

SYNTHESIS OF 1,1'-DIDEAZA-QUININE: A PROOF OF CONCEPT

by

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SYNTHESIS OF 1,1'-DIDEAZA-QUININE: A PROOF OF CONCEPT

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Abstract

Quinine is a naturally occurring plant alkaloid found in the bark of the Cinchona tree.¹ Its medicinal relevance cannot be overstated as it is one of the most widely used anti-malarial drugs in the world.¹ While the laboratory synthesis of quinine is not of practical value since this drug is easily extracted in large quantity from the natural source, the puzzle of designing reactions to create a route to stereochemically pure quinine has captivated synthetic chemists for generations. The purpose of this study is to prove the validity of a new route proposed by Stotter, Friedman, and Minter² for the total synthesis of stereochemically pure quinine via a non-nitrogenous analog where the two nitrogen atoms of quinine are substituted with carbon atoms. The product of this model study is 1,1'-dideaza-quinine. Quinine is stereochemically complex with four separate stereocenters. Without control of stereochemistry, a non-selective synthesis of quinine could generate up to sixteen different isomeric structures.³ While the total synthesis of quinine with the correct stereochemistry was accomplished in 2001,³ the proposed route in our study will simplify the process by relying on a stereospecific aldol addition reaction to eliminate potential isomers.² If successful, the results of this study will validate the concept of using the aldol as a key reaction to control the stereochemistry for three out of the four stereocenters in quinine. In addition, this synthetic route will demonstrate for the first time an approach to quinine that uses a convergent strategy rather than the linear strategy used by others who have investigated the total synthesis of this molecule.

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Introduction

The discovery of quinine and its use as a drug was first recorded in the seventeenth century during the era of European invasion into the Americas.¹ Native American populations used quinine to treat fever associated with malaria in tropical regions. They extracted it from the bark of the Cinchona tree, and the Europeans soon learned to do the same.¹ Quinine thus became the first recorded chemical compound to treat infection successfully.¹ Due to its medicinal value, quinine was brought back to Europe where it was widely distributed.¹ By the nineteenth century, procedures for extracting quinine from Cinchona bark were well established, and it was the primary drug used to combat malaria until early in the twentieth century when more effective synthetic antimalarial drugs became available.¹ However, the more efficacious drugs have struggled recently with respect to antimicrobial resistance. This has led to a shift back toward the use of quinine due to the slower rate at which the protozoans that cause malaria are able to develop drug resistance.¹

During the age of British imperialism in India, quinine was found to have a secondary role. In the mid-nineteenth century, British soldiers and colonists living in tropical areas of India took protective doses of quinine powder as a malarial defense mechanism.⁴ Since the powder was extremely bitter to the taste, they began mixing their medicine with soda and sugar, the result of which became known as tonic water with quinine serving as the source of bitterness.⁴ By 1870, the recipe for tonic water had made its way back to England and was acquired and produced by Schweppes.⁴ Not long after, gin was added to the tonic and the first gin and tonics were being consumed routinely as a result of the anti-malarial efficacy of quinine.

Because of the prominence of quinine both medicinally and recreationally, chemists, too, were interested in knowing more about the molecule. The first step in understanding quinine from a

chemical approach was to solve its atomic connectivity, which was accomplished by Paul Rabe in 1907 and depicted in Figure 1.⁵ After determining the connectivity of quinine, he attempted to complete a total synthesis of the molecule. The four stereocenters in quinine at carbons 3, 4, 8 and 9 make it possible to create sixteen isomeric structures, and Rabe did not know which was the correct one.³ Thus, Rabe's attempt was extremely noble but ultimately of little use.

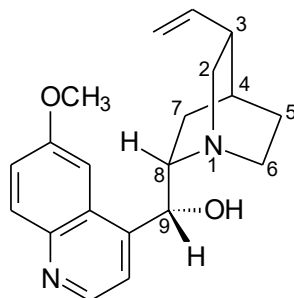
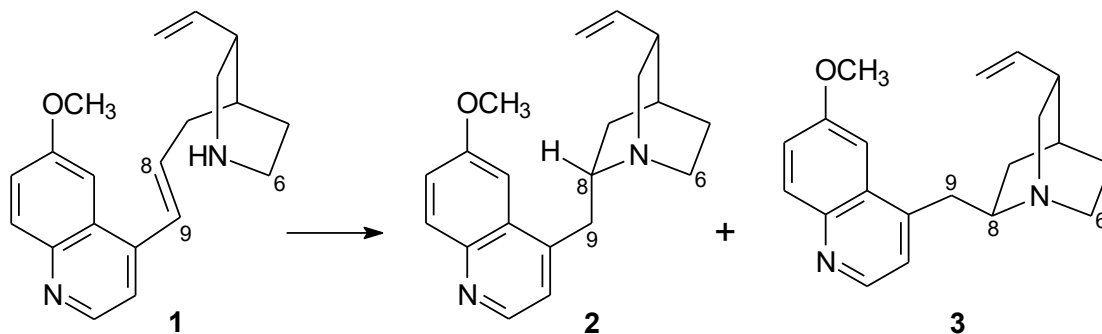
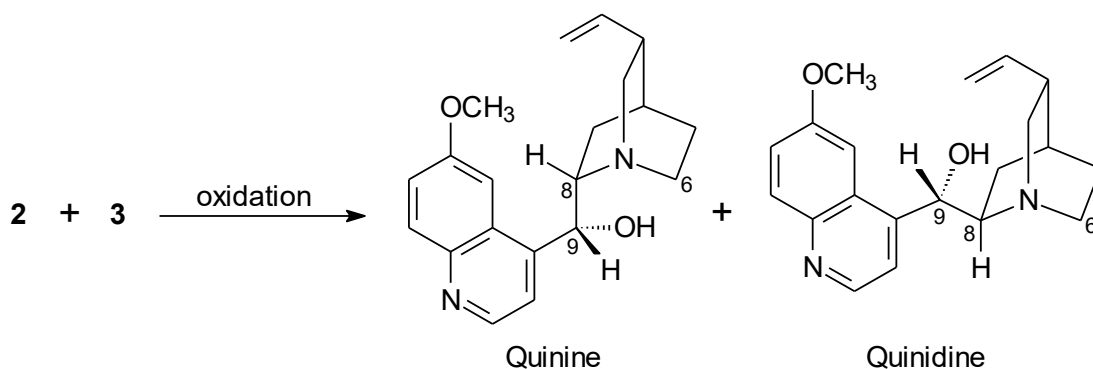


