

Total synthesis of Crotonine A

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Abstract. Crotonine A is a newly reported molecule. The insulin resistance activity it exhibited shows a promising prospect for synthesizing the molecule. In this work, based on the oxidation levels and some functional groups of the target molecule, in order to break the rings that make up the molecule and thus simplify the molecular structure, retrosynthetic routes were designed by simplifying the target molecule into three parts and analyzing them separately in an organized retrosynthetic manner. Then, complete theoretical synthetic routes were designed based on the retrosynthetic strategy. Furthermore, the relevant reaction selectivity and stereoselectivity were analyzed, and the synthetic routes were optimized. Among them, the relevant reaction mechanisms and their advantages were discussed and analyzed, emphasizing the stereoselectivity of some reactions and the protection of target functionalities. Some synthetic routes were also employed, and several different methods were used for selection. As a result, the method of synonymizing the target molecule was theoretically realized, and the route might be useful for the Crotonine A, which may serve as a reference for the actual synthesis of Crotonine A and may be extended to the application of related similar Terpenoids.

Keywords: crotonine A, terpenoid, retrosynthesis, synthesis.

1. Introduction

Terpenoids are the largest category of natural products, with various biological activities such as anti-cancer, anti-allergy, etc., which have gained widespread attention in the fields of food, medicine, etc., showing enormous application potential and vast market prospects. Many natural terpenoids have been identified and even applied as marketed drugs for a vast number of diseases. Thus, the chemical synthesis of these natural terpenoids has made a tremendous impact in the field [1]. Recently, scientists have isolated eight neo-clerodane diterpenes from the roots of Croton plants in Yunnan. Among them, Crotonine A (compound 1 shown in Fig. 1) has exhibited insulin-sensitizing activity. When treated together with low insulin concentrations, it significantly enhanced glucose uptake activity at a concentration of 20μM, indicating that this compound may help alleviate insulin resistance [2]. This molecule has broad future prospects and may be used to treat type 2 diabetes. Furthermore, the molecular structure of this compound is versatile, and the retro-synthetic pathway designed may be applicable to

the chemical synthesis of similar new clerodane diterpenoids, which requires further in-depth exploration and research.

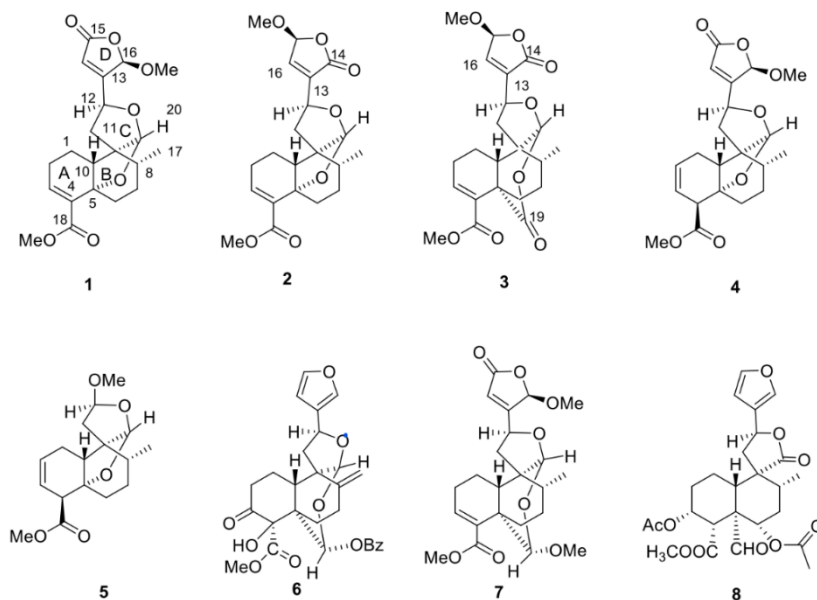


Figure 1. Eight neo-clerodane diterpenes from the root of Croton plants in Yunnan [2]

2. Retrosynthesis

A retrosynthesis was devised centred on the two six-membered rings. Firstly, two five-membered rings were broken according to their oxidation level and compound 1 was obtained. Grignard reagent could be used to divide molecule one into molecule A and molecule 2. Further treatment was done on molecule 2, an olefin α -site addition molecule. So, the Baylis–Hillman reaction broke the six-membered ring, and molecule three was obtained. The bond (see Fig. 2, highlighted in blue) was further broken, and two synthons were formed. Two synthetic equivalents could be easily obtained: molecule B and molecule C.

