CHAPTER 5

APPROACHES TOWARDS FEBRIFUGINE

5.1. Approach to febrifugine using a chiral auxiliary; Quirion methodology

5.1.1. Background

One strategy to achieve stereoselective synthesis involves the use of a chiral auxiliary group, which might direct by means of steric interactions the stereoselective introduction of a nearby group, in one of the intermediate molecules. If this approach is to be carried out successfully, the required absolute configuration in the chiral auxiliary needs to be determined such that the desired stereochemistry is obtained in the pivotal diastereoselective step. A good chiral auxiliary should initially be easily introduced and also easily removed at a latter stage. Both these additional synthetic steps should preferably proceed in high yield. Furthermore, the chiral auxiliary has to be stable and not participate in undesired side-reactions under the experimental conditions used in subsequent transformations during the synthesis. Obviously, racemization of the chiral centre in the auxiliary should not occur prior to application of the diastereoselective step.

We came across an easy and economical route devised by Quirion’s group in 1994\(^{134}\), which is based on the use of a chiral auxiliary to obtain enantiomerically pure 3-substituted piperidines and piperidin-2-ones. We were particularly interested in this route as the chiral auxiliary, phenylglycinol, serves both to control the stereoselective introduction of a variety of groups at C-3 of the piperidin-2-one ring, and as an electron-donating protecting group on the ring nitrogen. As seen in Chapter 4, it might be necessary to use such a protecting group in our proposed synthesis of febrifugine 1 and its derivatives.

For the proposed stereoselective synthesis of natural (+)\(^{-}\)-1, we needed to access a (3S)-oxygen substituted piperidin-2-one. Scheme 51(a) illustrates the applicable transformations used by Quirion’s group to synthesize one such piperidin-2-one. They
found that the most efficient preparation of starting lactam 233, in 45% yield, was the condensation of (R)-phenylglycinol with methyl 5-bromovalerate in the presence of 2 eq. DBU and refluxing ethanol as solvent.

Quirion found that deprotonation of C-3 and the hydroxyl group in 233 using 2.5 eq. of sec-BuLi, followed by the addition of 1 eq. Br₂, afforded after flash chromatography a 69% yield of 3-bromo-substituted derivative 234 in 90% diastereomeric excess. The model used to explain the diastereoselectivity of this reaction involves intramolecular chelation by Li of the auxiliary group oxygen and the enolate nitrogen (which is highly pyramidalized in amide enolates). This results both in an increase in the acidity of H-3 alpha to the carbonyl, and in facial differentiation during nucleophilic attack. The latter is a result of stereoelectronic control, owing to the position of the bulky phenyl group relative to the incoming nucleophile, as demonstrated here:

The major product obtained when using (R)-phenylglycinol is therefore the (3S)-bromopiperidin-2-one as shown in Scheme 51. Introduction of the benzyloxy group at C-3 of (S)-234 was achieved by S_N2-substitution of the bromide by the benzyloxyide.
ion, generated from benzyl alcohol and NaH. The resulting (3R)-oxygen substituted lactam 235 was obtained in more than 95% diastereoselectivity\(^{135}\). No mention was made of epimerization to any extent in product 235. The nucleophilic substitution reaction therefore occurred by the S\(_{N2}\) mechanism (which resulted in inversion of configuration at C-3) and importantly, the isolated compound 235 was not prone to epimerization.

In a first paper by Micouin et al.\(^{134}\), it was demonstrated that 3-alkylated lactams 236 can be transformed into their corresponding enantiopure piperidines 237, by first reducing the amide carbonyl using LAH, followed by deprotection of the chiral auxiliary using Pearlman’s catalyst (Scheme 51b). If we incorporate this methodology into our proposed synthesis, we would also ultimately need to deprotect an amine 238, obtained by reduction of the target enaminone 239 (Scheme 52):

Two important differences should be noted in the structures of 238 and 239 above, compared to the Quirion compounds discussed before. We require the (3S)-configuration, thus we need to use (S)-phenylglycinol as the chiral auxiliary. Secondly, we will need to protect the hydroxyl group in the chiral auxiliary as this group might interfere with other transformations in our synthesis (see later).

Another example of the hydrogenolysis of an oxygen-containing benzyl group is found in a paper by Agami et al.\(^{136}\). Again, Pearlman’s catalyst was used to sever the N-C bond, effectively deprotecting the carbamate N in oxazolidinone 240 to afford 241 (Scheme 53). It is important to note that, in the process, the chiral centre alpha to the nitrogen in 241 is epimerized.
5.1.2. Preparation of \((R)-3\text{-bromo-1-}[(S)-2\text{-hydroxy-1-phenylethyl}]piperidin-2\text{-one}\n
For our synthesis, we opted to start from ethyl 5-bromopentanoate 242 (as opposed to the methyl ester used by Quirion), which was prepared from δ-valerolactone by existing procedures \(^{137,138}\), as shown in Scheme 54. Acid-catalyzed hydrolysis of the lactone in the presence of hydrobromic acid afforded 84% of almost pure 5-bromopentanoic acid. Esterification by refluxing the carboxylic acid in EtOH and H\(_2\)SO\(_4\) using a Dean-Stark apparatus afforded pure 242 in 94% yield from unpurified 5-bromopentanoic acid.

Scheme 53.

Scheme 54: The synthesis of 245.
(S)-Phenylglycinol 243 was prepared in 70% yield, based on an existing procedure\textsuperscript{139}, by reducing (S)-2-phenylglycine using LAH. The condensation of 242 and 243 in the presence of DBU (2 eq.) afforded an improved yield (63% as opposed to 45% by Quirion’s group) of key lactam 244. It therefore seems that ethyl ester 242 is a better reactant to use in order to obtain 244 than the methyl ester analogue used by Quirion (see Scheme 51) to obtain the (R)-enantiomer (233) of 244. Using very similar conditions on 244 to those employed by Quirion on 233, we obtained only a 25% yield of diastereomerically pure (R)-3-bromo-1-[(S)-2-hydroxy-1-phenylethyl] piperidin-2-one 245 as a colourless solid (mp 122-125 °C), as opposed to the 69% yield obtained by Quirion [who observed a mp of 129 °C for the antipode (S)-3-bromo-1-[(R)-2-hydroxy-1-phenylethyl] piperidin-2-one 234]. The only difference was that we allowed the bromination step to occur for 10 min., as opposed to the 5 min. allowed by Quirion. The \textsuperscript{1}H NMR spectrum of 245 agreed with that obtained by Quirion for 234. The NCH proton, alpha to the phenyl group, appears as a double doublet ($J = 5.1$ and 4.6 Hz) at $\delta_H$ 5.84 owing to coupling with the two protons alpha to the hydroxyl group. The ring NCH$_2$ protons appear as two distinct multiplets, one of which was observed at $\delta_H$ 3.26-3.25 and the other at $\delta_H$ 3.07-3.13. Although we obtained the desired lactam 245 in low yield, we did not observe any evidence of the (3S)-diastereomer.

\textbf{5.1.3. Preparation of (S)-2-[3-(S and R)-acetyl-2-oxopiperidin-1-yl]-2-phenylethyl acetate (248)}

Unfortunately, the next step in our proposed synthesis, i.e. the preparation of benzyloxy-substituted diastereomer 246 (Scheme 55), was unsuccessful for unknown reasons. Quirion’s exact procedure was applied to compound 245. However, only a 9% crude yield of the desired lactam 246 was obtained! The bulk crude product of this reaction, which was obtained after a standard work-up procedure, was mostly insoluble in CH$_2$Cl$_2$ and the \textsuperscript{1}H NMR spectrum of the purified product 246, after column chromatography of the CH$_2$Cl$_2$-soluble fraction, indicated the presence of contaminants. Furthermore, the presence of the Bn protecting group was expected to lead eventually to crowded, difficult-to-interpret NMR spectra during the latter stages
of the proposed synthesis. Consequently, we decided to alter the synthetic route and opted for the use of an alternative, small protecting group (acetyl) on the 3-oxygen.


At a late stage during this proposed route, thionation of an appropriate lactam would need to be carried out prior to the Eschenmoser reaction. It can be presumed that, similar to the presence of free amino groups, free hydroxyl groups during Lawesson’s thionation reaction might lead to drastically reduced yields. For this reason, it was decided to firstly acetylate the hydroxyl group in 245 prior to carrying out the proposed S_N2 reaction with acetate. Using a known procedure, acid-catalyzed acetylation of 245 afforded a low yield (46%) of O-acetyl protected lactam 247. The acid catalyst was a mixture of acetic acid and perchloric acid (see Scheme 55) and acetic anhydride was the acetylation reagent. The mixture was stirred for 43 h at rt. Perhaps not too surprisingly though, as explained in Section 4.2.1., epimerization at C-3 in 247 appeared to have occurred under these reaction conditions. Two diastereomers were obtained in a 0.52:0.48 ratio. It was obvious from the characterization data of 247 that we obtained the expected product. In the ^1H NMR spectrum, H-3 (alpha to the carbonyl) appeared as a double doublet at δ_H 4.64 for diastereomer 1, and was obscured in a multiplet at δ_H 4.61-4.67 for diastereomer 2. These chemical shifts are similar to what was observed for precursor 245 (δ_H 4.68). Interestingly, acetylation of the hydroxyl group caused significant deshielding of the benzylic proton (NCΗ) in 247 (δ_H 6.21 for diastereomer 1, and δ_H 6.12 for diastereomer 2), compared to that observed for 245 (δ_H 5.84). Furthermore, the vicinal
coupling constants observed for this proton vary greatly between diastereomer 1 of \[247\] (\(J = 10.1\) and 5.1), diastereomer 2 of \[247\] (\(J\ ca. 7.3\) for both couplings) and \[245\] (\(J = 5.1\) and 4.6). The protons alpha to the respective acetyl groups also appeared very differently in the \(^1\)H NMR spectra of diastereomers 1 and 2 of \[247\]. In diastereomer 1, these were observed as two distinct double doublets at \(\delta_H\ 4.84\) and 4.45, respectively, whereas in diastereomer 2 the signals were observed at a similar chemical shift, overlapping with the H-3 signal, i.e. as a multiplet at \(\delta_H\ 4.61-4.67\). In \[245\], these protons were more shielded (\(\delta_H\ 4.24\) and 4.06-4.16, respectively), owing to the vicinal presence of the less electron-withdrawing hydroxyl group. The possibility that we obtained rotamers of \[247\], owing to the restriction of rotation about the exocyclic N-C bond, cannot be ruled out. Owing to time constraints, and after having chosen a different route to 1, we did not do any high-temperature NMR studies on \[247\], nor did we do any additional NMR experiments to determine the absolute structures of diastereomers 1 and 2. The IR spectrum clearly shows the presence of both an ester carbonyl group (1741 cm\(^{-1}\)) and a lactam carbonyl group (1646 cm\(^{-1}\)). Both carbonyl carbons were also observed for each diastereomer in the \(^{13}\)C NMR spectra (\(\delta_C\ 171.0\) and 167.1 for diastereomer 1, and \(\delta_C\ 170.8\) and 166.9 for diastereomer 2). Conclusive evidence for the formation of \[247\] was found in the FAB mass spectra. In both cases, the M+1\(^+\) molecular ion was observed at \(m/z\ 340\).

Diastereomer 1 of \[247\] was next subjected to nucleophilic substitution of the bromo-group by the addition of anhydrous NaOAc to a DMSO-solution of \[247\]. As almost no reaction was observed at rt, the reaction mixture needed to be warmed to 55 °C and kept at this temperature for another hour before complete disappearance of \[247\] was observed. It was clear from the characterization data that we had indeed obtained diacetylated lactam \[248\] although all the peaks in the NMR spectra were duplicated, i.e. it was found that \[248\] had epimerised at C-3, and an inseparable 50/50 mixture of diastereomers was isolated in 73% yield. In the \(^1\)H NMR spectrum, the two signals (for the two diastereomers of \[248\]) corresponding to H-3 were even further deshielded at \(\delta_H\ 5.24-5.31\) owing to the strongly deshielding 3-acetyloxy group in \[248\], compared to \(\delta_H\ 4.64\) in precursor diastereomer 1 of \[247\]. In the \(^{13}\)C NMR spectrum, six carbonyl signals were observed, four of which (\(\delta_C\ 170.9,\ 170.8,\ 170.23,\ 170.16\)) were attributed to the four acetyl carbonyl carbons, and two of which (\(\delta_C\ 168.0\) and 167.7)
were attributed to the two lactam carbonyl carbons in the two diastereomers, respectively.

It is well-established that the nucleophilicity of oxygen nucleophiles decrease in the following order: $\text{CH}_3\text{O}^- > \text{C}_6\text{H}_5\text{O}^- > \text{CH}_3\text{CO}_2^- > \text{NO}_3^-$, i.e. nucleophilicity parallels basicity in this instance. An alkyl group is most electron-donating, which makes the oxygen in an alkoxide ion most electron-rich and therefore, most nucleophilic in the series. By using benzyloxide as the nucleophile in their 3-bromide substitution reaction, Quirion observed predominantly $\text{SN}_2$ reaction and obtained high diastereoselectivity with inversion of configuration at C-3 in the lactam ring in 235 (Scheme 51). However, it is highly unlikely that our use of the acetate ion, which is a weaker nucleophile than the benzyloxide ion, would lead to an increase in the rate of $\text{SN}_1$ reaction. The existence of a carbocation on C-3, alpha to the amide carbonyl group, is highly improbable. Therefore, this model cannot be used to explain the racemization we observed at C-3 in 248.

It is thought that an AcOH/AcO$^-$ equilibrium might be responsible instead for the racemization at C-3. It is possible that the rate of deprotonation at C-3 by the acetate ion might be faster than the rate of $\text{SN}_2$ reaction, which is supported by the fact that heating to 55 °C was required to initiate this reaction to form 248 (Scheme 55). This results in the loss of stereoselectivity. Alternatively, it cannot be ruled out that racemization might have occurred after $\text{SN}_2$ reaction, i.e. in product 248, e.g. during the aqueous work-up procedure. At this stage we opted for a different approach to 1 and this route was discontinued.

