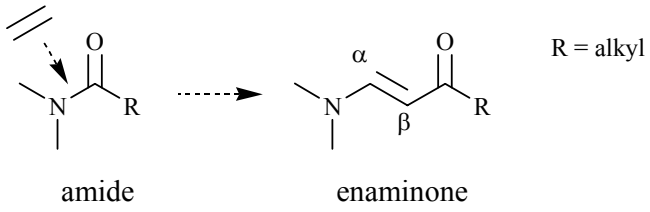
CHAPTER 2

A PROPOSAL FOR A NEW SYNTHESIS OF FEBRIFUGINE

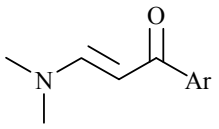
2.1. Introduction to enaminones and the Wits approach to alkaloid synthesis

Our synthetic approach to **1** and **14** involves the intermediacy of "enaminones" which may be viewed as amides into which a vinyl fragment has been interpolated [70] (Scheme 16). The terms "enaminone" and "vinylogous amide" are thus practically interchangeable descriptions of this functional group. During this project we shall deal with the enaminone system shown in Scheme 16, i.e. a β-acylated enamine where R = alkyl.

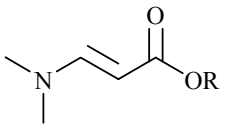


Scheme 16: Explanation of the enaminone functional group.

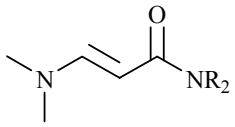
The Organic Chemistry Group at the University of the Witwatersrand (Wits) has for almost three decades successfully used enaminones for the synthesis of naturally occurring alkaloids and their derivatives. Most of their work reported thus far involved the synthesis of enaminones bearing electron-withdrawing groups, as β-substituents, leading to the structures illustrated in Figure 12. The β-substituents are responsible for alterations in the reactivity of the enamine core, and to different extents, as demonstrated by the sustained research efforts of the Wits Group.



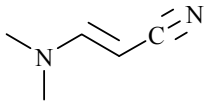
aromatic vinylogous amide



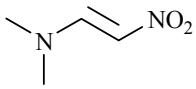
vinylogous urethane



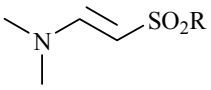
vinylogous urea



vinylogous cyanamide



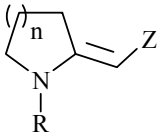
vinylogous nitramine



vinylogous sulfonamide

Figure 12: Enaminones bearing electron-withdrawing substituents

Because most naturally occurring alkaloids contain the nitrogen atom in five- or six-membered rings, the Wits Group invariably deal with pyrrolidine or piperidine derivatives. For the enaminone compounds this means that the alkylidene substituent is present at C-2 of the ring (Figure 13).



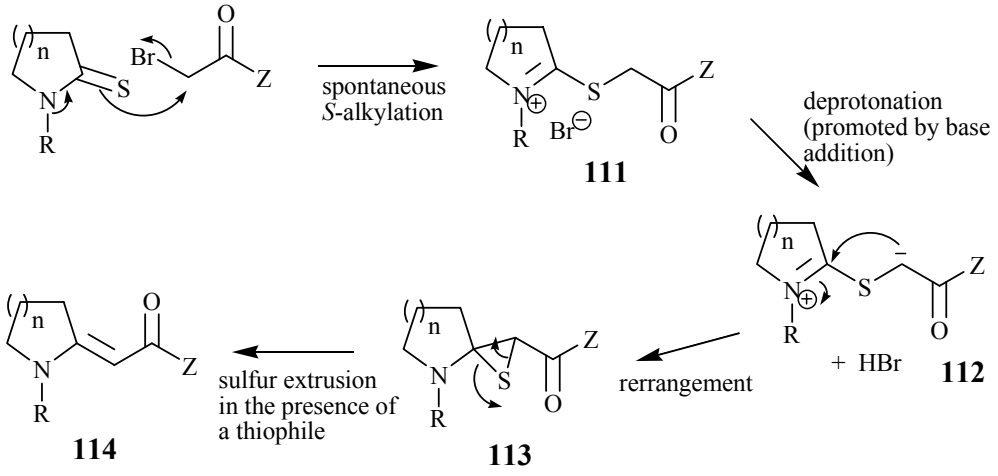
n = 1, 2

R = H, alkyl, aryl
Z = COR, CO_2R,
CN, NO_2, etc.

