Studies on the Total Synthesis of Amphidinolide O (II): A Stereoselective Synthesis of C1-C11 Fragment

Mi-Yeon Jang, Jong-Woo Kim, and Duck-Hyung Lee*

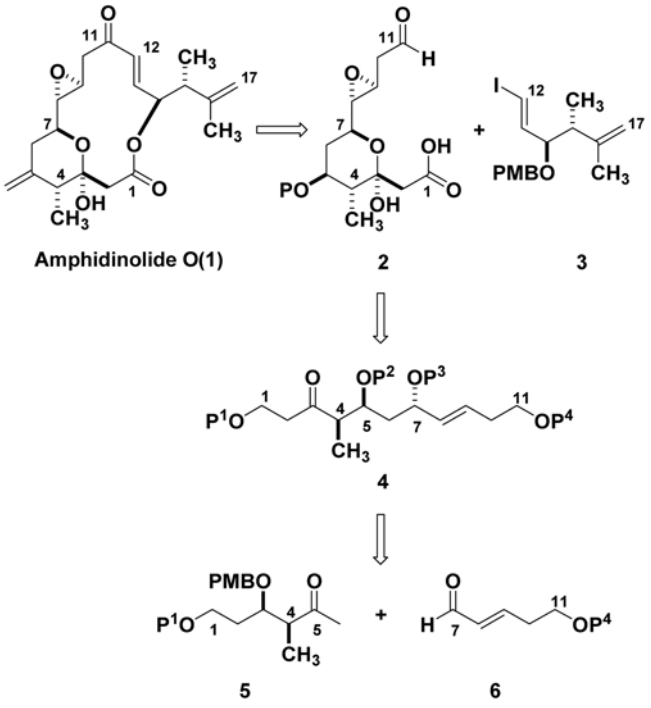
*Department of Chemistry, Sogang University, Seoul 121-742, Korea. *E-mail: dhlee@ccs.sogang.ac.kr*
Received June 18, 2005

Key Words : Amphidinolide O, Cytotoxic macrolide, Stereoselective synthesis, 1,5-*anti*-Selective aldol reaction, 1,3-*anti*-Selective reduction of β-hydroxy ketone

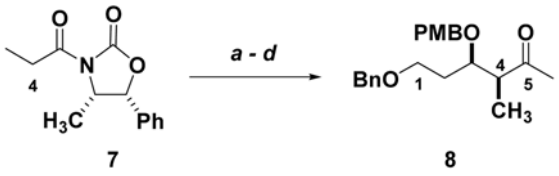
The amphidinolides were isolated from the marine dinoflagellate *Amphidinium* sp., which produces a host of secondary metabolites endowed with potent cytotoxicity against various cancer cell lines. Amphidinolide O (**1**) displayed potent *in vitro* cytotoxicity against L1210 marine leukemia cells and human epidermoid carcinoma KB cells with 1.7 and 3.6 μg/mL of IC50s, respectively.[1] In addition to our recent reports[2] regarding to the synthesis of C12-C17 and C3-C11 fragments of amphidinolide O (**1**), we describe herein a new route to diastereoselective synthesis of C1-C11 fragment of **1**.

The retrosynthetic analysis of **1** led to the C1-C11 fragment **2** and C12-C17 fragment **3** (Scheme 1). The hemiketal **2** was expected from acyclic precursor **4** which, in turn, would be derived by diastereoselective aldol reaction between ketone **5** and aldehyde **6**.

The C1-C6 fragment **8** (equivalent to **5** in scheme 1) was prepared as summarized below (Scheme 2). Enolization of carboximide **7** with Bu_2BOTf and $EtN(i\text{-}Pr)_2$ was followed by reaction with aldehyde to provide the *syn*-aldol product in



Scheme 1. Retrosynthesis of Amphidinolide O (**1**).



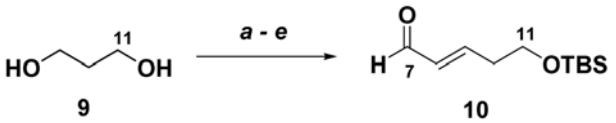
Scheme 2. Synthesis of C1-C6 fragment (**8**). (a) Bu_2BOTf, $EtN(i\text{-}Pr)_2$, CH_2Cl_2, −20 °C, 20 min; $BnO\text{-}(CH_2)_2CHO$, −78 °C, 1 h, 86%; (b) MeN(OMe)H-HCl, $AlMe_3$, THF, −10 °C to rt, 3 h, 91%; (c) $CCl_3C(4\text{-}MeO\text{-}PhCH_2)$=NH, TsOH, CH_2Cl_2, rt, 2 d, 75%; (d) MeMgCl, THF, 0 °C, 1 h, 85%.

