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Retrosynthetic Pathways of Decahydrofluorene-Alkaloid Microascones B

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Abstract:

Microascones B is a compound that can be a candidate for antibacterial material and is discovered and obtained from marine-derived fungus with complex 12- or 13- membered ring structures. Since no one has provided the forward synthesis and retrosynthesis pathway, we have introduced a possible retro-synthesis pathway in this work. The retrosynthesis of this complicated compound can be done in several steps into starting materials. Some of the core retrosynthesis strategies contain the analysis of di-oxygenation patterns to break bonds retro-synthetically by applying aldol reactions and Grignard as well as anion addition. Moreover, the Diels-Alder reaction is also one of the core reactions to break those multiple rings in this retrosynthesis pathway.

Keywords:-Microascones B; marine fungus; retrosynthesis; Diels-Alder; di-oxygenation.

1. Introduction

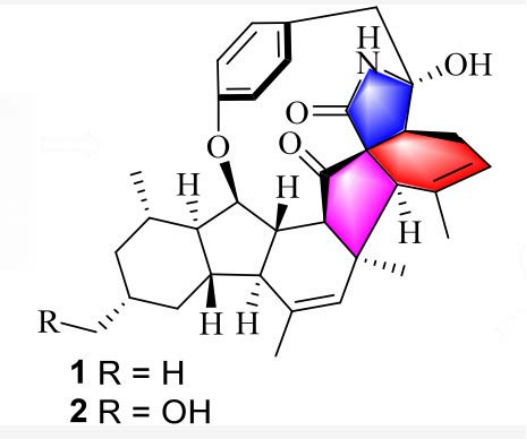

Fig.1 Structure of Microascones A(1) and B(2).

Decahydrofluorene-class alkaloids are a class of macrocyclic alkaloids with complex 12- or 13- membered ring structures. Newly discovered such class of compounds are extracted and obtained from marine-derived fungus from the South China Sea named *Penicillium sp.* SCSIO 41512[1]. More specifically, there are eight decahydrofluorene-class alkaloids containing antibacterial and enzyme inhibitory activities extracted from *Penicillium sp.* SCSIO 41512, including the microascones B which this essay's retrosynthetic ideas discuss (see Figure 1). Basically, the microascones B is a compound containing continuous and interconnected five- and six- membered rings attached with hydrogen, oxygen, hydroxyl groups, and other function groups [2]. In this work, our group chose such a compound to conduct its retrosynthesis procedure in consideration of its structural complexity of its complicated but mannered ring structures that evoke our interest in analyzing its possible retrosynthesis methods. Moreover, retro-synthesis analysis and forward synthesis of this molecule have not yet been studied.

2. Retrosynthesis Pathways of Microascones B

2.1 Basic ideas and methodologies

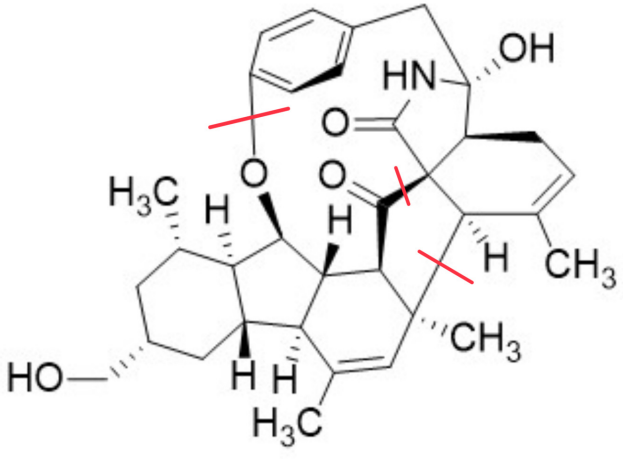

Fig.2 The bounds to be broken for breaking the molecule apart.

Initially, to cope with such an intricate molecule with multiple rings, it will be transformed into a simpler problem if we can break the bounds in one of the rings to break the whole molecule apart into two simpler parts with fewer rings so that a clearer picture of how retrosynthetic methods work can be shown. For microascones B, its characteristic of how rings are connected proposed a possible and efficient pathway that breaks the carbon-oxygen bond connecting the benzene ring and major ring-chain as well as two single bonds of the five-membered ring in the middle can effectively get the whole molecule into two separate parts (see Figure 2).

