CHAPTER 3

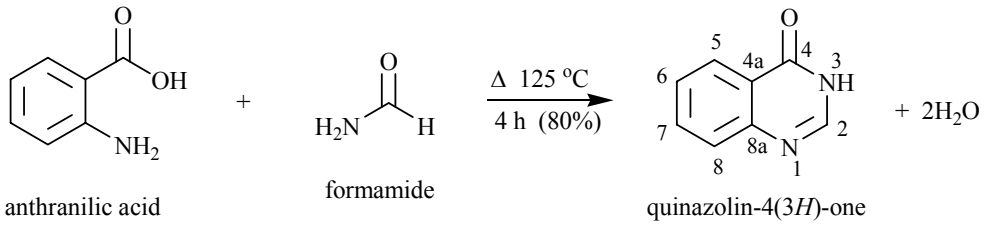
MODEL SYNTHETIC STUDIES

3.1. Aims

A good approach when attempting the synthesis of a complex natural product is by first testing the proposed transformations on model systems, i.e. simpler versions of the synthons which will be used for the natural product synthesis. The advantage of this approach is that steps in the synthesis can be optimized prior to their application on costly or more complex substances. Furthermore, if a model synthesis works well, one might anticipate generality in its application, which makes continued research into the methodology worthwhile. In our case for the intended synthesis of (+)-**1**, the easiest approach is to first produce the 3″-unsubstituted analogue, (±)-deoxyfebrifugine (**14**), which is itself a desirable synthetic target (see Chapter 1). We also wanted to ascertain whether our proposed method might work for the synthesis of analogues containing different ring sizes, other than the 6-membered piperidine ring in **14** and **1**. Finally, experiments with different protecting groups on the nitrogen of the lactams, thiolactams and vinylogous amides required for the synthesis of **14** and analogues would hopefully tell us which *N*-protecting group might work best when attempting to synthesize **1**.

3.2. Synthesis of quinazolin-4(3*H*)-one

We opted to prepare the commercially available heteroaromatic starting material, quinazolin-4(3*H*)-one, by the double condensation reaction of anthranilic acid (2-aminobenzoic acid) with formamide at 125 ºC [82] as shown in Scheme 19. Complementary nucleophilic attack of the respective amino groups onto the given carbonyl functions results in synchronous amide and imine formation. The melting point (209-210 ºC) of the crystalline quinazolin-4(3*H*)-one product we obtained in this way corresponded well with the literature value (212 ºC [82]).



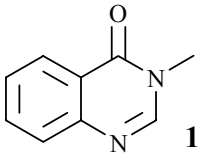
anthranilic acid formamide quinazolin-4(3*H*)-one

Scheme 19: Preparation of, and the atomic numbering scheme given to, quinazolin-4(3*H*)-one.

Quinazolin-4(3*H*)-one was found to be practically insoluble in most frequently used organic solvents, especially aprotic solvents such as dichloromethane. NMR spectra were thus recorded in DMSO-d_6. For the same reason, subsequent reactions involving quinazolin-4(3*H*)-one needed to be carried out in the polar solvent DMF.

Although, as commonly observed, the NMR spectral chemical shifts of the aromatic protons of the quinazolin-4(3*H*)-one group varied among the deuterated solvents used during this project (DMSO-d_6, $CDCl_3$, D_2O) to acquire NMR data, the ^{1}H NMR spectrum of quinazolin-4(3*H*)-one exhibited a characteristic aromatic proton splitting pattern which was observed throughout the project. The most deshielded H-5 signal is split into a doublet (J = 8.0 Hz) by neighbouring H-6. Highly deshielded H-2 (bonded to two N's) showed the expected singlet at δ 8.04. These signals were followed by, in increasing order of nuclear shielding, a triplet for H-7 (J = 7.6 Hz), a doublet for H-8 (J = 7.9 Hz) and finally, a triplet for H-6 (J = 7.5 Hz). The order of shielding was deduced from a reliable publication [53], i.e. the synthesis of racemic febrifugine [(±)-**1**] by Takeuchi, which was also applied to the aromatic ^{1}H and ^{13}C NMR assignments of other quinazolin-3-yl containing compounds synthesized during this project.

In addition to the preparation of quinazolin-4(3*H*)-one, the above reaction (Scheme 19) was successfully applied to the synthesis of 3-methylquinazolin-4(3*H*)-one **118** from 2-aminobenzoic acid and *N*-methylformamide in a related project conducted in our laboratory [83]. In this case, product **118** was sufficiently soluble in EtOAc to be extracted with EtOAc, following dilution of the reaction mixture with



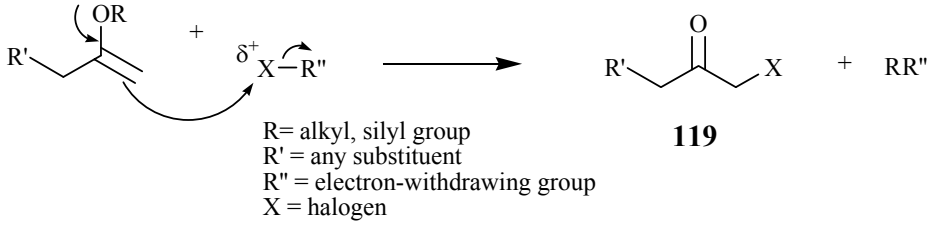
118

water. A good yield (73%) of **118** was obtained after column chromatography of the evaporated combined organic extracts. The NMR data of our obtained product **118** agreed with those of Mali *et al*. [84]. Interestingly, no publications in the literature using this method for the preparation of **118** were found. This result was therefore significant as the reported procedures for preparing **118** [84-86] are all inferior (both in number of steps and yield) to our preparation.

3.3. Synthesis of the bromide precursor, 3-(3-bromo-2-oxopropyl)quinazolin-4(3*H*)-one (105)

Pivotal to conducting our proposed synthesis of **1** and analogues is the ready availability of key starting material 3-(3-bromo-2-oxopropyl)quinazolin-4(3*H*)-one **105** (see Scheme 18, section 2.2.).

Numerous methods exist for the preparation of α-haloketones **119**. Regioselective reaction of alkyl enol ethers, trimethylsilyl enol ethers, enol acetates or enamines with various electrophilic halogenating reagents is the method of choice (Scheme 20) [87]. The previously mentioned synthesis by Takeuchi *et al*. of **105** (Scheme 18) [31] employed this reaction (where R = TMS and X-R″ = NBS) to afford the desired compound in 74% yield from the corresponding ketone **104**. As this procedure required the synthesis firstly of **104** and also the expensive reagent TMSOTf, which we did not have at our disposal, we set out to find an alternative, and hopefully an improved, synthesis of **105**.

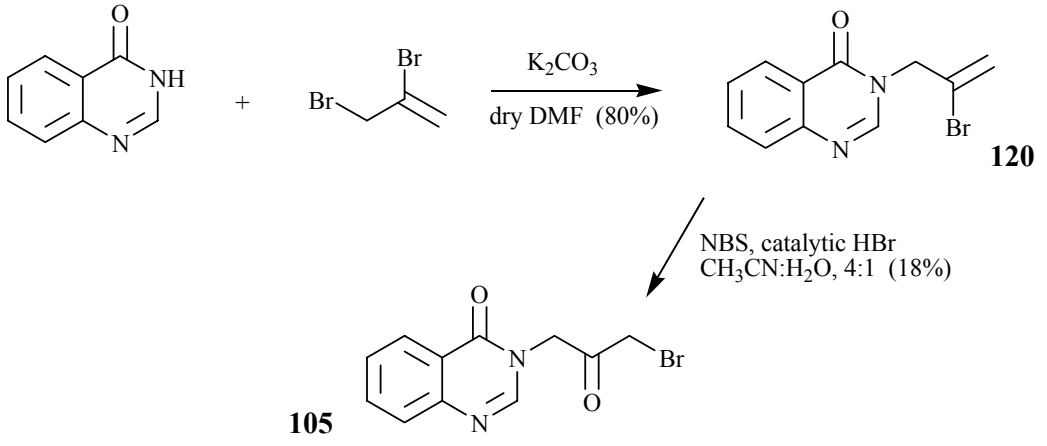


Scheme 20: Popular method for the preparation of α-haloketones **119**.

3.3.1. From 3-(2-bromoallyl)quinazolin-4(3*H*)-one

The first approach to **105** involved the preparation of vinyl halide **120** by alkylation of quinazolin-4(3*H*)-one, followed by oxidative hydrolysis, thought to occur by the *in situ* generation of hypobromous acid (HOBr), to afford the desired bromide (Scheme 21) [87]. Commercially available 2,3-dibromopropene was added to a mixture of quinazolin-4(3*H*)-one and K_2CO_3 in dry DMF. After stirring at rt overnight, the reaction mixture was diluted with water and extracted with EtOAc. Column chromatography afforded stable and crystalline **120** in high yield. When **120** was stirred in the presence of NBS and a catalytic amount of HBr in aqueous CH_3CN, the desired **105** was obtained in a very low optimized yield of 18%. The side-products of this reaction were not characterized as they were insoluble during the EtOAc extraction or the column chromatography stage. Presumably the acidic conditions used during this step, coupled with the presence of brominating agent NBS, resulted in unwanted hydrolysis and/or bromination of **120**. The yield of **105** was therefore considerably lower than the reported yields (52-86%) of other less complex α-bromoketones [87] synthesized by this procedure.

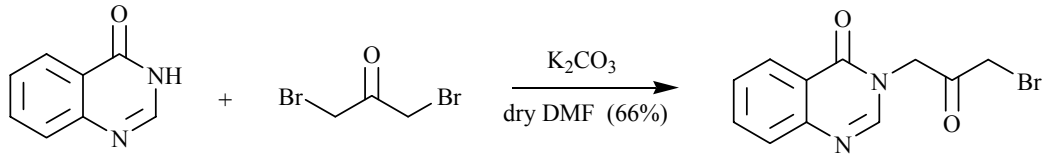
Disappointed by this result and aware that we would need an economical route useful for obtaining **105** in large quantities, we sought an alternative method for its preparation.



Scheme 21: First preparation of **105**.

3.3.2. Using 1,3-dibromopropan-2-one

We discovered a simple and high-yielding preparation of **105**. Standard *N*-alkylation of quinazolin-4(3*H*)-one using commercially available 1,3-dibromopropan-2-one (which we prepared by a standard procedure from acetone [88], see experimental) under similar conditions to those used before (K_2CO_3, DMF) afforded, after recrystallization from EtOAc-MeOH, pure **105** in 66% yield (Scheme 22).



105

Scheme 22: New, improved preparation of **105**.

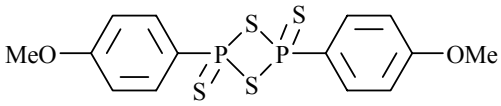
Conveniently, **105** could be isolated by selective precipitation during partial evaporation of the EtOAc, which was used for extraction, on the rotary evaporator. Recrystallization of the beige powder thus obtained from EtOAc-MeOH was usually sufficient to obtain pure product as a colourless powder, the characterization data of which agree with those obtained by Takeuchi's group [31] (see experimental, Chapter 7). The Takeuchi paper did not include ^{13}C NMR spectral data.

It should be noted that none of the possible dimer, formed by potential reaction of 1 equivalent of dibromoacetone with 2 equivalents of quinazolinone, was isolated. Presumably the dimer has solubility and polarity properties sufficiently different to **105** so that it does not interfere with the isolation of **105**. Although some of the dimer probably did form, this side-reaction was minimized by adding a large excess of 1,3-dibromoacetone (3.1 equivalents).

The advantages of this procedure are numerous. As mentioned above, the isolation of **105** was made easy by its rather low solubility in EtOAc. It requires only one step (compared to 2 steps in the Takeuchi preparation, Scheme 15, section 1.7.3.), is moderate-yielding (66%, compared to Takeuchi's overall yield of 55%) and inexpensive. Excess 1,3-dibromoacetone may be recovered by simple distillation from the crude product.

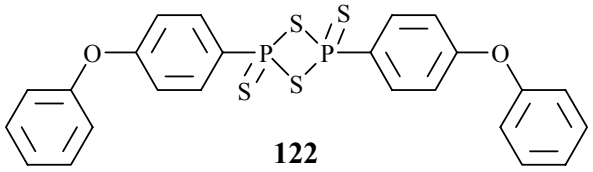
3.4. Synthesis of the thiolactam precursors

A popular method for converting the carbonyl group in lactams, amides, ketones, esters and lactones to the corresponding thiocarbonyl derivatives, is by use of the phosphetane called Lawesson's reagent **121** [89]. Lactams (applicable to this project) and amides are generally the most easily thionated of the above-mentioned carbonyl compounds. Lecher first prepared **121** in 1956 [90] and Lawesson demonstrated its versatility as a thionation reagent in the late 1970s. Thionation of oligopeptides was said to proceed without epimerization of chiral carbons in the constituent amino acids [91]. This finding will be discussed further in a later section.



121

The disadvantages of this method include the high cost of **121**, the requirement for absolutely anhydrous conditions during the reaction (**121** is also a hygroscopic compound which requires moisture-free storage conditions) and purification difficulties during the isolation of the products. The last-mentioned fact is most disadvantageous. Owing to the nonpolar by-products formed during a thionation reaction with **121**, coupled with the high mass of **121**, large columns are needed during purification, resulting in increased cost and effort. Finally, the limited solubility of **121** in common organic solvents (e.g. CH_2Cl_2) used to pose problems until it was discovered that most thionations proceed efficiently using **121** in refluxing benzene or toluene. Furthermore, when dealing with thermolabile protecting groups, it was demonstrated that the phenyl ether derivative **122** can be used instead of **121** [92].



