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Systhesis and characterization of analogues of the antimalaria alkaloid febrifugine

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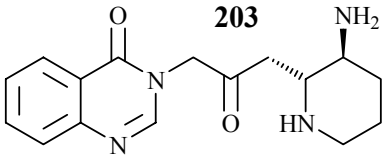
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CHAPTER 4

APPROACHES TOWARDS THE 3″-AMINO ANALOGUE OF FEBRIFUGINE

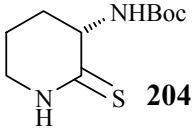
4.1. Background

After achieving the synthesis of model compound (±)-deoxyfebrifugine **14** using our synthetic methodology, we were ready to test this method for the synthesis of 3″-substituted derivatives of febrifugine **1**. We opted to begin with approaches to the 3″-amino analogue of **1** (**203**) because the alkaloid analogue **203** represents a potentially important antimalarial candidate, which has not been synthesized before. One heteroatomic group (hydroxyl) in the natural product **1** is substituted by another such group (amino) in derivative **203**. Furthermore, the hydroxyl and amino groups are isoelectronic and of similar size.

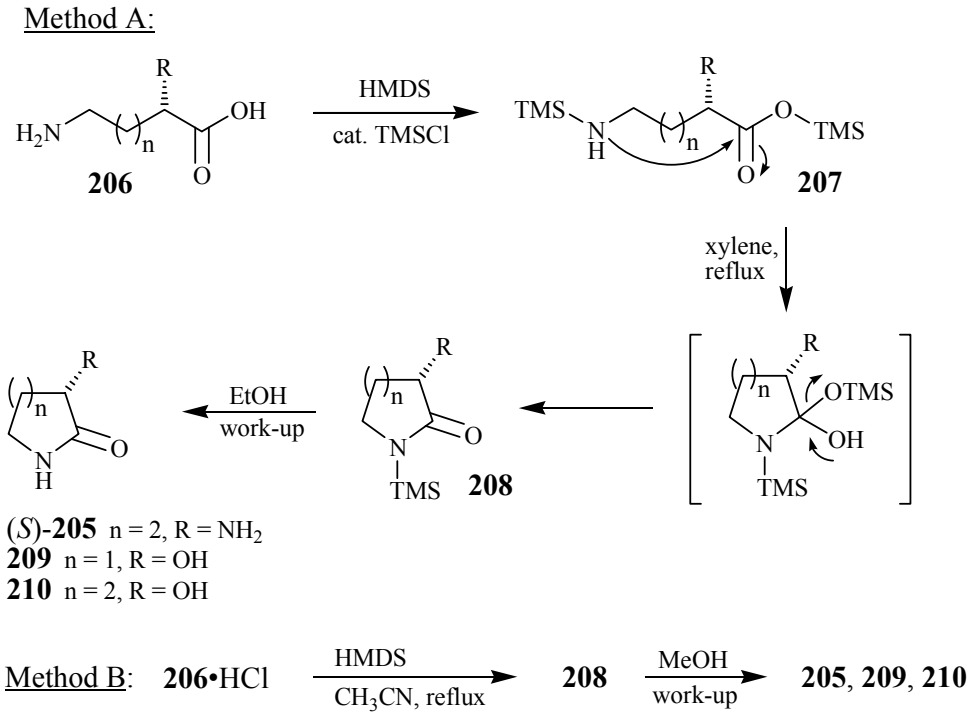


203

Although the prerequisite thiolactam **204** in our proposed synthesis of **203** had not been synthesized before, we found a potentially easy, two-step preparation of **204** in the literature. In 1978, Pifferi's group [119] published a new method for the preparation of lactams, including (3*S*)-aminopiperidin-2-one [(*S*)-**205**, R= NH_2, Scheme 41], from their corresponding amino acids. This involves conversion of the appropriate amino acid **206** (R = NH_2) into its trimethylsilyl amino ester **207**, followed by *exo*-trigonal ring closure (i.e. during ring closure, the C=O bond broken is *exo* to the formed ring, and the carbon of the C=O is *trigonal*) affording lactams **208** of varying ring size, as shown in Scheme 41. This method was claimed to proceed in a *non-racemizing* fashion, i.e. the 3″-position in (*S*)-**205** does not undergo racemization. Two different methods were used. When using the free amino acid **206**, refluxing xylene was used as the solvent and a few drops of TMSCl were added to catalyze the reaction (Method A, Scheme 41). When starting from the amino acid hydrochloride salt **206**•HCl, refluxing CH_3CN was used as solvent and HMDS was the only other additive (Method B, Scheme 41).



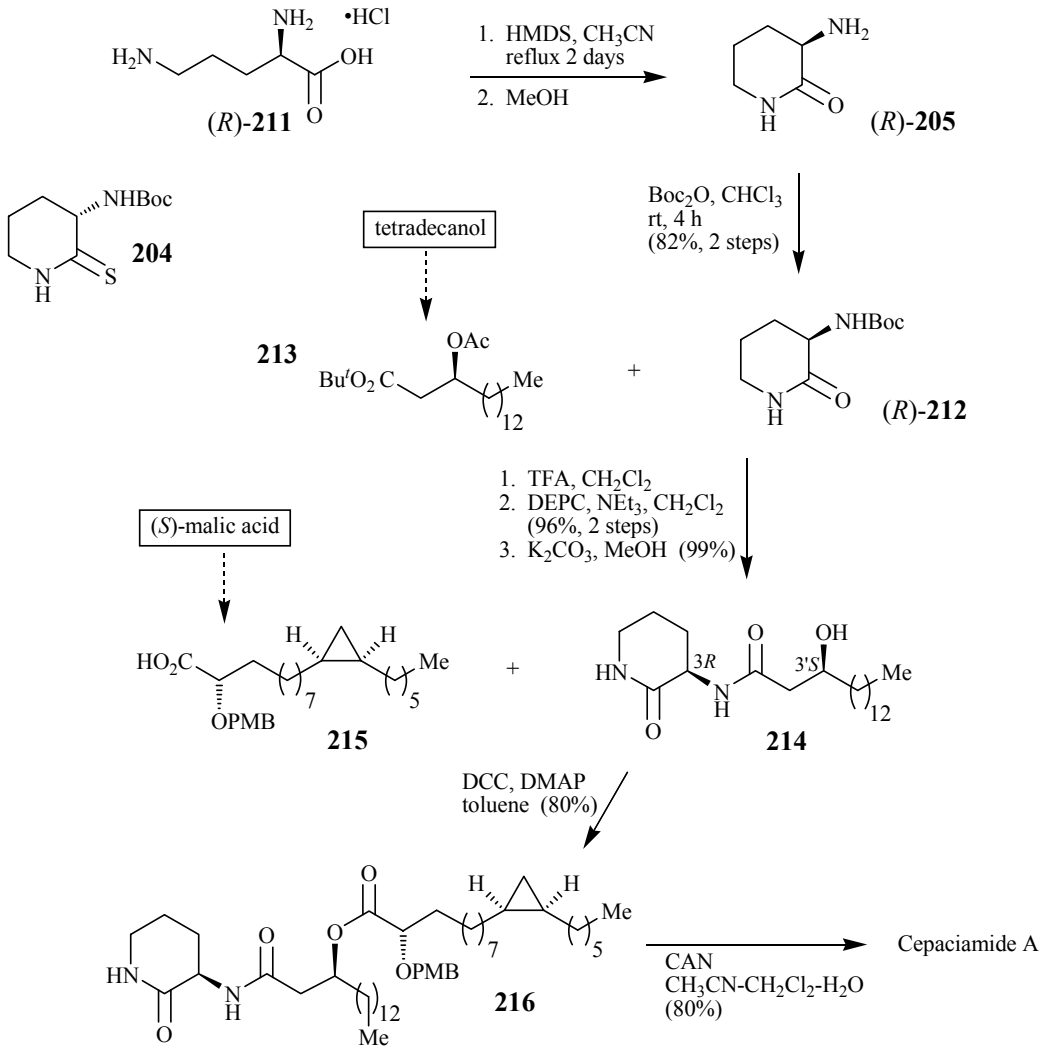
204



Scheme 41: Proposed mechanism of lactamization using HMDS, including structures of important lactams (*S*)-**205**, **209** and **210**.