2.2 Initial Bond-breaking

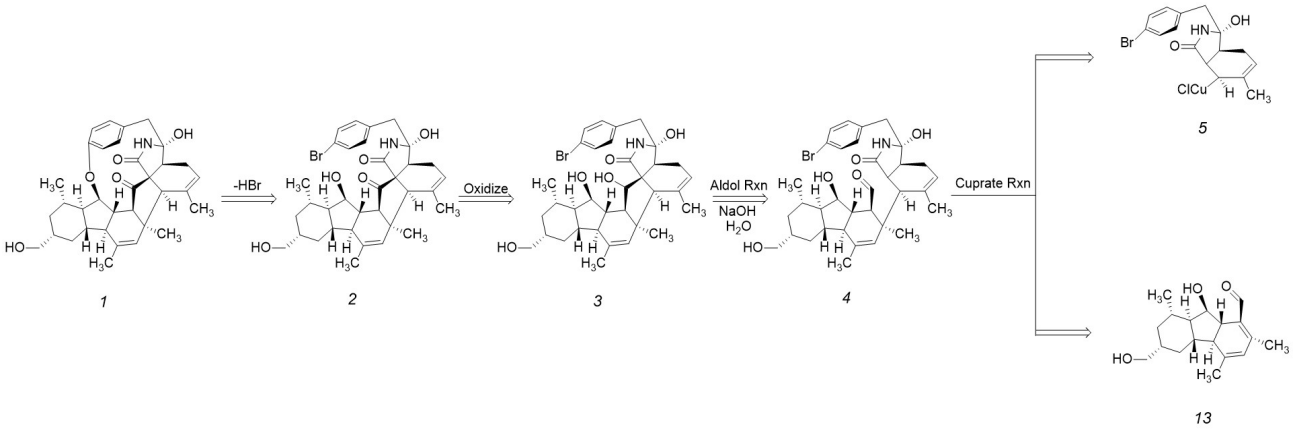

Fig.3 The break-up procedures of the target molecule.

To start with, the carbon-oxygen bond up on the chain needs to be removed. By applying hydrogen bromide, this bond can be converted retro-synthetically into the form that a bromine attached to the end of the benzene ring, and the oxygen is then transformed into a hydroxyl group on the five-membered ring of **2**. Then, by oxidization, the oxygen on the fourth ring from the left, which is the five-membered ring that we wish to deconstruct, can be converted into a hydroxyl group and form a 1,3-dioxy pattern and then undergoes an aldol reaction to break the carbon single bond Number 1 in **3** [3,4]. After that, by utilizing cuprate reagent, the last connecting bond Number 2 of two parts of the molecule can be broken in **4**, and formally get apart into an upper section **5** attached with copper and chlorine and a lower section **13** (see Figure 3).

2.3 Decomposition of the upper section

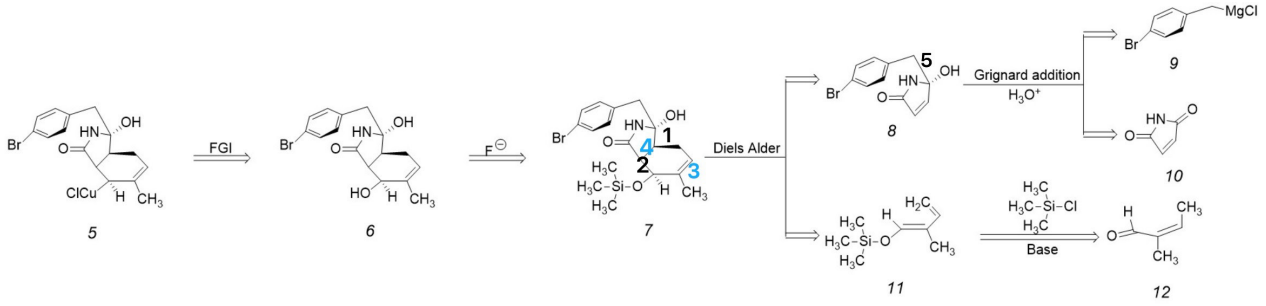

Fig.4 The application of Diels-alder reaction to break up the upper part.

