Natural Products Synthesis

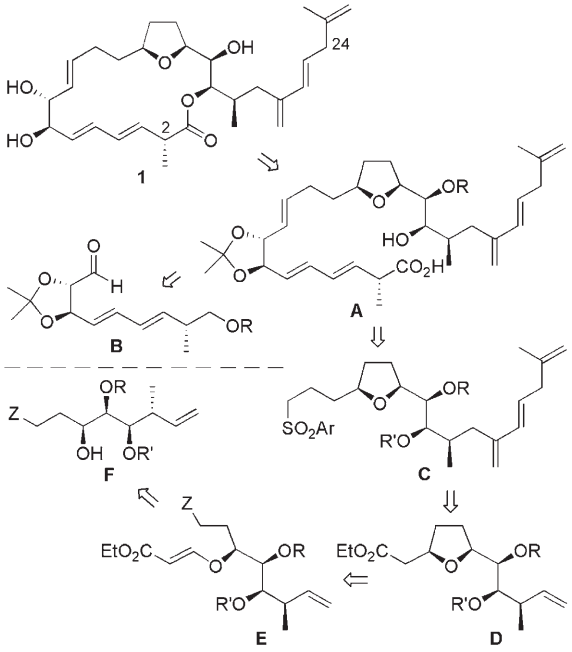
DOI: 10.1002/ange.200603363

Total Synthesis of (−)-Amphidinolide E**

*Chan Hyuk Kim, Hyo Jung An, Won Kyo Shin, Wei Yu, Sang Kook Woo, Soon Kyu Jung, and Eun Lee**

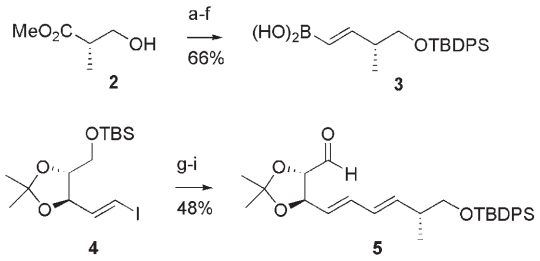
Amphidinolide E (**1**) is a unique 18-membered macrolide isolated from the Y-5′ strain of the dinoflagellate *Amphidinium* sp.[1] It exhibits cytotoxic activity against L1210 (IC_{50} = 2.0 μg mL^{-1}) and L5178Y (IC_{50} = 4.8 μg mL^{-1}) murine leukemia cells in vitro. Owing to its unique structural features and limited availability, amphidinolide E (**1**) has been the target of intense synthetic studies.[2] We report herein the results of our recent efforts towards the total synthesis of **1**.

According to our retrosynthetic analysis, **1** could be synthesized by lactonization of the *seco* acid **A**, which we intended to prepare by the Julia coupling of fragments **B** and **C**. In this way, potential problems arising from the intrinsic lability at C2 of **1** would only be faced at the end of the synthetic sequence. We also decided to introduce the triene side chain relatively early in the synthesis, thus forestalling difficulties which might arise from manipulations of the unstable macrolide intermediates. Fragment **B** may be obtained from the known tartrate acetonide precursors, and fragment **C** may be prepared from fragment **D**. Fragment **D** may in turn be obtained by radical cyclization of the β-alkoxy acrylate derivative **E**, which should be accessible from fragment **F** (Scheme 1).



Scheme 1. Retrosynthetic analysis of **1**.

For the synthesis of fragment **B**, methyl (*S*)-3-hydroxy-2-methylpropanoate (**2**; commercially available) was converted into the corresponding TBDPS ether, from which vinyl boronic acid **3** was obtained through reduction, oxidation, Corey–Fuchs homologation,[3] and hydroboration–hydrolysis.[4] Suzuki coupling[5] of **3** with the known vinyl iodide **4**[6] proceeded smoothly, and the resulting diene was transformed into aldehyde **5** by removal of the TBS protecting group and oxidation (Scheme 2).