Figure 1. Chemical structure of quinine with proper stereochemistry.

The first total synthesis of quinine was completed by Woodward and Doering in 1944.⁶ They relied heavily on Rabe's work and were able to improve it by generating a product mixture with only four isomers, which proved extremely difficult to separate.³ Although Woodward's route was a major step forward, it lacked stereochemical control. A highly stereoselective synthesis was not achieved until 1970, when Uskoković and Gutzwiller reduced the isomeric mixture of products to only two.⁷ The problem of selectivity occurred during the ring closing reaction between C8 and N1 as shown in Scheme 1.³ The resulting mixture of bicyclic compounds contained both **2** and **3** with *endo* and *exo* substituents, respectively. Since these products form at about the same rate, they are present in approximately equal amounts. In the final step of the synthesis shown in Scheme 2, an oxidation reaction produced the hydroxyl group at C9; and this process was also less than 100% selective. After purification, the synthesis produced a mixture of quinine and quinidine.³



Scheme 1. Uskoković and Gutzwiller ring closure.³



Scheme 2. Uskoković and Gutzwiller oxidation of compounds **2** and **3**.^{3,7}

In 1985, a synthetic approach was proposed and modeled by Stotter, Friedman and Minter to generate quinine under stereoselective conditions via an aldol addition reaction to solve the stereochemical quandary at C8 and C9.² However, this was only a model study to test the reaction conditions that would be required to achieve control of stereochemistry. The first to publish a completely stereoselective synthesis of quinine was Gilbert Stork et al. in 2001,³ although their route did not take advantage of an aldol addition reaction. Instead, Stork decided to perform a ring closing reaction between N1 and C6³ (Scheme 3) as opposed to the closure between N1 and C8⁷ (Scheme 1) used by Uskoković. Additionally, he introduced a stereocenter that was maintained throughout the entire reaction sequence such that when the ring closure occurred, only the *endo* configuration was available for the substituent attached to C8.³ The differences between the

substrates used by Stork et al. versus Uskoković and Gutzwiller are explicit in structures **4** and **1** (Figure 2.) The forced *endo* position of the C8 substituent in **2** (Scheme 3) is a result of the mechanism that operates in the ring closure reaction. Therefore, the oxidation reaction in the last step was carried out on a pure substrate giving a 14:1 mixture of quinine and epiquinine.³ The Stork synthesis produced quinine with higher stereoselectivity than any previous method.

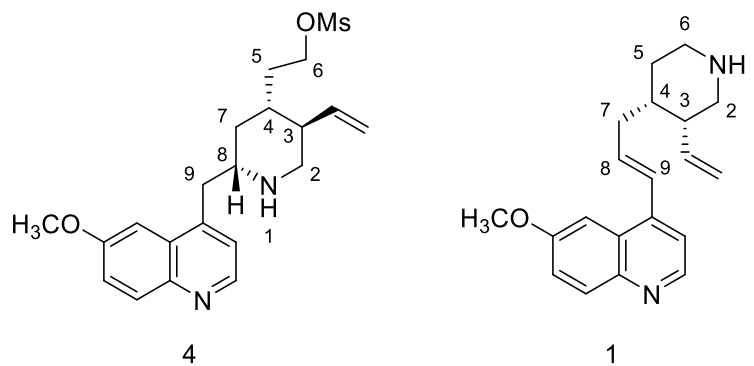
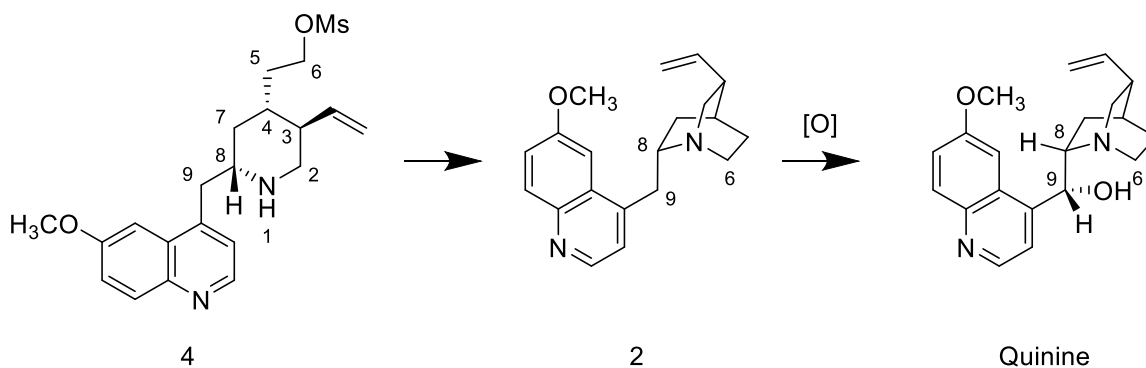