For the upper section, the first procedure to take is to change the copper and chlorine on the end of the six-membered ring in 5 into a hydroxyl group in 6 through function group interconversion (FGI). As there is an olefin on the six-membered ring, it is possible to do a Diels-Alder reaction to break bonds 1 and 2 in 7, and transfer bond 3 into a single bond and bond 4 into a double bond, so that this six-membered ring can be deconstructed [5]. Nevertheless, standing on a forward synthesis aspect of thinking, the hydroxyl group tends to be tautomerized and directly forms a molecule like **12**, which can disturb the Diels-alder reaction. Thus, it is crucial to add a silylether protection group on that hydroxyl group under basic condition shown in **11**, and the protection group can be eventually removed by fluorine ions from **7** to **6** in the forward reaction; hence, for the retrosynthesis, the fluorine ions take place at earlier steps. Simultaneously, for the remnant with a benzene ring and a five-membered ring with a nitrogen, Grignard reagent can be applied to form bond 5 and change the carbonyl group to alcohol as shown in **8**,

and it becomes two starting materials: one benzene ring with bromine, magnesium, and chlorine attached shown in **9**, and a symmetric five-membered ring with two carbonyls shown in **10** (see Figure 4).

2.4 Decomposition of the lower section

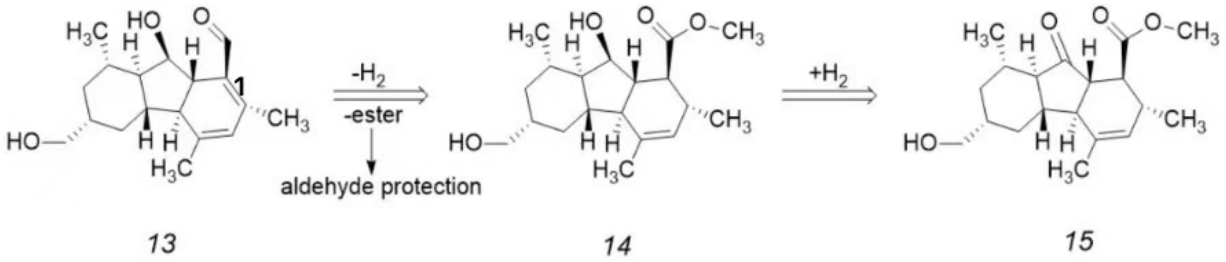

Fig.5 Protecting the aldehyde by ester retro-synthetically.

For the lower section, as the presence of aldehyde on the six-membered ring tends to be reactive and lead to the instability of the reaction, we decide to make the aldehyde from an ester forward-synthetically immediately when we need to aldehyde instead of keeping it as an aldehyde throughout the whole retrosynthetic pathway. Therefore, we retro-synthetically change the aldehyde back to the ester shown in **14**. At the same time, dehydrogenation can lead to the double bond number 1 as marked in **13** turning back to a single bond retro-synthetically. Then by one more hydrogenation, the hydroxyl group on the five-membered ring transforms back to a carbonyl group.

For the following steps, for there appears an olefin on the six-membered ring on the right shown in **15**, a Diels-Alder reaction can be done to break the six-membered ring on the right. On the other hand [5], it is considered that the compound at this step has two possible routes of Diels-alder reaction. It can be either doing one breaking by Diels-alder and simultaneously deforming the six- and five-membered rings to **16** or take two Diels-alder reactions at the same time to break away the multiple bonds and results in two chains of carbon and function groups shown in **33** and **38** (see Figure 5).

