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Phomactinine: proposed Retrosynthesis and Forward Synthesis Routes

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Abstract:

Phomactinine, a newly discovered substance separated from marine fungal secretion, is the first discovered nitrogen-bearing phomactin.[1] In this work, a total synthesis for phomactinine is proposed. Initiating from making an α, β-unsaturated Weinreb amide, the synthesis undergoes a [4+2] cycloaddition, followed by a carbon chain elongation. After a [2+2] addition under photochemical condition, a side chain is added, in which process an epoxide forms. Then, ways to close the nitrogen bearing ring are suggested. The route ends with forming a phosphorous ylide intermediate, which leads to the closure of the 11-carbon-ring by Wittig reaction. In this synthesis scheme, an innovative approach of differentiating carbonyl groups with similar reactivity by utilizing the different stability of carbon rings is suggested. This paper proposed the first total synthesis for phomactinine.

Keywords: phomactinine; retrosynthesis; total synthesis; differentiating carbonyl groups

1. Introduction

Phomactinine(see Figure.1) is a recently isolated phomactin from a media where marine-derived fungus Biatriospora sp. CBMAI 1333 grow on[1]. Phomactinine is found to be the first phomactin with a nitrogen, where phomactins are a class of molecules exhibiting ability to inhibit platelet aggregation factor (PAF). In other words, phomactinine displays potential use in medical field. Thus, the structure of the molecule is analyzed via retrosynthesis, and a chemical approach to synthesize phomactinine is proposed.

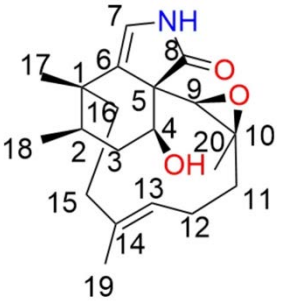

Figure. 1 Phomactinine

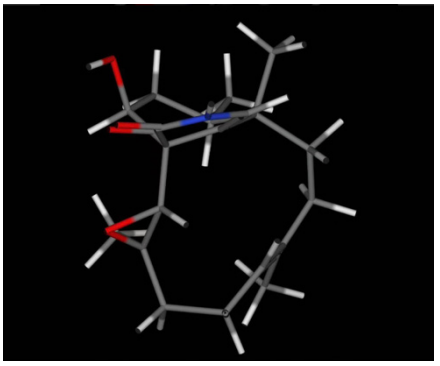

Figure. 2 Phomactinine 3D model

2. Retrosynthesis of phomactinine

A 3D model is bulit for analysis(see Figure. 2). Noticing that the 6-carbon-ring and the connected nitrogen-bearing ring is nearly situated in a plane, while the 11-carbon-ring is beneath the plane, the unique big ring is broken first (perform ring closure in the last step of forward synthesis) as the beneath ring will create hindrance for many reactions. Therefore, the retrosynthesis starts with breaking the carbon double bond at position 13-14 in the 11-carbon-ring into 2 side chains (see Figure. 3). Further, the retrosynthesis route divides into 2 separate routes A and B, with route A being the major route. In route A, we continue to break the nitrogen-bearing ring to form structure 3. As carbon 5 is fully substituted, side chain 5 is further disassembled from structure 3. The olefin-containing 4-membered-ring 4 is then broken down to an alkyne and an olefin-containing 6-carbon-ring 8. We notice this unique olefin in the ring, and devise a way to set it apart retrosynthetically using Diels-Alder reaction, leading to an α,β-unsaturated Weinreb amide 9 and a Danishefsky's diene 10 (commercially available) as the product of our retrosynthesis. In retrosynthesis route B, the first key strategy remains the same. However, other than route A, in the next step, strategy to remove side chain 5 is proposed. The remaining part is molecule 7, in which the nitrogen-bearing ring can be further broken down into a 4-carbon-ring with an olefin. The further retrosynthesis steps in route B is the same as that in route A.

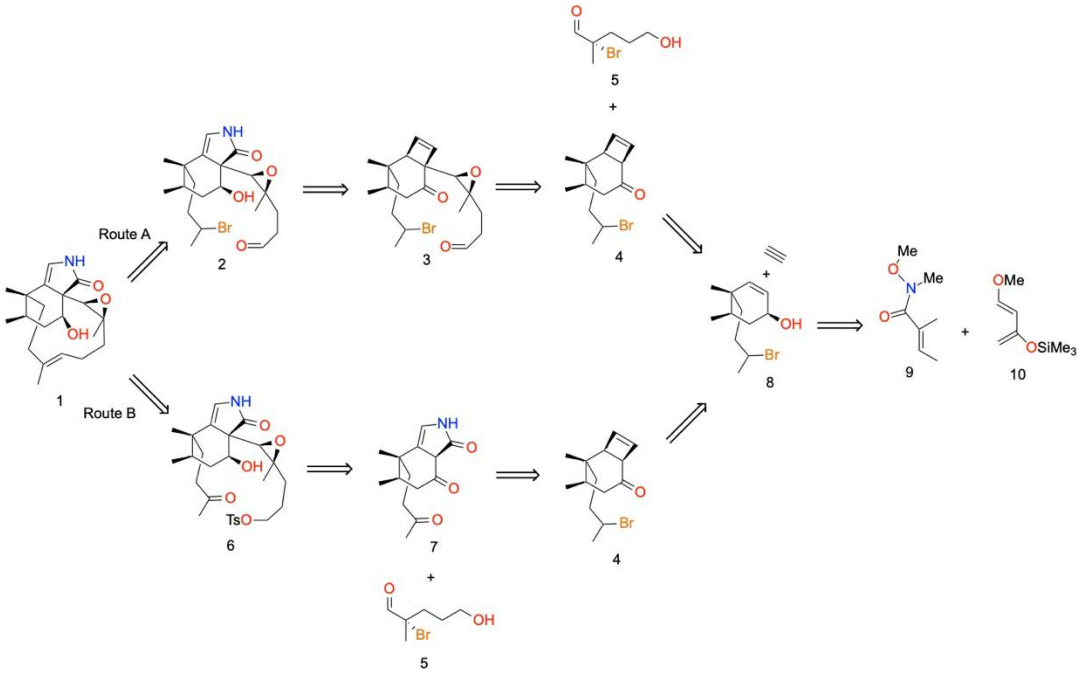

Figure. 3 Scheme. 1 Retrosynthesis of phomactinine, 2 routes.

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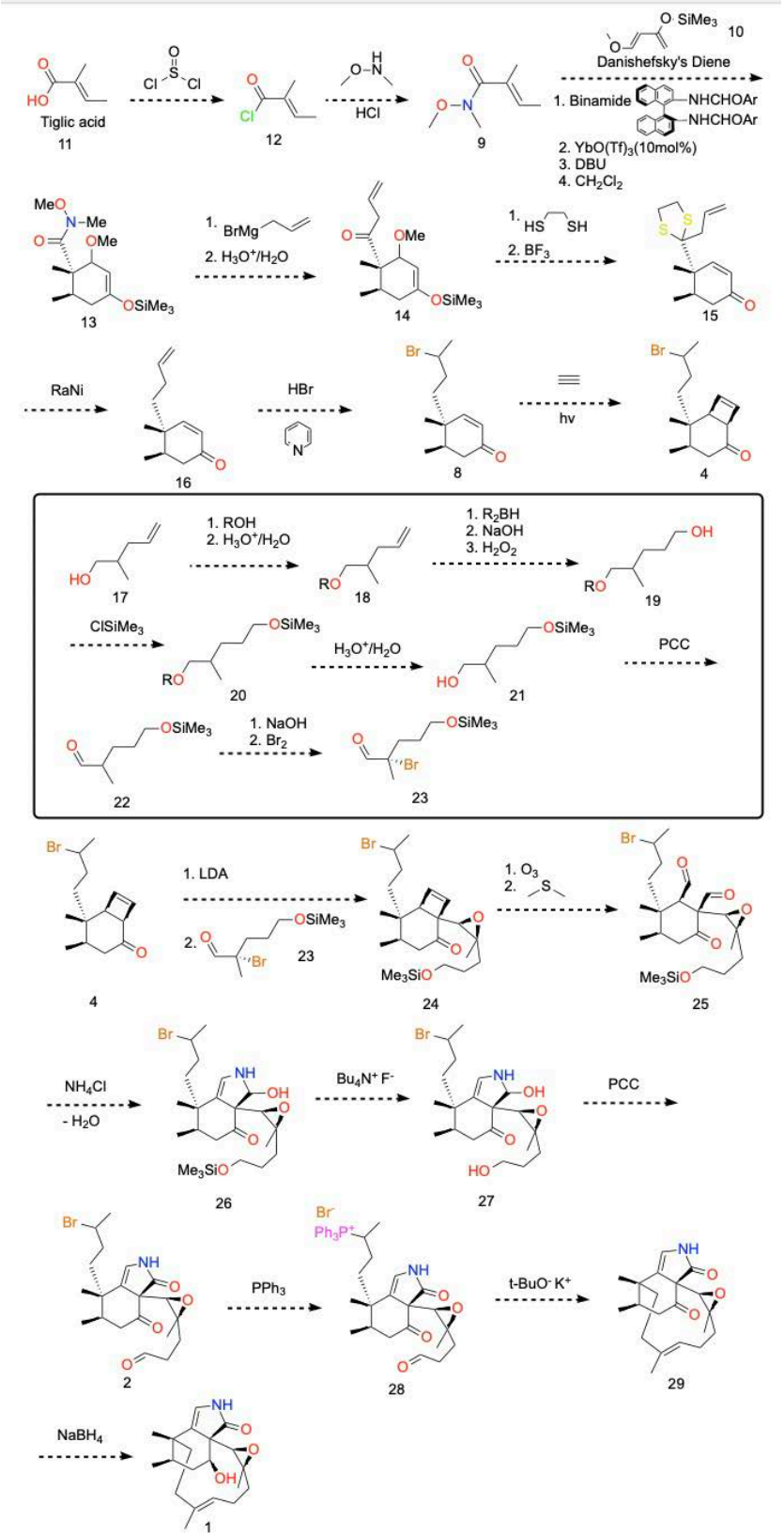