5.1.4. Final comments on this approach

Although this approach to 1 did not work as efficiently, in the limited time spent, as expected, it still represents a feasible approach to 1. The one step in the reaction which did not work well, i.e. the substitution of bromide by benzyloxide to afford 246 (Scheme 55), could probably be easily optimized. This reaction was only attempted once, in hygroscopic DMSO without distilling the benzyl alcohol used. The advantage of this approach was the ease of purification of the relatively non-polar products
obtained. Even when diastereomers were obtained, they were usually easily separable, e.g. during the purification of 247. If this approach is to be pursued again, one would need to use a strong nucleophile, e.g. an alkoxide ion, in the bromide substitution reaction in order to obtain high diastereoselectivity. Secondly, the use of an O-protecting group on lactam 245, e.g. the TMS group, which requires very mild conditions for its introduction and removal, is recommended in order to minimize possible racemization at C-3.

It is important to note that, during this discussion we have assumed without concrete evidence that epimerization occurred at C-3 (in both 247 and 248). It is possible, but theoretically very unlikely (Quirion’s group also never observed this in the wide range of reactions they carried out), that racemization might have occurred at the benzylic carbon in the chiral auxiliary.

5.2. Approach to febrifugine from L-arginine

5.2.1. Background

An alternative approach to stereoselective synthesis is the “chiral pool” approach, i.e. starting from natural products which already contain the desired stereochemistry and which are suitable for incorporation into the proposed synthesis. This approach usually has the advantage of being inexpensive and environmentally friendly. Using our methodology for the synthesis of biologically active (+)-1, one strategy is to first access (3S)-hydroxypiperidin-2-one 210 (Scheme 56).

Several references to this compound have been found in the literature. Long ago, in 1928, Felix and Müller 142 isolated 210 (Scheme 56) as colourless prismatic needle-like crystals by the sublimation at 190 °C of (S)-5-amino-2-hydroxypentanoic acid 249. Acid 249, in turn, was obtained from naturally occurring L-arginine monohydrochloride as shown in Scheme 56.
Neutralization of (+)-arginine hydrochloride using an aqueous solution of silver nitrite results in the formation of insoluble silver chloride and the *in situ* generation of nitrous acid (HNO₂). Heating on a water bath (no temperature was given) led to the release of N₂ gas from the reaction mixture and formation of L-argininic acid 250, i.e. diazotization followed by substitution of the resultant diazonium ion by water occurred. The mechanism of this well-known reaction is shown in Scheme 57. The amine reacts with nitrous acid to form N-nitrosoamine intermediate 251, which undergoes rearrangement and dehydration to form diazonium salt 252. Salt 252 is very unstable and immediately decomposes to give an intermediate alkyl cation (R⁺) and nitrogen gas. Then R⁺ is attacked by water to form alcohol 253 after regeneration of H⁺. No intimate ion pair is generated, as is the case in halide or sulfonate substitutions, which often occur by the S_N2 mechanism and subsequent inversion of configuration. Only R⁺ is generated which has no closely associated anion.

Scheme 56: The synthesis of 210 by Felix and Müller.

\[
\begin{align*}
\text{(+)-arginine hydrochloride} & \quad \text{1. aq. AgNO}_2, \text{rt, several hours} \\
\text{2. heating on a water bath (96%)} & \quad \text{210}
\end{align*}
\]

\[
\begin{align*}
\text{249} & \quad \text{saturated aq. Ba(OH)}_2 \quad \text{reflux 1.5 h} \\
\text{249} & \quad \text{sublimation} \\
\text{250} & \quad \text{urea}
\end{align*}
\]

Scheme 57: Mechanism of deamination using nitrous acid in aqueous medium.
Depending on the solvent, this reaction is often observed to proceed with retention of configuration, which has been rationalized by the formation of a solvent-separated ion pair that is produced owing to concerted protonation and nitrogen elimination \(^\text{143}\) (Scheme 58). The result is that the water is eliminated and also attacks \(R^+\) primarily from the same side, which leads to the retention of configuration.

![Scheme 58](image)

The synthesis by Felix and Müller was completed by removing the guanidino group by basic hydrolysis using saturated aqueous \(\text{Ba(OH)}_2\) to form acid \(249\) (Scheme 57) and urea. Dehydration of \(249\), when heating above its melting point during the sublimation step, subsequently produced \(210\).

In 1941, Hunter and Woodward \(^\text{144}\) proved that optically active \(210\) was indeed formed during Felix and Müller’s synthesis. They studied the specificity of arginase on natural substrate \(\text{L-argininic acid} (250)\). Arginase removes the guanidino group from \(250\) to produce \(249\). The product \(249\) that Hunter and Woodward obtained also afforded, upon sublimation, lactam \(210\) with similar melting point (171.5 °C) to that obtained by Felix and Müller (mp 160-169 °C). Hunter and Woodward determined the optical rotation of \(210\) to be \([\alpha]_D^{21} -6\) in aqueous solution. Their melting point of racemic \(210\) was considerably lower (134.3 °C), as also determined by Fischer and Zemplen in 1909, who obtained a melting point of 141-142 °C for racemic \(210\) \(^\text{142}\).

Importantly, in both the Felix and Müller and the Hunter papers, no mention of yields is made in their preparation of \(210\) from \(249\). Felix also did not mention the yield of the hydrolysis reaction to form \(249\) from \(250\). The synthesis of \(250\) by Felix and Müller was reported in subsequent studies to be low-yielding, with difficulties being encountered during the decomposition of arginine nitrite, as mentioned in a publication by Hamilton and Ortiz \(^\text{145}\) of an alternative preparation of \(250\). This preparation involves the chlorination of arginine hydrochloride using nitrosyl chloride to yield intermediate chloride \(254\), followed by hydrolysis to produce \(250\) (Scheme 59). The chlorination reaction also involves the intermediacy of a diazonium ion
which, in this case, is attacked by the chloride ion. Subsequently, when an aqueous solution of chloride 254 is refluxed for 48 h, hydrolysis occurs leading to the formation of L-argininic acid 250 in 75% yield. Although the paper suggests that the S-configuration is retained throughout, owing to the retention of laevorotation in both products 254 ([α]D −7.5) and 250 ([α]D −11.0), it is thought that this is an example of double inversion instead. The mechanism differs from the usual deamination mechanism shown in Scheme 57, as chloride is the attacking nucleophile here, and not the water generated by synchronous protonation and nitrogen elimination (Scheme 58). The first substitution reaction therefore probably occurs by the S_N2 mechanism, which results in inversion to form (R)-254. A second S_N2 reaction, with water being the nucleophile, then leads to the formation of (S)-250, i.e. an overall retention of configuration occurs.

Scheme 59: The preparation of 250 by Hamilton and Ortiz 145.

5.2.2. Preparation of (3S)-2-thioxopiperidin-3-yl acetate (260)

We tested both the previously mentioned literature preparations of 250, as shown in Scheme 60 (Methods A and B). As mentioned before, it is necessary to protect the hydroxyl group in 210, prior to carrying out the thionation reaction. We opted again for the simple O-acetyl protecting group, which eventually led to the formation of lactam 255 (Method A) and thiolactam 256 (Method B), as shown in Scheme 60.

Using the Felix and Müller method, we obtained (3S)-2-oxopiperidin-3-yl acetate 255 in an unacceptably low 1.5 % yield over 4 steps from (S)-arginine hydrochloride. During the initial trials using this methodology, we attempted to isolate key lactam
by sublimation of recrystallized carboxylic acid 249 under high vacuum in a sublimation apparatus. As we followed their procedure meticulously, we were initially certain that pure 249 was indeed obtained in good yield. They reported a very high yield (96%, Scheme 56) of 250, and even though no yield was reported for 249, we assumed that this was a standard, high-yielding reaction. However, it was observed that product 249, instead of forming crystals of sublimed material on the cold finger of the apparatus, simply expanded on heating to form a very hygroscopic, amorphous material, the NMR data (after rigorous drying under high vacuum) of which is given in Table 15.

Interestingly, it was recently (in 2002) discovered by Alam et al. 146 that (3S)-hydroxypiperidin-2-one 210 is a natural product, which occurs in the defence secretions of two coccinellid beetles, *Harmonia axyridis* and *Aiolocaria hexaspilota*. In this work lactam 210 was isolated as a yellow-brown solid by reverse-phase flash column chromatography of the residues obtained from methanolic extracts of the beetles. The NMR data of natural product 210 in CD$_3$OD are compared to that of our product, after sublimation of crude 249, in Table 15 below. It should be noted that Alam *et al.* recorded the NMR spectra using CD$_3$OD as a solvent, whereas we used D$_2$O. These results are therefore not directly comparable.
Method A:

(+)-arginine hydrochloride

1. aq. AgNO₃, rt, 3 h
2. Δ, 60 °C, 2 h

250

saturated aq. Ba(OH)₂, reflux 2 h

249

1. HMDS (7.9 eq.), cat. TMSCl, xylene, reflux 13.5 h
2. EtOH

255

Pyridine, Ac₂O, EtOAc, rt, 6.5 h

(1.5% over 4 steps)

210

Method B:

(+)-arginine hydrochloride

conc. HCl/conc. HNO₃ (v/v, 2/1)
60 °C, 30 min

254

1. Reflux in H₂O (48 h)
2. Ag₂CO₃

250

saturated aq. Ba(OH)₂, reflux 3 h

249

1. HMDS (7.6 eq.), cat. TMSCl, xylene, reflux 15.5 h
2. EtOH

255

Lawesson's reagent, benzene, rt 12 h, reflux 1.5 h
(42% over 6 steps)

210

260

Scheme 60: Preparations of 255 and 260.

<table>
<thead>
<tr>
<th>Proton(s)</th>
<th>Sublimed product (δ_H)</th>
<th>210 (δ_H)¹⁴⁶</th>
<th>Carbon</th>
<th>Sublimed product (δ_C)</th>
<th>210 (δ_C)¹⁴⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOH</td>
<td>3.79 (t)</td>
<td>3.94 (dd)</td>
<td>C=O</td>
<td>177.0</td>
<td>174.5</td>
</tr>
<tr>
<td>NCH₂</td>
<td>3.28 (t)</td>
<td>3.36 (dt),</td>
<td>CHOH</td>
<td>57.0</td>
<td>62.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.20 (dt)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH₂CHOH</td>
<td>1.90–1.98 (m)</td>
<td>2.28 (dd),</td>
<td>NCH₂</td>
<td>43.2</td>
<td>46.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.09 (ddd)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
It can be seen from Table 15 that, for the product obtained by the sublimation of crude 249, we did not observe the expected multiplicities (double doublets, and double triplets) for the CHOH and NCH2 signals, respectively, in the 1H NMR spectrum. This indicates that the material we isolated was probably acyclic. The 1H NMR spectrum of 210 reported by Alam et al. clearly reflects the cyclic nature of 3-substituted lactam 210 owing to increased coupling, compared to that observed for our product obtained by sublimation of 249. The most deshielded proton is H-3 (alpha to the lactam carbonyl group), which was observed by Alam as a double doublet at δH 3.94. The two protons (H-6) vicinal to the nitrogen were observed as two double triplets, respectively, at δH 3.36 and 3.20. This is in contrast to the corresponding triplets observed (at δH 3.79 and 3.28) for our product. It can also be seen from Table 15 that the 13C NMR signals correspond very well between compound 210 and the sublimed material. Importantly, we could not obtain a melting point of the sublimed material under normal atmospheric conditions as it was too hygroscopic. No mention is made by Alam et al. (or by any other groups which isolated 210) that lactam 210 is hygroscopic, although it is strange that the melting points for 210 found in the literature differ considerably (as shown by Alam et al. in their experimental section 146). It is thought that we, in fact, isolated a polymerized form of amino acid 249, after condensation occurred either during sublimation, or by intermolecular polymerization during the Ba(OH)2 step (see Scheme 60).

Alam et al. reported an optical activity for 210 much higher in methanol ([α]D18 53) than that observed for enzymatically resolved 210, by Hunter and Woodward 144, recorded in water ([α]D21 6). The melting points reported by the two groups also differed greatly (122-124 ºC, Alam et al.; 171.5 ºC, Hunter and Woodward 144).

| NCH2CH2 | 1.60–1.88 (m) | 1.94–1.99 (m) | CH2CHOH | 30.2 | 31.0 |
| NCH2CH2 | - | - | - | 26.6 | 24.5 |

Table 15: Comparison of the NMR data of natural product 210 (in CD3OD) and the product obtained by sublimation of 249 (in D2O). (Note that δH and δC are given in ppm, and the multiplicities of the proton signals are given in brackets.)
Therefore, the melting point of natural, highly optically active 121 isolated by Alam 
et al. was lower, yet similar to that of racemic 121 (141-142 °C) 142. This conflicts 
with the reasoning by Hunter and Woodward, as explained earlier, that optically 
active 121 exhibits a much higher melting point than racemic 121. It is also suggested 
by the wide range of melting points reported for both optically pure and racemic 121 
that this lactam might be hygroscopic and difficult to handle under normal 
atmospheric conditions. This is supported by the fact that analogous 3-amino 
substituted lactam 205 (see Scheme 42, Section 4.1.) was reported to be very hygroscopic by Pifferi 119.

