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Total Synthesis of Ormosianine A

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Abstract. Ormosianine A–P, each being a quinolizidine alkaloid (QA), were isolated from the stems and leaves of Ormosia yunnanesis in 2023. Biological evaluation revealed that Ormosianine A demonstrates more potent acetylcholinesterase (AChE) inhibitory activity (IC50 = 1.55 μM) than its analogs, supported by follow-up molecular docking studies. This study aims to investigate the retrosynthesis of Ormosianine A and proposes a synthetic route toward its construction. Establishing such pathways facilitates future explorations into its neuroactive potential and related alkaloids within medicinal chemistry. The work also provides an insight into the synthesis of compounds with an azabicyclo[3.3.1]nonane structure.

Keywords: retrosynthesis, total synthesis, Ormosianine, AChE inhibitor, quinolizidine alkaloid, natural product

1. Introduction

Quinolizidine alkaloids represent an important class of nitrogen-containing plant metabolites that exhibit diverse biological activities. These compounds are particularly abundant in the genus Ormosia, where they serve as chemical defense agents against herbivores and insects. Their insecticidal properties are largely attributed to acetylcholinesterase (AChE) inhibition, a mechanism shared with synthetic pesticides but with potentially lower environmental toxicity. Recent investigations of Ormosia yunnanensis have uncovered a series of novel quinolizidine alkaloids designated as ormosianines A–P. In biosynthesis, L-lysine serves as the precursor for the characteristic quinolizidine core. These compounds display remarkable structural diversity, several of which demonstrated significant AChE inhibitory activity, with ormosianine A emerging as the most potent (IC50 = 1.55 μM) [1]. Shown below in Figure 1, this azabicyclo[3.3.1]nonane skeleton has a bridged structure with various substituents, creating multiple stereocenters (4 in total). The presence of such intricate architectures, combined with their promising bioactivity, makes these natural products attractive targets for both pharmacological development and synthetic challenges. Herein, the total synthesis of ormosianine A is proposed, with a strategic combination of enolate chemistry employed.

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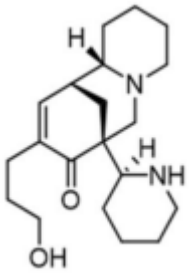


Figure 1. Structure of ormosianine A

2. Retrosynthetic analysis

A strategic first connection should be connected to one of the bridging points to simplify the structure of the molecule, as shown in Figure 2. Moreover, formation of >7-membered-rings is difficult to achieve, so any bond common to a pair of rings whose envelope is greater than 7 is not strategic. Based on these considerations, the suggested first disconnection is shown in Figure 3, where the γ-position of the α,β- unsaturated ketone serves as the nucleophile and attacks the imine intermediate, which is intramolecularly formed by an aldehyde group and a secondary amine group in compound 1.

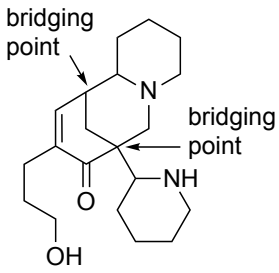


Figure 2. Structural analysis of the target molecule (without stereochemistry)

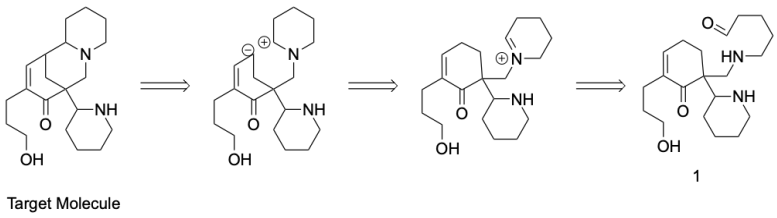


Figure 3. Disconnection 1

Compound 1 can be further broken down by noticing its 1,3-diO pattern, suggesting a Mannich reaction. It can therefore be made from compound 3, 5-aminopentanal, and formaldehyde, as shown in Figure 4. The latter two compounds are readily available. The synthetic equivalent of 5-aminopentanal, 1-piperideine, can potentially be used if it is available and results in higher yields.

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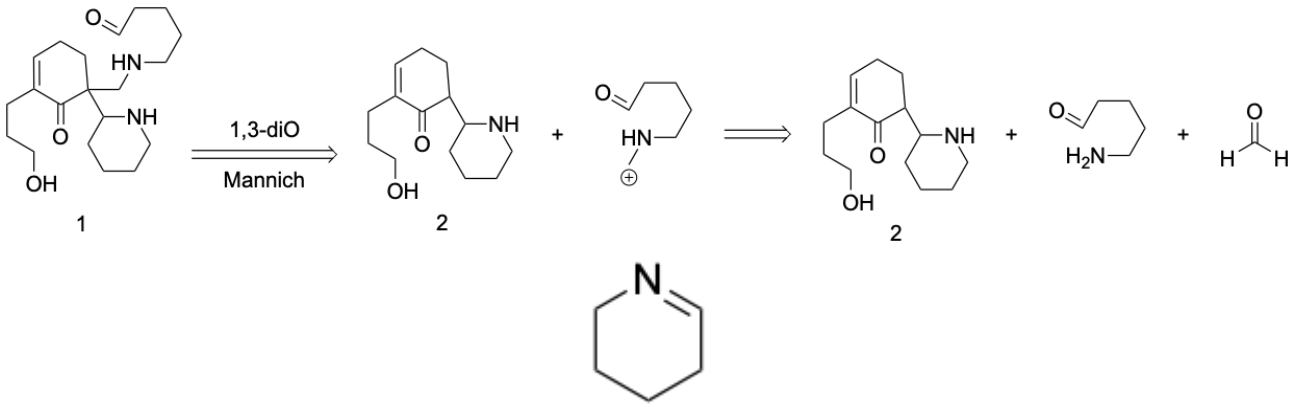