Figure. 4 Scheme 2 Synthesis Route A.

3. Total Synthesis of phomactinine

3.1 Route A

The first target is to synthesize structure 8 (see Figure. 4). After analysis and finding out the specific olefin group in the ring, the use of Diels-Alder reaction is suggested. The synthons of molecule 8 are molecule (1) and (2) (see Figure. 5). However, in molecule (1), carbon1 is disubstituted, and there is no recorded reaction that can prove that an end-disubstituted-diene can perform Diels-Alder reaction.

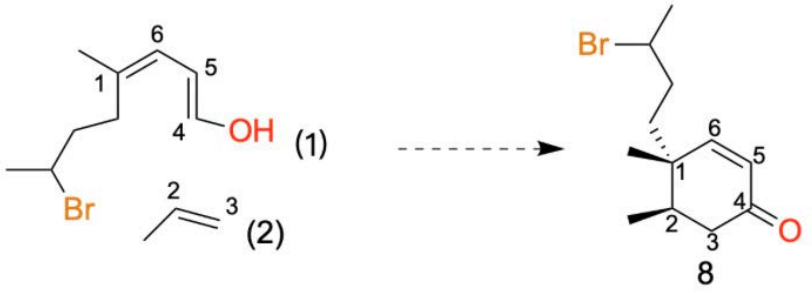

Figure. 5 Synthons of molecule 8 via Diels-Alder.

Moreover, for a diene to react with dienophile, the diene has to be electron-rich, while the dienophile being electron-poor[2]. However, molecule (2) does not electron-withdrawing-group (EWG), meaning that it is not electron-poor. Hence, Diels-Alder reaction cannot be carried out between molecule (1) and (2) to make molecule 8. Inspired by the α,β-unsaturated ketone, we shifted the π system to form a π bond between carbon 4 and 5, while adding HX into the system (see Figure. 6). With this change, the target molecule becomes 8* instead of 8, where 8* can be synthesized by Diels-Alder reaction. Molecule 8* can be easily converted to molecule 8, as the lone pair electrons on oxygen on carbon4 in molecule 8* can attack the olefin, and the π bond will shift to the position 5-6, expelling the X leaving group

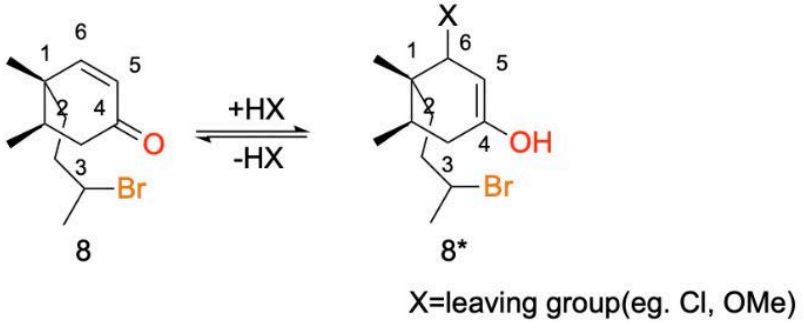

Figure. 6 Shifting the π system.

Originally, the synthesis uses molecule (3) and (4) to synthesize 8* (see Figure. 7), where X is a leaving group. The ester group on molecule (3) is to create an electron-poor dienophile, as ester is a strong EWG, and ester group allows further addition of carbon chain by organometallic reagents.

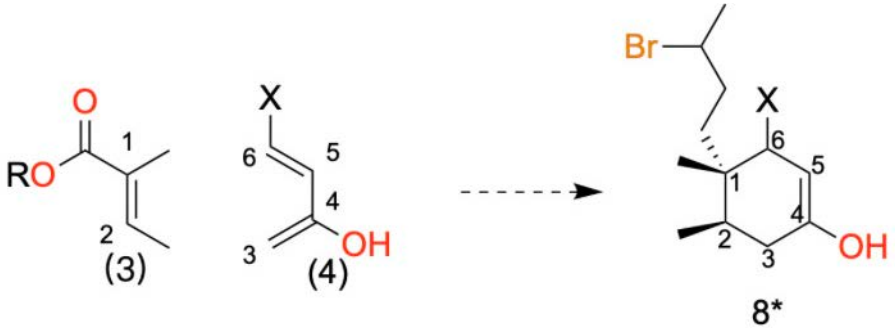

Figure. 7 Diels-Alder reaction to synthesize 8*.

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For the X group on molecule (4), a halogen leaving group such as Cl is used in the procedure at first, therefore obtaining molecule e (see Figure. 8). To create molecule e, we have to start from an ethyne group with a chloride as in molecule a. Then, LDA is used as a strong base to deprotonate it, allowing the aldehyde to bind. Further, we tautomerize c to form a diene d, and then protect the hydroxyl group with trimethylsilyl (TMS) group. However, this way of synthesizing the diene is not ideal. Firstly, there are no vendors selling alkyne a. Moreover, the tautomerization favors the ketone product, lowering our yield. Therefore, we choose another diene with a different leaving group.

Figure. 8 Molecule e synthesis.

The structure of molecule (4) reminds us a particular diene that is commonly used: the Danishefsky's diene (see Figure. 9). This diene has a TMS protecting group that will protect the hydroxyl or carbonyl group in the following reactions, while the ether group acts as a leaving group.

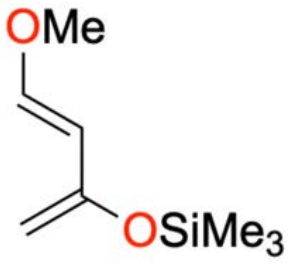

Figure. 9 Danishefsky's diene.

For molecule (3) to react with Danishefsky's diene, we would get molecule (5) with an ester (see Figure. 10). To form molecule 8*, we still have to elongate the carbon chain using Grignard reagent, where the ester becomes problematic as Grignard reagents add twice to the ester group.

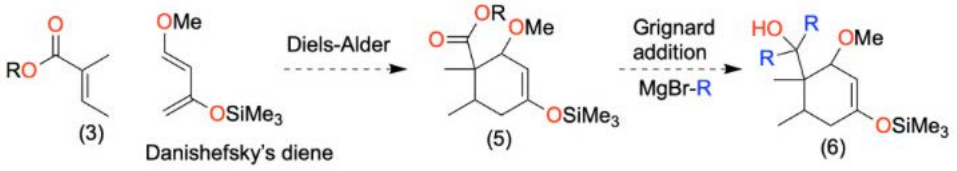

Figure. 10 Grignard addition.