Figure 13: Representation of the relevant enaminones.

The compounds represented in Figure 13 are accessible by many routes, the most convenient of which is the Eschenmoser sulfide extrusion reaction [71]. The mechanism of this reaction is shown in Scheme 17. The required pyrrolidine- or piperidine-2-thiones (thiolactams) are prepared by thionation of the corresponding pyrrolidine- or piperidin-2-ones by using the various methods discussed later. A spontaneous reaction between the thiolactam and an appropriate α-bromocarbonyl compound results in *S*-alkylation to form the α-thioiminium salt **111**. Deprotonation promoted by the presence of a base, e.g. NEt_3 or 1-methylpiperidine, occurs at the position α to the ketone to produce intermediate **112** which undergoes spontaneous intramolecular cyclization to thiirane **113**. Sulfur extrusion is accelerated by the presence of an

equivalent amount of a suitable thiophile, eg. PPh_3, to yield the desired enaminone **114**.



Scheme 17: Mechanism of the Eschenmoser reaction.

When viewing the enaminone structure, it is at once apparent that it should display ambident reactivity. It may react both as a nucleophile and as an electrophile as demonstrated in Figure 14.

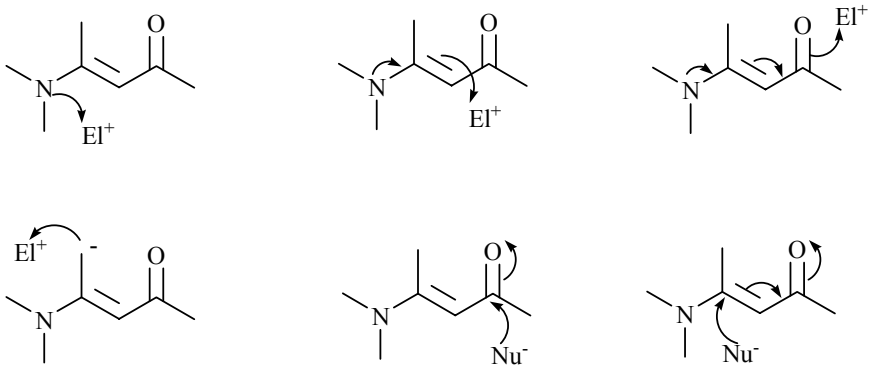
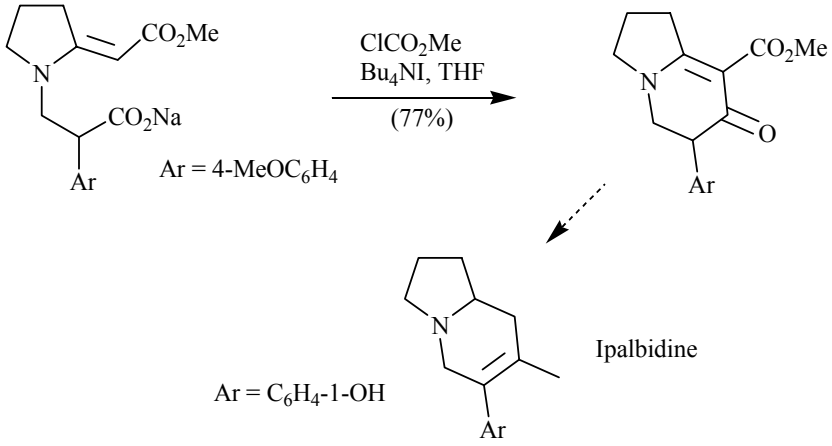