122

The good solubility of **122** in THF at rt, coupled with an easy preparation of **122** from phenyl ether using Lecher's procedure [90], makes **122** a good, yet little utilized, alternative.

The oldest and least expensive thionation method is the use of P_2S_5 in conjunction with bases such as pyridine, NEt_3, *n*-BuLi, $NaHCO_3$ or Na_2CO_3. The latter is most

convenient. Reaction of P_2S_5 with Na_2CO_3 in a 2:1 ratio at rt in THF forms within 20 minutes a homogeneous solution of the phosphorus salt **123** shown below [93].

$$P_4S_{10} + Na_2CO_3 \xrightarrow{THF} \underset{\mathbf{123}}{(P_4S_{10}O)^{2-}Na_2^{2+}} + CO_2$$

In situ generated **123** is the active thionation species and is both soluble in THF and in water. This allows for an easy work-up procedure with obvious advantages above the use of **121** and **122** discussed above. The only disadvantages when using this combination of reagents are the large volume of THF required and the possibility of obtaining lower product yields. Decreased yields may be explained by the basic conditions used during this procedure. Especially when dealing with costly starting materials, it may be viewed as a "risky" alternative to Lawesson's method.

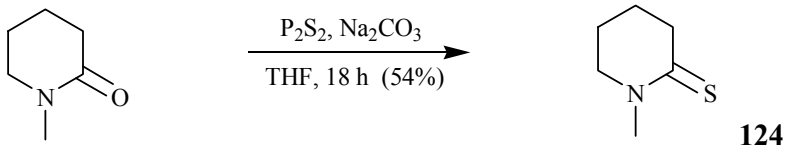
A new thionation method was recently published by Curphey [94]. It was discovered that P_2S_5 in conjunction with hexamethyldisiloxane (HMDO), in solvents such as CH_3CN, toluene, xylene or CH_2Cl_2, efficiently convert carbonyl-containing compounds into their thiocarbonyl analogues. Phosphorus-containing by-products are easily removed, either by mild alkaline hydrolysis, or by filtering through silica gel. The mechanism by which HMDO enhances the thionating ability of P_2S_5 is still uncertain. We tested the applicability of this procedure, and compared it with the older thionation methods, as will be seen in several subsequent sections of this project.

3.4.1. Preparation of the *N*-protected thiolactams

As mentioned before, when aiming to prepare derivatives of febrifugine (**1**) which are *N*-protected in the piperidine moiety, we were limited to the use of thiolactams bearing electron-donating groups on the nitrogen, necessary for the Eschenmoser reactions to proceed satisfactorily. The amine protecting groups in this project were therefore all alkyl groups. In this context, we also view benzyl, 2-naphthylmethyl and 2-cyanoethyl groups as "*electron-donating alkyl*" groups.

The synthesis of *N*-methyl derivatives of (±)-deoxyfebrifugine (**14**) required the preparation of 1-methylpiperidine-2-thione **124** and 1-methylpyrrolidine-2-thione **125**.

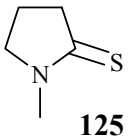
Thionation of commercially available 1-methylpiperidin-2-one using 2 eq. P_2S_5 and 1.5 eq. Na_2CO_3 gave a disappointing yield (54%) of **124** after distillation of the crude product mixture under high vacuum (Scheme 23). This procedure is not recommended as, in a related project [83], **124** was obtained in high yield (79%) by using Curphey's conditions [94] (see above) and by purifying the crude product by column chromatography. The yield may be further improved by distilling 1-methylpiperidin-2-one prior to use.



124

Scheme 23: Preparation of **124**.

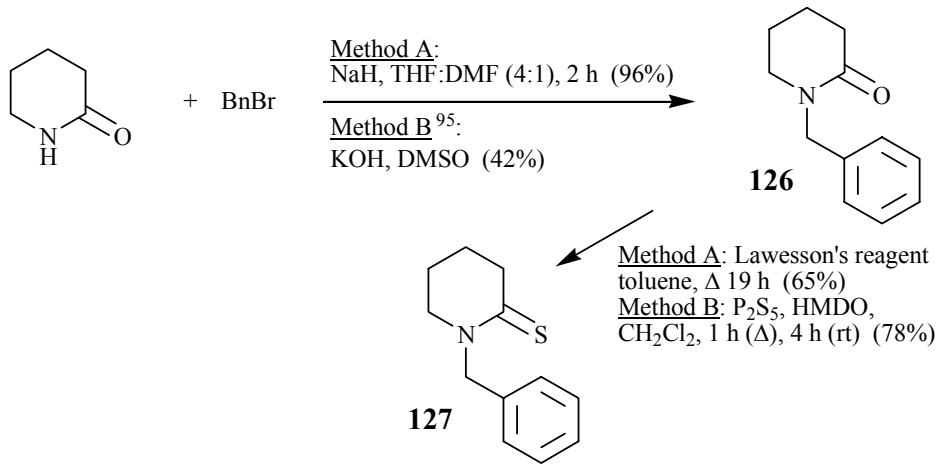
Analogue **125** was available from laboratory stock which obviated the need to prepare it from commercially available 1-methylpyrrolidin-2-one.



125

Our study towards the use of the *N*-benzyl protecting group in this synthesis commenced with the preparation of known 1-benzylpiperidin-2-one **126** from commercially available piperidin-2-one and benzyl bromide. Using a literature procedure (KOH, DMSO) [95], we obtained **126** in low yield (42%, Scheme 24). A much more convenient preparation method for **126** was then discovered. By stirring piperidin-2-one in the presence of NaH using THF and a small amount of dry DMF, **126** was obtained in 96% yield after column chromatography (Scheme 24).

Thionation of **126** by Lawesson's reagent (**121**) in refluxing toluene resulted in a moderate yield (65%) of known compound, 1-benzylpiperidine-2-thione **127** (Scheme 24). We were not too disturbed by this apparently poor yield as aged **121** was used. It is also thought that the conditions of high temperature (refluxing toluene) and extended time (19 h) could result in a lower yield. Once again, a better yield (79%) of **127** was obtained by using Curphey's method (P_2S_5, HMDO, CH_2Cl_2).

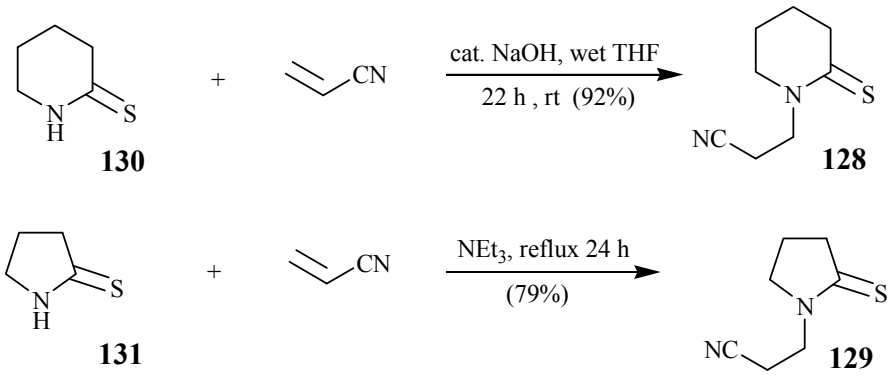


Scheme 24: Preparation of **126** and **127**.

When comparing the ^{1}H NMR spectra of **126** and **127**, the well-known deshielding effect of sulfur is observed. The triplet observed for the methylene protons alpha to the thiocarbonyl function in **127** is at a considerably higher chemical shift (δ_H 3.11) than that observed for lactam **126** (δ_H 2.47), in which these protons are alpha to a carbonyl group. Similarly, the benzylic protons are more deshielded in **127** (δ_H 5.34) than in **126** (4.60). Furthermore, characteristic for thiolactams (and thioamides) is the high ^{13}C NMR spectral chemical shift observed for the thiocarbonyl carbon in **127** (δ_C 200.9).

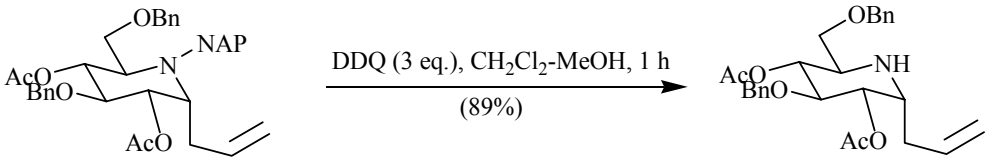
Because the *N*-benzyl protecting group proved to be difficult to remove at a later stage (see section 3.8.4.), we experimented with the use of an alternative *N*-protecting group for vinylogous amides, which was developed in our laboratory [79], i.e. the 2-cyanoethyl group. We decided to prepare both the piperidine- and pyrrolidine-2-thione thiolactam derivatives **128** and **129**, respectively (Scheme 25), by existing procedures [96,97]. A Michael reaction between the corresponding secondary thiolactams, **130** and **131** (see section 3.4.2.), and acrylonitrile was employed to afford **128** and **129** in good yields. This type of Michael addition will only proceed when a sufficiently nucleophilic nitrogen is present in the Michael donor, i.e. the thiolactam. Lactams would not react rapidly in this manner as the amide nitrogen is not nucleophilic enough. The procedure used for the preparation of **129** was both more expensive (using NEt_3 as

solvent) and lower yielding than that used for the preparation of **128**, which required only a catalytic amount of NaOH.



Scheme 25: Preparation of **128** and **129**.

Finally, we also wanted to test the utility of a *N*-alkyl type amine protecting group which recently proved to be a good alternative to the use of the *N*-Bn protecting group [98,99] for secondary amines, i.e. the 2-naphthylmethyl (NAP) group. Godin *et al*. [99] used the NAP protecting group on the amine nitrogen in the iminosugar *C*-glycoside starting material shown below, to selectively deprotect, using 2,3-dichloro-5,6-dicyanoquinone (DDQ), the amine nitrogen (in the presence of *O*-Bn and *O*-Ac groups) in order to form the desired secondary amine product, as shown below, in 89% yield.

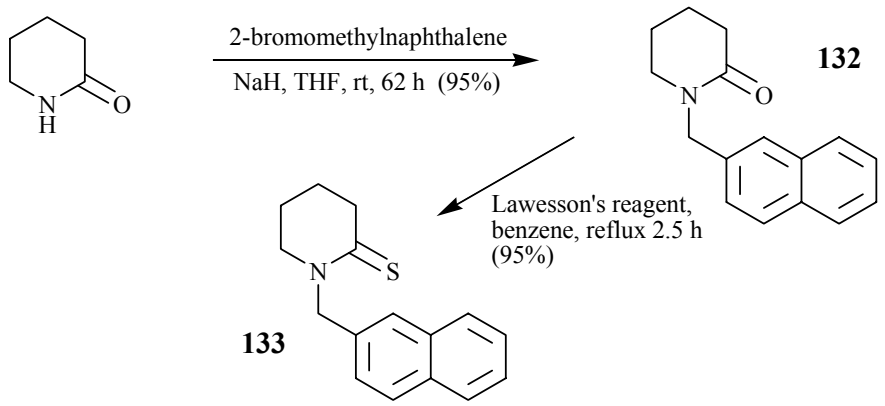


Unfortunately, owing to time constraints, we did not attempt the deprotection of *N*-NAP during this model study and only progressed to the preparation of the model *N*-NAP vinylogous amide (see section 3.5.).

In order to access the corresponding *N*-NAP thiolactam, we first prepared lactam **132** by the recently published procedure of Godin *et al*. [99]. Reaction of piperidine-2-one with 2-bromomethylnaphthalene in the presence of NaH in dry THF afforded **132** in 95% yield (Scheme 26). The ^{1}H NMR spectrum of **132** shows a peak at δ_H 4.76, which integrates for two protons, corresponding to the exocyclic NCH_2 protons. The

^{13}C NMR spectrum clearly showed the presence of the naphthalene ring, as three quaternary carbons were observed, together with seven additional aromatic peaks. The amide carbonyl was observed at δ_C 169.9 and the benzylic carbon at δ_C 50.2.

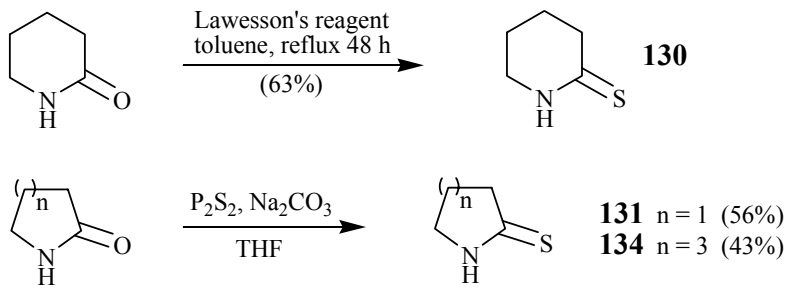
Subsequent thionation of **132** using Lawesson's reagent in refluxing benzene gave **133** in a satisfactory yield of 95%. Confirmation of the structure was found in the ^{13}C NMR spectrum, in which the thiocarbonyl carbon was observed at the expected highly deshielded chemical shift, δ_C 201.0. All the remaining spectral data were also as expected for structure **133**, e.g. the exocyclic NCH_2 protons were observed as a singlet, strongly deshielded owing to the presence of the neighbouring thioamide group, at δ_H 5.51.



Scheme 26: Preparation of **132** and **133**.