To tackle this problem, we decide to use Weinreb amide instead of molecule (3), we Weinreb amide also has C=O bond to act as EWG, and it only allows Grignard reagents to add once[2]. The mechanism of adding Grignard reagent to Weinreb amide is introduced.(see Figure. 11)

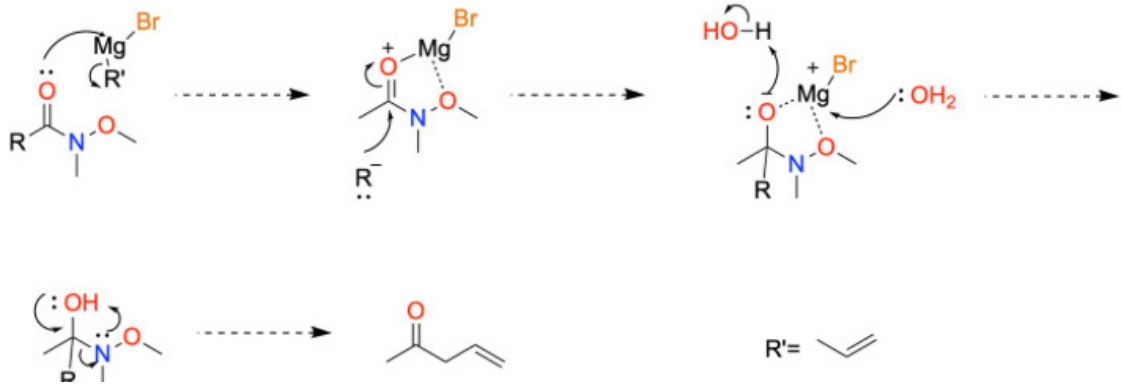

Figure. 11 Grignard addition to Weinreb amide.

Therefore, the Diels-Alder reaction would react molecule 9 and 10 together to form a racemic mixture of 2 enantiomers: molecule 13 and 13* (see Figure. 12)

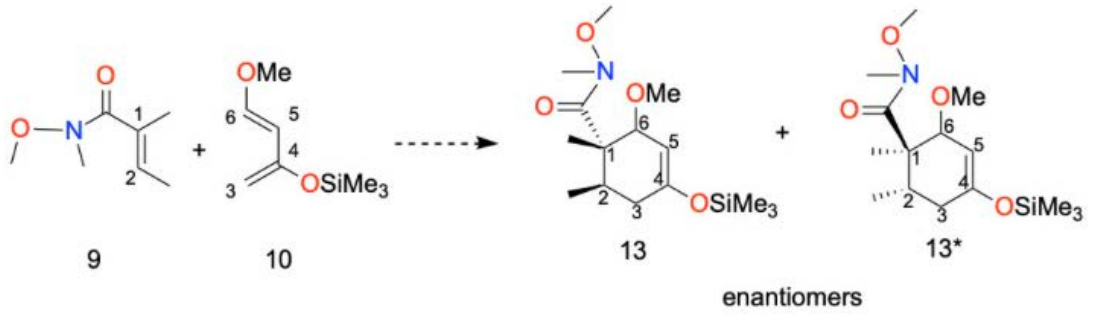

Figure. 12 Racemic mixture of 2 enantiomers.

The reason why there are only 2 isomers produced is due to the regioselectivity of our Diels-Alder reaction. Considering the resonance form of the diene and dienophile, the distribution of charge is shown below(see Figure. 13). During Diels Alder reaction, the most electron-rich end of the diene attacks the most electron-poor end of the dienophile, making the reaction regioselective.

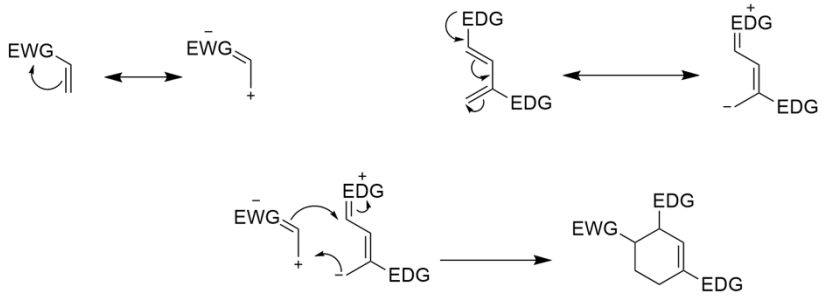

Figure. 13 Resonance and regioselective Diels-Alder reaction.

For the synthesis of molecule 9, the scheme starts from tiglic acid (see Figure. 14). First, the carboxylic acid is halogenated using thionyl chloride (SOCl2) and an acyl chloride 12 is obtained. Next, the addition of N,O-Dimethylhydroxylamine is carried out to make an unsaturated Weinreb amide 9, which can further react with Danishefsky's diene to produce molecule 13.

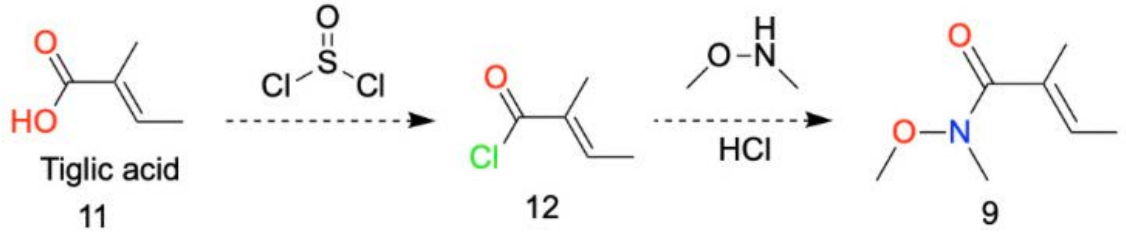

Figure. 14 Synthesis of an α,β-unsaturated Weinreb amide.

The yield of molecule 13 can be increased by increasing the enantioselectivity of our Diels-Alder reaction.(see Figure. 12) A BINAMIDE catalyst(see Figure. 13) is introduced[3]. This catalyst catalyzes a Diels-Alder reaction with a Danishefsky's diene and a dienophile with an acyl-oxazolidinone group. It generates the enantiomers which has R group out of the plane and the acyl-oxazolidinone is into the plane that is up to 97%ee to another. Although the reagents in the Diels-Alder reaction in this paper are not exactly the same as the one used in the BINAMIDE catalyst paper, they are alike. Therefore, it is assumed that this catalyst might be useful to create a single enantiomers 13 (see Figure. 15)

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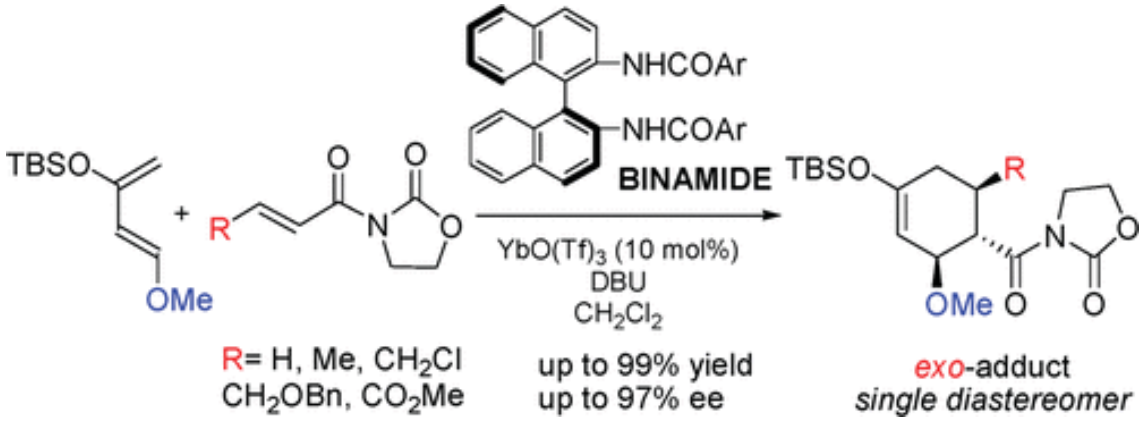

Figure. 15 BINAMIDE catalyst, figure from paper[3].

From molecule 13, Grignard reagent is used to add carbon chain to the Weinreb amide, forming molecule 14 (see Figure. 14).