Figure 4. Disconnection 2

Compound 3 has an obvious 1,3-diX pattern. By exploiting it once more we can arrive at another slightly modified Mannich reaction, where 5-aminopentanal is utilized again as a reagent, as shown in Figure 5.

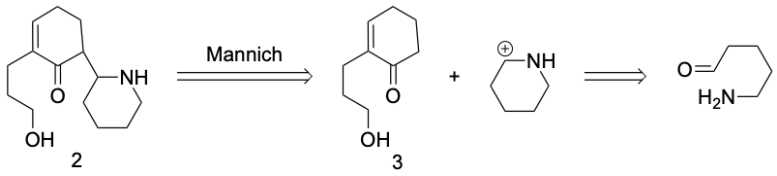


Figure 5. Disconnection 3

As for the retrosynthesis of Compound 3, a functional group interconversion that converts the carbon-carbon double bond into a bromine atom, followed by alkylation of the α position of the cyclohexanone will suffice, as shown in Figure 6.

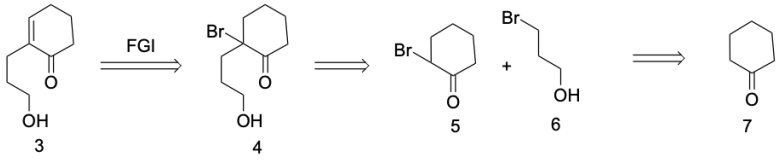


Figure 6. Disconnection 4

3. Forward synthesis

In the forward synthesis, protection of functional groups should be included to improve regio-selectivity and avoid side reactions.

The starting molecule of choice is methyl 2-oxocyclohexanecarboxylate instead of cyclohexanone to prevent polyalkylation. It is treated with a base (NaOMe) and an alkyl electrophile with the hydroxyl group protected in the form of silyl ether to alkylate its α position. Next, β-carbonyl decarboxylation takes place under acidic conditions upon heating. Bromination will take place in the more substituted α position. Finally, elimination of the α-brominated product yields the α,β- unsaturated ketone (Compound 3'). The series of reactions is shown in Figure 7 below.

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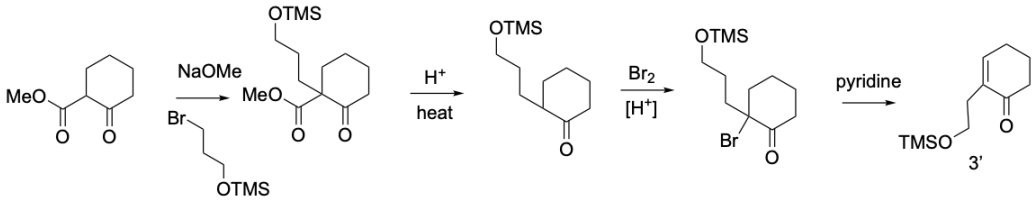


Figure 7. Forward scheme 1

In 1968, K. Morita reported the reaction of acetaldehyde and ethyl acrylate to form α-hydroxyethylated products with tertiary phosphines as the catalyst [2]. In 1972, Baylis and Hillman modified the reaction using DABCO (1,4-diazabicyclo[2.2.2]octane, a tertiary amine) as a better catalyst. The reaction is famously known as the Baylis-Hillman Reaction. A modified strategy may be applied in the synthesis of the α,β-unsaturated ketone (compound 3'), where the ketone attacks the halide at the α-position, as shown in Figure 8. The strategy is not guaranteed to work because of weakened electrophilicity of the electrophile (alkyl bromide instead of an aldehyde or a ketone) and potential side reactions.

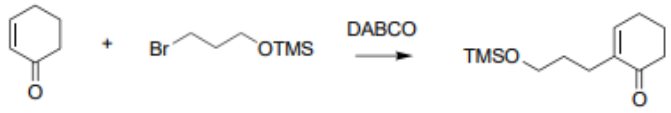


Figure 8. Forward scheme 2

In 1978, T. Saesuga reported the reaction of silyl enol ethers and Pd(OAc)2 and p-benzoquinone in acetonitrile at room temperature to form the α,β-unsaturated ketone [3]. The reaction is known as the Saesuga Oxidation. In the total synthesis of (-)-gambeierol by M. Sasaki, the reaction is used to introduce α,β-unsaturation into the seven-membered ketone in the final step [4], as shown in Figure 9. The possible side reaction is oxidizing the wrong side of the cyclohexanone. To minimize the co-product, a thermodynamic enolate forming conditions may be applied (a small base, higher temperature, dissociating additives such as HMPA that promotes equilibration). The reaction may be allowed to last a longer time before trapping the substrate with TMSCl.