For simplicity, Scheme 41 also shows the structures of two other important lactams, which will be discussed in this project, i.e. (3*S*)-hydroxypyrrolidin-2-one (**209)** and (3*S*)-hydroxypiperidin-2-one (**210**). These lactams will be discussed again in Chapter 5. To our knowledge, **210** has never been synthesized by using the method in Scheme 41, but in 1983, Maurey and Srairi [120] prepared **209** in this way. Our use of this method for preparing **210** is further discussed in Chapter 5.

In 1999, Toshima *et al*. [121] published the first total synthesis of two novel fungitoxic (3-aminopiperidin-2-one)-containing lipids, cepaciamides A and B, by preparing (*R*)-**205** according to Pifferi's method. The synthesis of cepaciamide A is outlined in Scheme 42. Using the conditions mentioned earlier, they obtained (*R*)-**205** from ornithine hydrochloride [(*R*)-**211**] as a brownish oil which could not be crystallized. Pifferi's group did manage to crystallize (*S*)-**205**, but they mentioned that it was hygroscopic and needed to be stored in a desiccator under vacuum. Toshima opted to convert crude (*R*)-**205** directly into its amino *N*-Boc derivative **212** by using 2.6 eq. Boc_2O in $CHCl_3$. The yield of (*R*)-**212** over two steps was 82%.

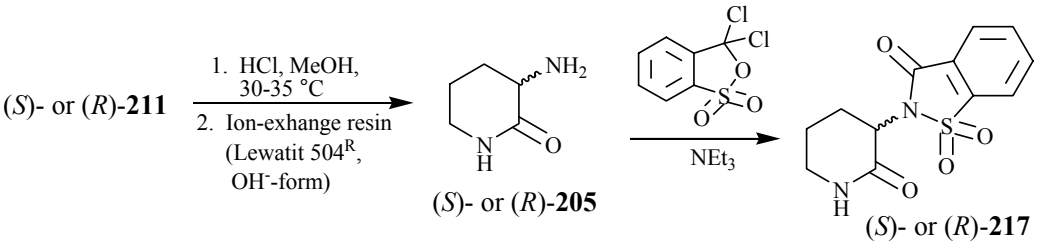


Scheme 42: Toshima's synthesis of cepaciamide A.

From tetradecanol, Toshima managed to prepare key ester **213**, which was condensed with (*R*)-**205**, after both compounds were deprotected using TFA. Diethyl phosphoryl cyanide (DEPC) was found to be most effective for this amide formation reaction, which proceeded in 96% yield. Deprotection of the *O*-Ac, using K_2CO_3 and MeOH, yielded the desired amide **214**. The other prerequisite fragment, carboxylic acid **215**, was prepared from (*S*)-malic acid. After esterification between **214** and **215** using DCC, the obtained compound **216** was deprotected using CAN to afford cepaciamide A.

It is important to note in Toshima's synthesis of cepaciamide A that apparently no racemization occurred at position 3 on the piperidin-2-one, even under the basic conditions employed during deprotection of the intermediate amide to form **214** (Scheme 42). The stereochemistry at position 3 remained (*R*) in **214**, as indicated. However, only the stereochemistry at position (3′*S*) in **214** was confirmed using a modified Mosher's method. If there were traces of the other (3*S*)-diastereomer, one presumes Toshima would have observed this compound, and the single diastereomer yields in going from **212** to **214** would not be as high as were found.

In 1983, Winter *et al.* [122] prepared both (*S*)- and (*R*)-**205**, using acid-catalyzed ring-closure of (*S*)-**211**. The intermediates were then used in a synthesis of enantiomerically pure (*S*)- and (*R*)- supidimide **217** (Scheme 43). Importantly, Winter mentioned that the temperature during the HCl-catalyzed ring-closure step to form **205** should not exceed 40 °C so as to prevent racemization from occurring in **205**. Unfortunately, Winter presented no evidence that racemization was indeed observed, nor did he mention any references to such a possibility.



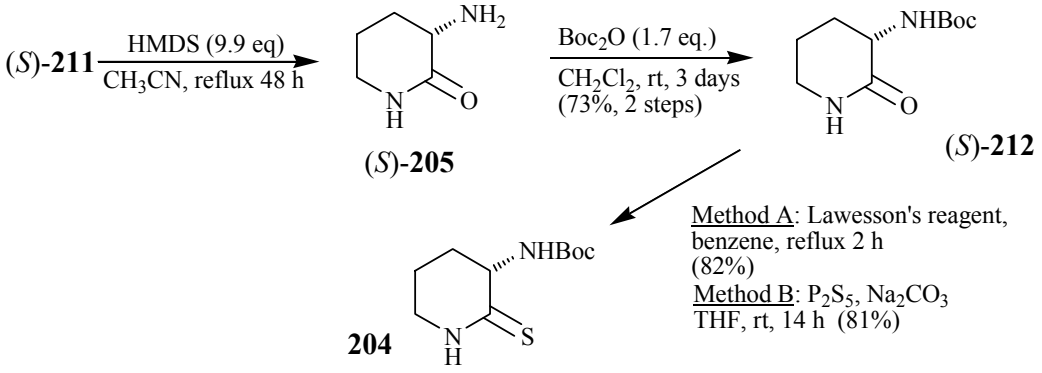
Scheme 43: Winter's preparation of supidimide.

4.2. Approach without *N*-protection of the piperidine ring

4.2.1. Preparation of *tert*-butyl (*S*)-2-thioxopiperidin-3-ylcarbamate (204)

Seeing that the absolute stereochemistry in natural, biologically active (+)-**1** is 3″*S*, we started our synthesis of the 3″-amino analogue from (*S*)-(+)-**211**. This also happens to be the naturally occurring, less expensive enantiomer of ornithine. Using Pifferi's procedure [119], we managed to obtain the intermediate lactam (*S*)-**205**

(Scheme 44) as an orange-coloured oil, which we did not attempt to crystallize. As this compound is hygroscopic, it was completely dried under high vacuum and with gentle heating, before proceeding to the next step.

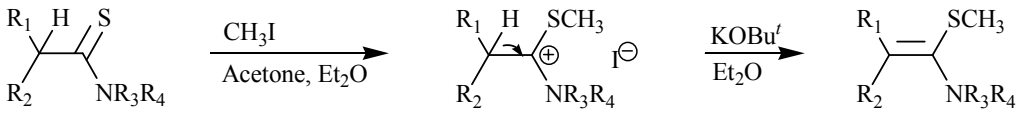


Scheme 44: Synthesis of **204**.