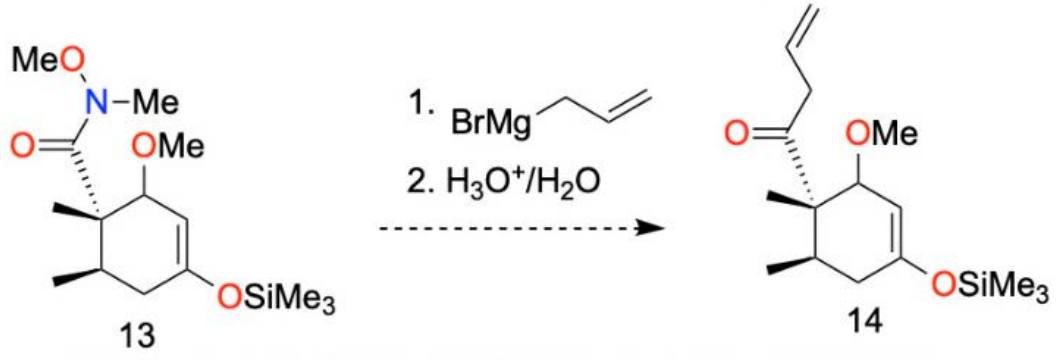

Figure. 16 Grignard addition to molecule 13.

As the ketone group on molecule 14 is not in the target, it is eliminated using Mozingo reaction, which is a mild reaction that specifically converts the carbonyl group into a dithioacetal, and then reduce the dithioacetal group into an alkane (Figure. 17).

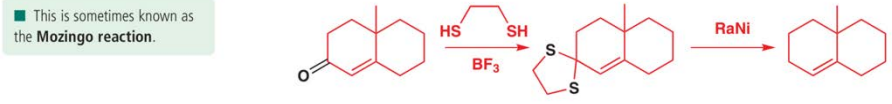

Figure. 17 Mozingo reaction from Organic Chemistry p.540 [2].

BF3 is needed to add the dithioacetal group. During this process, the Si-O bond will be dissociated by the fluorine in BF3 since silicon binds firmly with fluorine. The bonding pair of electrons will attack carbon4, moving the π bond up along the 6-membered-ring. The leaving group on carbon6 will be expelled, forming an α,β-unsaturated ketone 15 (see Figure. 18). Further, Raney nickel (RaNi) is used to selectively reduce the dithioacetal into alkane 16.

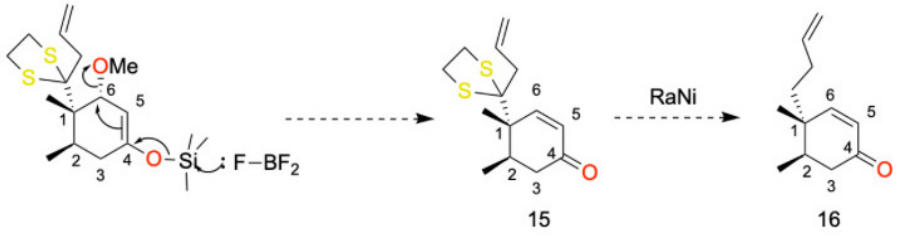

Figure. 18 Shifting of π bond and reduction by RaNi.

Next, HBr is added to get molecule 8 (see Figure. 4). However, there are 2 olefins in molecule 16, so chemoselectivity becomes a problem. The olefin at position 5-6 is much more electron-deficient than that at position 14-19 since olefin 5-6 has a carbonyl besides it. As addition of HBr is electrophilic addition, olefin at position 14-19 will have higher affinity to HBr. Moreover, olefin 5-6 is more hindered, making it unfavorable. Pyyridine is used as solvent to further increase hinderance of HBr and slower the rate of addition at olefin at 5-6 position, thus improving yield of our target (see Figure. 18)

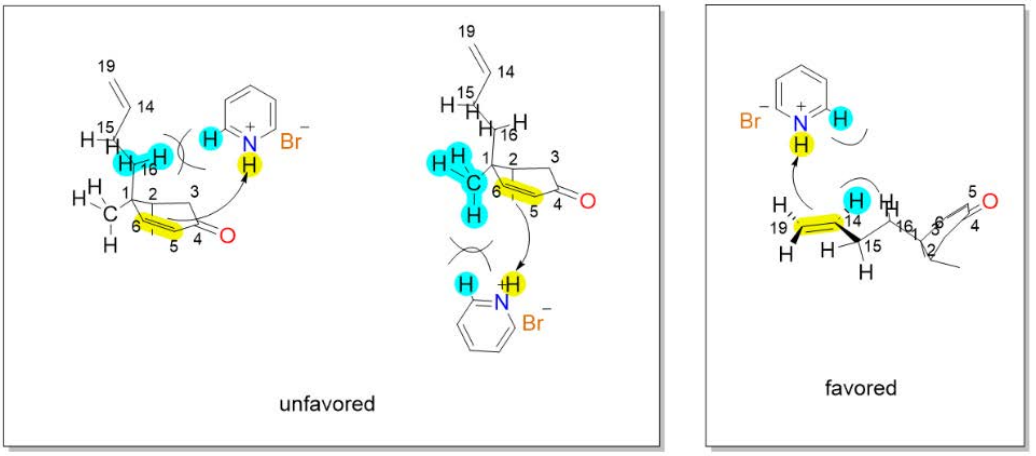

Figure. 19 Unfavored and favored addition of HBr to olefin.

Finally, we need to create a 4-membered-ring at the α,β position of the ketone to obtain molecule 4 (see Figure. 20). We propose a way of using photochemical [2+2] cycloaddition to the α,β-unsaturated ketone, and the mechanism is introduced (see Figure. 21)

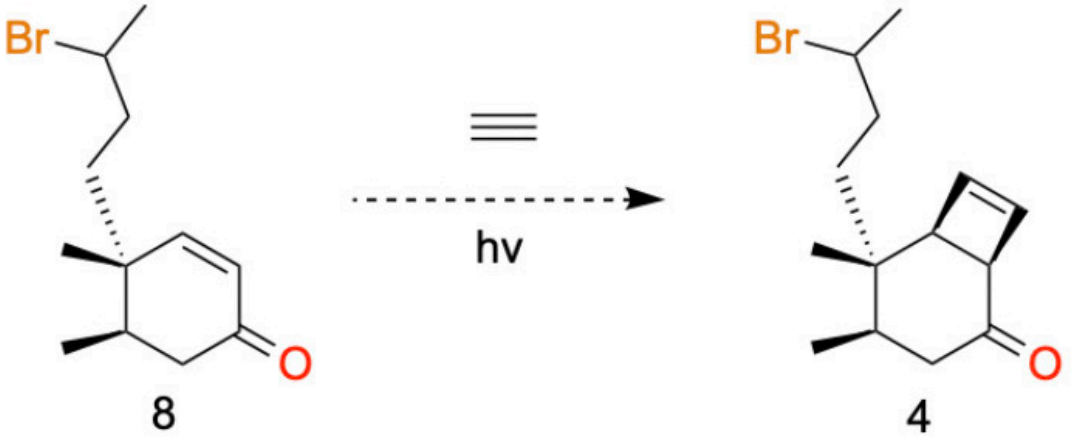

Figure. 20 Photochemical [2+2] cycloaddition.

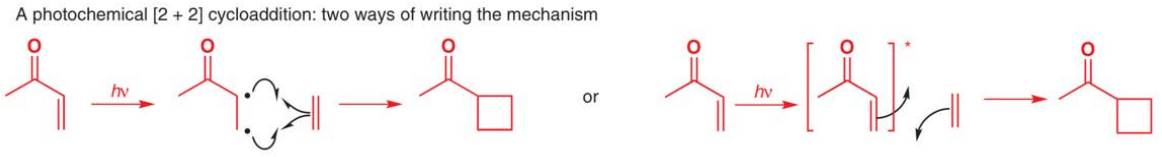

Figure. 21 Photochemical [2+2] cycloaddition from Organic Chemistry p.897[2]

In route A, the next step will be adding a side chain. For side chain 23, there is an aldehyde with a leaving at its α-position (Figure. 22). The leaving group is for the formation of the epoxide when the carbonyl attacks molecule 4. The TMS group at the other end of side chain 23 is for the Wittig reaction afterwards. To synthesize side chain

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23, we initiate with 2-methyl-4-penten-1-ol 17 (see Figure. 22). We first protect the alcohol with an ether group, and then carry out hydroboration of the olefin to get anti-Markovnikov product. We further protect the alcohol on the other end with TMS group and deprotect ether group to bring back the previous alcohol. We then use pyridinium chlorochromate (PCC) to oxidize the alcohol into an aldehyde, followed by the bromination of the α-H of the aldehyde.