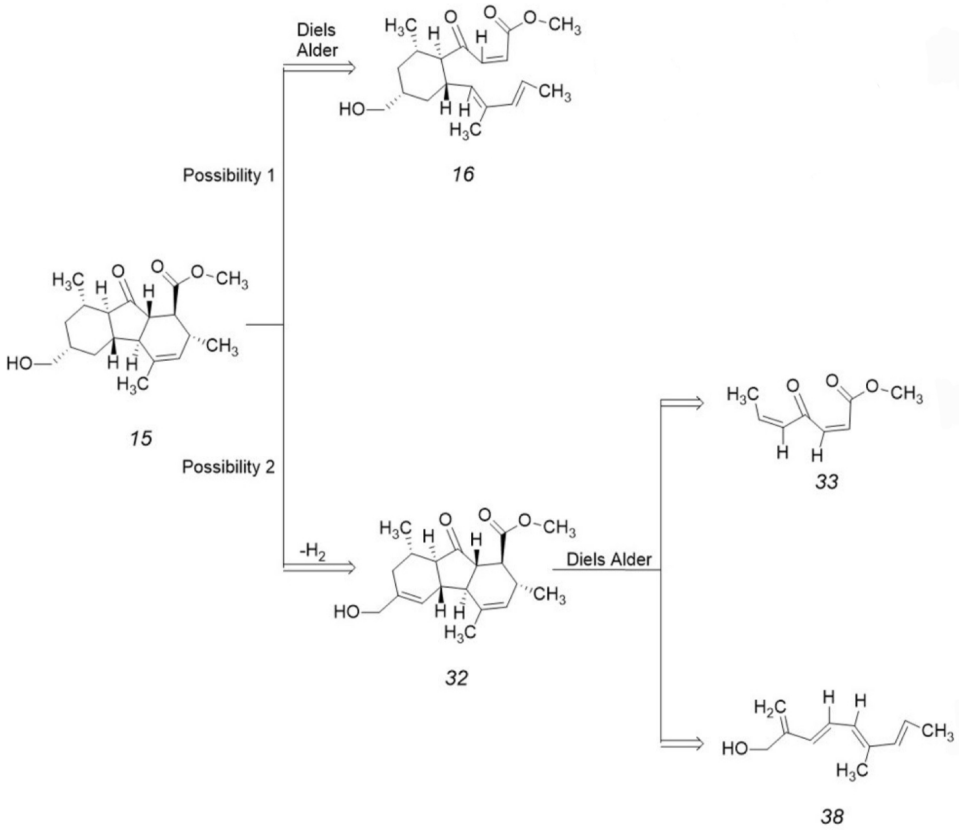

Fig.6 single Diels-Alder reaction and double Diels-Alder reactions.

2.4.1 Single diels-alder reaction

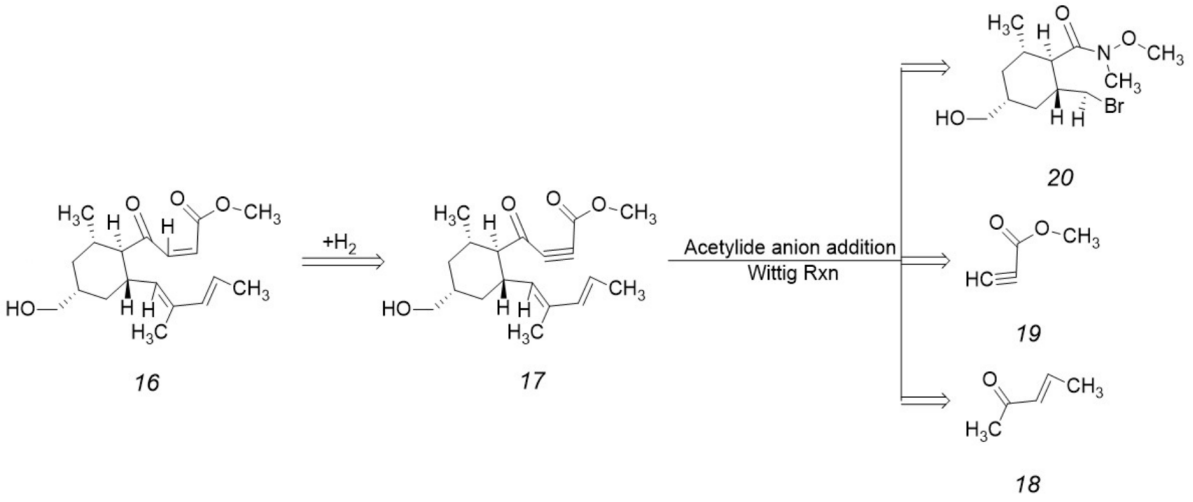

Fig.7 Application of acetylide anion addition and Wittig reaction.