3.4.2. Preparation of the *N*-unprotected thiolactams

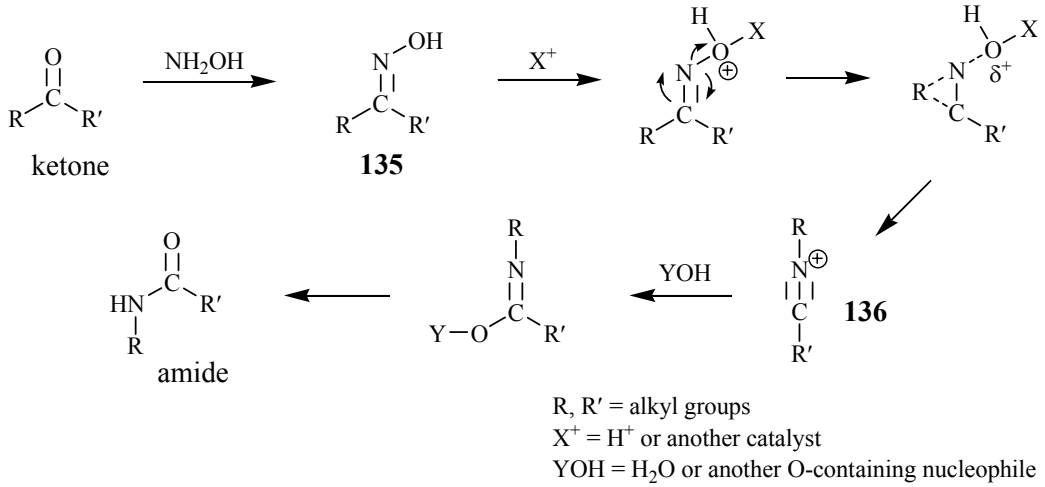
As explained later in Section 3.6., we also wanted to test the Eschenmoser reaction on secondary model thiolactams (unprotected on nitrogen and of varying ring size). These thiolactams are easily accessible from their corresponding lactams. The 5-, 6- and 7-membered thiolactams (**131**, **130** and **134**) were prepared from commercially available lactams as shown in Scheme 27 by the standard procedures discussed in section 3.4.1.



Scheme 27: Preparation of simple secondary thiolactams.

The low yield of **130** can once again be ascribed to the unnecessarily harsh conditions employed for this reaction during the initial stages of the project. General optimization of the thionation reactions only occurred during the latter stages of the project. Here, we were only interested in obtaining sufficient amounts of the simple thiolactams required. Similarly, the yields of the P_2S_5 procedures applied to the synthesis of **131** and **134** could be improved by repeated recrystallization in the case of **134**, or by more meticulous experimentation in the case of **131**. The basic conditions used, coupled with the presence of free *N*H groups in **131** and **134**, could further explain the disappointing yields.

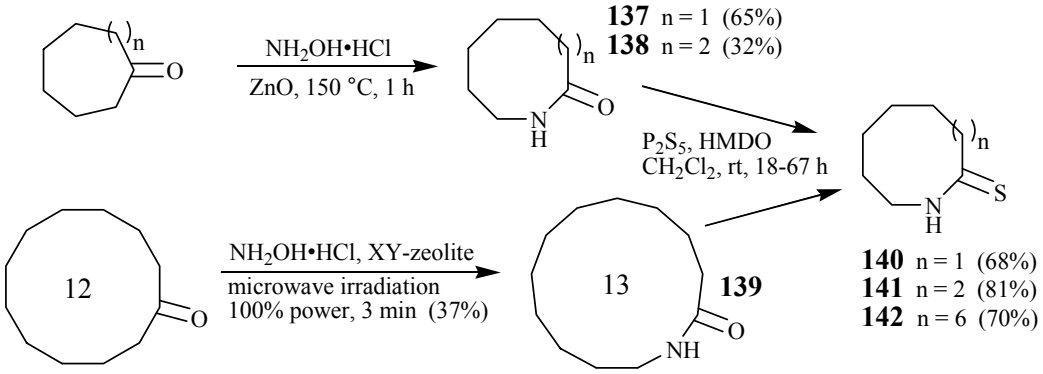
Although the remaining lactams required for the synthesis of the 8-, 9- and 13-membered model thiolactams are all commercially available compounds, we decided to prepare them by simple Beckmann procedures from the corresponding ketones. The Beckmann rearrangement reaction is a well-known method by which oximes are converted into amides, the mechanism of which is shown in Scheme 28 [100]. A ketone is first reacted with hydroxylamine to form an oxime **135**, which is protonated by a Brønsted or a Lewis acid (X^+), thereby converting the hydroxyl group into a leaving group. This is followed by concerted ionization and migration to form nitrilium ion **136**, which is attacked by a nucleophile YOH (e.g. H_2O). Hydrolysis forms the amide.



Scheme 28: Mechanism of the Beckmann rearrangement.

Using a recent method developed by Sharghi and Hosseini [101], which employs ZnO as the catalyst and proceeds without the use of solvent, we prepared azocan-2-one **137** and azonan-2-one **138**, in moderate to low yields (Scheme 29). The low yield of **138** is probably because aged and undistilled starting material was used. The 13-membered lactam **139** was prepared from cyclododecanone by another recently developed method [102], which uses XY-zeolite as a catalyst and proceeds very rapidly by microwave irradiation (Scheme 29). It should be noted that we did not use a commercial microwave apparatus, but carried out this experiment in a domestic microwave oven, which explains the very low yield of **139** obtained. A large amount of starting material was still present in the crude product. Prolonged periods of irradiation did not increase the yield, as starting material simply evaporates from the reaction mixture and condenses on the sides of the test-tube used, without reacting. We were happy to be able to separate product **139** from excess reactant cyclododecanone by column chromatography, and to obtain sufficient amounts of **139** to proceed to the next step. It should be noted that, when attempting to prepare **139** from cyclododecanone by an established routine procedure [103] using sodium azide and concentrated HCl, no product was obtained, even on prolonged heating. This can only be explained if the sodium azide used was inactive, or if the cyclododecanone was simply not soluble enough to react under these conditions. During two attempts, we did not observe any exotherm, nor did homogeneous mixing of the reagents occur on heating. In each case, all the starting material was recovered.

As shown in Scheme 29, thionation of **137-139** using Curphey's conditions afforded the corresponding thiolactams **140-142** in moderate to good yields. Interestingly, although IR and melting point data are available on thiolactam **142**, the NMR spectral data of **142** have, to our knowledge, never been published. The ^{1}H NMR spectrum of **142** exhibits a large multiplet at δ_H 1.26–1.42, which integrates for fourteen protons. Two protons, assigned to the β- or 4-position of the 13-membered ring, are observed as a multiplet at δ_H 1.65–1.72. Two more protons, assigned to the 12-position of the ring near the nitrogen atom, are observed as a multiplet at δ_H 1.81–1.85. Finally, the NC*H*$_2$ protons were observed as a multiplet at δ_H 3.74–3.79. The ^{13}C NMR spectrum of **142** clearly showed the presence of twelve carbons. The thiocarbonyl carbon was observed at the highly deshielded chemical shift of δ_C 205.8.



Scheme 29: Preparation of **137-142**.

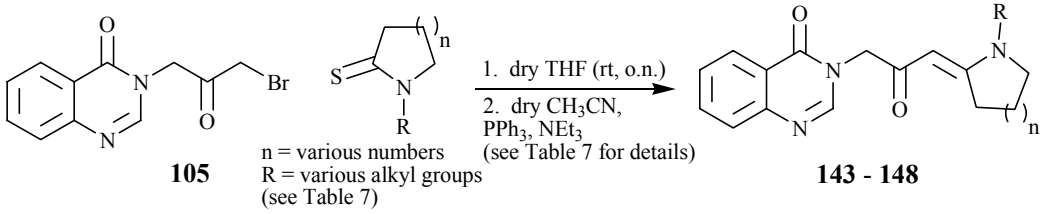
3.5. The preparation of the model *N*-protected vinylogous amides

The Eschenmoser reactions between bromide **105** and the prepared *N*-alkylated thiolactams (Scheme 30) proceeded satisfactorily in all cases, albeit that the yields of some of the reactions were unexpectedly low (see Table 7 below). We used a two-step standard procedure, which has been optimized in the Wits laboratory over many years of research:

1. Dry THF was used as a solvent to mediate the first *S*-alkylation step. This reaction is often easily monitored owing to the gradual precipitation of the

sparingly soluble and colourless thioiminium salt product. Disappearance of the starting materials from solution was also monitored by TLC, but this was not always completely reliable for reasons explained below. Although these reactions were usually close to completion after stirring at rt for *ca*. 3 h, it was thought beneficial to leave the *S*-alkylation reactions stirring overnight, or even for several days, to ensure good yields.

2. The thioiminium salt must be solubilized better for the sulfur extrusion step to occur at an acceptable rate. Therefore, after evaporation of the THF *in vacuo*, the more polar solvent CH_3CN was added. Although the salts did not completely dissolve at this stage, once NEt_3 was added, the reaction always commenced immediately. PPh_3 was used as a thiophile to scavenge the extruded sulfur and therefore, together with the base, accelerated the reaction significantly. In all these experiments, an immediate colour change to yellow, orange or red, was observed as soon as NEt_3 was added to the reaction mixture. Although the sulfur extrusion reaction is thought to go to completion very rapidly in the case of *N*-alkylated enaminones, it was left stirring overnight to ensure completion.



105 **143 - 148**

Scheme 30: Reaction of **105** with model *N*-alkylated thiolactams (See Table 7 below for details).

Table 7 summarizes the results obtained for the synthesis of the model tertiary *N*-alkylated vinylogous amides shown in Scheme 30. As indicated, many of these products were easily purified by an acid-base extraction procedure, i.e. using 2 M HCl solution to selectively extract the product into the aqueous phase, then removing organic impurities from the acidic aqueous phase by CH_2Cl_2 extraction, followed by back-extraction of the product into CH_2Cl_2 after neutralizing with aqueous ammonia solution. The enamine system is rapidly protonatable, which makes it soluble in acidic solution, so that organic impurities (eg. PPh_3 and its side-products) can be separated from the desired product.

The *N*-Bn (**145**) and *N*-NAP (**148**) derivatives were, however, surprisingly difficult to extract into the acidic aqueous phase using the above-mentioned work-up procedure. A reason could be that the enamine systems in **145** and **148** are slightly less basic than that in the other derivatives of the series owing to the inductive electron-withdrawing effect of the Bn and NAP groups. The aromatic residues draw electron density away from the *N*-methylene groups (and therefore also from the enamine systems) in these compounds, which leads to slightly lower pK_a values compared to the derivatives bearing aliphatic alkyl groups. Furthermore, the increased hydrocarbon content (aromatic rings) in **145** and **148** might reduce the solubility of their salts in the aqueous phase. Therefore, these compounds were purified by subjecting the crude product mixtures (after filtration through celite) directly to column chromatography on silica gel.

The low yield of the piperidinylidene, *N*-Me analogue **144** can only be explained by presuming that the starting material bromide **105** was not of impeccable purity. During the recrystallization purification process of **105**, a trace amount of 1,3-dibromoacetone can co-crystallize with **105**. This might drastically reduce the yield of the Eschenmoser reaction as 1,3-dibromoacetone would react with the thiolactam reagent to form undesired side-products. It is therefore recommended that re-crystallized **105** should always be purified further by column chromatography (see experimental, Section 7.1.3.).

Thio-lactam used	**R**	**N**	**PPh_3 equiv.**	**NEt_3 equiv.**	**Work-up pro-cedure**	**Product**	**Yield (%)**
125	Me	1	1.4	1.4	Acid-base extract.	**143**	63
124	Me	2	1.4	1.6	Acid-base extract.	**144**	58

127	Bn	2	1.4	1.6	Column chrom. alone	**145**	72
128	2-cyano ethyl	2	1.5	1.5	Acid-base extract.	**146**	73
129	2-cyano ethyl	1	1.4	1.4	Acid-base extract.	**147**	81
133	NAP	2	1.2	1.2	Column chrom. alone	**148**	58

Table 7: *N*-alkylated model vinylogous amides prepared.

Two factors can be used explain the low yield of **148** (R = NAP). Firstly, this product was the least polar of the series and was difficult to separate from the non-polar by-products of PPh_3. Several purifications by the standard column chromatography procedure used were necessary which resulted in losses. Secondly, the low yield of **148** might be as a result of steric repulsion during the *S*-alkylation step in THF, which was only allowed to proceed for 19.5 h at rt. It is also true that the sulfur in **133**, for reasons explained earlier, is a little less nucleophilic than the sulfur in the nonbenzylic-type alkyl groups (Me, 2-cyanoethyl), which might slow down the reaction. This is therefore also valid for thiolactam **127** (R = Bn). However, in the case of **127**, we obtained a good yield (72%) of **145** by stirring for 17 h at rt during the *S*-alkylation step. Because the NAP group is bulkier than the Bn group, we suggest that this was the deciding problem. Usually in these reactions, a slight excess of thiolactam was used, compared to the bromide **105**. If the thiolactam is very UV-active, as is the case for **133**, its presence on TLC, even if it seems to be in significant

concentration, might *not* be an indication that the reaction is *incomplete*. In addition to this, bromide **105** was found to be only sparingly soluble in THF. This fact most certainly slowed down most of the *S*-alkylation reactions carried out in the project. Furthermore, for this reason, the absence of **105** on TLC might *not* necessarily mean that the reaction is *complete*. In short, the first step to form **148** was probably still incomplete and had to be stirred for a prolonged period of time at rt, or heated for a while to ensure completion.

