Natural Products

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Total Syntheses of Amphidinolides B, G, and H**

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Beginning in 1986, investigations by Kobayashi and coworkers led to the isolation of a series of amphidinolide natural products which possess complex macrolide structures. These substances were found to display several interesting biological effects on tumor cell lines.[1] In particular, amphidinolides B,[2] G,[3] and H[3] (**1**–**3**; Figure 1) exhibited strong,

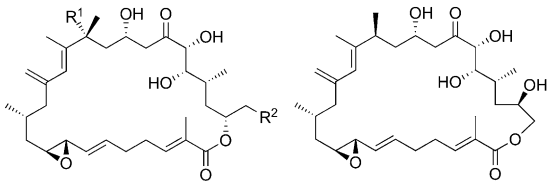
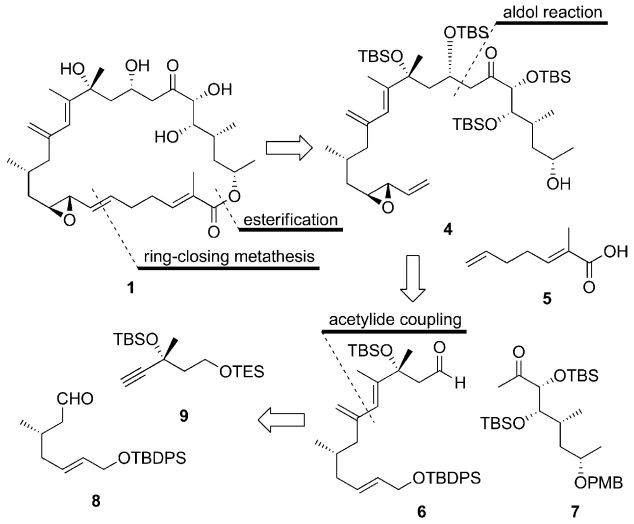


Figure 1. Structures of amphidinolides B (**1**), G (**2**), and H (**3**).

nanogram range cytotoxicity against L1210 murine lymphoma and KB human epidermoid carcinoma, and **3** was observed to stimulate actin polymerization by covalently bonding to the actin cytoskeleton.[4] From a structural perspective, the amphidinolides **1**–**3** contain 26- and 27-membered macrolide systems incorporating allylic epoxide and *s-cis*-diene moieties. Along with the presence of five hydroxy groups and nine stereogenic centers, the structural features of these substances present a considerable challenge to the development of efficient routes for their preparation, particularly from the perspective of stereochemical control and reaction conditions which address the sensitivity of key functional groups to basic conditions.

Owing to their interesting biological properties and intriguing structural motifs, the amphidinolides have attracted the attention of synthetic chemists.[5,6] Among many synthetic studies targeted at members of this family, work from Fürstner et al. in 2007 resulted in the total synthesis of amphidinolides G and H (**2** and **3**).[7] Synthesis of amphidinolide B (**1**) was successively achieved by Carter and coworkers[8] in 2008, and Fürstner et al.[9] in 2009.

In the investigation described below, we have devised and executed the total syntheses of **1**–**3** by utilizing sequences which relied on the implementation of a diene construction protocol developed in our laboratory,[5g] and a diastereoselective aldol process. The synthetic strategy used for **1** is shown in Scheme 1. We envisioned that the 26-membered macrolide in **1** would be constructed by using ring-closing



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

metathesis (RCM)[10] following condensation of the alcohol **4** with carboxylic acid **5**. In addition, the plan was to install the allylic epoxide unit at a late stage of the sequence because of its anticipated fragile nature. Moreover, the protected β-hydroxyketone moiety in **4** could be generated by condensation of the aldehyde **6** and ketone **7** with subsequent protection.

In earlier synthetic studies focusing on the amphidinolides,[5s,7] chelation-controlled, aldol processes were employed to construct fragments containing the desired C18 stereochemistry. Although approaches for stereoselective synthesis of the β-hydroxyketones in these targets that did not depend on chelation effects remained challenging, they had the advantage of avoiding the need for complicated protecting-group regimes.[11] Consequently, we decided to construct the key fragment without using chelation control in the aldol process.[12] The approach utilizes the aldehyde **6**, which would be efficiently synthesized from the aldehyde **8** and alkyne **9** by

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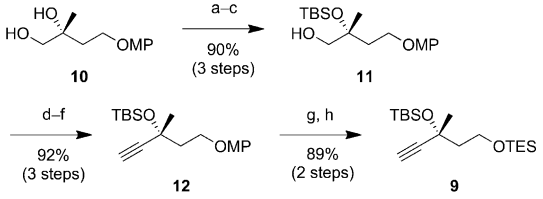
using the diene construction protocol we have previously described (Scheme 1).[5g] The viability of this convergent and flexible strategy was demonstrated by its application to syntheses of **1**–**3**.