For the pathway of a single Diels-alder reaction [5], the double bond on the upper side can possibly turn back retro-synthetically to a triple bond as shown in **17**, which is hydrogenation in forward synthesis. By now, the compound performs as a six-membered ring attached with two chains, one with ketone group, triple bond, and ester group on the end, and one with alternating single and double bonds (see Figure 6).

Hence, steps are taken to peel off these two leaving parts from the six-membered ring. First, by taking an acetylide anion addition, the ester on the upper end with a triple bond can be taken off as a starting material**19**, and the end of the ketone group will relate to a Weinreb amide protection group on the end. Second, by taking a Wittig reaction on the olefin on the left of the chain, this double bond can be deconstructed [3], and yield a ketone **18** and a halogen on the end of the chain of **20** (see Figure 7).

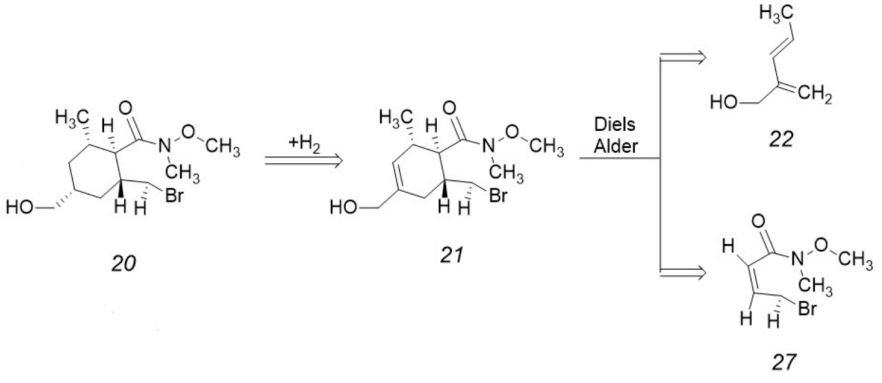

Fig.8 Diels-alder reaction applied on the olefin of the six-membered ring.

By changing the single bond into an olefin on the six-membered ring, another Diels-alder reaction can be taken [5], so that the ring can be disassembled into a chain connected with hydroxyl group shown in **22** and another group with amide on its one end shown in **27** (see Figure 8).

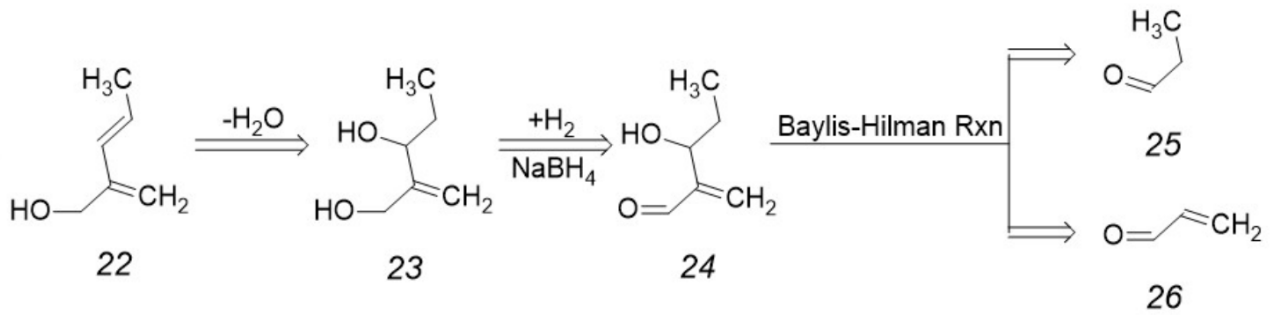

Fig.9 Baylis-Hilman Reaction after some adjustments.

For the upper chain, dehydration process in forward synthesis allows the addition of one hydroxyl group onto the carbon chain retro-synthetically, and $NaBH_4$ workup can transform the down hydroxyl group into a carbonyl group retro-synthetically in **24**. After that, the compound undergoes a Baylis-Hilman reaction to disconnect the bond in the middle and ends up with two aldehydes as starting materials **25** and **26** (see Figure 9).