The moderate yields of the other products (**125**, **128** and **129**) are due to unavoidable losses, which occurred during the acid-base extraction procedures. The best yields were obtained when 1.4 eq. of PPh_3 and NEt_3 was used in the sulfur extrusion steps.

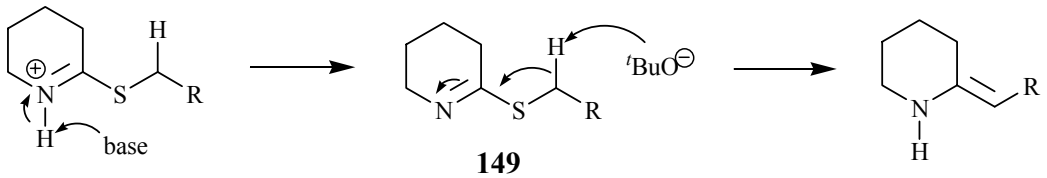
Enaminones are easily identified by their characteristic IR [104] and NMR spectra. As an example, the characterization data of the *N*-methyl protected pyrrolidinylidene analogue **143** is discussed here. The infrared spectrum shows two distinct carbonyl stretching frequencies, one for the enaminone conjugated C=O group (at ν_{max} 1611 cm^{-1}) and one for the quinazolinone conjugated C=O group (at ν_{max} 1676 cm^{-1}). The ^1H NMR spectrum of **143** clearly shows the presence of a vinyl proton, which appears as a singlet at δ_H 5.07. The methylene protons between the quinazolinone and central ketone groups [i.e. NCH_2C(O)] are observed as a highly deshielded singlet at δ_H 4.71. The aromatic signals are very similar, both in chemical shifts and in multiplicities, to that found in the parent compound, quinazolin-4(3*H*)-one. In the ^{13}C NMR spectrum, the enaminone carbonyl carbon is observed at δ_C 186.4, and the quinazolinone carbonyl carbon is considerably more shielded and observed at δ_C 161.2. The tertiary vinyl carbon (NC=*C*H) is observed at δ_C 85.6, whereas the quaternary vinyl carbon (N*C*=CH) is highly deshielded at δ_C 168.0. All the structures of the new enaminones prepared in this (and in the following) section were further confirmed by high resolution mass spectrometry, in which the molecular ions were observed as expected. Selected characterization data of the enaminones synthesized in this chapter will be further discussed in Chapter 6.

3.6. The preparation of the model *N*-unprotected vinylogous amides

Side-reactions are often prevalent when reactive functional groups, such as amines and alcohols, are left unprotected. We wanted to test the Eschenmoser reaction on a variety of model *N*-unprotected (or secondary) thiolactams for several reasons:

1. The synthesis can be shortened by two steps (protection and deprotection).
2. The natural product **1** contains a free secondary amine and similar derivatives are potentially more valuable for antimalarial research.
3. Interesting hydrogen bonding patterns might be observed if the amine is left unprotected. We also wanted to see how variations of ring size might influence the structures of the unprotected vinylogous amides (see Chapter 6).

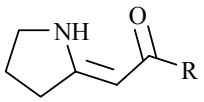
In an Eschenmoser reaction in which the nitrogen is left unprotected, an additional intermediate, thioimidate **149**, is formed (Scheme 31). As the thioiminium salt intermediate has two acidic protons, the one on nitrogen being more acidic, harsher conditions, e.g. elevated temperatures and a strong base such as KOBu^t, might be required to force the desired sulfur extrusion to occur [96].



149

Scheme 31: Mechanism of the Eschenmoser reaction to form secondary enaminones.

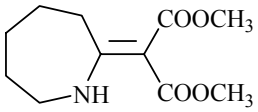
There are surprisingly few examples in the literature of Eschenmoser reactions involving *N*-unprotected thiolactams. The original Eschenmoser publication in 1971 [71] included the preparation of secondary pyrrolidinylidene enaminones **150**. Sulfur extrusion usually occurred rapidly by simply heating the thioiminium salt at 60 ºC in the presence of PPh_3, or by using the bases KOBu^t or $NaHCO_3$, or by using both a thiophile and a



150

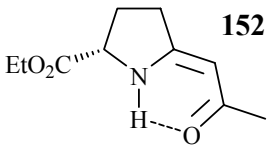
R = Ar, CH_3, $(CH_2)_2COOCH_3$, $OC(CH_3)_3$, etc.

base. It is not clear from this paper how substituent R (see **150** above) influenced the rate of the reaction. It seems that the reactions generally proceeded more easily, and in higher yields, when R = Ar or $OC(CH_3)_3$, and also when dimethyl bromomalonate was used as alkylating agent. The presence of these substituents probably facilitates α-deprotonation (to form thiirane **113**, Scheme 17), compared to when R = alkyl, which promotes the reaction. To synthesize the methyl derivative (**150**, R = Me), Eschenmoser used $KOBu^t$ and refluxing benzene as solvent in the sulfur extrusion step. In our case, we want to prepare derivatives where R = CH_2Q (Q = quinazolinone), i.e. an alkyl group. Eschenmoser's group also prepared a seven-membered cyclic enaminone **151** in good yield (90% crude yield after column chromatography) from thiocaprolactam and dimethyl bromomalonate.



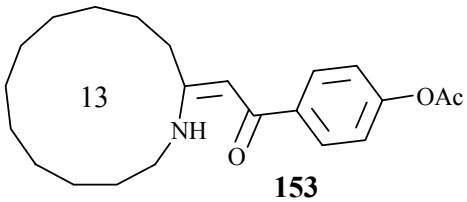
151

More recently, an enantioselective synthesis of (−)-adalinine [105] included the Eschenmoser reaction to form secondary enaminone **152**. In this case, the authors found it necessary to use harsh conditions, i.e. 4 eq. of both PPh_3 and 1-methylpiperidine (i.e. a slightly stronger base than triethylamine) combined with refluxing in benzene for 24 h, to drive the reaction to completion. Note that an intramolecular hydrogen bond constrains secondary vinylogous amide **152** to the *Z*-configuration. This structural phenomenon is proved and discussed in Chapter 6.

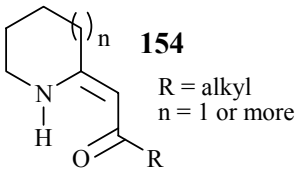


152

In 1983, Yamamoto's group [106] published a new method for the preparation of enaminones from enol silyl ethers and oxime mesylates using organoaluminium reagents. This paper included the preparation of a cyclic 13-membered secondary enaminone **153**.



153



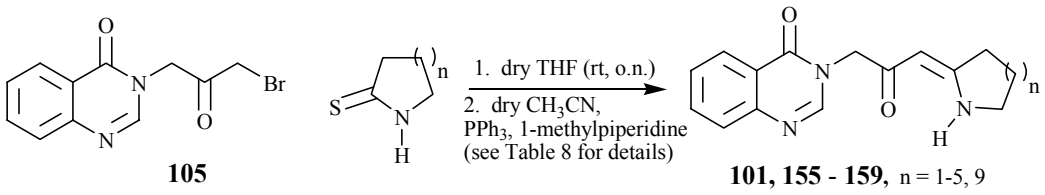
154

R = alkyl
n = 1 or more

It can be seen that few, if any, examples exist in the literature of the preparation using Eschenmoser's reaction of cyclic secondary enaminones **154**, which contain 6-

membered or larger rings, and where R = an alkyl group. This further fuelled our interest in synthesizing and characterizing (see Chapter 6) a variety of compounds based on **154**.

Our synthesis of the secondary enaminones **101** and **155-159**, all of which are dehydro-derivatives of deoxyfebrifugine **14** (Section 1.4.1., p. 13), is described in Scheme 32 and Table 8.



105 **101, 155 - 159,** n = 1-5, 9

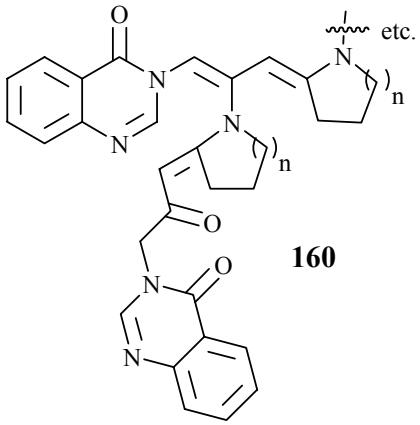
Scheme 32: Synthesis of model secondary enaminones.

As seen from Table 8, all the desired compounds were isolated, albeit in low to moderate yields. We opted to use 1-methylpiperidine, which is a stronger base than NEt_3 (used for synthesizing the *N*-alkyl derivatives) owing to its cyclic nature. On one occasion for the synthesis of **101**, we used NEt_3 and obtained a reduced yield of **101**, compared to when 1-methylpiperidine was used as the base. As seen from Table 8, by changing the number of equivalents of thiophile and base, the yields were not profoundly affected. Unfortunately, the by-products were not cleanly isolable and therefore not characterized. It was evident from TLC, however, that most of the unwanted by-products were probably either highly polar and/or products of high molecular weight (e.g. polymers). Intense spots of UV-active products were observed by TLC, which were not eluted by column chromatography using the polar eluents employed for isolating the secondary enaminone products.

Thiolactam Used	**PPh_3 equiv.**	**N-Me-piperidine equiv.**	**Product**	**n**	**Yield (%)**
130	2.5	2.5	**101**	2	64

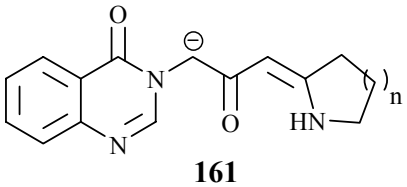
131	4.6	4.6	**155**	1	59
134	3.0	3.4	**156**	3	55
140	1.2	1.3	**157**	4	58
141	1.2	1.3	**158**	5	50
142	1.2	1.2	**159**	9	37

Table 8: Secondary model vinylogous amides prepared.



160

One might expect some intermolecular reactions to occur under the basic conditions required for these reactions to proceed. For example, nucleophilic attack of the unprotected nitrogen of one molecule onto the central 2′-ketone group of another might result in the formation of poly-enamines **160**. It should be noted that the protons at position 1′ of the side-chain (between the Q nitrogen and the central ketone) are acidic, owing to the inductive electron-withdrawing effects on either side of these protons. Under strongly basic conditions, such as the presence of 1-methylpiperidine, this 1′ centre can be deprotonated to give **161**, which might also cause by-products to form by aldol-type intermolecular reactions. Furthermore, if a trace of moisture is present in the reaction mixture, basic hydrolysis of, e.g. the Q core, might occur.



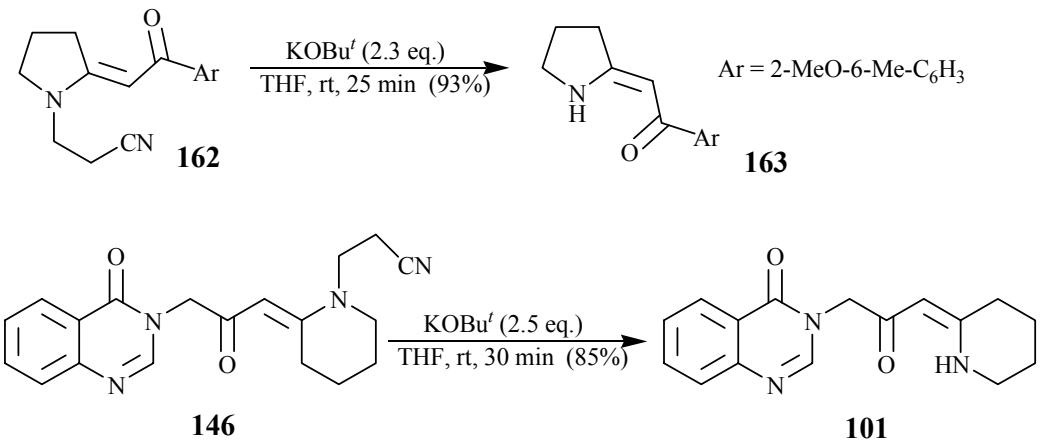
161

We were pleased to be able to isolate products **101** and **155-159** in sufficient quantities for characterization and synthetic purposes. The characterization data are discussed in Chapter 6.

The very low yield (37%) of **159** might be attributed to the increased steric bulk of 13-membered thiolactam **142**, in which case it could be beneficial to extend the reaction time during the *S*-alkylation step, and/or to use a larger equivalent of thiophile and base. Alternatively, low product recovery simply occurred by chance as this reaction was not optimized. It is recommended that the *S*-alkylation step be prolonged, even heated, in order to ensure maximum salt formation at this stage. The second sulfur extrusion step is more problematic. In an attempt to minimize side-reactions, we carried this reaction out at 0 ºC for 10 min. initially after adding the base (during which time the reaction had not yet gone to completion) before warming to rt. It might be useful to see whether this reaction will proceed at even lower temperatures by leaving it stirring for a long period of time. Another option is to attempt the sulfur extrusion in the absence of base, e.g. by refluxing in xylene. Owing to time constraints, we decided to stick to our conditions and this method was consequently not optimized any further. The characterization data of the secondary enaminones prepared in this section is discussed in Chapter 6.