Dried, crude (*S*)-**205** was converted into (*S*)-**212** by acylation with 1.7 eq. of Boc_2O, i.e. considerably less than the 2.6 eq. used by Toshima [121]. The yield of (*S*)-**212** was 73% over 2 steps, comparable to the 82% yield obtained by Toshima. The ^1H NMR spectral data agreed with those obtained by Toshima. The Boc N*H* was observed as a broad singlet at δ_H 6.59 and the lactam N*H* was observed similarly at δ_H 5.51. The Boc C(C*H*$_3$)$_3$ protons were observed as a singlet, which integrated for nine protons, at δ_H 1.45. The optical rotation we observed for (*S*)-**212** in $CHCl_3$ ($[\alpha]_D$ +54.4) agreed very well with what was expected from Toshima's measurement for (*R*)-**212** ($[\alpha]_D$ – 57.4 in $CHCl_3$). Next, thiolactam **204** was obtained from (*S*)-**212** in 82% yield using Lawesson's reagent, or in 81% yield using the P_2S_5/Na_2CO_3 method. It was obvious from the ^1H and ^{13}C NMR data that we did indeed obtain the desired thiolactam **204**. The thiocarbonyl carbon was observed at δ_C 203.5 and the Boc carbonyl carbon at δ_C 155.5. Furthermore, the deshielding effect of the sulfur atom was again apparent in the ^1H NMR spectrum. The thiopiperidone N*H* was highly deshielded and observed as a broad singlet at δ_H 8.65, whereas the Boc N*H* was less deshielded at δ_H 5.93. The hydrogen alpha to the thiocarbonyl group was also highly deshielded at δ_H 4.16, as expected.

As will be seen in the next section, a single crystal of **204** was found to be centrosymmetric. This was a very disappointing result, as we had hoped that racemization of **204** might not occur at all. The specific rotation observed for the obtained product **204** in $CHCl_3$ was $[\alpha]_D$ –2.2 (for the material obtained by the Lawesson's thionation method, Method A, Scheme 44). This laevorotation was similar to that observed for precursor (*S*)-**205** ($[\alpha]_D$ –12.4, in $CHCl_3$ [119]) but different to that expected for precursor (*S*)-**212** (+ rotation expected, as $[\alpha]_D$ +54.4 was found for (*S*)-**212**, in $CHCl_3$). We did not do HPLC work to determine the ratio of enantiomers obtained. It was sufficient evidence from the crystal data that undesired racemization was occurring, the extent of which was not important at this stage as we were simply testing our synthetic methodology. We also hoped that, should diastereomers arise at a later stage in the synthesis, these might be easily resolved.

How might racemization at position 3 in **204** occur? As mentioned before, Winter *et al*. [122] thought that racemization of precursor lactam **205** occurred above 40 °C under acidic conditions, without presenting conclusive evidence. We know that Toshima [121] encountered no such problems under basic conditions with precursor lactam **212**. The answer might lie in the fact that **204** is a *thio*lactam, bearing a highly deshielding group (NHBoc) at the position alpha to the thiocarbonyl function. It is well known that the sulfur in thioamides is considerably more nucleophilic than the oxygen in corresponding amides. This is why thioamides are easily *S*-alkylated [123,124], e.g. in 1969, Gompper and Elser [123] prepared isolable ketene *S*,*N*-acetals **218**, from thioamides **219** using methyl iodide and potassium *tert*-butoxide, as shown in Scheme 45.



219 **218**

Scheme 45: Synthesis of ketene-*S*,*N*-acetals **218**.

Similarly, the sulfur in **219** might be easily protonatable under acidic conditions, and the alpha-hydrogen in **219** might be deprotonated under basic conditions. As deduced

from Scheme 45, such proton exhange processes would ultimately result in racemization at the position alpha to the thiocarbonyl group. These processes are not as favoured in amides as in thioamides, which contain strongly nucleophilic and electron-withdrawing sulfur atoms. The "enol" form can be viewed as being more pronounced in thioamides, compared to in the corresponding amides. Furthermore, if the alpha carbon in **219** is substituted by an electron-withdrawing group, e.g. the Boc group in **204**, racemization at the alpha carbon might be accelerated owing to the increased acidity of the alpha-hydrogen.

Acidic or basic conditions might therefore cause racemization during the three-step preparation of **204** in Scheme 44. Lawesson's reagent is known to be slightly acidic [125], and the heating required during this method might promote racemization. The basic conditions used in the P_2S_5 thionation work-up procedure might cause racemization in that case. Furthermore, the slightly acidic silica gel used for purification could be detrimental to the enantiomeric purity of **204**. Finally, it is possible that racemization is a slow process, which occurs upon storage of 3-substituted thiolactams such as **204**. We obtained single crystals of **204** by keeping it for a prolonged period in EtOAc-hexane solution. It might be coincidental that a centrosymmetric crystal was selected for X-ray diffraction characterization purposes, and that the product **204** was not completely racemized, as suggested by the optical rotation data.

Future work includes the search for milder conditions, especially during thionation, in the preparation of **204** and related thiolactams. Importantly, studies on the racemization of the alpha-position in thioamides, using HPLC, are required. No such studies were found in the literature. Even though the loss of stereochemical purity in **204** was a discouraging outcome, we decided to continue this route to check whether the subsequent steps might work, before trying to solve the racemization problem.

4.2.2. Crystal structure of 204

The crystal data for **204** are summarized in Table 12. Note that all the detailed crystal data for structures determined during this project are available on the accompanying compact disc.

Crystal system	Orthorhombic	
Space group	*Pbca*	
Unit cell dimensions	a = 11.1118(14) Å	α = 90°.
	b = 11.0591(14) Å	β = 90°.
	c = 20.603(3) Å	γ = 90°.
Volume	2531.8(6) Å^3	
Z	8	
Density (calculated)	1.209 Mg/m^3	
Absorption coefficient	0.241 mm^{-1}	
F(000)	992	
Crystal size	0.40 x 0.36 x 0.30 mm^3	
Theta range for data collection	1.98 to 28.30°.	
Index ranges	-14<=h<=14, -14<=k<=14, -16<=l<=27	
Reflections collected	16492	
Independent reflections	3140 [R(int) = 0.0324]	
Completeness to theta = 28.30°	99.8 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3140 / 0 / 139	
Goodness-of-fit on F^2	1.021	
Final R indices [I>2sigma(I)]	R1 = 0.0391, wR2 = 0.1065	
R indices (all data)	R1 = 0.0645, wR2 = 0.1213	
Largest diff. peak and hole	0.267 and -0.218 e.Å^{-3}	

Table 12: Crystal data and structure refinement for **204**.

In 1989, Valle *et al.* [126] published the crystal structure of precursor lactam, (3*S*)-3-*tert*-butyloxycarbonylaminopiperidin-2-one, (*S*)-**212**. It is interesting to compare the structures of lactam (*S*)-**212** and the corresponding thiolactam **204**. In the case of enantiomerically pure (*S*)-**212**, the crystal system is monoclinic (as opposed to orthorhombic for **204**), and the space group is $P2_1$ (as opposed to the centrosymmetrical space group *Pbca* for racemic **204**. In the crystal of (*S*)-**212**, Valle

et al. found two molecules in the asymmetric unit. The δ-lactam ring of Molecule A was in an approximate half-chair conformation, while that of Molecule B was in the boat conformation. We found that related thiolactam **204** crystallized only in an approximate half-chair conformation, as shown in the Ortep diagram for **204** given in Figure 17. It can be seen that N1, C2, C3, C5 and C6 are approximately planar, whereas C4 is out-of-plane.

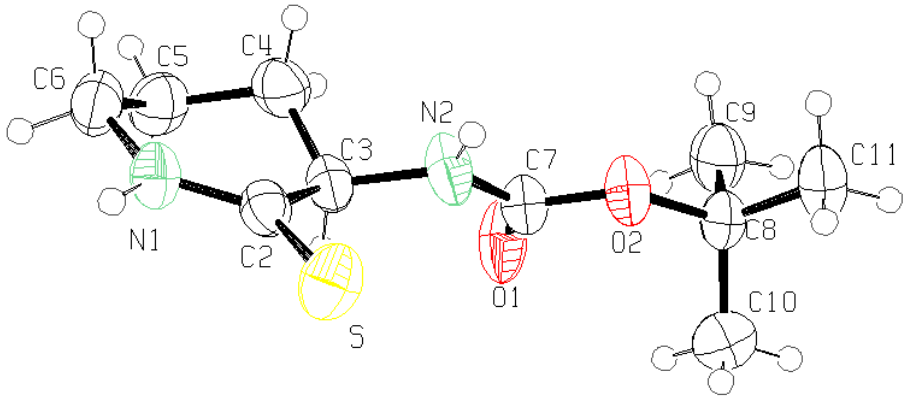


Figure 17: Ortep diagram (50% ellipsoid probability) of **204**, showing the atomic numbering scheme.

