Total Synthesis

DOI: 10.1002/ange.200701640

What is Amphidinolide V? Report on a Likely Conquest**

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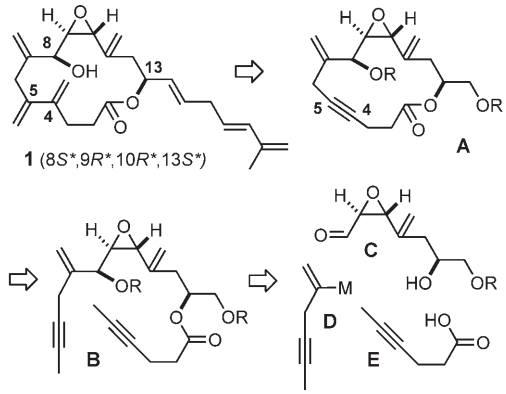
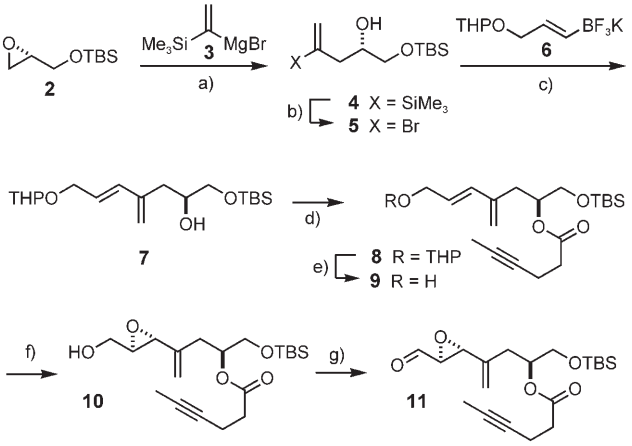
More than 30 macrolides have been isolated to date from laboratory-cultured dinoflagellates of the *Amphidinium* sp.[1] Despite their common origin and a uniformly high cytotoxicity against various cancer cell lines, the individual "amphidinolides" are structurally quite diverse and have therefore inspired many synthetic approaches toward them.[2,3] One of the rarest members of this series is amphidinolide V (0.00005% of the wet weight of the harvested algae), for which structure **1** (Scheme 1) was proposed on the basis of the spectroscopic data of a sample of no more than 0.2 mg.[4]



Scheme 1. Proposed structure and retrosynthetic analysis of amphidinolide V.

As part of our ongoing program on bioactive natural products of marine origin,[5] amphidinolide V was chosen as a target for further evaluation. To this end, a flexible entry was sought that would provide meaningful amounts of this scarce metabolite for testing, and allow for systematic modification of its molecular edifice at a later stage. It was envisaged that the distinctive s-*trans* diene unit of **1**, spanned by the vicinal *exo*-methylene branches at C-4 and C-5, would provide a unique opportunity in this regard. If formed by a sequence of ring-closing alkyne metathesis (RCAM)[6] and subsequent intermolecular enyne metathesis of the resulting cycloalkyne **A** with ethylene,[7] the overall assembly process should gain substantial flexibility (Scheme 1). At the outset, however, it was by no means clear if the available alkyne metathesis catalysts tolerate the labile *trans*-configured vinylepoxide and the allylic alcohol residing in the cyclization precursor **B**, while serious selectivity issues might plague the late-stage enyne metathesis event proposed to complete the polyunsaturated framework.

The synthetic venture commenced with a copper-catalyzed opening of epoxide **2** with the Grignard reagent **3**, followed by the addition of bromine for silyl exchange to afford product **5** in excellent yield on a large scale (Scheme 2).



