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A proposed total synthesis of a clerodane-type diterpenoid—Scaparin C

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Abstract. A theoretically feasible synthetic route for Scaparin C, a clerodane-type diterpenoid newly discovered in nature is depicted. A Diels-Alder reaction followed by oxidative cleavage of the olefin generates a 1,3,6-tricarbonyl compound as the substrate. Based on the relative reactivities of the three carbonyl groups, the primary aldehyde group is protected as the acetal. It is expected that the right aldol and alkylation reactions take place for the remaining carbonyl groups, collaboratively giving a bi-fused ring system which is the most important constituent of Scaparin C. After deprotection, the primary aldehyde group is connected with the 3-bromofuran through a Friedel-Crafts reaction. Finally, reactions including sequential reduction of the carbonyl groups, selective protection, acylation and oxidation of the alcohols can preserve the diol and the ketone groups needed, intramolecularly forming the cyclic acetal and epoxidation of alkene with the m-CPBA completing the synthesis.

Keywords: Aldol, alkylation, oxygenation pattern, bi-fused ring system, diterpenoids

1. Introduction

Extracted from Chinese liverworts, terpenoids and aromatic compounds have attracted wide attention from fields of scientific research since they were first discovered [1]. This is because they generally exhibit distinct biochemical properties that are beneficial to humans as for therapeutic purposes, ranging from antifungal, cytotoxic, and antimicrobial to insect antifeedant activities [2].

As the category of these compounds that are widely distributed in Chinese liverworts, clerodane-type diterpenoids, as shown in Figure 1, have intrigued scientists and thus make them eager to explore them in detail [3, 4]. For instance, Yanan Qiao and her co-workers had investigated the spectroscopic data of some diterpenoids as a way to characterize them. This was the basis for them performing analysis on the vasorelaxant assay of the diterpenoids and their appreciation of the medicinal value of these compounds [5]. Rui-Juan Li and her co-workers, on the other hand, took advantage of statistical methods to study the phytotoxic potential of five cis-clerodane diterpenoids, stephanialides A-E which could inhibit growth and reproduction of some other organisms [6]. Unfortunately, although there have been previous researches on the chemical structure and activity of these diterpenoids carried out as mentioned above, ideas about effective total synthesis of them have remain to be figured out. The potential reason lying behind the difficulty of the synthesis can be the typically complex structure of the diterpenoids which features a heavily substituted bi-fused ring motif and various oxygenation patterns. In addition, an observation of around seven stereogenic centers in each of the diterpenoids indicates that steps involved careful stereochemical control need to be taken, which have always been confusing scientists if they are

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to successfully synthesize novel products that have a significant change in lives of humans. This may account for why scientists have not disclosed a complete scheme for the synthesis.

The main target of this paper is to provide a logically plausible synthetic route for one of the clerocane-type diterpenoids after gaining an inspiration for the linkage between dioxygenation patterns and formation of the polycyclic skeleton from the case of sarracein, a natural product [7]. According to Figure 2, Saracein also has a cyclic acetal that shows a hidden aldehyde group and further disconnection can give two more aldehydes and some alcohols which can be selectively reconnected to give two five-membered rings fused together. In this paper, a retrosynthetic analysis on Scaparin C is developed as an example, disconnecting the cyclic acetal and subsequently separating a substituted six-membered ring and a 3-carbon Grignard reagent. It is envisioned that they are connected via a Grignard reaction and subsequently an intramolecular alkylation reaction. The six-membered ring can be obtained from intermolecular and intramolecular aldol reactions with an unusual tricarbonyl compound made from oxidative cleavage of a cyclohexene available with a Diels-Alder reaction between two simple starting materials. Ultimately, connection between the bi-fused ring with the 3-position of furan can be a spontaneous Friedel-Crafts acylation without harsh conditions. To avoid the occurrence of some issues of chemoselectivity and regioselectivity that can lead to unwanted side products as much as possible, suitable protective groups will be selectively added and the sequence of steps will be strictly determined depending on how each intermediate will be converted in a particular condition. Even more importantly, a stoichiometric amount of some reagents is required so that they will have no alternative but to react with the most reactive functional groups cleanly. Given that the structures of the diterpenoids are highly similar, it is possible to synthesize the other products by slightly altering the conditions of reaction or reagents used in the procedure as for Scaparin C.