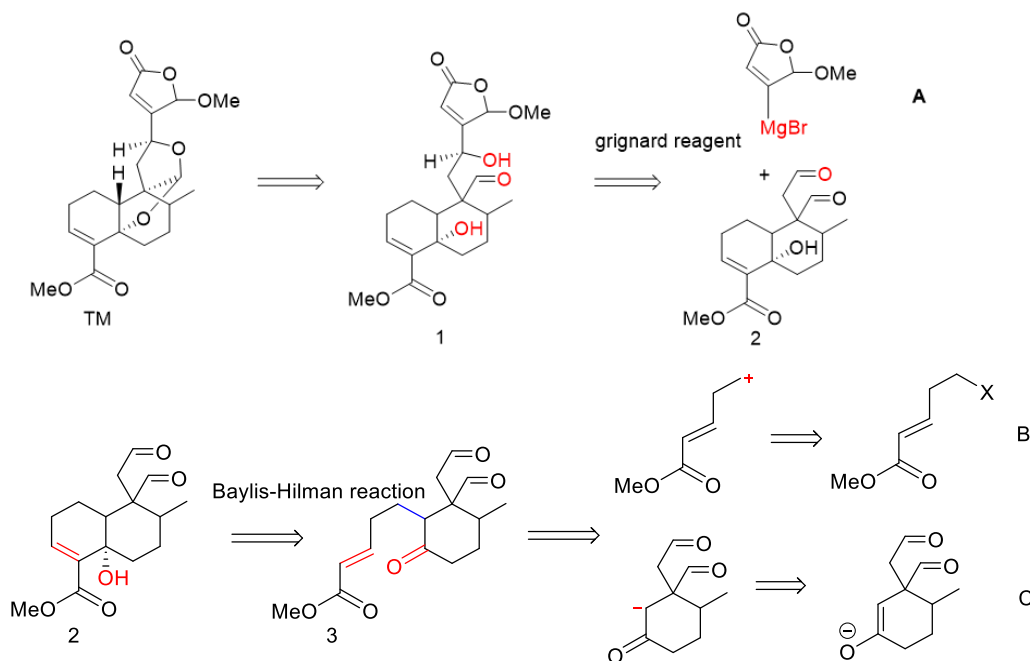


Figure 2. Initial retrosynthesis.

Next, further retrosynthesis on molecules A, B, and C was designed. For molecule A (see Fig. 2), molecule four was obtained by FGI. Its lactone was opened to get molecule 5. Considering its oxidation level, molecule five was converted into molecule 6, and the enol was turned into ketone, molecule 7. Molecule 7 is a 1,3—di-oxygenation compound. With Dieckmann Condensation, molecule eight and an ester could be easily obtained.

