A Proposed Total Synthesis of Sesquiterpenoids from Chrysanthemum indicum

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Abstract: The proposed retrosynthesis of a guaianolide-type sesquiterpenoid. The first route begins with the construction of a 5,7,5-ring sesquiterpenoid through the connection α, β-cyclopentenone derivative from Pauson-Khand reaction and trans lactone by a special Barbier reagent. Firstly, angelic acid is used to complete the synthesis via esterification with enclosing central ring sesquiterpenoid. The second route starts with the fabrication of a modified trans configured lactone with methylene. A following Pauson-Khand reaction appends α, β-cyclopentenone on the lactone. Finally, angelic acid completes the synthesis by esterification with exterior hydroxy of sesquiterpenoid.

1 INTRODUCTION

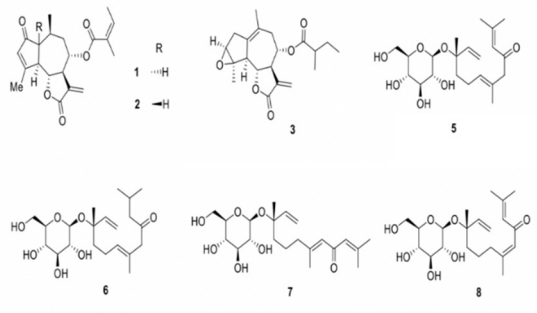
Chrysanthemum indicum is a genus of flowers that belongs to the Asteraceae family. The dried flower heads of *Chrysanthemum indicum* have been used for tea preparations and have also been used in traditional Chinese and Korean medicine for the treatment of fever, migraine, eye irritation, hypertension, vertigo, and respiratory diseases (Youssef et al. 2020, Kim et al 2021). Over 190 isolated chemical constituents have been identified from the *Chrysanthemum indicum* plant to date, including phenylpropanoids, terpenoids, flavonoids, and phenolic acids. Various extracts and monomeric compounds from *Chrysanthemum indicum* have different pharmacological characteristics, such as having anti-inflammatory, anti-oxidation, antipathogenic, anticancer, immune regulation, and hepatoprotective effects (Shao, Sun, Li, Chen 2020).

New compounds recently isolated from *Chrysanthemum indicum* include three guaianolide lactones and four 9-oxonerolidol glucosides. The target molecule, compound **1**, is a guaianolide-type sesquiterpenoid isolated from *Chrysanthemum indicum* flowers. (Kim et al 2021) Compound **1** may provide some pharmacological value, as its molecular structure is similar to the tumor inhibitors eupatorin acetate and eupachlorin acetate, which are found in *Eupatorium rotundifolium*. (Kupchan, Kelsey, Cassady 1968)

In this paper, two detailed retrosynthetic strategies and proposed synthetic routes of producing the target molecule are presented

2 THE ANALYSIS OF SESQUITERPENOIDS FROM CHRYSANTHEMUM INDICUM

2.1 Sesquiterpenoids from Chrysanthemum Indicum



Scheme 1: Three new guaianolide lactones (1−3) and four new 9-oxonerolidol glucosides (5−8) isolated from the flowers of Chrysanthemum indicum.

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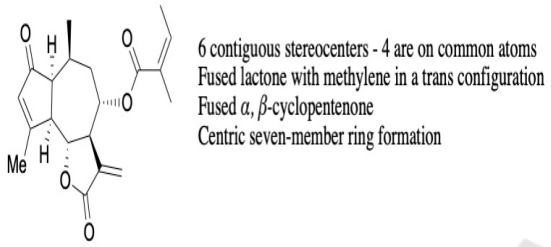
Compound **1** features six contiguous stereocenters, four of which are situated on common atoms connecting two rings. A feature of critical importance is the stereochemistry surrounding the lactone ring in the synthetic design. Specifically, the 5,7-fused lactone being trans-configured poses difficulties. Furthermore, the *α, β*-cyclopentenone structure is also synthetically challenging.