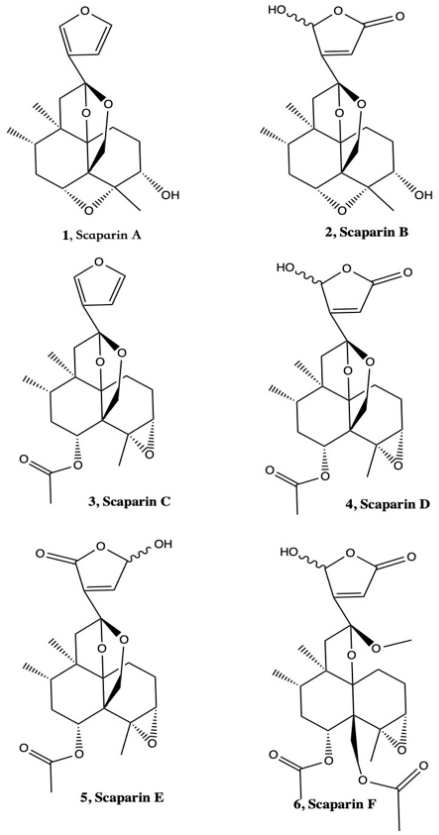

Figure 1. clerodane-type diterpenoids A-F, 1-6

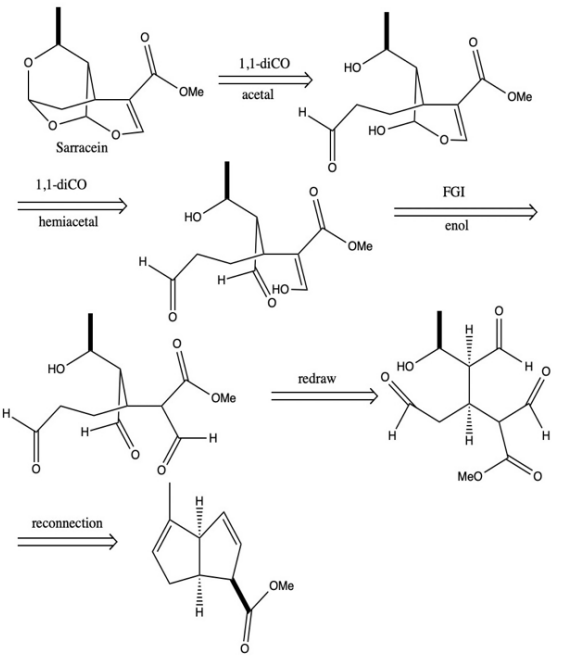

Figure 2. Disconnection of Saracein

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2. Retrosynthetic analysis

2.1. Scheme 1(Figure 3)

At first glance, there is an obvious 1,1-dicarbonyl relationship found in the cyclic acetal, which is commonly afforded by a reaction between a ketone(or aldehyde) and a diol, simplifying the structure of Scaparin C as **7** critically. On the right hand side of the bi-fused ring system, the epoxide is known to stem from the epoxidation of an alkene with hydrogen peroxide or m-CPBA therefore it can be directly disconnected to an alkene group **8** retrosynthetically. As for the ketone group just revealed that has a neighboring furan molecule, it can be considered as oxidation of a secondary alcohol group in **10** and it is then recognized that the primary aldehyde group of bi-fused ring system **11** and furan molecule **12** can be connected in the form of Friedel-Crafts acylation. A 3-bromo furan **13** will be used instead to ensure that reaction can occur at the correct at the right 3-position since a typical furan molecule usually prefers 2 and 5 positions when it experiences electrophilic substitution.

2.2. Scheme 2(Figure 4&5)

The molecule **11** is interesting for its 1,4- and 1,6-dioxygenation patterns and both can be applied for the following disconnections. This paper chooses the latter approach pertaining to the focus of simplifying the bi-fused ring structure to a greater extent. The secondary alcohol on carbon 6 and the primary alcohol on carbon in **11** can be changed into a ketone and benzyl ester group respectively in **14** and reduction of them can be realized by the end of the synthesis. The formation of carbon-carbon bond between carbons 7 and 13 can be the result of intramolecular alkylation and a bromo group can be added on carbon 13. Before this alkylation takes place, there is probably a reaction between the Grignard reagent **17** and a bromo group in **16** to which an aldehyde **18** is converted in two steps, making the carbon-carbon bond between carbons 10 and 11. The six-membered ring **18** is thought to be furnished by a total of three aldol reactions, a Grignard reaction and an alkylation with the substrate **22** where there are desired 1,6-related aldehyde and ketone groups. They allow **22** to be reconnected to a cyclohexene molecule that can be made from a Diels-Alder reaction between two available starting materials **24** and **25.**

