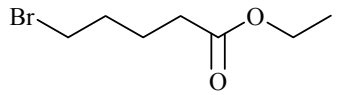
CHAPTER 9

EXPERIMENTAL SECTION RELATING TO CHAPTER 5

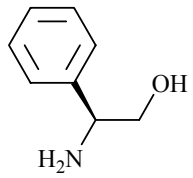
9.1. Approach to febrifugine using Micouin methodology [i.e. using (*S*)-phenylglycinol as a chiral auxiliary]

9.1.1. Ethyl 5-bromopentanoate (242)



This compound was prepared based on a combination of two known procedures [137,138]. δ-Valerolactone (15.0 g, 13.6 cm^3, 0.150 mol) was dissolved in a HBr solution (48%, 90 cm^3) to which was added H_2SO_4 (98%, 4.5 cm^3). The solution was heated under reflux for 140 min followed by stirring at rt for 22 h. After the addition of water (20 cm^3), the mixture was extracted with Et_2O (5 × 80 cm^3). The combined ethereal extracts were washed with brine (2 × 30 cm^3), dried (Na_2SO_4) and evaporated *in vacuo* to yield crude 5-bromopentanoic acid as a light-brown solid (22.7 g, 84%), which was used without further purification. The obtained 5-bromopentanoic acid was dissolved in a mixture of absolute ethanol (25 cm^3) and toluene (10 cm^3), after which H_2SO_4 (98%, *ca.* 1 cm^3) was added. The solution was refluxed in an appropriate Dean-Stark apparatus for 8h and the residue was dissolved in Et_2O:hexane (1:1, 50 cm^3) and subsequently washed with water (30 cm^3) and saturated $NaHCO_3$ (3 × 30 cm^3). The organic layer was dried (Na_2SO_4) and evaporated *in vacuo* to yield pure **242** as a clear orange-coloured oil (24.5 g, 94%), δ_H (300 MHz; $CDCl_3$) 4.14 (2H, quartet, *J* 7.1, OC*H*$_2$), 3.42 (2H, t, *J* 6.6, C*H*$_2$Br), 2.34 (2H, t, *J* 7.3, O=CC*H*$_2$), 1.91 (2H, 2 × t, *J* 7.9 and 6.5, C*H*$_2$CH$_2$Br), 1.78 (2H, 2 × t, *J* 7.9 and 7.3, O=CCH$_2$C*H*$_2$), 1.26 (3H, t, *J* 7.1, OCH$_2$C*H*$_3$). The spectroscopic data agree with those reported elsewhere [138].

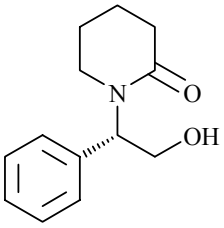
9.1.2. (*S*)-2-Amino-2-phenylethanol (243)



This compound was prepared by a known procedure [139]. A suspension of LAH (95%, 10.5 g, 0.263 mol) in dry THF (250 cm^3) was stirred at rt for 5 min before adding portionwise, over a period of 1 h, (*S*)-2-amino-2-phenylacetic acid (12.5 g, 82.5 mmol). The mixture was stirred for another hour at rt before refluxing gently for 22 h. After cooling to 0 °C, water (5 cm^3) was added cautiously and the mixture was stirred for another 30 min

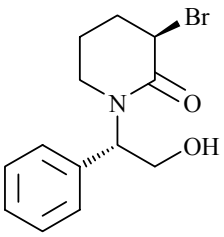
before evaporating most of the solvent *in vacuo*. The residue was partitioned between water (50 cm^3) and CH_2Cl_2 (80 cm^3). The aqueous layer was extracted with CH_2Cl_2 (4 × 80 cm^3) and the combined organic extracts were washed with water (50 cm^3), dried (Na_2SO_4) and evaporated *in vacuo* to yield a yellow solid which was recrystallized from CH_2Cl_2–hexane to yield **243** as a colourless solid (7.9 g, 70%), mp 78–80 °C [lit., 77–78 °C[ref]]; δ_H (300 MHz; $CDCl_3$) 7.22–7.35 (5H, m, 5 × H_{arom}), 4.02 (1H, dd, *J* 8.3 and 4.2, H_2NCH), 3.70 (1H, dd, *J* 10.9 and 4.2, 0.5 × CH_2OH), 3.52 (1H, dd, *J* 10.9 and 8.4, 0.5 × CH_2OH). The spectroscopic data agree with those reported elsewhere [139].

9.1.3. 1-[(*S*)-2-Hydroxy-1-phenylethyl]piperidin-2-one (244)



This compound was prepared by a known procedure [135]. A solution of (*S*)-2-amino-2-phenylethanol **243** (1.37 g, 9.99 mmol), ethyl 5-bromopentanoate **242** (2.10 g, 10.0 mmol) and DBU (98%, 3.1 g, 20 mmol) in pre-dried (5 Å molecular sieves) absolute ethanol (20 cm^3) was stirred at reflux for 48 h. After evaporation of the ethanol *in vacuo*, the orange-coloured residue was dissolved in CH_2Cl_2 (50 cm^3) and washed with saturated NH_4Cl (10 cm^3). The organic layer was dried ($MgSO_4$) and evaporated *in vacuo*. The residual oil was purified by column chromatography (CH_2Cl_2:MeOH, 19:1) to yield **244** as a viscous colourless oil (1.38 g, 63%) which contained trace impurities, but was used without further purification, R_f 0.15 (CH_2Cl_2:MeOH, 9:1); δ_H (300 MHz; $CDCl_3$) 7.23–7.36 (5H, m, 5 × H_{arom}), 5.79 (1H, dd, *J* 5.7 and 2.8, NC*H*), 4.09–4.15 (2H, m, 0.5 × CH_2OH), 3.34–3.39 (1H, m, O*H*), 3.18–3.23 (1H, m, 0.5 × NCH_2), 2.91–2.95 (1H, m, 0.5 × NCH_2), 2.48–2.52 (2H, m, 1 × $O{=}CCH_2$), 1.65–1.82 (4H, m, 4 × ring CH_2). Spectroscopic data agree with those reported elsewhere [135].