As observed by Valle for (*S*)-**212**, the Boc group in **204** is in the expected extended conformation. How does the sulfur in thiolactam **204** affect the surrounding molecular environment, compared to what was observed by Valle for lactam (*S*)-**212**? Selected bond lengths in the two structures are compared in Table 13, whereas selected bond angles and torsion angles are compared in Table 14.

Bond	(*S*)-**212** Molecule A (Å)	(*S*)-**212** Molecule B (Å)	**204** (Å)
C(2)-N(1)	1.337 (9)	1.327 (10)	1.3154 (19)
C(2)-C(3)	1.529 (11)	1.520 (10)	1.522 (2)
C(2)-S, or C(2)-O(3)	1.238 (10)	1.220 (9)	1.6755 (16)
C(3)-N(2)	1.454 (9)	1.458 (8)	1.4547 (18)

C(3)-C(4)	1.536 (11)	1.533 (11)	1.520 (2)
C(6)-N(1)	1.467 (11)	1.460 (12)	1.462 (2)
C(7)-O(1)	1.219 (7)	1.207 (7)	1.2084 (19)
C(7)-N(2)	1.342 (9)	1.345 (10)	1.336 (2)
C(7)-O(2)	1.350 (8)	1.360 (8)	1.3411 (18)
C(8)-O(2)	1.465 (10)	1.450 (9)	1.4814 (19)

Table 13: Comparison of bond lengths between (*S*)-**212** and **204**. Note that "S" in **204** becomes "O(3)" in (*S*)-**212**.

The bond lengths are very similar in the two compounds (Table 13). However, the presence of strongly electron-withdrawing sulfur in **204** does cause a slight shortening of the N(1)-C(2) (1.32 Å), as well as the C(3)-C(4) (1.52 Å) bonds in the ring, compared to these bonds in (*S*)-**212** [*ca*. 1.34 and 1.54, respectively]. It can also be seen that bond C(7)-O(2) is shorter (1.34 Å) in **204** than in (*S*)-**212** (1.35 and 1.36 Å), and that bond C(8)-O(2) is longer (1.48 Å) in **204** than in (*S*)-**212** (1.47 and 1.45 Å). This is a consequence of the slightly stronger intermolecular H-bonds involving O(1) in **204** (see later), as opposed to those found in (*S*)-**212**. The thiolactam C=S bond, C(2)-S, is of expected magnitude [1.6755(16) Å, compared to the mean value of 1.671 Å for $(X)_2$N**C**(=**S**), *X* = C, N, O, S [127]].

Angle	(*S*)-**212** Molecule A (º)	(*S*)-**212** Molecule B (º)	**204** (º)
N(1)-C(2)-C(3)	117.7 (9)	113.4 (8)	117.05 (13)
N(1)-C(2)-S, or N(1)-C(2)-O(3)	121.9 (8)	122.8 (8)	121.43 (12)
C(3)-C(2)-S, or C(3)-C(2)-O(3)	120.2 (10)	123.6 (10)	121.50 (11)
N(2)-C(3)-C(4)	112.4 (7)	109.1 (8)	112.66 (13)
N(2)-C(3)-C(2)	110.2 (8)	112.3 (8)	109.55 (12)
C(4)-C(3)-C(2)	114.1 (8)	110.7 (7)	112.66 (13)
C(3)-C(2)-N(1)-	12.4 (14)	0.2 (13)	-10.7 (2)

C(6)			
S-C(2)-N(1)-C(6), or O(3)-C(2)-N(1)-C(6)	-172.6 (9)	-177.3 (9)	170.84 (14)
C(2)-C(3)-N(2)-C(7)	52.3 (11)	-86.5 (10)	143.13 (15)

Table 14: Comparison of selected bond angles and torsion angles between *S*-**212** and **204**.

From Table 14, it can be seen that most of the bond angles and torsion angles are very similar in (*S*)-**212** and **204**. The angles correspond better between Molecule A of (*S*)-**212** and **204**. This is because both these molecules consist of δ-lactam rings in the half-chair conformation, whereas Molecule B is in the boat conformation. Importantly, similar to what was found for the amide group in lactam (*S*)-**212**, the thioamide group in **204** is non-planar as indicated by the torsion angles C(3)-C(2)-N(1)-C(6) (-10.7º) and S-C(2)-N(1)-C(6) (170.8º). The respective rotations of the ring relative to the *tert*-butyloxycarbonylamino substituent [torsion angles C(2)-C(3)-N(2)-C(7)] for Molecules A (52.3 º) and B (-86.5 º) in (*S*)-**212**, and for **204** (143.1 º), differ greatly in value.

Figure 18 is a representation of the unit cell and its contents in **204**. It clearly demonstrates the centrosymmetry (i.e. symmetry from the inversion centre) in structure **204**, which indicates that racemization had occurred at carbon 3.

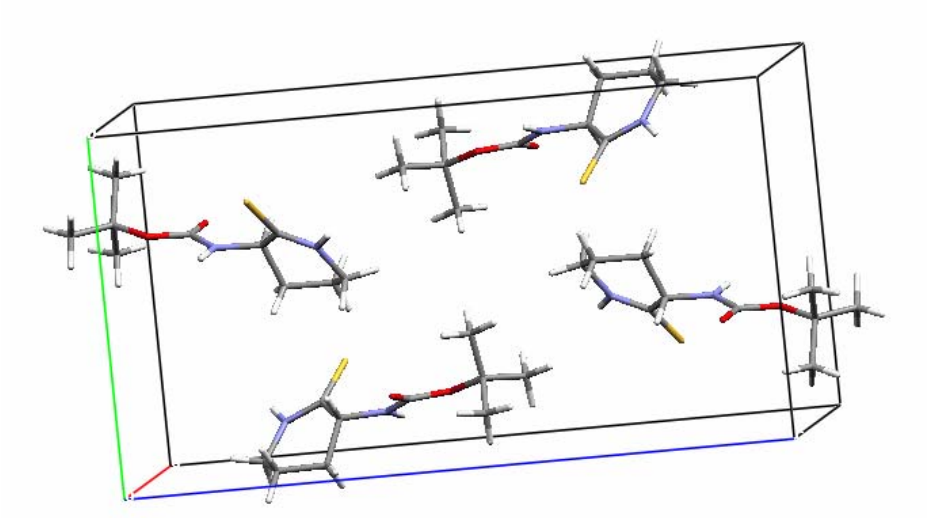


Figure 18: Representation of the unit cell in **204** showing centrosymmetry in the crystal. Four molecules were removed for clarity.

