Retrosynthesis of a Newly Discovered Molecule in Betula Alnoides Achieved by Considering a Similar Molecule, 3-Farnesyl-2,4,6-Trihydroxybenzophenon

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Abstract: A recent found type of benzophenone (molecule A), a component of the alcohol extract of Betula alnoides, has shown antiausterity activity against PANC-1 human pancreatic cancer cells. The molecular structure of this new type of bezophenone is very similar to that of an already found bezophenone, 3-farnesyl-2,4,6-trihydroxybenzophenon (molecule B), which demonstrates the availability of examining the production method of this new bezophenone (molecule A) via considering the molecular structure of the already found bezophenone (molecule B). In this paper, retrosynthesis (a theoretical analytic method) is applied to these two bezophenones, in order to determine the types of molecules of the raw materials and a few efficient ways of production.

1 INTRODUCTION

In a study published in the Journal of Nature Products on May 19th. 2021, an ethanol extract of Betula alnoides showed antiausterity activity, a method used to discover lead compounds by using unprecedented anticancer activities which target the tolerance of cancer cells to nutrition starvation, against PANC-1 human pancreatic cancer cells under nutrient-deprived conditions. According to the study, the Phytochemical investigation of this active extract led to the isolation of eight benzophenones (1−8), in which 6 of them (2-7) are newly discovered and three xanthones (9−11) (Omar, 2021).

The unknown molecule A (Figure1), one of the main components of ethanol extract of Betula alnoides, demonstrates great similarities in molecular structure with 3-farnesyl-2,4,6-trihydroxybenzophenone (Figure 2). Therefore, we intend to use the concept of retrosynthesis to break down the unknown molecule A (Figure1) through such similarities.

Retrosynthesis is an analytic approach based on the desired product. When synthesizing this planning process, the following rules should be clearly understood. First of all, fragment ions produced should be stable. Secondly, fragments are always in a form of cations and anions so that they will be able to switch between each other. Thirdly, the relationship between the functional groups plays a role in deciding the order of disconnection. For example, a functional group that would boost the other to connect should be disconnected last. Fourthly, electron-withdrawing groups should be the first ones to be disconnected. Fifthly, a balance of applying these rules should be achieved in order to make the entire process as simple as possible (Tutor, 2020).

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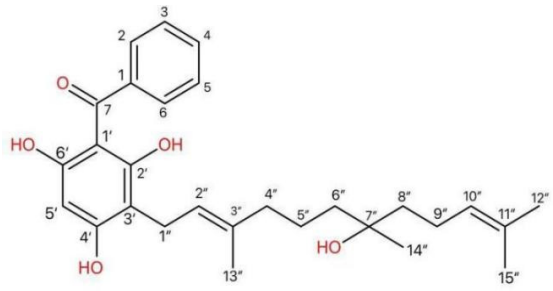

Figure 1: Molecular Structure of Molecule A.

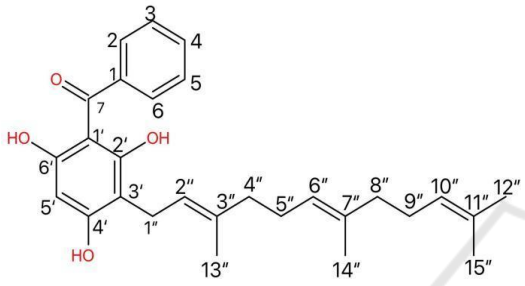

Figure 2: Molecular Structure of Molecule B.

Considering the structures of molecule, A (Figure 1) and molecule B (Figure 2), they are both mainly composed of benzophenone and a large chain with 15 carbons. Benzophenone is composed of two aromatic rings, a structure with closed rings and conjugated double bonds or lone pairs. One is a simple benzene ring, the other is a trihydroxybenzene, called phloroglucinol. The difference here is that between C 6"and C 7", molecule A has a single bond whereas molecule B has a double bond. In addition, C 7"of molecule A is connected to a hydroxide group whereas that of molecule B is connected to hydrogen.

2 METHODS

2.1 General Disconnecting Sequence

As regards to the rules of retrosynthesis, the general sequence of disconnecting bonds is listed here. First, the bond between C 3' and C 1". Then, the bond between C 1 and C 7 and the bond between C 1' and C 7 could both be the second ones to be broken down. The third step would be to break down the other aromatic ring. Finally, the three hydroxide groups could be considered to be disconnected, but not necessarily. The following content includes the considerations of the sequence and the mechanism.