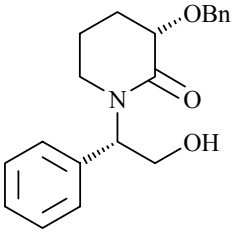
9.1.4. (*R*)-3-Bromo-1-[(*S*)-2-hydroxy-1-phenylethyl]piperidin-2-one (245)



This compound was prepared by a known procedure [134]. To a solution of 1-[(*S*)-2-hydroxy-1-phenylethyl]piperidin-2-one **244** (1.08 g, 4.93 mmol) in dry THF (65 cm^3) was added *sec*-BuLi (1.3 M in cyclohexane, 9.5 cm^3, 12 mmol) at –78 °C. The mixture was stirred for 20 min after which the temperature was lowered to –100 °C. Br_2 (0.26 cm^3, 5.1 mmol) was added dropwise over 5 min and the reaction was stirred for another 5 min at –100 °C before quenching with saturated NH_4Cl (20 cm^3). After

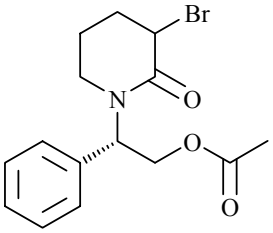
warming to rt, the mixture was extracted with EtOAc (2 × 30 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The product was purified by column chromatography (EtOAc) to yield **245** as a colourless solid (0.37 g, 25%), mp 122–125 °C (from EtOAc–Hexane) [lit., 129 °C [134]]; δ_H (300 MHz; $CDCl_3$) 7.20–7.40 (5H, m, 5 × H_{arom}), 5.84 (1H, dd, *J* 5.1 and 4.6, NC*H*), 4.68 (1H, td, *J* 3.3 and 1.0, BrC*H*), 4.24 (1H, dd, *J* 6.4 and 5.1, 0.5 × CH_2OH), 4.06–4.16 (1H, m, 0.5 × CH_2OH), 3.26–3.35 (1H, m, 0.5 × NCH_2), 3.07–3.13 (1H, m, 0.5 × NCH_2), 2.11–2.39 (3H, m, 1.5 × ring CH_2), 1.74–1.81 (1H, m, 0.5 × ring CH_2). Spectroscopic data agree with those reported elsewhere [134]. An optical rotation of the compound was not determined as it was obvious from the melting point and the ^{1}H NMR spectral data that we indeed obtained the correct diastereomer. No evidence of the other diastereomer was observed.

9.1.5. (*S*)-3-Benzyloxy-1-[(*S*)-2-hydroxy-1-phenylethyl]piperidin-2-one (<u>246</u>)



This compound was prepared by a known procedure [134]. To a suspension of NaH (50% mineral oil suspension, 0.25 g, 5.2 mmol) in dry DMF (12 cm^3) was added benzyl alcohol (0.36 cm^3, 5.1 mmol). After stirring at rt for 30 min, a solution of (*R*)-3-Bromo-1-[(*S*)-2-hydroxy-1-phenylethyl]piperidin-2-one **245** (0.76 g, 2.5 mmol) in dry DMF (12 cm^3) was added dropwise over 5 min, before leaving the reaction mixture stirring at rt for 1h30min. After the addition of saturated aq. NH_4Cl (40 cm^3), the product was extracted with Et_2O (2 × 40 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to afford crude product (0.76 g) as an oil. Column chromatography (EtOAc:cyclohexane, 9:1) afforded crude **246** as an oil (70 mg, 9%), which contained impurities evident from the ^{1}H NMR spectrum. Owing to the low yield of **246**, this approach was discontinued (see Section 5.1.3.).

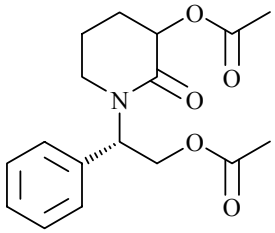
9.1.6. (*S*)-2-[3-(*R* and *S*)-Bromo-2-oxopiperidin-1-yl]-2-phenylethyl acetate (<u>247</u>)



This compound was prepared based on a known acetylation procedure [140]. To a stirred mixture of (*R*)-3-bromo-1-((*S*)-2-hydroxy-1-phenylethyl)piperidin-2-one **245** (1.48 g, 4.96 mmol), Ac_2O (1.40 cm^3) and glacial AcOH (1.40 cm^3) at 0 °C was added AcOH-$HClO_4$ catalyst (0.15 cm^3, which was prepared by mixing 0.10 cm^3 of 60% $HClO_4$ and 0.23 cm^3 Ac_2O at 0 °C). The reaction was warmed to rt and left stirring for 43 h. Water (20 cm^3) was added and the product was extracted with CH_2Cl_2 (3 × 25 cm^3). The combined organic extracts were washed with saturated

NaCl (10 cm^3), dried (Na_2SO_4) and evaporated *in vacuo* to afford a residue which was purified by gradient elution column chromatography (Hexane:EtOAc, 9:1 to 7:3). Two diastereomers, corresponding to structure **247**, were isolated (both as light yellow oils) in an approximately 1:1 ratio. Diastereomer 1 (0.40 g, 24%), R_f 0.32 (Hexane:EtOAc, 7:3); δ_H (300 MHz; $CDCl_3$) 7.32–7.39 (3H, m, 3 × H_{arom}), 7.24–7.27 (2H, m, 2 × H_{arom}), 6.21 (1H, dd, *J* 10.1 and 5.1, NC*H*), 4.84 (1H, dd, *J* 11.4 and 10.2, 0.5 × CH_2OAc), 4.64 (1H, dd, *J* 3.9 and 2.7, BrC*H*), 4.45 (1H, dd, *J* 11.5 and 5.1, 0.5 × CH_2OAc), 3.31–3.38 (1H, m, 0.5 × NCH_2), 2.80–2.88 (1H, m, 0.5 × NCH_2), 2.06–2.25 (3H, 2 × m, 1.5 × ring CH_2), 2.11 (3H, s, O=CCH_3), 1.68–1.74 (1H, m, 0.5 × ring CH_2); δ_C (75 MHz; $CDCl_3$) 171.0 (ester *C*=O), 167.1 (lactam *C*=O), 135.3 (*ipso*-C_{arom}), 128.8, 128.3 (*para*-C_{arom}), 127.8, 60.6 (*C*H_2OAc), 54.1 (N*C*H), 45.4 (*C*Br), 42.2 (N*C*H_2), 30.9 (ring *C*H_2), 20.9 (O=C*C*H_3), 19.0 (ring *C*H_2); *m/z* (FABMS) 340 (16%, M+1^+), 316 (5), 298 (6), 280 (44, M^+–CH_3COO), 266 (8), 261 (17), 236 (6), 200 (33), 188 (22), 163 (100, M^+–lactam), 132 (11), 121 (21), 104 (37, $PhCHCH_2^+$), 91 (62, piperidonium ion) (Found: M+1^+, 340.0540. $C_{15}H_{19}{}^{79}BrNO_3$ requires 340.0548). Diastereomer 2 (0.37 g, 22%), R_f 0.22 (Hexane:EtOAc, 7:3); ν_{max}(film)/cm^{-1} 3061 and 3031 (w, Aryl-H str), 2953 (m, CH sym str), 2872 (w, CH asym str), 1741 (s, ester C=O), 1646 (s, lactam C=O); δ_H (300 MHz; $CDCl_3$) 7.32–7.41 (3H, m, 3 × H_{arom}), 7.26–7.29 (2H, m, 2 × H_{arom}), 6.12 (1H, br t, *J* 7.2, NC*H*), 4.61–4.67 (3H, m, BrC*H* and 1 × CH_2OAc), 3.22–3.31 (1H, m, 0.5 × NCH_2), 3.05–3.12 (1H, m, 0.5 × NCH_2), 2.26 (2H, quintet, *J* 3.8, 1 × ring CH_2), 2.06 (3H, s, O=CCH_3), 2.04–2.15 (1H, m, 0.5 × ring CH_2), 1.73–1.80 (1H, m, 0.5 × ring CH_2); δ_C (75 MHz; $CDCl_3$) 170.8 (ester *C*=O), 166.9 (lactam *C*=O), 135.9 (*ipso*-C_{arom}), 129.0, 128.2 (*para*-C_{arom}), 127.5, 61.3 (*C*H_2OAc), 54.2 (N*C*H), 45.5 (*C*Br), 42.4 (N*C*H_2), 31.1 (ring *C*H_2), 20.9 (O=C*C*H_3), 18.9 (ring *C*H_2); *m/z* (FABMS) 340 (34%, $M^{79}Br$+1^+), 298 (9), 280 (62, M^+–CH_3COO), 266 (11), 261 (26), 200 (39), 188 (24), 163 (100, M^+–lactam), 132 (10), 121 (18), 104 (32, $PhCHCH_2^+$), 91 (47, $C_7H_7^+$) (Found: $M^{79}Br$+1^+, 340.0554. $C_{15}H_{19}{}^{79}BrNO_3$ requires 340.0548).