Scheme 2. a) CuCN (10%), THF, 0°C→RT, 99%; b) 1. Br_2, CH_2Cl_2, −78°C; 2. NaOMe, MeOH, −20°C; 3. HOAc, 91% (overall); c) **6**, $Pd(OAc)_2$ (10%), dppf (10%), *t*$BuNH_2$, THF, reflux (sealed tube), 84%; d) 4-hexynoic acid, EDC, 1-hydroxy-7-azabenzotriazole, $(iPr)_2NEt$, DMAP, CH_2Cl_2/DMF (4:1), 95%; e) PPTS (cat.), *i*PrOH, 70°C, 98%; f) D-(−)-DET (40%), $Ti(OiPr)_4$ (40%), *t*BuOOH, MS (4 Å), CH_2Cl_2, −25°C, 77%; g) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 90%. dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, EDC = *N*-(3-dimethylaminopropyl)-*N*′-ethyl-carbodiimide, DMAP = 4-dimethylaminopyridine, PPTS = pyridinium *p*-toluenesulfonate, DET = diethyl tartrate, TBS = *tert*-butyldimethylsilyl, THP = tetrahydropyranyl, MS = molecular sieves.

This compound was subjected to a Suzuki reaction with trifluoroborate **6**.[8] In contrast to the recommended protocol that emphasizes the importance of aqueous media for reactions of alkenyl trifluoroborates as Suzuki donors,[9] this particular cross-coupling reaction would not proceed well unless performed in anhydrous THF with *t*$BuNH_2$ as the base. Under these modified conditions, however, a yield of 84% was secured in batches that produced up to 10 g of the desired diene **7**. Esterification with 4-hexynoic acid, unmasking of the allylic alcohol terminus, and Sharpless epoxidation[10] with D-(−)-DET furnished alcohol **10**, which was oxidized under

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[**] Generous financial support from the MPG and the Fonds der Chemischen Industrie (Kekulé fellowship to S.F.) is gratefully acknowledged. We thank Prof. J.-I. Kobayashi for an exchange of information.

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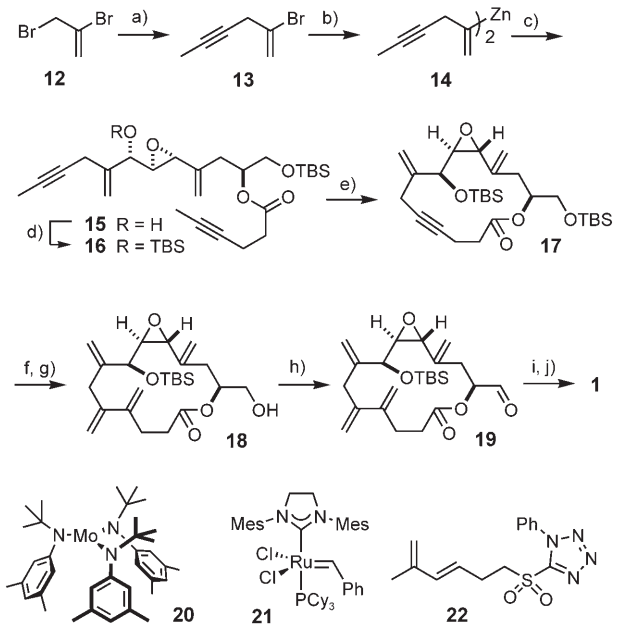
buffered conditions to give epoxy-aldehyde **11** in high overall yield.

Initial attempts to subject this labile aldehyde to chelation-controlled additions of various organometallic reagents derived from bromide **13** were unrewarding. Gratifyingly though, it was found that **13** reacts with $ZnBr_2$ and Li sand under ultrasonication to produce the bis(alkenyl)zinc reagent **14**.[11] Slow addition of aldehyde **11** to a salt-free solution of **14** in toluene in the presence of (+)-*N*-methylephedrine furnished alcohol **15** in good yield and appreciable diastereoselectivity (up to 7:1) in favor of the desired *syn* adduct (Scheme 3). Subsequent O-silylation provided diyne **16** as the substrate for the envisaged ring closure by RCAM.