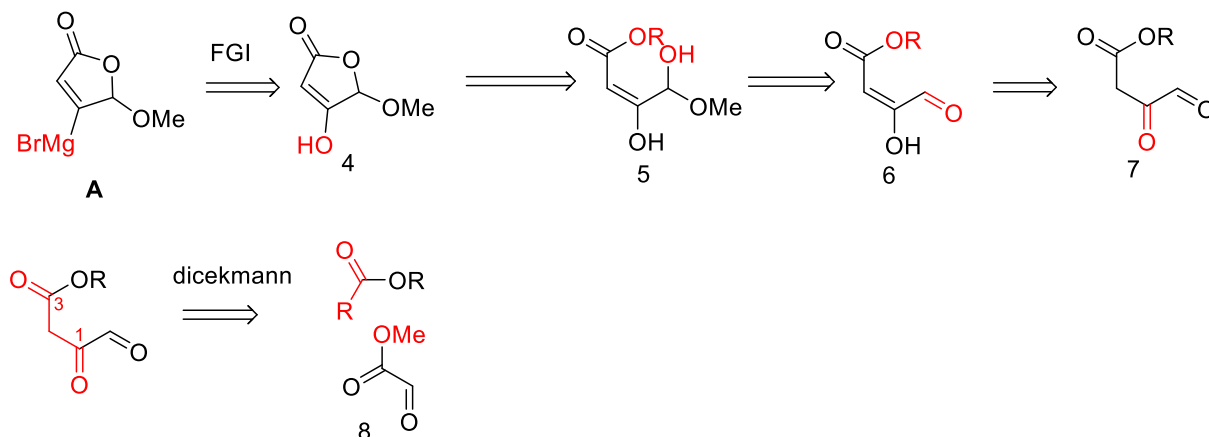


Figure 3. Retrosynthesis of molecule A.

For molecule B (see Fig. 4). The carbon-carbon double bond was broken through the Horner-Wadsworth-Emmons reaction, and molecules 9 and 10 were obtained. Horner-Wadsworth-Emmons reaction is good as the phosphonate anion is more nucleophilic than the original phosphor ylide so that it can react with almost all aldehydes and ketones under mild conditions [3,4]. The by-product, dialkyl phosphate, is water-soluble and can, therefore, be easily separated from the olefinic product. Then, the halide was converted into alcohol, and molecule 11 was obtained, a 1,3- di-oxygenation compound. The bond (Fig. 4, highlighted in blue) could be easily broken, and acetaldehyde and formaldehyde were obtained.

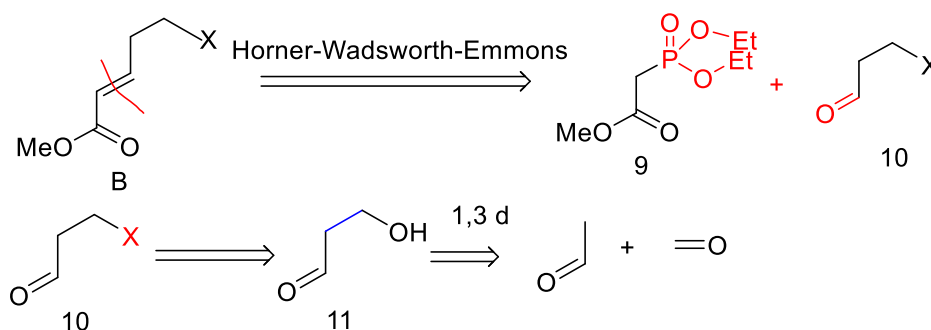


Figure 4. Retrosynthesis of molecule B.

For molecule C (see Fig. 5). The enol compound was converted into a carbonyl compound, and a bromine atom was introduced on its α carbon to get molecule 12. Then, the carbonyl functional group was converted to an ester group to reduce carbonyl reactivity, and that is molecule 13. Molecule 13 is a 1,5- di-oxygenation compound. The bond (Fig. 5, highlighted in blue) was broken and ester and molecule 14 was got. With several steps, the carbon-carbon double bond and Br group could be easily converted to hydroxyl and molecule 15 was got, a 1,3- di-oxygenation compound. The six-membered ring by aldol condensation was broken to get molecule 16, a 1,5- di-oxygenation compound. Michael addition was used to break the bond (Fig. 5, highlighted blue) and an acetone and molecule 17 was got. By converting the carbon-carbon double bond into a hydroxyl group, a 1,3- di-oxygenation compound,

molecule 18 was got. The blue bond was broken by aldol condensation to get molecule 19 and formaldehyde.

