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Studies toward asymmetric synthesis of hoiamides A and B

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ABSTRACT

A convenient method for diastereoselective synthesis of the key intermediate **5** from triheterocyclic fragment and polyketide **6** for hoiamides A (**1**) and B (**2**) was developed. The main feature is the successive construction of four stereogenic centers from C33 to C36 for hoiamides A (**1**) through the well-established Oppolzer's *anti*-aldol and Paterson's *anti*-aldol methodology. Furthermore, asymmetric allylation was also utilized as a key step to form the stereogenic center at C32 for hoiamides A (**1**).

Introduction

Natural products isolated from marine cyanobacteria, as a class of structurally novel and biologically active secondary metabolites in drug discovery, display a variety of physiological activities including antimicrobial, antimalarial, cytotoxic and neurotoxic properties.[1] Hoiamides A (**1**) and B (**2**), an interesting family member of bioactive cyclic depsipeptide, were isolated by Gerwick and co-workers in 2009 from an environmental assemblage of the marine cyanobacteria *Moorea producens* and *Phormidium gracile* collected in Papua New Guinea.[2] These two natural products stimulated sodium influx in mouse neocortical neurons (EC_{50} values are 1.7 and 3.9 μM, respectively)[2b] and exhibited modest cytotoxicity to cancer cells.[2c] While the family member of hoiamides C (**3**) and D (**4**) showed no significant activity in the same assay. The structure and stereochemical assignments were assigned by using extensive NMR studies, chemical degradation methods, and modified Mosher ester analysis. As shown in Fig. 1, the structures of hoiamides A (**1**) and B (**2**) are 26-membered cyclodepsipeptides, while C (**3**) and D (**4**) are linear peptides.[2b]

The complexity of hoiamides A (**1**) or B (**2**) includes 15 (or 16 for B) asymmetric carbons, a highly oxygenated and methylated polyketide substructure, a triheterocyclic fragment bearing two *R*-methylated thiazolines and one thiazole as well as a γ- amino acid with four chiral centers.[2a] Owing to the complexity of structures, there is only one asymmetric method to hoiamide C[3] and one approach for constructing the polyketide fragment of six chiral centers.[4] As a continuation of our interests in pursuing diverse methods for syntheses of bioactive alkaloids,[5] divergent syntheses of natural products isolated from cyanobacteria and investigating their structure-activity relationships,[6] we decided to explore an enantioselective approach for the asymmetric synthesis of hoiamides due to its specific bioactivities and challenging structure. Herein we present an efficient method for synthesis of the key fragment **5** for hoiamides.

Our synthetic strategy for hoiamides A (**1**) and B (**2**) is illustrated in Fig. 2, with effectively stereoselective synthesis of oxygenated and methylated polyketide substructure **6** as our main focus in constructing our target molecule. Retrosynthetic analysis led to three key fragments of γ- amino acid **7** with four chiral centers, the key fragment **5** including *R*-methylated two thiazolines and one thiazole ring **8** and polyketide **6**. We envisioned that the highly oxygenated and methylated polyketide **6** could be formed through the successive well-established Oppolzer's *anti*-aldol,[7] Paterson's *anti*-aldol[8] methodology and asymmetric allylation.[6c,9]

Results and discussion

As shown in Scheme 1, chiral aldehyde **11**, easily prepared through the known method of asymmetric methylation,[6b,10] was treated with propinylated chiral auxiliary **12** in the presence of

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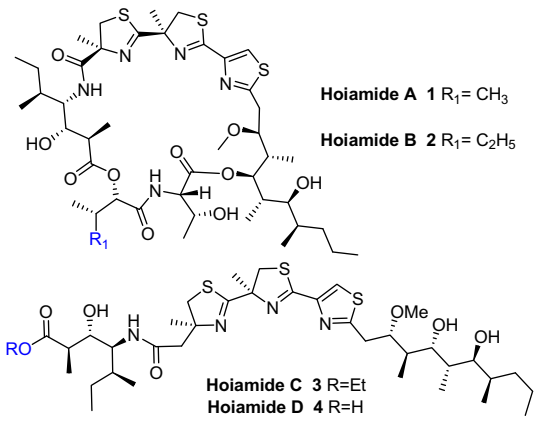


Figure 1. The structures of hoiamides A-D.

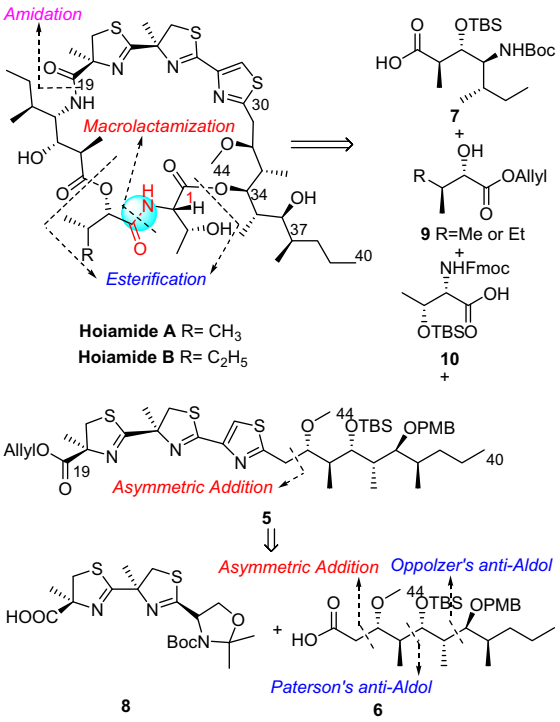
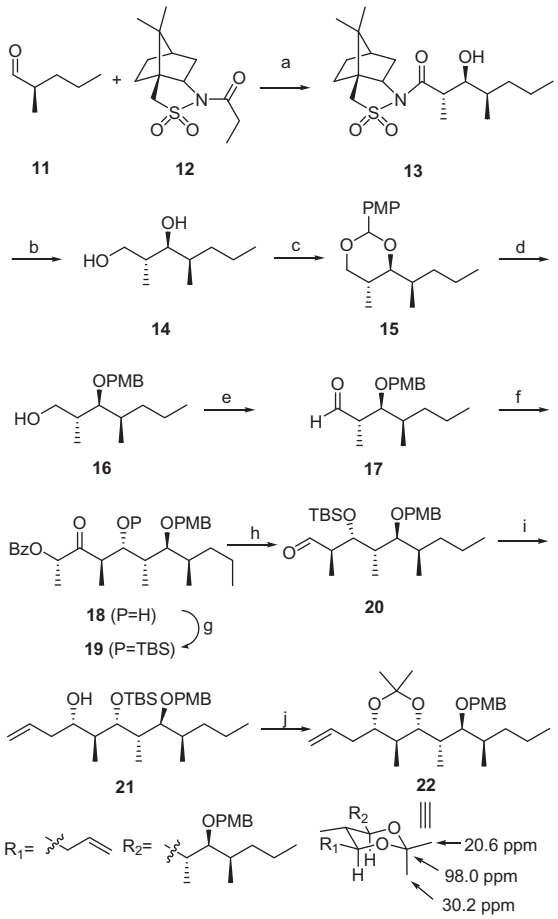