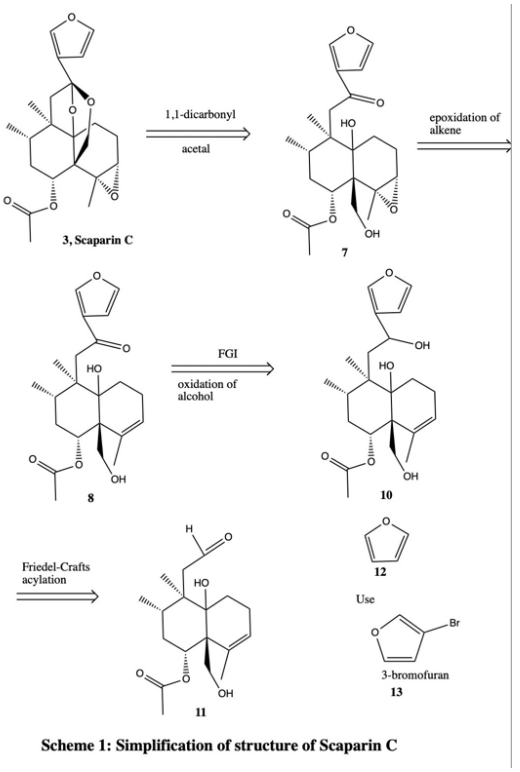

Figure 3. Separation of the important bi-fused ring structure retrosynthetically

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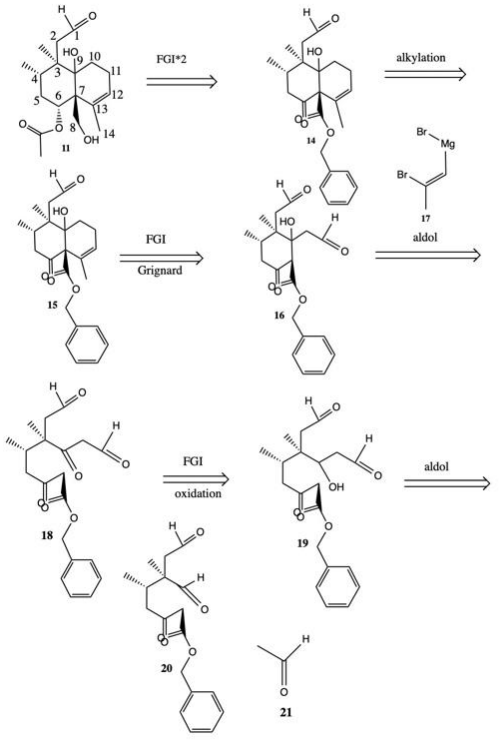
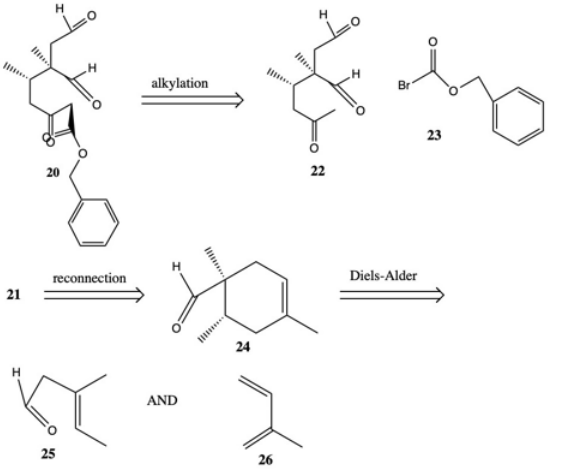