Figure 2. Ring closing substrate of Stork et al. (left) and Uskoković and Gutzwiller (right).^{3,7}



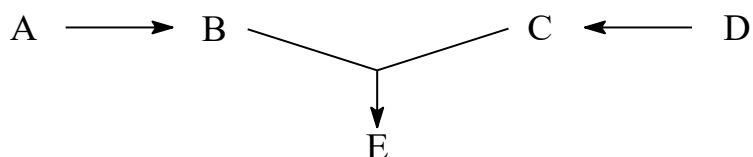
Scheme 3. Ring closure and oxidation to yield quinine.^{3,7}

Stork et al. may have created a solution to the puzzle of controlling the stereochemistry in quinine, but the purpose was never to determine a way to synthesize quinine on an industrial scale. Rather, the motivation for solving stereochemical problems is to increase the knowledge base of organic synthesis with respect to stereocenters and find solutions that may be applicable in other reactions where stereochemistry is relevant. Because of the significant value found in expanding

our store of chemical information, the conceptual model for an alternative pathway to a stereoselective synthesis of quinine proposed by Stotter, Friedman, and Minter should also be explored.² This model is significantly different from the work accomplished by Stork as well as Uskoković and Gutzwiller, Woodward and Doering, and Rabe all of whom used the so-called linear approach to their syntheses. In the linear strategy, each step of the reaction pathway is carried out in sequence from a single starting material:



In the convergent strategy, which is inherently more efficient, two or more linear pathways are combined at the end:



The molecule of quinine is conveniently divided into two fragments of approximately equal size by cleaving the bond between C8 and C9. Compound **6** in Figure 3 represents the "top half"

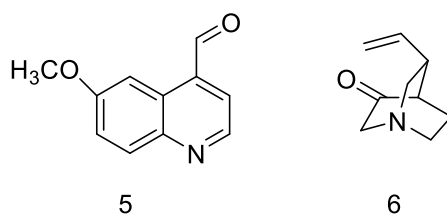
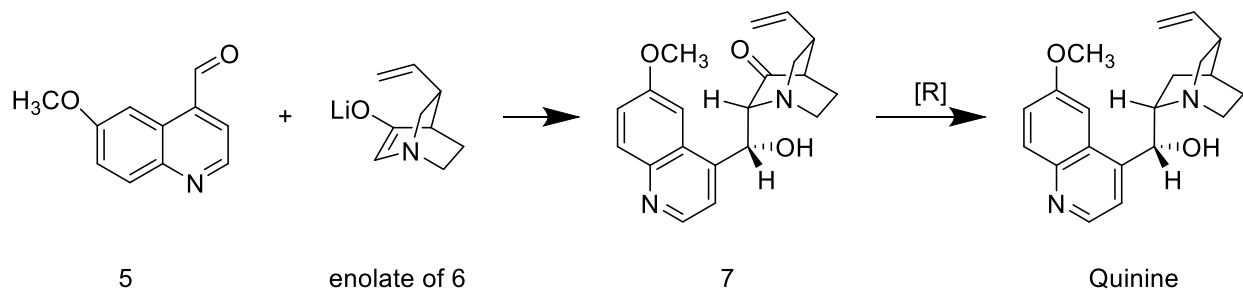


Figure 3. Components necessary for aldol addition.

of quinine in the form of a ketone.⁸ This will provide the enolate nucleophile required for the aldol addition reaction. The aldehyde **5**, which will be prepared separately, is the electrophile in the aldol addition reaction. By synthesizing these two components in separate pathways, the structural complexity is reduced until it is necessary to combine them in the reaction leading to compound **7**

(Scheme 4).² Provided that the new bond is *endo* and also possesses the correct stereochemistry, a reduction of the carbonyl group in **7** will produce the target molecule quinine.



Scheme 4. Aldol addition reaction.²

The aldehyde **5** is a known compound whose synthesis has been published. The ketone **6** is also known⁸ but its synthesis is cumbersome and would require improvement to be practical. However, the concept for synthesizing quinine using this approach can be tested without the actual components depicted in Scheme 4 by using mimics for aldehyde **5** and ketone **6**. The aldehyde **8** (Figure 4) is a known compound and should be readily available. Although it lacks the nitrogen atom in **5**, its chemistry should be approximately the same as **5**. Likewise, the ketone **9** could serve as a mimic for **6** even though it also lacks the nitrogen atom. Ketone **9** is not a known compound, but it appears to be a molecule that is accessible using a seven- or eight-step synthesis comprised of straightforward reactions.

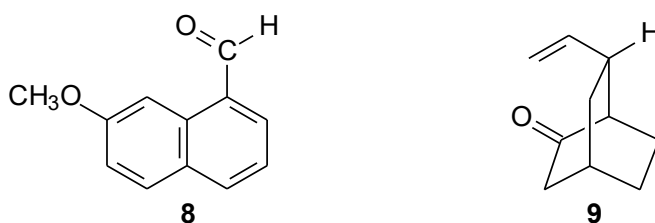


Figure 4. Aldehyde and ketone mimics.

Therefore, the purpose of this study is to validate the novel concept proposed by Stotter, Friedman, and Minter² for a stereoselective approach to quinine by synthesizing an analogous compound 1,1'-dideaza-quinine using the same reactions. A structural comparison of quinine and 1,1'-dideaza-quinine is shown in Figure 5 and indicates that the differences between the two compounds are limited to the substitution of two carbon atoms for two nitrogen atoms of quinine. The results of this study are described in the sections to follow.