9.1.7. (*S*)-2-[3-(*S* and *R*)-Acetyl-2-oxopiperidin-1-yl]-2-phenylethyl acetate (248)

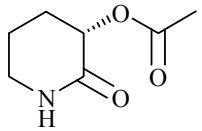


To a solution of (*S*)-2-(3-(*R* or *S*)-bromo-2-oxopiperidin-1-yl)-2-phenylethyl acetate **247** (diastereomer 1 as characterized above, 390 mg, 1.15 mmol) in dry DMSO (30 cm^3) at 0 °C, was added a solution of anhydrous sodium acetate (0.21 g, 2.6 mmol) in DMSO (10 cm^3) at 0 °C. After warming the reaction to rt, it was stirred for another 30 min, then warmed to 55 °C and kept at this temperature for 1 h. After pouring the reaction mixture into water (50 cm^3) and extracting with EtOAc (3 × 25 cm^3), the organic extracts were dried (Na_2SO_4) and

evaporated *in vacuo*. Column chromatography (Hexane:EtOAc, 7:3) yielded **248** as a colourless oil (268 mg, 73%) which was identified as an inseparable mixture of diastereomers in an approximately 1:1 ratio, R_f *ca*. 0.11 (Hexane:EtOAc, 7:3); ν_{max}(film)/cm^{-1} 3061 (w, Ar–H str), 3031 (w, Ar–H str), 2953 (w, CH_3 asym str), 2872 (w, CH_3 and CH_2 sym str), 2853 (w, sh, CH_2 sym str), 1741 (m, sh, ester C=O), 1646 (s, lactam C=O), 1485 (w, Ar C=C str), 1453 (m, Ar C=C str); δ_H (300 MHz; $CDCl_3$) 7.24–7.40 (10H, m, 10 × H_{arom}, both diastereomers), 6.09–6.15 (2H, m, 2 × NC*H*, both diastereomers), 5.24–5.31 (2H, m, 2 × C*H*OAc, both diastereomers), 4.64–4.73 (2H, m, 1 × CH_2OAc, both diastereomers), 4.48–4.60 (2H, m, 1 × CH_2OAc, both diastereomers), 3.18–3.25 (2H, m, 1 × NCH_2, both diastereomers), 2.89–2.98 (2H, m, 1 × NCH_2, both diastereomers), 2.17 (3H, s, first O=CCH_3, first diastereomer), 2.16 (3H, s, first O=CCH_3, second diastereomer), 2.083 (3H, s, second O=CCH_3, first diastereomer), 2.076 (3H, s, second O=CCH_3, second diastereomer), *ca.* 2.0–2.2 (2H, m, 1 × ring CH_2, both diastereomers), 1.72–1.95 (6H, m, 3 × ring CH_2, both diastereomers); δ_C (75 MHz; $CDCl_3$) 170.9 (first ester *C*=O, first diastereomer), 170.8 (first ester *C*=O, second diastereomer), 170.23 (second ester *C*=O, first diastereomer), 170.16 (second ester *C*=O, second diastereomer), 168.0 (lactam *C*=O, first diastereomer), 167.7 (lactam *C*=O, second diastereomer), 135.9 (ipso-C_{arom}, first diastereomer), 135.7 (ipso-C_{arom}, second diastereomer), 128.82, 128.79, 128.1, 127.8, 127.6, 69.5 (O=C*C*OAc, first diastereomer), 69.2 (O=C*C*OAc, second diastereomer), 61.31 (*C*H_2OAc, first diastereomer), 61.27 (*C*H_2OAc, second diastereomer), 54.05 (N*C*H, first diastereomer), 54.02 (N*C*H, second diastereomer), 42.1 (N*C*H_2, first diastereomer), 41.9 (N*C*H_2, second diastereomer), 26.9 (ring *C*H_2, first diastereomer), 26.4 (ring *C*H_2, second diastereomer), 21.0 (first O=C*C*H_3, both diastereomers), 20.8 (second O=C*C*H_3, both diastereomers), 20.2 (ring *C*H_2, first diastereomer), 20.1 (ring *C*H_2, second diastereomer); *m/z* (HREIMS) 259 (58, M^+–HOC(O)CH_3), 246 (70, M^+–H_2COC(O)CH_3), 216 (7), 204 (31), 200 (100), 176 (18), 158 (18), 120 (13), 104 (16, PhCHCH_2^+), 103 (12), 91 (13, $C_7H_7^+$), 70 (35) (Found: M^+–HOC(O)CH_3, 259.1213. $C_{15}H_{17}NO_3$ requires 259.1208).

9.2. Approaches to febrifugine from L-arginine

9.2.1. Method A; the preparation of (3*S*)-2-oxopiperidin-3-yl acetate (<u>255</u>)

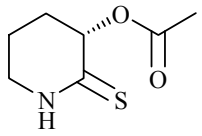


Crude (3*S*)-3-hydroxypiperidin-2-one was prepared from L-arginine monohydrochloride based on the combination of two previously published

methods[142,119], followed by *O*-acetylation, without isolating the intermediates. This compound was synthesized only once before by following a completely different route [147].