Figure 4. Disconnection of bi-fused ring skeleton



Scheme 2: Disconnection of the bi-fused ring via dioxygenation patterns

Figure 5. The revealed acylation and Diels-Alder steps

2.3. Scheme 3: Route for Synthesis (Figure 8&9)

To begin with, an alkene with a substituted tertiary aldehyde **24** and a diene **25** combine in a Diels-Alder manner to give the cyclohexene **23** in a Diels-Alder manner. The stereochemistry of methyl groups in Scaparin C are cis so they are supposed to remain cis in **23**. This is analogous to the situation with the methyl group and carboxylic acid that are cis in the dienophile used to synthesize a bicyclic double lactone with both groups cis to each other as well [8]. Oxidative cleavage of **23** in an atom of ozone affords the long-chain molecule **22** which can be apparently challenging to be made through traditional aldol methods. Of the three carbonyl groups in **22**, the primary aldehyde is the most reactive while it should not undergo aldol reactions. One molecule of glycol protects the primary aldehyde with priority in a catalytic amount of p-toluene sulfonic acid. Given that the tertiary aldehyde will be more electrophilic than the ketone in **22**, there can be an aldol reaction between it and one molecule of ethanal **21** preferentially, regardless of its greater steric hindrance. Reduction of aldehyde in **18** with sodium borohydride and reaction of it with phosphorus tribromide produce the bromo group in **16**, which can be attacked by the Grignard reagent **17**.

To prevent the secondary alcohol in **29** from bromination with phosphorus tribromide, one equivalent of this reagent is used since the primary alcohol possesses greater reactivity identical to the situation with the primary aldehyde group. The ketone group in **18** may be reduced simultaneously to a secondary alcohol but it will be oxidized together with the alcohol on carbon 9 by adding chronium(VI) oxide, having few influences on the progress of synthesis. Treatment with a base sodium hydroxide can enable the intramolecular aldol reaction between the two ketone groups, forging the bi-fused ring with a convergent intramolecular alkylation between the alkene and ketone in **14** which means approximately half of the completion of the synthesis. To introduce the benzyl ester moiety to the more substituted end of the ketone, the ketone group may be converted into an enamine with the use of a secondary amine, which

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is morpholine in this case. Direct combination of **31** and benzyl bromoformate **23** in basic solution will cause an issue—the reaction does not stop in the aldol step and instead an epoxide in Figure 6 is detected from successive O-alkylation, which is known as the Darzens reaction [9]. The epoxide will not facilitate but seriously interfere with the synthesis so the significance of enamine is highlighted. The ambiguity in terms of where the benzyl bromoformate attacks the ketone can be eliminated as the intermediate contains a new alkene. It is believed that a more substituted alkene in Figure 7 is more stable and is therefore favored.

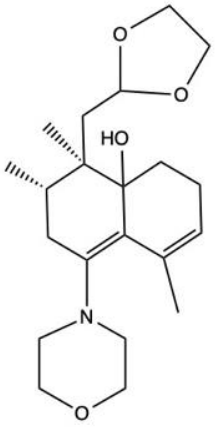

Figure 6. The stable enamine intermediate

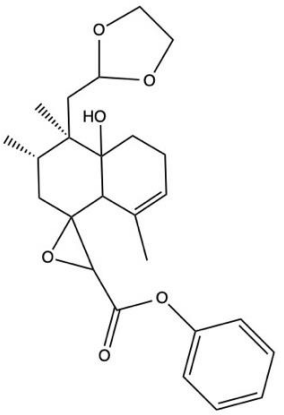

Figure 7. The undesired epoxide formed

Under the condition of acidic solution, the cyclic acetal is removed to give the primary aldehyde. 3-bromo furan is then reacted with **32** after its deprotection to yield **33**, achieved by a regular Friedel-Crafts acylation without catalysts. The secondary alcohol group formed will then be oxidized to its corresponding ketone group. Originally the paper intends to oxidize the alkene on the right-hand side of the bi-fused ring in the very last step, but deprotection of the benzyl ester will need hydrogen gas which can accidentally reduce the alkene and it will be impossible to regain it. Therefore, it is necessary to carry out the reaction prior to the hydrogenation step which liberates the carboxylic acid in **35**. When dealing with the individual reduction of it to a primary alcohol, borane is selected as the ideal reducing agent as it will destroy neither of the ketone groups as in **36**, unlike sodium borohydride [10]. To the author's satisfaction, **36** includes the requisite diol and ketone partners which cyclize to an acetal **37** intramolecularly in an acidic environment. By the end of the synthesis, reduction of the remaining ketone group in **37** with sodium borohydride and esterification using ethanoic acid in a concentrated strong acid yield the target molecule.