Confused by the results obtained thus far, we decided to carry out the proposed 
synthesis, without isolating the intermediates, simply to check whether lactam 255 
might be isolated in any appreciable yield. Instead of subjecting crude 249 to 
sublimation conditions, we opted for Pifferi’s 119 intramolecular cyclization procedure 
mentioned before (see Section 4.1.). This procedure was also used successfully by 
Maurey and Srairi 120 to prepare analogous (3S)-hydroxypyrrolidin-2-one (209). Thus, 
the obtained 249, in the presence of HMDS and a catalytic amount of TMSCl, was 
refluxed in xylene for 13.5 h. After TMS-deprotection, by the addition of EtOH and 
evaporation of the mixture in vacuo, a brown oil (only ca. 0.10 g) was obtained after 
filtering a methanolic solution of the residue through celite. As the free amino lactam 
205 was found to be hygroscopic as mentioned above, we decided not to isolate 210, 
but to convert it directly into the less polar and therefore, more easily isolable, acetyl-
protected lactam 255 before purification. Although the product was obtained in very 
low yield, the spectroscopic data of purified 255 did agree with those reported 
recently by Kamal’s group 147. They published in 2003 the chemoenzymatic synthesis 
of 3-hydroxypyrrolidin-2-ones and 3-hydroxypiperidin-2-ones. Their synthesis of 255 
is shown in Scheme 61.
Scheme 61: Kamal’s synthesis of 255.

Acid bromide 256 was obtained from δ-valerolactone by reaction with red phosphorus and bromine. This was followed by conversion of 256 into amide 257 using aqueous ammonia. Intramolecular cyclization of 5-bromo-substituted amide 257 was achieved in 40% yield using NaH to afford lactam 258. Nucleophilic substitution of the bromide in 258, by the acetate ion in the presence of 18-crown-6, afforded racemic 259 in 94% yield. Lipase resolution of 259 occurred by selective hydrolysis of (R)-259 to yield (3R)-hydroxypiperidin-2-one [(R)-210] in 60% yield, and also lactam 255, the yield of which was not mentioned. Although optically active 255 was not characterized in this paper, we could compare our 1H NMR results with those obtained by Kamal et al. for racemic 259. These corresponded very well, although we obtained 255 as a viscous oil, contrasting with Kamal’s report of racemic 259 as a solid (mp 69-71 ºC). We also obtained a 13C NMR spectrum, which has not been previously published, and a mass spectrum of 255 (see experimental section). Although we did not determine the optical rotation of 255, it is presumed that it would be optically active, as product 260 discussed below did display such activity.

Disappointed by the low yield of 255, together with the difficulties experienced when attempting to recrystallize and characterize the intermediates in the Felix and Müller synthesis, we opted to use the Hamilton procedure for the preparation of L-argininonic acid 250 (Method B, Scheme 60). Although we again could not isolate pure, recrystallized samples of the polar, water-soluble intermediates (254, 250 and 249), this method worked much better overall. It was found that the intermediates need not
be isolated. Following their procedure exactly, we obtained crude 250, which was subsequently refluxed in saturated aq. Ba(OH)₂ solution to hydrolyze the guanidino group. The obtained acid 249, after removal of the urea by-product by repeated washing of the residue with hot absolute EtOH, was subjected to the 1,6-cyclization conditions used before. Again, crude 210 was obtained as a brownish oil, which was directly subjected to O-acetyl protecting conditions. In this case, the crude product 255 was almost pure by TLC. It was thionated directly, without further purification, using Lawesson’s reagent and benzene as the solvent. After column chromatography, stable and easily isolable (3S)-thioxopiperidin-3-yl acetate 260 was obtained in 42% yield over 6 steps (Scheme 60, Method B). This was a very satisfying result. As we were really only interested at this point in accessing a 3-oxygen substituted piperidine-2-thione, no further detailed studies were performed in order to clarify the initial difficulties experienced using this “chiral pool” approach. However, it can be said with certainty that Felix and Müller’s preparation of (3S)-hydroxypiperidin-2-one is not a reliable method, as we obtained very low yields of the desired products after several attempts. This is in agreement with work done by other groups 145.

The reason why we opted to pursue the synthetic route from L-arginine is that, according to the literature procedures followed, racemization at the stereogenic alpha-carbon should not occur at any stage during this route. We were not interested in using expensive and effectively, overall yield-reducing, enzymatic resolution, e.g. as utilized by the Kamal group 147. It was reasoned that, if other methods such as the procedures outlined before from L-arginine are available, these should be prioritized. The obtained yellow solid 260 was indeed optically active and in the expected laevorotatory sense ([α]D –22.0 in CHCl₃). However, a single crystal obtained by slow evaporation of an EtOAc-hexane solution of 260 was found to be centrosymmetric, as described in the next section. This result pointed again to the eventual racemization of 260, similar to the observation made earlier for analogous thiolactam 204 (Section 4.2.1.).

5.2.3. Crystal structure of 260

The important crystal and refinement data for 260 are given in Table 16.
- **Crystal system**: Triclinic
- **Space group**: P1
- **Unit cell dimensions**:
  - $a = 5.1118(10)$ Å, $\alpha = 84.625(4)^{\circ}$
  - $b = 6.7423(13)$ Å, $\beta = 84.167(4)^{\circ}$
  - $c = 13.275(3)$ Å, $\gamma = 79.534(4)^{\circ}$
- **Volume**: 446.26(15) Å³
- **Z**: 2
- **Density (calculated)**: 1.289 Mg/m³
- **Absorption coefficient**: 0.315 mm⁻¹
- **F(000)**: 184
- **Crystal size**: 0.48 x 0.28 x 0.10 mm³
- **Theta range for data collection**: 1.55 to 25.00°
- **Index ranges**: $-6 \leq h \leq 5$, $-8 \leq k \leq 5$, $-15 \leq l \leq 14$
- **Reflections collected**: 2376
- **Independent reflections**: 1536, $R(int) = 0.0269$
- **Completeness to theta = 25.00°**: 99.1%
- **Absorption correction**: None
- **Max. and min. transmission**: 0.9691 and 0.8633
- **Refinement method**: Full-matrix least-squares on $F^2$
- **Data / restraints / parameters**: 1536 / 0 / 101
- **Goodness-of-fit on $F^2$**: 1.070
- **Final R indices [$I>2\sigma(I)$]**: $R1 = 0.0700$, $wR2 = 0.2036$
- **R indices (all data)**: $R1 = 0.0923$, $wR2 = 0.2228$
- **Largest diff. peak and hole**: 0.367 and -0.299 e.Å⁻³

### Table 16: Crystal data and structure refinement for 256.

As seen from Table 16, 260 crystallizes in a less symmetrical space group (P1), and in a different crystal system (triclinic), compared to analogous thiolactam 204 (Pbca and
monoclinic, respectively). The presence of an inversion centre indicates that **260** is racemic, i.e. (3S)- and (3R)-acetyloxypiperidin-2-one molecules had co-crystallized.

Similar to the structure of (3S)-tert-butyloxypiperidin-2-one (S)-**212**, as discussed in Section 4.2.2., only two molecules (Z = 2) constitute the asymmetric unit in **260**. A standard Ortep drawing of **260** is shown in Figure 20. Similar to what was observed for **204**, it can be seen that molecule **260** crystallized in the half-chair conformation, i.e. atoms N1, C2, C3 and C6 are approximately planar, whereas atom C5 is above and atom C4 is below this plane.

![Figure 20: Ortep drawing (showing 50% ellipsoid probability) of 260.](image)

Selected bond lengths are compared between **204** and **260** in Table 17. Interestingly, the thiocarbonyl bond C(2)-S is slightly longer in 3-acetyl substituted **260** than in 3-Boc substituted **204**. Furthermore, the N(1)-C(2) bond together with the C(2)-C(3) and C(3)-C(4) bonds in the proximity of the thioamide group, are shorter in **260** than in **204**. This points to an increased inductive electron-withdrawing effect by the 3-acetyl group (and possibly also the sulfur) in **260**, compared to this effect in **204**. Such increased deshielding in **260** might increase slightly the acidity of alpha-proton H-3 in **260**, compared to the case for **204**. This finding was also reflected in the $^1$H NMR data of these thiolactams; whereas H-3 absorbed as a broad triplet at $\delta_H$ 5.50 in **260**, the analogous H-3 in **204** was considerably more shielded (quintet at $\delta_H$ 4.16). The possibility exists that this difference might also enhance the rate of racemization at carbon 3 in **260**, compared to that in **204**. The Boc carbonyl bond C(7)-O(1) in **204**
although involved in hydrogen bonding, is shorter than the acetyl carbonyl C(7)-O(2) bond in 260.

\[
\text{\begin{tabular}{|c|c|c|}
\hline
Bond & 204 (Å) & 260 (Å) \\
\hline
C(2)-N(1) & 1.3154 (19) & 1.305 (4) \\
\hline
C(2)-C(3) & 1.522 (2) & 1.499 (6) \\
\hline
C(2)-S & 1.6755 (16) & 1.683 (4) \\
\hline
C(3)-C(4) & 1.520 (2) & 1.512 (5) \\
\hline
C(6)-N(1) & 1.462 (2) & 1.463 (5) \\
\hline
C(7)-O(1) for 204 & 1.2084 (19) & - \\
\hline
C(7)-O(2) for 256 & - & 1.215 (6) \\
\hline
C(3)-O(1) for 256 & - & 1.449 (5) \\
\hline
C(7)-O(1) for 256 & - & 1.321 (5) \\
\hline
\end{tabular}}
\]

Table 17: Bond lengths in analogues 204 and 260.

Table 18 compares selected bond angles and torsion angles in 204 and 260. It can be seen that bond angles N(1)-C(2)-C(3) and N(1)-C(2)-S in the thioamide function of 204 are smaller than in 260, whereas, the bond angles in the vicinity of the 3-substituent [C(3)-C(2)-S, N(2)-C(3)-C(4) and N(2)-C(3)-C(2) in 204] are larger in 204 than in 260 [C(3)-C(2)-S, O(1)-C(3)-C(4) and O(1)-C(3)-C(2), respectively]. This might be a reflection of increased steric repulsion between the bulky 3-substituent (Boc group) and the thioamide function (as well as the ring) in 204, compared to the case for the less sterically demanding acetyl group in 260. From torsion angles C(3)-C(2)-N(1)-C(6) and S-C(2)-N(1)-C(6), it can be seen that the thioamide group is considerably more planar and closer to the ideal situation in 260 (in which these angles approximate -180º and 0º, respectively) than in 204 (in which these angles approximate 170º and -10º, respectively). Once again, this might be a reflection of the increased bulkiness of the Boc substituent in 204, which causes deviations from the
ideal conformation during molecular packing. In contrast, fewer disfavoured intra- and intermolecular steric interactions in 260 exist, which allow the bond angles and torsion angles to approximate more closely the normal lowest-energy conformation. From torsion angles C(5)-C(6)-N(1)-C(2) and N(1)-C(2)-C(3)-C(4), it is evident that both 204 and 260 crystallize in approximate half-chair conformations with atoms C(5) and C(4) being more out-of-plane than the other ring carbons and N(1).

<table>
<thead>
<tr>
<th>Angle</th>
<th>204 (degrees)</th>
<th>260 (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(1)-C(2)-C(3)</td>
<td>117.05 (13)</td>
<td>118.1 (3)</td>
</tr>
<tr>
<td>N(1)-C(2)-S</td>
<td>121.43 (12)</td>
<td>122.1 (3)</td>
</tr>
<tr>
<td>C(3)-C(2)-S</td>
<td>121.50 (11)</td>
<td>119.7 (3)</td>
</tr>
<tr>
<td>N(2)-C(3)-C(4)</td>
<td>112.66 (13)</td>
<td>-</td>
</tr>
<tr>
<td>O(1)-C(3)-C(4)</td>
<td>-</td>
<td>107.3 (3)</td>
</tr>
<tr>
<td>N(2)-C(3)-C(2)</td>
<td>109.55 (12)</td>
<td>-</td>
</tr>
<tr>
<td>O(1)-C(3)-C(2)</td>
<td>-</td>
<td>108.1 (3)</td>
</tr>
<tr>
<td>C(4)-C(3)-C(2)</td>
<td>112.66 (13)</td>
<td>114.6 (3)</td>
</tr>
<tr>
<td>C(3)-C(2)-N(1)-C(6)</td>
<td>-10.7 (2)</td>
<td>3.3 (6)</td>
</tr>
<tr>
<td>S-C(2)-N(1)-C(6)</td>
<td>170.84 (14)</td>
<td>-177.8 (3)</td>
</tr>
<tr>
<td>C(2)-C(3)-N(2)-C(7)</td>
<td>143.13 (15)</td>
<td>-</td>
</tr>
<tr>
<td>C(2)-C(3)-O(1)-C(7)</td>
<td>-</td>
<td>-111.6 (4)</td>
</tr>
<tr>
<td>C(5)-C(6)-N(1)-C(2)</td>
<td>21.8 (2)</td>
<td>-21.2 (6)</td>
</tr>
<tr>
<td>N(1)-C(2)-C(3)-C(4)</td>
<td>25.11 (19)</td>
<td>-13.6 (5)</td>
</tr>
</tbody>
</table>

Table 18: Comparison of bond angles and torsion angles in 204 and 260.

Figure 21 represents a unit cell in the structure of 260. Owing to the obvious inversion centre between the two molecules, the crystal is centrosymmetric. Interestingly, no moderate H-bonds (intra- or intermolecular) were found in structure 260. This is unusual, seeing that the acetyl carbonyl group is a good H-bond acceptor, and we did find in structure 204 that a thiolactam NH can be a very good H-bond donor [see Section 4.2.2., the intermolecular H-bonds were even stronger than corresponding H-bonds in lactam precursor (S)-212]. This conflicts with accepted theory, e.g. as
demonstrated in the detailed statistical study performed in 1990 by Etter. In general, it was determined in this study that the best proton donors and the best proton acceptors in any given organic molecule can be expected to bind to one another. Importantly, if possible, all proton donors will form hydrogen bonds, and usually all good proton acceptors will also form hydrogen bonds.

**Figure 21:** Unit cell representation of 260, clearly showing centrosymmetry in the structure.

### 5.2.4. Reaction between thiolactam 260 and bromide 105, and attempted hydrogenation of the product

Using our developed standard conditions (Scheme 62) for the Eschenmoser reaction between thiolactam 260 and bromide 105, we obtained a product (261), the $^1$H NMR data and the general properties of which were very similar to those obtained for product 220 (see Section 4.2.3.).

