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

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Received June 12, 2009, Accepted September 5, 2009

Key Words: Amphidinolide O, Anti-cancer activity, Asymmetric allylation, *syn*-Aldol reaction

The amphidinolides are well-known series of cytotoxic macrolides isolated from the marine dinoflagellate *Amphidinium sp.*, which is a symbiotic with Okinawan marine flatworm *Amphiscolops sp.*, and attracted interests from the synthetic community due to their potent cytotoxic activities against various cancer cell lines.[1]

The isolation and structural elucidation with the relative stereochemistry of amphidinolide O (**1**) were reported by Kobayshi *et al.* in 1995 (Figure 1).[2] Amphidinolide O (**1**) is a 15-membered macrolide possessing seven chiral centers, one tetrahydropyran ring with one exo-methylene group, three equatorial alkyl substituents, and one axial hydroxyl group, one epoxide, and three double bonds. In addition, amphidinolide O (**1**) showed *in vitro* cytotoxicity against L1210 cells (IC50: 1.7 μg/mL) and human epidermoid carcinoma KB cells (IC50: 3.6 μg/mL), and total synthesis of amphidinolide O (**1**) has not been reported yet.

In relation to our program for the synthesis of amphidinolide O (**1**), we published the stereoselective synthesis of C12-C17, C3-C11, and C1-C11 fragments of amphidinolide O (**1**) in the past few years.[3] We report herein a more efficient route along with the formation of the tetrahydropyran ring in the synthesis of C1-C11 fragment **3** using Brown asymmetric allylation[4] and Evans *syn*-aldol reaction.[5]

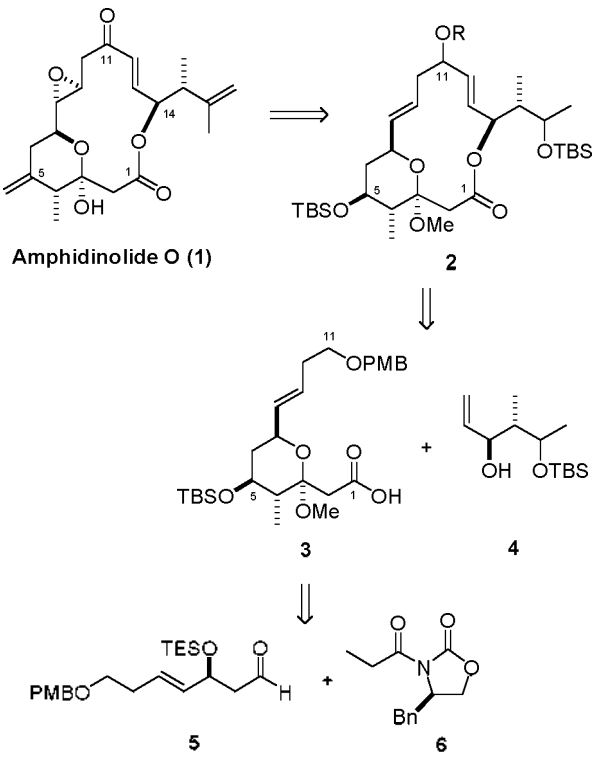
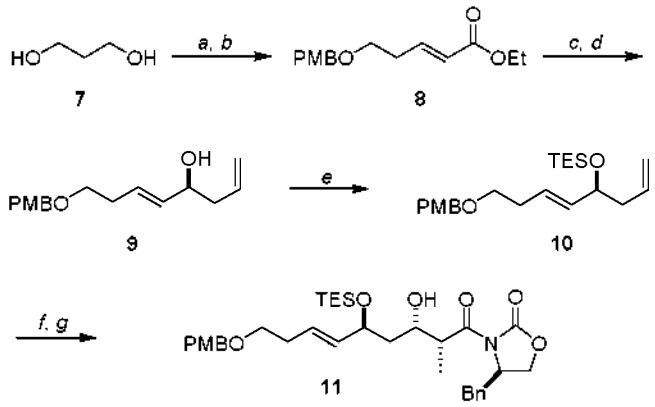