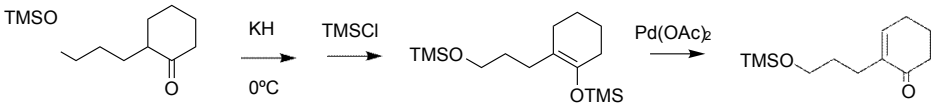


Figure 9. Forward scheme 3

To move on with the synthesis, compound 3' is treated with 5-aminopentanal to install the piperidine group to the α position of the ketone. The δ-amino aldehyde condensates with itself to form a reactive six-membered imine intermediate. Then it is protected with the Boc (t-butyloxycarbonyl) group, giving compound 2' and preventing the reactive amine group from participating in later reactions, as shown in Figure 10.

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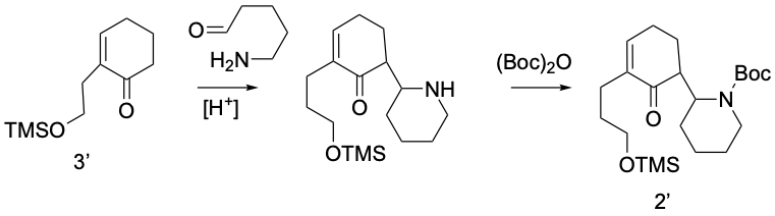


Figure 10. Forward scheme 4

Reacting compound 3' with the protected 5-aminopentanal and formaldehyde (a classic Mannich reaction) yields the β-amino ketone (compound 1'), as shown in Figure 11.

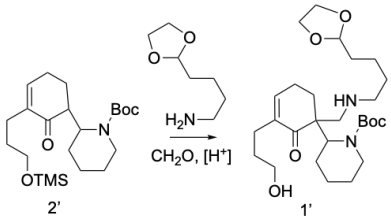


Figure 11. Forward scheme 5

In the next step, as shown in Figure 12, deprotecting the aldehyde with acid, followed up with imine formation and γ position of the ketone attacking the imine leads to the target molecule and finishes the construction of the [3.3.1] bridge structure. The intramolecular Mannich type reaction is utilized in the total synthesis of (±)-aspidospermidine by C.H. Heathcock. [5]

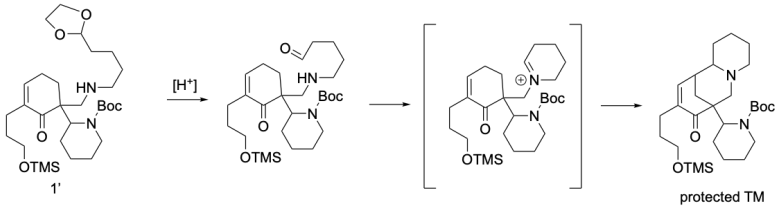


Figure 12. Forward scheme 6

Finally, removal of the protecting groups (TMS and Boc) affords the target molecule, Ormosianine

A, as shown in Figure 13. Some additional base might be needed to deprotonate the protonated amine in acidic conditions.

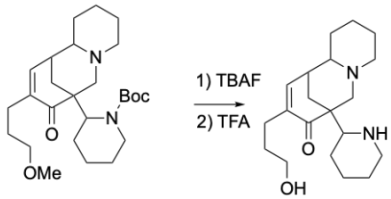


Figure 13. Forward scheme 7

4. Stereochemistry (preliminary)

Several notes can be made on the stereochemical control of the synthesis:

(1) The relative stereochemistry of the two bridge carbons is definite.

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(2) Stereoselective aldol reactions is usually carried out in strongly basic and kinetic conditions (LDA, –78°C, THF) through the Li+ chelated chair transition state. For cyclic ketones, only the E-enolate will be formed, which means the syn product will dominate; however, stereoselectivity is much lower with E-enolate than Z-enolate [6]. Additionally, under acidic conditions, the transition state is loose (no Li+ holding the two electronegative atoms together), and the reaction is readily reversible, meaning that the reaction is under thermodynamic control. Whether the syn or anti product is more stable is uncertain. In a similar reaction where the cyclohexanone lithium enolate undergoes aldol reaction with benzaldehyde [7], the ratio between anti and syn products is 52:48, which is nearly even.

(3) The reaction scheme proposed above cannot control all the stereochemistry in the molecule. Further resolution (e.g. chiral chromatography) may be needed to extract the enantiomerically pure product.

5. Conclusion

In this work the total synthesis of Ormosianine A is proposed. It has fair chemo- and regio-selectivity but touches little on stereochemistry. The reaction scheme may be applied to the synthesis of similar molecules with the azabicyclo[3.3.1]nonane skeleton.

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