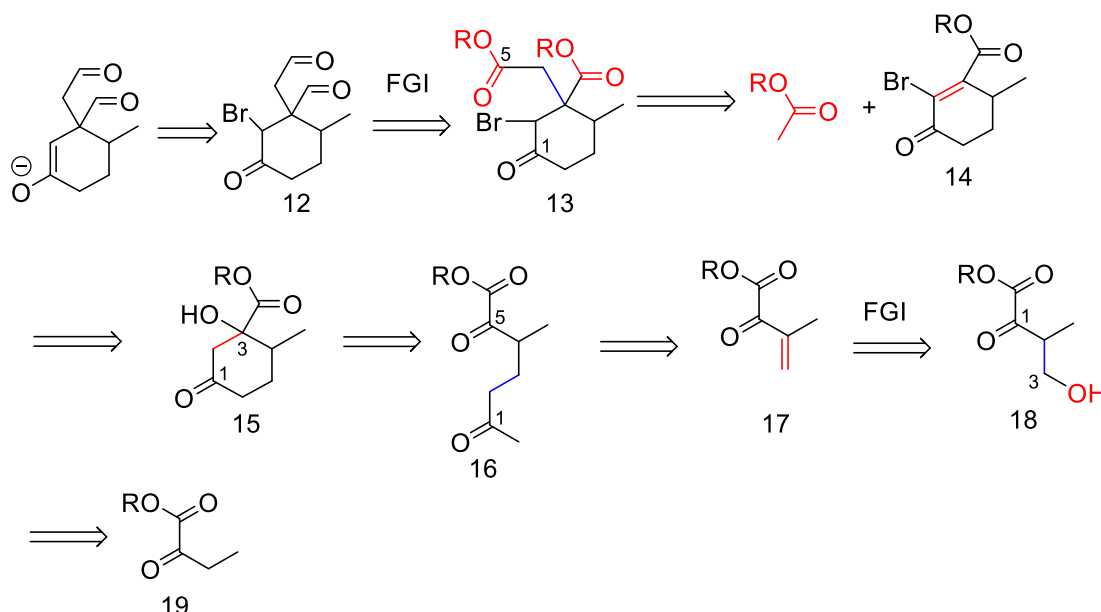


Figure 5. Retrosynthesis of molecule C.

3. Total synthesis

3.1. Synthesis of (2-methoxy-5-oxo-2,5-dihydrofuran-3-yl)zinc(II) bromide

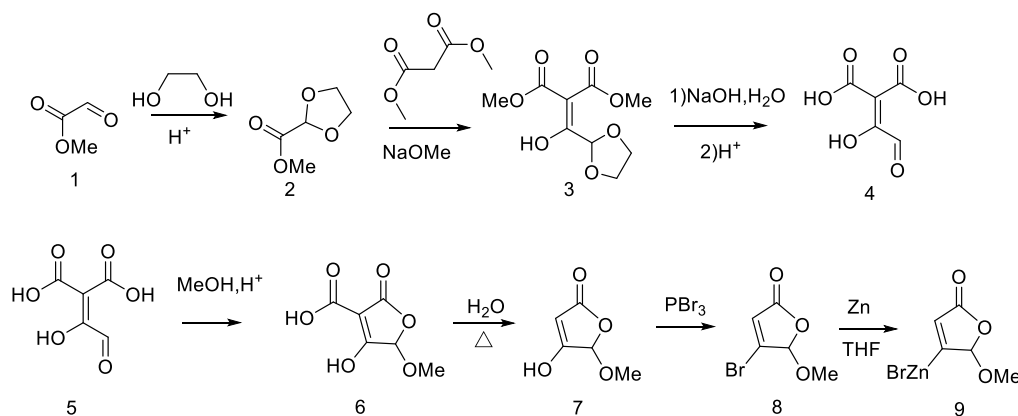


Figure 6. Synthesis of (2-methoxy-5-oxo-2,5-dihydrofuran-3-yl)zinc(II) bromide.

Firstly, let us discuss the synthesis route of (2-methoxy-5-oxo-2,5-dihydrofuran-3-yl) zinc(II) bromide (compound 9) shown in Fig.6. Methyl 2-oxoacetate(Compound 1) is a common chemical material used in pharmaceuticals⁴. The conversion from compound 1 to compound 2 protects the aldehyde group [5]. Dimethyl malonate undergoes a Claisen condensation with compound 2 to form compound 3. The transformation from compound 3 to compound 4 involves the alkaline hydrolysis of the ester, with concurrent acidification facilitating the deprotection of the aldehyde group. The transformation from compound 5 to compound 6 is a balanced reaction. Methanol and hydrogen ions promote the equilibrium. Upon heating, a decarboxylation reaction occurs, followed by the replacement of the hydroxyl group with bromine. Finally, the Grignard reagent is prepared, and then the first part of the synthesis is finished.