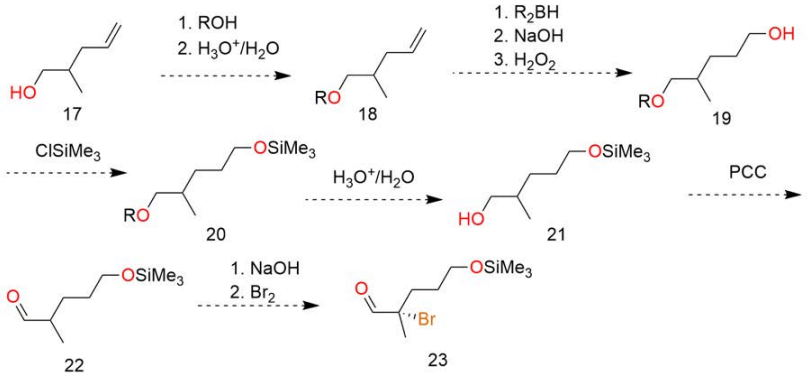

Figure. 22 Synthesis of side chain 23.

In structure 4 (see Figure. 23), both olefin at carbon 7 and 8 and carbonyl at carbon 4 are EWGs, making the hydrogen at carbon5 more acidic than carbon3.

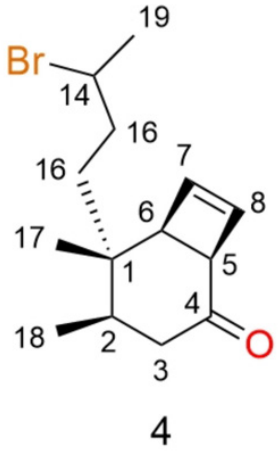

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Figure. 23 Structure 4.

Hence, we use equivalent LDA to deprotonate hydrogen at carbon 5 to give a carbanion, and add in side chain to form structure 24 (see Figure. 24). Meanwhile, an epoxide forms.

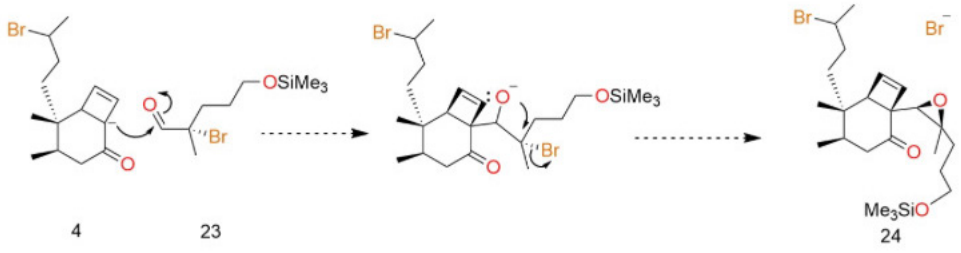

Figure. 24 Addition of side chain 23 to structure 4.

Next, the 4-membered-ring is opened up by ozonolysis to form a di-aldehyde, followed by condensation of ammonia. Noticing that in the final step of synthesis of pyrrole, the intermediate loses two H2O molecules to form a pyrrole (see Figure. 25). Since the carbon 5 is fully substituted, the molecule will probably lose one molecule of H2O to form structure 26 (see Figure. 26).

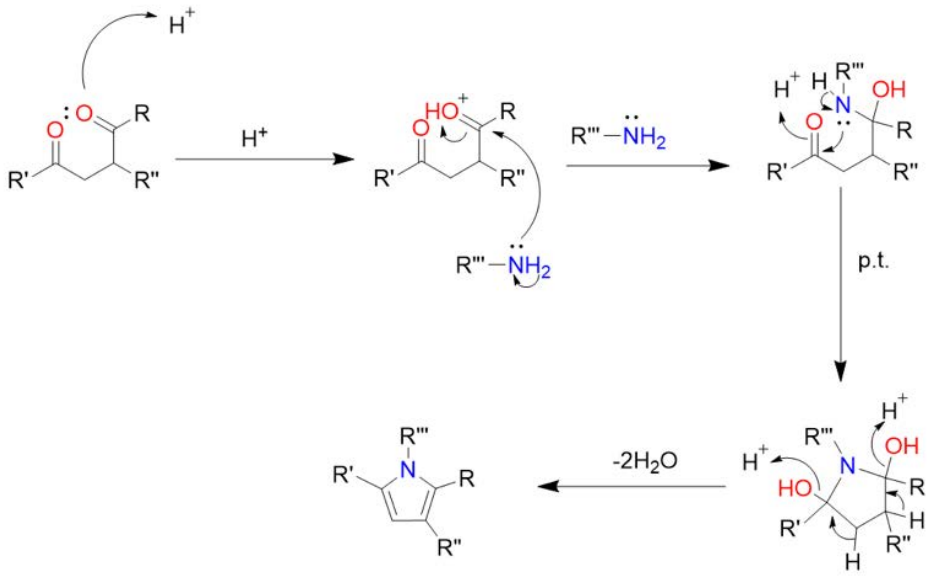

Figure. 25 Condensation of NR_3 to form pyrrole.

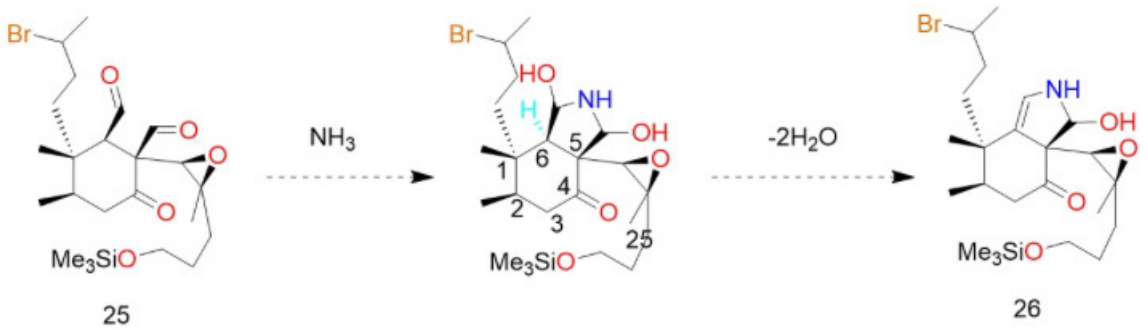

Figure. 26 Condensation of NH_3.

After that, the TMS group is deprotected with a mild fluorine reagent, tetrabutylammonium fluoride (Bu4NF), followed by the oxidation of 2 hydroxyl groups into aldehyde and enamide using PCC, a mild oxidizing reagent. The mechanism of PCC is as follows.(see Figure. 27)

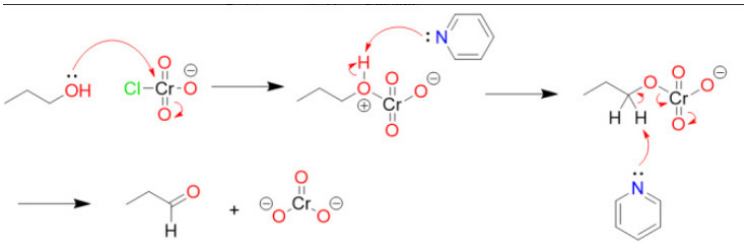

Figure. 27 PCC mechanism.

Then, through Wittig reaction with triphenylphosphine (PPh_3) and potassium tert-butoxide (t-BuOK), the ring is closed. It is worth mentioning that potassium tert-butanol (t-BuOH) has a pKa of around 19, which means that when it is deprotonating the aldehyde, it creates an equilibrium; when it deprotonates the carbon attached to PPh3, it deprotonates it fully. Lastly, molecule 29 is reduced by $NaBH_4$ to get our target molecule 1.(see Figure. 4). One thing to be mentioned is that there is a face-selectivity of this reduction. The reducing agent H- might attack from either the upper plane of the ketone or the lower plane (see Figure. 28), resulting in two different products (see Figure. 29).