Scheme 3. a) MeC≡CMgBr, $CuBr{\cdot}Me_2S$, Et_2O, 99%; b) Li, $ZnBr_2$, THF, 0°C, ultrasound; c) **11**, toluene, (+)-*N*-methylephedrine (60%), −25°C, 69%; d) TBSCl, imidazole, CH_2Cl_2, 10°C, 79%; e) **20** (20%), CH_2Cl_2/toluene, 85°C, 66%; f) **21** (2%), C_2H_4 (1.8 atm), toluene, 45°C, 90%; g) PPTS (cat.), MeOH, 62%; h) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2; i) **22**, KHMDS, DME/DMPU, −78°C→RT, 57% (over both steps, $E{:}Z \approx 10{:}1$); j) TASF, DMF, −5°C, 82%; KHMDS = potassium hexamethyldisilazide; TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate, Mes = mesityl = 2,4,6-trimethylphenyl.

This transformation proceeded nicely, even though the resulting product is fairly strained, thus attesting to the excellent application profile of the molybdenum-based catalyst formed in situ upon activation of complex **20** with CH_2Cl_2 as previously described by our research group.[12] Equally gratifying was the outcome of the subsequent enyne metathesis between cycloalkyne **17** thus formed and ethylene gas,[7] which installed the vicinal one-carbon branches characteristic of amphidinolide V without any appreciable interference from the preexisting double bonds. Attachment of the lateral chain involved a routine protecting-group and oxidation-state management as well as a Julia–Kocienski olefination[13] with sulfone **22**,[8] which was best performed with KHMDS as the base in DME/DMPU (50:1); this particular medium led to substantially higher E/Z ratios (ca. 10:1) than were observed in THF (ca. 3:1). The isomers were readily separable, thus securing a good supply of **1** in pure form (Table 1).

Table 1: Reference data set of compound **1**.

$[\alpha]_D^{20} = -9.3\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($CHCl_3$, $c = 0.6\ g\,cm^{-3}$); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 1.83$ (3H, s), 2.12 (1H, d, $J = 5.4$ Hz, OH), 2.39–2.41 (2H, m), 2.43–2.47 (2H, m), 2.50–2.67 (1H, m), 2.70–2.77 (1H, m), 2.79–2.82 (1H, m), 2.82–2.85 (2H, m), 3.11 (1H, d, $J = 16.4$ Hz), 3.25 (1H, d, $J = 16.4$ Hz), 3.46 (1H, brs), 4.00 (1H, dd, $J = 5.4$, 5.8 Hz), 4.89 (2H, s), 4.93 (1H, s), 5.08 (1H, s), 5.10 (1H, s), 5.13 (1H, s), 5.16 (1H, s), 5.19 (1H, s), 5.24 (1H, s), 5.40–5.43 (1H, m), 5.43–5.45 (1H, m), 5.46 (1H, s), 5.60 (1H, dt, $J = 6.7$, 15.6 Hz), 5.67–5.77 (1H, m), 6.12 ppm (1H, d, $J = 15.6$ Hz); ^{1}H NMR (C_6D_6, 400 MHz): $\delta = 1.73$ (3H, s), 1.93 (1H, brs, -OH), 2.01 (1H, ddd, $J = 4.0$, 5.6, 14.4 Hz), 2.08–2.18 (2H, m), 2.24 (1H, dd, $J = 2.6$, 14.1 Hz), 2.34 (1H, dt, $J = 4.2$, 14.1 Hz), 2.52 (1H, ddd, $J = 4.0$, 12.1, 14.1 Hz), 2.64 (2H, t, $J = 6.5$ Hz), 2.77 (1H, dd, $J = 6.5$, 2.1 Hz), 2.86 (1H, d, $J = 16.1$ Hz), 3.01 (1H, $J = 16.1$ Hz), 3.50 (1H, brs), 3.93 (1H, brs), 4.71 (1H, s), 4.89 (2H, brs), 4.92 (2H, s), 4.95 (1H, s), 4.98 (1H, s), 5.04 (1H, s), 5.28 (1H, s), 5.42 (1H, dd, $J = 6.6$, 15.4 Hz), 5.52 (1H, dt, $J = 6.6$, 15.6 Hz), 5.53–5.59 (1H, m), 5.62 (1H, s), 5.69 (1H, dt, $J = 6.6$, 15.4 Hz), 6.15 ppm (1H, d, $J = 15.6$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 18.6$, 30.5, 33.7, 35.1, 39.1, 39.2, 58.0, 63.3, 71.4, 74.3, 114.0, 114.8, 114.9, 115.1, 115.1, 127.5, 128.1, 132.0, 134.1, 140.8, 141.9, 142.1, 144.6, 145.0, 171.9 ppm; IR (NaCl): $\tilde{\nu} = 3476$, 3082, 2923, 2856, 1735, 1670, 1639, 1608, 1453, 1374, 1262, 1239, 1156, 1089, 969, 901, 679 cm^{-1}; MS (ESI+): 419.3 $[M+Na]^+$; HRMS (ESI+) calcd for $[M+Na]^+$: 419.2193, found: 419.2192.