Arginine monohydrochloride (5.0 g, 24 mmol) was dissolved in distilled water (250 cm^3). Freshly prepared $AgNO_2$ [192] (4.0 g, 26 mmol) was added and the mixture was stirred vigorously for 3 h. The formed AgCl was filtered and the resulting filtrate was heated in a conical flask at 60 ºC for 2 h until the evolution of N_2 gas ceased. After filtering to remove any remaining insoluble salts, $Ba(OH)_2$ was added to the filtrate until the solution was just saturated at rt. The resulting mixture was refluxed for 2 h. While still warm, CO_2 gas was bubbled through the reaction mixture for 10 min. After cooling to rt, the formed $BaCO_3$ was filtered off twice under suction through celite, after which the filtrate was evaporated *in vacuo* at 60 ºC. The remaining residue was washed with hot absolute ethanol (3 × 30 cm^3). The remaining flask contents, a very viscous light yellow oil, was dried thoroughly under high vacuum for several hours. To the crude product was added xylene (170 cm^3), HMDS (40 cm^3) and a few drops of TMS-Cl. The mixture was refluxed for 13.5 h, after which EtOH (96%, 170 cm^3) was added to the cooled reaction mixture. The solvents were evaporated *in vacuo* and the residue was dissolved in MeOH (50 cm^3), followed by filtration through celite. After evaporation of the solvent *in vacuo*, crude (3*S*)-3-hydroxypiperidin-2-one **210** (0.10 g) was obtained as a light brown oil. After drying thoroughly under high vacuum, the crude product was suspended in EtOAc (10 cm^3). Pyridine (0.70 cm^3) and Ac_2O (0.40 cm^3) were sequentially added under N_2 and the mixture was stirred for 24 h at rt. After evaporation of the solvents and reactants *in vacuo*, a residue remained which was purified by column chromatography (EtOAc) to yield **255** as a light yellow viscous oil (55 mg, 1.5% over 4 steps), R_f 0.10 (EtOAc); ν_{max}(film)/cm^{-1} 3241 (m, br, N–H str), 2953 (w, br, CH_3 asym str), 2879 (w, CH_3 and CH_2 sym str), 1744 (m, ester C=O), 1670 (s, br, lactam C=O); δ_H (300 MHz; $CDCl_3$) 6.91 (1H, br s, N*H*), 5.23 (1H, dd, *J* 9.0 and 6.1, O=CC*H*), 3.33–3.39 (2H, m, NCH_2), 2.12–2.29 (1H, m, discernible overlapping m, 0.5 × CH_2), 2.15 (3H, m, CH_3), 1.84–2.04 (3H, 1.5 × CH_2); δ_C (75 MHz; $CDCl_3$) 170.2 (ester *C*=O), 169.9 (lactam *C*=O), 68.5 (O=C*C*H), 41.9 (N*C*H_2), 26.8 (*C*H_3), 20.8 (*C*H_2), 20.1 (*C*H_2); *m/z* (EI) 158 (15%, M+1^+), 129 (8, M+1^+–C_2H_5), 114 (21, M+1^+–CO_2), 102 (9), 97 (42), 86 (6), 71 (44, $C_5H_{11}^+$), 69 (25, $C_5H_9^+$), 59 (12, $C_2H_5CH{=}OH^+$), 43 (100, CH_3CO^+), 31 (15, $CH_2{=}OH^+$) (Found: M+1^+, 158.0846. $C_7H_{12}NO_3$ requires 158.0817). ^{1}H NMR spectroscopic data agree with the previously incomplete data reported elsewhere [147].

9.2.2. Method B; the preparation of (3*S*)-2-thioxopiperidin-3-yl acetate (<u>260</u>)

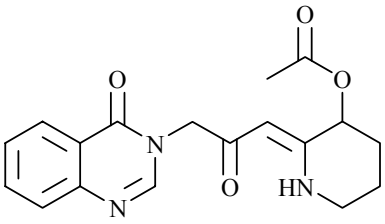


Crude (3*S*)-3-hydroxypiperidin-2-one **210** was prepared from L-arginine monohydrochloride by two well established methods [145,119], followed by *O*-acetylation and subsequent thionation, without isolating the intermediates.

In a 50 cm^3 round bottom flask, L-arginine monohydrochloride (4.42 g, 21.0 mmol) was dissolved in a mixture of conc. HCl (6.6 cm^3) and conc. HNO_3 (3.3 cm^3). The solution was kept at 60 ºC for 30 min. Excess acid was evaporated *in vacuo*, without allowing the water bath temperature to exceed 80 ºC. Conc. HCl (8.8 cm^3) was added to the residue, the partial solution was shaken for a while and then the acid was again evaporated *in vacuo* as before. This last process was repeated twice. After drying thoroughly under high vacuum, the residue was dissolved in distilled water (440 cm^3) and the solution was refluxed for 48 h. After cooling to rt, Ag_2CO_3 (5.5 g, 20 mmol) was added and the mixture was vigorously stirred for 1 h, before removing the AgCl precipitate by filtration through celite. The precipitate was washed with additional water (30 cm^3) and the resultant filtrate was evaporated *in vacuo*, keeping the water bath temperature below 60 ºC. After thorough drying under high vacuum, the residue was dissolved in saturated aq. $Ba(OH)_2$ (160 cm^3) and the solution was refluxed for 3 h. After filtering through celite, water was again evaporated *in vacuo* without allowing the bath temperature to exceed 60 ºC. The residue was washed with hot absolute ethanol (3 × 30 cm^3) before dissolving the flask residue in water (50 cm^3). Conc. H_2SO_4 was added dropwise until the pH tested slightly acidic (*ca*. 6). The formed $BaSO_4$ was removed by filtration and the filtrate was evaporated *in vacuo* at 60 ºC as before. After thorough drying of the residue under high vacuum, the crude product was suspended in xylene (140 cm^3), HMDS (33 cm^3) and TMS-Cl (3 drops) was added, and the resulting mixture was refluxed for 15.5 h. After cooling the reaction mixture to rt, absolute EtOH (320 cm^3) was added and the solvents were evaporated *in vacuo* at 60 ºC. The residue was dissolved in MeOH (120 cm^3), after which the solution was filtered through celite. After evaporation of the filtrate *in vacuo*, an orange-brown oil [crude (3*S*)-3-hydroxypiperidin-2-one **210**] was obtained. The crude product was suspended, after thorough drying under high vacuum, in EtOAc (100 cm^3). Addition of pyridine (9.0 cm^3) and Ac_2O (5.3 cm^3) was followed by stirring at rt for 6.5 h. After filtering the reaction mixture through celite and washing the solids with EtOAc, the filtrate was evaporated *in vacuo* and dried thoroughly under high vacuum. The residue was dissolved in benzene (50 cm^3) and Lawessons reagent (4.95 g, 12.2 mmol) was added. After stirring at rt for 12 h, the mixture was refluxed for 1.5 h. Evaporation of the solvent *in vacuo* followed by column chromatography (hexane:EtOAc, 4:1) yielded **260** as a

yellow solid (1.53 g, 42% over 6 steps from L-arginine monohydrochloride), mp 106.5-108 ºC (from hexane); R_f 0.49 (EtOAc:hexane, 1:1); $[\alpha]_D^{20}$ –22.0 (*c* 0.27, $CHCl_3$); ν_{max}(film)/cm^{-1} 3172 (w, br, N–H str), 3084 (w), 2950 (w, CH_3 asym str), 2862 (w, CH_2 sym str), 1739 (s, C=O), 1563 (s, C=S); δ_H (300 MHz; $CDCl_3$) 9.00 (1H, br s, N*H*), 5.50 (1H, br t, *J* 6.6, S=CC*H*), 3.37 (2H, m, NCH_2), 2.17 (3H, CH_3), 1.85–2.11 (4H, m, 2 × CH_2); *m/z* (EI) 173 (100%, M^+), 131 (69, M^+–CH_2CO), 113 (9, M^+–$HO(O)CCH_3$), 102 (6), 86 (8), 71 (66, $C_5H_{11}^+$), 60 (11, $CH_2{=}C(OH)_2^+$), 55 (21, $C_4H_7^+$), 43 (67, CH_3CO^+), 28 (13, CO^+) (Found: M^+, 173.0510. $C_7H_{11}NO_2S$ requires 173.0510). This compound was also characterized by single crystal X-ray diffraction and found to have racemized to an undetermined extent, as deduced from the crystal centrosymmetry (see Section 5.2.3.).