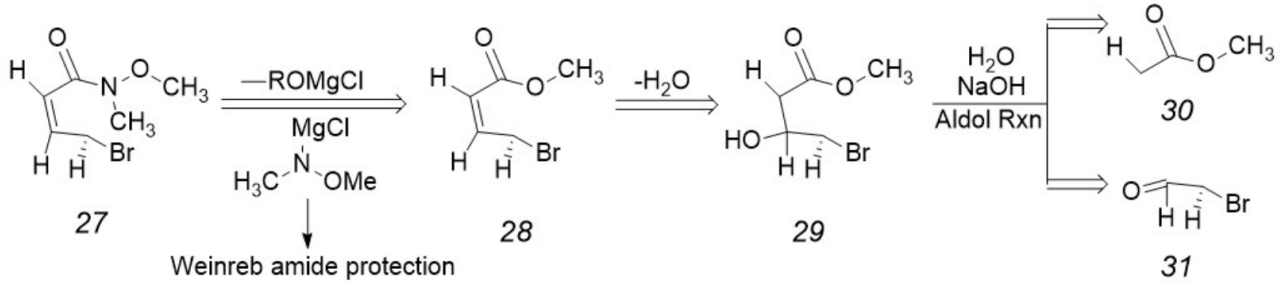

Fig.10 Application of Weinreb amide protection group and 1,3 dioxy-pattern aldol reaction.

For the lower chain, the Weinreb protection group can first be taken away back to an ester group shown in **28**. By dehydration turning the hydrogen on the olefin into a alcohol, it turns out to be a 1,3-dioxy pattern and can be treated with an aldol reaction to break the bond in the middle [4], resulting in **30**, an ester, and **31**, an aldehyde, as starting materials. As reminders, for **31**, we will stop here in our retrosynthesis; however, if it is in forward synthesis, it might have to be formed by another starting material that is more stable since 31 itself doesn't have high stability (see Figure 10).

2.4.2 Double Diels-Alder Reaction

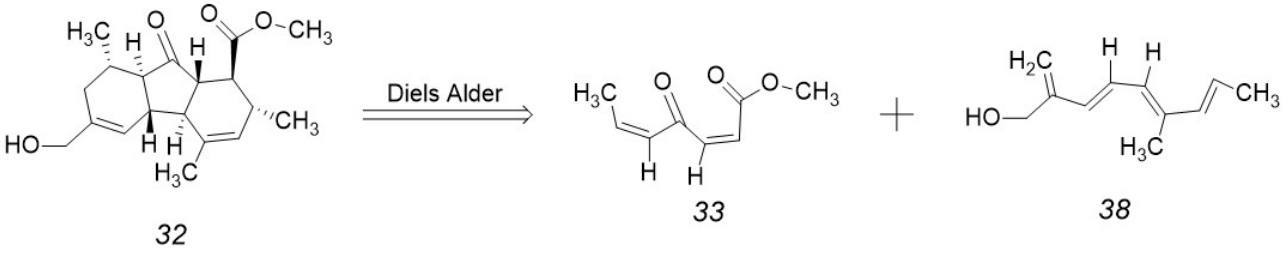

Fig.11 Applying Diels-Alder reaction on two olefins simultaneously.

In comparison to doing one Diels-alder reaction at one time and deconstruct the rings separately and gradually, another possible pathway is to do two Diels-alder reactions at the same [5], so that the three rings that currently exist can be all deconstructed at the same time. Eventually, there are two separate chains containing multiple olefins, one with carbonyl groups on the chain and amide on the end of **33**, and the other one with multiple methyl groups on the chain and hydroxyl group on the end of **38** (see Figure 11).

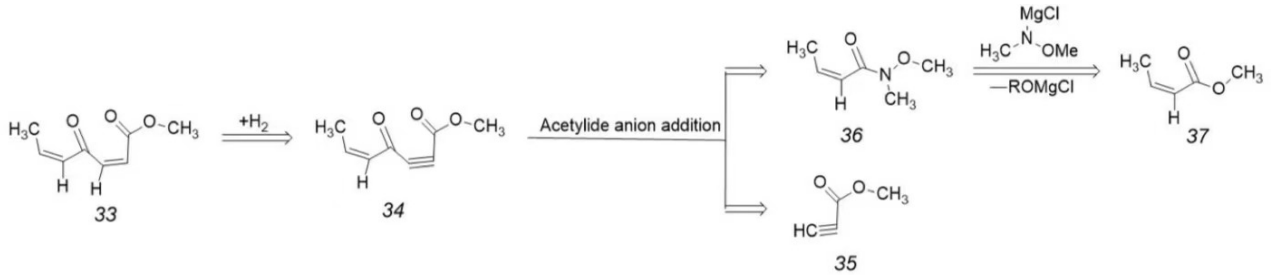

Fig.12 Acetylide anion addition and the add-on of the Weinreb amide protection group.

