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Total Synthesis of Heterolactone

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Abstract. Verticillane diterpenoids, heterolactone was isolated from the soft coral Heteroxenia Ghardaqensis. The structures, including the absolute configurations, were determined by extensive spectroscopic analysis, singlecrystal X-ray diffraction analysis, calculated ECD spectra, and DP4+ probability analyses. This paper will present the occurrences and functions of the compound in daily life, investigate its retrosynthesis and total synthesis, and illustrate them in graphical form.

Keywords: total synthesis, heterolactone, retrosynthesis, boronate, natural product.

1. Introduction

Verticillane diterpenoids, a category of fascinating natural product, demonstrates widespread bioactivities, such as anti-inflammatory， antimicrobial and cytotoxic activities. Verticillane (bicyclic [9.3.1] diterpenes) is similar to taxane diterpenoids isolated from various species of terrestrial Taxus plants. Heterolactone, a diterpenioid which is shown in figure 1(a), was obtained as colorless crystals. The molecular formula, $C_{20}H_{30}O_4$, was deduced from the (+)-HRESIMS ions at m/z 357.2036 [M + Na^+] in 2023, revealing six degrees of unsaturation [1].

Hepatotoxicity, which means liver injury induced by drugs or alcohol, is a potential threat to human health, it may be mild or severe. If it goes on for a while, it could cause permanent liver scarring or cirrhosis. This can lead to liver failure or even death. In some severe cases, as with acetaminophen, even short-term use can be enough to cause liver failure. These cases mean treatment and medicine for hepatotoxicity is dramatically important. Among all compounds shown in figure 2, A, G, and K showed moderate effects similar to the positive control S-adenosyl-L-methionine (SAM) [1].

In addition, compounds D, I and J (see figure 1(b)) display moderate anti-inflammatory activity. They are potential anti-inflammatory drugs especially against new virus or bacteria. The core of compound 1 resembles all these hetelactams, which means synthesis analysis of compound 1 has dramatically guidance for synthesis of hetelactams, which may be utilized as new anti-inflammatory or hepatoprotective drugs in the future.

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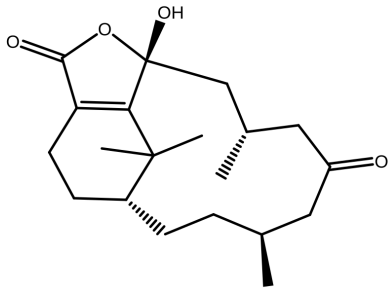

