Studies on the Total Synthesis of Amphidinolide O. A Stereoselective Synthesis of C3-C11 Fragment

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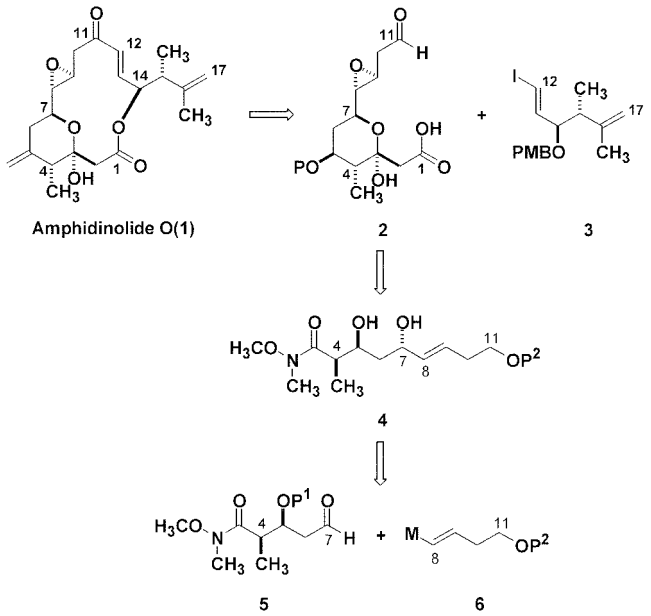
The amphidinolides were isolated from the marine dinoflagellate *Amphidinium* sp., and Amphidinolide O (**1**) displayed potent *in vitro* cytotoxicity against L1210 marine leukemia cells and human epidermoid carcinoma KB cells (IC_{50} : 1.7 and 3.6 μg/mL, respectively).[1] Until now, the total synthesis of amphidinolide J,[2] K,[3] and P[4] were reported by Williams' group, and many synthetic studies for amphidinolide A,[5] B,[6] C,[7] G,[8] H,[8] and L[8,9] have been published. Recently, the synthesis of C12-C17 fragment **3** of amphidinolide O (**1**) was reported in this laboratory[10] and we describe herein the diastereoselective synthesis of the other C3-C11 fragment **20** of amphidinolide O (**1**).

The retrosynthetic analysis of amphidinolide O (**1**) led to the C1-C11 fragment **2** and C12 C17 fragment **3** through cleavage of C1-O and C11-C12 bond (Scheme 1) as proposed in the our paper.[10] The hemiketal moiety of fragment **2** was expected from the Weinreb amide **4**, and the coupling reaction of an aldehyde **5** and vinyl organometallic compound **6** would provide the Weinreb amide **4**. The amide **5** should be easily available *via* Evans asymmetric *syn*-aldol protocol.

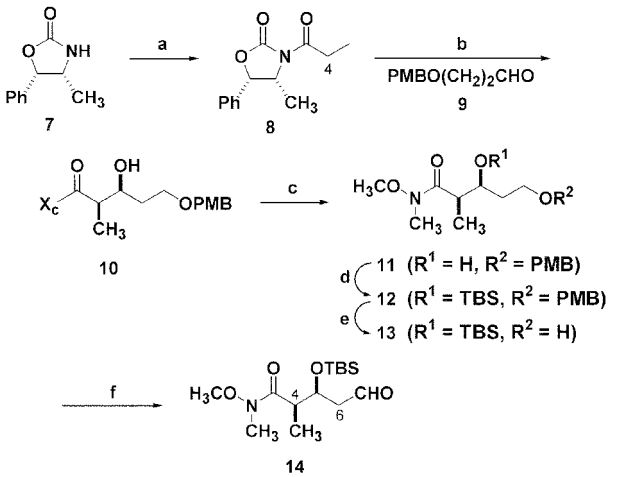
First, Evans oxazolidinone **7** was treated successively with



Scheme 1. Retrosynthetic Analysis of Amphidinolide O (**1**).

n-BuLi (1.05 equiv.) and propionyl chloride (1.3 equiv.) to afford the carboximide **8** in 85% yield (Scheme 2).[11] Enolization of **8** with $TiCl_4$ (1.05 equiv.) and Hunig's base (1.15 equiv.) was followed by reaction with the aldehyde **9** to provide the *syn*-aldol product **10** with high diastereoselectivity (> 97 : 3 by NMR analysis).[12] The aldehyde **9** was prepared in two steps from 1,3-propanediol *via* selective protection of one primary alcohol with *p*-methoxybenzyl chloride and Swern oxidation of the remaining primary alcohol.[13] The *syn*-aldol product **10** was successively treated with *N*,*O*-dimethylhydroxylamine hydrochloride (5.0 equiv.) and $Al(Me)_3$ (5.0 equiv.) to give the Weinreb amide **11** in 90% yield.[14] Purification of **11** was facilitated by efficient crystallization of the recyclable oxazolidinone auxiliary **7** (80-90%) from the reaction mixture. The hydroxyl group of **11** was then treated with TBSOTf (1.2 equiv.) and 2,6-lutidine (2.0 equiv.) to provide the TBS ether **12** in 92% yield[15] and the PMB group of **12** was deprotected with 10% Pd-C in ethyl acetate and ethanol at room temperature in 88% yield.[16] And the primary alcohol **13** was oxidized by Swern protocol into the aldehyde **14** in 85% yield.[17]

Next, the vinyl stannane **15** was prepared from 3-butyn-1-



Scheme 2. Synthesis of C1-C11 fragment of amphidinolide O. (a) *n*-BuLi, CH_3CH_2COCl, THF, -78 °C, 30 min, 85%; (b) $TiCl_4$, *i*-Pr_2NEt, 0 °C, 1 h; **9**, CH_2Cl_2, -78 °C, 1 h, then -40 °C, 1 h, 70%; (c) $HN(CH_3)OCH_3$-HCl, $AlMe_3$, THF, rt, 5 h, 90%; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min, 92%; (e) H_2, 10% Pd/C, EtOAc/EtOH (1 : 1), rt, 12 h, 88%: (f) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, -78 °C, 1 h, 85%.