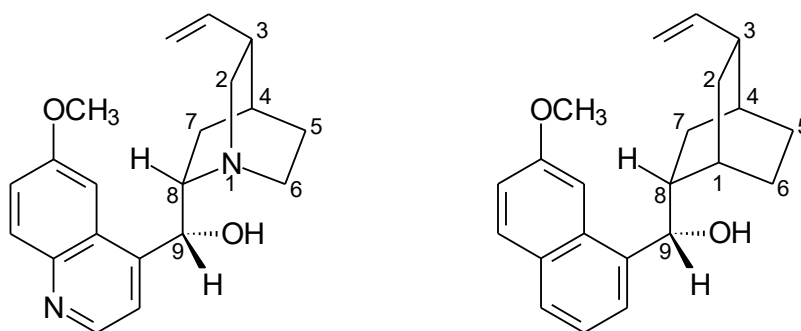
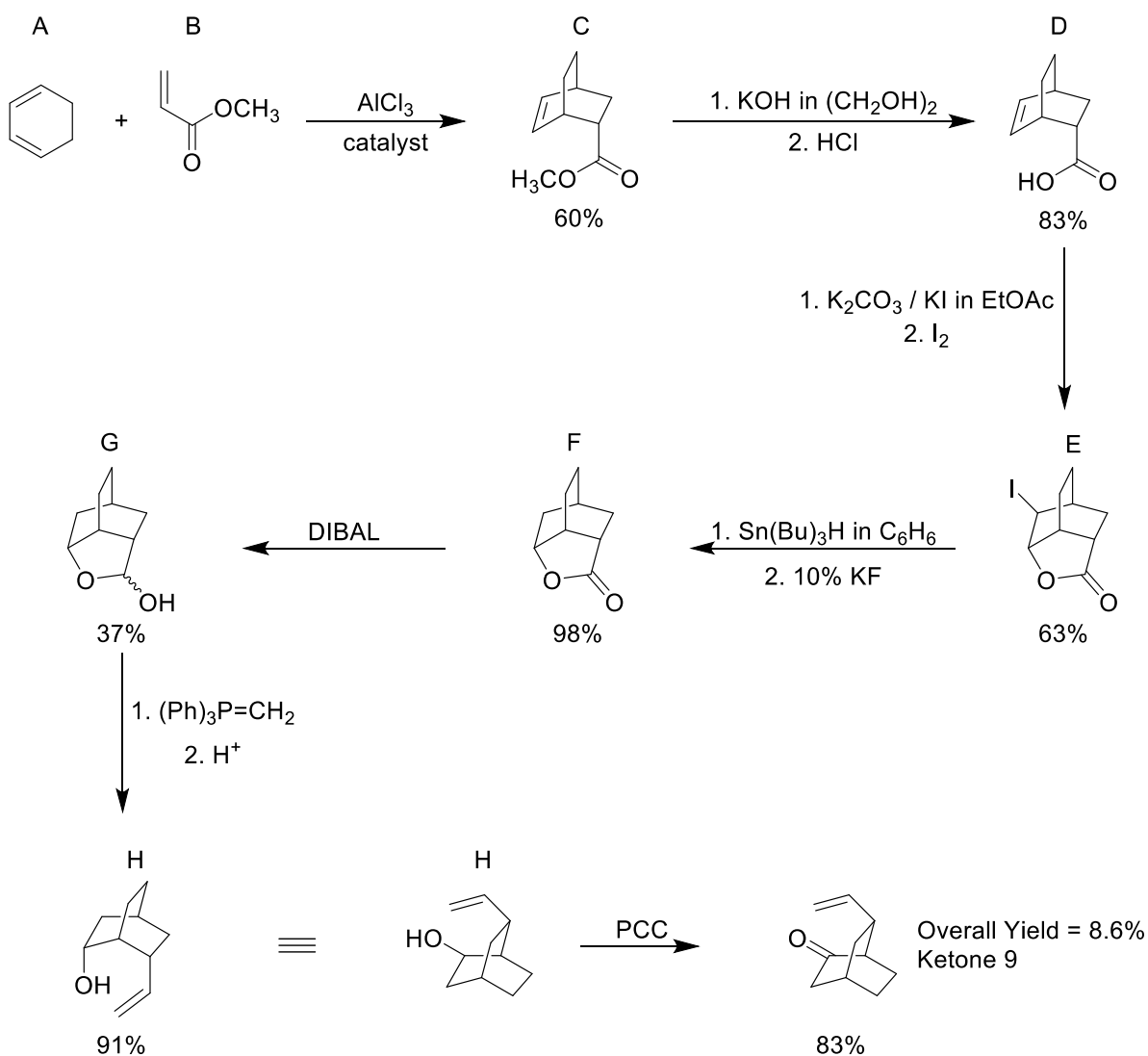


Figure 5. Structural comparison of Quinine (left) and 1,1'-Dideaza-Quinine (right).

Experimental

The synthetic pathway to ketone **9** is shown in Scheme 5 below. The starting materials A and B are commercial available and relatively inexpensive. This synthesis requires 7 steps and was accomplished with an overall yield of 8.6%. Each step was optimized with the exception of the conversion of F to G, which proceeded in only 37% yield.



Scheme 5. Synthetic pathway for ketone **9**

Preparation of Compound C (Bicyclo[2.2.2]oct-5-ene-2-carboxylic acid, methyl ester).