9.2.3. Attempted preparation of 3-{(*Z*)-3-[(3*S*)-3-acetylpiperidin-2-ylidene]-2-oxopropyl} quinazolin-4(3*H*)-one (<u>261</u>)



A mixture of 3-(3-bromo-2-oxopropyl)quinazolin-4(3*H*)-one **105** (0.20 g, 0.71 mmol) and (*S*)-2-thioxopiperidin-3-yl acetate **260** (125 mg, 0.73 mmol) in dry THF (20 cm^3) was stirred at rt o.n. After evaporating the solvent *in vacuo*, dry CH_3CN (20 cm^3), PPh_3 (0.28 g, 1.1 mmol) and 1-methylpiperidine (0.15 cm^3, 1.2 mmol) were sequentially added to the remaining residue at 0 ºC. After warming to rt, stirring was continued for 1.5 h. The solvent was evaporated *in vacuo* after which the residue was dissolved in CH_2Cl_2 (20 cm^3) and filtered through celite. After evaporation of CH_2Cl_2 *in vacuo*, the residue was subjected to column chromatography (EtOAc, followed by CH_2Cl_2:MeOH, 4:1) to yield putative compound **261** as a very viscous light brown oil (0.51 g, 64%) which could not be crystallized, δ_H (300 MHz; $CDCl_3$) 8.88 (1H, s, N*H*), 8.44 (1H, s, H-2), 8.11 (1H, d, *J* 7.8, H-5), 7.62–7.72 (2H, m, H-7 and H-8), 7.42 (1H, t, *J* 7.3, H-6), 6.31 (1H, t, *J* 4.5, C*H*OAc), 5.83 (1H, d, *J* 16.0, 0.5 × NCH_2C=O), 5.73 (1H, d, *J* 16.0, 0.5 × NCH_2C=O), 4.95 (2H, m, 0.5 × ring NCH_2 and =C*H*), 3.31 (1H, br s, 0.5 × ring NCH_2), 2.57 (1H, m, 0.5 × ring CH_2), 2.45 (2H, m, 1 × ring CH_2), 2.22 (1H, m, 0.5 × ring CH_2), 2.13 (3H, s, CH_3). The ^{1}H NMR spectroscopic data corresponded very closely with those of the *tert*-butoxycarbonylamino analogue **220** described before (see Section 8.1.3.). As observed for **220**, after attempted purification, compound **261** decomposed rapidly (darkened) upon standing and was not characterized further. Similar to **220**, it was hoped that a product from the hydrogenation reaction of **261**, reacted directly after its purification, might be accurately characterizable and give clues to the structure of **261**.

9.2.4. Attempted reduction of 261

Method A:

A solution of 3-{(*Z*)-3-[(3*S*)-3-acetylpiperidin-2-ylidene]-2-oxopropyl}quinazolin-4(3*H*)-one **261** (0.10 g, 0.29 mmol) in MeOH (6 cm^3), to which conc. HCl (0.08 cm^3) had been added, was hydrogenated over PtO_2 (Adam's catalyst, 10 mg) under H_2 gas (1 atm) for 3 days. After work-up as before (see for NHBoc derivative), a brown residue was obtained, which was subjected to column chromatography as before. Very little isolable material was obtained which indicated, by ^1H NMR, decomposition of the starting material to unidentifiable products.

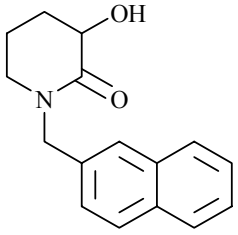
Method B:

A solution of 3-{(*Z*)-3-[(3*S*)-3-acetylpiperidin-2-ylidene]-2-oxopropyl}quinazolin-4(3*H*)-one **261** (32 mg, 0.094 mmol) in EtOH (96%, 1.5 cm^3), to which glacial AcOH (2 drops) had been added, was hydrogenated over Pd/C (10 %, 20 mg) under H_2 gas (1 atm) for several hours. After filtering the mixture through celite, the solution was partitioned between 10% NaOH (3 cm^3) and Et_2O (5 cm^3). After extraction of the aqueous layer with Et_2O (5 cm^3), the combined ethereal extracts were dried ($MgSO_4$) and evaporated *in vacuo* to yield a residue which was subjected to column chromatography (EtOAc:MeOH, 19:1) to afford unidentifiable (by ^1H NMR) products which once again indicated the decomposition of starting material.

9.3. Approaches to febrifugine using piperidin-2-one α-hydroxylation methodology

9.3.1. Using *O*-Ac and *N*-NAP as the piperidin-2-one protecting groups

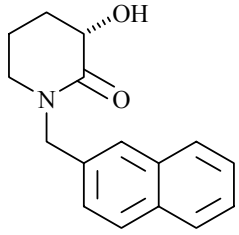
9.3.1.1. 3-Hydroxy-1-[(naphthalen-3-yl)methyl]piperidin-2-one [(±)-277]



This compound was prepared based on a known procedure [156]. *n*-BuLi (1.6 M in hexane, 4.2 cm^3, 6.8 mmol) was added dropwise to a solution of diisopropylamine (0.95 cm^3, 6.8 mmol) in THF (5 cm^3) at –20 ºC. After 5 min, the solution was warmed to 0 ºC and kept for another 30 min after which it was transferred under N_2 and dropwise to a solution of 1-[(naphthalen-3-

yl)methyl]piperidin-2-one **132** (0.65 g, 2.7 mmol) in THF (25 cm^3) at –70 ºC. The mixture was stirred for 30 min at –70 ºC, then warmed to 0 ºC. Gaseous O_2 was bubbled through the reaction mixture for 2 h at 0 ºC. After evaporation of the solvent *in vacuo*, saturated aq. Na_2SO_3 (30 cm^3) followed by acetone (0.5 cm^3) were added to the residue. The resulting mixture was stirred vigorously for 10 min. Water (20 cm^3) and CH_2Cl_2 (30 cm^3) were added and the mixture was transferred to a separatory funnel. After extraction of the aqueous layer with CH_2Cl_2 (3 × 30 cm^3), the combined organic extracts were washed with saturated NaCl (50 cm^3), dried (Na_2SO_4) and evaporated *in vacuo*. Gradient elution column chromatography (hexane:acetone, 9:1 to 7:3) yielded starting material (*ca*. 60 mg) and the desired product (±)-**277** as colourless crystals (364 mg, 53%), mp 118-119 ºC (from acetone-hexane); R_f 0.27 (EtOAc:hexane, 1:1); $\nu_{max}(CH_3Cl)/cm^{-1}$ 3378 (m, vbr, O–H str), 3053 (w, Ar–H str), 2944 (m, CH_2 asym str), 2867 (w, CH_2 sym str), 1633 (s, lactam C=O), 1494 (m, sh, Ar C=C str), 1465 and 1446 (w, Ar C=C str); δ_H (300 MHz; $CDCl_3$) 7.79–7.83 (3H, m, 3 × H_{arom}), 7.68 (1H, s, NAP H–1), 7.44–7.51 (2H, m, 2 × H_{arom}), 7.38 (1H, dd, *J* 7.8 and 1.3, 1 × H_{arom}), 4.81 (1H, d, *J* 14.5, 0.5 × NCH_2Ar), 4.67 (1H, d, *J* 14.5, 0.5 × NCH_2Ar), 4.13 (1H, dd, *J* 10.5 and 4.4, O=CC*H*), 3.86 (1H, br s, O*H*), 3.23 (2H, dd, *J* 4.8 and 2.5, ring NCH_2), 2.24–2.32 (1H, m, 0.5 × ring CH_2), 1.71–1.92 (3H, m, 1.5 × ring CH_2); δ_C (75 MHz; $CDCl_3$) 172.6 (*C*=O), 134.0 (1 × quaternary C_{arom}), 133.2 (1 × quaternary C_{arom}), 132.8 (1 × quaternary C_{arom}), 128.6 (1 × C_{arom}), 127.7 (2 × C_{arom}), 127.0 (1 × C_{arom}), 126.3 (1 × C_{arom}), 126.0 (2 × C_{arom}), 68.2 (O=C*C*), 50.5 (N*C*H_2Ar), 47.0 (ring N*C*H_2), 28.3 (ring *C*H_2), 19.9 (ring *C*H_2)]; *m/z* (EI) 255 (0.4%, M^+), 239 (40, M^+–H_2O), 219 (7), 213 (6, M^+–C_3H_6), 155 (13, NCH_2Naph^+), 149 (25), 142 (41, $NaphCH_3^+$), 134 (53), 121 (18), 108 (100), 93 (45), 82 (43, $H_2CCH_2CH{=}CHC{=}O^+$), 67 (42), 55 (24), 53 (22), 41 (40, $C_3H_5^+$, alkenes), 27 (20, $C_2H_3^+$) (Found: M^+, 235.1223. $C_{13}H_{17}NO_3$ requires 235.1208).