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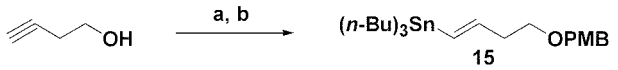
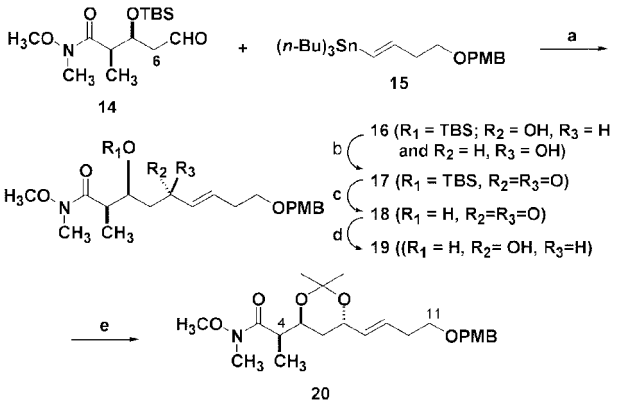


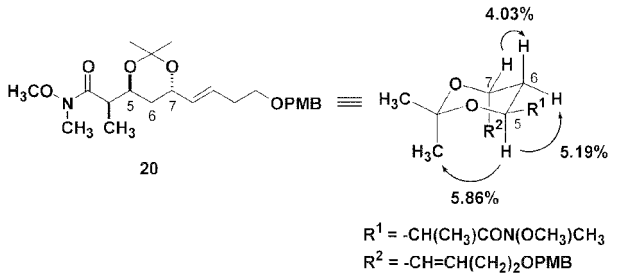
Scheme 3. Synthesis of Tin Reagent 15. (a) NaH, DMF, 0 °C, 30 min; PMBCl, rt, 1 d, 70%; (b) (*n*-Bu)$_3$SnH, AIBN, toluene, 130 °C, 2 h, 70%.

ol in two step sequences (Scheme 3): PMB protection of alcohol with *p*-methoxybenzyl chloride (1.0 equiv.) in DMF[18a] and hydrostannylation of the alkyne moiety with *n*-tributyltin hydride (1.5 equiv.) in the presence of a catalytic amount of AIBN.[18b]

And the vinyl stannane **15** was lithiated with *n*-BuLi (1.5 equiv.) at -40 °C for 1 h and the resulting lithium reagent was added to the aldehyde **14** to furnish the diastereomeric mixtures of secondary alcohols **16** in 70% yield (Scheme 4).[19] The alcohols **16** were oxidized with Dess-Martin periodinane (1.3 equiv.) to give the ketone **17** in 84% yield,[20] while oxidation of **16** with PCC or PDC resulted in significant isomerization at the α-chiral center. Desilylation of the ketone **17** was achieved by 48% aqueous HF in acetonitrile (5 : 95 v/v) at 0 °C, leading to β-hydroxy ketone **18** in 65% yield. A hydroxyl group-directed 1,3-*anti*-reduction of **18** with NaBH(OAc)$_3$ (1.5 equiv.) provided the 1,3-*anti*-diol **19** in 72% yield with moderate 1,3-stereoselectivity (84:16).[21] The diol **19** was then treated with 2,2-dimethoxypropane (10.0 equiv.) in the presence of a catalytic amount of PPTS to give the acetonide **20** in 65% yield.



Scheme 4. Synthesis of C3-C11 fragment of amphidinolide O. (a) *n*-BuLi, THF, -78 °C, 20 min, then -40 °C, 40 min; (E)-Bu$_3$SnCH =CH(CH$_2$)$_2$OPMB (**15**), 70%; (b) DMP, CH_2Cl_2, rt, 12 h, 84%; (c) 48% aq. HF/MeCN (5 : 95), 0°C, 2 h, 65%; (d) NaBH(OAc)$_3$, EtOAc, rt, 12 h, 72%; (e) Me$_2$C(OMe)$_2$, PPTS, CH_2Cl_2, rt, 12 h, 65%.



Scheme 5. Determination of relative stereochemistry of 1,3-*anti* acetonide **20**.

The relative stereochemistries of 1,3-*anti* diol **19** and the acetonide **20** were determined unambiguously from ^{1}H NOE difference spectroscopy of the acetonide **20**. As shown in Scheme 5, NOSEY correlations were observed between C_5-*axial* H and C_6-*equatorial* H (5.19%), C_6-*axial* H and C_7-*equatorial* H (4.03%), and C_5-*axial* H and *axial* methyl group (5.86%), which confirm the *anti* relationship between C_5-H and C_7-H.

In summary, Weinreb amide **20**, *the C3-C11 fragment of Amphidinolide O (**1**)*, was prepared stereoselectively *via* 11 step sequences in 4.0% overall yield.

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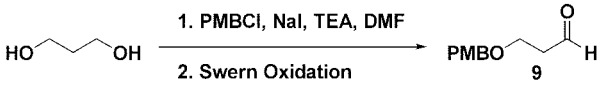

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