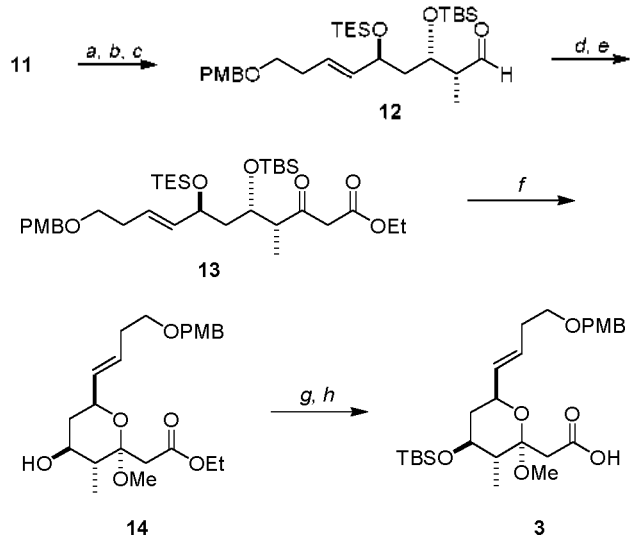
Figure 1. Retrosynthesis of Amphidinolide O (1).

In a retrosynthetic analysis (Figure 1), amphidinolide O (**1**) can be derived from the common intermediate **2**. Intermediate **2** may be prepared from C1-C11 segment **3** and C12-C17 segment **4** by Yamaguchi esterification[6] and ring-closing metathesis (RCM).[7] Construction of the correct stereochemistry at C-4 and C-5 would be established from the Evans *syn*-aldol reaction of **5** and **6**.[5]

The intermediate **11** was prepared from the commercially available 1,3-propanediol (**7**) (Scheme 1). After mono-protection of the diol **7** using sodium hydride, PMBCl, and TBAI in THF in 70% yield, the primary hydroxyl group was converted quantitatively to the aldehyde by Swern oxidation, and the subsequent olefination using stabilized Wittig reagent in benzene provided the *trans*-α,β-unsaturated ester **8** in 91% overall yield.[3,8] The ester moiety in **8** was reduced to a primary alcohol by Dibal-H in 94% yield. Swern oxidation of the resulting alcohol was followed by asymmetric Brown allylation protocol using (-)-B-methoxydiisopinocampheyl-



Scheme 1. Synthesis of intermediate **11**. (a) NaH, PMBCl, TBAI, THF, rt, 24 h (70%). (b) (i) DMSO, $(COCl)_2$, TEA, CH_2Cl_2, −78 °C, (ii) $Ph_3P{=}CHCO_2Et$, benzene, 45 °C (91%, two steps). (c) Dibal-H, CH_2Cl_2, −78 °C (94%). (d) (i) DMSO, $(COCl)_2$, TEA, CH_2Cl_2, −78 °C, (ii) (-)-Ipc$_2$BOMe, allyl-magnesium bromide, ether, −90 °C (*ent* ratio = 8:1, 98%, two steps). (e) TESCl, imidazole, CH_2Cl_2, rt (87%). (f) OsO_4, NMO, THF: H_2O = 3:1, −5 °C (68%). (g) (i) $Pb(OAc)_4$, $NaHCO_3$, CH_2Cl_2, 0 °C, (ii) $TiCl_4$, (-)-sparteine, **6**, CH_2Cl_2, 0 °C (83%, two steps).



Scheme 2. Synthesis of C1-C11 Fragment **3**. (a) MeONHMe-HCl, $AlMe_3$, CH_2Cl_2, −20 °C (68%). (b) TBSOTf, TEA, CH_2Cl_2, −78 °C (96%). (c) Dibal-H, CH_2Cl_2, −78 °C (96%). (d) BuLi, diisopropylamine, Ethyl acetate, THF, −78 °C (92%). (e) DMP, CH_2Cl_2, 0 °C (81%). (f) *p*-TsOH, MeOH : MC = 2 : 8, rt, 16 h (65%). (g) TBSOTf, TEA, CH_2Cl_2, 0 °C, 10 min (99%). (h) LiOH, THF: H_2O: MeOH = 1:1:1, rt (53%).