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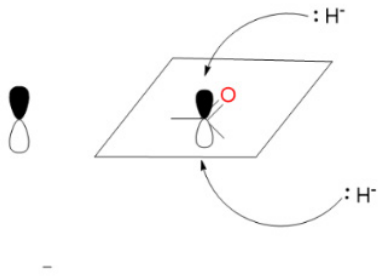

Figure. 28 Attack from different faces

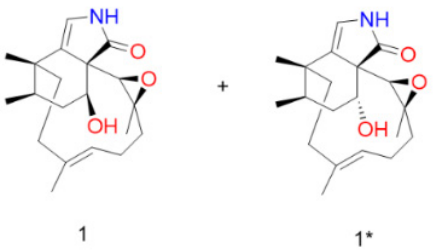

Figure. 29 Conformers

Due to steric hinderance, structure 1, is likely to be the major product. This can be explained in detail by the stability of conformations. In a 6-membered-ring, the more bulky substituents tend to be in equatorial position instead of axial position[2]. Hence, conformer b will be the more stable one as more substituents are in the equatorial position (see Figure. 30).

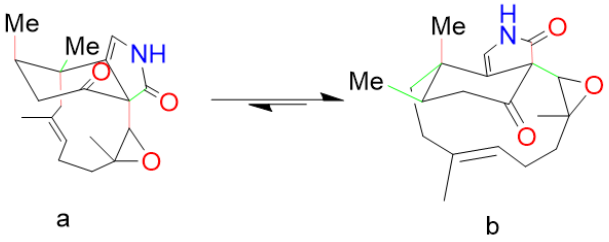

Figure. 30 Conformers a and b

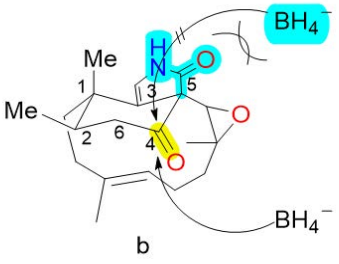

Figure. 31 face selectivity

For conformer b (see Figure. 31), since the carbonyl at carbon5 has a hindered substituent on its adjacent carbon in axial position, the attack is going to be easier to happen from the lower face, pushing the hydroxyl group towards the outside. Thus, molecule 1 will be the major product in the reduction.

3.2 Route B

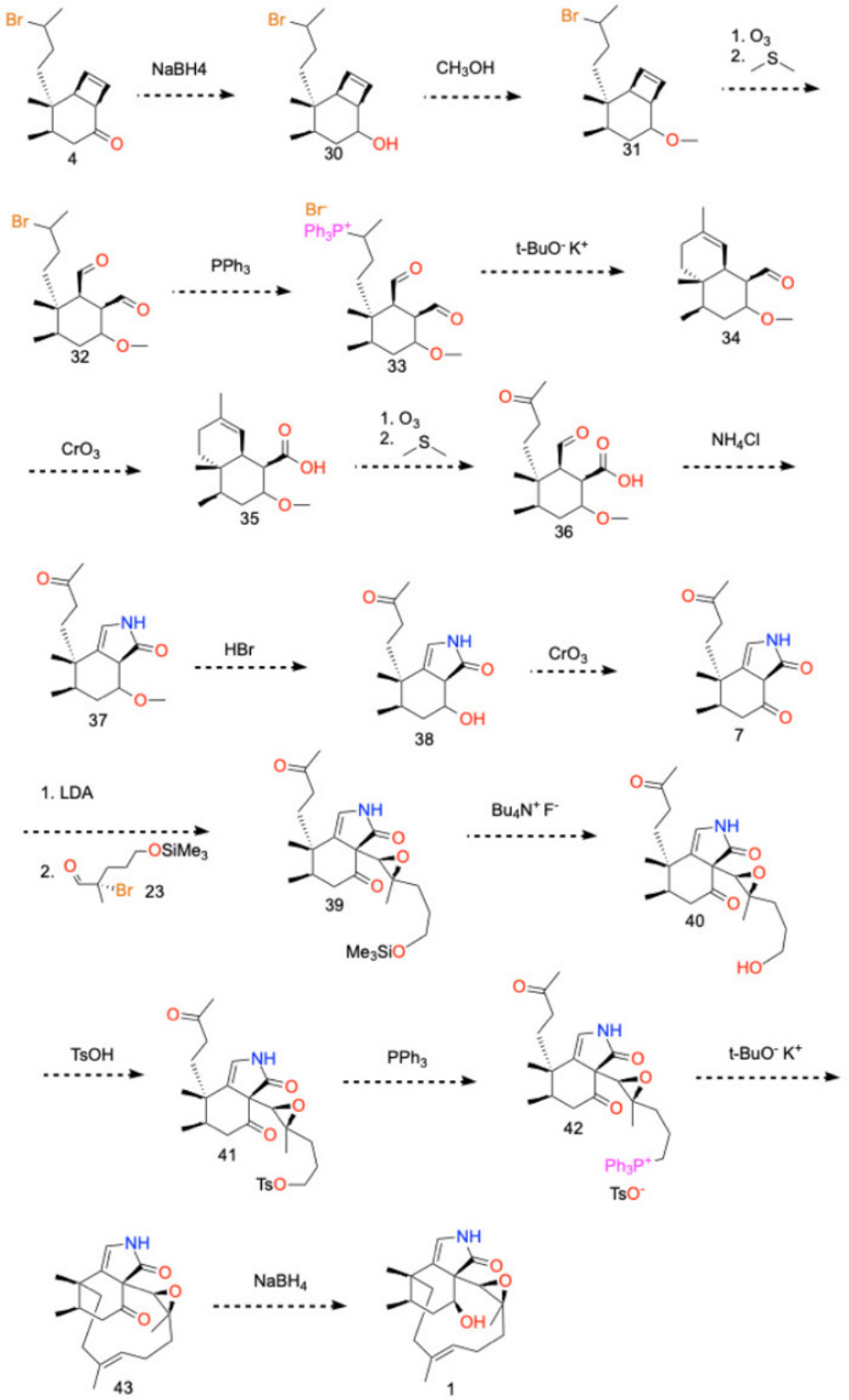

Figure. 32 Scheme. 3 Forward Synthesis of phomactinine, route B.

In forward synthesis route B, the previous steps until molecule 4 are the same (see Figure. 32). However, in the next step, instead of adding the side chain, an alternative choice is to directly open the 4-membered-ring into two

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aldehydes using ozonolysis. Starting from molecule 4, the next step of route B is to make the nitrogen-containing ring as molecule 7 (see Figure. 33). Ideally, in molecule a, one of the aldehyde should become carboxylic acid, while the other remains aldehyde so that ammonia can condense on it to make an imine that will further undergo enolization to create an equilibrium with enamine[2](p.234). In this way enamine and carboxylic acid can react to close the ring.

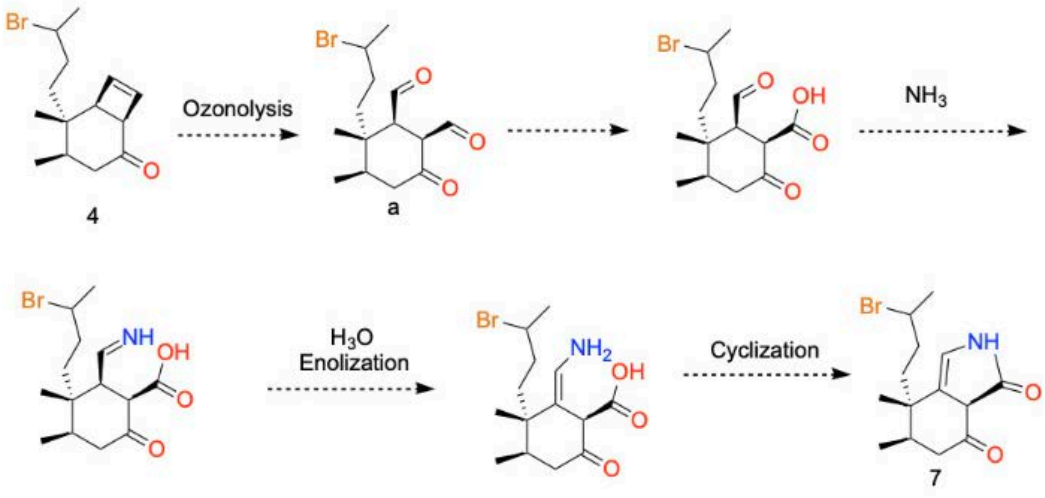

Figure. 33 Synthesis of the nitrogen-bearing-ring

However, the properties and hinderance of the two aldehydes are very similar, that it is impossible to selectively oxidize one side into carboxylic acid while leaving the other side as aldehyde. It is also not possible to allow ammonia to condense on the left side of the ammonia only as there is small selectivity in reaction. Therefore, we form a six member ring by connecting carbon 7 and carbon 14 via Wittig reaction so that only the aldehyde at carbon8 can be oxidized (see Figure. 34).