2.2 Synthetic Difficulties of Compound 1

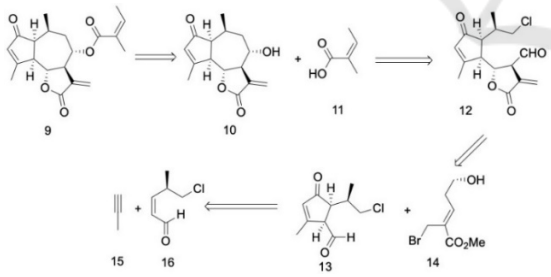


Scheme 2: Molecular formula of Compound 1.

3 SYNTHETIC ROUTE OF COMPOUND 1

3.1 Synthetic Route 1 of Compound 1

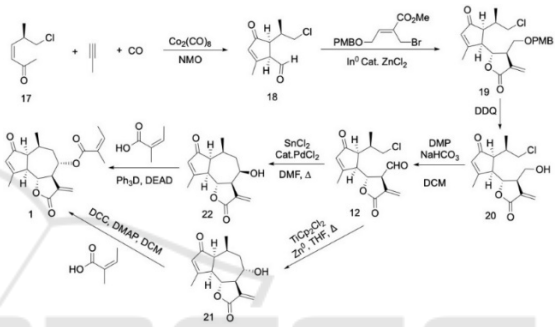
3.1.1 Retrosynthetic Strategy for Synthetic Route 1.



Scheme 3: Retrosynthetic Strategy for Synthetic route 1.

After evaluating the structure of compound **1**, the first retrosynthetic analysis was proposed. The target molecule can be divided into three major fragments, the eastern angelic acid, the western *α, β*-cyclopentenone structure, and the southern *trans* configured lactone. Disconnecting the 5,7,5-ring system and the angelic acid eliminates the possibility of the eastern angelic acid side structure interfering with other synthesis reactions. The hydroxyl group on the seven-membered ring is a good cleavage point from a retrosynthetic perspective as it provides a convenient separation of the *α, β*-cyclopentenone structure and the southern *trans* configured lactone. The construction of southern *trans* configured lactone relies on the nucleophilic attack of the Barbier reagent **14** to the aldehyde of the *α, β*-cyclopentenone, leading to transesterification. The stereostructure of the lactone is also a synthetic challenge. The construction of the *α, β*-cyclopentenone **13** with exterior 2-chloro-isopropyl chain could be achieved through a PK reaction of designed alkynes and alkenes. However, since the reaction does not possess chiral selectivity, it may lead to the formation of impurities.

3.1.2 Synthetic Route 1



Scheme 4: Synthetic route 1.

The first proposed synthetic route begins at compound **17**, an *α, β*-cyclopentenone **18** decorated with various groups that is derived from the Pauson-Khand (PK) reaction between **17** and propyne. Theoretically, compound **14** is one of the derived isomers formed from the reaction. Since the PK reaction does not possess chiral selectivity, the formation of **18** may be in a low yield. Noteworthily, the Nazarov Cyclization reaction of specific modified divinyl ketones constructs **18**, which reduces the byproducts resulting from the PK reaction. Compound **19** can be merged with allylic bromide under In^0-mediated allylation conditions to produce lactone **20** in good yield and with the correct *trans* configuration in the major diastereomer. (Hu, Musacchio, Shen, Tao, Maimone, 2019)

The following steps focus on correcting the different attached functional groups and closing the centric seven-member ring. DDQ (2,3-dichloro-5,6-dicyanobenzoquinone) hydrolyzes the PMB (4-methoxybenzyl ester) protecting group in compound **19**, and compound **20** is formed with a free alcohol group. A Dess-Martin periodinane oxidation is applied for aldehyde generation in compound **12**. To close the centric seven-member ring and form compound **21**, zinc and titanocene (III) complexes are

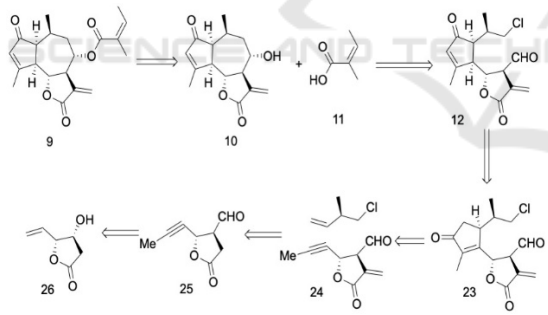
used as catalysts, which allows the allylic chloride group in compound **12** to act as a nucleophilic zinc reagent that adds to the aldehyde in a Barbier reaction. (Estévez et al. 2009) This reaction mitigates potential compatibility issues that may have been present if a Grignard reagent had been used instead, as a Barbier reaction can work with a reactive group. The resulting compound, compound **21**, is the core framework of the target molecule. Finally, Steglich esterification between angelic acid and compound **21** completes the formation of the target molecule.