A suspension of compound **B** [ethyl acrylate (31.17 g, 0.362 mol)] and five spatula tips of AlCl_3 was prepared in a 250-mL round bottom flask and was cooled to 0 °C under nitrogen while being stirred magnetically. Compound **A** [1,3-cyclohexadiene (15.29 g, 0.191 mol)] was added dropwise slowly to the solution to reduce risk of overheating. After complete addition, the temperature was allowed to increase to room temperature over 4 hours. The color changed to a pinkish red and an aluminous precipitate began to form. The reaction proceeded overnight for a total of 24 hours. The reaction mixture was then transferred to separatory funnel. The flask was rinsed with 50 mL of ether and 50 mL of DI water, and both rinses were added to the separatory funnel. The organic layer was separated and the aqueous layer was extracted twice more with 20 mL of ether. The combined organic layers were washed twice with 20 mL of DI water, and then dried with anhydrous sodium sulfate. The ether and other volatiles were removed by rotary evaporation to yield 19.05 g (60.1%) of crude Compound **C** as a colorless oil. The crude material was used without further purification for the next step after verification of the structure and purity using the ^{13}C NMR spectrum, which contained peaks at 24.4, 25.4, 29.4, 29.9, 32.5, 42.7, 51.6, 131.4, 135.2 and 175.9 ppm.

Preparation of Compound D (Bicyclo[2.2.2]oct-5-ene-2-carboxylic acid).

A solution containing 19.64 g (0.350 mol) of KOH in 172 mL of ethylene glycol was prepared in a 250-mL round bottom flask and 19.05 g (0.115 mol) of crude compound **C** was added in one portion. The reaction mixture was stirred magnetically and heated under nitrogen at 50 °C in a water bath for 1 hour. The solution was cooled to room temperature, transferred to a separatory along with 200 mL of DI water, and extracted with dichloromethane (3 x 100 mL). The extracts

were combined and set aside in case the reaction was incomplete. The aqueous layer was acidified to pH \approx 1-2 via dropwise addition of 6 M HCl and transferred to a separatory funnel. The product was then extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate and the solvent was removed by rotary evaporation to give 14.55 g (83%) of Compound **D** as an amorphous, yellow solid. The crude material was used without further purification for the next step after verification of the structure and purity using the ^{13}C NMR spectrum, which contained peaks at 24.3, 25.3, 29.3, 29.6, 32.4, 42.7, 131.4, 135.3, 181.7 ppm. The melting point of Compound **D** was not able to be determined despite there being a literature melting point of 56-57 °C.⁹

Preparation of Compound E (Iodolactonization of Compound D).

A basic aqueous solution containing 26.45 g (191.4 mmol) of K_2CO_3 dissolved in 200 mL of DI water was prepared and 14.55 g (95.7 mmol) of the carboxylic acid Compound **D** was added. Solid KI (7.94 g, 47.85 mmol) was then added all at once followed by 200 mL of ethyl acetate and solid I_2 (36.43 g, 143.55 mmol) in one portion. The dark solution was then stirred magnetically at room temperature for 72 hours under nitrogen. The reaction mixture was then transferred to a separatory funnel along with 200 mL of ether and 200 mL of 10% sodium thiosulfate. The aqueous layer was removed and the organic layer was washed twice with 200 mL of 10% sodium thiosulfate, then once with 200 mL of brine. The organic layer was then isolated and dried over anhydrous sodium sulfate. The ether was evaporated to yield 16.78 g (63 %) of the crude iodolactone, Compound **E**, as a white solid. The crude material was used without further purification for the next step after verification of the structure and purity using the ^{13}C NMR spectrum, which contained peaks at 14.9, 24.0, 28.0, 29.6, 31.9, 34.5, 35.6, 85.7, and 179.5 ppm.

The melting point of Compound E was 73-74.5 °C which is slightly lower than the literature value of 80-81 °C most likely due to trace impurities observed in the ¹³C NMR spectrum.¹⁰

Preparation of Compound F (Dehalogenation of Compound E).

To a solution of Compound E (12.47 g, 44.85 mmol) in 75 mL of benzene at room temperature, was added tributyltin hydride (18.08 g, 62.13 mmol) in one portion. The reaction mixture was then stirred magnetically for 20 hours under nitrogen. The solvent was then removed under reduced pressure and the resulting residue was dissolved in 75 mL of ether. Then 75 mL of 10% KF was added to the reaction flask. The tributyltin fluoride (TBTF) precipitate was filtered off and the organic filtrate was dried over anhydrous sodium sulfate and concentrated. The resulting solid exceeded the theoretical yield, suggesting that TBTF remained. The solid mixture was then dissolved in acetonitrile prior to washing with hexanes. The acetonitrile layer was isolated and concentrated to yield 6.73 g (98%) of the crude lactone, Compound F, as white solid. The crude material was used without further purification for the next step after verification of the structure and purity using the ¹³C NMR spectrum, which contained peaks at 15.7, 23.5, 26.1, 27.6, 33.2, 34.3, 37.4, 78.6, and 181.4 ppm. The melting point of Compound F was 158-166 °C which is broad but feasible given the trace impurities observed in the ¹³C NMR spectrum.

Preparation of Compound G (Reduction of Compound F).