Similar to the results obtained by Valle *et al*. for (*S*)-**212**, no intramolecular H-bonding is observed in the structure of **204**. Instead, (thiolactam)N(1)-H···O(1)=C(Boc) intermolecular H-bonds are observed along the B plane, as seen in Figure 19. The N(1)···O(1) separation is 2.823 Å, i.e. shorter than that observed by Valle for (*S*)-**212** (2.990 and 2.880 Å between Molecules A and Molecules B, respectively). The corresponding N(1)-H(1)···O(1) distance is 1.984 Å. This results in a layered structure, each layer formed by intermolecular H-bonds extending in one plane. Valle additionally observed (Boc)N(2)-H···O(3)=C(lactam) intermolecular H-bonds in (*S*)-**212**. No such close contacts were found between sulfur and the (Boc)N(2)-H in **204**. It is important to note that, seeing that the hydrogen atoms in all the structures determined during this project were first located in a difference map and then placed on the parent atoms, hydrogen bonds are indicated between the heteroatoms which share the bond (as shown in Figure 19), and not directly between the hydrogen atom and the hydrogen bond acceptor.

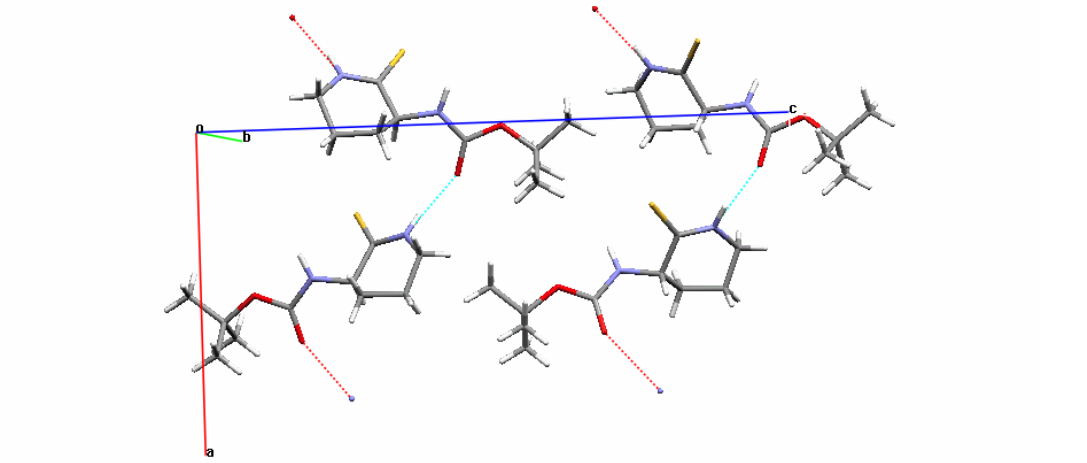
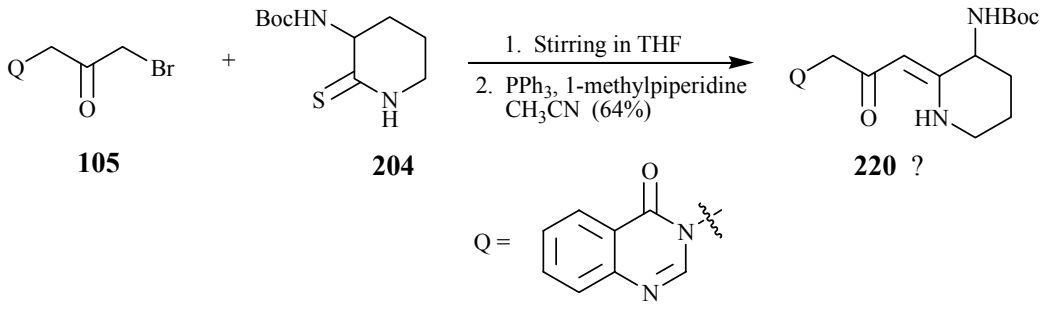


Figure 19: Intermolecular H-bonding in **204**, as viewed along the b-axis. Four molecules were removed for clarity.

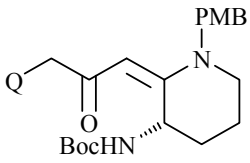
4.2.3. Sulfide contraction reaction between 204 and 105, and attempted hydrogenation of the product

With the desired racemic thiolactam **204** in hand, the Eschenmoser reaction with bromide **105** could be attempted. As this reaction worked quite pleasingly in the model studies (see Chapter 3), we decided to use exactly the same experimental conditions as used for the *N*-unprotected model thiolactams. The use of the stronger base, 1-methylpiperidine, was explained in section 3.6. Thus, following this procedure, we obtained a moderate yield (apparently 64%) of what initially appeared to be the desired vinylogous amide **220** (Scheme 46) as a viscous oil, which unfortunately could not be induced to crystallize.



Scheme 46: Reaction between **105** and **204**.

The ^{1}H NMR spectrum of product **220** gave cause for alarm. It should be noted that we could not prove unequivocally that we had indeed obtained structure **220**. For convenience, the ^{1}H NMR spectrum of **220** is compared to that of an analogue of **220** [the 1-(4-methoxybenzyl) derivative **221**, see later in Section 4.3.1.], here. All the quinazolinyl proton signals in **220** were observed at the expected chemical shifts, and in the correct multiplicities. The only deviation from the normal trend was H-2 (δ_H 8.35, i.e. the hydrogen attached to the imine *C* in Q, Scheme 46). Usually, we would expect this singlet to appear at a lower chemical shift (e.g. at δ_H 7.91 in **221**). Although the remaining signals integrated correctly for the remaining 21 protons in **220**, the chemical shifts were very different from those observed for analogue **221**. Furthermore, all the signals were broadened. As expected, two distinct doublets were observed for the NC*H*$_2$C(O) protons, but at considerably higher chemical shifts (δ_H 5.78 and 5.66, respectively) than in **221** (δ_H 4.67 and 4.56, respectively). The H-3″ alpha to the *tert*-butoxycarbonylamino substituent also absorbed at a higher chemical shift (δ_H 5.30) than its counterpart in **221** (δ_H 4.98). The next four assignments were more ambiguous and questionable. Two broadened multiplets at δ_H 4.86 and 4.66, integrating for one proton each, were attributed to the ring NC*H*$_2$ protons, owing to the multiplicities (two multiplets) of the signals. The corresponding protons in **221**, however, absorb much lower at δ_H 3.63 and 3.22. Then a broad singlet at δ_H 3.5 and integrating for two protons, was assigned to the two N*H* protons in **220**. However, as mentioned before, all signals were very broadened compared to those observed in other analogous compounds. The fact that this signal appears to be a singlet is not conclusive evidence that it belongs to N*H* protons. Also, the corresponding Boc N*H* in **221** absorbs at δ_H 5.88, i.e. at a considerably more deshielded position. Then, two multiplets (δ_H 2.47 and 2.33) were attributed to the remaining four ring methylene protons. These chemical shifts are again much higher than expected (e.g. δ_H 2.26, 2.00, 1.85 and 1.70, for the four protons in **221**, respectively). The nine Boc protons were observed as a singlet at the expected chemical shift (δ_H 1.44, compared to δ_H 1.40 for **221**). Importantly, the only peak that could be assigned to the vinyl proton in **220**, was a very highly deshielded singlet at δ_H 8.77. This singlet is observed at δ_H 5.06 for **221**. This was a major deviation, which puzzled us. This signal could also be assigned to the BocN*H*, although it is perhaps



221

too sharp a signal for these two assignments to be exchanged. It seems possible that the presence of the free NH group in the piperidinyl ring of **220** could H-bond in such a way that it results in substantial deshielding of the atoms surrounding the enaminone functional group, as compared to the case where this nitrogen is protected by an electron-donating alkyl group, such as the PMB group in **221**. It is important to note that the enaminone in product **220** is not necessarily in the *Z*-configuration as drawn in Scheme 46. The BocNH group can also H-bond, which might lead to a mixture of *Z*/*E* products. This might also explain the differences in chemical shifts observed for **220** compared to **221**, and might also lead to a broadening of signals.