2.2 Breaking Farnesyl Group (Explanation)

The farnesyl group is a nucleophile that would attract electrons, or withdraw electrons, from the aromatic ring. As regards to the fourth rule listed in the introductions, an electron-withdrawing group should be disconnected first so the farnesyl group would be the first one to disconnect. In addition, when considering whether the first disconnecting functional group would be the farnesyl group or the hydroxide group, rule number three gives an answer. The linkage of nucleophiles for aromatic rings would deactivate the aromatic ring whereas the hydroxide group would activate the ring. Here, a deactivating step could be achieved after there is something that has already activated the aromatic ring. Therefore, the hydroxides on the benzene rings should not be removed before the farnesyl. Besides, when removing the farnesyl group, a more symmetrical structure with two aromatic rings would be present, which allows the following step to be more conveniently presented (fifth rule). All of these rules support that the farnesyl group should be disconnected first (Kolesnikov, 2016).

The following steps show Benzene alkylation (Libretexts, 2020), where the R group represents the farnesyl group.

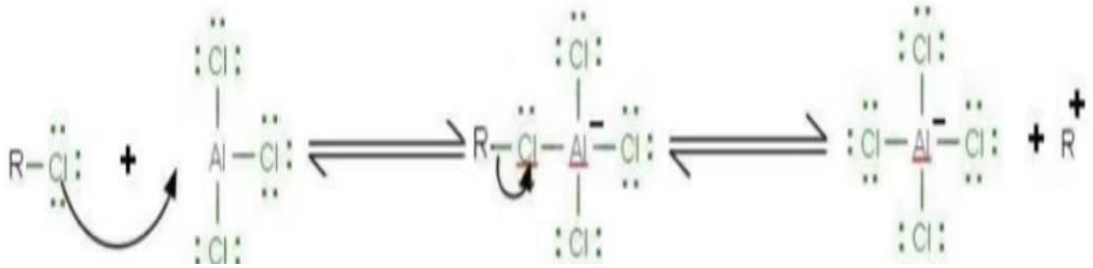

Figure 3: Benzene Alkylation.

As shown in Figure 3, firstly, the Cl, linked to the farnesyl group, link to AlCl3, forming a farnesyl cation.

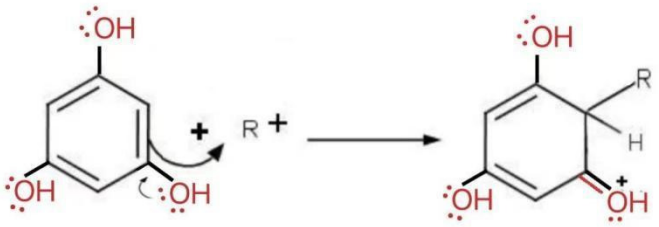

Figure 4: Farnesyl Cation Formation.

As shown in Figure 4, secondly, the cation link to the trihydroxybenzene by electrophilic addition reaction.

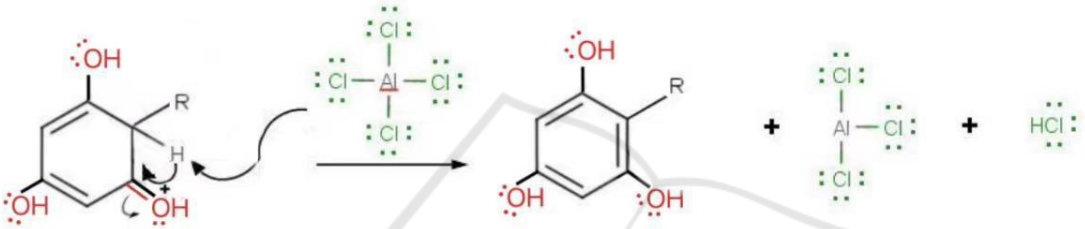

Figure 5: HCl Formation.

As shown in Figure 5, finally, the AlCl4 pushes the electrons back, splitting the hydrogen, forming a by-product of HCl (Libretexts, 2020).

2.3 The Separation of the Two Aromatic Rings

After removing the farnesyl group, the rest of the structure is mainly composed of benzophenone with two aromatic rings. The reason why the hydroxides should still not be separated is that it could also boost the following linkage of the aromatic ring and the acyl group. Moreover, steps should be as simple as possible. The next retrosynthesis step is to separate the two aromatic rings. As there is a ketone (-R-C=O-R-) in the middle of this complex, there will be two pathways of disconnection: the benzene ring or the trihydroxy benzene ring.

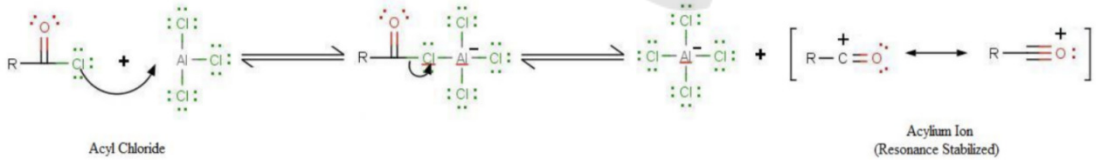

Figure 6: Formation of Acylium Ion and AlCl4-.