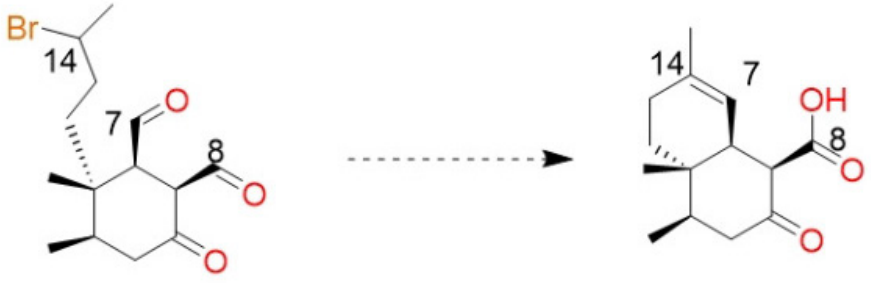

Figure. 34 Using Wittig reaction to close the 6-member ring

It is possible that the aldehyde on carbon8 will also react to form a structure as in 34* (see Figure. 35). However, 34* has a bridged system, making its structure less stable and hence its formation less favored than 34. The ketone in the molecule is also unlikely to react since it is less reactive than aldehyde. One problem with this route would be the aldehyde on carbon8. During the intramolecular Wittig reaction, it may react with some other molecules due to its high reactivity. If the reaction is ideal, meaning that molecule 34 is formed, the selective oxidation to the aldehyde at carbon8 can be carried out.

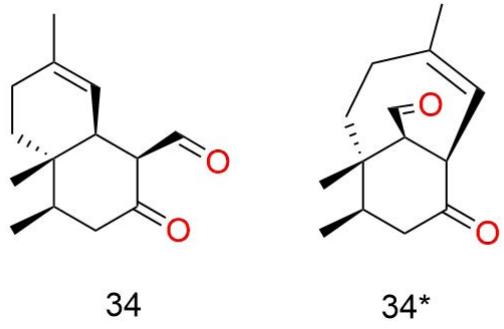

Figure. 35 Molecule 34 and 34*

In Wittig reaction, PPh_3 is used to make a phosphonium salt and further use t-BuOK to deprotonate the hydrogen on carbon 14 to create an ylide. However, in this step, the hydrogen at carbon5 (α-H of β-di-ketone) has a pKa value lower than carbon 14 (H in ylide salt)[4]. This means that when t-BuOK is added, the hydrogen at carbon 5 would be deprotonated more readily than hydrogen at carbon 14, so that molecule b cannot be formed (see Figure. 36).

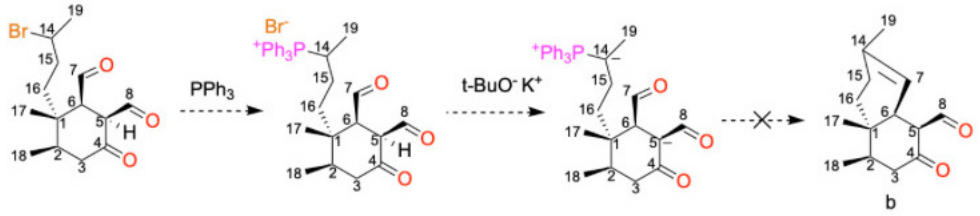

Figure. 36 Failed way to create the 6-membered ring

The solution to this is to reduce the ketone at carbon4 directly in molecule 4, so that molecule 30 can be formed. Since the hydrogen on the hydroxyl group is also acidic, we protect the hydroxyl group by forming an ether (see Figure. 37). Then, we can carry out ozonolysis from molecule 31.

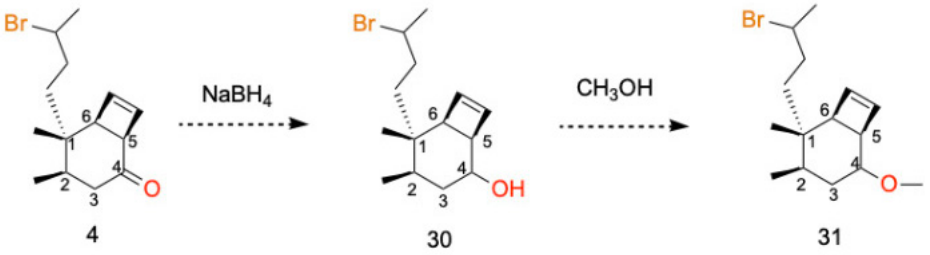

Figure. 37 Reduction of ketone at carbon4 from molecule 4

In this case, we can carry out Wittig reaction successfully by only deprotonating the hydrogen at carbon14 and not that at carbon5, as the former one is more acidic (see Figure. 38).

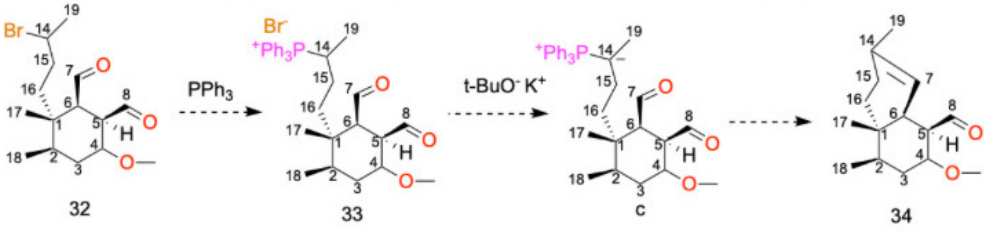

Figure. 38 Successful Wittig reaction.

CrO_3 is used on molecule 34 to oxidize the aldehyde into carboxylic acid, and then use ozonolysis to open the ring at the olefin position (see Figure. 39). This time, in 36, one ketone and one aldehyde is formed, and they can be differentiated due to their difference in reactivity. Then we add NH4Cl in an attempt to condense nitrogen onto the ring. As this phomactinine molecule exists in nature, the nitrogen-bearing-ring structure is assumed to be stable. Hence, when condensing NH3 onto the aldehyde, ideally the heteroatom ring structure in 37 will form directly due to its stability. Further, we use HBr as acid to deprotect the ether, forming 38.

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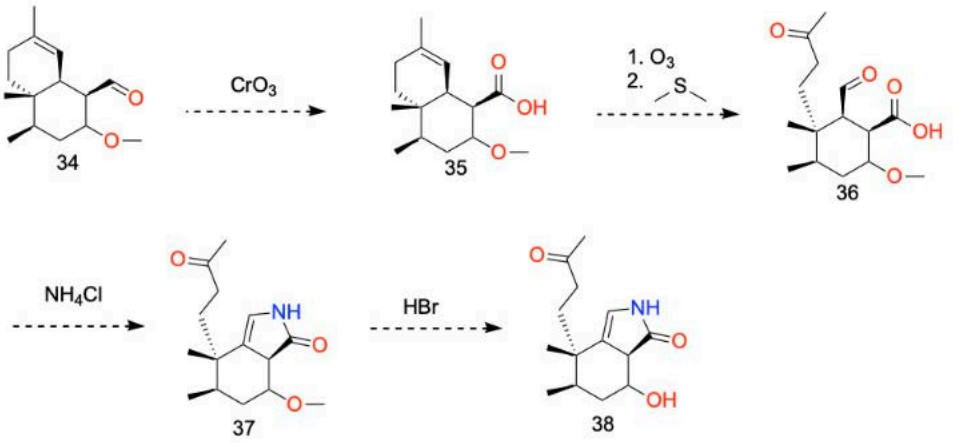

Figure. 39 Selective oxidation and condensation of NH_3.

If the ideal product 37 does not form, then a backup plan may be used to force the nitrogen onto the ring (see Figure. 40). In the backup plan, we start with molecule 36. When NH_4Cl is added, carboxylic acid would be converted into an amide. Since NH_4Cl is an acid, it also catalyzes the enolization of aldehyde to form a vinyl alcohol group in d. Then, we may add triflate (Tf) to the alcohol group, forming an enol triflate in e, which can further be coupled with amide[5], forming molecule 37. With HBr, we convert the ether group back to hydroxyl group.