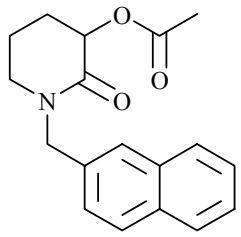
9.3.1.2. (3*S*)-Hydroxy-1-[(naphthalen-3-yl)methyl]piperidin-2-one [(*S*)-**277**]



This compound was prepared based on a known procedure [154]. To a solution of HMDS (0.58 cm^3, 2.7 mmol) in THF (9 cm^3) at –70 ºC was added *n*-BuLi (1.6 M in hexane, 1.70 cm^3, 2.72 mmol). The mixture was stirred for 30 min at –78 ºC after which a solution of 1-[(naphthalen-3-yl)methyl]piperidin-2-one **132** (0.50 g, 2.1 mmol) in THF (15 cm^3) was added dropwise and the stirring was continued for 1 h at –78 ºC. A solution of (+)-CS oxaziridine (0.63 g, 2.7 mmol) in THF (8 cm^3) was added dropwise and the stirring was continued for 3 h between –78 and –70 ºC. The reaction was quenched with saturated NH_4Cl aq. solution (25 cm^3) and warmed to rt. After extracting the products with CH_2Cl_2

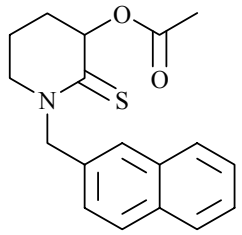
(4×15 cm^3), the combined organic layers were washed with brine (20 cm^3), dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (hexane:EtOAc, 1:1) yielded starting material (57 mg, 11%) and (*S*)-**277** a colourless solid (448 mg, 84%), mp 206–210 ºC (from EtOAc-hexane); R_f 0.69 (EtOAc), $[\alpha]_D^{20}$ –28.0 (*c* 0.714, $CHCl_3$). All the other characterization data agree with those given above for the racemic compound.

9.3.1.3. 1-[(Naphthalen-3-yl)methyl]-2-oxopiperidin-3-yl acetate (<u>281</u>)



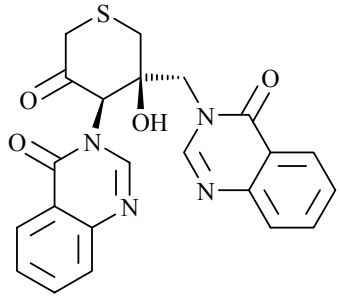
To a solution of 3-hydroxy-1-[(naphthalen-3-yl)methyl]piperidin-2-one (±)-**277** (165 mg, 0.646 mmol) in pyridine (2.4 cm^3) was added Ac_2O (0.52 cm^3, 5.5 mmol). The reaction mixture was stirred at rt for 17.5 h. After dilution with water (10 cm^3) followed by extraction with CH_2Cl_2 (3×10 cm^3), the combined organic extracts were dried ($NaSO_4$) and evaporated *in vacuo*. Column chromatography (hexane:acetone, 9:1) afforded **281** as a viscous colourless oil (185 mg, 96 %), R_f 0.59 (EtOAc:hexane, 3:2); $\nu_{max}(CH_3Cl)/cm^{-1}$ 3378 (m, vbr, O–H str), 3054 (w, Ar–H str), 3012 (w, Ar–H str), 2941 (m, CH_2 asym str), 2870 (w, CH_2 sym str), 1744 (s, ester C=O), 1655 (s, lactam C=O), 1509 (w, sh, Ar C=C str), 1492 (w, sh, Ar C=C str), 1466 (m, sh, Ar C=C str); δ_H (300 MHz; $CDCl_3$) 7.80–7.83 (3H, m, $3 \times H_{arom}$), 7.70 (1H, s, NAP H–1), 7.44–7.51 (2H, m, $2 \times H_{arom}$), 7.40 (1H, dd, *J* 8.5 and 1.5, $1 \times H_{arom}$), 5.36 (1H, dd, *J* 9.5 and 5.9, O=CC*H*), 4.80 (1H, d, *J* 14.5, $0.5 \times$ NCH_2Ar), 4.69 (1H, d, *J* 14.5, $0.5 \times$ NCH_2Ar), 3.25 (2H, m, ring NCH_2), 2.18 (3H, s, CH_3), 2.13–2.20 (1H, overlapping m, $0.5 \times$ ring CH_2), 177–2.01 (3H, m, $1.5 \times$ ring CH_2); δ_C (75 MHz; $CDCl_3$) 170.2 (first *C*=O), 167.1 (second C=O), 134.1 ($1 \times$ quaternary C_{arom}), 133.2 ($1 \times$ quaternary C_{arom}), 132.8 ($1 \times$ quaternary C_{arom}), 128.6 ($1 \times C_{arom}$), 127.67 ($1 \times C_{arom}$), 127.65 ($1 \times C_{arom}$), 127.1 ($1 \times C_{arom}$), 126.22 ($1 \times C_{arom}$), 126.19 ($1 \times C_{arom}$), 125.9 ($1 \times C_{arom}$), 68.3 (O=C*C*), 50.4 (N*C*H_2Ar), 46.7 (ring N*C*H_2), 27.2 (*C*H_3) 21.0 (ring *C*H_2), 20.1 (ring *C*H_2)]; *m/z* (EI) 297 (5%, M^+), 253 (7, M^+–$HCOCH_3$), 237 (83, M^+–$HOCOCH_3$), 209 (100), 180 (40, NaphCNCHCH_2^+), 168 (11, NaphCNCH_3^+), 154 (34, NaphCNH^+), 141 (100, NaphCH_2^+), 127 (10, Naph$^+$–H), 115 (50, Naph$^+$–CH), 55 (7), 43 (57, $C_3H_7^+$, alkanes) (Found: M^+, 297.1392. $C_{18}H_{19}NO_3$ requires 297.1365).