**Scheme 62:** Attempted synthesis of O-acetyl protected febrifugine, 262.
Table 19 compares selected $^1$H NMR data of proposed vinylogous amides 220 and 261.

![Chemical Structures](image)

<table>
<thead>
<tr>
<th>Proton(s)</th>
<th>220 [δH (ppm) and multiplicity]</th>
<th>261 [δH (ppm) and multiplicity]</th>
</tr>
</thead>
<tbody>
<tr>
<td>NH</td>
<td>8.77 (s)</td>
<td>8.88 (s)</td>
</tr>
<tr>
<td>H-2</td>
<td>8.35 (s)</td>
<td>8.44 (s)</td>
</tr>
<tr>
<td>H-5</td>
<td>8.17 (d)</td>
<td>8.11 (d)</td>
</tr>
<tr>
<td>H-7 and H-8</td>
<td>7.63-7.73 (m)</td>
<td>7.62-7.72 (m)</td>
</tr>
<tr>
<td>H-6</td>
<td>7.45 (t)</td>
<td>7.42 (t)</td>
</tr>
<tr>
<td>H-3″</td>
<td>5.30 (t)</td>
<td>6.31 (t)</td>
</tr>
<tr>
<td>NCH$_2$C=O</td>
<td>5.78 (d) and 5.66 (d)</td>
<td>5.83 (d) and 5.73 (d)</td>
</tr>
<tr>
<td>0.5 × ring NCH$_2$ and =CH</td>
<td>4.86 (m) and 4.66 (m)</td>
<td>4.95 (m)</td>
</tr>
<tr>
<td>0.5 × ring NCH$_2$</td>
<td><em>ca. 3.5</em> (br s)</td>
<td>3.31 (br s)</td>
</tr>
<tr>
<td>remaining ring CH$_2$’s</td>
<td>2.47 (2H, m), 2.33 (2H, m)</td>
<td>2.57 (1H, m), 2.45 (2H, m), 2.22 (1H, m)</td>
</tr>
</tbody>
</table>

Table 19: Comparison of selected NMR data obtained for the proposed structures 220 and 261.

The vinyl proton signal (=CH) and all the aromatic quinazolinyl proton signals (H-2, H-5, H-7, H-8 and H-6) are all very similar in 220 and 261. In addition, most of the aliphatic proton signals (NCH$_2$C=O, ring NCH$_2$, remaining ring CH$_2$’s), and even the assigned NH signal, are very comparable between the two compounds. The only obvious difference is the H-3″ signal, which is considerably more shielded ($\delta_H$ 5.30) in Boc-protected 220 than in acetyl-protected 261 ($\delta_H$ 6.31). However, this finding is expected, as the acetyl group is more electron-withdrawing than the Boc-group. This was also reflected in the data for corresponding thiolactams 204 and 260 (see Section...
5.2.3. $\delta_H$ 4.16 and 5.50, respectively). All the aliphatic signals in 261 are again surprisingly highly deshielded, as was the case for 204. It is thought that strong hydrogen bonding in the free NH enaminone functional group of these compounds might cause such an effect.

Similar to what was observed for 204, it was found that 261 darkened and decomposed slowly on standing under normal atmospheric conditions. The broadening of $^1H$ NMR signals was also evident, similar to what was observed for 204. Attempted chemoselective hydrogenation of 261 to produce 262 (Methods A and B, Scheme 62) again failed. Mixtures of very polar, unidentifiable products were obtained (see experimental, Section 9.2.4.).

In conclusion, the “chiral pool” approach to febrifugine from L-arginine was found to be much more problematic than expected. Even though we obtained a few of the key intermediates (e.g. 260 and 261) required for the synthesis of 1, we opted to discontinue this route for various reasons. Thiolactam 260 was found to have racemized, either during the preparation conditions employed, or upon storage. The vinylogous amide 261 was unstable and could not be cleanly reduced to form febrifugine analogue 262. After several repetitions of both methods in Scheme 62, the experimental procedures used in this approach were found to be tough to reproduce and optimize satisfactorily. Furthermore, the water-soluble intermediates were not isolable by standard column chromatography, nor easily purified by recrystallization.

5.3. Approaches to febrifugine by $\alpha$-hydroxylation of piperidin-2-ones

5.3.1. Background

Our final strategy towards obtaining 3-oxygenated functionalized lactams and thiolactams for the synthesis of 1 and its derivatives involved the $\alpha$-hydroxylation of piperidine-2-ones. It was discovered in 1979 by Davis et al. 81 that carbanions can be efficiently, and often stereoselectively, hydroxylated using a novel class of 2-sulfonyloxaziridines. These reagents were found to be stable, aprotic and neutral
oxidizing agents\textsuperscript{149}. Many other reagents have been used for the diastereoselective oxidation of chiral enolates, e.g. Vedejs’ MoOPH reagent\textsuperscript{150} and dibenzyl peroxycarbonate\textsuperscript{151}. However, the disadvantage is that a chiral auxiliary, which has to be prepared and eventually removed, needs to be present in the enolate. Davis hydroxylation avoids this problem by using an enantiomerically pure reagent to control the introduction of chirality into a prochiral substrate. The most popular reagents used nowadays for stereoselective oxidation purposes are (+)- and (–)-camphorsulfonyloxaziridine [(+)- and (–)-CS, Figure 22]. Improved stereoselectivity might further be achieved through the utilization of sterically more challenging derivatives, of which (+)-DCCS (Figure 22) is an example.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure22.png}
\caption{Examples of 2-sulfonyloxaziridines.}
\end{figure}

The proposed general mechanism for oxygenation of nucleophiles by electron-deficient oxaziridines\textsuperscript{263} (EWG = electron-withdrawing group) is outlined in below\textsuperscript{152}.

\begin{equation}
\begin{aligned}
\text{Mo}^6 & \text{Ni} \rightarrow \\
263 & \rightarrow 264 \rightarrow 265 + 266
\end{aligned}
\end{equation}

A nucleophile, e.g. an enolate, attacks the electrophilic oxygen in 263, with simultaneous N-O bond cleavage (i.e. by the S\textsubscript{N}2 mechanism), to give hemiaminal 264. However, the formation of a stable hemiaminal 264 has been questioned\textsuperscript{153}. After spontaneous breakdown of 264, an imine by-product 265 and the desired oxygenated product 266 result.

The synthesis of the marine alkaloids (–)-lepadins A, B and C by Kibayashi’s group in 2001\textsuperscript{154}, as represented in Scheme 63, illustrates well the utility of sulfonyloxaziridines in modern total synthesis. A key reaction in their synthesis of
(−)-lepadin A was the diastereoselective oxidation of bicyclic isoxazino lactam 267 (Scheme 63) to afford the desired (S)-isomer 268. The rate of formation of the (R)-isomer 269 therefore needed to be minimized. Table 20 summarizes selected reaction conditions and results obtained by Kibayashi’s group during their optimization of this pivotal step. In all cases, regardless of the absolute configuration of the sulfonyloxaziridine used, a preference for the formation of (S)-isomer 268 was observed. Unfortunately, no detailed explanations were given for this observed stereoselectivity. Presumably sterically disfavoured interactions between the benzyloxy group in the E-enolate of 267 and the incoming oxygenated electrophile leads to the favoured introduction of oxygen from the si face, i.e. trans to the benzyloxy group, of the formed E-enolate (Scheme 64). It can be seen that the use of (+)-CS and (+)-DCCS further increased this stereoselectivity, the effect being most pronounced for (+)-DCCS.

\[
\begin{align*}
\text{(S)-malic acid} & \quad \text{to} \quad \text{267} \\
\text{267} & \quad \text{1. base, THF, -78°C} \quad \text{2. sulfonyloxaziridine} \quad -78°C, \text{several hours (see Table 20)} \\
\text{268} & \quad + \quad \text{OTBDPS} \\
\text{269} & \quad \text{OTBDPS} \\
\text{(-)-lepadin A} & \quad \text{to} \quad \text{268, 269}
\end{align*}
\]

Scheme 63: Brief outline of the total synthesis of (−)-lepadin A by Kibayashi’s group.
| sulfonyle- | base     | 268:269 ratio | yield (%) |
| oxaziridine|          |              |          |
| (-)-CS     | NaHMDS   | 1.2:1        | 80       |
| (+)-CS     | NaHMDS   | 5.0:1        | 79       |
| (+)-CS     | LiHMDS   | 11:1         | 84       |
| (+)-DCCS   | LiHMDS   | 17:1         | 91       |

Table 20: Selected results for the oxidation step in Kibayashi’s synthesis.

Scheme 64: Electrophilic oxygen introduction onto the re or the si faces of a trisubstituted E-enolate.

In a detailed mechanistic study on the asymmetric oxidation of ketone enolates by Davis et al. in 1990 \(^{153}\), it was found that the stereoselectivity was higher for the oxidation of trisubstituted enolates (analogous to lactam enolate 267) than for tetrastubstituted enolates. Furthermore, Z-enolates seemed to exhibit higher stereoselectivities than E-enolates, which is often also the case during aldol and Michael reactions. Sodium and potassium enolates of the studied ketones were found to give both higher yields and greater stereoselectivities than lithium or zinc enolates. This was explained by the finding that increased ion separation occurs down the series lithium, sodium and potassium enolates. It was also thought that this might occur simply because sodium enolates are oxidized more easily and at a lower temperature than lithium or zinc enolates.

The mechanism by which stereoinduction occurs in the Davis hydroxylation reaction is not always completely understood or predictable \(^{153}\). Although a strong correlation between enolate geometry and the stereochemistry of the major product in, e.g. aldol
and Michael reactions, often exists, this is not perceived to be the predominant factor in Davis reactions. It is thought that stereoinduction in the Davis reaction is more influenced by the enolate substitution pattern (e.g. it was found that a change in $R_1$ in Scheme 64 from Ph to alkyl might lead to a change in configuration in the product $^{153}$). Equally important is the enolate solution structure, as reflected by the counterion effects mentioned before, together with the finding that the addition of highly polar HMPA has a significant effect on stereoselectivity $^{153}$.

Oxidations of carbanions using molecular oxygen are well-known in organic chemistry. The $\alpha$-hydroperoxide intermediates formed in this way from enolates are easily reduced to the $\alpha$-hydroxy derivatives using e.g. trimethyl phosphite [P(OCH$_3$)$_3$] or Na$_2$SO$_3$. Examples of such transformations are given in Scheme 65.

Scheme 65: Examples of the $\alpha$-oxidation of lactams using molecular oxygen.

In their synthetic approach towards cytochalasins, Kim et al. $^{155}$ managed to oxidize bicyclic lactam 270 stereoselectively in order to access key intermediate $\alpha$-hydroxylactam 271 in 60% yield. Firstly, lithium hexamethyldisilazide was generated in situ from $n$-BuLi and HMDS in THF at $-78 \, ^\circ\text{C}$. A solution of 270 in THF was subsequently added and the reaction was stirred at 0 $\, ^\circ\text{C}$ for 1 h to complete enolization. Oxygen gas was passed through the reaction mixture for 1 h at the same temperature, after which a few drops of P(OCH$_3$)$_3$ were added to reduce the intermediate hydroperoxide. The mixture was stirred for another two hours and subsequently worked up by standard methods to afford 271. It is thought that oxygen
was exclusively attacked from the unhindered *si* face of the lactam enolate, *trans* to the neighbouring ether substituent, to afford the desired *S* alcohol isomer 271. This is therefore an example of diastereoselective oxygenation.

In 1975, Wasserman and Lipshutz\(^{156}\) published a procedure for the \(\alpha\)-hydroxylation of a variety of amides and esters [of which the preparation of 3-hydroxy-1-methylpiperidin-2-one 272 (Scheme 65) is an example] using lithium diisopropylamide (LDA) and molecular oxygen. In this case, a suspension of the pre-formed lithium enolate in THF at 0 °C was added to a reaction well, in a custom-made apparatus, containing ether through which dry oxygen was continuously circulated beforehand. By monitoring the oxygen uptake with a gas burette, they established that oxygenation was quantitative and practically instantaneous \(^{156}\). Prolonged reaction times, such as those applied by Kim *et al.*, might therefore be unnecessary during this stage of the reaction. It was also mentioned that the oxygen uptake reaction may be carried out at –78 °C. After a standard work-up procedure, Wasserman and Lipshutz simply treated the residual crude hydroperoxide intermediate with an aqueous Na\(_2\)SO\(_3\) solution until the starch-iodide test was negative, which indicated the absence of peroxides, to afford the \(\alpha\)-hydroxylated product.

### 5.3.2. Oxidations to produce \(O\)-acetyl and \(N\)-(2-methylnaphthyl) protected piperidin-2-ones

We felt that the Davis hydroxylation reaction should proceed optimally when applied to tertiary amides, as opposed to secondary or primary amides. Owing to the use of a strong base to form the \(\alpha\)-carbanion, the presence of other proton donors (such as that found in a secondary lactam) might lead to side-reactions. Furthermore, as we previously experienced problems, particularly with the purification, isolation and stability of the advanced intermediates, e.g. the vinylogous amide products before (see Sections 4.2.3. and 5.2.4.) when applying our methodology to \(N\)-unprotected thiolactams, it was deemed necessary to keep this nitrogen protected throughout the synthesis and only remove the protecting group in a penultimate step in the proposed
synthesis of 1. We also believed that a N-protecting group would facilitate the purification of advanced intermediates by standard chromatographic procedures by decreasing their polarity. For this purpose, we selected initially the 2-methylnaphthyl group, explained earlier in Chapter 3. As a free hydroxyl group will significantly reduce the yield in the thionation step of our procedure, this group also needs to be protected. We opted again for the use of the acetyl group for this purpose as it is a simple hydroxyl protecting group, which is likely to be stable under the reaction conditions required for our synthetic route and which is also expected to facilitate the easy identification of complex intermediates by NMR spectroscopy.