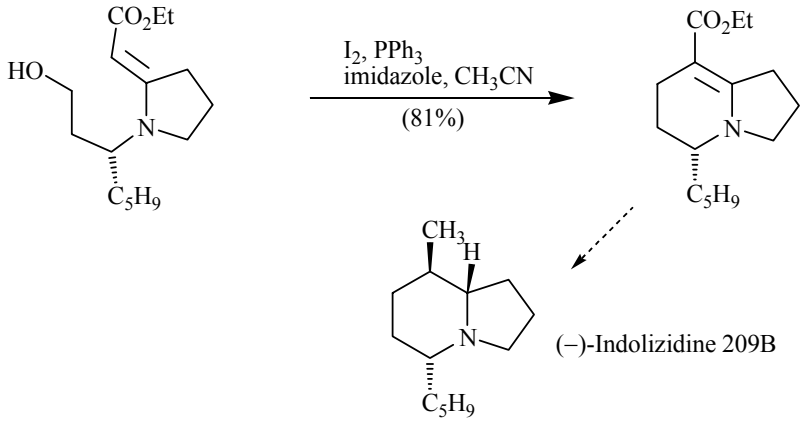
Figure 14: The versatile reactivity of the enaminone group.

The interesting reactivity of enaminones has been exploited by the Wits Group to effect, amongst other results, intramolecular annulation in order to access important core structures of alkaloids, a few examples of which are shown on the following pages.

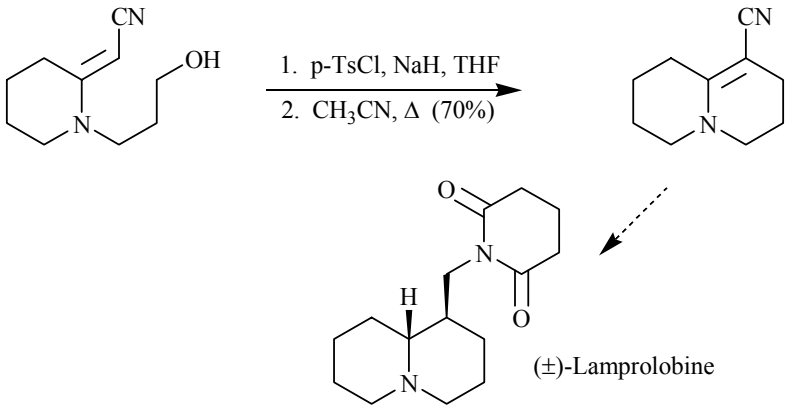
1. An indolizidine alkaloid was accessed by acylative cyclization [72]:



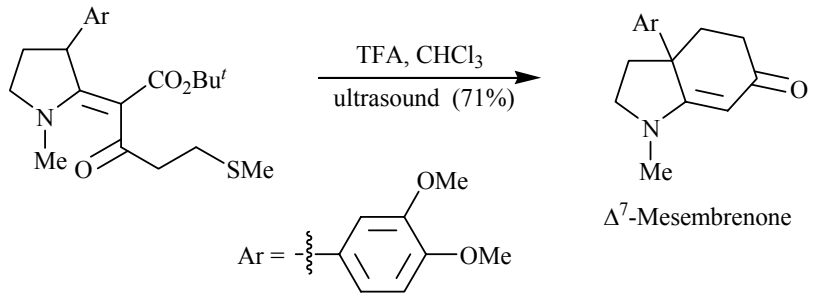
2. An indolizidine alkaloid could also be obtained by alkylative cyclization [73]:



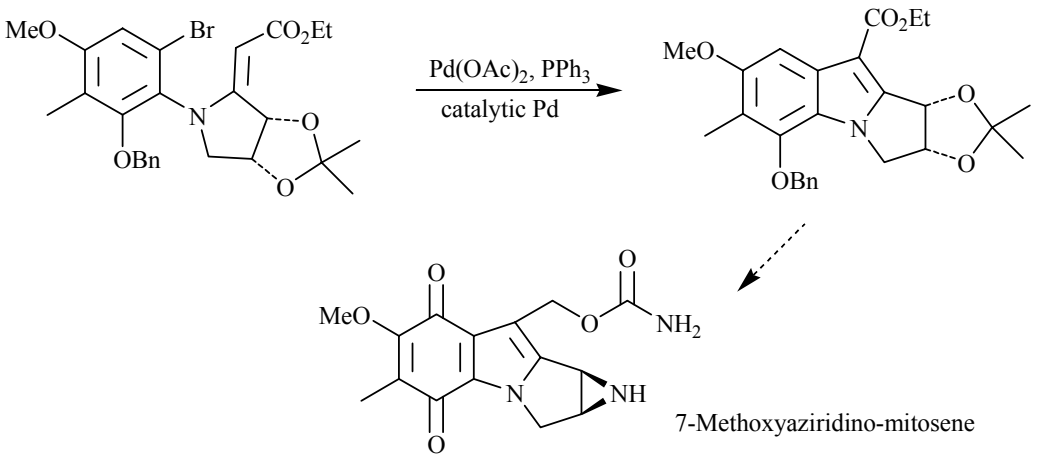
3. A quinolizidine alkaloid was accessed by alkylative cyclization [74]:



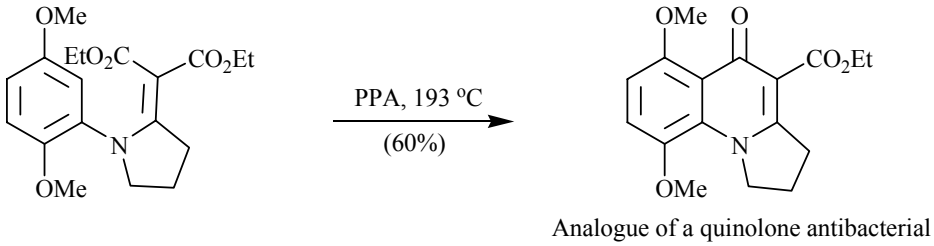
4. A perhydroindole alkaloid was formed in the following reaction [75]:



5. The pyrrolo[1,2-*a*]indole skeleton was recently accessed by an intramolecular Heck-type reaction [76]:



6. A quinolinone was synthesized by using the electrophilic nature of the parent enaminone [77]:



Analogue of a quinolone antibacterial

The contrasting sensitivity of various enaminones towards reducing agents is an important topic in this project which will be discussed in detail later (see Chapter 3). Some examples of alkaloids prepared by the Wits Group through the chemoselective reduction of enaminones are shown in Figure 15.