Scheme 2. Preparation of fragment **B**: a) TBDPSCl, imidazole, CH_2Cl_2, 0 °C→RT; b) $LiBH_4$, Et_2O; c) SO_3·pyridine, Et_3N, DMSO/CH_2Cl_2 (1:1), 0 °C→RT; d) CBr_4, Ph_3P, Zn, CH_2Cl_2, 0 °C→RT; e) *n*BuLi, THF, −78 °C; f) $BHBr_2$·SMe_2, CH_2Cl_2, 0 °C→RT; H_2O/Et_2O (1:3), 0 °C→RT; g) **3**, $[Pd(PPh_3)_4]$, TlOEt, THF/H_2O (4:1); h) PPTS, EtOH; i) SO_3·pyridine, Et_3N, DMSO/CH_2Cl_2 (1:1), 0 °C→RT. DMSO = dimethyl sulfoxide, PPTS = pyridinium *p*-toluenesulfonate, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl.

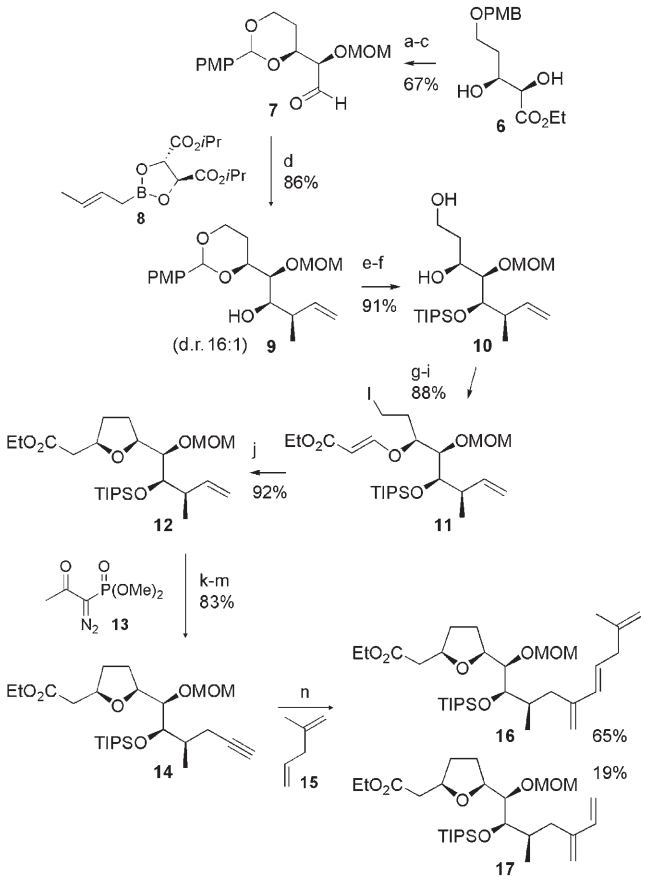
The known diol **6**[7] served as the starting material in the synthesis of fragment **C**. DDQ oxidation of **6** provided the corresponding PMP cyclic acetal, which was converted into aldehyde **7** by MOM protection of the remaining hydroxy group and reduction with DIBAL. Roush crotylation[8] of **7** by treatment with boronate **8** provided a product mixture that contained mainly the desired homoallylic alcohol **9** (d.r. 16:1). TIPS protection of **9** and oxidative deprotection of the acetal with CAN produced diol **10**. Selective tosylation of the primary hydroxy group in **10**, treatment with ethyl propiolate, and substitution of the tosylate group with iodide led to the β-alkoxy acrylate **11**. Radical cyclization[9] of **11** proceeded smoothly in the presence of tris(trimethylsilyl)silane and triethylborane, and the oxolane product **12** was obtained in high yield (Scheme 3).