For the chain with carbonyl and amide groups, the method to cope with is fundamentally identical to the other pathway, which uses Acetylide anion addition to cope with the Weinreb amide protection as the process shown in Figure 12. Then, the Weinreb amide can turn back to **37,** an ester, retro-synthetically (see Figure 12).

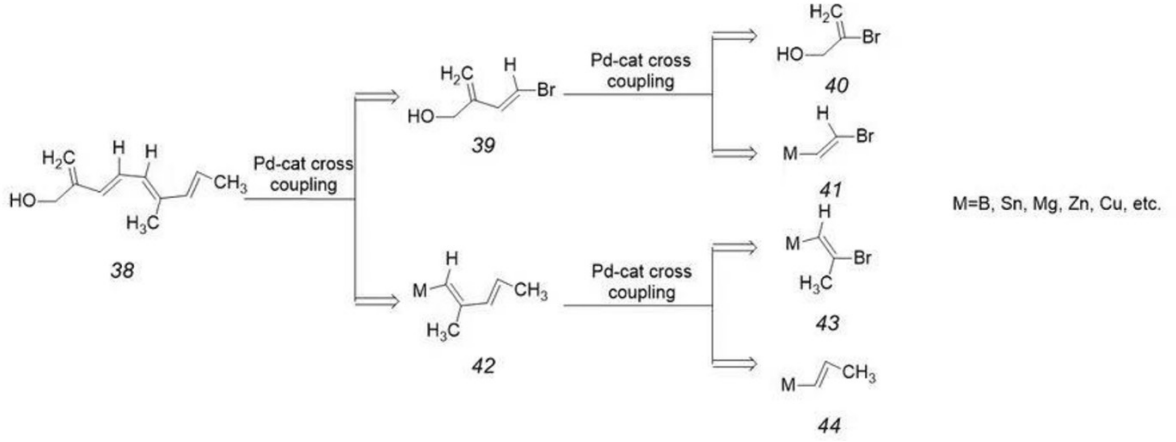

Fig.13 Breaking up single bonds by palladium-catalyzed cross-coupling.

For the chain with multiple methyl groups attached, a palladium-catalyzed cross-coupling reaction can be applied to the carbon-carbon single bonds [6]. Basically, this reaction can form carbon-carbon single bonds by one of the carbons connected to a halide of an olefin molecule and the other carbon in another olefin molecule connected with certain elements represented by M which includes boron, tin, magnesium, zinc, copper, etc. Therefore, it helps to break the carbon-carbon bonds from the middle of the molecules **38**, **39**, and **42** in Figure 13 retro-synthetically. As seen in Figure 13, though tricky to get rid of the double bonds in the chain, by palladium-catalyzed cross coupling reaction [6], the single bonds can be broken and eventually come up with starting materials **40**, **41**, **43**, and **44** (see Figure 13).