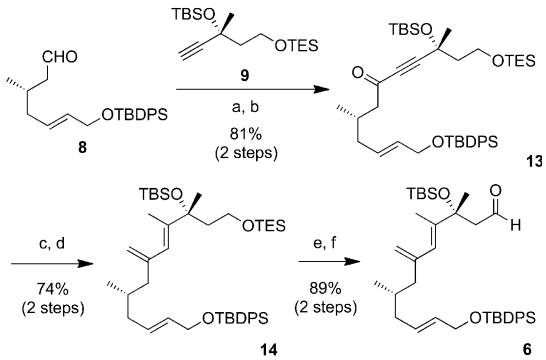
The route for the synthesis of **1** commenced with preparation of the alkyne **9** (Scheme 2). Treatment of the



Scheme 2. Synthesis of alkyne **9**. Reagents and conditions: a) PivCl, pyridine, RT, 95%; b) TBSOTf, 2,6-lutidine, RT, 98%; c) DIBAL-H, CH_2Cl_2, −78°C, 95%; d) SO_3-pyridine, DIPEA, DMSO, CH_2Cl_2, RT, 98%; e) CBr_4, PPh_3, Et_3N, toluene, RT, 98%; f) EtMgBr, THF, 0°C, 96%; g) CAN, MeCN, H_2O, RT, 94%; h) TESCl, imidazole, CH_2Cl_2, RT, 95%. CAN = cerium ammonium nitrate, DIBAL-H = diisobutylaluminum hydride, DIPEA = diisopropylethylamine, DMSO = dimethyl sulfoxide, MP = methoxyphenyl, Piv = pivaloyl, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran, Ts = *para*-toluenesulfonyl.

known diol **10**[5m] with PivCl and Et_3N, followed by protection of the resulting tertiary monoalcohol as a TBS ether, and reductive removal of the pivalate ester provided the alcohol **11**. Parikh–Doering oxidation[13] of **11** and subsequent reaction with PPh_3 and CBr_4 gave the corresponding 1,1-dibromo alkene, which was treated with EtMgBr[14] to afford the alkyne **12** in 92% yield (3 steps). Removal of the methoxyphenyl group in **12** using CAN gave the corresponding alcohol, which upon protection as a TES ether afforded the desired alkyne **9**.

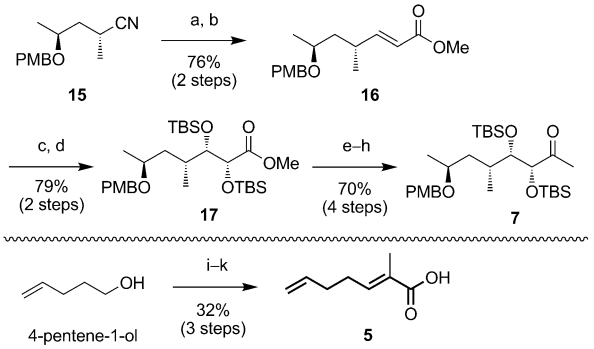
An acetylide coupling reaction between the previously prepared aldehyde **8**[6i] and **9** was employed to construct the aldehyde **6** (Scheme 3). The acetylide anion, generated by



Scheme 3. Synthesis of aldehyde **6**. Reagents and conditions: a) *n*BuLi, THF, −78→0°C, 96%; b) TPAP, NMO, M.S. 4 Å, CH_2Cl_2, RT, 84%; c) MeLi, CuI, THF, Et_2O, −78→-30°C, 90% (*E*/*Z* = 9:1); d) *n*BuLi, Ph_3PCH_3Br, THF, 0°C→RT, 91%; e) PPTS, CH_2Cl_2, MeOH, 0°C, 93%; f) DMP, CH_2Cl_2, pyridine, RT, 96%. DMP = Dess–Martin periodinane, M.S. = molecular sieves, NMO = *N*-methylmorpholine *N*-oxide, Ph = phenyl, PPTS = pyridinium *para*-toluenesulfonate, TPAP = tetrapropylammonium perruthenate.

treatment of **9** with *n*BuLi, was reacted with **8** to furnish an alcohol which was then subjected to TPAP oxidation[14] to produce the ketone **13** in 81% yield (2 steps). Treatment of **13** with the Gilman reagent led to formation of the desired *E* enone (81%, *E*/*Z* = 9:1), which was then converted into the diene **14** by Wittig olefination.[5g] Removal of the TES group in **14** and subsequent Dess–Martin oxidation[16] afforded the key intermediate **6**.