Hydroboration–oxidation of alkene **12** produced the corresponding primary alcohol, which was converted into the corresponding aldehyde. At this point, a variety of methods were tested to find an effective way to build up the

[*] C. H. Kim, H. J. An, W. K. Shin, W. Yu, S. K. Woo, S. K. Jung, Prof. E. Lee
Department of Chemistry
College of Natural Sciences
Seoul National University
Seoul 151-747 (Korea)
Fax: (+82) 2-889-1568
E-mail: eunlee@snu.ac.kr

[**] This work was supported by a grant from MarineBio21, Ministry of Maritime Affairs and Fisheries, Korea and a grant from the Center for Bioactive Molecular Hybrids (Yonsei University and KOSEF). BK21 graduate fellowship grants to C. H. Kim, H. J. An, W. Yu, and S. K. Jung and Seoul Science Fellowship grants to C. H. Kim are gratefully acknowledged.

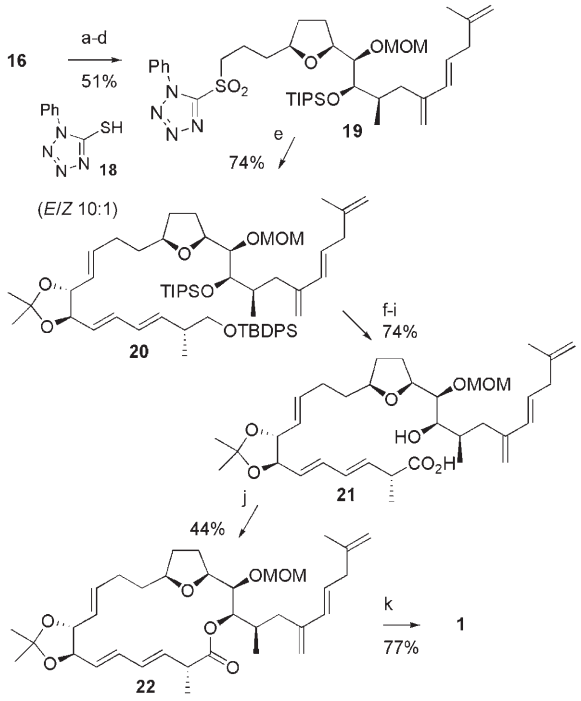
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 3. Preparation of fragment **C**: a) DDQ, 3-Å MS, CH_2Cl_2, 0 °C; b) MOMCl, DIPEA, DMAP, CH_2Cl_2, reflux; c) DIBAL, CH_2Cl_2, −78 °C; d) **8**, 4-Å MS, toluene, −78 °C; e) TIPSOTf, collidine, CH_2Cl_2; f) CAN, $MeCN/H_2O$ (9:1), 0 °C; g) TsCl, Et_3N, CH_2Cl_2, 0 °C; h) $CHCCO_2Et$, NMM, CH_2Cl_2; i) NaI, acetone, reflux; j) $(TMS)_3SiH$, Et_3B, toluene, −20 °C; k) $(Sia)_2BH$, THF, 0 °C; $NaBO_3 \cdot 4H_2O$, H_2O; l) Dess–Martin periodinane, pyridine, CH_2Cl_2, 0 °C→RT; m) **13**, Cs_2CO_3, EtOH, 0 °C→RT; n) CH_2CH_2, $[(H_2IMes_2)RuCl_2(P(c\text{-}Hex)_3)]$, CH_2Cl_2; **15**, sealed tube, 40 °C. CAN = ceric ammonium nitrate, DIBAL = diisobutylaluminum hydride, DIPEA = *N*,*N*-diisopropylethylamine, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMAP = 4-dimethylaminopyridine, Mes = mesityl, MOM = methoxymethyl, NMM = *N*-methylmorpholine, PMB = *p*-methoxybenzyl, PMP = *p*-methoxyphenyl, Sia = siamyl, TIPS = triisopropylsilyl, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl, Ts = *p*-toluenesulfonyl.

side chain. For example, a Nozaki–Hiyama–Kishi reaction[10] of the aldehyde with 1-iodo-4-methyl-1,4-pentadiene[11] proceeded efficiently to yield a mixture of allylic alcohols, which was eventually converted into the desired triene **16** by oxidation and Wittig olefination. Alternatively, the alkyne **14** was obtained from the aldehyde by treatment with diazophosphonate **13**.[12] Alkyne **14** was first treated with ethylene in the presence of the second-generation Grubbs catalyst,[13] and the crude product was treated with 2-methyl-1,4-pentadiene (**15**; commercially available). In this way, the desired triene **16** was obtained in 65% yield accompanied by diene **17** in 19% yield. Subjection of the isolated sample of diene **17** to the same reaction conditions provided an additional amount of triene **16** (10%).