The broadened signals in the ^{1}H NMR spectrum (which could suggest a mixture or an unstable compound), together with the fact that no expected molecular ion was present in the mass spectrum of **220** (see experimental, Section 8.1.3.), were both discouraging results. The absence of a molecular ion in the mass spectrum also supports the suspicion that **220** is unstable. Despite several repetitions of this experiment, the same product was isolated in each case and, even though it appeared as a single spot on TLC, product **220** was very polar, difficult to purify, and darkened upon storage, which further suggested decomposition. We nevertheless decided to attempt the next reaction in our synthetic sequence, i.e. hydrogenation, on freshly prepared material of **220,** in the hope of isolating a more stable, or crystalline compound, and with the aim of casting more light on the possible structure of **220**.

Unfortunately, attempted chemoselective hydrogenation of the putative enaminone C=C bond in **220**, using conditions similar to those used on the model vinylogous amides, failed. These reaction conditions seemed to lead to the decomposition of **220**, as evident from the five, uncharacterizable spots isolated by column chromatography of the crude product (see experimental, Section 8.1.4.). At this stage, the structure of the product (**220**) obtained remains a mystery.

4.3. Approach using *N*-(4-methoxybenzyl) protection

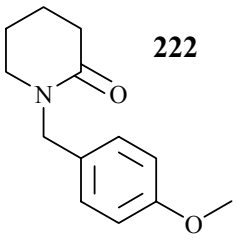
As the route without piperidinyl *N*-protection failed, we decided to use a protecting group on N1″ instead. It was hoped that the advanced intermediates thus obtained

would be more easily isolable and more stable than those obtained in the previous section. A popular amino protecting group is the PMB (4-methoxybenzyl) group. This group can also be used to protect amides. We chose this group primarily because it represents an electron-donating protecting group (as explained in Section 2.2.), which should be easily removable from the amide nitrogen using e.g. CAN [128] (ceric ammonium nitrate) and from the amine nitrogen using e.g. standard catalytic hydrogenation methods [129], or chloroethyl chloroformate [130]. The PMB group is also very stable under basic conditions such as those required during the Eschenmoser reaction to produce our key vinylogous amide intermediate.

4.3.1. Preparation of 3-{(*E*)-3-[3-(*tert*-butoxycarbonylamino)-1-(4-methoxy benzyl)piperidin-2-ylidene]2-oxopropyl}quinazolin-4(3*H*)-one (221)

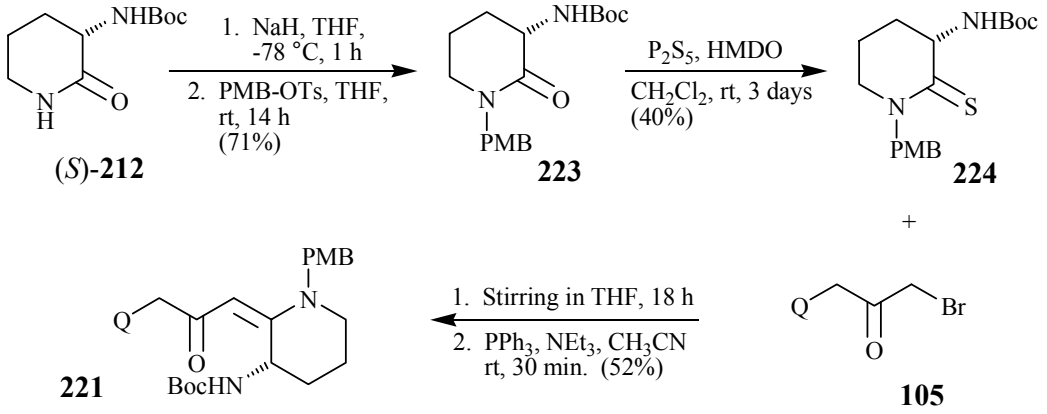
Scheme 47 summarizes the results obtained in this section. The lactam, 1-(4-methoxybenzyl)piperidin-2-one **222**, is a known compound, which has previously been prepared before from piperidin-2-one [131] (see later, Section 5.3.4.). Using similar experimental conditions, we managed to prepare our starting lactam **223** (Scheme 47) as a stable and crystalline compound, in 71% yield from (*S*)-**212** and 4-methoxybenzyl alcohol. Tosylation *in situ* of 4-methoxybenzyl alcohol affords 4-methoxybenzyl tosylate. The tosyl group is easily nucleophilically substituted by the amine nitrogen in deprotonated (*S*)-**212** to afford alkylated lactam **223**. Fortunately, the Boc nitrogen did not seem to undergo side-reactions under these highly basic (NaH) reaction conditions. Although **223** was optically active ($[\alpha]_D^{20}$ 14.4), it cannot be stated with certainty that no racemization had occurred, considering that the presence of NaH could induce base-catalyzed racemization to some extent as explained in section 4.2.1. The ^{13}C NMR spectrum of **223** clearly showed the presence of both a Boc carbonyl carbon (δ_C 159.1) and a lactam carbonyl carbon (δ_C 169.6).

222



Thionation of **223** using Curphey's method (P_2S_5, HMDO)[94] afforded a disappointing yield (40%) of prerequisite thiolactam **224**. The ^{13}C NMR spectrum clearly indicated

the presence of a thiocarbonyl carbon (δ_C 201.0). The Boc $(CH_3)_3$ protons were observed as a singlet at the expected chemical shift (δ_H 1.47) in the ^{1}H NMR spectrum of **224**. Although these thionation conditions are mild, the work-up procedure included use of saturated aq. K_2CO_3 to separate impurities from the product in the organic phase. This could again induce racemization and perhaps the decomposition of **224** by basic hydrolysis. It is recommended that the crude solution be simply filtered through celite prior to column chromatography, without using base in the work-up. Alternatively, Lawesson's reagent should be used to effect thionation of base-sensitive 3″-substituted lactams. This might increase the yield of the desired thiolactams, whilst reducing the extent of racemization. We did find that the obtained **224** was stable, crystalline, optically active ($[\alpha]_D^{20}$ –14.5) and exhibited a sharp melting point (see experimental, Section 8.2.2.).



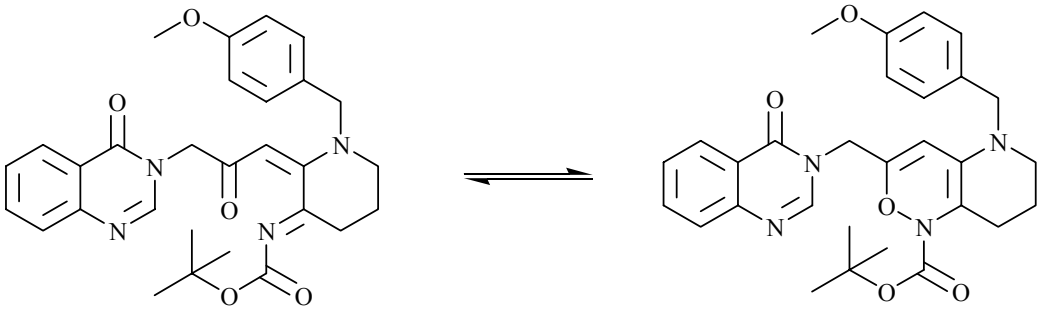
Scheme 47: Preparation of **221**.

Eschenmoser reaction between **224** and bromide **105** afforded a moderate yield (52%) of the desired vinylogous amide **221** as a colourless, stable solid. This was a very pleasing result, as optically active **221** ($[\alpha]_D^{20}$ –5.49) may be viewed as an advanced intermediate in our synthesis of 3″-substituted analogues of febrifugine **1**. No 3″-nitrogen-containing substituted analogues of **1** had been synthesized before, which makes **221** an interesting candidate for antimalarial testing. As mentioned in Chapter 1, the biological activity of dehydro derivatives of **1**, such as enaminone **221**, has not been determined. Our synthesis of relatively complex molecule **221** is simple and inexpensive. Owing to time constraints, the yields were not optimized, nor did we

attempt potentially straight-forward Boc-deprotection of **221** to obtain the 3″-amino-dehydro- derivative of **1**. Future work includes all the aforementioned studies.