3.7. Deprotection of 3-{(2*E*)-2-[2-oxo-3-(4-oxoquinazolin-3(4*H*)-yl)propylidene]piperidin-1-yl}propanenitrile

As mentioned before, the use of the 2-cyanoethyl group as enaminone nitrogen protecting group was previously demonstrated in our laboratory by Michael and Parsons [79]. Base-induced elimination of acrylonitrile from vinylogous amide **162**, using 2.3 eq. KOBu^t and stirring in THF for 25 min at rt, afforded secondary enaminone **163** in 93% yield (Scheme 33). Under similar conditions, we found that **146** could be deprotected to afford **101** in 85% yield (Scheme 33). For the synthesis of deoxyfebrifugine **14**, we therefore successfully prepared key intermediate **101** *via* two routes, i.e. the direct Eschenmoser reaction between piperidine-2-thione and bromide **105**, or by first synthesizing 2-cyanoethyl protected enaminone **146** followed by *N*-deprotection.

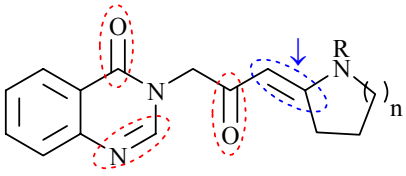


Scheme 33: The use of *N*-(2-cyanoethyl) as a protecting group of enaminones.

3.8. Chemoselective C=C reduction of the model vinylogous amides

3.8.1. Background

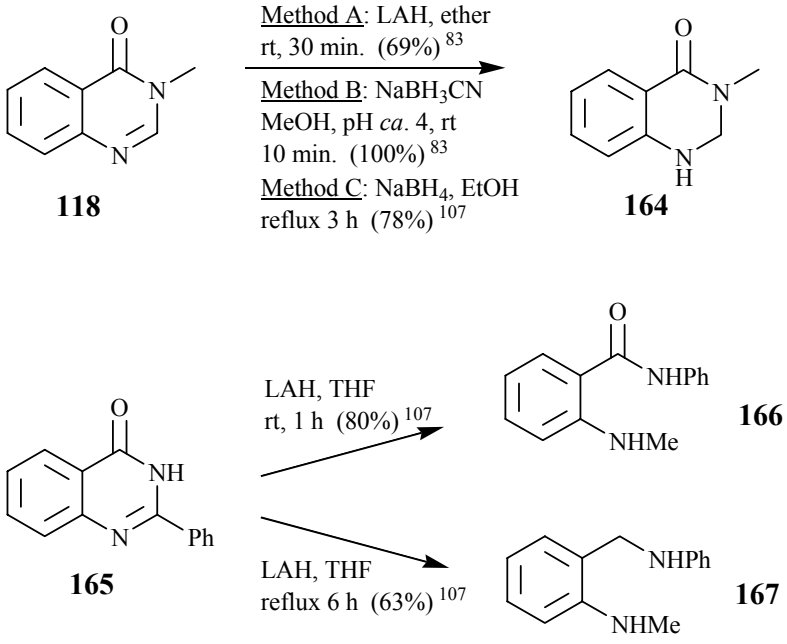
With the required model vinylogous amides in hand, we turned our attention to the next step in our proposed synthesis of model analogues of **1**, i.e. the chemoselective reduction of the enaminone C=C bond. Many methods exist for this purpose, but we were limited by the side-reactions which might occur when using certain reducing agents. Encircled here are those groups, most sensitive to reducing agents, in our model compounds. Our aim is to reduce selectively the C=C double bond of the enaminone indicated in blue.



One of the most popular reducing agents used over the years in our laboratory for this purpose is lithium aluminium hydride (LAH), as illustrated in Section 2.1., Figure 15. However, it is well known that LAH can reduce the imine bond in quinazolinone. In a related project conducted in our laboratory [83], it was found that when model quinazolinone **118** was stirred in the presence of 1 eq. LAH in ether for 30 min. at rt, approximately 69% of **118** was reduced to amine **164** (Scheme 34) and all of the unreduced starting material was recovered. Furthermore, Pakrashi and Chakravarty [107] found that LAH converted 3-phenyl-4-quinazolinone **165** into either *o*-

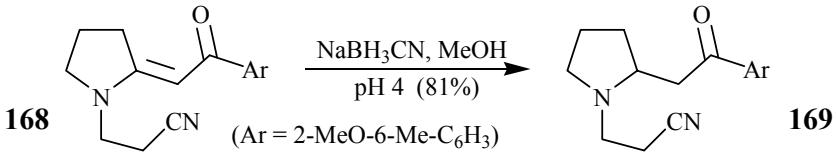
methylaminobenzanilide **166** or into *o*-methylamino-*N*-phenylbenzylamine **167**, depending on the reaction conditions employed (Scheme 34).

It is therefore clear that, should we opt to use LAH in our reaction, we not only risk reducing out the imine bond in the quinazolinone moiety, but reductive cleavage of the 2,3 bond (in addition to amide carbonyl reduction), which would result partial decomposition, cannot be ruled out.



Scheme 34: Reactions of quinazolinone derivatives with various reducing agents.

We next considered another reductant, $NaBH_3CN$, which was used successfully before in our laboratory, e.g. to reduce **168** to afford **169** [79]:



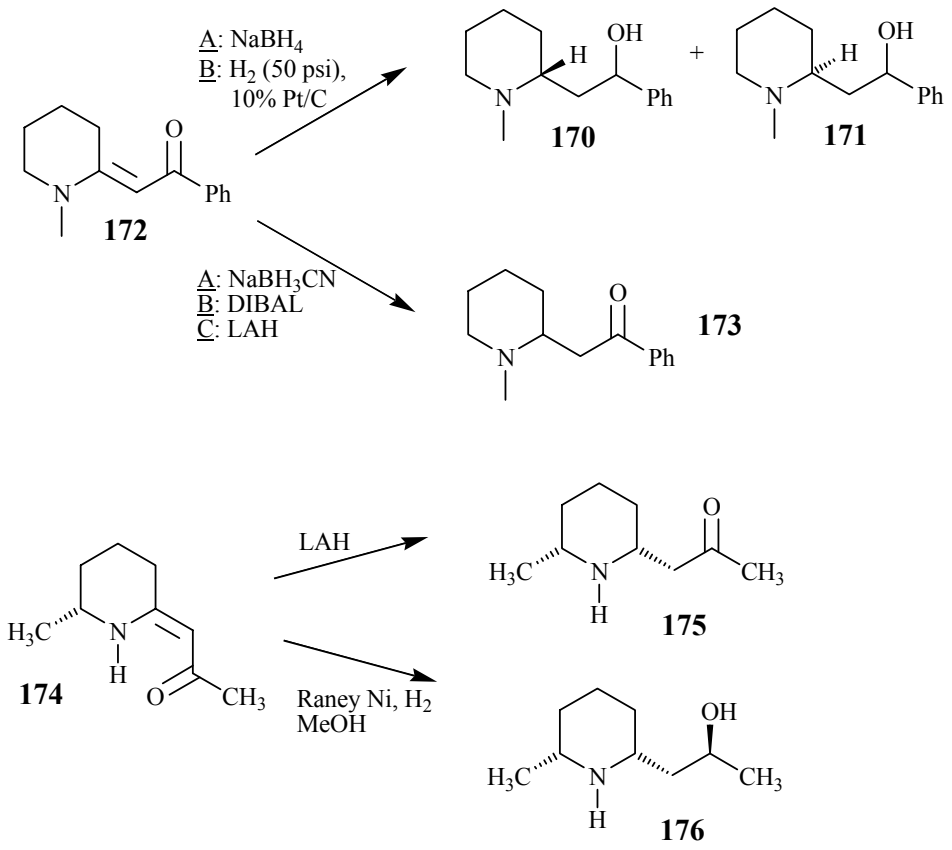
However, it was found recently in our laboratory [83] that, similarly to LAH, $NaBH_3CN$ reduced out the imine bond in quinazolinone **118** to afford **164** in 100% yield (see Scheme 34). Furthermore, $NaBH_4$ is also less suitable for our purposes as Pakrashi

and Chakravarty [107] observed that, under reflux conditions for 3 h in EtOH, $NaBH_4$ reduced **118** to **165** in 78% yield (Scheme 34).

In 1996, Ghiaci and Adibi [108] published the syntheses of (±)-sedamine **170** and (±)-allosedamine **171** based on an Eschenmoser reaction followed by chemoselective reduction of enaminone intermediate **172** (Scheme 35). Both the C=C bond and the carbonyl group were reduced when using $NaBH_4$, or hydrogen on Pt/C in trifluoroacetic acid. Selective reduction of the C=C bond in **172** to β-aminoketone **173** occurred when $NaBH_3CN$, DIBAL or LAH were used. However, as mentioned already, the latter reductants might react with the quinazolinone moiety in our model compounds (see above).

In another example from a communication in 2001, Lhommet's group [109] found that reduction of enaminone **174** using LAH afforded (–)-pinidinone **175** (Scheme 35) with high diastereoselectivity. Hydrogenation over Raney nickel in MeOH, however, caused reduction both of the C=C bond and the carbonyl group to yield (–)-epipinidinol **176**.

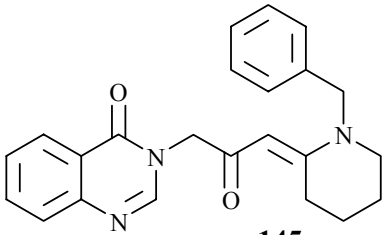
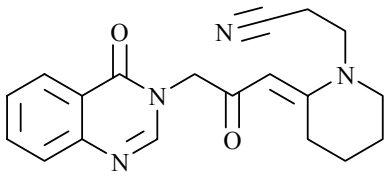
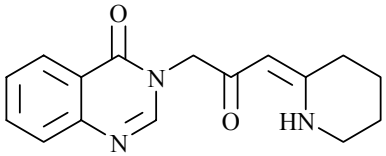
It is clear from the examples given here that the reduction of enaminones is not always a predictable reaction, especially when dealing with complex molecules which contain additional centres sensitive to reducing agents, such as our model compounds. Our only option was to experiment by trial-and-error, using a range of reducing agents and reaction conditions, as seen in the following sections.

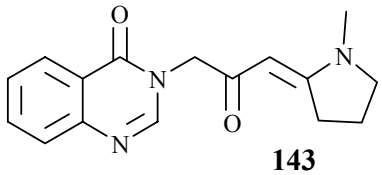
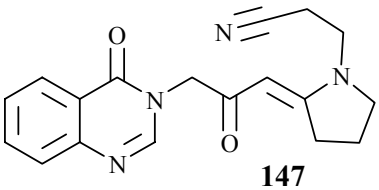
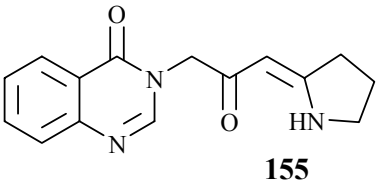


Scheme 35: Examples of the reduction of enaminones.

3.8.2. Failed attempts at the chemoselective reduction of various model enaminones

It will become apparent later that the chemoselective reduction of the enaminone C=C bond proved to be an obstacle in this project. During our model studies, we tested numerous reducing agents on the various enaminones synthesized in the previous section. Owing to time constraints, and because this project was synthetic target driven, we often did not attempt to characterize by-products or undesired products fully during these reduction trials. Furthermore, owing to the polar nature of most of these products, they were often very difficult to purify and to separate from each other by conventional column chromatography techniques. The results of the failed trial experiments are summarized in Table 9. Comments are based on the evidence obtained from NMR spectroscopy, mostly of the crude or partially purified products.

Starting material (s.m.)	Reaction conditions [mass of starting material, reagent, solvent, temperature, time]	Comments
 **145**	0.26 g s.m., LAH (1 eq.), THF, rt, 30 min.	major product (0.19 g and some impurities) shows evidence of both enaminone C=C, and quinazolinone N=C reduction
	97 mg s.m., LAH (1 eq.), THF, rt, 15 min	major product (81 mg containing trace impurities; could not be purified further) is the desired product (by NMR and mass spectroscopy); predominantly only enaminone C=C reduced
 **146**	89 mg s.m., $NaBH_3CN$ (1 eq.), MeOH and a catalytic amount of HCl (pH *ca.* 4), rt, 1 h	isolated product (*ca*. 30 mg) shows evidence of over-reduction and decomposition (the piperidyl moiety is absent)
 **101**	17 mg s.m., LAH (1 eq.), THF, rt, 20 min	mostly starting material (12 mg) recovered
	60 mg s.m., $NaBH_3CN$ (1 eq.), MeOH and cat. HCl (pH *ca*. 4), rt, 1 h	crude product showed only evidence of overreduction (i.e. reduction of quinazolinone N=C and/or C=O)

	12 mg s.m., $NaBH(OAc)_3$ (1.1 eq.), AcOH:THF (3:1), 0 ºC, 1 h	crude product shows evidence of reduction of quinazolinone moiety and decomposition of s.m. (mostly aromatic peaks and little signs of the piperidyl moiety)
 **143**	0.30 g s.m., fresh LAH (1 eq.), Et_2O, rt, 15 min.	crude product shows that the quinazolinone N=C *and* C=O were probably reduced, together with the enaminone C=C; the central ketone goup still showed up on ^{13}C NMR (δ 205)
	100 mg s.m., PtO_2 (7 mg), H_2 (1.5 atm), AcOH, rt, 72 h	s.m. (35 mg including some impurities) and over-reduced (quinazolinone) mixture of products (7 mg) isolated
 **147**	108 mg s.m., LAH (1.1 eq.), THF, 0 ºC, 10 min	Inseparable mixture of many products; major (43 mg) and minor (12 mg) fractions (isolated by column chromatography, 1% NH_3-EtOAc) exhibit peaks reminiscent of quinazolinone C=N and/or C=O reduction
 **155**	20 mg s.m., $NaBH(OAc)_3$ (1.1 eq.), AcOH:THF (3:1), 0 ºC, 30 min	crude product spectrum shows mostly s.m. and some evidence of quinazolinone reduction