DIBAL reduction of **16** produced the corresponding aldehyde, which was transformed into the homologous aldehyde by Wittig methoxymethylidenation and hydrolysis. Further reduction with $NaBH_4$, Mitsunobu-type substitution of the primary hydroxy group with thiol **18**, and selective oxidation led to sulfone **19**. Conditions for the Kocienski–Julia reaction[14] between sulfone **19** and aldehyde **5** were then investigated; the best result was obtained when the lithio derivative of sulfone **19** prepared in THF was treated with aldehyde **5** in DMF/DMPU (3:1) at −78 °C. In this way, a product mixture in which the major isomer was the desired *E* alkene **20** was obtained in 74% yield (*E*/*Z* 10:1). The selective removal of the TBDPS group in **20** was possible under alkaline conditions, but the oxidative conversion of the primary hydroxy group into a carboxylic acid group proved painfully difficult; for example, Dess–Martin oxidation resulted in a scrambling of the NMR spectroscopic signals from the side-chain region. Eventually, it was found that treatment of the primary alcohol with IBX[15] provided the corresponding aldehyde cleanly. The aldehyde was then converted into the hydroxy carboxylic acid **21** by oxidation with sodium chlorite and removal of the TIPS protecting group (Scheme 4).



Scheme 4. Synthesis of amphidinolide E (**1**): a) DIBAL, THF, −78 °C; b) $(Ph_3P^+CH_2OMe)Cl^-$, *t*BuOK, THF, 0 °C→RT; $Hg(OAc)_2$, THF/H_2O (10:1), 0 °C; c) $NaBH_4$, MeOH; d) **18**, PPh_3, DIAD, THF; H_2O_2, $(NH_4)_6[Mo_7O_{24}] \cdot 4H_2O$, EtOH; e) LiHMDS, THF, −78→−40 °C; **5**, DMF/DMPU (3:1), −78 °C→RT; f) 15% NaOH/DMPU (1:10); g) IBX, DMSO/THF (1:1); h) $NaClO_2$, NaH_2PO_4, *t*BuOH/2-methyl-2-butene/H_2O (1:1:1); i) TBAF, THF; j) EtOCCH, $[\{RuCl_2(p\text{-cymene})\}_2]$, toluene, 0 °C→RT; CSA, RT→50 °C; k) 4 N HCl, MeOH. CSA = camphorsulfonic acid, DIAD = diisopropylazodicarboxylate, DMF = *N*,*N*-dimethylformamide, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, HMDS = hexamethyldisilazide, IBX = 2-iodoxybenzoic acid, TBAF = tetrabutylammonium fluoride.

For the lactonization of **21**, the protocol of Kita et al.[16] gave the best result; thus, macrolide **22** was produced in 44% yield. It was not possible to obtain **22** in reasonable yield under Yamaguchi lactonization conditions. Finally, removal of the MOM protecting group and cleavage of the acetonide under acidic conditions produced amphidinolide E (**1**) in 77% yield.[17]

In summary, a radical cyclization reaction of a β-alkoxy acrylate was employed for the stereoselective construction of the oxolane unit in our synthesis of amphidinolide E (**1**). The general fragility of **1**, particularly at C2 and C24, necessitated careful analysis and the judicious choice of reaction conditions for the successful culmination of the total synthesis.

Experimental Section

Macrolide **22**: Ethoxyacetylene (40% in hexanes, 0.030 mL, 0.13 mmol) was added to a solution of the *seco* acid **21** (52.6 mg, 0.0873 mmol) and $[\{RuCl_2(p\text{-cymene})\}_2]$ (1.0 mg, 0.0016 mmol) in toluene (8 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred for a further 30 min. The dark red solution was then filtered through a pad of silica gel, and the silica gel was washed with dry Et_2O (50 mL) under a nitrogen atmosphere. The filtrate was concentrated under reduced pressure. The crude ethoxyvinyl ester was dissolved in toluene (3 mL) and added to a solution of CSA (2.0 mg, 0.0087 mmol) in toluene (14 mL). The reaction mixture was heated to 50 °C and stirred at this temperature for 2 h, then filtered through a pad of silica gel and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc, 10:1) to afford lactone **22** (22.5 mg, 44%).