3.2. Synthesis of 2-(4-chlorobut-1-en-1-yl)-1,3-dioxolane

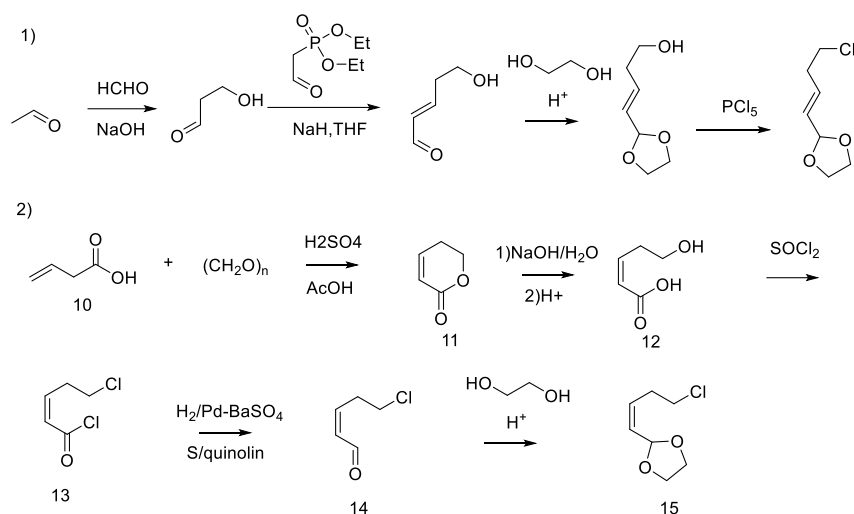


Figure 7. Synthesis of 2-(4-chlorobut-1-en-1-yl)-1,3-dioxolane

As is shown in Fig. 7, we have two routes to synthesize 2-(4-chlorobut-1-en-1-yl)-1,3-dioxolane (15). The first route involves the construction of the alkene by using the Horner-Wadsworth-Emmons reaction, followed by the protection and chlorination of the aldehyde group [6]. In the second route, the reaction from compounds 10 to 11 is a patented process known for its high yield and purity. The reduction from compound 13 to 14 using the Rosenmund reduction where acyl chlorides are selectively reduced into aldehyde. The addition of the carbon-carbon double bond and the reduction of the aldehyde to alcohol can be prevented by the use of a catalyst poison or regulator such as quinoline-sulfur, which selectively deactivates the catalyst, whereby the formation of the alcohol is suppressed [7], thereby increasing the selectivity to the aldehyde. Barium sulphate is also added as a poison due to its low surface to reduce palladium activity. Overall, fully deactivating Pd improves the reaction's selectivity.