In our proposed synthesis, we need to access a 3-oxygen containing piperidin-2-one with the (3S) configuration. As Kibayashi’s group found that diastereoselective bias towards the (S)-isomer (Scheme 63) increased significantly when using (+)-CS (Table 20), compared to (–)-CS, we decided to use (+)-CS in the hope that it might also afford the desired (S)-stereoisomer as major product. Although (+) and (–)-CS are commercially available reagents, we prepared (+)-CS from the corresponding camphorsulfonic acid by a standard procedure (Scheme 66). Conversion of 273 into the sulfonyl chloride 274 was achieved through the reaction with thionyl chloride. The addition of aqueous ammonia solution to crude product 274 afforded sulfonamide 275, which could also be used for the next step without further purification. Intramolecular 1,5-cyclization to sulfonimide 276 occurred upon dehydration of 275 using a Dean-Stark apparatus in the presence of an Amberlyst H\(^+\) ion-exchange resin. Finally, oxidation of the imine group occurred in the presence of a large excess of oxone (KHSO\(_5\)) and K\(_2\)CO\(_3\) to afford (+)-CS. Our overall yield was comparable to that given in this procedure (77%). It is imperative that CS be stored in a desiccator, and preferably under vacuum, to prevent re-formation of 276 and therefore retain the oxidative activity of CS. We used (+)-CS directly after purification followed by recrystallization and drying of the filtered product under high vacuum.
Applying Kibayashi’s hydroxylation procedure for 267 on lactam 132, which was prepared as described before (see Section 3.4.1.), we obtained (S)-277 in 84% yield (Scheme 67). Unreacted starting material (11%) was also recovered. The $^1$H NMR spectrum of (S)-277 contained a double doublet ($J = 10.5$ and $4.4$ Hz) at $\delta_{H} 4.13$, which can be attributed to the proton alpha to the lactam carbonyl group. In the $^{13}$C NMR spectrum, the carbon at this 3-position on the lactam ring was also highly deshielded at $\delta_{C} 68.2$ owing to the hydroxyl substituent. It should be noted that we did not prove unequivocally that the (S)-isomer was in fact the major product. This was an assumption based on literature precedence, as mentioned before. For simplicity, we choose here to distinguish this reaction product as (S)-277 from the racemic product [(±)-277], which was also prepared (see later). The enantiomers in (S)-277 were not resolved by chiral HPLC and 100% enantioselectivity cannot be assumed. It was again hoped that we might prove the absolute configuration of C-3, e.g. by crystallography, at a latter stage when easily separable diastereomers might be obtained. The colourless, crystalline product (S)-277 did display optical activity, i.e. $[\alpha]_{D}^{20} -28.0$ (c 0.714, CHCl$_3$). It can therefore be stated with certainty that the Davis hydroxylation reaction on 132 was, albeit to an undetermined extent, enantioselective. The optical rotations of a few 3-oxygen substituted piperidine-2-ones (presumed to be in their enantiomerically pure forms by the authors) found in the literature are given in

Scheme 66: Standard synthesis of (+)-CS.
Figure 23. It can be seen that all the optical rotations are laevorotatory for the (3S) isomers (210, 255 and 278) and dextrorotatory for the (3R) isomers (279 and 280). In fact, (3R)-N-Bn protected alcohol 280 is very similar in structure (but opposite in configuration) to our N-NAP protected alcohol (S)-277 and rotates polarized light in the opposite (+) sense. Based on this data, we expect the optical rotation of (S)-277 to be laevorotatory in CHCl₃ and this was indeed the case. We can therefore tentatively assume that the selection of (+)-CS for the oxidation of 132 (Scheme 67), based on Kibayashi’s results described earlier, proved to be successful in giving us the desired (3S)-isomer as the major product. It should also be noted that, to our knowledge, no enantioselective (as opposed to diastereoselective) 3-oxidations of simple, carbon-unsubstituted piperidin-2-ones using this methodology have been reported in the literature. This method therefore represents a new, efficient and inexpensive route to such piperidine-2-ones without the need for enzymatic resolution.

Scheme 67: Synthesis of 1-[(naphthalen-3-yl)methyl]-2-thioxopiperidin-3-yl acetate 282.

210 R₁ = H, R₂ = H
[α]D²¹⁸⁻⁵³ (c 0.8, MeOH)¹⁴⁶
[α]D²¹⁻⁶.⁰ (c 7.66, H₂O)¹⁴⁴
255 R₁ = Ac, R₂ = H
[α]D²⁵⁻ⁱ.⁵ (c 1, CHCl₃)¹⁴⁷
278 R₁ = Ac, R₂ = Bn
[α]D²⁵⁻¹⁰.⁰ (c 1, CHCl₃)¹⁴⁷
279 R₃ = H
[α]D²⁵⁺₆.⁰ (c 1, CHCl₃)¹⁴⁷
280 R₃ = Bn
[α]D²⁵⁺₁₂.⁰ (c 1, CHCl₃)¹⁴⁷
We next decided to test the simple oxidation procedure using molecular oxygen on lactam 132 to obtain racemic alcohol 277. After the use of LDA to form the enolate of 132, oxygen gas was bubbled through the reaction mixture for 2 h at 0 °C. After a standard work-up procedure, followed by column chromatography, we obtained a 53% yield of (±)-277 (Scheme 67) and some starting material was also recovered (see experimental, Section 9.3.1.2.). The spectroscopic data of (±)-277 was the same as for (S)-277 obtained previously. The presence of a hydroxyl group was easily detected in the IR spectrum of (±)-277 by the very broad band observed at 3378 cm\(^{-1}\). We decided to continue the synthesis using (±)-277 simply to test our new proposed synthesis of 1.  

O-Acetylation using a standard protocol of (±)-277 afforded an excellent yield (96%) of protected lactam 281. The acetyl CH\(_3\) protons were observed as a singlet at δ\(_H\) 2.18. The presence of the acetyl carbonyl carbon was evident from the absorption at 1744 cm\(^{-1}\) in the IR spectrum of 281. Subsequent thionation of 281 using Lawesson’s reagent afforded thiolactam 282 in 89% yield. The thiocarbonyl carbon of 282 was observed at δ\(_C\) 197.7. The alpha hydrogen (at position 3 of the ring) in 282 was, as expected, observed at a more deshielded position (δ\(_H\) 5.69) than in precursor 281 (δ\(_H\) 5.36) owing to increased electron-withdrawing by the neighbouring thiocarbonyl group in 282.

### 5.3.3. Attempted sulfide contraction on 1-[(naphthalen-3-yl)methyl]-2-thioxopiperidin-3-yl acetate 282

The Eschenmoser reaction between 282 and the key bromide 105 led to an unexpected result. Using the standard procedure, which was optimized during the model studies, we obtained none of the desired vinylogous amide 283 (Scheme 68). Instead, a mixture of inseparable compounds (two spots on TLC) was isolated as a viscous reddish-coloured oil. The R\(_f\) values for these products were approximately as expected for polar compound 283. Whilst conducting the experiment, we were initially quite certain that the vinylogous amide 283 had formed for this reason. In an effort to separate what appeared to be two diastereomers, we attempted the selective crystallization of one of the products from the mixture by dissolving it in acetone-MeOH and initiating crystallization by the addition of hexane. A colourless crystalline
product, which was almost insoluble in CHCl₃ and CH₂Cl₂, was obtained. The ¹H and ¹³C NMR spectra in DMSO-d₆ were initially puzzling and it was decided to grow single crystals in order to elucidate the structure by X-ray crystallography. The results showed that we had, in fact, isolated racemic tetrahydrothiopyran-5-one 284 (Scheme 68, see later for the crystal data). After repeated crystallizations from the crude product mixture mentioned before, we obtained a combined yield of approximately 70% for compound 284 based on the bromide 105. However, the ¹H and ¹³C NMR spectra of the crystals crops obtained were not in all cases that of completely pure 284. We believe that undetermined amounts of the other (anti) diastereomer of 284, i.e. compound 285 (Scheme 69), as well as the uncyclized thioether intermediate 286, were also isolated by co-crystallization. The determined yield of 284 is therefore not the accurate true yield, although it is certain that this was the major product (isomer).

Scheme 68: The sulfide contraction between thiolactam 282 and bromide 105.

The simplest explanation for the formation of 284 is shown in Scheme 69. It is believed that the thiolactam was hydrolyzed under conditions of basic catalysis during the second step of the Eschenmoser reaction. Only a trace amount of water in the reaction mixture would be required for this to occur in the presence of bromide 105 according to the mechanism given in Scheme 69. Hydrolysis of the thioiminium salt, formed during the S-alkylation step, results in the formation of O,S-hemiacetal 287. In the presence of base, the sulfur in 287 can react with a second equivalent of bromide 105 to form thioether 286 and lactam 281. A catalytic amount of triethylammonium
hydroxide (NHEt$_3^-$OH$^-$) then results in an intramolecular aldol reaction, through the intermediate formation of enolate 288, to afford the isolated tetrahydrothiopyran-5-one 284. The $\alpha$-hydrogens between the ketone and quinazolinyl groups in 286 are expected to be quite acidic owing to the electron-withdrawing effects on either side of this methylene group. This is reflected in the $^1$H NMR spectrum of 284, in which the corresponding methylene protons were observed as two doublets ($J = 13.0$ and 12.9) deshielded at $\delta_H$ 4.16 and 3.09. Unfortunately, we did not prove the mechanism shown in Scheme 69 by isolating lactam 281. It is thought that other side by-products were also formed, as an inseparable mixture of non-polar products (probably including 281) was obtained during purification by column chromatography.

Scheme 69: One explanation for the formation of 284.

It is therefore thought that $S$-alkylation according to the Eschenmoser mechanism of thiolactam 282 with bromide 105 did not occur to any appreciable extent during the first step (stirring in THF, Scheme 67) of the attempted Eschenmoser reaction. It is possible that the bulkiness of the $N$-NAP group, combined with the electron-
withdrawing effect of the 3-acetyl substituent on the sulfur in thiolactam 282 rendered 282 less reactive towards bromide 105. As mentioned before, TLC monitoring of these reactions during this project was not a trivial task (see Section 3.5.), especially seeing that bromide 105 is sparingly soluble in THF. Compound 105 does not completely dissolve initially during the Eschenmoser reaction. If 105 is reactive towards the specific thiolactam used, we nevertheless obtained some good results using these conditions (see Sections 3.5. and 3.6.). The problem is that one insoluble compound (105) initially, is replaced by another (the thioiminium salt) if reaction occurs, so that the presence of an insoluble precipitate after some time is not necessarily an indication that the reaction is complete. In this case for thiolactam 282, an increased amount of precipitate was visible after 18 h of stirring at rt, and TLC did not show any appreciable amount of 105 in solution. We also used a slight excess of 282 so that its presence on TLC, in turn, was not surprising. We therefore decided to continue with the sulfur extrusion reaction, as we did not want to heat the reaction mixture to ensure completion, by adding the thiophile (PPh₃) and base (NEt₃). We believe that hydrolysis occurred at this stage, as discussed above.

It is well-known that Z-enolates, such as 288, often react predominantly to yield syn-addition products, such as 284, especially when one of the carbonyl substituents is bulky 158. In the case of ketone 286, the steric bulk of the quinazolinyl group probably favours the kinetic formation of the Z-enolate 288. It can be argued that the intramolecular 6-membered cyclic chair-like transition state, as represented in Scheme 70, results. The quinazolinyl (Q) group in the enolate part of the molecule points axially away from the thioether moiety in the Z-enolate, whereas the geminal hydrogen occupies an equatorial position. This is presumably favoured for steric reasons. The quinazolinyl group alpha to the non-enolized ketone part of the molecule occupies a favourable equatorial position in the 6-membered cyclic transition state. Nucleophilic attack therefore occurs such that the bulky quinazolinyl groups end up favourably in a trans-relationship, as far apart as possible, to afford syn product 284 as the major isomer.

![Scheme 70](image_url)

Scheme 70: Proposed mechanism for the formation of the syn aldol product.

In a paper published by Asinger et al. in 1960, a similar tetrahydrothiopyran compound was described. This group studied the reactivity of $\alpha,\alpha'$-diketodisulfides. They were surprised to find that, when a mixture of disulfide 289 and 1.4 eq. of NaCN was stirred in wet diethyl ether for 120 h, they obtained tetrahydropyran-5-one 290 in 18-20% yield (Scheme 71). They realized that sodium cyanide had, in fact, cleaved the disulfide bond to yield intermediate sulfide salt 291 and thiocyanate 292. The thiocyanato group then reacted as a halogen would, by being substituted by the sulfide group in 291 to afford, in situ, thioether 293 and sodium thiocyanate. Owing to trace amounts of water in the solvent, together with the presence of NaCN, a base-catalyzed intramolecular aldol reaction occurred to afford 290. These observations are very similar to ours for the formation of 284 and further support the proposed mechanism given in Scheme 69.

Scheme 71: The preparation of 290 by Asinger et al.

The important crystal and refinement data for tetrahydrothiopyran 284 are given in Table 21.

<table>
<thead>
<tr>
<th>Crystal system</th>
<th>Triclinic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Space group</td>
<td>$P1$</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>$a = 9.6476(17)$ Å $\alpha = 77.583(3)^\circ.$</td>
</tr>
<tr>
<td></td>
<td>$b = 10.8520(19)$ Å $\beta = 69.246(3)^\circ.$</td>
</tr>
<tr>
<td></td>
<td>$c = 12.217(2)$ Å $\gamma = 71.510(3)^\circ.$</td>
</tr>
<tr>
<td>Volume</td>
<td>1126.7(3) Å$^3$</td>
</tr>
<tr>
<td>$Z$</td>
<td>2</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.416 Mg/m$^3$</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.189 mm$^{-1}$</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>$F(000)$</td>
<td>504</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.34 x 0.22 x 0.20 mm$^3$</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>1.79 to 25.00°</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-10&lt;=$h&lt;=$11, -</td>
</tr>
<tr>
<td></td>
<td>11&lt;=$k&lt;=$12, -</td>
</tr>
<tr>
<td></td>
<td>12&lt;=$l&lt;=$14</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>6064</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>3936 [$R$(int) = 0.0236]</td>
</tr>
<tr>
<td>Completeness to theta = 25.00°</td>
<td>99.1 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>None</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on $F^2$</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
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</tr>
<tr>
<td>Goodness-of-fit on $F^2$</td>
<td>1.080</td>
</tr>
<tr>
<td>Final $R$ indices [$I&gt;2\sigma(I)$]</td>
<td>$R1 = 0.0449$, $wR2 = 0.1108$</td>
</tr>
<tr>
<td>$R$ indices (all data)</td>
<td>$R1 = 0.0512$, $wR2 = 0.1144$</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.346 and -0.225 e.Å$^{-3}$</td>
</tr>
</tbody>
</table>

Table 21: Crystal data and structure refinement for 284.