As shown in Figure 6, firstly, the reverse reaction of both of the disconnections would start with a formation of an Acylium ion and AlCl4, where the AlCl3 acts as a catalyst. Here the R group would be either trihydroxybenzene or benzene, which depends on the pathway retrosynthesis is performed.

i. Breaking benzophenone into Benzene and Benzoyl chloride, 2,4,6-trihydroxy (acyl chloride)

The reverse reaction mechanism would be a simple electrophilic substitution.

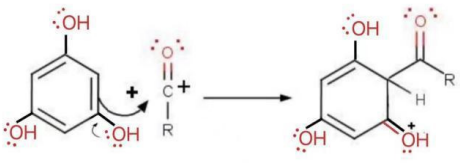

Figure 7: Linking of the Aromatic Ring.

In Figure 7, the R group refers to the benzene ring. In this mechanism, the acylium ion acts as a nucleophile while the tri hydroxybenzene acts as an electrophile. The inductive effect of the hydroxide groups could "push" the electron onto the conjugated double bond in the trihydroxybenzene which will attach to the nucleophile. The move of electrons allows the acylium ion and the aromatic ring to link together.

Then, a deprotonation step formed by AlCl4- would produce a by-product HCl and target molecule benzophenone.

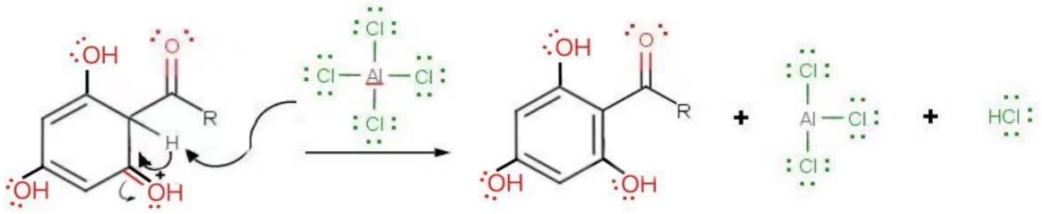

Figure 8: Formation of HCl.

Again, in figure 8, here the R group refers to the benzene ring. In this mechanism, the AlCl4 act as an electrophile, attaching the hydrogen on the trihydroxybenzene, "pushing" back a pair of electrons along the same way back, finally to the oxygen. And the hydroxide and chloride are split, forming a molecule of HCl (Libretexts, 2020).

ii. Breaking benzophenone into Phloroglucinol and Benzoyl chloride (acyl chloride)

This mechanism is very similar to the last one.

The reverse reaction mechanism is also a simple electrophilic substitution.

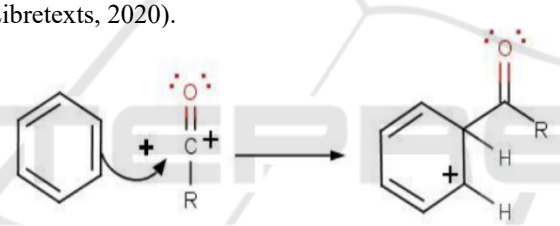

Figure 9: Phloroglucinol and Benzoyl Chloride (https://www.chemistry.msu.edu/faculty/reusch/VirtTxtJml/chapt15.htm).

In the Figure 9, the R group refers to trihydroxybenzene. In this mechanism, the acylium ion also acts as a nucleophile while the benzene acts as an electrophile. The difference is that there is no hydroxide group to "push" the electron pairs to the nucleophile. The linkage of benzene and the acylium ion is achieved by moving an electron pair from the conjugate double bond itself to the acylium ion.

After that, the deprotonation step is very similar.

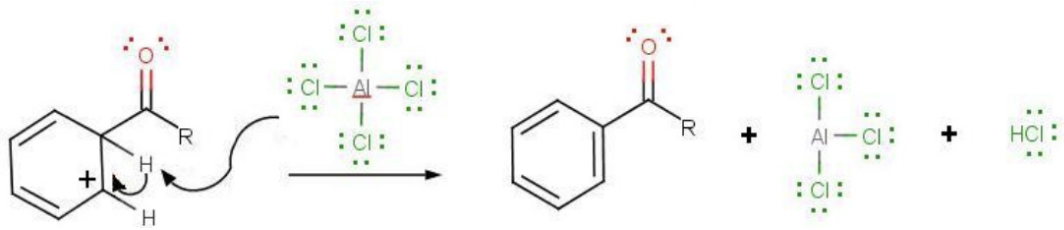

Figure 10: Formation of the conjugated double bond and HCl
(https://www.chemistry.msu.edu/faculty/reusch/VirtTxtJml/chapt15.htm.)