Figure 1: (a) Heterl

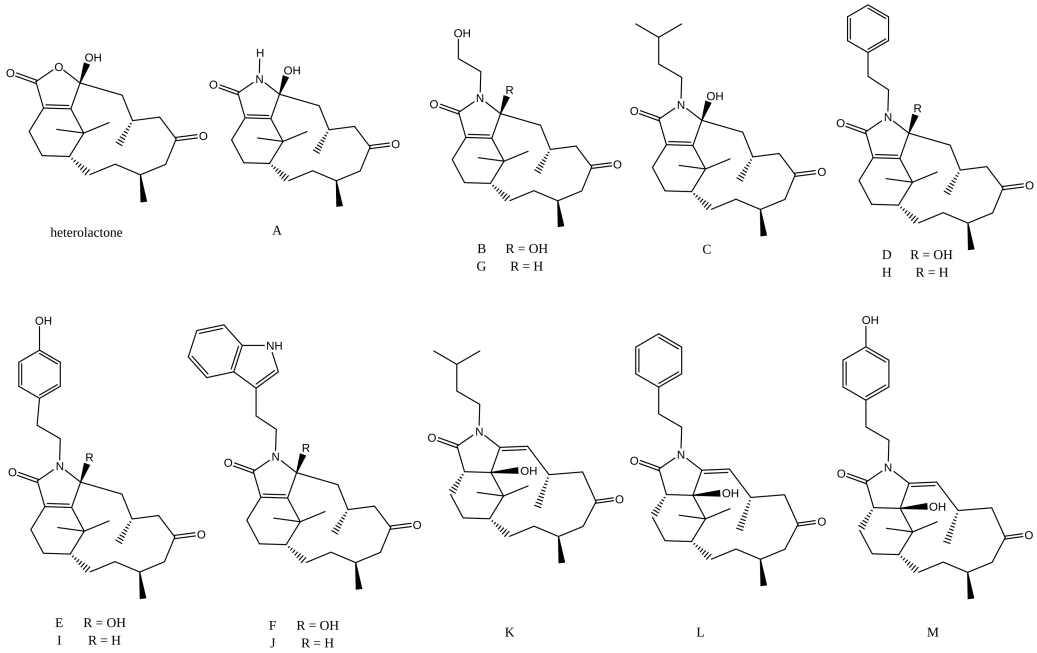

Figure 1: (b) Heterolactams [1]

2. Retrosynthesis

As is shown in figure 2 and 3, two retrosynthesis strategy was designed. The first strategy centers on the six-member ring. Olefin carboxylation was elected in order to form the bond between six-member and carboxyl group. Getting rid of the carboxyl group makes the diene more nucleophilic, which enables us to utilize Diels-Alder reaction to convert liner diene 3 to the two-ring system 2. Then, boronate is applied to track back to aldehyde 4 in this route. Finally, a carbonyl is added as a handle in order to break the bond between C4 and C5.

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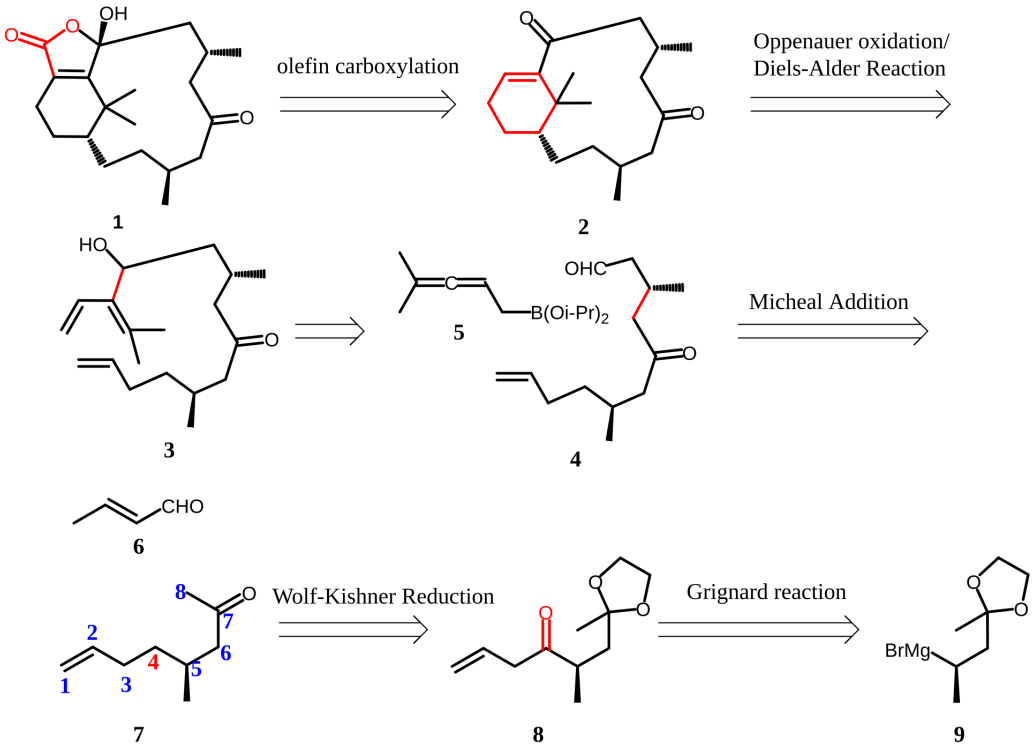
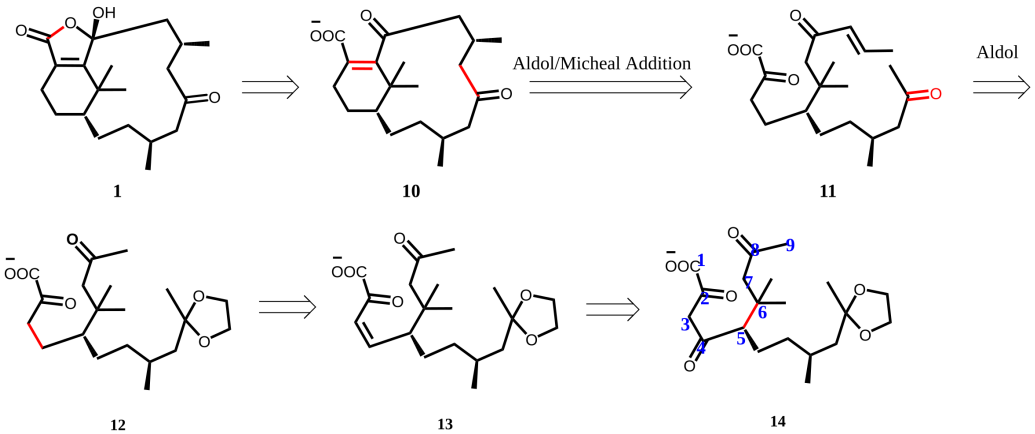