9.3.1.4. 1-[(Naphthalen-3-yl)methyl]-2-thioxopiperidin-3-yl acetate (<u>282</u>)



A mixture of 1-[(naphthalen-3-yl)methyl]-2-oxopiperidin-3-yl acetate **281** (150 mg, 0.504 mmol) and Lawesson's reagent (104 mg, 0.257 mmol) in benzene (7 cm^3) was refluxed for 2 h. After evaporation of the solvent *in vacuo*, the residue was purified by column chromatography (hexane:acetone, 19:1) to afford **282** as a pale yellow solid (0.14 g, 89%), mp 87–88 ºC; R_f 0.52 (hexane:EtOAc, 3:2); ν_{max}(film)/cm^{-1} 3053 (w, Ar–H str), 2950 (m, br, CH_3 and CH_2 asym str), 2873 (w, CH_2 sym str), 1742 (s, sh, C=O), 1633 (vw), 1601 (w, sh), 1506 (C=S), 1445 (m, br, Ar C=C str), 1234 (s, C–O–C asym str); δ_H (300 MHz; $CDCl_3$) 7.81 (3H, d, *J* 8.0, 3 × H_{arom}), 7.74 (1H, s, NapH-1), 7.47–7.51 (3H, m, 3 × H_{arom}), 5.69 (1H, t, *J* 6.4, S=CC*H*), 5.52 (1H, d, *J* 14.4, 0.5 × NCH_2Ar), 5.38 (1H, d, *J* 14.4, 0.5 × NCH_2Ar), 3.43 (2H, m, 1 × ring NCH_2), 2.20 (3H, s, CH_3), 2.07 (1H, m, 0.5 × ring CH_2), 1.77–2.00 (3H, m, 1.5 × ring CH_2); δ_C (75 MHz; $CDCl_3$) 197.7 (*C*=S), 169.9 (*C*=O), 133.2 (1 × quaternary C_{arom}), 132.9 (1 × quaternary C_{arom}), 132.6 (1 × quaternary C_{arom}), 128.7 (1 × C_{arom}), 127.68 (1 × C_{arom}), 127.65 (1 × C_{arom}), 127.0 (1 × C_{arom}), 126.3 (1 × C_{arom}), 126.1 (1 × C_{arom}), 125.7 (1 × C_{arom}), 73.8 (S=C*C*), 57.6 (N*C*H_2Ar), 49.2 (ring N*C*H_2), 25.9 (ring *C*H_2), 21.3 (ring *C*H_2), 19.1 (ring *C*H_2); *m/z* (EI) 313 (8%, M^+), 253 (100, M^+–CH_3COOH), 237 (26), 220 (24), 209 (42), 180 (7, $NaphCNCHCH_2^+$), 168 (10, $NaphCNCH_3^+$), 154 (7, $NaphCNH^+$), 141 (68, $NaphCH_2^+$), 115 (23, $Naph^+$–CH), 43 (19, $C_3H_7^+$, alkanes) (Found: M^+, 313.1129. $C_{18}H_{19}NO_2S$ requires 313.1136).

9.3.1.5. 3-{[(4*R**,5*R**)-5-hydroxy-3-oxo-5-(4-oxoquinazolin-3(4*H*)-yl)methyl]tetrahydro-2*H*-thiopyran-4-yl}quinazolin-4(3*H*)-one (<u>284</u>)



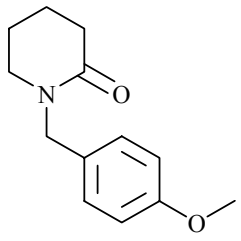
A mixture of 1-[(naphthalen-3-yl)methyl]-2-thioxopiperidin-3-yl acetate **282** (0.13 g, 0.41 mmol) and 3-(3-bromo-2-oxopropyl)quinazolin-4(3*H*)-one **105** (0.12 g, 0.43 mmol) in dry THF (10 cm^3) was stirred at rt for 18 h. After evaporation of the solvent *in vacuo* the residue was dissolved in dry CH_3CN (10 cm^3) and PPh_3 (0.14 g, 0.53 mmol) was added to the solution. After cooling the mixture to 0 ºC, NEt_3 (0.070 cm^3, 0.50 mmol) was added and the reaction was stirred for 10 min before warming to rt and stirring for 1 h. The reaction mixture was evaporated *in vacuo* and the residue was purified by column chromatography (CH_2Cl_2:MeOH, 49:1) to yield two inseparable products [R_f *ca*. 0.3 (CH_2Cl_2:MeOH, 19:1)] as a reddish coloured viscous oil. After dissolving the product mixture in MeOH:acetone (3:1, 10 cm^3), hexane was added dropwise until crystallization was observed. The

mixture was left in the freezer o.n. to complete crystallization. This crystallization process was repeated several times to yield, each time on filtering, **284** as a colourless solid (65 mg in total, 70% based on the bromide **105**) * which was also identified by single crystal X-ray diffraction (see Section 5.3.3.), mp 236–238 ºC (decomp., from acetone); R_f 0.34 (CH_2Cl_2:MeOH, 19:1); ν_{max}(film)/cm^{-1} 3415 (m, vb, O–H str), 3059 (w, Ar–H str), 2928 (w, br, CH_2 asym str), 2853 (w, CH_2 sym str), 1728 (m, sh, unconjugated C=O), 1678 (s, conjugated C=O), 1660 (s), 1611 (s, sh, Ar C=C str), 1561 (s), 1549 (s), 1510 (w, Ar C=C str), 1474 (m, sh, Ar C=C str); δ_H (400 MHz, DMSO-d_6) 8.42 (1H, s, H-2), 8.19 (1H, dd, *J* 7.7 and 0.61, H-5), 8.10 (1H, d, *J* 7.8, H-5′), 8.01 (1H, s, H-2′), 7.87 (1H, t, *J* 7.6, H-7), 7.80 (1H, t, *J* 7.6, H-7′), 7.69 (1H, d, *J* 8.3, H-8), 7.63 (1H, d, *J* 8.0, H-8′), 7.56 (1H, t, *J* 7.7, H-6), 7.51 (1H, t, *J* 7.6, H-6′), 6.27 (1H, s, O=CC*H*), 6.23 (1H, s, O*H*), 4.55 (1H, d, *J* 13.9, 0.5 × NCH_2), 4.16 (1H, d, *J* 13.0, 0.5 × SCH_2C=O), 3.81 (1H, d, *J* 14.3, 0.5 × SCH_2COH), 3.74 (1H, d, *J* 12.3, 0.5 × NCH_2), 3.09 (1H, dd, *J* 12.9 and 2.2, 0.5 × SCH_2C=O), 2.55 (1H, dd, *J* 14.4 and 2.2, 0.5 × SCH_2COH); δ_C (100 MHz, DMSO-d_6) 196.9 (unconjugated *C*=O), 160.8 (conjugated *C*=O), 160.6 (conjugated *C*=O′), 148.7 (C−8a), 147.8 (C−8a′), 147.6 (C–2), 147.2 (C–2′), 134.5 (C–7), 134.2 (C–7′), 126.95, 126.85, 126.7, 126.6, 126.4, 126.1, 121.3 (C−4a), 121.1 (C−4a′), 82.6 (*C*OH), 64.0 (O=C*C*H), 50.1 (N*C*H_2), S*C*H_2C=O peak hidden under the DMSO-d_6 peaks, 36.9 (S*C*H_2COH). *m/z* (EIMS) M^+ absent; major signals: 466 (100), 437 (36), 394 (18), 286 (28), 209 (28), 183 (78), 108 (33), 69 (21). This compound was also characterized by single crystal X-ray diffraction (see Section 5.3.3.).