The ketone **7**, utilized in our convergent approach (Scheme 1), was prepared from the known nitrile **15**[5f] (Scheme 4). DIBAL-H reduction of the nitrile produced the



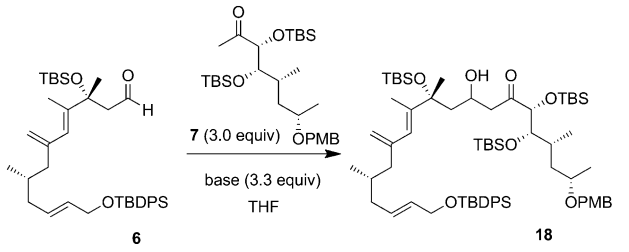
Scheme 4. Syntheses of carboxylic acid **5** and ketone **7**. Reagents and conditions: a) DIBAL-H, CH_2Cl_2, −78°C; b) Ph_3PCHCO_2Me, CH_2Cl_2, RT, 76% (2 steps); c) AD-mix-α, $MeSO_2NH_2$, *t*BuOH, H_2O, 0°C, 90%; d) TBSOTf, 2,6-lutidine, CH_2Cl_2, RT, 88%; e) DIBAL-H, CH_2Cl_2, −78°C, 91%; f) SO_3-pyridine, DIPEA, DMSO, CH_2Cl_2, RT; g) MeLi, Et_2O, −78°C; h) SO_3-pyridine, DIPEA, DMSO, CH_2Cl_2, RT, 75% (3 steps); i) PCC, CH_2Cl_2, RT; j) $Ph_3PC(CH_3)CO_2Me$, benzene, RT, 34% (2 steps); k) NaOH, THF, H_2O, 80°C, 93%. AD = asymmetric dihydroxylation, PMB = *para*-methoxybenzyl, PCC = pyridinium chlorochromate.

corresponding aldehyde, which was transformed into the unsaturated ester **16** by using a Wittig olefination. Sharpless asymmetric dihydroxylation[17] of **16** proceeded smoothly to afford the corresponding diol as a single diastereomer, which was then converted into the ester **17** (79%, 2 steps) using TBSOTf and 2,6-lutidine. The DIBAL-H reduction of **17**, followed by oxidation and addition of MeLi furnished the corresponding secondary alcohol, which was oxidatively transformed into the ketone **7**. The carboxylic acid **5**, the final component needed in the convergent approach, was prepared from 4-penten-1-ol by a PCC oxidation,[18] Wittig olefination, and hydrolysis sequence.

With the requisite fragments in hand, the key aldol reaction between **6** and **7**, which were produced in six and twelve steps, respectively, from readily available derivatives, was investigated (Table 1).[12] An initial reaction using LDA as the base afforded the desired aldol **18** in 43% yield, but the C18 stereochemistry (*R* configuration) of the resulting β-hydroxyketone was different than was expected (entry 1). In an extensive exploration, we observed that reaction at −20°C led to formation of the aldol product in a 72% yield with an optimal C18 *S*/*R* diastereomer ratio of 2.5:1 (entry 6).

The next phase involved construction of the macrocyclic lactone system in the target (Scheme 5). The aldol product (*S*)-**18** was converted into the corresponding TBS ether, from which the TBDPS group was selectively removed using

Table 1: Optimization of the reaction conditions for the aldol reaction between **6** and **7**.