3.3. The rest Synthesis of Crotonine A

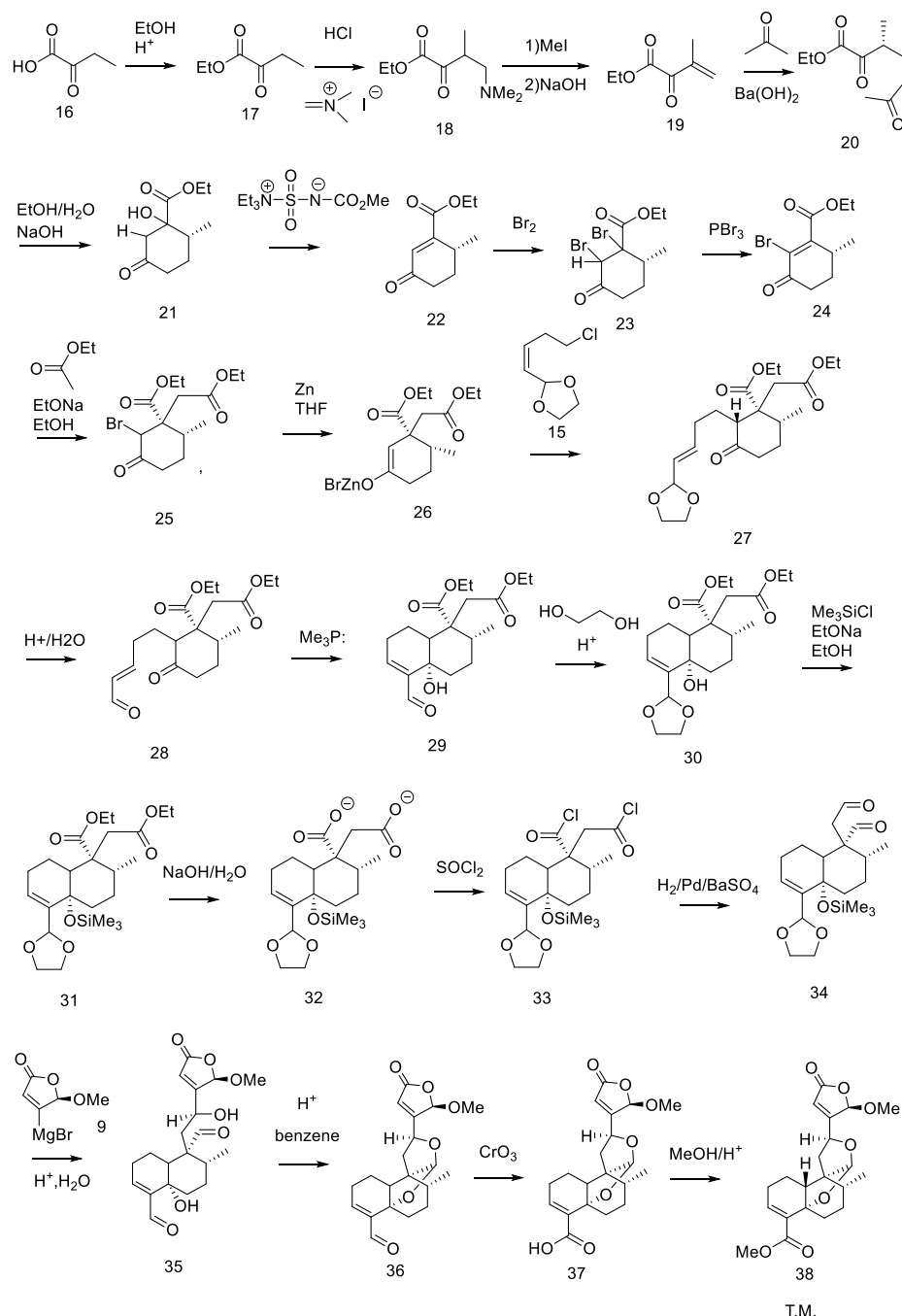


Figure 8. Synthesis of Crotonine A

Initially, I chose α -Ketobutyric acid (**16**) as the starting material. This is a common food additive and flavouring agent. It first undergoes esterification with ethanol to protect the carboxyl group, forming compound **17**. To synthesize compound **19**, I initially considered using formaldehyde with compound **17** for an aldol condensation reaction (Fig. 9), followed by elimination to make a carbon-carbon double bond to make compound **19**.