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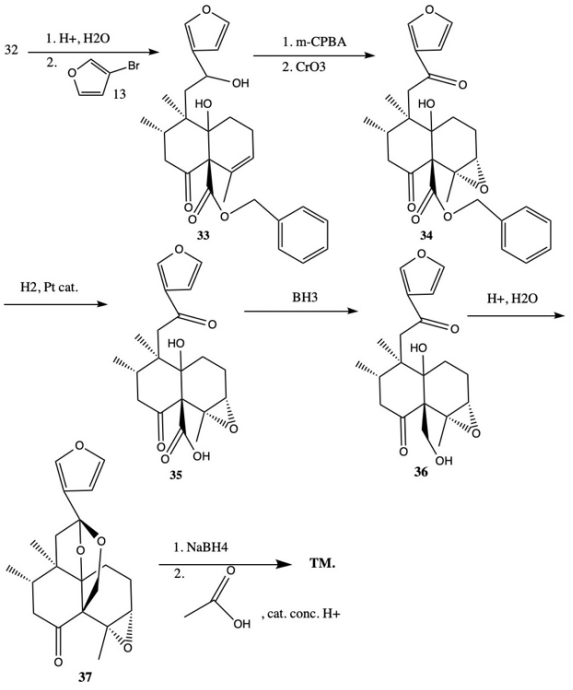

Scheme 3: Total synthesis of Scaparin C

Figure 8. Synthetic route to Scaparin C

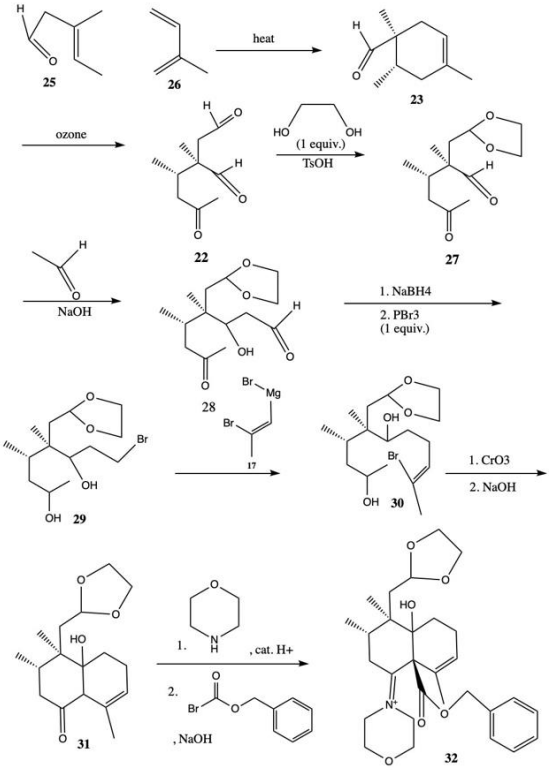

Figure 9. (Continued) Synthetic route to Scaparin C

3. Conclusion

The paper presents a total synthesis for one of the members of clerodane-type diterpenoids, Scaparin that can be utilized as a reference for researchers, especially those who look forward to understanding the manufacture of them. Despite lack of experimental results as for the yields and possible mixture of enantiomers or diastereoisomers of some intermediates, the synthetic efforts should be valued for their identification of the implicit dioxygenation patterns that serve as a clue to aldol and alkylation reactions which play a key role in the formation of carbon-carbon bonds and therefore complex ring structures. Bearing in mind the competing reactivity of the four oxygen-containing functional groups, protection of the rather electrophilic primary aldehyde as a cyclic acetal in the beginning before it reacts with tribromo furan, acylation of ketone in the left-hand side ring with a benzyl bromoformate that survives in acidic and basic solutions and one equivalent of phosphorus tribromide can overcome the barrier. As for the regiochemical control of aldol reaction of the ketone and benzyl bromoformate, the enamine will direct the benzyl ester to the more substituted side of the ketone which corresponds to the more substituted intermediate alkene. The slight adjustment of steps of reactions helps to continue the synthesis smoothly by getting rid of the wrong intermediates. If the theoretically based route for synthesis is to be improved in the future, researchers can in practice use chiral organic catalysts such as a chiral secondary amine which is common in asymmetric aldol reactions and measure the enantiomeric excess to purify the final product.

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