As can be seen from Table 2, all the ^{1}H NMR data of synthetic **1** recorded in [D_6]benzene are in excellent agreement with the reported spectra of the natural product;

Table 2: Deviation of selected NMR shifts of synthetic **1** and isomers from the values reported for amphidinolide V.[a]

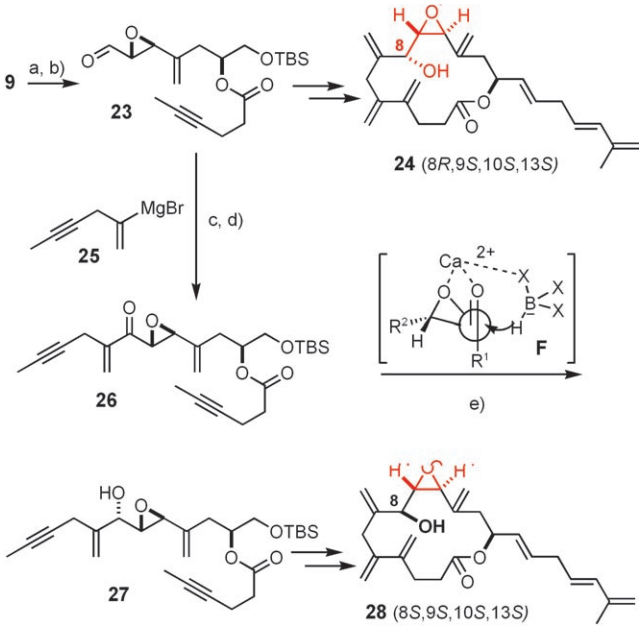
	$\Delta\delta_H$		$\Delta\delta_C$		$\Delta\delta_C$	
No.	**1**[b]	**1**[c]	**1**[b]	**24**[b]	**28**[b]	**30**[b]
2	0.00	−0.04	0.2	0.8	0.6	3.0
4	—	—	0.1	2.0	1.5	−0.3
8	**−0.50**	−0.04	0.3	5.1	−0.7	0.7
9	0.00	−0.05	0.0	−3.4	−5.4	−0.9
10	0.00	−0.05	0.2	2.0	−1.3	−2.1
12	0.00	−0.05	0.1	−5.7	−7.2	−3.8
14	0.00	−0.05	0.4	1.1	1.3	2.0

[a] For the full data set, see the Supporting Information. [b] $CDCl_3$. [c] C_6D_6; $\Delta\delta = \delta$(synthetic isomer) − δ(natural product).[4]

likewise, the ^{13}C NMR data recorded in $CDCl_3$ are also in good accord.[4,8] Surprisingly, however, a single resonance in the ^{1}H NMR spectrum recorded in $CDCl_3$, assigned to H-8, is displaced by $\delta = 0.50$ ppm (!), whereas all the other shifts and coupling constants show an almost perfect match in this particular medium. Unfortunately, we were unable to resolve this rather suspicious singular discrepancy at this point because neither an authentic sample nor the original spectra of amphidinolide V could be made available to us.