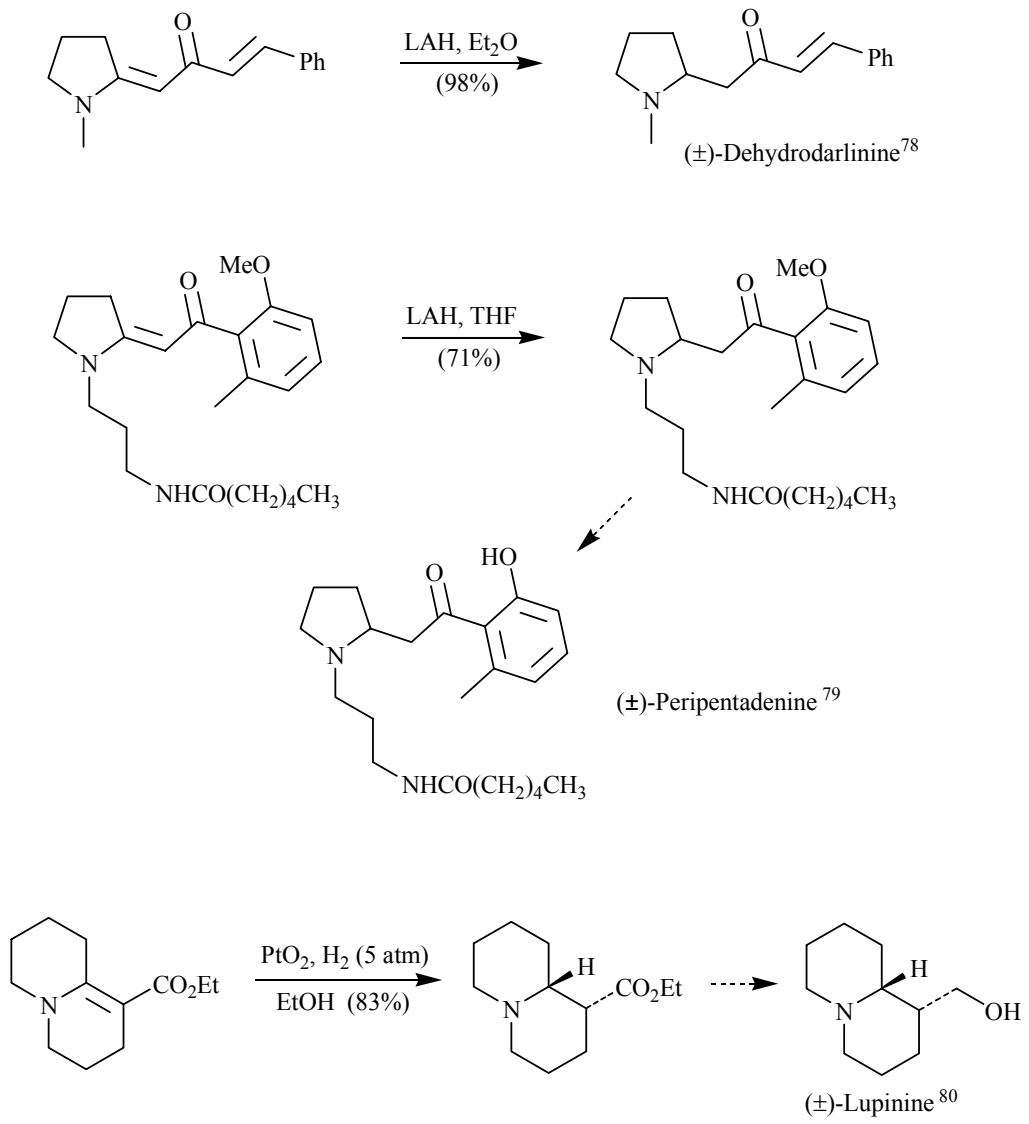


Figure 15: Chemoselective reduction of the enaminone C=C bond *en route* to various alkaloids.

2.2. Strategy and aims

Most of the published syntheses of **1** mentioned in Section 1.6 involved disconnection between N3 (of the quinazolinone moiety) and C1′ (of the side chain) in **1** as indicated in Figure 16.