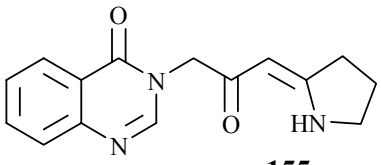
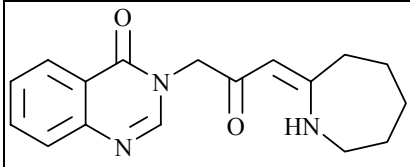
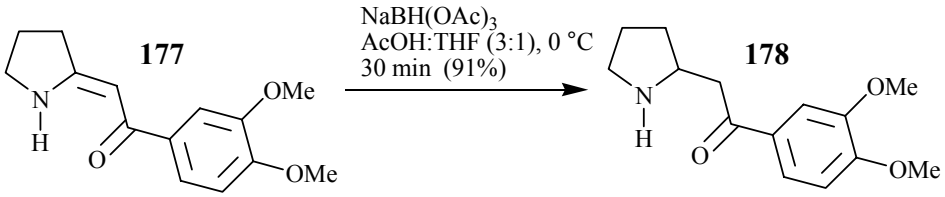
 **155**	crude product from the above exp. was subjected to the same conditions as above, but at 0 ºC for 2 h	quinazolinone C=N reduction
	50 mg s.m., $PdCl_2$ (20 mg of 59%), MeOH, H_2 (2 atm), rt, 5.5 h	crude NMR: quinazolinone C=N was reduced in the majority of material; the minor component is s.m.
	58 mg s.m., $NaBH_3CN$ (19 mg), MeOH and cat. HCl, rt, 19 h	Crude NMR shows mostly aromatic peaks and little of the pyrrolidine moiety remained
	190 mg s.m., PtO_2 (8 mg), H_2 (1.2 atm), AcOH, rt, 23 h	only s.m. recovered
	90 mg s.m., PtO_2 (7 mg), H_2 (1.5 atm), AcOH, rt, 3 days	inseparable mixture of 2 products; possibly the desired product and its over-reduced (C=N of quinazolinone) derivative
	80 mg s.m., PtO_2 (13 mg), H_2 (2 atm), MeOH and cat. HCl, rt, 18 h	evidence of quinazolinone reduction; no signs of the desired product
	0.23 g s.m., Zn dust (0.26 g), AcOH, rt, 1h, then reflux o.n.	no reaction
 **156**	110 mg s.m., PtO_2 (7.5 mg), H_2 (2 atm), AcOH, rt , 48 h	reduction of the quinazolinone moiety (C=N) and traces of s.m.
	70 mg s.m., $NaBH_3CN$ (1.1 eq), MeOH, rt, 30 min	Only s.m. recovered

Table 9: Results of the various reduction trials conducted on the model enaminones.

Not too surprisingly, the major crude product formed by reduction of *N*-benzyl derivative **145** with LAH, at rt for 30 min, was the undesired quinazoline, i.e. the C=N bond in the quinazolinone moiety was also reduced. When the reaction time was shortened to 15 min, the desired β-aminoketone was obtained as major product, but it was contaminated by trace impurities which could not be removed by re-purification. This was therefore not a sufficiently suitable reductant, especially seeing that when LAH was used in attempts to reduce the pyrrolidinylidene analogues **143** and **147** (under the same conditions) the crude products were in each case over-reduced. It is a well-known observation in the research done at Wits, that the reaction time, the temperature and the quantity of LAH used in these reductions, are all critical determinants of selectivity [78]. Sometimes the use of slightly aged, less active LAH may lead to increased chemoselectivity. This could explain the ambiguities in our results when LAH was used as reductant, albeit that the loss of chemoselectivity in the reductions conducted in this project was usually due to reduction of the *quinazolinone imine* group, not that of the *enaminone ketone* group.

In all but one case [i.e. for azepanylidene derivative **156** when only reactant (starting material, s.m.) was recovered], when $NaBH_3CN$ was used in acidic MeOH, the starting materials were over-reduced and/or decomposed. The quinazolinyl moiety is sensitive under these conditions as illustrated before (Scheme 34). The surprising outcome (no reaction) when **156** was exposed to this reductant cannot be explained.

We were particularly interested in finding conditions to reduce the pyrrolidinylidene derivatives, especially the secondary enaminone **155** to the five-membered cyclic analogues of **14**, as few of these have been synthesized and the effects of ring size on the antimalarial properties of such derivatives of **1** have not been clarified. We therefore set up numerous small-scale experiments, all of which were discouraging as seen in Table 9. Couture *et al*. [110] published in 1996 the chemoselective reduction, using sodium triacetoxyborohydride, of secondary 5-membered cyclic enaminone **177** to form ruspolinone **178**.



As seen from Table 9, our attempts using these reductive conditions on enaminones **101** and **155**, both failed. It seems that $NaBH(OAc)_3$ is more reactive towards the quinazolinyl imine group than towards the enaminone C=C bond.

Another popular method used in our laboratory (see Figure 15, p. 52) for the selective C=C reduction is the use of catalytic hydrogenation over PtO_2 (Adams catalyst). This was a promising option for us, as it was recently observed in a control experiment in our laboratory that model quinazolinone **118** (see Scheme 34) was completely resistant to hydrogenation in the presence of PtO_2 and HCl in MeOH [83]. The use of acidic conditions is explained in section 3.8.4. We assumed that, when using a weaker acid, AcOH, the quinazolinone moiety should be even less sensitive to the reducing conditions. However, as seen from Table 9, both pyrrolidinylidene analogues **143** and **155**, and the seven-membered cyclic analogue **156**, were either untouched by, or quinazolinone imine reduced under, these conditions. This is surprising and confusing, as we observed no or very little imine reduction in the piperidine analogues (see next section). The resistance of the exocyclic double bond in the pyrrolidinylidene analogues to reduction is once again clearly illustrated in these examples. It will be seen in the next section that no such resistance was observed in the piperidinylidene analogues. This is an important topic which will be thoroughly discussed in Chapter 6.

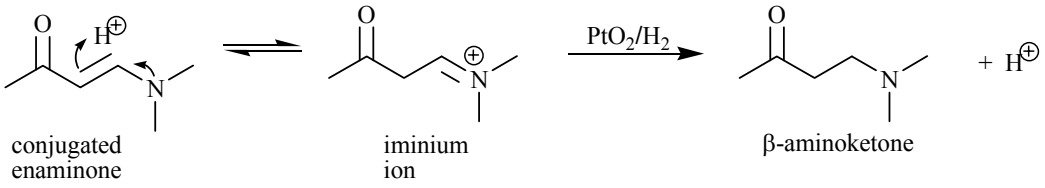
Finally, we found that hydrogenation with 10% Pd/C in EtOH did not reduce out the C=C bond in the *N*-alkyl piperidinylidene analogue **145** (see this result later in Section 3.8.4., the deprotection of **145**), but that hydrogenation with $PdCl_2$ in MeOH caused the reduction once again of the imine bond in **155** (Table 9).

3.8.3. Reduction of the *N*-alkylated model enaminones

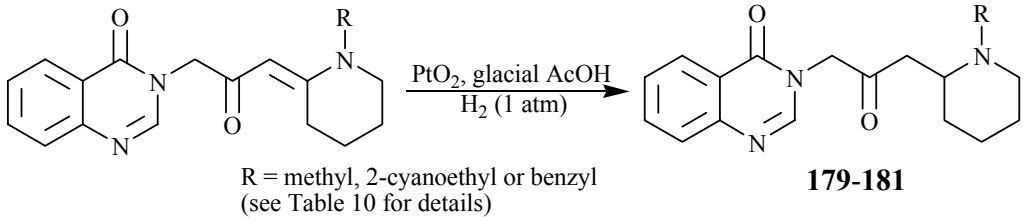
As opposed to the pyrrolidinylidene derivatives mentioned in the previous section, the *N*-alkylated piperidinylidene derivatives were easily and selectively reduced to give the desired β-aminoketones **179-181** in good yields (see Scheme 36 and Table 10).

Success was achieved when hydrogenating over PtO_2 in glacial AcOH and stirring under 1 atm hydrogen gas for 30 min to a couple of days.

The role of the acid (AcOH) is to protonate the stable vinylogous amide thereby destroying conjugation in the enaminone group and rendering it more reactive. This facilitates hydrogenation to give the β-aminoketone. It is thought that the resulting iminium ion itself is reduced:



As the *N*-alkylated enaminone is rather basic, a weak acid such as AcOH is appropriate to catalyze the reaction. However, as seen in section 3.8.5. for the less basic secondary enaminone **101**, it might be advantageous to use a strong acid (e.g. HCl) to drive the equilibrium towards the formation of the iminium ion in some cases. It was not established conclusively, however, whether use of a strong acid is essential for the hydrogenation of **101** to occur (see section 3.8.5.).



Scheme 36: Reduction of model *N*-alkylated enaminones.

The reaction times are also given in Table 10. It can be seen that the lowest yield was that of the *N*-Bn analogue **180**, obtained after stirring for 30 min under the same hydrogenation conditions as for **179** and **181**, obtained in higher yields after allowing the reaction to continue for 48 h in both cases. It is possible, but doubtful (see next section), that a fraction of **180** was Bn-deprotected during this procedure, which resulted in a lower yield of the protected product (the deprotected product, **14**, is not easily isolable by column chromatography, see section 3.8.5.). No starting material

was recovered in the preparation of **180**. In contrast, in the synthesis of **181**, unreacted starting material (10%) was recovered (see experimental, Section 7.6.3.), even after leaving the reaction to continue for 48 h. It is worthwhile noting that no signs of quinazolinone imine reduction were observed in any of these reactions, even with prolonged reaction times.

Enaminone	R	Time	Product	Yield (%)
144	Me	48 h	**179**	81
145	Bn	30 min	**180**	70
146	2-cyanoethyl	48 h	**181**	86

Table 10: Synthesis of **179-181**.

The characterization data of **179-181** indicate clearly that the desired compounds were obtained. The reduction of the enaminone C=C bond destroys conjugation in this group, which is clear from the NMR- and IR spectral data. The most important characterization data is summarized in Table 11.

In the ^{1}H NMR spectra of **179-181**, the singlet peak of the vinyl proton (H3′) in the corresponding enaminones disappeared. Furthermore, a stereogenic centre results at C2″ of the piperidine ring in **179-181**, which causes increased proton-proton coupling and a more complex spectrum. The diastereotopic protons on C1′ (i.e. H1′), α to both the central ketone and the quinazolinone N-3, are now non-equivalent in **179-181**, as opposed to in **144-146**. Still highly deshielded (see Table 11), these protons now appear as two doublet signals in the ^{1}H NMR spectra of both **179** and **180**, with characteristic geminal coupling constants (*J* 17.5 and 17.4, respectively, for **179** and **180**). However, intriguingly, a singlet is still observed for H1′ in the ^{1}H NMR spectrum of the *N*-(2-cyanoethyl) analogue **181**.

Further evidence that we achieved the desired (chemoselectively reduced) outcome is found in the ^{1}H NMR spectroscopic peaks of the imine hydrogens (H-2) in the quinazolinone moieties of **179-181**. These protons are observed as singlets at the expected chemical shifts, i.e. the imine bonds were not reduced.

Furthermore, the loss of conjugation on C=C reduction of enaminones **144-146** is also evident in the ^{13}C NMR chemical shifts, together with the IR peaks, observed for the central carbonyl group (C2′=O) of **179-181**. The δ_C NMR chemical shifts for this group increased to 201-202 ppm, and the IR ν_{max} increased to a value characteristic for an unconjugated ketone group, i.e. 1729 cm^{-1}. When looking at the remarkable similarities, especially in the IR spectra of **179-181**, there can be no doubt that these compounds are structurally very similar.

The ^{13}C NMR chemical shifts, together with the IR peaks, observed for the quinazolinyl carbonyl group (C4=O) of **179-181** are unchanged compared to those observed for the enaminone precursors **144-146**. This indicates that this conjugated carbonyl group was also unaffected by the Pt hydrogenation conditions used.

Compound	δ_H (H1′) (ppm)	Multiplicity (H1′)	δ_H (H2) ppm	δ_C (C4=O) ppm	δ_C (C2′=O) ppm	IR: ν_{max} (C4=O) cm^{-1}	IR: ν_{max} (C2′=O) cm^{-1}
179	4.80 and 4.85 (J = 17.5 Hz)	2 × d	7.88	160.9	201.3	1677	1729
180	4.70 and 4.61 (J = 17.4 Hz)	2 × d	7.79	160.9	201.7	1677	1729
181	4.82	S	7.95	162.3	201.6	1677	1729

Table 11: Conclusive spectroscopic evidence for compounds **179-181**.

3.8.4. Deprotection attempts on compounds 180 and 181

With the *N*-Bn (**180**) and *N*-(2-cyanoethyl) (**181**) models in hand, we next wanted to see whether these alkyl groups might be useful as amino protecting groups in the synthesis of **1** and derivatives. The results of the trial deprotection experiments conducted on **180** and **181** are summarized in Table 12.