$R_f = 0.45$ (hexanes/EtOAc, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 6.30 (dd, $J = 14.9$, 10.8 Hz, 1H), 6.19 (dd, $J = 14.9$, 10.8 Hz, 1H), 6.04 (d, $J = 15.7$ Hz, 1H), 5.68–5.76 (m, 2H), 5.55 (dd, $J = 14.7$, 9.3 Hz, 2H), 5.31 (ddd, $J = 15.2$, 8.6, 1.5 Hz, 1H), 5.12 (d, $J = 7.1$ Hz, 1H), 4.98 (s, 1H), 4.87 (s, 1H), 4.73 (s, 1H), 4.70 (s, 1H), 4.67 (d, $J = 6.8$ Hz, 1H), 4.64 (dd, $J = 10.3$, 1.2 Hz, 1H), 4.02 (t, $J = 8.5$ Hz, 1H), 3.98 (t, $J = 8.5$ Hz, 1H), 3.72 (dd, $J = 8.9$, 1.3 Hz, 1H), 3.52 (td, $J = 9.3$, 6.4 Hz, 1H), 3.36 (s, 3H), 3.24–3.32 (m, 2H), 2.77 (d, $J = 7.1$ Hz, 2H), 2.30–2.39 (m, 3H), 1.86–1.98 (m, 2H), 1.82 (dd, $J = 14.3$, 11.9 Hz, 1H), 1.71 (s, 3H), 1.62–1.70 (m, 1H), 1.46–1.54 (m, 2H), 1.43 (s, 3H), 1.43 (s, 3H), 1.26–1.32 (m, 1H), 1.24 (d, $J = 6.6$ Hz, 3H), 1.11–1.19 (m, 1H), 0.91 ppm (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 174.5$, 144.5, 144.1, 138.5, 135.8, 135.4, 133.3, 131.3, 127.9, 127.7, 125.4, 115.7, 110.8, 109.0, 97.2, 83.0, 82.3, 80.7, 79.2, 78.0, 77.7, 77.2, 56.3, 44.0, 41.3, 35.8, 32.1, 31.6, 28.8, 27.7, 27.1, 27.1, 22.5, 17.1, 14.7 ppm. IR (neat): $\tilde{\nu}_{max} = 3443$, 3063, 3078, 2981, 2929, 1732, 1653, 1604, 1454, 1377, 1238, 1171, 1090, 1030, 991, 885, 758, 580 cm^{-1}; MALDI-TOF MS: m/z 607 $[M+Na]^+$; HRMS (FAB): m/z calcd for $C_{35}H_{52}O_7Na$ $[M+Na]^+$: 607.3611, found: 607.3627; $[\alpha]_D^{25} = -178.7$ ($c = 0.46$, $CHCl_3$).

Received: August 17, 2006
Published online: November 9, 2006

Keywords: anticancer agents · macrolides · marine natural products · radical cyclization · total synthesis

[1] a) J. Kobayashi, M. Ishibashi, T. Murayama, M. Takamatsu, M. Iwamura, Y. Ohizumi, T. Sasaki, *J. Org. Chem.* **1990**, *55*, 3421–3423; b) T. Kubota, M. Tsuda, J. Kobayashi, *J. Org. Chem.* **2002**, *67*, 1651–1656.

[2] For reports on the partial synthesis of **1**, see: a) M. K. Gurjar, S. Mohapatra, U. D. Phalgune, V. G. Puranik, D. K. Mohapatra, *Tetrahedron Lett.* **2004**, *45*, 7899–7902; b) C. L. Heitzman, W. T. Lambert, E. Mertz, J. B. Shotwell, J. M. Tinsley, P. Va, W. R. Roush, *Org. Lett.* **2005**, *7*, 2405–2408; c) J. A. Marshall, G. Schaaf, A. Nolting, *Org. Lett.* **2005**, *7*, 5331–5333.