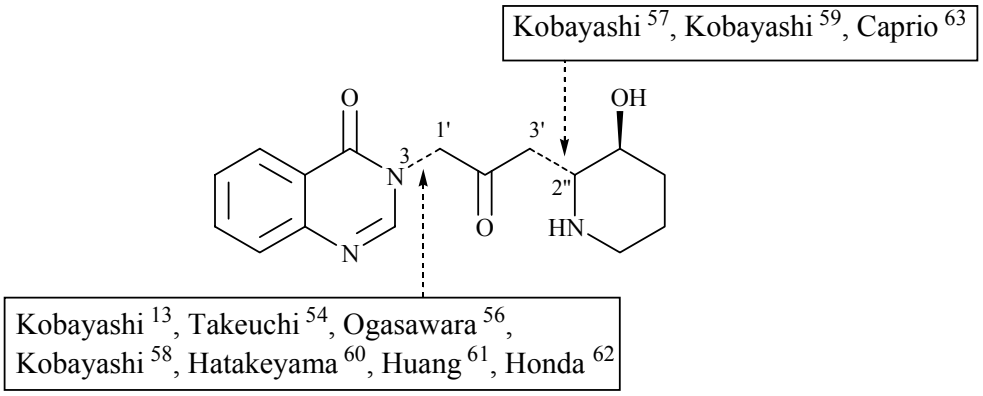
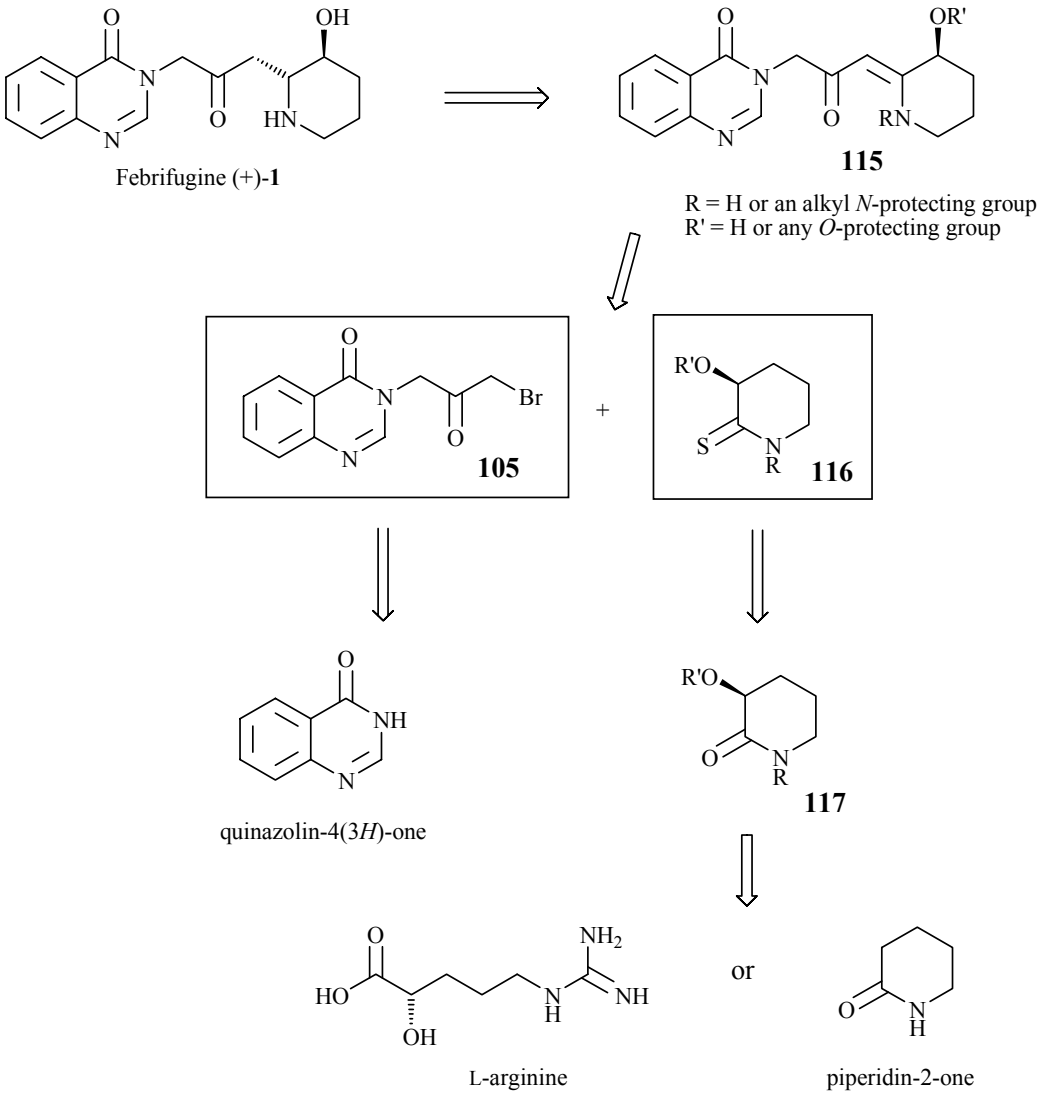


Figure 16: Disconnections to **1** used in published syntheses.

