A Potential Synthesis Routine of Microketide A and B, Polyketide from a Fungus in Southern China Sea

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Abstract. In this paper, a synthesis routine of microketide A (1a) and B (1b) is purposed. The microketides are divided into two parts, 2 and 3, and synthesized separately. 2 is synthesized by an ortho-specific alkylation of phenols. 3 is synthesized by first oxidizing and then reducing phenols. The chirality of carbon 6 is ensured by Noyori asymmetric hydrogenation. After 2 and 3 are synthesized, a MBH reaction connects them, providing the microketides A and B.

1. Introduction
Polyketides are a large group of acetate derived natural products with bioactivities. These natural products usually contain alternating carbonyl groups and methylene groups. Or they are derivations of the compounds which have such alternating groups. Polyketides have a wide range of structure and can be isolated from various kinds of microorganisms, such as bacteria, fungi, or plants. Some polyketides have antibiotic or antifungal activity and thus used as pharmaceutical drugs, while some of them are toxic. Due to its antimicrobial activity, polyketides have a wide range of application. For example, it could be applied in agriculture as insecticides, die to its toxicity. Since polyketides shows great potential in many fields, the synthesis of polyketides becomes more and more important and attracts the attention of more and more scientists.

Among the family of polyketides, microketides A (1a) and B (1b), a pair of C-11 epimeric polyketides, were isolated form the gorgonian-derived fungus Microsphaeropsis sp. RA10-14 from the South China Sea. Microketide A showed the ability to inhibit activity of some bacteria such as Nocardia brasiliensis and Bacillus anthraci. In this paper, a synthesis method of microketide A and B is proposed.

2. Discussion
The first step of the proposed retrosynthesis is to make a disconnection between the two rings of the Microketide, separating it into 2-(bromomethyl)-3-methylphenol (2) and (6S)-5,6-dihydroxy-3,6-dimethylocyclohex-2-en-1-one (3). The advantage of this disconnection is that it converts a compound...
with two rings to two rig structure, which is easier to synthesis dividedly than as a whole. Another advantage is that 3 is a polyketide which have been isolated from *Penicillium* sp. JP-1 in 2007. This shows that this compound is existed stably in nature, which might favors the synthesis. In the synthesis of 2, an ortho-position specific catalyst will be used to attach the bromomethyl group on the 2-position. The synthesis of 3 mainly consists of an oxidization reaction and a reduction reaction.

Scheme 1. RETROSYNTHETIC ANALYSIS OF MICROKETIDE A & B.

A. Disconnection of Microketide A and B

B. Ortho-position specific catalyzed aromatic substitution for the synthesis of 2

C. Oxidization and then reduction of phenols for the synthesis of 3

Figure 2. Retrosynthetic analysis of Microketide A & B.

Scheme 2. Synthesis of 2 by ortho-specific alkylation of phenols.

Figure 3. Synthesis of 2 by ortho-specific alkylation of phenols.
2 is an aromatic compound with three functional groups next to each other on the ring, while no functional groups on the other side of the ring. To obtain this structure, m-cresol (5) is chosen as the materials because of its structural similarity to 2 and high accessibility in comparatively low price. However, if electrophilic aromatic substitution directly applied on 5, the conversion rate of 2 will not be high due to the huge steric hinderance of position 2. Although both hydroxyl group and methyl group are activating group in electrophilic aromatic substitution reaction and thus position 2 is favored, due to much less steric hindrance, position 4 and 6 will be much more favored than position 2, which makes 2 with low selectivity. To solve this problem, phenylboronic acid is introduced as an ortho-specific catalyst. According to the literature, phenol can react with phenylboronic acid and aldehyde in refluxing toluene and form a corresponding 2-phenyl-4-alkyl-1,3,2-benzodioxaborins which, in this case, is 4. Then, with aluminum chloride, 4 will eventually be converted to an o-alkylphenol, 5.6 (scheme 2).

However, the problem of steric hindrance still exists. Although ortho-specific catalyst eliminates the possibility of which the bromomethyl group is added on the position 4. Position 6 is still a more favored choice than position 2. Thus, in the product, there will exist a lot of 2-(bromomethyl)-5-methylphenol, which is the side product of this reaction. According to the literature, there will also be about 25% of the m-cresol remain unreacted.6 However, since m-cresol is highly accessible, if a large amount of m-cresol is used in the reaction, even with comparatively low conversion, enough 5 can still be obtained for further synthesis.