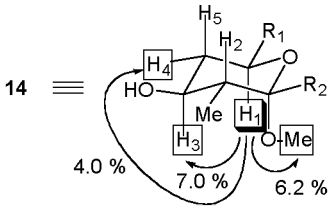


Figure 2. Assignment of the Relative Stereochemistry of **14**.

borane[4] at −90 °C to provide the homoallylic alcohol **9** in a 8:1 enantiomeric ratio[9] and in 98% two step yield. The secondary hydroxyl group was converted to TES ether **10** in 87% yield, and the double bond was dihydroxylated using OsO_4 and NMO in 68% yield. Dihydroxylation at −5 °C was necessary in order to suppress the concomitant formation of the tetraol. Oxidative cleavage of the diol afforded the aldehyde and the aldehyde was immediately treated with titanium enolate of (*R*)-4-benzyl-3-propyloxazolidin-2-one (**6**) to give the *syn*-aldol product **11** in 83% two step yield.[5]

Next, oxazolidinone **11** was transformed to a Weinreb amide by reaction with trimethylaluminium and *N*,*O*-dimethylhydroxylamine hydrochloride in 68% yield (Scheme 2).[3] After protection of the resulting secondary alcohol to the corresponding *tert*-butyldimethylsilyl ether in 96% yield, the Weinreb amide was treated with Dibal-H in CH_2Cl_2 to give the aldehyde **12** in 96% yield. Condensation of **12** with the enolate of ethyl acetate (92% yield) and the subsequent Dess-Martin oxidation of the resulting secondary alcohol gave the *β*-ketoester **13** in 81% yield. Removal of the TES protecting group in **13** using *p*-TsOH in methanol-dichloromethane led to the simultaneous cyclization into the tetrahydropyran acetal **14** and cleavage of TBS-protection group in 65% yield. Protection of the secondary hydroxyl group by TBSOTf and TEA in 99% yield, and final hydrolysis of ester moiety in **14** with lithium hydroxide gave the C1-C11 fragment **3**.[10]

The relative stereochemistry of tetrahydropyran **14** was further confirmed by ^{1}H NOE study (Figure 2).

In summary, the C1-C11 fragment **3** (18 steps, 4% overall yield from **8**) of amphidinolide O (**1**) has been synthesized through Brown asymmetric allylation and Evans *syn*-aldol reaction as key steps.

Acknowledgments. This research was assisted financially by Korea Research Foundation (KRF-2006-311-C00381). The instrument facilities of the Organic Chemistry Research Center (OCRC) in Sogang University were also helpful.

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8. Stabilized Wittig reagent turned out to be better than HWE reagents in the synthesis of *trans*-*α*,*β*-unsaturated ester.
9. The enantiomeric ratio was determined by using Mosher's ester method (Mosher Ohtani, I.; Takenori, K.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092-4096).
10. Spectroscopic data for **3** : R_f 0.66 (EA/hex = 1 : 2); $[\alpha]_D^{25}$ = 1.07 (c = 0.43, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.5 Hz, 2 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 5.75 (dt, *J* = 15.5 & 6.5 Hz, 1 H), 5.54 (dd, *J* = 15.5 & 6.5 Hz, 1 H), 4.45 (s, 2 H), 4.12 (m, 1 H), 3.80 (s, 3 H), 3.72 (dt, *J* = 4.5 & 10.0 Hz, 1 H), 3.50 (t, *J* = 6.5 Hz, 2 H), 3.22 (s, 3 H), 2.90 (d, *J* = 15.0 Hz, 1 H), 2.66 (d, *J* = 15.0 Hz, 1 H), 2.37 (dt, *J* = 6.5 & 6.5 Hz, 2 H), 1.88 (dm, 1 H), 1.63 (m, 1 H), 1.46 (m, 1 H), 1.02 (d, *J* = 6.5 Hz, 3 H), 0.87 (s, 9 H), 0.03 (s, 6 H) ppm; ^{13}C NMR (125 MHz, CDCl3): δ 170.20, 159.36, 130.56, 130.50, 129.45, 113.96, 101.92, 72.75, 70.72, 69.32, 69.10, 55.44, 48.43, 45.54, 41.19, 40.58, 32.79, 25.91, 18.09, 12.07, -3.95, -4.59 ppm; HRMS: *m/z* calcd for $C_{27}H_{44}NaO_5Si$ $[M+Na]^+$ 531.2754, found 531.2755.