Disconnection at N3-C1′ constitutes a linear synthesis as commercially available quinazolin-4(3*H*)-one is built into the molecular skeleton during the final step(s), whereas disconnection at C2″-C3′ (Figure 16) would result in a more convergent synthesis with well-known benefits.

We opt to disconnect at C2″-C3′ as allowed for by the key Eschenmoser sulfide contraction reaction. Our synthetic approach to **1** is shown in Scheme 18. Disconnection of (+)-**1** to vinylogous amide **115** involves chemoselective and diastereoselective reduction of the enaminone C=C bond in **115**. It is anticipated that this reduction reaction might initially result in the intermediate formation of isofebrifugine (+)-**2** which can easily be isomerized to (+)-**1** as demonstrated in the Takeuchi synthesis described before (see Section 1.6.3.).

Compound **115** is formed by the Eschenmoser reaction of the known bromide **105**, prepared from quinazolin-4(3*H*)-one, with key 3-*O*-substituted thiolactam **116**, which in turn can be prepared from lactam **117** by thionation. Access to **117** is gained either from piperidin-2-one or from the naturally occurring amino acid, L-arginine, as demonstrated in subsequent chapters.



Scheme 18: Our disconnection approach to **1**.

In order for the Eschenmoser reaction to proceed satisfactorily, it is imperative that the thiocarbonyl sulfur in **116** be nucleophilic enough to react with alkylating agent **105**. It is therefore essential to use an electron-donating protecting group, e.g. an alkyl group on nitrogen in **116**.

The correct stereochemistry in **116** may be accessed by various approaches. The most appealing "chiral pool" approach is from inexpensive L-arginine which has the correct configuration (*S*) about the hydroxyl-substituted α-carbon. The second approach is the

stereoselective, sterically controlled introduction of the (3*S*)-hydroxyl in **117** by using a chiral auxiliary protecting group on the nitrogen of piperidin-2-one. The third approach is the implementation of the Davis hydroxylation reaction [81], which entails the utilization of a chiral oxaziridine to introduce stereoselectively at the 3-position electrophilic oxygen *via* formation of the enolate of a *N*-protected piperidin-2-one.

If the correct stereoisomers **117** and **116** are obtained, the question arises whether these readily enolizable compounds would refrain from epimerizing. The other anticipated difficulty is the chemo- and stereoselective reduction of **115**. This compound also contains other functional groups which might interfere with our intended transformations.

The advantages of our synthetic approach to **1** are as follows:

1. This would be an extremely general synthesis allowing for the preparation of important febrifugine derivatives, which have not been prepared before. Both the quinazolinone and the piperidine moieties can be easily modified prior to the Eschenmoser coupling reaction. The quinazolinone may be easily substituted by different groups, or another heteroaromatic moiety may be used instead. Lactams are common and stable organic compounds, abundant in the literature and often very readily prepared. The possibility exists to use lactams of different ring sizes and also to vary the substituents on the nitrogen and elsewhere on the lactam ring. Furthermore, the use of readily accessible sugar lactams could lead to promising febrifugine analogues.

2. This is a convergent synthetic approach which, in theory, would require few steps. Even if the chemoselective reduction reaction in the final stages does not work satisfactorily, the dehydro-febrifugine derivatives **115** might still prove to be important candidates in antimalarial research. It should be noted that none of these derivatives have been prepared or tested before.

3. This is an economical approach which requires no particularly expensive, nor any highly toxic, reagents.

In summary, as **1** and its derivatives are presently such promising lead compounds in antimalarial research, the primary aim of this project is finding a simple, general and economical synthetic route (preferably incorporating "green" chemistry) for the preparation of **1** and its derivatives. As our proposed synthesis involves the intermediacy of enaminones, we shall also endeavour to expand our existing knowledge of the reactivity and structures of these interesting compounds. The long-term aim of this project is the antimalarial testing of potentially promising febrifugine analogues obtained in order to cast more light on the structure-activity relationships of the potent antimalarial alkaloid **1**.