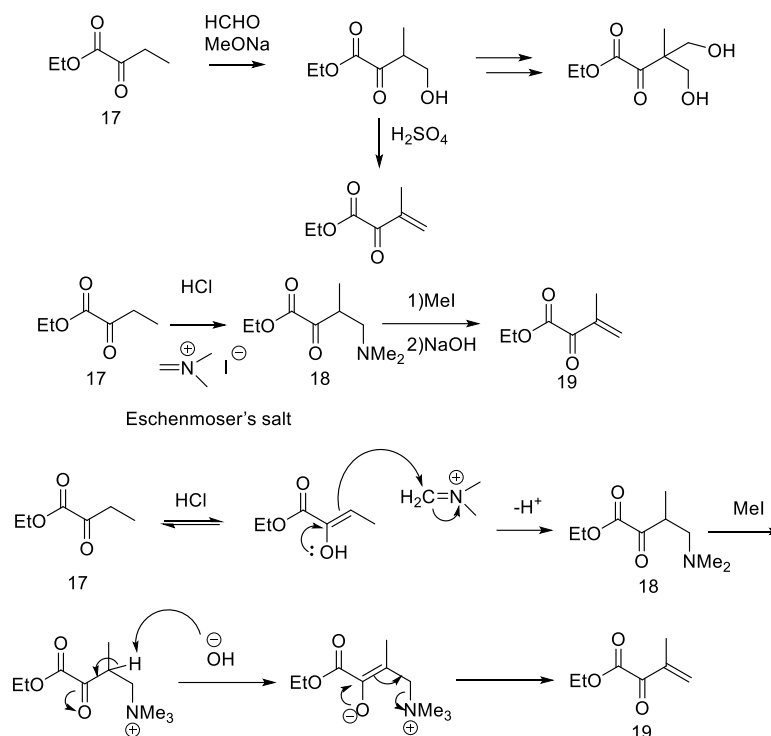


Figure 9. A wrong route and mechanism of Mannich reaction.

However, the trouble is that methanal needs to be more reactive. The reaction would continue uncontrollably, and the elimination of primary alcohols is not straightforward. Fortunately, the Mannich reaction is ideal for synthesizing the target compound 19 using a Eschenmoser's salt, a common compound used in organic synthesis [8]. The mechanism is illustrated in the figure. Next (19-20), a Michael addition reaction using acetone as the solvent and barium hydroxide as the base is conducted to elongate the carbon chain. At this point, the first stereoisomer that will influence the final product appears. However, simply relying on this reaction cannot determine the stereoselectivity.

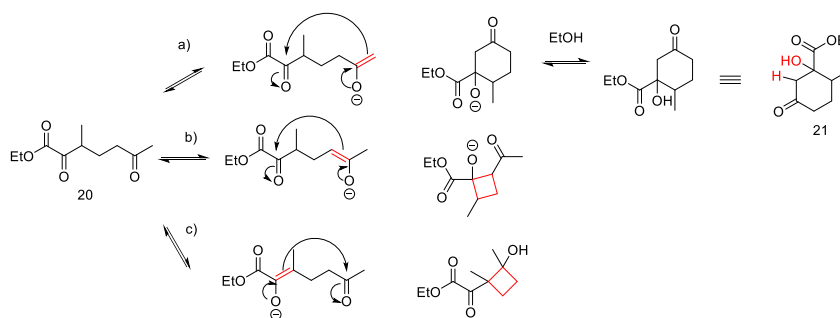


Figure 10. Selectivity of aldol condensation to make compound 21 from compound 20

As shown in Fig. 10, another aldol condensation is used to form a six-membered ring in compound 21. However, analyzing the compound reveals selectivity in the reaction, as the base can attack three α -H atoms, allowing the enolate to form at three positions. Upon ring formation, situations b) and c) form four-membered rings, unstable due to the ring strain, leaving only one major product (21). Then, an important six-membered ring is constructed. Next, Burgess reagent, Methyl N-(triethylammonium sulphonyl) carbamate (21-22), also known as Burgess reagent, a mild and selective dehydrating agent, is utilized for the preparation of alkene from alcohol [9]. Bromine addition and elimination are then substituted for bromine at another carbon position (22-24).

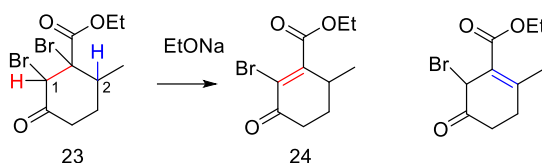


Figure 11. Selectivity of E2 Elimination.

Clearly, the α -H of the carbonyl group is more acidic than general hydrogens, making the E2 elimination reaction more likely to occur at carbon 1 rather than at carbon 2 (Fig. 11).