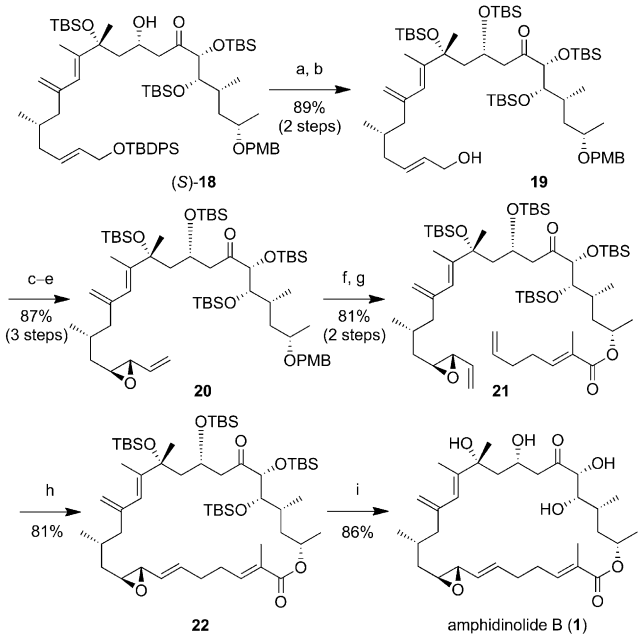


Entry	Base	T [°C][a]	Yield [%][b]	S/R[c]
1	LDA	−78	43	1:5.4
2	NaHMDS	−78	–[d]	–[d]
3	KHMDS	−78	–[d]	–[d]
4	LiHMDS	−78	81	1:4.1
5	LiHMDS	−40	63	1.3:1
6	LiHMDS	−20	72	2.5:1

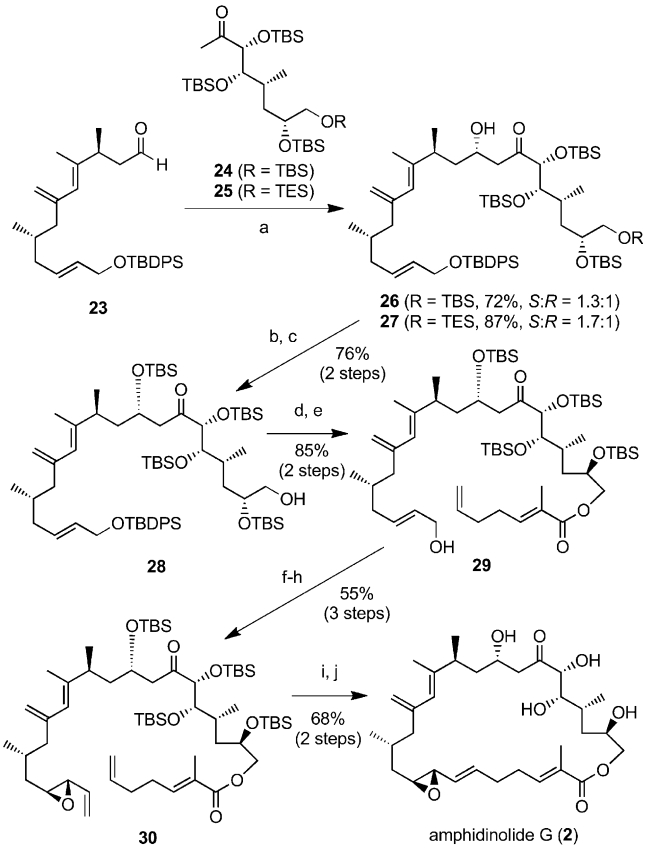
[a] Aldehyde **6** was added to a solution of the enolate of ketone **7** in THF at the indicated temperature. The enolate was obtained by treatment of **7** with a base at room temperature. [b] Combined yield of (*S*)-**18** and (*R*)-**18**. [c] The ratio was determined by ^{1}H NMR spectroscopy. [d] No reaction. KHMDS = potassium hexamethyldisilazide, LDA = lithium diisopropyl amide, LiHMDS = lithium hexamethyldisilazide, NaHMDS = sodium hexamethyldisilazide.

TBAF/AcOH/H_2O in THF and DMF.[19] This process generated the alcohol **19**, which was then subjected to Sharpless asymmetric epoxidation[20] to afford the corresponding epoxy alcohol as a single diastereomer. A Dess–Martin oxidation and Wittig olefination sequence efficiently provided the allylic epoxide **20** which was subjected to selective removal of the PMB group. Yamaguchi esterification[21] of the resulting alcohol with **5** gave the ester **21** in 81% yield (2 steps). RCM utilizing Grubbs' second-generation catalyst[22] transformed **21** into the target 26-membered **22** (81%) without producing the undesired *Z* isomer. Finally, cleavage of the TBS group in **22** produced **1**, which was determined to be identical in all respects (^{1}H NMR and ^{13}C NMR spectroscopy, IR, optical rotation, and mass spectrometry)[2b] to the natural product.