86% yield (ds = > 97 : 3 by ^1H NMR analysis) (Scheme 2).[3] The aldol product was treated with *N,O*-dimethylhydroxylamine hydrochloride and $Al(Me)_3$ to provide the Weinreb amide in 91% yield.[4] The free hydroxyl group was protected as PMB ether, and finally Weinreb amide was converted to ketone **8** in 85% yield by reaction with MeMgCl.

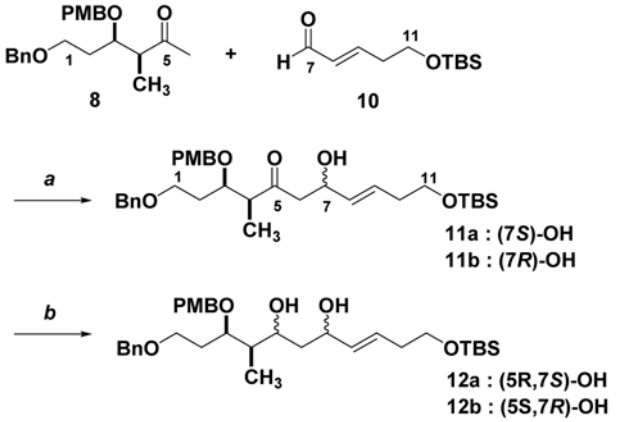
Synthesis of C7-C11 fragment **10** (equivalent to **6** in scheme 1) was completed via 5-step sequences (Scheme 3). Monoprotection of propane-1,3-diol (**9**),[5] Swern oxidation of the remaining alcohol to aldehyde, and Wittig-olefination was undertaken to give α,β-unsaturated ester,[6] which was subsequently reduced by DIBAL and oxidized to provide the C7-C11 fragment **10**, another key intermediate in the next aldol reaction.

Aldol-reactions of fragments **8** and **10** were investigated with four chiral boron reagents[7] in ether at −78 °C (Scheme 4), and the use of chlorodicyclohexylborane provided the desired product with the best diastereoselectivity (**11a** : **11b** = 67 : 33) in 61% (**11a**) and 30% (**11b**) yield, respectively. Hydroxyl group-directed 1,3-*anti* reduction of either **11a** or **11b** with $NaBH(OAc)_3$ provided the 5,7-*anti* diol **12a** or **12b** in 91% yield.

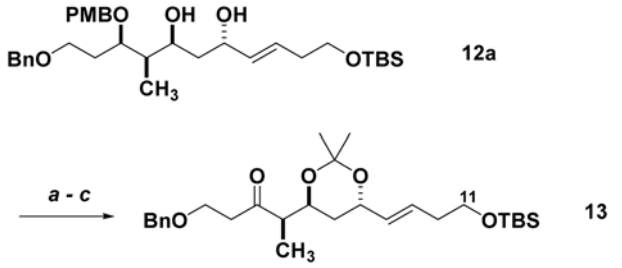
The (5*R*,7*S*)-isomer **12a** was treated with 2,2-dimethoxypropane in the presence of PPTS (Scheme 5). The PMB-



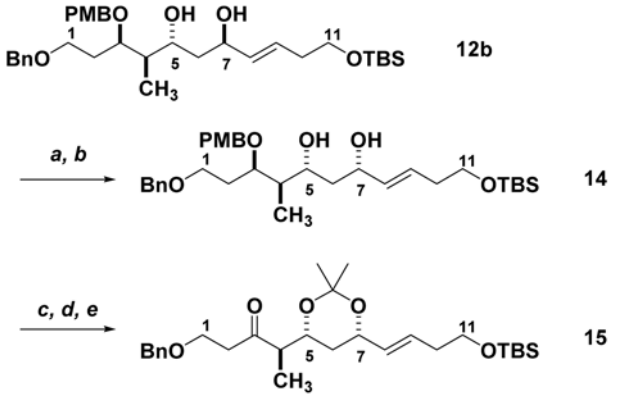
Scheme 3. Synthesis of C7-C11 fragment (**10**). (a) TBSCl, imidazole, CH_2Cl_2, rt, 3 d, 87%; (b) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C, 1.5 h, 100%; (c) Ph_3PCHCO_2Et, benzene, 45 °C, 1 h, 89%; (d) DIBAL, CH_2Cl_2, −78 °C, 30 min., 91%; (e) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C, 1.5 h, 100%.



Scheme 4. Synthesis of **12a**/**12b**. (a) EtN(*i*-Pr)$_2$, (*c*-Hex)$_2$BCl, Et_2O, −78 °C, 1.5 h, 93%; (b) $Me_4NB(OAc)_3H$, CH_3CN/AcOH (1 : 1), −20 °C, 2 d, 91%.