As shown in Figure 10, the electron pair on the chloride of AlCl4 passes along the same path to the benzene ring, forming the conjugated double bond again. The chloride also attracts the hydrogen and form a by-product of HCl.

2.4 Comparison of 3i. and 3ii.

There are two explanations for the effects that a substituent exerts on the reactivity of a benzene ring: Firstly, it depends on the inductive effect of the

substituent. Except for metals and carbon, most elements have much higher electronegativity than hydrogen. As a result, sigma bonds are formed between substituents containing nitrogen, oxygen, halogen atoms, and an aromatic ring that gives an inductive electron. Secondly, the conjugation of a substituent function with the aromatic ring is another important result. The electron pair donates or withdraws electrons with the help of conjugated interaction to form a benzene ring. If the atom bonded to the ring contains nitrogen, oxygen, and halogens which have one or more non-bonding valence shell electron pairs, electrons may move into the aromatic ring according to p-pie conjugation. Finally, the benzene ring may receive electrons from polar double and triple bonds.

In this paper, 3-farnesyl-2,4,6-trihydroxybenzophenone(B) only has several double bonds on its farnesyl chain while there is a hydroxyl group located at 3'' on the unknown compound. The rules for oxygen are utilized on it and the hydroxyl group actives benzene, making the following reaction easier to happen (https://www.chemistry.msu.edu/faculty/reusch/VirtTxtJml/chapt15.htm.)

2.5 The Separation Between the Other Aromatic Ring and the Acyl Group

No matter which passway it has gone through in the last step, the next step would be just to break down the linkage between the acyl group with the other aromatic ring. And the step would be basically the same as before. Therefore, the advantage of hydroxide boosting the linkage between the aromatic ring and the acyl group would ultimately appear for both sequences.

2.6 The Separation of the Three Hydroxides

This step is optional because the trihydroxybenzene, phloroglucinol (which is made from glucosides, plant extracts and resins), is a common raw material, and could simply be considered as a final molecule in the process of planning retrosynthesis (Hoool, 2018).

2.6.1 Converting Molecule B to A

This step could be achieved by altering the reactant of farnesyl of the benzene alkylation (https://www.chemistry.msu.edu/faculty/reusch/VirtTxtJml/chapt15.htm.), which means converting the farnesyl group into a similar one with a hydroxide on C 7" and no double bonds between C 6" and C 7". The reason why adding the hydroxide onto the farnesyl group first is that the reaction would be easier to target without disruptions.

This step is an electrophilic addition reaction

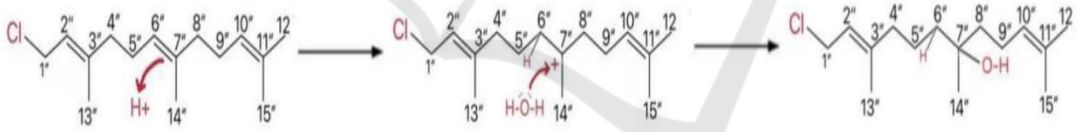

Figure 11. Conversion of Molecule B to A

In Figure 11, the proton acts as a nucleophile and the double bond between C 6" and C 7" acts as an electrophile, where hydrogen is linked onto C 6". Then a carbocation is formed at C 7", which acts as a nucleophile, attacked by the lone pair of the water molecule, and the hydroxide is linked onto C 7".

According to the inductive effect, the hydroxide group is more likely to locate on C 7" than C 6" as there is more inductive effect on C 7" that would stabilize it. This theory is the same as the inductive effect on C 2" and C 10", which means these two are also not "favorited". In addition, when considering the inductive effect of C 3" and C 11" compared with C 7", the inductive effect is not as symmetrical as that of C 7". Therefore, both of these two considerations support that the hydroxide group would be the mostly located on C 7", with a small proportion of the other Cs.

When considering the way of extracting only the target molecule with hydroxide group located on C 7", their slightly different boiling points would allow fractional distillation to separate them and isolate the wanted products.

2.6.2 Conclusion and Evaluation

In conclusion, we aim to use a known compound to deduce a new one that obtains a similar structure by connecting and breaking functional groups or inducing and moving electrons. This research paper promotes the understanding of the retrosynthesis process of 3-farnesyl-2,4,6-trihydroxybenzophenone.

The results suggest that it may be a relatively simple way to find a new medicine that targets pancreatic cancer.

Since the retrosynthesis shown above have not been proven in a real experiment, the feasibility of such methods is unknown. Other factors such as financial restrictions, potential safety hazards, and the duration of a total experiment should be considered to achieve practicality. Furthermore, only two routes were analyzed so it was possible that simpler ways were neglected. In addition, distillation should be performed in conditions as perfect as possible so common experimental tools may not be able to separate the desired product because it may be mixed with other molecules that have similar boiling points. Overall, further testification and research are required to determine the hypothesis provided in this paper.

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