It can be seen that 284 crystallized in the primitive space group $P1$, with one inversion centre, and the crystal system is triclinic. An Ortep diagram of 284 is given in Figure 24(a), together with a Mercury “wireframe” drawing (b) of 284 showing the chair conformation of the tetrahydrothiopyran-5-one ring. It can be seen that atoms C10, C11, C13 and C14 are planar, with the sulfur atom (S9) and C12 out-of-plane (Figure 24b). The C10-S9-C14 bond angle is 96.36(11)$^\circ$, i.e. considerably smaller than the tetrahedral ideal ($ca$. 109$^\circ$), owing to the constraints imposed on the sulfur bonding electrons within the six-membered ring. The C10-C11-C12 bond angle is 114.76(19)$^\circ$, i.e. also smaller than the ideal (120$^\circ$) for $sp^2$-hybridized C11 for the same reason. It can also be seen that the bulky quinazolinyl and N3-methylquinazolinyl substituents on the chair-like 6-membered ring lie trans-equatorial so as to minimize steric repulsion between each other, as well as with the ring. The thioether C-S bonds, C10-S9 and S9-C14, are 1.815(2) and 1.814(2) Å, respectively. This is slightly smaller than the mean value for this bond distance, i.e. 1.823 Å, in tetrahydrothiopyrans \textsuperscript{127}.\textsuperscript{127}
The endocyclic carbonyl bond, C11-O2, is 1.209(3) Å in length. As expected, the quinazolinyln amide carbonyl bonds, C4-O1 [1.220(3) Å] and C4'-O1' [1.231(3) Å], are longer owing to conjugation with nitrogen within the respective heteroaromatic rings. The C13-O3 bond in the alcohol is shorter [1.412(2) Å] than average (mean bond length for C2-CH-OH is 1.432 Å) because the O3 atom is involved as a donor in relatively strong hydrogen bonding (see later).

Figure 24: Ortep (showing 50% ellipsoid probability) and Mercury diagrams of 284.

Figure 25 (a) shows clearly the centrosymmetry between the two molecules comprising the asymmetric unit in 284, whereas Figure 25 (b) illustrates, by expansion, the intermolecular H-bonding found in the structure of 284.

Figure 25: Packing in structure 284.
It can be seen that intermolecular hydrogen bonds (of magnitude 2.798 Å) are found between O3 as donor and N1 as acceptor. It is well-known that conjugated imine nitrogens (N1 in 284), e.g. those found in purine and pyrimidine bases in DNA, are good H-bond acceptors. Furthermore, it can be seen that the electron-rich heteroaromatic quinazolinone ring of one molecule interacts through π-stacking with the electron-poorer tetrahydrothiopyran ring of a neighbouring molecule (Figure 25b) so that tandem hydrogen bonds are formed between each molecular pair. These forces result in very dense packing in the crystal lattice, which explains the high melting point observed for 284.

5.3.4. Oxidations of N-(4-methoxybenzyl) protected piperidin-2-ones

It is possible that S-alkylation of thiolactam 282 (see previous section) was hampered by the steric bulkiness of the N-NAP group, combined with the presence of the O-acetyl group, both in close proximity to the sulfur atom in 282. Furthermore, the strongly electron-withdrawing nature of the acetyl group on carbon 3 (alpha to the thiocarbonyl group) in 282 might decrease the nucleophilicity of the neighbouring sulfur atom. It can be recalled that we also obtained a reduced yield of the N-NAP model vinylogous amide (see Section 3.5.), as compared to the other N-alkyl protected analogues. For these reasons, it was decided to alter our proposed synthesis by using different protecting groups. We opted for the 4-methoxybenzyl (PMB) group on the nitrogen in the piperidine moiety, as this functions as a protecting group for both amides and amines. The aim was to prepare lactam 294 (Scheme 72), which could serve as a key intermediate both for the preparation of 210 (by amide nitrogen deprotection) and for the eventual synthesis of febrifugine (+)-1. Furthermore, in this proposed route towards (+)-1, we would again need to protect the hydroxyl group in 294 for reasons explained earlier. For this purpose, we initially opted for the benzyl (Bn) group. This represents an electron-donating protecting group on oxygen, as opposed to electron-withdrawing such as the acetyl group, which led to disappointing results; i.e. racemization in the respective thiolactams occurred during the Quirion (Section 5.1.3.) and arginine (Section 5.2.2.) approaches, and presumably no Eschenmoser reaction occurred with the O-acetyl thiolactam in Section 5.3.2 (see above). It is often a good idea in organic synthesis to change the protecting groups
when a route is not working as planned. The nature of the selected protecting group might significantly affect the reactivity of synthetic intermediates, in addition to altering the stability, isolability and/or yields of these.

Starting lactam 222 was prepared in 63% yield according to the procedure used before (see Section 4.3.1.) from piperidin-2-one (Scheme 72). The benzylic protons in 222 appeared as a singlet at $\delta_H 4.53$ in the $^1H$ NMR spectrum and the methoxy OCH$_3$ protons were observed as a singlet at $\delta_H 3.79$. Using similar conditions to those implemented previously for the preparation of (S)-277 (Scheme 67), but extending the oxidation time to 16 h at −60 to −70 ºC, we managed to obtain a satisfactory yield (75%) of key alcohol 294. The optical activity of 294 was similar (laevorotatory; $[\alpha]_D^{294} -6.89$ in CHCl$_3$) to that observed previously for (S)-277. This again pointed to the probability that the desired (3S)-enantiomer was obtained as the major product. The hydroxyl proton was observed at 294 as a singlet at $\delta_H 3.22$ and the infrared spectrum also indicated the presence of an O-H stretching frequency as a broad band at 3412 cm$^{-1}$. The alpha ring proton in 294 was observed as a double doublet ($J = 10.7$ and 6.0) highly deshielded at $\delta_H 4.07$. In the $^{13}$C NMR spectrum, the corresponding alpha carbon was observed at $\delta_C 68.2$.

Scheme 72: Using the N-PMB protecting group.

With 294 in hand, we were in a position to attempt the preparation of natural product (3S)-hydroxypiperidine-2-one 210. Unfortunately, all the attempts at deprotecting the PMB group in 294 failed (see also the experimental, Section 9.3.2.3.). Standard N-PMB deprotection conditions using CAN and CH$_3$CN:H$_2$O (10:1) failed to produce the desired lactam 210. It seemed that aromatization of the lactam
ring to pyridine derivatives might have occurred, as mostly aromatic signals (reminiscent of a mixture of such derivatives) were observed in the $^1$H NMR spectrum of the unidentifiable, isolated crude product. The signals in this spectrum did not indicate the presence of a PMB residue. Only starting material was recovered when 294 was hydrogenated, following a known procedure $^{160}$, over PdCl$_2$ using EtOAc:AcOH (9:1) as the solvent. Finally, using a method published recently $^{161}$ for the N-PMB deprotection of peptides, 294 was refluxed in neat TFA for 1 h, followed by evaporation in vacuo of the excess TFA. Column chromatography of the residue led to the isolation of what appeared to be the trifluoroacetate salt of 294. Although all the signals in the $^1$H NMR spectrum, except those belonging to the PMB protons, displayed less coupling than expected and appeared as broad singlets, the chemical shifts and integrals pointed to the structure of starting material 294. The R$_f$-value of this very polar compound was, however, very different to that of the starting material. The resistance of the PMB group to be cleaved from lactam 294 using the latter procedure cannot be easily explained. Owing to time constraints, we did not further attempt this preparation of 210.

Scheme 73: Attempted preparation of 298.

Benzylation of alcohol 294 using BnBr and NaH proceeded in moderate yield to afford lactam 295 (Scheme 73). Two groups of “benzylic” protons were observed in the $^1$H NMR spectrum of 295, the first two protons appeared as doublets at $\delta_H$ 5.01 ($J = 12.0$ Hz) and 4.79 ($J = 12.0$ Hz) and can be attributed to the benzyl group. The next
two protons were observed as doublets at $\delta_H 4.55$ ($J = 14.4$ Hz) and $4.49$ ($J = 14.4$ Hz) and can be attributed to the PMB group. The subsequent thionation procedure on 294 using Lawesson’s reagent in benzene afforded a satisfying yield (98%) of key thiolactam 296. Owing to the presence of the strongly electron-withdrawing sulfur atom, both groups of benzylic protons were observed at more deshielded positions ($\delta_H 5.30, 5.11$ and $4.98, 4.77$) than the corresponding protons in 294 (see above). The presence of the thiocarbonyl group is evident from the $^{13}C$ NMR spectrum, which exhibited a peak at $\delta_C 198.6$. The Eschenmoser reaction between 296 and bromide 105 proved to more successful in this case. We isolated, after column chromatography, a 62% yield of the desired (albeit crude) vinylogous amide 297. Trace amounts of what appeared to be (from the $^1H$ and $^{13}C$ NMR spectra) a geometric isomer, remained in the isolated product after several repeated column chromatographic purifications. Unfortunately, repeated attempts at crystallizing the major product from the product mixture failed. It was therefore impossible to characterize fully the major geometric isomer of 297, owing to the crowded NMR spectra obtained of the crude oil. In the $^1H$ NMR spectrum of the product 297 obtained after several attempted purifications [$R_f 0.52$ (EtOAc)], all the expected signals were observed quite clearly in the aromatic region, e.g. the major isomer showed the expected doublet ($J = 8.2$ Hz) at $\delta_H 8.28$ corresponding to H-5 in the quinazolinone moiety. A singlet at $\delta_H 7.94$ corresponded to H-2 in the same isomer of 297. Another smaller doublet and a smaller singlet in this region can be attributed to the corresponding signals of the minor isomer. The three remaining multiplets at $ca. \delta_H 7.2-7.8$ integrated for the remaining quinazolinone and benzyl protons, whose signals overlapped. The PMB aromatic protons were clearly observed as two doublets ($J = 8.5$ and 8.6, respectively) for the meta protons ($\delta_H 7.05$) and the ortho protons ($\delta_H 6.80$), respectively. These doublets integrated for approximately two protons each. It is thought that the minor isomer’s corresponding signals overlapped exactly with that of the major isomer for these PMB protons, as no other smaller doublets were observed in this region. Although the two groups of benzylic protons in the major isomer were observed as a group of doublets at the expected chemical shifts ($\delta_H ca. 4.3-5.3$), some of these signals overlapped and the corresponding peaks attributed to the minor isomer interfered with the accurate characterization of these doublets in this region of the spectrum. The same applies to the aliphatic peaks corresponding to the
piperidinylidene ring, which were observed in the expected lower field region of the spectrum. A relatively clearly distinguishable multiplet, integrating for one proton, at $\delta_H$ 3.73 corresponds to the expected peak for H-3” in the piperidinylidene ring of 297. However, the multiplicity could once again not be accurately ascertained owing to the presence of some smaller overlapping peaks here, which could be attributed to the corresponding proton in the minor isomer. We were therefore convinced that we had indeed obtained the correct product, but as a mixture of practically completely inseparable geometric isomers.

It was anticipated that, owing to the bulkiness of the O-Bn group, the preference for the E-isomer when the piperidinylidene nitrogen is protected, might not be as prevalent here as was observed for all the other N-protected vinylogous amides prepared during this project. It is therefore probable that a small amount of the Z-isomer, inseparable from the E-isomer, also formed in this case.

As predicted before, the use of aromatic protecting groups (PMB and Bn) certainly complicated the NMR spectra obtained for quinazolinyl-containing vinylogous amide 297, which made conclusive characterization tricky. It was decided to continue with the proposed route in the hope of obtaining a crystalline and characterizable intermediate. Unfortunately, two attempts at O-Bn deprotection failed. Following a standard protocol, crude 297 was subjected to hydrogenation (first in EtOAc then in EtOH) over 10% Pd/C under 1 atm of H$_2$ gas in an attempt to form alcohol 298. In both cases, only starting material was recovered.

Disappointed by these results, we decided to opt again for a different protecting group on oxygen, the tert-butyldimethylsilyl (TBDMS) group. This group would certainly aid NMR spectrum characterization during the latter stages of the synthesis, and it also represents an electron-donating group (different to the acetyl group). Scheme 74 summarizes the results obtained using the TBDMS group.
Scheme 74: Using O-TBDMS protection.