4.3.2. Attempted hydrogenation of 221; the isolation of an apparently dehydrogenated derivative (225/226)

The next step in the synthesis of amino analogue **203** is the chemoselective hydrogenation of the enaminone C=C bond in **221**. Using the standard conditions we established in section 3.8.3. for the reduction of the *N*-alkylated model compounds (PtO_2, glacial AcOH, H_2), we obtained three isolable spots on TLC after stirring the reaction mixture for 72 h under 1 atm of hydrogen gas. The two most polar products, obtained only in trace amounts, were unidentifiable by NMR spectroscopy. The NMR spectra were complex and possibly indicated decomposition of **221**. We did, however, manage to isolate an oil, which was apparently a dehydrogenated derivative of **221**, characterizable by NMR and mass spectroscopy. It is thought to possess either structure **225** or **226** as shown in Scheme 48, in which case it was obtained in 25% yield from **221**. Presumably, the conversion of **225** to isoxazine **226** by an electrocyclic reaction is reversible. Unfortunately, crystallization of the obtained product could not be achieved.

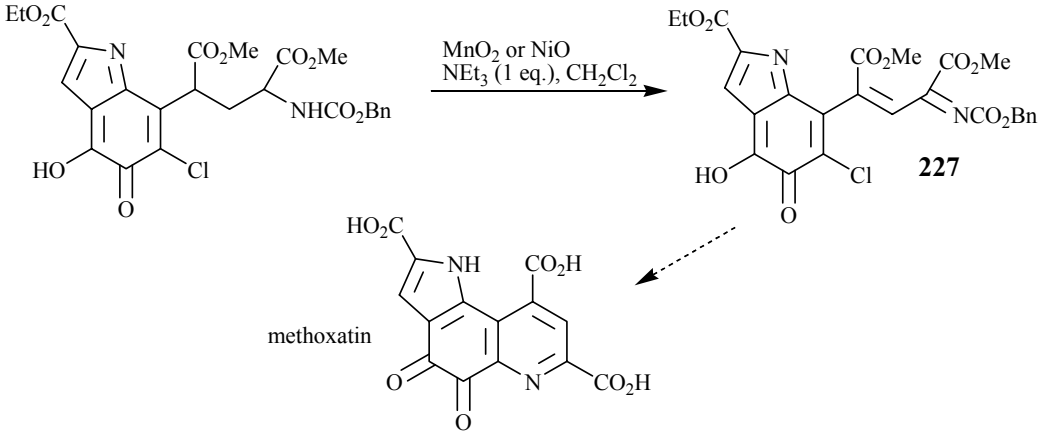


225 **226**

Scheme 48: Two alternative proposed structures formed during the attempted hydrogenation of **221**.

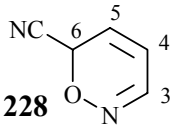
It is well known that dehydrogenation of carbamates such as **221** can occur in the presence of metal oxides and base, e.g. Büchi *et al.* [132] prepared bright red imine **227**

from a carbobenzyloxy compound using MnO_2 or NiO and NEt_3 (see Scheme 49), in their synthesis of the biologically important cofactor methoxatin.



Scheme 49: Büchi's synthesis of methoxatin.

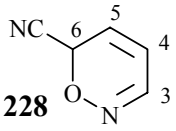
Evidence that we might have prepared **225** or **226** comes from the spectroscopic data. The mass spectrum showed a molecular ion, M^+ 516, which corresponds to dehydrogenated **221**. The IR spectrum contained no broad N-H absorption peak. The ^{1}H NMR spectrum contained signals integrating for the required number of protons. The quinazolinone protons were observed at the expected chemical shifts and of expected multiplicities. Decreased coupling throughout the remaining part of the structure pointed to the absence of a stereogenic centre at carbon 3″. Thus, two singlets (at δ_H 5.37 and 3.97) were observed for the C*H*$_2$Ar and NC*H*$_2$C(O) protons, respectively. For precursor **221**, these protons were observed as four doublets at δ_H 4.67, 4.56, 4.52 and 4.34, respectively. The differences in chemical shifts of these protons between **221** and **225**/**226** are quite surprising, though. As expected for structure **225**/**226**, we did not observe a highly deshielded multiplet for H-3″ (in **221**), which is therefore absent. The vinyl hydrogen singlet in **225**/**226**, NC=C*H*, was observed at δ_H 5.94 (similar, but more deshielded than in **221**, where δ_H = 5.06). This ^{1}H chemical shift agrees with that expected for an oxazine ring proton at the corresponding 4-position of the ring. In 1981, Abramovitch and Dupuy [133] obtained 1,2-oxazines "isoxazines" by the thermolysis of 2-azidopyridine 1-oxides in benzene at 90 °C. The simplest isoxazine **228**, which they isolated, is shown here (the numbering scheme is included). In the ^{1}H



228

NMR spectrum, H-5 was observed [as a ddd, $J_{5,6}$ = 5.1 Hz)] at δ_H 6.1, in good agreement with our tentative assignment of the corresponding proton (at δ_H 5.94) if the structure of our isolated compound is that of **226** (Scheme 49). The remaining signals in the ^{1}H NMR spectrum of **225**/**226** (i.e. methoxy protons, ring methylene protons and Boc protons) were as expected, and comparable to those observed for precursor **221**, both in chemical shift and multiplicity.

The ^{13}C NMR spectrum of **225** was complex, owing to the large number of signals in the carbonyl and aromatic region. However, we could assign a few of these (see experimental, Section 8.2.4.), which were comparable to those observed for **221**. As expected, the enaminone *C*=O signal was not observed in **225**. Furthermore, it is reasonable to expect the quaternary carbons C-2″ and C-3″ to be highly deshielded and to absorb in the aromatic region. These could not be assigned with certainty, but two "additional" quaternary carbon peaks were indeed observed in this region. In the



228

^{13}C NMR spectrum of **228** (obtained by Abramovitch and Dupuy[133]) carbons 3, 4 and 5 were observed at δ_C 148.2, 116.45 and 124.2, respectively. Although we could not be sure about whether the signal we observed in the ^{13}C NMR spectrum of **225**/**226** at δ_C 148.1 was attributed to the analogous C-3, i.e. C-3″ in **226**, or to the quinazolinone C-8a, we did observe a quaternary carbon at δ_C 115.1 (i.e. similar to C-4 in **228**) which might therefore be assigned to C-2″ in **226**. Five carbon signals were observed at *ca*. δ_C 126-129 in the spectrum of **226** and it cannot be speculated which one might be attributed to C-3′ (similar to C-5 in **228**) in **226**. The other carbons in **226** were all tentatively assigned, all within reason, by comparing the assignments to those in precursor **221**. Importantly, no carbonyl carbon peak was found corresponding to the carbonyl carbon in structure **225**, unless this carbon is more shielded than expected and absorbs at δ_C 135.2 (a quaternary carbon peak which could not be unequivocally assigned). It is therefore more likely that we isolated the isoxazine **226**.

