **23**, NaOMe, THF; b) O_3, CH_2Cl_2, −78 °C, then Me_2S; c) TBSOTf, Et_3N, CH_2Cl_2, −20 °C; d) O_3, CH_2Cl_2, −78 °C, then Me_2S; e) $(EtO)_2P(O)CH_2COOEt$, NaH, THF, 25 % (over 5 steps, see text); f) DIBAL-H, CH_2Cl_2, −78 °C, 69 %; g) (+)-DET, $Ti(OiPr)_4$ cat., $tBuOOH$, MS (4 Å), CH_2Cl_2, −20 °C, 72 % (98 % *de*); h) TBSCl, imidazole, CH_2Cl_2, 83 %; i) $Bu_3SnSiMe_3$, $[Pd(Ph_3P)_4]$ (2 mol %), DMF, sealed tube, 79–85 %; j) TBAF, DMSO, 80 °C, 91 %.



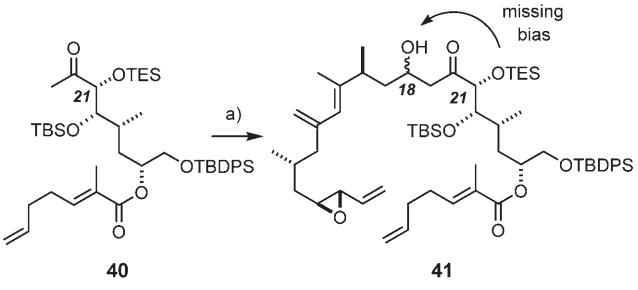
Scheme 5. a) $[Pd(Ph_3P)_4]$(10 mol %), CuTC, $Ph_2PO_2NBu_4$, DMF, 82 %; b) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C→RT; c) $[Ph_3PCH_3]Br$, $Na[N(SiMe_3)_2]$, THF, 0 °C, 65 %; c) TBAF, THF, 87 %; d) DMP, $NaHCO_3$, aq CH_2Cl_2, 0 °C→RT; 75 %; e) **17**, LDA, THF, −78 °C, 52 %; f) **38**, (10 mol %); C_6H_6, 73 %. CuTC = copper thiophene-2-carboxylate, Cy = cyclohexyl, LDA = lithium diisopropylamide, Mes = mesityl = 2,4,6-trimethylphenyl.

recently developed in our laboratory in response to a similarly challenging case.[21] To this end, tributylstannane **34** was prepared in gram quantities by a regioselective, palladium-catalyzed silylstannation of **32** with commercial $Bu_3SnSiMe_3$,[22] followed by a concomitant cleavage of the C–Si and O–Si bonds in **33** with TBAF in DMSO at 80 °C.

With all building blocks in hand, the development of a reliable assembly process became the next goal. First and foremost, the potentially challenging Stille reaction of **34** and the sterically compromised iodide **25** was tested, which gave the desired diene **35** in good yield, provided that it was performed with a combination of $[Pd(PPh_3)_4]$, CuTC, and $Ph_2PO_2NBu_4$ in DMF (Scheme 5).[21] The reaction proceeded at ambient temperature under these chloride-free conditions thus minimizing the risk of thermal decomposition of the sensitive diene product; other protocols essentially failed to afford the desired compound.[23] Compound **35** was elaborated into the fully functional "western" part of **1** by oxidation of its epoxy alcohol using Dess–Martin periodinane[24] and a Wittig olefination, followed by conversion of the terminal TBDPS ether into the corresponding aldehyde **36**. This compound was then treated with the lithium enolate derived from **17** to give aldol **37** in 52 % yield (unoptimized). The observation that **37** was produced as a single isomer is ascribed to the strong 1,4-*anti* induction exerted by the adjacent OPMB substituent.[25]

Even though only a few metathesis reactions of vinyl epoxides had previously been reported,[8,26] exposure of **37** to catalytic amounts of the Grubbs carbene complex **38**[27] in benzene at ambient temperature resulted in a remarkably clean cyclization, with formation of the 26-membered cycloalkene **39** in 73 % yield as a single isomer; its *E* configuration is evident from the large coupling constant of the olefinic protons ($^3J_{H6,H7} = 18$ Hz). Although at this stage we were seemingly only two routine operations away from **1**, insurmountable problems with the removal of the remaining protecting groups were encountered. Whereas the cleavage of the silyl ethers proceeded uneventfully with TASF in THF/DMF,[28] it was the removal of the PMB group that met with failure. We assume that an uncontrolled oxidation of the diene occurs at a competitive rate on treatment with either DDQ or ceric ammonium nitrate.[29,30] Acidic or reductive conditions for cleavage of the PMB group were equally inappropriate.