To a stirred solution of lactone (5.00 g, 32.9 mmol), Compound F, in 75 mL of anhydrous ether under nitrogen at 0 °C, was added 33 mL (33 mmol) of 1 M diisobutylaluminum hydride (DIBAL) dropwise via a syringe through a septum over 10 minutes. The reaction remained at 0 °C for 15 minutes and was then brought to room temperature for 1 hour. The progress of the reaction was

monitored at this point via thin layer chromatography (silica gel, Hex:EtOAc, 3:1) which showed that starting material was still present. The reaction was then allowed to continue overnight for a total of 20 hours. The reaction was then quenched by dropwise addition of 75 mL of DI water before potassium sodium tartrate (10.0 g) was added in one portion. The suspension was stirred rapidly for 3 hours. The biphasic mixture was then transferred to a separatory funnel and the organic layer was isolated. The aqueous layer was extracted three times with 15 mL of ether. The combined organic layers were dried over sodium sulfate and concentrated. The resulting residue was purified by column chromatography (silica gel, Hex:EtOAc, 3:1-3:2) to yield 1.87 g (37%) of the lactol, Compound **G**, as a colorless oil. The crude material was used without further purification for the next step after verification of the structure and purity using ^{13}C NMR spectrum, which contained peaks at 15.4, 22.7, 26.8, 30.0, 31.4, 36.5, 41.1, 76.8, and 104.4 ppm.

Preparation of Compound H (Wittig Olefination of Compound G).

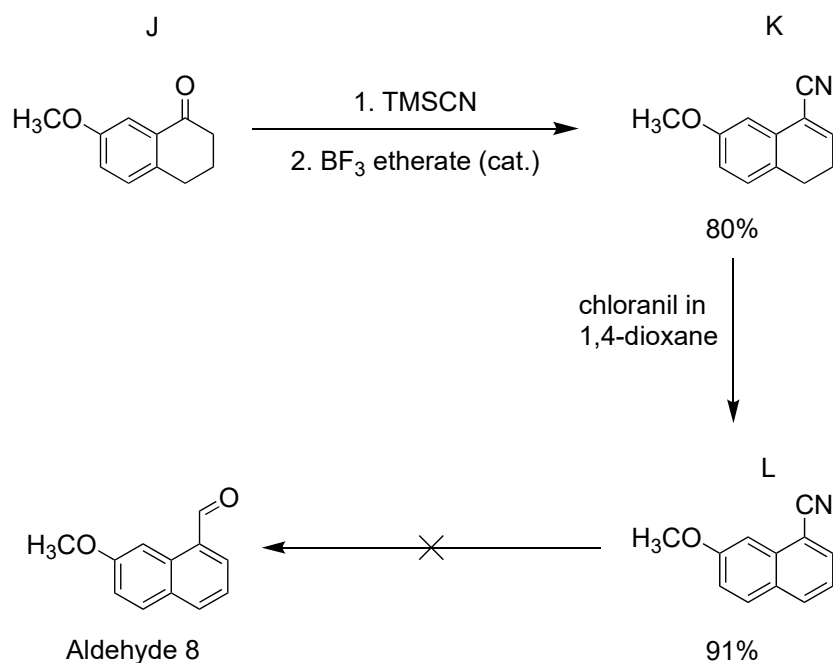
Methyltriphenylphosphonium bromide (2.2 eq, 9.53 g, 26.7 mmol) was added to a 250 mL three-neck flask equipped with a thermometer, addition funnel, and a septum to cover the right arm under nitrogen. Tetrahydrofuran (THF, anhydrous, 62.8 mL) was then added to the flask as well as a magnetic stir bar. The contents were stirred in the reaction flask magnetically while the flask was cooled in a dry ice/acetone bath to $-78\text{ }^{\circ}\text{C}$. N-Butyllithium (2.2 eq, 10.7 mL 2.5 M n-BuLi in hexanes, 26.7 mmol) was then added dropwise over 30 minutes to the reaction mixture. The solution was then stirred 1 hour at $-78\text{ }^{\circ}\text{C}$ to allow the Wittig reagent to form. The lactol (1.87 g, 12.1 mmol), Compound **G**, was suspended in 10 mL of dry THF and transferred into the addition funnel. The reactant mixture was added dropwise to the reaction flask over 15 minutes while maintained at temperature of $-78\text{ }^{\circ}\text{C}$. The reaction then proceeded at $-78\text{ }^{\circ}\text{C}$ for 1 hour. The

temperature was then raised to 0 °C by transitioning from the dry ice/acetone bath to an ice/water bath and the reaction proceeded for an additional 2 hours. The reaction was then quenched with 81.6 mL of saturated NH₄Cl before being transferred to a separatory funnel. The aqueous layer was extracted three times with 25 mL of ether. The combined organic layers were then dried over sodium sulfate and concentrated. The mass was higher than the theoretical yield due to triphenylphosphine oxide impurity. The product mixture was then filtered through a silica plug under vacuum and rinsed with DCM. The solution was then concentrated to yield 1.69 g (91%) of the alkene product, Compound **H**, as crystalline white solid. The crude material was used without further purification for the next step after verification of the structure and purity using the ¹³C NMR spectrum, which contained peaks at 23.5, 24.8, 25.1, 31.5, 37.8, 38.3, 38.5, 71.3, 112.3, and 146.2 ppm. The melting point of Compound **H** was 143-146 °C.

Preparation of Ketone 9 (Oxidation of Compound H).