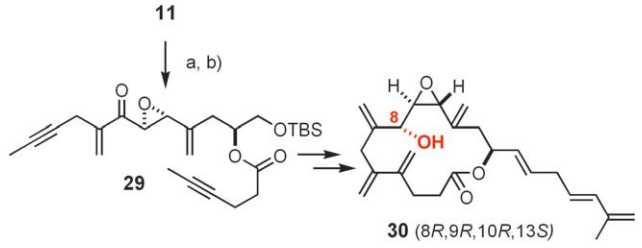
Therefore, it was necessary to obtain a more comprehensive data set for further comparison, which required prepa-

ration of all other conceivable diastereomers that incorporate a *trans*-epoxide entity but differ in the configuration of the individual tetrahedral centers.[14] To this end, it sufficed to replace D-(−)-DET by L-(+)-DET in the Sharpless epoxidation of alcohol **9**, and to pursue an analogous assembly process from there on to obtain isomer **24** (Scheme 4).[8]



Scheme 4. a) L-(+)-DET (40%), $Ti(OiPr)_4$ (40%), *t*BuOOH, MS (4 Å), CH_2Cl_2, −20°C, 92%; b) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2; c) Grignard reagent **25**, THF, −15°C, 86%; d) Dess–Martin periodinane, CH_2Cl_2; e) $NaBH_4$, $CaCl_2$, MeOH, 0°C, 71% (over 2 steps, d.r. = 11:1); for further details, see the Supporting Information.

Access to isomer **28** containing an *anti*-configured hydroxy-epoxide unit was gained by a chelation-controlled reduction of ketone **26**. The combination of $NaBH_4$ and $CaCl_2$ served well for this purpose,[15] which is thought to lock a transition state of type **F** without damaging the fragile epoxide unit. The completion of the synthesis then followed the blueprint outlined above for the diastereomeric series.[8] Chelate-controlled reduction of the diastereomeric epoxyketone **29** gave access to the last isomer **30** (Scheme 5); this latter compound turned out to be much less stable than its congeners, and readily decomposed even when kept cold. It



Scheme 5. a) Grignard reagent **25**, THF, −15°C, 70%; b) Dess–Martin periodinane, CH_2Cl_2; 97%; for further details, see the Supporting Information.

is important to note, however, that the RCAM reactions (66–93%) and the ensuing enyne metatheses (73–96%) were highly efficient for all isomers prepared during this venture.[8]

The spectral characteristics of **24**, **28**, as well as **30** showed a clear mismatch with the published data and hence none of them represents the actual target (Table 2). Therefore, we must conclude that the constitution and relative stereochemistry of amphidinolide V is most likely represented by structure **1**, as originally proposed.[4] Whether the conspicuous mismatch of a single resonance in only one of the two reported ^1H NMR spectra is due to a typographical error in the original data set can only be clarified after re-isolation of the natural product from the producing *Amphidinium* strain, which is beyond our possibility.

Received: April 13, 2007
Published online: June 20, 2007

Keywords: alkynes · macrolides · metathesis · natural products · structure elucidation

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[14] Not considered were isomers with different double-bond geometries as well as isomers containing a *cis*-epoxide unit. The presence of the latter was ruled out on the basis of the $^{3}J_{H9,H10}$ coupling constant of 2.2 Hz reported for natural amphidinolide V, which is characteristic of a *trans*-epoxide, see Ref. [4]. This assignment was corroborated by the NMR data of the synthetic *trans* epoxides prepared during this investigation, the corresponding coupling constants of which were invariably about 2 Hz.

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