Our attention then turned to the synthesis of amphidinolides G (**2**) and H (**3**). In an initial effort, we observed that the intermediate **26** could be generated by an aldol reaction between the aldehyde **23** and ketone **24**[6i] (Scheme 6). However, an ensuing investigation revealed that the aldol product **27** could be produced in a higher yield and



Scheme 5. Total synthesis of amphidinolide B (**1**). Reagents and conditions: a) TBSOTf, 2,6-lutidine, CH_2Cl_2, RT, 98%; (b) TBAF, AcOH, H_2O, DMF, THF, RT, 79% (89% conv.); c) Ti(O*i*Pr)$_4$, TBHP, (+)-DIPT, M.S. 4 Å, CH_2Cl_2, −20 °C, 84% (92% conv.); d) DMP, pyridine, 0 °C, 97%; e) NaHMDS, Ph_3PCH_3Br, CH_2Cl_2, 0 °C→RT, 98%; f) DDQ, CH_2Cl_2, phosphate buffer (pH 7.0), RT, 83%; g) **5**, 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N, 0 °C, 98%; h) Grubbs' 2nd generation catalyst, benzene, RT, 81%. i) TASF, THF, DMF, H_2O, RT, 86%. DDQ = 2,3-dichloro-5,6-dicyano-p-benzoquinone, DIPT = diisopropyl tartrate, DMAP = *N*,*N*-dimethyl-4-aminopyridine, DMF = *N*,*N*-dimethylformamide, TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate, TBAF = tetra-*n*-butylammonium fluoride, TBHP = *tert*-butyl hydroperoxide.



Scheme 6. Total synthesis of amphidinolide G (**2**). Reagents and conditions: a) **25**, LiHMDS, THF, −10 °C, 87% (*S*/*R* = 1.7:1); b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −10 °C, 98%; c) PPTS, CH_2Cl_2, MeOH, 0 °C, 78%; d) **5**, 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N, RT, 98%; e) TBAF, AcOH, H_2O, DMF, THF, RT, 82% (87% conv.); f) Ti(O*i*Pr)$_4$, TBHP, (+)-DET, M.S. 4 Å, CH_2Cl_2, −20 °C, 54% (75% conv.); g) DMP, pyridine, 0 °C, 91%; h) NaHMDS, Ph_3PCH_3Br, CH_2Cl_2, 0 °C, 80%; i) Grubbs' 2nd generation catalyst, benzene, RT, 95%. j) TASF, THF, DMF, H_2O, RT, 72%. DET = diethyl tartrate.

stereoselectively when the TES-protected ketone **25** was employed as the coupling partner. After protection of **27** as a TBS ether, selective deprotection with PPTS afforded the alcohol **28**. Esterification of **28** with **5** by using the Yamaguchi protocol took place smoothly to give nearly quantitatively the corresponding ester, which was treated with TBAF/AcOH/H_2O to afford the alcohol **29**. Essentially the same synthetic procedure used to transform **21** into **1** was used for the allylic epoxide **30** to afford **2**, which was shown to have spectroscopic properties that were identical to those of the natural product. Because the transformation from **2** into **3** under mildly basic conditions has been reported by Kobayashi and co-workers,[3b] the successful synthesis of **2** corresponds to a formal synthesis of **3**.

The investigation described above has resulted in the syntheses of the amphidinolides B (**1**; 6.9% overall yield in 21 steps), G (**2**; 3.2% overall yield in 23 steps) and H (**3**) based on routes that employ a previously developed diene construction protocol and a diastereoselective aldol reaction in the key steps. Notable features of the strategy are its high degrees of flexibility and convergency, both of which should make it applicable to the preparation of a broad range of other amphidinolides and related substances. Additional studies of approaches to the syntheses of amphidinolide congeners will be reported in due course.

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[10] The macrolactone ring was constructed by the same RCM approach as those used by Fürstner et al. (Ref. [7, 9]).

[11] The O-PMB (Refs. [5r] and [7]) and O-MOM (Refs. [6g and h]) substituents at C21 are known to induce the formation of diastereomers, having the *S* configuration at C18, as a result of a strong 1,4-*anti* chelation effect. However, removal of these groups at the final stage of the synthesis employing standard reaction conditions was found to be troublesome owing to the labile character of the *s-cis* diene and allylic epoxide moieties.

[12] Although Carter and co-workers described the same nonchelation and temperature control strategy (Ref. [8]), our substrates **6** and **7** provided effective results to construct C18 with an *S* configuration.

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