3. Conclusion

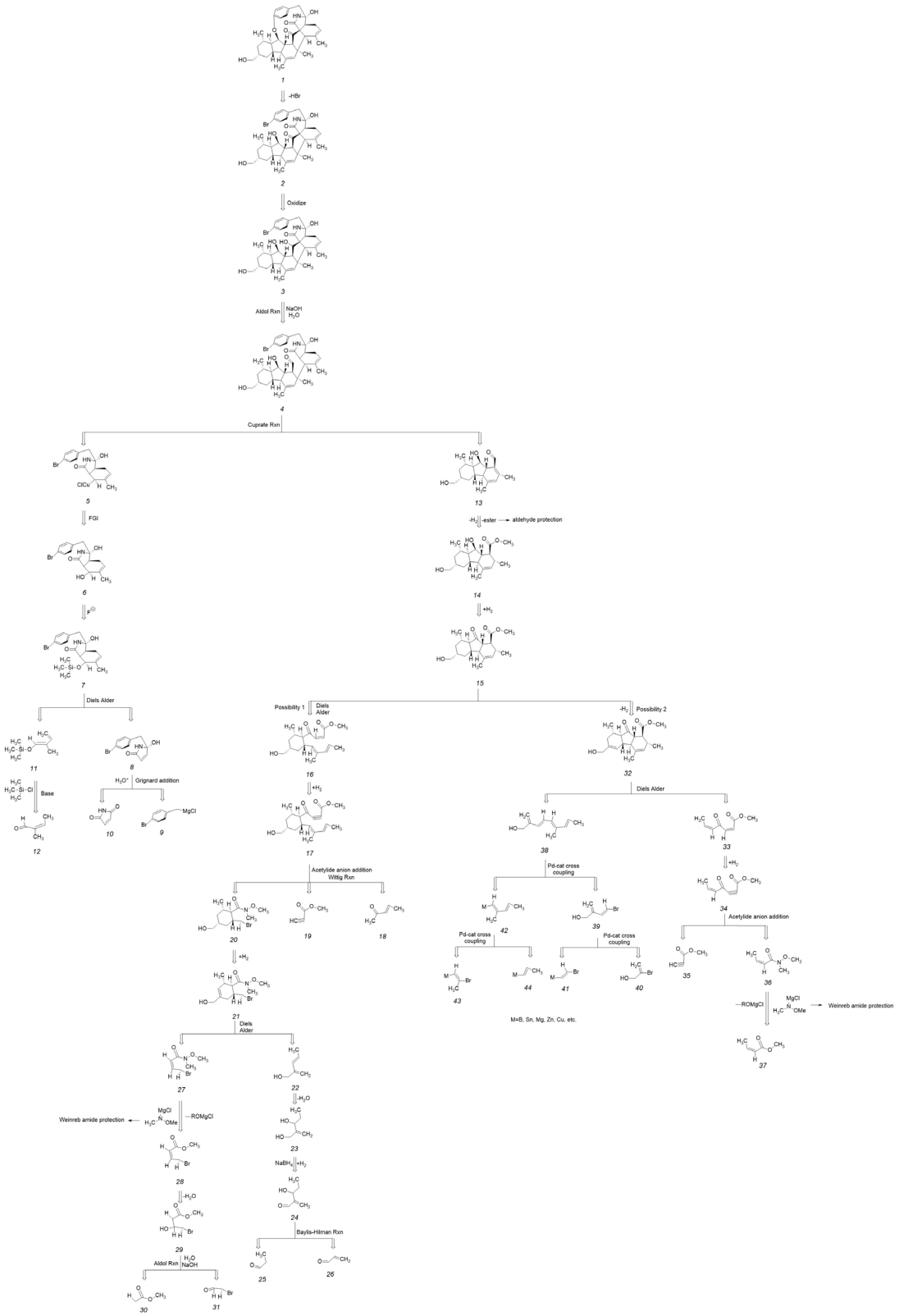

Fig.14 Overview: the retrosynthetic “tree”.

Throughout the whole retrosynthesis pathway, we have used various common retrosynthesis strategies and reactions such as the Diels-alder reaction, aldol reaction, anion addition, Wittig reaction, and palladium-catalyzed cross-coupling reaction to apply strategic disconnections on crucial bonds (Figure 14). By breaking the essential ring in the middle, we are able to split the target molecule into two separate compounds and create two convergence pathways (see Figure 14). In the end, we are able to breakdown the complex and complicated target molecule **1**, Microascones B, into some small starting materials with very simple structures and functional groups such as **9**, **12**, **25**, **26**, **30**, **31**, **37**, **35**, **40**, **41**, **43**, and **44**. This retro-synthesis pathway proposal will generate some insights for the forward synthesis of Microascones B in future research, which will further promote the field of antibacterial material since Microascones B is one of the candidate compounds for developing antibacterial agents[2] (see Figure 14).

4. Acknowledgments

Wentian He and Yinuo Cai contributed equally to this work and should be considered co-first authors.

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