Figure 2: Retrosynthesis 1

In the second strategy, Aldol reaction and Michael addition is uesd to break the two-ring system. Then the carbon-carbon double bond using Aldol reaction is disconnected. After 2 steps of functional group interconversion, it turns out to have one more carbonyl on C4 in ketone 14. Next, Michael addition is applied to disconnect C5 and C6. Following that, the carbonyl of C4 is converted to the hydroxyl in alcohol 17, following by the Aldol reaction to break the bond between C3 and C4. Finally, a carbon-carbon double bond is added as a handle, which can be formed by aldol reaction.



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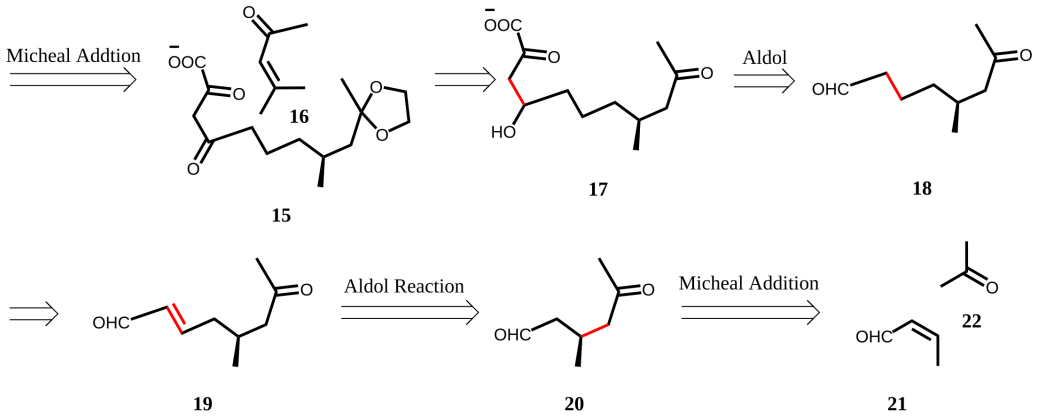

Figure 3: Retrosynthesis 2

3. Total synthesis

According to the retrosynthesis strategy shown in figure 2, a total synthesis scheme was proposed, which is shown is figure 4(a) (b) and (c). It begins with targeting boronate 5 (see figure 4(a)). Adding sodium acetylene to the acetone 22 and protonating it enables us to get alcohol 23. Then phosphorus tribromide is chosen to substitute hydroxyl. While elimination of hydroxyl is also likely to happen, the demanding bromide substitution 24 surpluses the other option, according to the total synthesis of Bryostations [2]. Following the substitution, magnesium and mercury dichloride are added to make the Grignard reagent 25 [3].