Figure 2. Retrosynthetic analysis of hoiamides A **1** and B **2**.



Scheme 1. *Reagents and conditions:* a. Cy_2BCl, $TiCl_4$, *i*-Pr_2NEt, −10 °C-room temperature, 78%; b. LAH, THF refluxe, 8 h, 90%; c. 1-(dimethoxymethyl)-4-methoxybenzene, PTSA, 1 h, 95%; d. DIBAL-H, DCM, −78 °C, 1 h, 90%; e. DMP, DCM, 0 °C–room temperature, 3 h, 90%; f. (*S*)-3-oxopentan-2-yl benzoate, Cy_2BCl, Me_2NEt, DCM, −78 °C, 2 h, −22 °C, 16 h, 75% (*dr* = 95:5); g. TBSOTf, 2,6-Lutidine, DCM, 0 °C–room temperature, 2 h, 90%; h. (1) $LiBH_4$, THF, 0 °C–room temperature, overnight; (2) $NaIO_4$, CH_3OH-H_2O, room temperature, 2 h, 95%; i. allylmagnesium chloride, $ZnCl_2$, THF, −78 °C, 1 h, 80% (*dr* = 80:20); j. (1) 4 N HCl, CH_3OH, 0 °C, 1 h, (2) PTSA, 2,2-dimethoxypropane, acetone, room temperature, 2 h, 81% (two steps).

chloride dicyclohexyl boron (Cy_2BCl),[7] titanium tetrachloride ($TiCl_4$) and *N,N*-diisopropylethylamine (*i*-Pr_2NEt) to give *anti*-aldol product **13** in 78% yield with high diastereoselectivity (*dr* > 99:1). Removal of chiral auxiliary in **13** with lithium aluminum hydride (LAH) and subsequent of the resulting diol protection with 1-(dimethoxymethyl)-4-methoxybenzene in the presence of *p*-toluenesulfonic acid (PTSA) afforded ketal **15** in 86% overall yield. Then the acetal **15** was reduced with diisobutylaluminium hydride (DIBAL-H)[11] to give the corresponding primary alcoholether **16** in 90% yield, which was converted to aldehyde **17** through Dess-Martin oxidation[12] in 90% yield, and then **17** was treated with (*S*)-3-oxopentan-2-yl benzoate in the presence of chloride dicyclohexyl boron (Cy_2BCl), and *N,N*-dimethylethanamine (Me_2NEt) to give Paterson's *anti*-aldol[8] product **18** in 75% yield with high diastereoselectivity (*dr* = 95:5). Protection (TBSOTf/2,6-Lutidine) of alcohol gave its ether **19** in 90% yield. Further conversion of the ether **19** to aldehyde **20** was achieved through the reduction ($LiBH_4$) and subsequent oxidation ($NaIO_4$) in 95% overall yield. Treatment of aldehyde **20** with allylmagnesium bromide in the presence of Zinc dichloride ($ZnCl_2$) to give alcohol **21** in 80% yield with moderate diastereoselectivity (*dr* = 80:20). The stereochemistry of addition product **21** was assigned through chemical transformations to acetonide **22.** Compound **21** was treated with an aqueous solution of hydrogen chloride (4 N in MeOH) to remove TBS group, and the resulting 1,3-diols were protected with 2,2-dimethoxypropane in the presence of catalytic amount of 4-methylbenzenesulfonic acid (cat. TsOH) to provide acetonide **22**. The stereochemistry of *syn*-1,3-diol was determined based on the chemical shifts of ketal methyl groups in ^{13}C NMR spectrum.[13]

Then, we turned our attention to prepare the acid with six chiral centers **6** (Scheme 2). Treatment of compound **21** with methyl trifluoromethanesulfonate (MeOTf) in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DBTP) produced **23** in 85% yield. Then the compound **23** was treated with $K_2OsO_4{\cdot}2H_2O$ and subsequent Pinnick oxidation ($NaClO_2$, NaH_2PO_4)[14] generated free carboxylic acid in 80% overall yield.

With the polyketide unit **6** in hand, we started to explore the coupling for formation of the key fragment **5** (Scheme 3). Bisthiazoline **8**, prepared through the known method,[3,15] was treated with allyl bromide in the presence of potassium carbonate (K_2CO_3) to give allyl ester **24** in 90% yield. Then the resulted ester **24** was