The alkene (1.69 g, 11.1 mmol), Compound **H**, was dissolved in 25 mL of DCM and stirred magnetically under nitrogen. Pyridinium chlorochromate (1.2 eq, 2.87 g, 13.3 mmol), PCC, was then added in one portion. The reaction was allowed to proceed for 21 hours at room temperature. The entire reaction contents were then filtered through a silica plug under vacuum to remove any PCC residue. The flask and plug were rinsed thoroughly with ~30 mL of DCM to isolate all product. The organic solution was then concentrated to yield 1.38 g (83%) of ketone **9** as a yellow oil. The structure and purity of the crude material were verified using the ¹³C NMR spectrum, which contained peaks at 23.3, 23.8, 27.9, 32.1, 40.0, 44.9, 48.0, 113.7, 141.8, and 216.3 ppm.

The proposed synthetic pathway to aldehyde **8** is shown in Scheme 6 below. The ketone **J** is commercially available.



Scheme 6. Proposed synthetic pathway for aldehyde **8**

Preparation of Compound **K** (7-methoxy-3,4-dihydronaphthalene-1-carbonitrile).

7-Methoxy-1-tetralone (5.00 g, 28.4 mmol), Compound **J**, was added to the reaction flask with a magnetic stir bar, and the reaction flask was evacuated with nitrogen. Trimethylsilyl cyanide (1.1 eq, 4.25 mL, 31.9 mmol), TMSCN, was added to the flask via a syringe under nitrogen over 5 minutes. The reaction flask was heated to 60 °C to dissolve the substrate. Following dissolution, 150 μL of BF_3 (boron trifluoride) etherate was added to the reaction flask and the reaction was allowed to proceed for 2 hours at 60 °C. Another portion of BF_3 etherate was added (100 μL) to the flask and the temperature was increased to 90 °C for 2 hours. The reaction mixture was then allowed to cool to room temperature whereupon 40 mL of pyridine and 4.5 mL of POCl_3 were added. A distillation head was attached and 30 mL of pyridine was removed slowly over 2-3 hours.

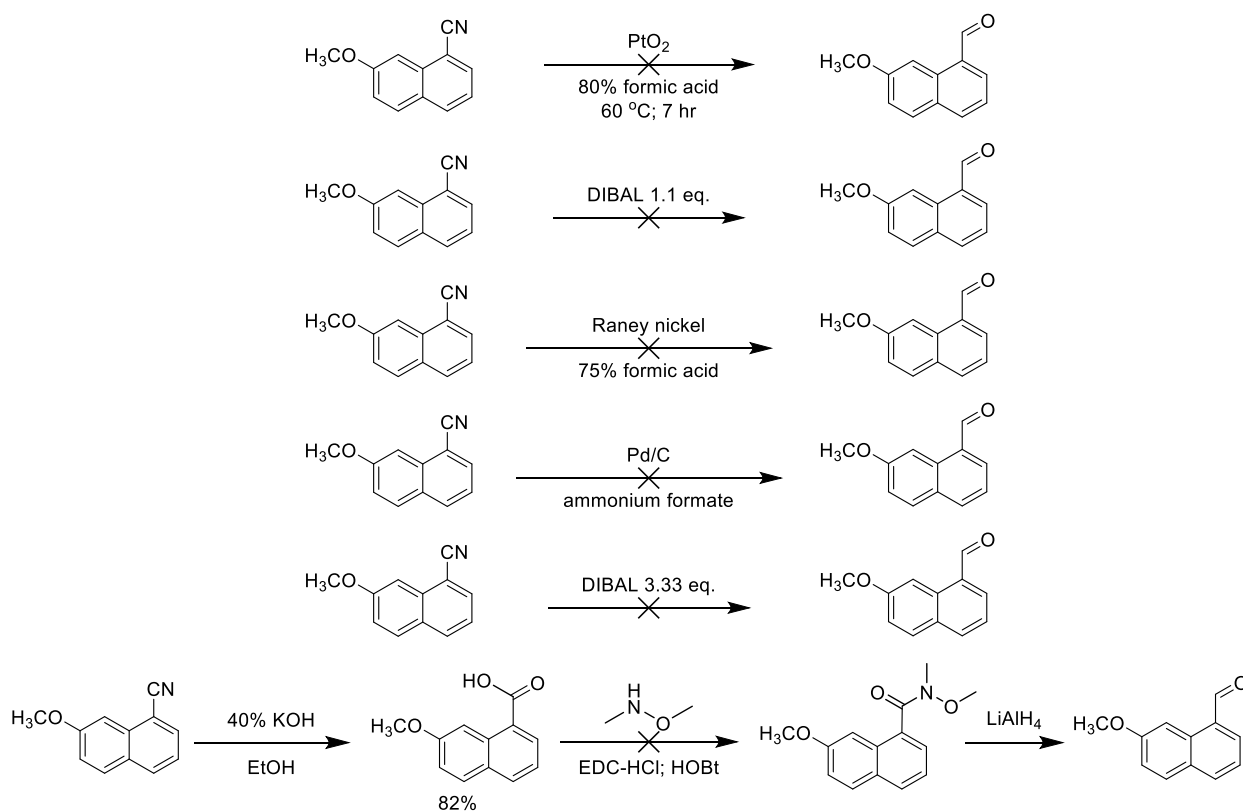
The reaction mixture was cooled, then poured into 200 mL of ice/water and extracted thrice with 15 mL of 25% ethyl acetate/hexanes. The organic layers were combined and rinsed with 15 mL of DI water, 15 mL of 1 M HCl, and 15 mL of DI water. After drying with anhydrous sodium sulfate, the organic solution was evaporated to ~10 mL and filtered through an alumina plug under vacuum. The alumina plug and flask were rinsed with 25% ethyl acetate/hexanes. The combined organic material was collected and evaporated resulting in 4.23 g (80%) of the nitrile product, Compound **K**.