Unfortunately, we could not find reported NMR spectral data for isoxazines, which are more similar to structure **226** than the oxazine **228.** A Beilstein database search revealed that isoxazine-containing compounds usually consist of the isoxazine ring fused to a benzene ring. None were found which were fused to a tetrahydropyridine

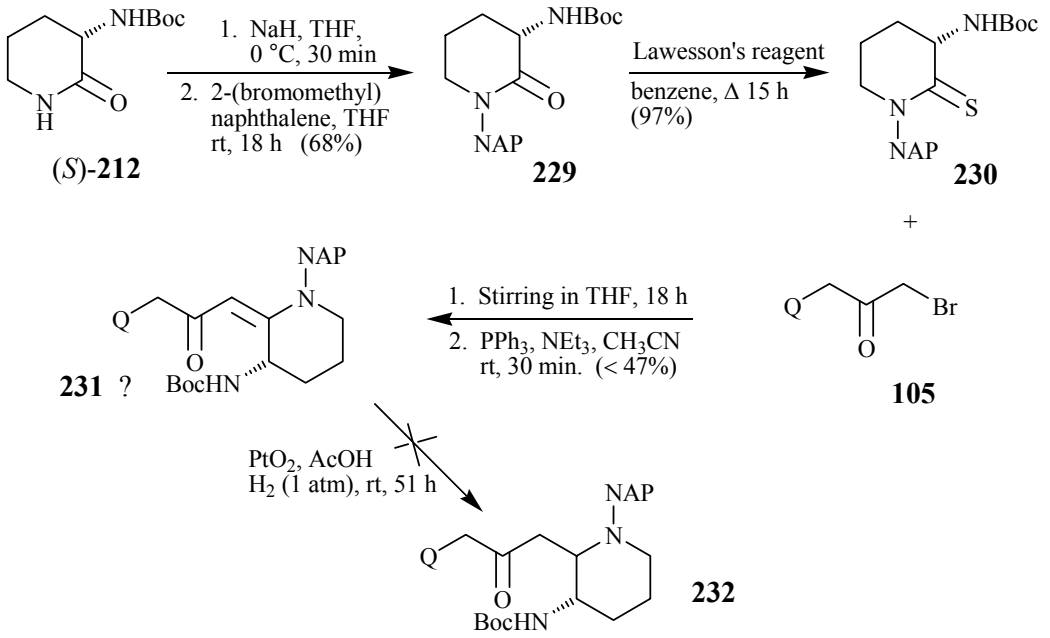
ring, such as **226**, nor to a cyclohexene-based ring. Furthermore, no NMR spectral data were found of a compound containing an imine which is substituted on an enaminone group in a way similar to structure **225**.

It should be noted that we cannot claim with total certainty that we did isolate **225** or **226** as proposed. The important point is that, for reasons not easily explained, vinylogous amide **221** was either decomposed or untouched when subjected to the hydrogenation conditions which worked well to reduce the model enaminones chemoselectively. The presence of a 3″-substituent therefore alters the properties and the reactivity of cyclic enaminones such as **221** to a greater extent than initially predicted. The presence of an inductively electron-withdrawing group, e.g. NHBoc, on C-3″ seems to prevent easy hydrogenation of the C=C bond in the neighbouring enaminone group.

4.4. Approach using *N*-(2-methylnaphthyl) protection

Our interest in the NAP (2-methylnaphthyl) group as an alternative alkyl amino-protecting group to the Bn group, which we were unable to remove during the model study, led us to attempt the synthesis of **203** using the NAP group. We also thought that the use of an alternative protecting group might alter the reactivity and isolability of advanced intermediates, which thus far proved to be problematic in our proposed synthesis of **203**.

Prerequisite lactam **229** was prepared in 68% yield from lactam (*S*)-**212** and 2-(bromomethyl)naphthalene (Scheme 50) according to the conditions mentioned before (Section 3.4.1.). In the ^{1}H NMR spectrum of **229**, the Boc N*H* proton was observed as a broad singlet at δ_H 5.59 The NC*H*$_2$Ar protons were observed as two distinct doublets (at δ_H 4.80 and 4.69, respectively, with J = 14.6 Hz for each) owing to the stereogenic centre at position 3 of the lactam ring. The signals of two carbonyl carbons were observed in the ^{13}C NMR spectrum (one signal at δ_C 169.8 can be assigned to the lactam carbonyl group and another, at δ_C 156.0, can be assigned to the Boc carbonyl group).



Scheme 50: Attempt towards **203** using NAP as an amino- protecting group.

Thionation of **229**, this time using the recommended Lawesson's method, afforded a high yield (97%) of the corresponding thiolactam **230**. The ^{13}C NMR spectrum clearly indicated the presence of a thiocarbonyl carbon, as reflected by the peak at δ_C 201.5. The Boc carbonyl carbon was observed at δ_C 155.3 in this case. Owing to the increased electron-withdrawing effect by the nearby thiocarbonyl sulfur atom, the Boc N*H* proton signal was observed as a broad singlet at δ_H 6.41, which is significantly more deshielded than the analogous proton in precursor lactam **229** (see above).

Although the Eschenmoser reaction between **230** and **105** seemed to lead to the formation of the desired vinylogous amide **231** in moderate yield (< 47% if the correct structure was obtained), product **231** (a viscous colourless oil) was difficult to isolate and contained trace impurities even after repeated purification attempts using column chromatography. Furthermore, the NMR spectra were complex, owing to the numerous aromatic signals observed. The ^1H NMR spectrum of **231** did show the presence of two identifiable protons in the quinazolinyl group, i.e. H-5 as a doublet at δ_H 8.28 (J = 7.9 Hz), and H-2 as the expected singlet at δ_H 7.87. The remaining nine aromatic signals overlapped to form a multiplet at δ_H 7.38-7.84. The Boc N*H* proton was observed as a broad singlet at δ_H 5.98, and the vinyl proton in the enaminone

group was observed as a singlet at δ_H 5.12. Furthermore, H-3 (alpha to the Boc substituent) formed a broad singlet at δ_H 5.01. The NC*H*$_2$Ar protons were observed as two distinct doublets (J =16.1 and 16.0) at the expected chemical shifts (δ_H 4.65 and 4.47, respectively). Two doublets (J = 16.6 for each) were also observed for the NC*H*$_2$C(O) protons (at δ_H 4.81 and 4.56). Although all the aliphatic and the vinyl (NC=*C*H) carbon signals could be assigned in the ^{13}C NMR spectrum of **231**, a few additional peaks (probably as a result of a small amount of an aromatic impurity) were observed in the aromatic region. However, both the quinazolinone and the Boc carbonyl carbons could be reliably assigned, as well as the peaks belonging to the N*C*=CH, C-8a and C-4a quaternary carbons (see experimental, Section 8.3.3).

Again in the hope of possibly isolating a crystalline and easily characterizable product, hydrogenation of **231** was carried out in an attempt to produce key amine **232**. Unfortunately, a mixture of unidentifiable products (the NMR data of which pointed to decomposition of **231**) was obtained. This experimental route was consequently discontinued.

4.5. Conclusion

In this chapter, we attempted the synthesis of an important 3-amino analogue of febrifugine (**1**) from L-ornithine. It was found that the use of an *N*-alkylated piperidine-2-thione was required if a stable, isolable vinylogous amide intermediate was to be obtained. The interesting 3-acylamino dehydro febrifugine analogue **221**, which is an analogue of **1** that might be worthwhile submitting for antimalarial testing, was prepared in this way. Attempted chemoselective C=C hydrogenation of the enaminone group in **221** unexpectedly resulted in the isolation of putative isoxazine **226**. Future work includes the repetition and/or the optimization of the hydrogenation reaction which produced **226**. The use of alternative conditions, e.g. NiO and base, to prepare **226** from **221** might be useful to confirm the structure of **226**. The attempted chemoselective reduction of **221** to form the desired azafebrifugine analogue should be repeated by employing an alternative reducing agent, preferably one that does not involve catalytic hydrogenation.