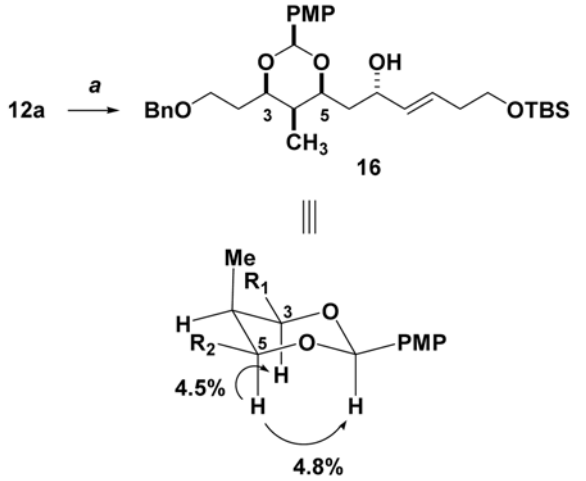


Scheme 5. Synthesis of C1-C11 fragment (**13**). (a) 2,2-dimethoxypropane, PPTS(cat), CH_2Cl_2, rt, 1 h, 85%; (b) DDQ, CH_2Cl_2/H_2O (10 : 1), rt, 1 h, 72%; (c) DMP, CH_2Cl_2, pyridine, rt, 40 min, 90%



Scheme 6. Synthesis of C1-C11 fragment (**15**). (a) MnO_2, Et_2O, rt, 2 d, 50%; (b) DIBAL, CH_2Cl_2, −78 °C, 30 min., 90%; (c) 2,2-dimethoxypropane, PPTS(cat), CH_2Cl_2, rt, 1 h, 90%; (d) DDQ, CH_2Cl_2/H_2O (10 : 1), rt, 1 h, 72%; (e) DMP, CH_2Cl_2, pyridine, rt, 40 min, 90%.

protecting group was cleaved under standard reaction condition,[8] and the free hydroxyl group was oxidized with Dess-Martin reagent to give the ketone **13**.[9] However, intramolecular cyclization of acetonide **13**, a crucial step toward the total synthesis of amphidinolide O (**1**), under various acidic conditions resulted in the decomposition of **13** at −78 °C without any indication for the presence of the



Scheme 7. Determination of relative stereochemistry of **12a**. (a) DDQ, CH_2Cl_2, 0 °C to rt, 1 h, 65%.

desired tetrahydropyran ring.

The minor (5*S*,7*R*)-isomer **12b** was oxidized with manganese dioxide and the ketone was reduced with DIBAL to yield diol **14** (Scheme 6). The conversion of **14** into acetonide **15** was completed by the method in scheme 5. However, the same result was obtained from the intramolecular cyclization of acetonide **15**.

The relative stereochemistry of **12a** was determined unambiguously from ^{1}H NOE spectroscopy of the acetonide **16**, which was prepared *via* deprotection of PMB ether of **12a** by DDQ and *in situ* cyclization (Scheme 7).

In summary, two ketones **13** and **15**, the C1-C11 fragment of Amphidinolide O (**1**), were prepared stereoselectively via 14 and 16 step sequences in 8.7% and 2.0% overall yield, respectively.

Acknowledgement. This research was assisted financially by Korea Science and Engineering Foundation (R01-2000-000-00048-0).

References

1. Ishibashi, M.; Takahashi, M.; kobayashi, J. *J. Org. Chem.* **1995**, *60*, 6022-6066.
2. (a) Pang, J. H.; Lee, D. H. *Bull. Korean Chem. Soc.* **2002**, *23*, 1173-1176. (b) Pang, J. H.; Ham, Y. J.; Lee, D. H. *Bull. Korean Chem. Soc.* **2003**, *24*, 891-892.
3. (a) Mapp, A. K.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 23-27. (b) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Cardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001-7032.
4. Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc.* **1990**, *112*, 2998-3017.
5. (a) Urbanek, R. A.; Sabes, S. F.; Forsyth, C. J. *J. Am. Chem. Soc.* **1998**, *120*, 2523-2533. (b) Chen, S.-M. L.; Schaub, R. E.; Grudzinskas, C. V. *J. Org. Chem.* **1978**, *43*, 3450-3454.
6. Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, 453-462.
7. Bu_2BOTf (ds = 58 : 42, 93% yield); (+)-DIPCl (ds = 45 : 55, 85% yield); (−)-DIPCl (ds = 55 : 45, 85% yield); (*n*-Ch)$_2$BCl (ds = 67 : 33, 91% yield).
8. Liu, X.; Peter, H.; Seeberger, P. H. *Chem. Comm.* **2004**, *15*, 1708-1709.
9. Dess, D. B.; Matin, J. C. *J. Org. Chem.* **1983**, *48*, 4155-4156.