Preparation of Compound L (7-Methoxy-1-naphthalenecarbaldehyde).

The nitrile (4.23 g, 22.9 mmol), Compound **K**, and two equivalents of chloranil (11.23 g, 45.67 mmol) were dissolved in 40 mL of 1,4-dioxane and stirred magnetically under nitrogen at reflux for 18 hours. The solvent was then removed under reduced pressure and the residue was dissolved in 20 mL of DCM. The resulting suspension was filtered through an alumina plug under vacuum to remove any chloranil and/or tetrachloroquinone residue. The alumina plug was subsequently rinsed with DCM. The collected organic solution was dried over anhydrous sodium sulfate and concentrated to yield 3.82 g (91%) of the aromatized nitrile product, Compound **L**, as a red solid. The crude material was used without further purification for the next step after verification of the structure and purity using the ^{13}C NMR spectrum, which contained peaks at 55.9, 102.9, 107.7, 118.3, 120.7, 123.6, 128.5, 131.3, 133.8, 134.0, 134.1, and 160.0 ppm. The melting point of Compound **L** was 62-65 °C which is lower than the literature value of 77-79 °C most likely due to impurities observed in the ^{13}C NMR spectrum.¹¹

Preparation of Aldehyde **8** (7-Methoxy-1-naphthalenecarboxaldehyde).

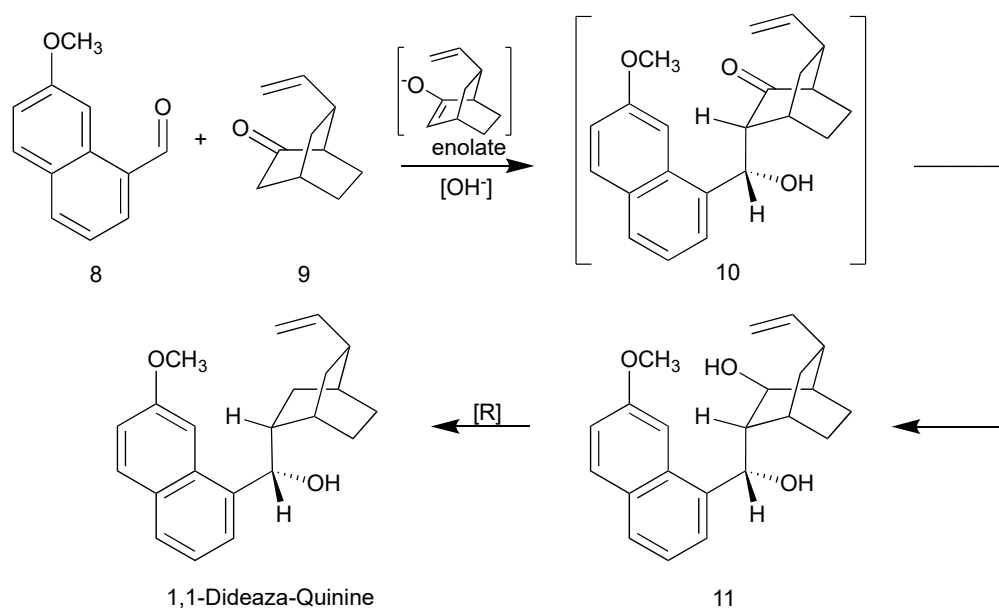
Multiple attempts to synthesize **8** are depicted in Scheme 7. None of these reactions generated any appreciable product, and most led only to the isolation of starting material.



Scheme 7. Experimental attempts at generating aldehyde **8**

Discussion and Conclusions

The purpose of this project was to develop a conceptually new route to the stereoselective synthesis of quinine using a convergent approach. As shown in Scheme 8, the key step is the aldol addition reaction between the aldehyde **8** and the enolate derived by deprotonation of the ketone **9**. The resulting hydroxyketone **10** would be reduced in situ to the diol **11** followed by a selective reduction of the non-benzylic alcohol to produce 1,1'-dideaza-quinine. Thus, the aldol addition reaction is responsible for controlling the stereochemistry for three out of the four chiral centers in the target molecule. This requires that the vinyl group in ketone **9** is sufficiently bulky to force the aldol reaction to occur only from the *endo* face of the enolate. Molecular models indicate that this is highly likely.



Scheme 8. Aldol addition between the enolate of Compound **9** and Compound **8** with subsequent reduction reactions to generate 1,1'-Dideaza-Quinine

While synthesis of the ketone **9** was successful, aldehyde **8** has eluded a number of attempts to prepare this compound (Scheme 7). The reaction with platinum oxide, PtO₂, gave the best results with an estimated 10% conversion to the aldehyde as indicated by the ¹H NMR spectrum of the reaction mixture. This suggests that increasing the temperature and the reaction time may force the reaction to completion. Reduction of the nitrile with DIBAL should also be repeated more carefully since this is a standard method for carrying out the reaction. It is not clear why DIBAL failed in this case. There are also other routes to this aldehyde that may deserve some investigation.

Because aldehyde **8** has not yet been synthesized due to problems in the reduction of the nitrile **L**, the hallmark aldol addition reaction that would validate this research has not been done. However, the synthesis of ketone **9** was carried out according to plan and represents significant progress toward the goal of the study. This includes the syntheses of three new compounds: the lactol **G**, and alcohol **H** and the ketone **9** as shown in Scheme 5. Future research will obviously include the completion of a viable synthesis of aldehyde **8**. In addition, the 37% yield realized in the conversion of the lactone **F** into **G** must also be improved. This will provide an excellent place to start for the students who will carry this project forward.

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