A solution of n-BuLi in hexane to a mixture of $(Oi\text{-}Pr)_3B$ (26) and CH_2I_2 in THF at -78 °C is slowly transferred while the solution is stirred. After addition, the mixture is stirred at -78 °C for another 0.5 h, followed by quenching the reaction with anhydrous HCl in Et_2O. The cold bath was removed, so that the mixture is warmed from -78 °C to room temperature. After 1 h the solid is obtained by precipitation. Then this solid is filtered off under N_2 and washed with ethereal. The combined Et_2O solution is concentrated, and the rest of the solution is distilled under reduced pressure in the presence of copper wires to afford an almost colorless liquid (27). Next, Grignard reagent and diisopropyl (iodomethyl) boronate 27 was mixed in THF, to generate the boronate 5 [4].

Then it comes to the synthesis of aldehyde 4. Because the starting material is not stable with the bromide on the β-C. If the route starts from 4-bromopentan-2-one, protecting the carbonyl and then reacting with magnesium to form the Grignard reagent, the result will be elimination product. Therefore, the sequence is adjusted and the synthesis of aldehyde 4 starts with aldehyde 28 instead. First, ethane-1,2-diol is used to protect the carbonyl, and hydrogen bromide is added to the carbon-carbon double bond. Then magnesium is added to generate Grignard reagent. Next, Grignard reagent and aldehyde 30 are connected to form the alcohol 31. As is shown in figure 4(b) alcohol has one more hydroxyl than aldehyde 4, which needs to be removed. If the hydrogen of alcohol 31 had been chosen to eliminate, it would be difficult to maintain the double bond in the end while reduce the double bond in the middle. So, Oppenauer oxidation and Wolf-Kishner reduction are selected to convert the hydrogen to the carbonyl (8) and reduce this carbonyl, forming ketal 32. Here Wolf-Kishner reduction is utilized instead of Clemmensen reduction because the former one requires alkaline condition, protecting the ketal sensitive to acid. What's more, Oppenauer oxidation is applied in this work because it's more moderate than oxidations using CrO_3. It won't oxidize the carbon-carbon double bond. Following that compound 32 is protonated to regenerate the carbonyl in red and the result will be ketone 7. Afterwards, ketone 7 reacts with unsaturated aldehyde 6. The

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acidity of both sides of the carbonyl is close to each other, and it is believed that aldehyde 4 can be obtained in the reaction system.

Now two smaller pieces – aldehyde 4 and boronate 5 have been prepared. The later steps are demonstrated in figure 4(c). Aldehyde 4 and boronate 5 react in toluene, forming the alcohol 3. This approach to the target molecule via boronate 5 is elected because the steps to add a diene to aldehyde 4 are fewer, while the diene doesn't have a carbonyl connected to it which exists in the target molecule. Therefore, it is easier for diene 3 to conduct a Diels-Alder reaction.

Considering that the diene is more nucleophilic when the carbon connected to it is under alcohol oxidation level, diene 3 is the best stage to utilize Diels-Alder reaction to connect the diene and dienophile, and to form the six-member ring. After D-A reaction, the hydroxyl is converted to carbonyl by Oppenauer oxidation. Then olefin carboxylation [5] is applied to add a carboxyl group to the carbon-carbon double bond, forming the carboxylic acid salt 34.

According to previous work on the formation of sodium acrylate [6,7], the main intermediates in the olefin carboxylation are the olefin complex, the lactone and the carboxylate complexes in figure 5. Finally, the salt is protonated by the acid added and then the acid attacks carbon of the ketone, generating the target molecule.