The results obtained during the deprotection attempts on **180** were, similarly to those obtained for the attempted reductions in section 3.8.2., both disappointing and puzzling. The most common method for amino *N*-benzyl deprotection is hydrogenation over a Pd catalyst. As it was obvious from the previous section that *N*-benzyl deprotection was unlikely to occur rapidly when using PtO_2, we opted for a variety of Pd catalysts in our deprotection attempts. Standard hydrogenation conditions over 10% Pd/C in EtOH resulted in no reaction. It is well-known that benzylamines are often very slowly cleaved under such conditions [111]. In an attempt to activate the benzylic position on **180**, we added a catalytic amount of perchloric acid and then repeated the hydrogenation under 3 atm H_2. In this case, even after 72 h, the crude ^{1}H NMR spectrum showed the presence of only starting material and possibly some of the quinazoline product (which is formed when the imine bond is reduced). The same result was obtained when Pearlman's catalyst [$Pd(OH)_2$] was used. It would seem, therefore, that Pd is more likely than PtO_2 to lead to the reduction of the imine bond in the quinazolinone moiety, especially under extended or harsher hydrogenation conditions. When the more reactive $PdCl_2$ was used in conjunction with a catalytic amount of HCl, a complex mixture of inseparable products resulted. One of the crude products did appear to be *N*-debenzylated, but this product was not the desired compound, i.e. (±)-deoxyfebrifugine **14**.

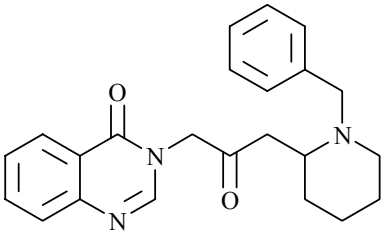
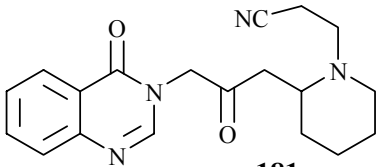
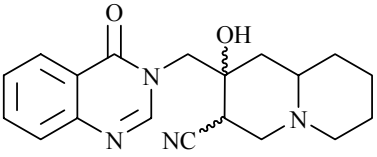
Starting material (s.m.)	Reaction conditions [mass of starting material, reagent, solvent, temperature, time]	Comments
 **180**	A. 0.19 g s.m., 10% Pd/C (30 mg), H_2 (1 atm), EtOH, 22 h; B. 71 mg s.m., 10% Pd/C (25 mg) and 1 drop 60% $HClO_4$, H_2 (3 atm), MeOH, 72 h	A. No reaction B. Only s.m. and traces of decomposed material recovered
	70 mg s.m., 20% $Pd(OH)_2$ (20 mg), H_2 (1.5 atm), MeOH:CH_2Cl_2 (1:1), 21 h	Crude NMR shows mostly s.m. and traces of product from quinazolinone reduction
	60 mg s.m., 59% $PdCl_2$ (5 mg), H_2 (1.5 atm), MeOH and cat. HCl, o.n.	Crude NMR shows complex mixture of products; some debenzylation occurred, but not a clean reaction
 **181**	45 mg s.m., K-*t*-BuO (2.5 eq.), THF, 20 min	Crude product shows evidence of possible intramolecular cyclization to form:  **182**

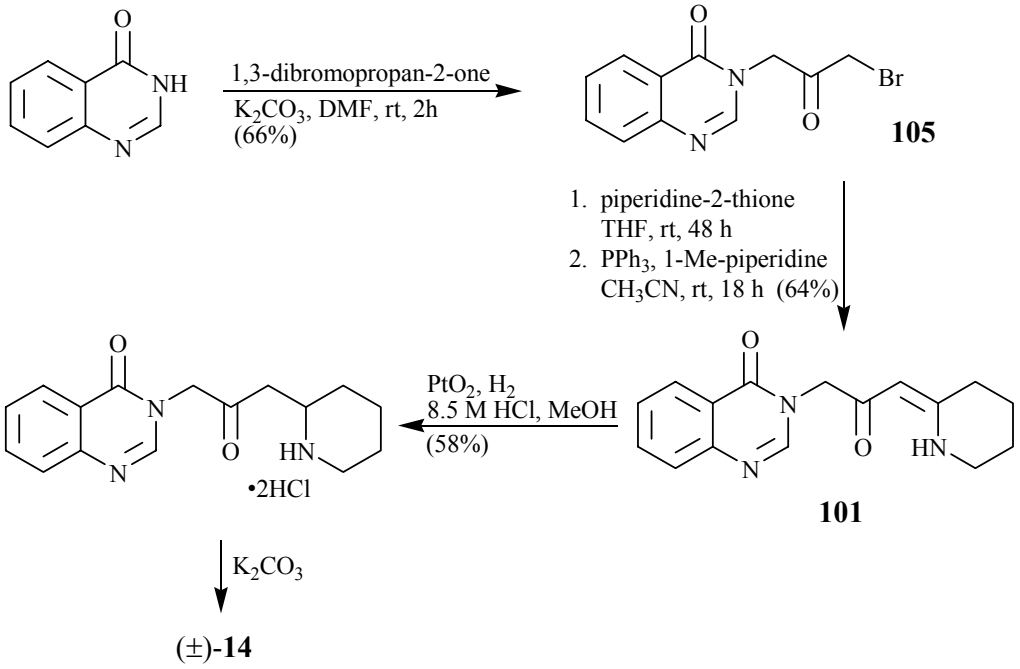
Table 12: Deprotection attempts on **180** and **182**.

We also wanted to test whether the *N*-(2-cyanoethyl) group was removable from **181** using our conditions for deprotecting enaminone **146** (see Scheme 33, p. 79). It was found that **181** possibly underwent intramolecular cyclization to give a mixture of diastereomers of alcohol **182** (Table 12) in the presence of KOBu^t. Deprotonation at the position α to the nitrile group likely resulted in nucleophilic attack onto the central carbonyl group to afford **182**. A ^{1}H NMR spectrum of the crude product (**182**) showed very little difference in the chemical shifts and multiplicities of the aromatic quinazolinone protons from that observed for precursor **181**. However, the NC*H*$_2$C(O) singlet signal at δ_H 4.82 was replaced by singlets at δ_H 4.96 and 4.67 (possibly corresponding to the two diastereomers of **182**) in the spectrum of **182**. Furthermore, owing to an increase in the number of stereogenic centres (together with the fact that this was a mixture of diastereomers) a significant increase in coupling was evident in the aliphatic region of the crude ^{1}H NMR spectrum of **182** (as compared to **181**), which was very crowded. Muliplets at *ca*. δ_H 2.3-2.8 and δ_H 1.4-1.9, which integrated roughly for the remaining fourteen protons, could account for the remaining protons in the quinolizidine ring of **182**. However, owing to the small scale of this experiment, the diastereomeric product (**182**) obtained here was not purified further to confirm its structure.

3.8.5. New synthesis of (±)-deoxyfebrifugine (14)

Fortunately, we were able to reduce secondary enaminone **101** chemoselectively, albeit in modest yield, to obtain important model compound (±)-deoxyfebrifugine **14**, the spectroscopic data of which agree with those reported by Takeuchi *et al*. [31] It should be noted that ^{13}C NMR spectroscopic data for **14** have not been reported before. Scheme 37 represents our expeditious synthesis of (±)-**14**. After numerous disappointments with other reducing agents and reaction conditions for the reduction of **101** (see section 3.8.2), we were successful by using conditions very similar (the hydrogenation catalyst being PtO_2) to those employed by Baker *et al*. in their second synthesis of **14** [66] from **101**, which they erroneously assigned the structure of **102** (see Section 1.7.2., p.). The only major differences are that we conducted this reaction under a hydrogen pressure of 3 atm for 6 h (as opposed to 1 atm in Baker's method

for an unspecified time), and that we used HCl of conc. 8.5 M (as opposed to 12 M in Baker's method). We followed Baker's work-up procedure, i.e. isolating the hydrochloride salt of **14** by triturating the crude product mixture with EtOH:MeOH (5:1) and thereby precipitating pure **14**•2HCl. The melting point observed for our product **14**•2HCl, 218-221 °C (decomp), was slightly lower than that observed by Baker's group [228-230 °C (decomp)], but we confirmed the correct structure by obtaining previously unpublished ^{1}H and ^{13}C NMR data of **14**•2HCl in D_2O (see experimental, Section 7.7.). Neutralization of the dihydrochloride salt using aqueous saturated K_2CO_3 solution, followed by repeated extraction of the free base with EtOAc afforded, after recrystallization from EtOAc, a quantitative yield of **14** from its hydrochloride salt. The optimized yield of **14** from **101** is 58%, i.e. slightly lower than the yield (66%) of **14**•2HCl (from **101**) obtained by Baker's group [66].



Scheme 37: New synthesis of (±)-**14**.

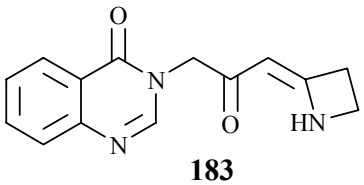
The structure of **14** was confirmed by conclusive spectroscopic evidence (see experimental, Section 7.7.). Similar to synthetic alkaloids **179** and **180** (see Table 11, section 3.8.3.), the deshielded diastereotopic protons H1′ in **14** appeared as two doublets at δ_H 4.84 and 4.73 (J = 17.4 Hz). Again, the chemoselectivity of the reduction used to synthesize **14** was proven by the presence of the quinazolinone

imine proton (H2), which appeared as a singlet at δ_H 7.89, and carbonyl carbons C4 and C2′, which appeared at δ_C 160.9 and 202.1, respectively. Furthermore, the IR absorptions confirmed that C4 was conjugated (ν_{max} 1677 cm^{-1}) and that C2′ was unconjugated (ν_{max} 1729 cm^{-1}), in exact agreement with the values obtained for compounds **179-181** (Table 11).

As can be seen from Scheme 37, this is indeed an easy and economical route to **14**. The overall yield from quinazolin-4(3*H*)-one is 24% over 5 steps. This promising result led us to test the generality of this route on more complex intermediates for the synthesis of **1** and its analogues (see Chapters 4 and 5). However, owing to time constraints, we did not test the final reduction step (employed here for the synthesis of **14**) on the 7-, 8-, 9- and 13-membered cyclic enaminone analogues (**156-159**) of **101** to prepare (±)-deoxyfebrifugine analogues of larger ring size. As mentioned in Section 3.8.2., we could not isolate the pyrrolidine analogue of **14** using these reduction conditions, as a mixture of complex products was obtained. Baker's group reported similar problems [66].

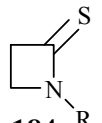
3.9. Synthetic studies towards the azetidinylidene enaminone analogue (183)

3.9.1. Background



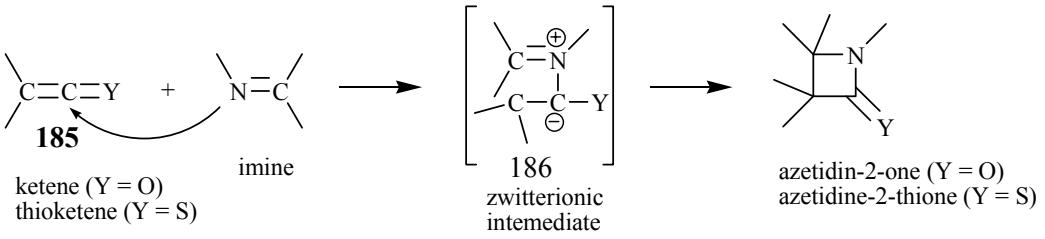
183

We were interested in synthesizing the azetidinylidene analogue (**183**) of the secondary enaminones, prepared in section 3.6., in order to compare its structure to the other members of this series (see also Chapter 6). Using our methodology, the preparation of **183** would require firstly the synthesis of a suitable azetidine-2-thione derivative **184** (R = any suitable substituent). Then we wanted to check whether this azetidine-2-thione might undergo the Eschenmoser reaction with **105**, as observed for the larger thiolactams, to give an enaminone intermediate useful for the synthesis of **183**.



184

The most common method for the preparation of both azetidine-2-ones and azetidin-2-thiones is the Staudinger reaction [112] (Scheme 38). This is theoretically a [2+2] cycloaddition reaction between a ketene or a thioketene (**185**) and an imine to produce the desired 4-membered cyclic structure of the azetidin-2-one or azetidine-2-thione.



Scheme 38: The Staudinger reaction.

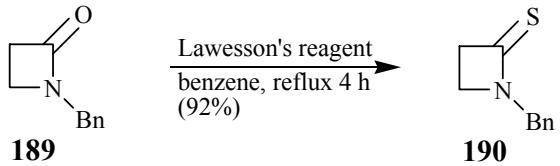
It is now accepted that the Staudinger reaction is not a concerted process, but that it occurs by a stepwise mechanism, after various theoretical studies on this reaction were published [113,114]. Thus, nucleophilic attack of the imine nitrogen onto the carbon attached to either the oxygen or the sulfur in the (thio)ketene results in the formation of a zwitterionic intermediate **186** (Scheme 38). Rate-determining electrocyclic closure then produces the azetidin-2-one or the azetidine-2-thione.

Although one of the above-mentioned theoretical studies [114] was based on the Staudinger reaction between thioketene and methylenimine to form azetidin-2-thione **187**, we were not certain that **187** was particularly stable or easily isolable. A Beilstein database search on structure **187** resulted in no entries found. Furthermore, no free *N*H azetidine-2-thiones were found on the same database.