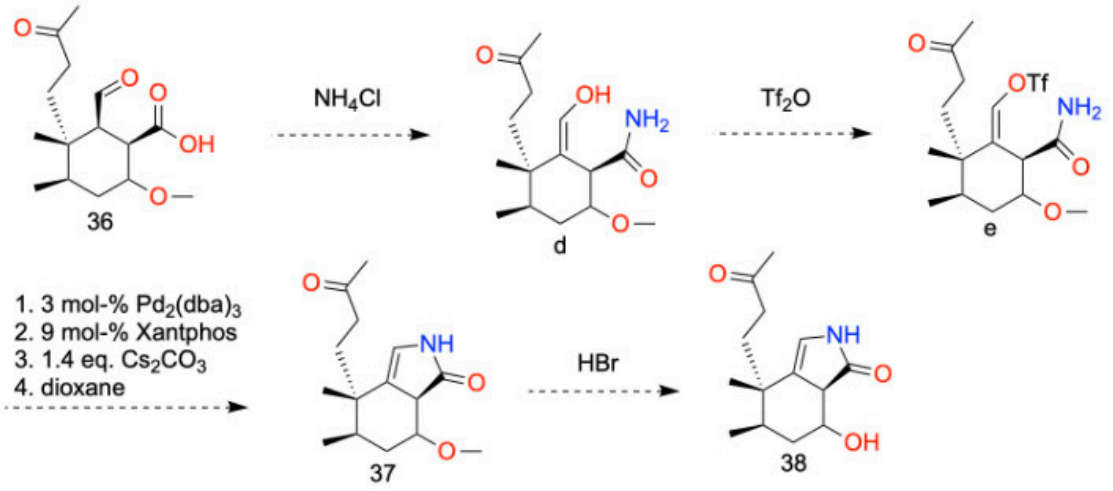

Figure. 40 Backup plan to couple enol triflate onto amide.

Next, our aim is to add the side chain. To add the side chain, we have to deprotonate the hydrogen at α-position of a carbonyl. In molecule 38, the hydrogen that will be cleaved would be the one on carbon 15 and carbon 19 due to the ketone. However, we want the side chain to be added at carbon 5 (Figure. 41). We have to oxidize the hydroxyl group at carbon 4 into ketone so that the hydrogen at carbon5 can be deprotonated by LDA, forming intermediate f. The carbanion f attacks carbon 9 in side chain 23. During the addition of the side chain, the oxygen on aldehyde carries out backside attack on the bromine leaving group, forming an epoxide as in molecule 39.

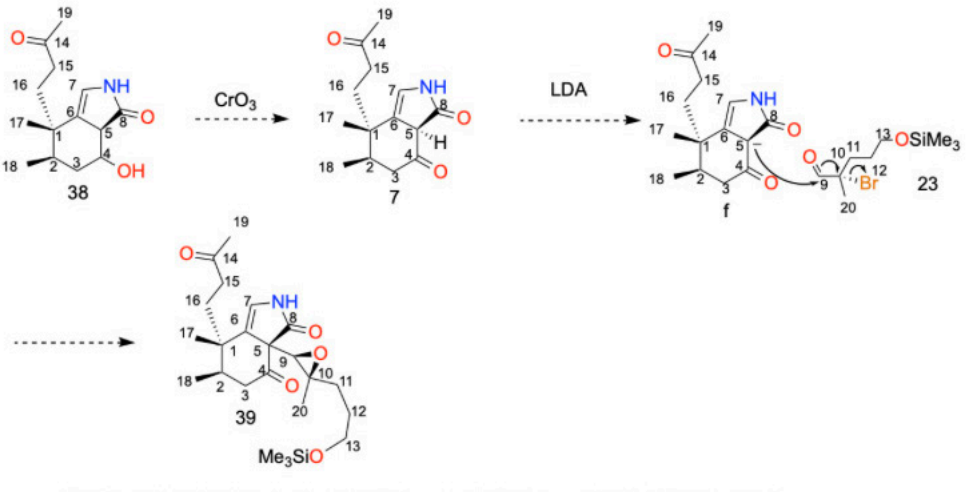

Figure. 41 Addition of side chain 23.

From 39, the 11-membered-ring need to be closed by connecting carbon 13 and carbon 14 via Wittig reaction (see Figure. 42). Since there is a ketone at carbon 14, we need a leaving group at carbon 13, thus PPh_3 can bind to carbon 13 and Wittig reaction can be carried out. Since neither TMS nor hydroxyl group is a leaving group, we first deprotect the TMS into hydroxyl group, and then use p-Toluenesulfonic acid (TsOH) to convert the hydroxyl group to a tosylate group, which is a good leaving group in molecule 41. Then PPh_3 is added to form a salt 42. Further, t-BuOK is used to deprotonate the hydrogen at carbon 13, forming a carbanion intermediate g, which attacks carbon14 that has a partial positive charge due to the ketone. It is worth to mention that carbon 4 also contains a ketone functional group that may react. However, based on our analysis, carbon 4 is more hindered than carbon 14 to be attacked by carbanion 13. Therefore, product 43 is favored.Lastly, we selectively reduce the ketone using $NaBH_4$, which would not reduce the enamide nor the olefin functional group. The reduction is stereoselective, meaning that our product will have a hydroxyl group pointing out. Its stereoselectivity is the same reason as explained in route A.

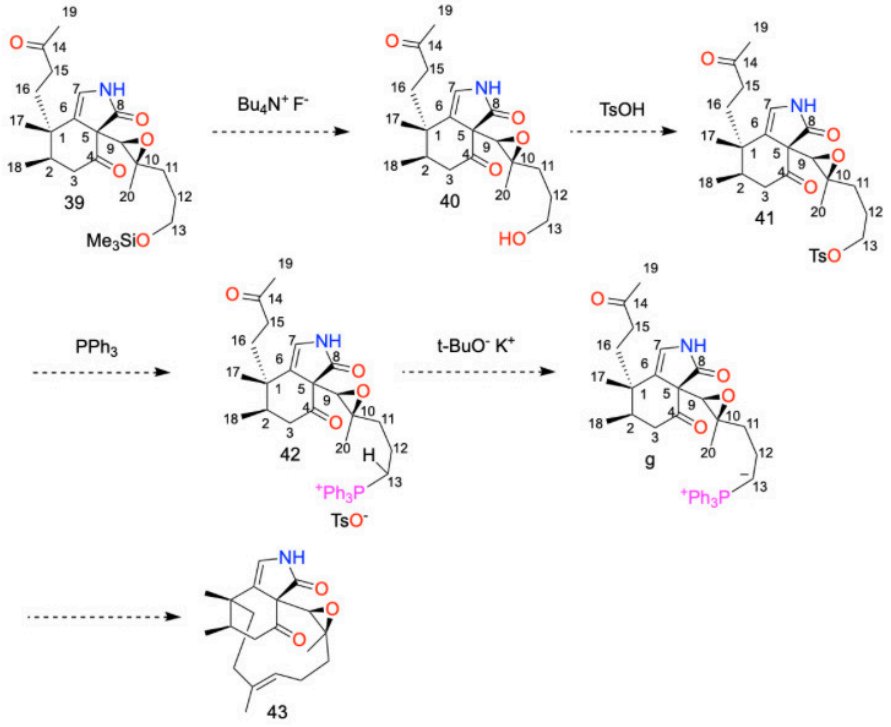

Figure. 42 Wittig closure and reduction.

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4. Conclusion

In this paper, we propose a total synthesis pathway of phomactinine. The main difficulties in the our proposal are dealing with the rings. The 5-member-heteroatom ring is the one that might be hardest to make among them. Our two main routes vary to ensure the formation of this ring: in route A, we fully substitute the common carbon to prevent dehydration; in route B, we form a six member ring to differentiate carbonyls to condense ammonia. Moreover, we have a back-up plan to force the coupling of amide to make the nitrogen-bearing-ring. As for the 11-member ring, we carry it as two side chain, which are then fused together in the final step. Although we do not have a chance to conduct the synthesis for this phomactinine molecule, we believe this total synthesis could provide a guidance for future chemists to synthesize.

5. Acknowledgments

Zixuan Wen and Yuxi Zhao contributed equally to this work, and should be considered co-first authors.

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