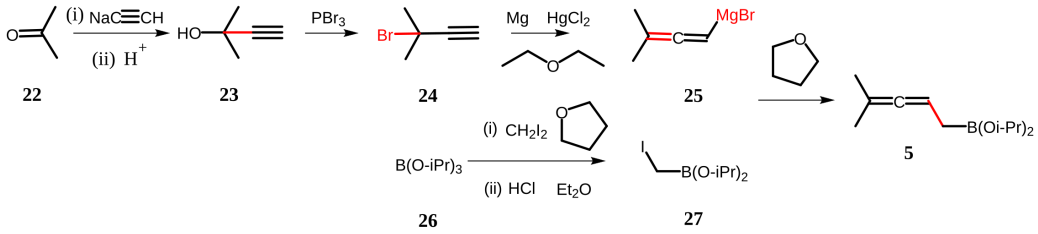

Figure 4: (a) Synthesis of boronate 5

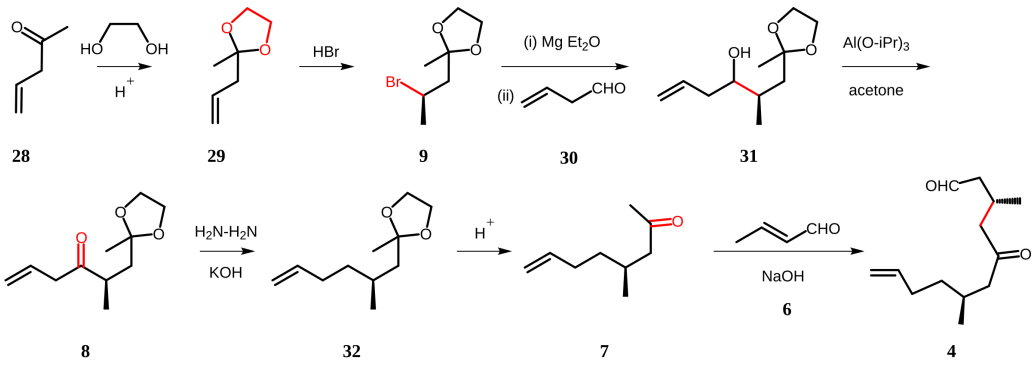

Figure 4: (b) Total synthesis scheme 1

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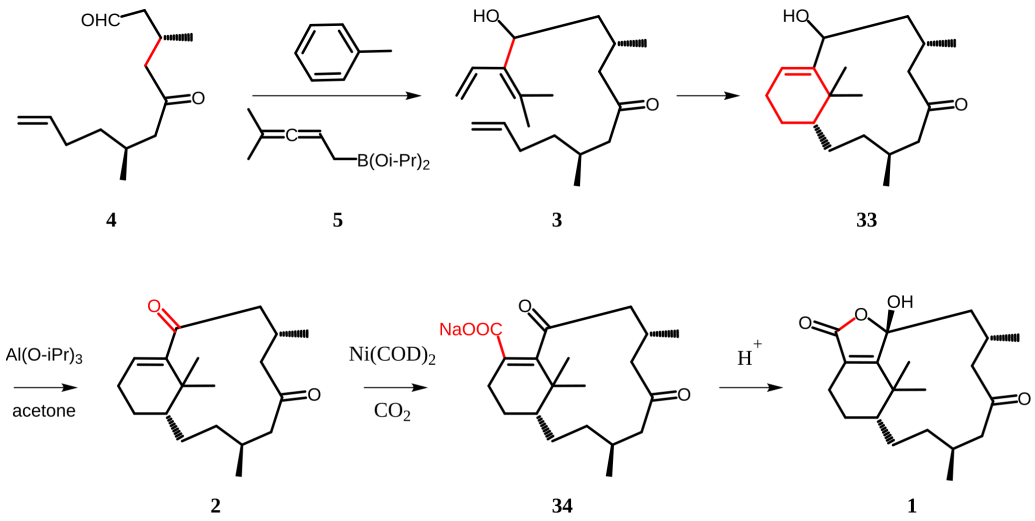

Figure 4: (c) Total synthesis scheme 1

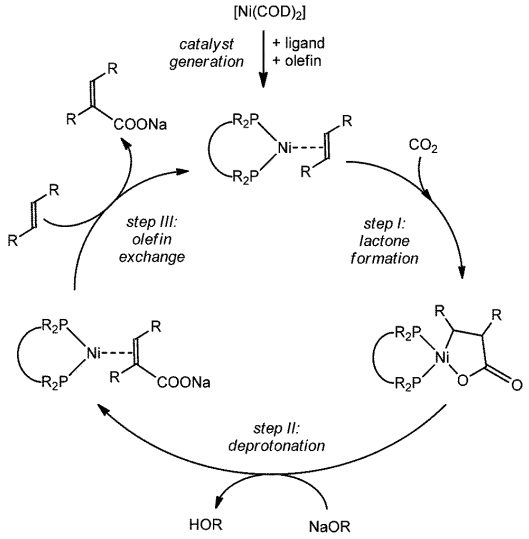

Figure 5: Intermediates of carboxylation [5]