An alternate proposed sub-route for forming the target molecule after compound **12** is created employs exogenous transition-metals in combination with $SnCl_2$ as catalysts, and the addition of catalytic quantities of $PdCl_2$, which can close the centric ring. This produces **22** in high yield, but gives the incorrect stereochemical outcome at the hydroxyl group, which contrasts the correct outcome in **21**. (Hu, Musacchio, Shen, Tao, Maimone, 2019)

However, the incorrect stereo configuration on the hydroxyl group of **22** can be amended by the Mitsunobu reaction to give the target molecule, **1**.

3.2 Synthetic Route 1 of Compound 1

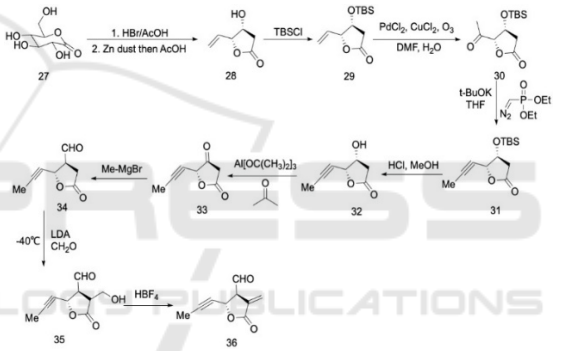
3.2.1 Retrosynthetic Strategy for Synthetic Route 2



Scheme 5: Retrosynthetic Strategy for Synthetic route 2.

A second viable retrosynthetic analysis was also proposed. In this retrosynthetic route, the target molecule is disconnected into two major fragments, the eastern angelic acid, and the 5,7,5-ring system. The fused centric seven-member ring is cleaved due to the presence of a hydroxyl group. The fabrication of the *α, β*-cyclopentenone is a challenge in the synthetic design. This could be resolved by a PK reaction of alkyne **24** and an alkene with chlorine, which then modifies the *α, β*-cyclopentenone. Consequently, the structure of the core framework, the 5,7,5-ring system, is formed. The unusual structure of compound **24** requires further synthetic consideration. The structure of compound **24** is similar to the β-hydroxy-γ-vinyl-γ-lactone **26**, which is a common building block in natural products. Hence, a retrosynthetic path connecting compound **24** and the β-hydroxy-γ-vinyl-γ-lactone **31** can be formed. Due to the high reactivity of the exterior vinyl bond at the α- position on the lactone, the modification of α-position will be at a later stage. To obtain **25**, the vinyl bond in β-hydroxy-γ-vinyl-γ-lactone **26** requires a chain extension and transformation of the vinyl to an alkyl. Furthermore, its hydroxyl also requires chain prolongation and further functionalization. Compound **26** has a structure similar to many natural products, which results in multiple potential synthetic strategies. The synthetic strategy for creating D-glucono-δ-lactone was chosen. (Song, Hollingsworth 2001)

3.2.2 Synthetic Route 2. Preparation of the Modified Stereo Lactone 36

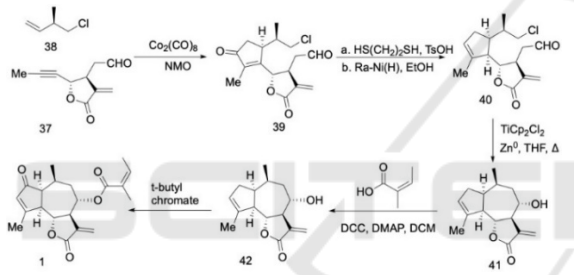


Scheme 6: Synthetic route 2: Preparation of the modified stereo lactone 36.