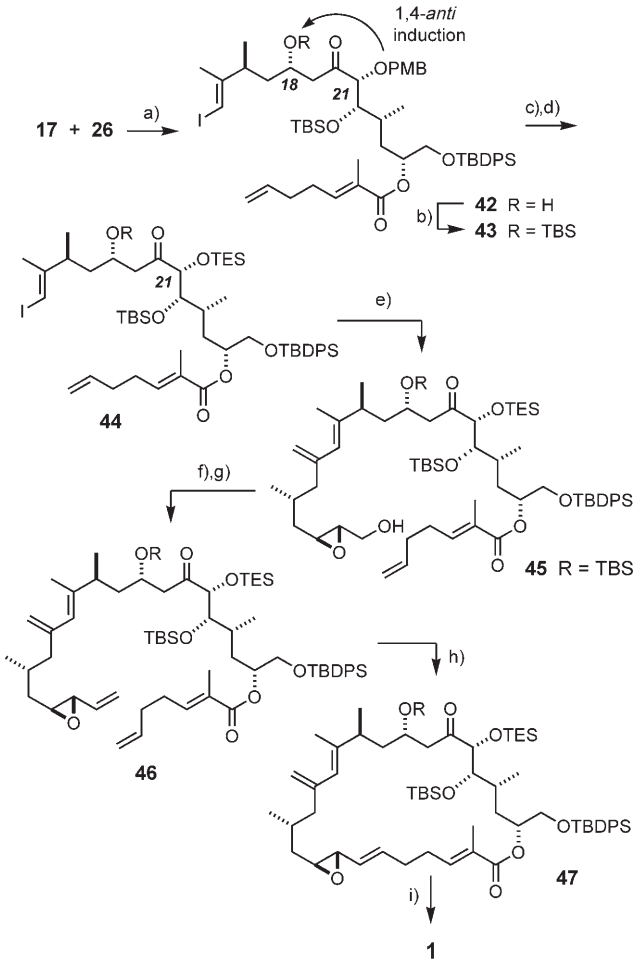
Cleavage of the PMB group of acyclic diene **37** also failed. In an attempt to rectify this situation we replaced **17** by a methyl ketone adorned with silyl only groups that could be more readily removed (Scheme 6). Based on our previous work on the total synthesis of amphidinolide Y, however, in which a similar 1,4-*anti*-selective aldol reaction had played a key role,[3b] we were apprehensive that this seemingly minor modification might have a detrimental impact on the stereochemical outcome. Alkoxy substituents at the α-position of a methyl ketone donor guide the stereodetermining addition process by chelation,[25] and a silyloxy moiety is hence unlikely to provide the same rigorous bias. In fact, the LDA-mediated reaction of the readily attainable ketone **40**[31] with aldehyde



Scheme 6. a) LDA, THF, −78 °C, then **36**, 50–60 % (d.r. ca. 2:1).

36 proceeded with poor selectivity (d.r. ca. 2:1). Since analysis of the Mosher ester showed that the major isomer had the undesired *R* configuration and separation of the diastereomers was tedious, it became clear that this revised fragment-coupling strategy was to no avail.

The necessary compromise between the beneficial influence of the PMB ether on the aldol reaction and the need to cleave this directing group prior to the installation of the 1,3-diene moiety enforced a final strategic adjustment. To this end, the Stille coupling was postponed until after the aldol step and the elaboration of the proper protecting-group regimen at the periphery (Scheme 7). Specifically, the lithium enolate of **17** was treated with the iodine-containing aldehyde **26** to give **42** in good yield and selectivity (d.r. > 10:1).[32] Masking the newly formed alcohol as the TBS ether allowed the protecting group at O-21 to be transformed from a PMB to a TES group. This critical interchange was followed by an effective cross-coupling reaction of the highly functionalized substrate **44** with stannane **34** under the previously optimized,



Scheme 7. a) LDA, THF, −78 °C, 70%; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 79–94%; c) DDQ, CH_2Cl_2/H_2O, 0 °C→RT, 55–62%; d) TESCl, imidazole, DMAP, DMF, 79%; e) **34**, $[Pd(Ph_3P)_4]$ (0.7 equiv), CuTC, $Ph_2PO_2NBu_4$, DMF, 89%; f) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C→RT; g) $[Ph_3PCH_3]Br$, $Na[N(SiMe_3)_2]$, THF, 0 °C, 65% (over 2 steps); h) **38** (10 mol%), C_6H_6, 68–72%; i) TASF, aq THF/DMF (10:1), 0 °C, 55%. TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate.

chloride-free conditions.[21] However, it was necessary to increase the catalyst loading to ensure complete conversion of these encumbered partners at ambient temperature. Yet, this result is auspicious if interpreted in light of the completely unsuccessful intramolecular Stille coupling at the exact same site en route to amphidinolide B1 (**4**) reported in the literature.[6a]

The epoxy alcohol of **45** was then converted into vinyl oxirane **46** which underwent a productive RCM reaction to give **47** as the required *E* isomer only. The sensitivity of the material meant, it was again imperative to perform this macrocyclization at ambient temperature.[33] Finally, TASF[28] was used to remove all four silyl protecting groups from the polyol sector of **47** to afford amphidinolide H (**1**), the analytical and spectroscopic properties of which were in good accord with the published data.[4] Since **1** is known to equilibrate by transesterification with amphidinolide G (**2**),[1,4] a synthesis of this ring-expanded congener has also been achieved. We found that this equilibration was best performed under slightly acidic conditions (see the Supporting Information).

To summarize, we have developed the first total synthesis of the exceptionally potent cytotoxic macrolide amphidinolide H.[34] This venture revealed the sensitivity of some of the advanced intermediates which could be mastered only after a scrupulous optimization of the key fragment coupling events and a careful adjustment of the peripheral protecting-group pattern. Most notable are the highly selective 1,4-*anti*-aldol step for the formation of the stereogenic center at C-18, the modified Stille coupling under chloride free conditions, and the application of the Grubbs catalyst in the challenging macrocyclization of a labile vinyl epoxide. As the underlying blueprint of this natural product synthesis is convergent, and hence inherently flexible, we are now in a favorable position to also prepare other members of the amphidinolide H, G, and B families. Work along these lines together with efforts to further streamline the synthesis of the parent compound **1** are underway and will be reported in due course.

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