[3] E. J. Corey, P. L. Fuchs, *Tetrahedron Lett.* **1972**, *13*, 3769–3772.

[4] H. C. Brown, N. G. Bhat, V. Somayaji, *Organometallics* **1983**, *2*, 1311–1316.

[5] a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483; b) S. A. Frank, H. Chen, R. K. Kunz, M. J. Schnaderbeck, W. R. Roush, *Org. Lett.* **2000**, *2*, 2691–2694.

[6] L. O. Haustedt, S. B. Panicker, M. Kleinert, I. V. Hartung, U. Eggert, B Niess, H. M. R. Hoffmann, *Tetrahedron* **2003**, *59*, 6967–6977.

[7] J. Uenishi, M. Ohmi, K. Matsui, M. Iwano, *Tetrahedron* **2005**, *61*, 1971–1979.

[8] W. R. Roush, K. Ando, D. B. Powers, A. D. Palkowitz, R. L. Halterma, *J. Am. Chem. Soc.* **1990**, *112*, 6339–6348.

[9] For examples of the radical cyclization of β-alkoxy acrylates and β-alkoxy methacrylates, see: a) E. J. Kang, E. J. Cho, M. K. Ji, Y. E. Lee, D. M. Shin, S. Y. Choi, Y. K. Chung, J.-S. Kim, H.-J. Kim, S.-G. Lee, M. S. Lah, E. Lee, *J. Org. Chem.* **2005**, *70*, 6321–6329; b) H. Y. Song, J. M. Joo, J. W. Kang, D.-S. Kim, C.-K. Jung, H. S. Kwak, J. H. Park, E. Lee, C. Y. Hong, S. Jeong, K. Jeon, J. H. Park, *J. Org. Chem.* **2003**, *68*, 8080–8087; c) E. J. Jeong, E. J. Kang, L. T. Sung, S. K. Hong, E. Lee, *J. Am. Chem. Soc.* **2002**, *124*, 14655–14662; d) E. Lee, S. J. Choi, H. Kim, H. O. Han, Y. K. Kim, S. J. Min, S. H. Son, S. M. Lim, W. S. Jang, *Angew. Chem.* **2002**, *114*, 184–186; *Angew. Chem. Int. Ed.* **2002**, *41*, 176–178.

[10] Y. Okude, S. Hirano, T. Hiyama, H. Nozaki, *J. Am. Chem. Soc.* **1977**, *99*, 3179–3181.

[11] Prepared by the hydrozirconation–iodination of 2-methylpent-1-en-4-yne.

[12] a) S. Ohira, *Synth. Commun.* **1989**, *19*, 561–564; b) S. Müller, B. Liepold, G. J. Roth, H. J. Bestmann, *Synlett* **1996**, 521–522.

[13] a) H. Y. Lee, B. G. Kim, M. L. Snapper, *Org. Lett.* **2003**, *5*, 1855–1858; b) T. W. Funk, J. Efskind, R. H. Grubbs, *Org. Lett.* **2005**, *7*, 187–190.

[14] a) P. R. Blackemore, W. J. Cole, P. J. Kocienski, A. Morley, *Synlett* **1998**, 26–28; b) P. Liu, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, *123*, 10772–10773.

[15] M. Frigerio, M. Santagostino, S. Sputore, *J. Org. Chem.* **1999**, *64*, 4537–4538.

[16] a) Y. Kita, H. Maeda, K. Omori, T. Okuno, Y. Tamura, *J. Chem. Soc. Perkin Trans. 1* **1993**, 2999–3005; b) B. M. Trost, J. D. Chisholm, *Org. Lett.* **2002**, *4*, 3743–3745.

[17] $[\alpha]_D^{30} = -131.1$ ($c = 0.21$, $CHCl_3$); the specific rotation of the natural sample was not reported.[1]