The TBDMS protection of 294, using TBDMSCl and imidazole, afforded 299 in 75% yield. The presence of the TBDMS group was evident from the $^1$H NMR spectrum of 299. One equivalent group of nine protons appeared as a singlet at $\delta_H$ 0.92, i.e. the C(CH$_3$)$_3$ group and the six methyl protons in the TBDMS group were observed as two singlets (i.e. these methyl groups are non-equivalent owing to the stereogenic centre at C-3 of the ring) at $\delta_H$ 0.17 and 0.19. Subsequent thionation of 299 using Lawesson’s method yielded thiolactam 300 in 83% yield. The thiocarbonyl carbon absorbed at $\delta_C$ 200.7 in the $^{13}$C NMR spectrum of 300, highly deshielded as seen before also for the other thiolactams in this project. The two ring NCH$_2$ protons were observed as two quintets (theoretically, as two ddd) at $\delta_H$ 3.55 and 3.24, respectively, in the $^1$H NMR spectrum of 300. Unfortunately, the Eschenmoser reaction between thiolactam 300 and quinazolinone-containing bromide 105 did not produce the desired vinylogous amide 301 in any appreciable amount. A complex mixture of unidentifiable products was obtained instead. It is quite possible that the steric bulk of the TBDMS group might prevent the desired Eschenmoser reaction from occurring. Base-catalyzed side-reactions might have resulted in partial decomposition of the reactants instead, which is why we obtained a mixture of inseparable products. This result is further discussed in section 5.3.7.
5.3.5. Crystal structure of 294

As demonstrated in previous sections, the Davis hydroxylation reaction using (+)-CS proved to be a useful and high-yielding route for the procurement of optically active 3-hydroxy substituted piperidine-2-ones. In an effort to prove that the configuration of our major product was as expected from the literature, i.e. the 3S configuration, we hoped to isolate an enantiomerically pure single crystal for X-ray diffraction purposes. It was argued that, if the enantiomeric excess of this reaction was as high as might be expected, the chances of obtaining such a crystal would be very high. However, to our great disappointment, a suitable single crystal was found to be that of racemic (±)-294. No obvious morphological differences were observed under the microscope between different crystals in the same batch from which the characterized crystal was selected. However, the optical data of this sample suggested that there was an excess of the 3S isomer ([\(\alpha\)]D\textsubscript{20} = −6.89 in CHCl\textsubscript{3}). We were nevertheless pleased to be able to characterize structure (±)-294 by single crystal X-ray diffraction. The important crystal and refinement data are shown in Table 22.

<table>
<thead>
<tr>
<th>Crystal system</th>
<th>Monoclinic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Space group</td>
<td>(P2_1/c)</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>(a = 12.980(3)) Å (\alpha = 90^\circ).</td>
</tr>
<tr>
<td></td>
<td>(b = 7.6143(17)) Å (\beta = 90.497(5)^\circ).</td>
</tr>
<tr>
<td></td>
<td>(c = 12.189(3)) Å (\gamma = 90^\circ).</td>
</tr>
<tr>
<td>Volume</td>
<td>1204.6(5) Å(^3)</td>
</tr>
<tr>
<td>(Z)</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.296 Mg/m(^3)</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.092 mm(^{-1})</td>
</tr>
<tr>
<td>(F(000))</td>
<td>504</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.32 x 0.26 x 0.18 mm(^3)</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>3.10 to 28.00(^\circ).</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-14(&lt;=h&lt;=17), -10(&lt;=k&lt;=10), -16(&lt;=l&lt;=9)</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>8378</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>2895 ([R(int) = 0.0265])</td>
</tr>
<tr>
<td>Completeness to theta = 28.00(^\circ)</td>
<td>99.9%</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>None</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on (F^2)</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>2895 / 0 / 156</td>
</tr>
</tbody>
</table>
Goodness-of-fit on $F^2$ & 1.077 \\
Final $R$ indices [$>2\sigma(I)$] & $R1 = 0.0422$, $wR2 = 0.1185$ \\
$R$ indices (all data) & $R1 = 0.0542$, $wR2 = 0.1260$ \\
Largest diff. peak and hole & 0.519 and -0.239 e.Å$^{-3}$

Table 22: Selected crystal and refinement data for (±)-294.

An Ortep diagram of molecule 294 is shown in Figure 26, together with a Mercury “wireframe” drawing showing a side view of 294.

![Figure 26: Ortep (showing 50% ellipsoid probability) and Mercury (side view with hydrogens removed) drawings of molecule 294.](image)

It can clearly be seen from the Mercury drawing that the lactam ring adopts a flat half-chair conformation, i.e. C6, N1, C2 and C3 are planar, whereas C4 and C5 are twisted slightly out-of-plane. This is reflected by the torsion angles given in Table 23; entries 1-4 show that the amide group in the lactam ring is practically planar, whereas entries 5 and 6 show that atoms C4 and C5 are approximately equally out-of-plane (ca. 20.8° and 19.3°, respectively) with the other atoms in the ring. Entry 7 in Table 23 shows that the PMB aryl ring lies roughly perpendicular to the plane of the lactam ring. The carbonyl bond length [1.2382 (16) Å] is slightly longer than the mean value (1.233 Å) reported for this bond in δ-lactams, owing to relatively strong intermolecular hydrogen bonds of which this group is the acceptor (see later). For the same reason, the C3-O2 bond (in the H-bond donor alcohol) is slightly shorter [1.4033 (16) Å] than the mean distance (1.432 Å) reported for such (C2-CH-OH) bonds.$^{127}$
<table>
<thead>
<tr>
<th>Entry</th>
<th>Torsion angle</th>
<th>Degrees</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O1-C2-N1-C6</td>
<td>176.47 (12)</td>
</tr>
<tr>
<td>2</td>
<td>C3-C2-N1-C6</td>
<td>-4.88 (18)</td>
</tr>
<tr>
<td>3</td>
<td>O1-C2-N1-C7</td>
<td>4.34 (18)</td>
</tr>
<tr>
<td>4</td>
<td>C3-C2-N1-C7</td>
<td>-177.01 (10)</td>
</tr>
<tr>
<td>5</td>
<td>N1-C2-C3-C4</td>
<td>20.78 (15)</td>
</tr>
<tr>
<td>6</td>
<td>C5-C6-N1-C2</td>
<td>19.25 (17)</td>
</tr>
<tr>
<td>7</td>
<td>C8-C7-N1-C2</td>
<td>98.17 (13)</td>
</tr>
</tbody>
</table>

Table 23: Selected torsion angles in structure 294.

Figure 27 represents the unit cell in crystal structure 294. One additional molecule is shown outside the cell to demonstrate H-bonding in 294. There are four molecules, which are related by an inversion centre, in each unit cell. Two hydrogen bonds, resulting from complementary amide-alcohol interactions, are formed between each pair of molecules to form dimers. The length of these O(2)···O(1) intermolecular contacts is 2.773 Å. The corresponding O(2)-H(2)···O(1) distance is 1.964 Å.

Figure 27: Representation of a unit cell in (±)-294, expanded to show intermolecular O(2)···O(1) contacts arising from hydrogen bonding.
5.3.6. Crystal structure of 296

As a sample of the obtained key thiolactam product 296 also displayed optical activity ([α]D<sup>20</sup> = -3.9 in CHCl₃), it was decided to characterize this compound by single crystal X-ray diffraction. The presence of a relatively heavy atom, sulfur, in the structure of 296 would facilitate the determination of absolute configuration should the crystal be enantiomerically pure. However, unfortunately a centrosymmetrical crystal was again selected, the important data of which are given in Table 24.

<table>
<thead>
<tr>
<th>Crystal system</th>
<th>Orthorhombic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Space group</td>
<td>Pbca</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>(a = 18.371(3) \text{ Å} \quad \alpha = 90^\circ).</td>
</tr>
<tr>
<td></td>
<td>(b = 10.4844(15) \text{ Å} \quad \beta = 90^\circ).</td>
</tr>
<tr>
<td></td>
<td>(c = 18.467(3) \text{ Å} \quad \gamma = 90^\circ).</td>
</tr>
<tr>
<td>Volume</td>
<td>3556.9(9) \text{ Å}³</td>
</tr>
<tr>
<td>(Z)</td>
<td>8</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.275 \text{ Mg/m}^3</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.194 mm⁻¹</td>
</tr>
<tr>
<td>(F(000))</td>
<td>1456</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.47 x 0.28 x 0.05 mm³</td>
</tr>
<tr>
<td>Theta range for data collection</td>
<td>2.21 to 28.00°.</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-24 &lt;= h &lt;= 19, -13 &lt;= k &lt;= 13, -23 &lt;= l &lt;= 24</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>22717</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>4286 ([R(\text{int}) = 0.0460])</td>
</tr>
<tr>
<td>Completeness to theta = 28.00°</td>
<td>99.9 %</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>None</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on (F^2)</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>4286 / 0 / 218</td>
</tr>
<tr>
<td>Goodness-of-fit on (F^2)</td>
<td>1.011</td>
</tr>
<tr>
<td>Final (R) indices ([I&gt;2\sigma(I)])</td>
<td>(R_1 = 0.0374, \ wR_2 = 0.0871)</td>
</tr>
<tr>
<td>(R) indices (all data)</td>
<td>(R_1 = 0.0674, \ wR_2 = 0.0981)</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.259 and -0.261 eÅ⁻³</td>
</tr>
</tbody>
</table>

Table 24: Selected crystal and refinement data for 296.
It can be seen that, similar to 3-amino-Boc protected thiolactam 204 (Section 4.2.2.), 296 crystallizes as orthorhombic crystals in the $Pbca$ space group. Ortep and Mercury diagrams are shown, as for structure 294 above, in Figure 28.

Figure 28: Ortep (showing 50% ellipsoid probability) and Mercury (side view with hydrogens removed) drawings of molecule 296.

Similar to the other thiolactams (204, 260) and the lactam (294) structures determined in this project, the lactam ring in 296 crystallizes in the half-chair-conformation, with atoms C4 and C5 out-of-plane. For completeness, the torsion angles selected before for precursor 294 (Table 23) are compared with those in 296, in Table 25 below.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Torsion angle</th>
<th>294 (degrees)</th>
<th>296 (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O1(S)-C2-N1-C6</td>
<td>176.47 (12)</td>
<td>-179.75 (12)</td>
</tr>
<tr>
<td>2</td>
<td>C3-C2-N1-C6</td>
<td>-4.88 (18)</td>
<td>-1.2 (2)</td>
</tr>
<tr>
<td>3</td>
<td>O1-C2-N1-C7</td>
<td>4.34 (18)</td>
<td>2.5 (2)</td>
</tr>
<tr>
<td>4</td>
<td>C3-C2-N1-C7</td>
<td>-177.01 (10)</td>
<td>-178.97 (12)</td>
</tr>
<tr>
<td>5</td>
<td>N1-C2-C3-C4</td>
<td>20.78 (15)</td>
<td>20.40 (19)</td>
</tr>
<tr>
<td>6</td>
<td>C5-C6-N1-C2</td>
<td>19.25 (17)</td>
<td>13.5 (2)</td>
</tr>
<tr>
<td>7</td>
<td>C8-C7-N1-C2</td>
<td>98.17 (13)</td>
<td>112.23 (15)</td>
</tr>
</tbody>
</table>

Table 25: Comparison between selected torsion angles in structures 294 and 296. Note that O1 in 294 is equivalent to S in 296.
It can be seen that, in contrast to thiolactam 204 (Section 4.2.2.), the thioamide group in 296 is practically completely planar (entries 1-4) and even more so than the amide group in precursor 294. Although C4 in 296 is almost equally out-of-plane in the ring as in lactam 294 (entry 5), C5 is slightly less out-of-plane in 296 (entry 6). The PMB aryl ring is bent slightly further away from the thioamide group in 296 (entry 7) than from the equivalent amide group in 294. It can clearly be seen from the Mercury drawing in Figure 28 that the benzyloxy substituent occupies an axial position on C3 in order to be as far away as possible from both the thiolactam ring and the PMB group. The thiocarbonyl bond length in 296 is 1.6788 (15) Å, intermediate to that found in thiolactams 204 (1.6755 Å) and 260 (1.683 Å).

It was interesting to find, during an extensive search of the Cambridge Crystallography Database, that very few thiolactam crystal structures have been published. None of the limited structures published are those of simple thiolactams such as 204, 260 and 296, of which the crystal structures were determined in this project. The published thiolactams are all either complex, ring multi-substituted compounds, or fused-ring compounds.

5.3.7. Oxidation of N-methylpiperidin-2-one and sulfide contraction attempt without using a hydroxyl protecting group

In 2000, Ma and Sun 162 published an efficient total synthesis of (2S,3S,4R)-plakoridine A (302), which is very relevant to this project for reasons mentioned below. An outline of the synthesis is given in Scheme 75.

It can be seen that 302 is an enaminone, the pyrrolidinylidene part of which is similar (owing to 3-hydroxyl group substitution in the ring) to the piperidine moiety in our natural target (+)-1. One major difference is that (+)-1 contains a 6-membered (piperidine) ring, as opposed to the 5-membered ring in 302. A second difference is that the other carbons in the piperidine ring of (+)-1 are unsubstituted, whereas both remaining ring carbons 302 bear substituents (a propyl and a methoxycarbonyl group, respectively).
Scheme 75: Ma’s synthesis of (2S,3S,4R)-plakoridine A.

The most obvious synthetic approach to 302 is the use of an enaminone-forming reaction as key step for the total synthesis. Similar to our strategy, Ma opted for the Eschenmoser methodology. Ma’s synthesis constitutes, to our knowledge, the only example in the literature of an Eschenmoser reaction using a thiolactam α-substituted with a heteroatom.
Starting from ethyl 4-hydroxyphenylacetate, Ma’s group managed to prepare lactam 303 over numerous steps, the details of which are not applicable to this discussion. Initially, Ma opted to acetylate both alcohol groups first in 303 to obtain 304, after thionation of the intermediate lactam. For the subsequent key Eschenmoser reaction between 304 and the appropriate α-keto-bromide, silver triflate was used to facilitate the S-alkylation step. The other conditions were according to standard protocol. However, the only product isolated after work-up was polysubstituted pyrrole 305. No yields were given for any of these steps. Ma mentioned that pyrrole 305 could result from the elimination of the acetoxy group on the ring. Presumably the intermediate thioiminium salt, upon the addition of base, was deprotonated on C-4 of the thiopiperidone ring (next to the acetoxy group, which is bound to C-3), which resulted in the (E2) elimination of the acetate ion. Aromatization followed by the subsequent deprotonation of the propyl-substituted carbon (C-5) to afford stable pyrrole 305. The desired exocyclic α-deprotonation therefore did not occur. The same result was obtained when thiolactam 306 (Scheme 75) was reacted with the bromide. It is important to note that both 304 and 306 contain a trans-3-acetoxy (or hydroxyl), 4-hydrogen geometrical relationship. This facilitates E2 elimination under basic conditions. When thiolactam 307 was used, in which this relationship is cis, E2 elimination was suppressed and success was achieved in preparing the desired vinylogous amide 308 (Scheme 75). After TBDPS deprotection of 308 using tetrabutylammonium fluoride in AcOH, the desired plakoridine A (302) was obtained.