The first step of the synthesis of 3 is to oxidize 2,5-dimethylbenzene-1,3-diol (8). The selected oxidizing agent is SIBX. According to the literature, SIBX and IBX both have ability to oxidize diphenyl.7 SIBX will convert 8 into 5,6-dihydroxy-3,6-dimethylcyclohexa-2,4-dien-1-one (7). 7, as an alkanol, is not stable. Keto-enol tautomerism will happen on it, converting 7 to 5,6-dihydroxy-3,6-dimethylcyclohexa-2,4-dien-1-one (6).

However, the tautomerism also bring constrain to this synthesis. In the tautomerism, when the base takes the proton on the hydroxyl group, both double bond between carbon 2 and carbon 3 and between carbon 4 and carbon 5 can get protonated, because the dislocated π bond structure. Thus, there will be two paths in the tautomerism, providing a pair of enantiomers. These two paths show that conversion existed between this pair of enantiomers, changing the chirality of carbon 6. Thus, 6a and 6b cannot be separated in this step and the obtained 6 will always be racemic.

After the 6 is obtained, there are two ketone functional group in the compound. To achieve the 3, the ketone on carbon 5 need to be reduced, while the ketone on carbon 1 need to be conserved. This can be achieved by the difference of the two ketones. Since the ketone on carbon 1 is conjugated with a carbon-carbon double bond, it tends to be less reactive than the ketone on carbon 5. Thus, the ketone on carbon 5 will firstly be reduced. By cooling down the temperature, which slows down the reaction rate, the moment that ketone at carbon 5 is reacted while the ketone remain unreacted can be captured, thus providing 3.
Scheme 3. Synthesis of 3 by oxidation of SIBX and then reduction.

Scheme 4. The mechanism of keto-enol tautomerism of 6

Scheme 5. Synthesis of 3a and 3b by Noyori asymmetric hydrogenation

Scheme 6. Protection of diol of 3 by 3-pentanone

Scheme 7. Synthesis of 1 by an MBH reaction to connect 2 and 3
The chirality of carbon 6 is another problem to concern. To make the reaction stereospecific, Noyori asymmetric hydrogenation is introduced. According to the literature, a BINAP-Ru(II) complex can reduce ketone asymmetrically. The complex can be obtained by heating a mixture of [RuCl₂(benzene)]₂ and (R)- or (S)-BINAP in a ratio of 1:1.05. Then, the 6 can be added to the complex and with a high pressure of hydrogen gas, the stereospecific reduction will take place. After the reduction step is finished, by removing the compound with R-configuration on carbon 6, 3 with desired chirality can be obtained.

After obtaining 2 and 3, before making the connection, the diol on the 3 requires protection, in case they get reacted in the later connection. To achieve the protection, protection agent such as 3-pentanone could be applied. After the diol of 3 is protected, 2 and 3 can be connected by the hydroxy chalcogenide-promoted Morita-Baylis-Hillman-type alkylation reaction. Professor Perez-Castells and his team has showed that with hydroxysulfide and base, such as CsCO₃, connection can be made between cyclohexenones and benzyl bromide. Thus, 2 and 3 can be connected under this conditions (scheme 7). In the reaction, the dipole of the sulfur on the hydroxysulfide will attack the carbon on position 3, pushing the double bond to form a enol as an intermediate. Then, the dipole on the oxygen go backward and push the double bond which attack the carbon with bromide on 2. Then, the bromide leaves and a carbon-carbon bond is formed. Finally, the base take the proton on carbon 2. The electrons go between carbon 2 and 3, reforming the double bond, making the hydroxysulfide leave and providing us the microketides A and B with diol protected. At the last step of the synthesis, the protected diol can be deprotected by TFA and THF in water, which finally bring the microketides A and B. (scheme 8)

3. Conclusions
In this paper, a potential synthesis routine of a pair of microketides A (1a) and B (1b) is purposed. This pair of microketides were separated from fungi in Southern China Sea. At first, the retrosynthesis analysis is applied to find a possible synthesis routine for this pair of microketides. Then, the forward reaction and its reaction condition are discussed. The microketides are divided into two parts, 2 and 3. 2 is purposed to be synthesized by an ortho-specific alkylation of phenols. 3 is synthesized by first oxidizing and then reducing phenols. Then, to achieve different chirality of carbon 6, Noyori asymmetric hydrogenation is purposed to applied. In final, a MBH reaction is purposed to connects 2 and 3, which finally bring us the pair of microketides, A and B.

Acknowledgments
Yudian Wu gratefully acknowledge Professor Brain M. Stoltz.

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