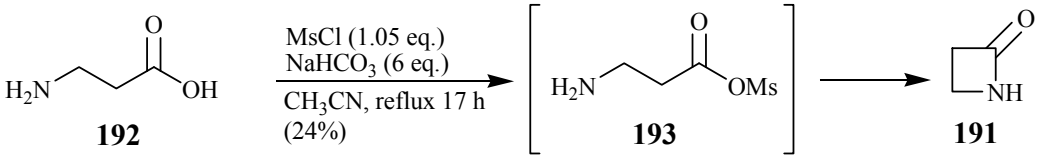
187

We assumed that *N*-substituted azetidine-2-thiones might be more stable and useful in synthesis. For this reason, we concentrated on finding routes to preparing azetidin-2-ones **188** (R = any suitable substituent), which can be thionated using Lawesson's reagent to form the corresponding thiolactams, e.g. Smith *et al*. published the conversion of 1-benzylazetidin-2-one **189** into its thiolactam **190** in 92% yield [115]:

188



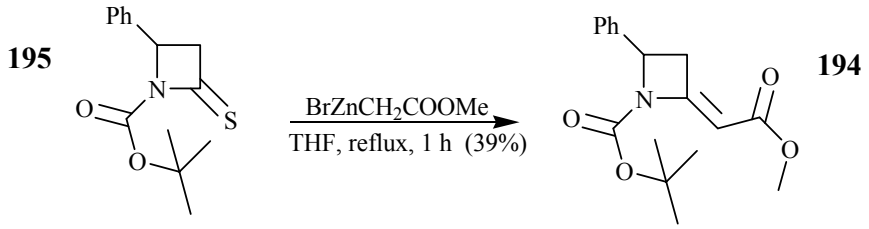
We opted not to use conventional Staudinger procedures to prepare our desired thiolactams, but to start from azetidin-2-one (**191**), a commercially available compound. We prepared **191** from β-alanine **192** using a previously published method by Loewe *et al.* [116] (Scheme 39). Mesylation of the carboxyl group in **192** (i.e. *in situ* generation of intermediate **193**) in the presence of a large excess of dry $NaHCO_3$, resulted in 1,4-cyclization to give **191** in 24% yield, as compared to the reported yield of 36%. Loewe explains that the low yield results from the very low solubility of the highly polar, zwitterionic form of **192** in CH_3CN. They carried this reaction out at 80 ºC for 4 h. Loewe also stressed the importance of using strictly anhydrous $NaHCO_3$ to optimize the yield. In an effort to improve on their yield, we decided to reflux the reaction mixture for 17 h. Our conditions were possibly too harsh and resulted in a lower yield! It is presumed that the product probably decomposed somewhat. As we found this to be an inexpensive, quick method to access **191**, we were not too concerned about the poor yield and decided to use these reaction conditions again later (see section 3.9.3.).



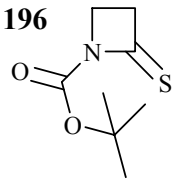
Scheme 39: Preparation of azetidin-2-one **191**.

3.9.2. Using *N*-Boc protection

With our starting material **191** in hand, we searched the literature to see which *N*-protecting group might be useful in our proposed synthesis. A search of the Beilstein database revealed the preparation of only one azetidinylidene enaminone, i.e. vinylogous carbamate **194**, by a thio-Reformatsky reaction [117]. The reaction of thiolactam **195**, the preparation of which is not reported in this paper, with methyl bromozincacetate (generated from activated Zn and methyl bromoacetate) produced **194** in 39% yield.

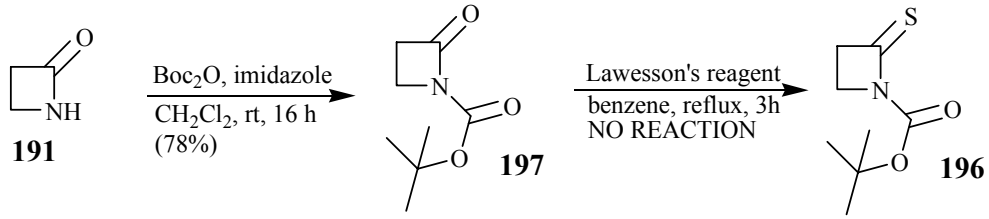


The preparation of reactive methyl bromozincacetate is facilitated by the stabilization of the α carbanion "CH_2^-" by the carboxylate group. This "enolate" can attack the thiocarbonyl group in **195**, which results in an intermediate thiol. Elimination of H_2S gives enaminone **194**. If we choose to follow this route towards vinylous amide **183**, we need to use 1-(*tert*-butyloxy)-azetidine-2-thione **196** instead of **195** above. The thio-Reformatsky reaction would then be between **196** and the Zn enolate of key bromide **105**. However, owing to the lower stability of Zn enolates formed from ketones, compared to those formed from esters, this step might prove to be problematic. Furthermore, the 4-Ph substituent in **195**, by drawing electron-density away from the thiocarbonyl function, probably activates carbon in the thiocarbonyl by increasing its electrophilicity. This is not the case in our desired unsubstituted, simple thiolactam **196**. Considering the fact that few reactions involving non-*C*-substituted azetidinones exist in the literature, and because the above reaction has not been attempted before using ketone enolates, curiosity led us to nevertheless attempt this route.



As seen from Scheme 40, Boc-protection of the nitrogen in **191** gave **197** in good yield. The ^{1}H NMR spectrum of **197** was as expected. The ring methylene protons appeared as two triplets at δ_H 3.56 and 2.98 (compared with δ_H 3.31 and 3.02 in **191**) with small coupling constant (*J* 5.1, compared to *J* 4.1 in **191**), characteristic for the eclipsed protons in azetidinones. The nine equivalent Boc protons appeared as an expected singlet at δ_H 1.53. The IR spectrum was also as expected for structure **197**, i.e. the Boc C=O absorption was observed at 1796 cm^{-1}, not unlikely for a highly deshielded C=O, and the lactam C=O absorption was observed at 1722 cm^{-1}. The increase in frequency for the lactam C=O absorption, compared to that observed for other lactams (e.g. 1630 cm^{-1} for *N*-NAP lactam **148** prepared in section 3.5.), is expected as a result of an increase in ring strain (4-membered ring in **197** *vs* 6-membered ring in **148**). The problem is that neither the lactam nor the Boc carbonyl

carbon was observed in the ^{13}C NMR spectrum, although the other carbons all appeared at the expected chemical shifts. The two methylene carbons were observed at δ_C 37.7 and 36.1, respectively. The quaternary Boc carbon was observed as a peak of reduced intensity, and far downfield (δ_C 83.2) as expected, owing to significant deshielding of this carbon by the neighbouring carbamate group. The three equivalent Boc carbons were observed as a singlet of high intensity at δ_C 28.0, which is realistic. Unfortunately, the molecular ion was not observed in the EI mass spectrum recorded of **197**. It was concluded that **197** might be unstable under EI conditions.



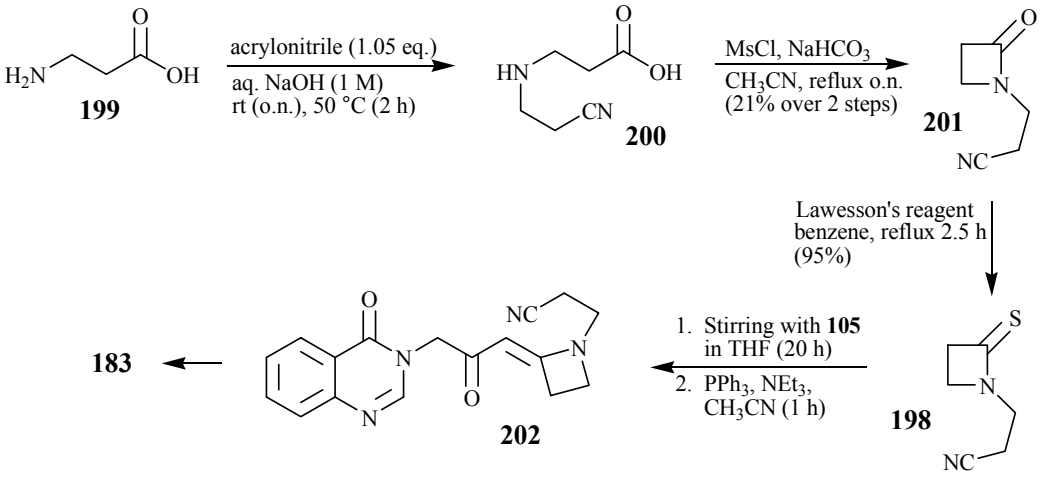
Scheme 40: Preparation of **197** and attempted preparation of **196**.

We decided to proceed to the next step, i.e. thionation of **197** to obtain thiolactam **196**. Using Lawesson's reagent in refluxing benzene, no reaction occurred after 3 h and only starting material was recovered after work-up. Thionation using these conditions is usually complete within 3 h, but it was clear that, in this case, no reaction whatsoever was taking place. This result created some doubt again over the structure of **197**. It is possible that the presence of the Boc group in **197** prevents thionation of the lactam carbonyl. Owing to time constraints and, in general, doubts regarding this approach to **183**, these reactions were not attempted again.

3.9.3. Using *N*-(2-cyanoethyl)-protection

As we successfully used the 2-cyanoethyl group as an enaminone nitrogen protecting group before (see section 3.7), we attempted the synthesis of enaminone **183** through the use of *N*-(2-cyanoethyl)-protection as shown in Scheme 41. It was thought that the Eschenmoser reaction between an *N*-alkyl azetidine-2-thione and bromide **105** might work to give us an azetidylidene enaminone.

Access to the required thiolactam, 3-(2-thioxoazetidin-1-yl)propanenitrile **198**, was gained from **199**. Following a published procedure [118], alkylation of **199** by a Michael reaction with acrylonitrile afforded crude nitrile **200**, which was cyclodehydrated to **201** using the same conditions mentioned above for the synthesis of **191**. The yield over two steps of **201** was low (21%). The ^{1}H NMR and IR spectral data was again as expected for an azetidin-2-one, and comparable to the other azetidin-2-ones synthesized in this section. Absolute confirmation of structure **201** was obtained by high-resolution mass spectroscopy (see experimental, Section 7.8.5.).



Scheme 40: Proposed synthesis of **183**, and the results obtained, using *N*-(2-cyanoethyl) protection.

Subsequent thionation of **201** using Lawesson's reagent afforded an excellent yield (95%) of the desired thiolactam **198**. In the IR spectrum of **198**, the C=O band observed at 1730 cm^{-1} for precursor lactam **201** was replaced by a strong band at 1506 cm^{-1}, indicating the presence of a thiocarbonyl group. In the ^{1}H NMR spectrum of **198**, the ring methylenes were again (see above for **196**) observed as triplets with a small coupling constant (J = 3.6 Hz). The ^{13}C NMR spectrum indicated the presence of a highly deshielded thiocarbonyl carbon at δ_C 202.7, and all other carbons were observed at the expected chemical shifts (see experimental, Section 7.8.6.). It should be noted that the NMR spectra obtained were those of a pure compound. However, EI mass spectroscopy indicated the presence of fragments of higher mass than the expected molecular ion, which was observed in 48% intensity. It was concluded that

thiolactam **198** was unstable under EI conditions. Furthermore, compound **198** was also found to be unstable upon storage in a vial, as a TLC run of this compound a few weeks after its synthesis revealed the presence of contaminants, not initially present in pure **198**.

The reaction between freshly prepared **198** and bromide **105**, under the same conditions as those used before for the other *N*-alkylated thiolactams (see section 3.5), failed to give any isolable tertiary enaminone **202**. The experimental observations, i.e. the formation of a yellow precipitate and the disappearance of starting materials, suggest that *S*-alkylation of **198** did indeed occur during the first step. However, undesired base-catalyzed side-reactions, e.g. ring-opening of the strained azetidine ring, occurred during the second step. A rapid colour change from yellow to red was observed after the addition of NEt_3, and several polar spots were observed on TLC in the region where we would expect to find the desired enaminone **202**. An inseparable mixture of products, unidentifiable by ^1H NMR spectroscopy, was obtained. As thiolactam **198** was itself found to be rather unstable, this result was not too surprising. Unfortunately, owing to time constraints, we could not repeat this reaction under different (milder) conditions and this experimental route was consequently discontinued.

3.10. Conclusion and future work

In this chapter, we devised a new and efficient synthetic route to the 3″-unsubstituted derivative [(±)-deoxyfebrifugine **14**] of the potent antimalarial alkaloid febrifugine **1**. Furthermore, we have successfully used our new synthetic strategy to prepare three *N*-alkylated alkaloid analogues of **14**. It is anticipated that this synthesis might be applicable for the preparation of other alkaloid analogues of **14**, especially those analogues in which the quinazolinone ring bears different substituents or is replaced by another heteroaromatic group, or by a different group altogether. Such analogues could be useful in important studies regarding the structure-antimalarial activity relationships in lead compounds **1** and **14**, as explained in Chapter 1.

A new and economical preparation was developed for the key bromide precursor **105** of the Eschenmoser reaction on which our synthetic strategy is based. The successful use of the 2-cyanoethyl group as a nitrogen protecting group for enaminones was again demonstrated in our laboratory. The 2-cyanoethyl group was, however, found to be prone to participating in side-reactions during the deprotection step when its use as a secondary amine protecting group was attempted. The Bn group was found to be a poor secondary amine protecting group for our intended synthetic strategy towards febrifugine **1**, as this group could not be removed by standard hydrogenation procedures during the model study discussed in this chapter.

Future work includes the chemoselective hydrogenation of the *N*-NAP protected vinylogous amide **148**, using the conditions developed in this chapter for the other *N*-alkylated analogues, followed by attempted removal of the NAP group to produce deoxyfebrifugine **14**. If this deprotection step is successful, it would again demonstrate the utility of the NAP group as an amine protecting group, and therefore also be a good protecting group to use in our synthetic approach towards febrifugine **1**. Furthermore, the chemoselective hydrogenation of the C=C bond in the enaminone groups of the model compounds synthesized in this chapter needs to be studied in more detail, as discussed again in Chapter 6.