Ma also reported that O-TBDMS protected thiolactam 309 did not react at all with the bromide during another Eschenmoser reaction trial. This was attributed to the bulkiness of the TBDMS group, which presumably prevents the sulfur in 309 from accessing the α-carbon in the bromide. This might also explain our disappointing result before, when we attempted to react thiolactam 300 with bromide 105 (Scheme 74, Section 5.3.4.). However, in this case, we did not recover much of the starting material, but isolated a mixture of unidentifiable products. Most importantly, Ma’s synthesis demonstrates that the standard Eschenmoser reaction can work efficiently when a thiolactam (307) which contains free hydroxyl group is used.
Finally, an important point needs to be raised here. Could epimerization at the \( \alpha \)-carbon (C-3) in the ring also occur during other stages of Ma’s route by the competitive deprotonation mechanism we discussed before for thiolactams (Section 4.2.1.) and thiolactams (Section 5.2.2.)? The electron-withdrawing effect of a substituent such as the acetoxy group on the \( \alpha \)-carbon (C-3) might enhance the acidity of the hydrogen on the \( \alpha \)-carbon. Intriguingly, Ma mentioned that the plakoridine A they prepared using the route in Scheme 73, displayed an optical activity ([\( \alpha \)]\( _{D}^{20} \) –43.0 in CHCl\(_3\)) very different to that observed by Kobayashi’s group ([\( \alpha \)]\( _{D}^{20} \) –0.4 in CHCl\(_3\)) for the natural product, \((2S,3S,4R)\)-plakoridine (302). Ma offered the explanation that the natural plakoridine A isolated by Kobayashi’s group could, in fact, have been racemic. Ma also mentioned that the spectral data of their obtained product were all in agreement with those of Kobayashi.

We decided to check whether Ma’s synthetic strategy towards plakoridine A could be applicable to the synthesis of \( \text{N-methylfebrifugine} \) 310, an important analogue of \((+)-1\), which has not been synthesized before. We opted for the methyl group on nitrogen because this simple group would not complicate the NMR spectral data of advanced intermediates, and because we had at our disposal the commercially available starting material, \( 1\)-methylpiperidin-2-one.

As an initial trial, we attempted the preparation of racemic lactam 311 (Scheme 76) from \( 1\)-methylpiperidin-2-one by the molecular oxygen \( \alpha \)-hydroxylation procedure, as described before for the preparation of analogue \((\pm)-277\) (see Section 5.3.2.), followed by TBDMS \( O \)-protection. The intermediate alcohol, \( 1\)-methyl-3-hydroxypiperidin-2-one (272, Scheme 65, Section 5.3.1.), has been synthesized before by Wasserman and Lipshutz 156 using the same conditions (i.e. LDA, followed by \( O_2 \)). When we repeated their reaction, we obtained a new compound, 3-hydroxy-3-isopropyl-1-methylpiperidin-2-one (312) in 42% yield (Scheme 76). Wasserman and Lipshutz made clear the necessity of using an excess of LDA (2.2 eq.) in order to ensure the maximum conversion of \( 1\)-methylpiperidin-2-one into 272. The only difference in our procedure was that we used even slightly more LDA (2.6 eq.). As we generated the
LDA *in situ*, and only allowed the reaction between BuLi and diisopropylamine (DIA) to proceed for 20 min. at –70 °C, it is possible that some of the amine might still have been present when the 1-methylpiperidin-2-one was added. The mechanism of the reaction, which occurred to produce 312, cannot be explained. It is certain, from the NMR, IR and mass spectrum data that 312 was indeed the product we obtained. After column chromatography, the obtained product 312 (a single spot on TLC) was dried for an extended period of time under high vacuum. This eliminated the slight possibility that some diisopropylamine still remained in the liquid product.

Scheme 76: Attempt without hydroxyl group protection.

The $^1$H NMR spectrum of 312 contains a singlet at $\delta_H$ 6.46, which integrates for one proton and could be assigned to the OH proton. Although this is an unexpectedly low chemical shift for an aliphatic alcohol, the neighbouring amide group might cause such deshielding. Furthermore, although we did not measure the concentration of 312 in our $^1$H NMR sample, intermolecular hydrogen bonding with the amide carbonyl in a concentrated NMR sample might also deshield the hydroxyl proton. Furthermore, a doublet integrating exactly for six protons at $\delta_H$ 1.18 points to the presence of the isopropyl group [i.e. the CH($CH_3$)$_2$ signal]. The other signals are at the expected chemical shifts and integrate for the correct number of remaining protons. The multiplicities of these remaining signals are difficult to interpret owing to extensive
coupling, but do follow the trend expected for 312, i.e. in general multiple doublets are observed, except for a crowded multiplet at \( \delta_H 1.90-2.07 \). This multiplet integrates for two protons and was assigned to the overlapping signals of one of the \( OCCH_2 \) protons and the \( CH(CH_3)_2 \) proton, the signal of which is expected to be a septuplet. The \(^1^3\)C NMR spectrum is as expected. The carbonyl carbon is observed at \( \delta_C 173.3 \), and the quaternary \( \alpha \)-carbon is observed in a highly deshielded position at \( \delta_C 72.4 \).

There is, however, one additional signal in the shielded aliphatic region. Four signals in this region (at \( \delta_C 28.1, 24.6, 24.4 \) and 22.4) cannot be easily assigned. Two of the signals are definitely attributable to the NCH\(_2\)CH\(_2\) and the isopropyl CH(CH\(_3\))\(_2\) carbons. The remaining two signals (possibly the closely spaced \( \delta_C 24.6 \) and 24.4 signals) are attributable to the diastereotopic isopropyl CH(CH\(_3\))\(_2\) carbons. The IR spectrum clearly shows the presence of a hydroxyl group (a broad band is observed at 3354 cm\(^{-1}\)). The mass spectrum contains a very small molecular ion (\( M^+ \)) peak at \( m/z 171 \) and of 1% intensity. The next largest mass peak (of 49% intensity) is at \( m/z 156 \) (i.e. \( M^+-\text{CH}_3 \)). Therefore, all the spectral data recorded for this product point to structure 312. We could, however, not find another example of such a trans-alkylation reaction in the literature.

Seeing that we achieved success before in the Davis hydroxylation procedures using LiHMDS as the base, we decided to use this base instead of LDA. After treatment of the resultant enolate with gaseous oxygen at 0 °C for 10 min, an inseparable mixture (as evident from the crude \(^1^H\) NMR spectrum) of 1-methyl-3-hydroxypiperidin-2-one and the starting lactam was obtained. It was decided to subject this crude product mixture directly to standard TBDMS hydroxyl group protection conditions (TBDMSCl, imidazole)\(^{163}\). The desired lactam 311 (Scheme 76) was obtained in a very low yield (7%) over two steps from 1-methylpiperidin-2-one. The \(^1^H\) NMR spectrum of 311 indicated the presence of the TBDMS group. A singlet at \( \delta_H 0.89 \), which integrated for nine protons, was attributable to the \( C(CH_3)\(_3\) \) protons. Two singlets, integrating for three protons each, were observed at \( \delta_H 0.12 \) and 0.15, and could be assigned to the diastereotopic methyl groups on silicon. In the \(^1^3\)C NMR spectrum of 311, the carbonyl carbon was observed at \( \delta_C 170.3 \) and the \( \alpha \)-carbon was observed, owing to the oxygen substituent, in a highly deshielded position at \( \delta_C 69.4 \).

In this case, we observed no signs of side-products such as 312 (Scheme 76). The
only intermediates isolated, or visible on TLC, were starting material and the desired intermediate alcohol. After TBDMS protection, we also did not detect any other isolable products. Oxygenation was allowed to proceed only for 10 min, as Wasserman and Lipshutz had established this step to be practically instantaneous. It was thought that extended reaction time would not likely improve the yield and we wanted to minimize possible oxidative side-reactions. It should be noted that we did not make use of any custom-made apparatus, as mentioned by Wasserman and Lipshutz, for the enolate oxygenation procedures conducted during this project. It is interesting that no starting material was recovered after the TBDMS protection step.

Seeing that we were sure that we could optimize all the poor yields obtained during the first trial of this approach at a later stage, should the approach prove to be promising, we decided to continue this route on a small scale with the material (311) in hand. Thionation of 311 using Curphey’s method (P₂S₅, HMDO)⁹⁴ gave a very disappointing yield (34%) of prerequisite thiolactam 313. The work-up procedure used (saturated aq. NaHCO₃) might sometimes significantly reduce the yields of certain thiolactams when this procedure is used. It is thought that e.g. base-catalyzed polymerization might occur, particularly if the thiolactam is slightly water-soluble. An alternative method, e.g. filtration of the reaction mixture through celite before column purification, is recommended. The neighbouring thiocarbonyl carbon in 313 caused a deshielding of the α-carbon, which was observed at δ_H 4.60 [as compared to the corresponding proton, observed at δ_H 4.07, in lactam precursor 311]. The thiocarbonyl stretching frequency was observed as a strong band at 1527 cm⁻¹ in the IR spectrum of 313. This time we decided to deprotect 313 prior to attempting the Eschenmoser reaction. A standard protocol¹⁶⁴ using p-toluenesulfonic acid hydrate, and a mixture of CH₂Cl₂ and MeOH as solvent, was used for this purpose. Again a lower-than-expected yield (43%) of the new compound 1-methyl-3-hydroxypiperidine-2-thione (314) was obtained as the only isolable material. The free hydroxyl group in 314 was clearly evident from the IR spectrum (a broad band was observed at 3297 cm⁻¹) and from the ¹H NMR spectrum (a broad singlet was observed at δ_H 4.62). The CH₃ protons in 314 were observed as a singlet at δ_H 3.47. In the IR spectrum, a strong thiocarbonyl band was observed at 1539 cm⁻¹.
Using our well-established conditions, the Eschenmoser reaction between 314 and bromide 105 did not seem to proceed to any appreciable extent at room temperature. As mentioned before, bromide 105 is quite insoluble in THF unless it is reactive enough towards the specific thiolactam used. As we were attempting this reaction on a very small scale, i.e. reacting only 8 mg of 314, we decided to use an excess of 105 so that the reaction could be easily monitored by observing the disappearance of soluble 314 alone by TLC. After stirring the reaction mixture at room temperature for 15 h, 314 was still present (in seemingly high concentration) by TLC. It was decided to add more of the bromide 105 at this stage and the temperature was elevated to reflux conditions for 1 h. At this stage, none of the thiolactam was present by TLC and the reactants had both formed a precipitate (presumably the intermediate thioiminium salt). The second step was then carried out as discussed before, by the addition of PPh3 and NEt3. After the base was added, all the material dissolved and the reaction mixture turned an orange colour, as observed before in similar experiments. TLC indicated one polar product of similar Rf-value to that expected for vinlylogous amide 315. However, after the standard work-up procedure, a very small amount (a few milligrams) of an unidentifiable aromatic compound was obtained. It was impossible to characterize this product properly. Unfortunately, owing to time constraints, this route was not repeated. Future work includes the optimization of the route given in Scheme 76. It is hoped that, should the Eschenmoser reaction between 314 and 105 be conducted on a larger scale, one might be able to isolate and characterize all the products more easily in order to understand what is happening during this reaction. Considering Ma’s results (see Scheme 75, pyrrole 305), it seems possible by dehydration to obtain tetrahydropyridine intermediate 316. In fact, as will be seen in Chapter 6, a six-membered cyclic thioiminium salt intermediate (such as the one expected to form here) is more likely than a five-membered analogue (e.g. in Ma’s reaction between thiolactam 304 and the bromide 162, Scheme 75) to react by endocyclic elimination. In other words, it is less favoured for any given six-membered cyclic compound to form an exocyclic double bond than it is for a five-membered analogous compound. The question is, if compound 316 formed, how would it react further, e.g. by additional eliminations to form a pyridine derivative, or by rearrangements? The possibility also exists that polymerization or dimerization could occur. The 1H NMR spectrum of the product obtained by the reaction between
314 and 105 did not indicate the presence of any methylene groups (i.e. those in the side-chain between the Q and the piperidine/pyridine residues), but only contained aromatic signals. These signals could not be traced to any theoretically feasible product. Unfortunately, owing to time constraints, we could not repeat this route on a larger scale in order to purify and characterize the Eschenmoser reaction product(s) more easily.

5.4. Conclusion

In this chapter, we attempted three plausible approaches towards an easy and economical synthesis of the potent antimalarial alkaloid febrifugine [(+)-1]. The results were often interesting and surprising. It is clear that, if our straight-forward synthetic strategy towards (+)-1 is to be successful, it is advisable to use an electron-donating hydroxyl protecting group, e.g. an alkyl group, on the prerequisite thiolactam before attempting the key Eschenmoser reaction with bromide 105. The most promising results were obtained when such a group, the benzyloxy group, was used (see Section 5.3.4.). An electron-donating group at this position not only seems to enhance the reactivity of the thiolactam sulfur towards alkylation during the Eschenmoser reaction, but most likely also minimizes the chance of epimerization which might occur at this position, α to the thioamide group. Furthermore, chemoselective hydrogenation of the key intermediate α-substituted vinylogous amide (see Sections 4.3.2. and 5.3.4.) proved to be more problematic than was initially anticipated from the model studies conducted (see Sections 3.8.3. and 3.8.5.). It is recommended that the mildest hydrogenation conditions possible should be applied to the α-substituted vinylogous amides, as these compounds contain many reactive sites and the six-membered piperidinyldiene ring is prone to reaction by endocyclic elimination.