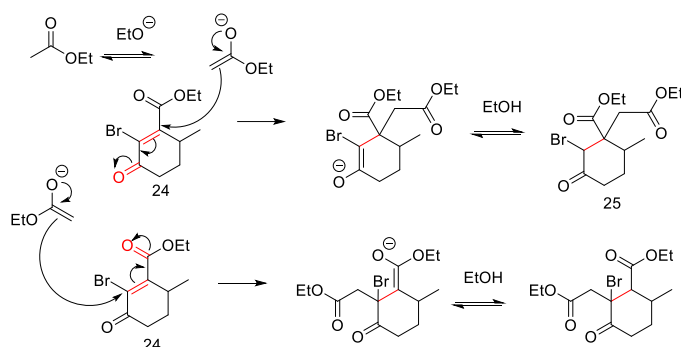


Figure 12. Selectivity of Michael addition.

Using another Michael addition(24-25), ethyl acetate primarily reacts with the more active ketone carbonyl group, yielding the major product (25) (Fig. 12). Meanwhile, another stereoselectivity is formed. Unfortunately, this synthesis method lacks an effective method to aid stereoselectivity.

Subsequently, the reaction of zinc with α -halogenated ketone forms an organozinc reagent, connecting 16 and 25 (25-27). This step also involves stereoselectivity.

After deprotecting the aldehyde group, the Baylis-Hillman reaction (28-29) completes the construction of the second six-membered ring (with stereoselectivity).

Next, both the aldehyde and hydroxyl groups are protected (29-31). Then, the ester group is deprotected, and Rosenmund reduction is used to reduce two acyl chlorides to aldehydes (32-34).

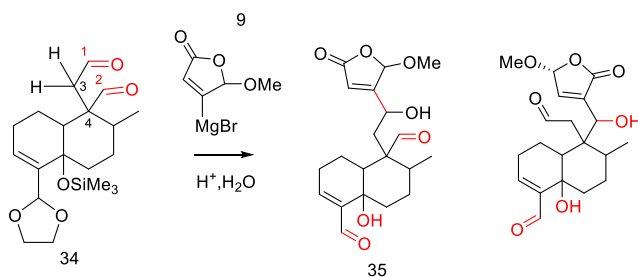


Figure 13. Selectivity of grignard reagnt.

The Grignard reagent is highly selective due to its high reactivity [10]. As shown in Fig., carbon 3 is linked to small hydrogenhydrogens of carbon 4, which connect large functional groups. The Grignard reagent predominantly reacts with the less sterically hindered aldehyde like carbon1. The main product 35 is thus formed. This step also involves stereoselectivity.

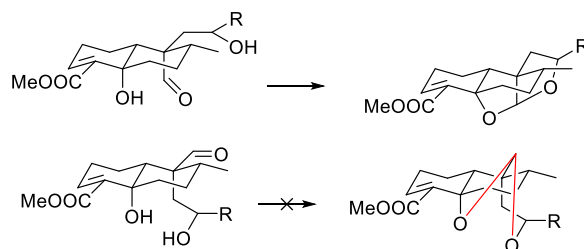


Figure 14. The influence of stereoselectivity for acetal reaction.

With protons and water, the deprotection of hydroxyl and aldehyde also happened simultaneously (34-35). Reaction 35-36 is an acetal reaction, but stereoselectivity would influence this reaction. In some cases, the acetal reaction will not happen because the aldehyde and hydroxyl are too far apart (Fig. 14). Finally, converting the protected aldehyde to an ester yields the target molecule(36-38).

4. Conclusion

Overall, crotonine A has a promising future in pharmaceuticals for anti-insulin resistance. This work carried out a simplified disassembly of the target molecule according to the oxidation level and the position of the characteristic functional groups, and finally de-cyclized it to obtain the common and easy-to-purchase synthesized substrate product, and then proceeded to synthesize it according to the direction of the retrosynthesis, and then improved the retrosynthesis and synthesis steps in terms of the reactivity and the selectivity of the reaction to complete the total synthesis. Finally, the total synthesis was completed. However, we need to develop some good ways to solve the problems about stereoselectivity, which is crucial for the synthesis and functions of the molecule. It should be discussed further. Furthermore, the details of the experiment, such as conditions of reactions and yields, are precise. So, this synthetic route is for reference only.

Acknowledgement

Wenyuan Chen and Yuanle Zhu contributed equally to this work and should be considered co-first authors.

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