Based on the second retrosynthesis strategy, another total synthesis scheme is proposed. It starts with unsaturated aldehyde 21 and acetone 22. Michael addition is applied to form 1,5 oxidized aldehyde 20. The aldehyde group is more active than the carbonyl. After mixing acetaldehyde and base which form negative carbon ion, the ion reacts with aldehyde group faster than carbonyl. Therefore, the result will be aldehyde 19. Next, the carbon-carbon double bond is removed by hydrogen with the catalyst palladium. Since the high selectivity of palladium, only the carbon-carbon double bond is reduced, while aldehyde group and carbonyl maintain their oxidation levels. Following this reduction, aldol reaction is used again to connect aldehyde 18 with the three-carbon carboxylic acid. Then the carbonyl is protected via ethane-1,2-diol. As for the carbonyl on C2 shown in figure 6(a), due to the carboxylic group next to it, it's hard to react with alcohol. So, only one carbonyl is protected in compound 35. In order to connect alcohol 35 with another small piece above, the oxidation level is adjusted by Oppenauer oxidation and the result is ketone 15.

Since C1 and C3 is more active than C5, while 3 equivalent strong base is added, C1, C3 will be the first to be deprotonated, followed by deprotonating C5. Later unsaturated ketone 16 is added to

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the system. C3 and C5 will both attack ketone 16 and it is believed that ketone 14, in which ketone 16 connects with C5 will be gained. Next, the synthesis moves forwards to remove the carbonyl C4. As two carbonyls on the left of the ketone are so close to each other, it is possible to convert one of them into carbon-carbon double bond (13) through enol substitution and Cu-H. Then hydrogen is applied to reduce the double bond and the result will be the carbonyl on C4 removed, which is shown in figure 6(b).

After the removal of carbonyl, it comes to aldol reaction of ketone 12 and acetaldehyde in figure 6(c). Carbonyl of C2 is less active than C8 because of the carboxyl group connected to it. So, it is most likely to gain the unsaturated ketone 11. Now the skeleton of the target molecule has been built. Next, acid is added to remove the protection of the carbonyl and then Michael addition and aldol reaction are applied to close the two rings at the same time, forming the two-ring system 10. Finally, the two ring system is treated with acid and the last ring is closed to form target molecule.