The second synthetic proposal begins with the construction of compound **27,** which undergoes a Pauson-Khand reaction. Starting from D-glucono-δ-lactone **27**, chiral pool material is used to complete the synthesis of the β-hydroxy-γ-vinyl-γ-lactone enantiomers **28**, which is further used to synthesize compound **36**. The synthetic route then treats **27** with 30% HBr in AcOH (acetic acid) at 60 °C. This is followed by a reaction with Zn dust and 50% aq. AcOH (acetic acid) at room temperature and then at reflux, producing compound **28** in 58% over yield. (Song, Hollingsworth 2001) The free alcohol is then protected with the TBS (tert-butyldimethylsilyl) group. The homologation of lactone **29** is carried out through the Wacker Oxidation of the terminal vinyl bond to aldehyde, to produce compound **30**. Following this, the Seyferth-Gilbert alkyne formation is used to generate molecule **31**. (Fernandes 2020) Removal of the TBS (tert-butyldimethylsilyl)

protection group is driven by hydrochloric acid in MeOH. Due to the presence of an unsaturated bond, Oppenauer oxidation is utilized to convert the alcohol into ketone **33**, in preparation for the elongation of the side chain on the lactone in the next step. The ketone responds to the Grignard reagent and participates in C-C coupling reactions, which lengthens the size of the chains surrounding the lactone, forming compound **34**. The active α-position of lactone is available for hydroxylation by LDA (Lithium diisopropylamide) in methanal under a controlled -40 ℃ temperature, resulting in **35** in 92% yield. (Baitinger, Mayer, Trauner 2010) In the presence of fluoroboric acid, vinyl group formation becomes possible via the dehydration of the hydroxyl group. The carbon radical reactivity is inhibited by the non-coordinating anion, thus producing **36**.

3.2.3 Synthetic Route 2. Completion of the Synthesis of Compound 1



Scheme 7: Synthetic route 2: Completion of the synthesis of compound 1.

With compound **37** in place, the *α, β*-cyclopentenone **39** is derived from alkyne **37** and alkene **38**, and undergoes a PK reaction using dicobalt octacarbonyl. Theoretically, there could be four products of the reaction, **39** is one of them. To eliminate the ketone on cyclopentene, treatment of **39** with dithiol in TsOH (p-Toluenesulfonic acid) is followed by Raney Nickel in EtOH, which leads to alkenyl shift due to the conjugation effect, yielding compound **40**. A Ti-catalyzed Barbier-Type allylation generates centric seven-member ring closure, thus producing the 5,7,5 fused ring system **41** with a hydroxyl group of the desirable configuration for further esterification. (Estévez et al. 2009) Angelic acid attaches to the 5,7,5 fused ring system via straightforward DCC-coupling (DDC: N, N′-Dicyclohexylcarbodiimide) and gives **42**. Compound **1**, the target molecule, is then formed via carbonylation on cyclopentenone by t-butyl chromate. (Dodson 1955)

4 CONCLUSIONS

The compound **1** which isolated from the *Chrysanthemum indicum* may exists some pharmacological value, for its molecular structure is similar to the tumor inhibitors eupatorin acetate and eupachlorin acetate, which are found in Eupatorium *rotundifolium*. In this paper, two retrosynthetic strategies and proposed synthetic routes are proposed. The target molecule, compound **1**, is comprised of three parts: an *α, β*-cyclopentenone structure, a *trans* configured lactone, and an angelic acid structure. By synthesizing each component and assembling them, the target molecule can be obtained. Future efforts to supplement the theoretical synthesis of Sesquiterpenoids from Chrysanthemum Indicum could focus on further researching the relevant stereochemistry. An emphasis could be placed on fine-tuning the stereochemical challenges of the proposed synthetic routes.

AUTHOR CONTRIBUTIONS

X.W., T. K., and W.J. evaluated the construction of the lactone, researched details regarding the characteristics of the target molecule, and participated in the discussion. T. K and W.J. researched the background of the target molecule. X.W. designed the major parts of route 1. T. K. and W.J. helped in the completion of route 1. X.W. designed route 2 and undertook the writing work of route 2. All authors worked on the retrosynthesis strategy and wrote the paper. All authors read and agreed on the content of the paper.

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