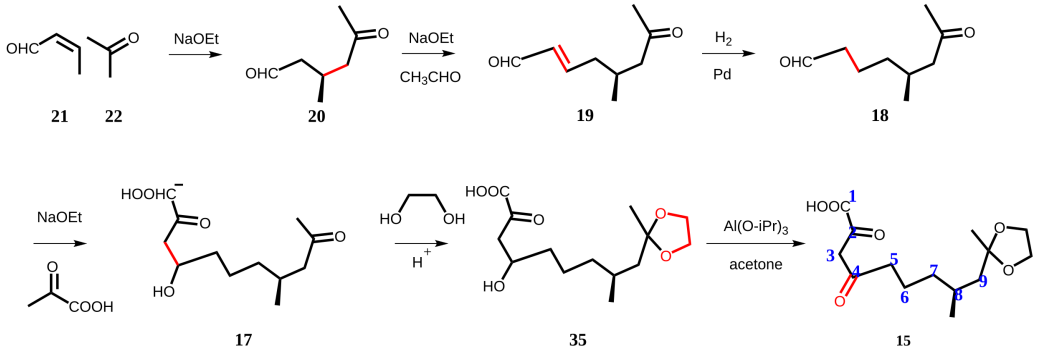
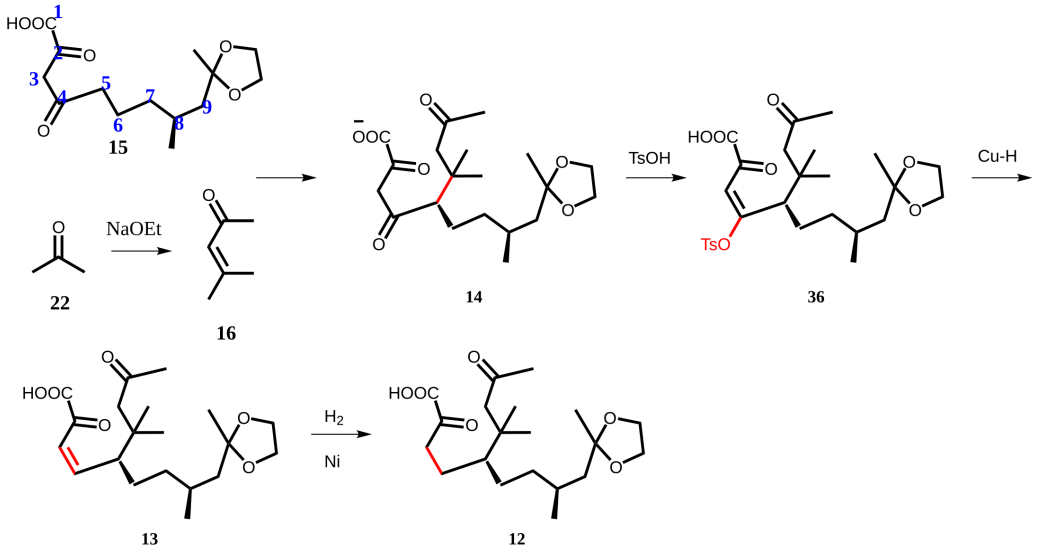


Figure 6: (a) Total synthesis scheme 2



Figuure 6: (b) Total synthesis scheme 2

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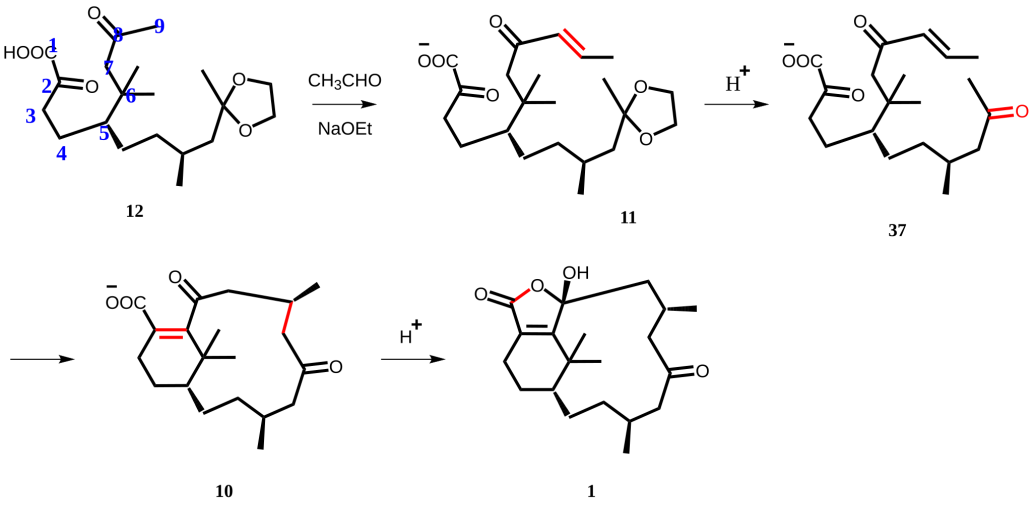

Figure 6: (c) Total synthesis scheme 2

4. Conclusion

To conclude, in this work two total syntheses of heterolactone is proposed. The first one starts from acetone using 13 steps to achieve the target molecule. And the second one commences with (Z)-but-2-enal, going through 14 steps in the second scheme to synthesis heterolactone. Furthermore, the first scheme provides an approach to diene through boronate. This approach simplifies the formation of diene and six-member ring. It may also be applied in the synthesis routes towards heterolactams.

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