* Trace amounts of impurities were observed in the ^{1}H NMR spectrum (see Section 5.3.3.). The compound could not be purified further preparatively either by column chromatography or by repeated recrystallization.

9.3.2. Using 4-methoxybenzyl (PMB) as the piperidin-2-one nitrogen protecting group

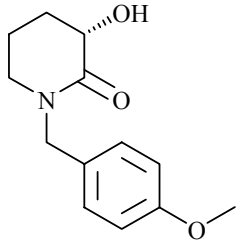
9.3.2.1. 1-(4-Methoxybenzyl)piperidin-2-one (222)



This compound was prepared based on a known procedure [131]. To a suspension of NaH (60% dispersion in mineral oil, 0.92 g, 23 mmol) in THF (25 cm^3) at 0 ºC was added dropwise a solution of 4-methoxybenzyl alcohol (2.9 cm^3, 23 mmol) in THF (25 cm^3). After stirring at 0 ºC for 30 min, a solution of *p*-TsCl (4.4 g, 23 mmol) in THF (25 cm^3) was added and the thick mixture was stirred for an additional 1 h. This mixture was subsequently added to a previously prepared mixture of

piperidin-2-one (2.3 g, 23 mmol) and NaH (60 % dispersion in mineral oil, 0.92 g, 23 mmol) at 0 ºC in THF (125 cm^3). After warming the reaction to rt, it was stirred o.n. and poured in water (150 cm^3). The aqueous layer was extracted with CH_2Cl_2 (4 × 100 cm^3). The combined organic extracts were washed with saturated aq. $NaHCO_3$ (150 cm^3), water (150 cm^3) and saturated aq. NaCl (150 cm^3). After drying ($MgSO_4$) the organic layer was evaporated *in vacuo* to yield crude product which was purified by column chromatography (EtOAc) to afford **222** as a very viscous pale yellow oil (3.51 g, 63%), R_f 0.37 (EtOAc); δ_H (400 MHz; $CDCl_3$) 7.19 (2H, d, *J* 8.5, 2 × *m*-H_{arom}), 6.85 (2H, *J* 8.6, 2 × *o*-H_{arom}), 4.53 (2H, s, NCH_2Ar), 3.79 (3H, s, OCH_3), 3.17 (2H, t, *J* 5.9, ring NCH_2), 2.45 (2H, t, *J* 6.1, O=CCH_2), 1.72–1.77 (4H, m, 2 × ring CH_2); δ_C (75 MHz; $CDCl_3$) 169.7 (*C*=O), 158.9 (*ipso*-C_{arom}), 129.4 (3C, 2 × *m*-C_{arom} and 1 × *p*-C_{arom}), 113.9 (2 × *o*-C_{arom}), 55.2 (O*C*H_3), 49.4 (N*C*H_2Ar), 47.0 (ring N*C*H_2), 32.4 (O=C*C*H_2), 23.2 (ring *C*H_2), 21.4 (ring *C*H_2). Spectroscopic data agree with those reported elsewhere [131].

9.3.2.2. (3*S*)- 3-Hydroxy-1-(4-methoxybenzyl)piperidin-2-one (294)



This compound was prepared by the method given before for (*S*)-**277**. To a solution of HMDS (0.63 cm^3) in THF (10 cm^3) at –70 ºC was added *n*-BuLi (1.6 M in hexane, 1.83 cm^3, 2.93 mmol). The mixture was stirred for 30 min at –70 ºC after which a solution of 1-(4-methoxybenzyl)piperidin-2-one **222** (322 mg, 1.47 mmol) in THF (20 cm^3) was added dropwise and the stirring was continued for 1 h between –70 and –60 ºC. A solution of (+)-CS oxaziridine (0.67 g, 2.9 mmol) in THF (20 cm^3) was added dropwise and the stirring was continued between –70 and –60 ºC for a further 16 h. The reaction was quenched with saturated NH_4Cl aq. solution (10 cm^3) and warmed to rt. After extracting the products with CH_2Cl_2 (4 × 15 cm^3), the combined organic layers were washed with brine (20 cm^3), dried ($MgSO_4$) and evaporated *in vacuo*. Gradient elution column chromatography (hexane:EtOAc, 9:1 to 1:1) yielded **294** as a colourless solid which was recrystallized from EtOAc-hexane to yield a trace amount of starting material together with **294** as colourless crystals (261 mg, 75%), mp 74–76 ºC (from EtOAc-hexane); R_f 0.49 (EtOAc); $[\alpha]_D^{20}$ – 6.89 (*c* 0.436, $CHCl_3$); ν_{max}(film)/cm^{-1} 3412 (m, vbr, O–H str), 2940 (m, CH_2 asym str), 2868 and 2837 (w, CH_2 sym str), 1636 (s, lactam C=O), 1586 (w, Ar C=C str), 1513 (s, sh, Ar C=C str), 1496 (m, sh, Ar C=C str), 1464 and 1443 (w, Ar C=C str), 1246 (s, C–O–C asym str); δ_H (300 MHz; $CDCl_3$) 7.18 (2H, d, *J* 8.4, 2 × *m*-H_{arom}), 6.86 (2H, *J* 8.5, 2 × *o*-H_{arom}), 4.57 (1H, d, *J* 14.4, 0.5 × NCH_2Ar), 4.46 (1H, *J* 14.4, 0.5 × NCH_2Ar), 4.07 (1H, dd, *J* 10.7 and 6.0, C*H*OH), 3.80 (3H, s, OCH_3), 3.22 (1H, s, O*H*), 3.17 (2H, dd, *J* 7.6 and 4.7, ring NCH_2), 2.23–2.35 (1H, m, 0.5 × ring

CH_2), 1.67–1.93 (3H, m, 1.5 × ring CH_2); δ_C (75 MHz; $CDCl_3$) 172.4 (*C*=O), 159.2 (*ipso*-C_{arom}), 129.5 (*m*-C_{arom}), 128.6 (*p*-C_{arom}), 114.1 (*o*-C_{arom}), 68.2 (*C*HOH), 55.3 (O*C*H_3), 49.8 (N*C*H_2Ar), 46.8 (ring N*C*H_2), 28.3 (O=C*C*H_2), 23.2 (ring *C*H_2), 20.0 (ring *C*H_2)]; *m/z* (EI) 235 (71%, M^+), 217 (13, M^+–H_2O), 189 (53, M^+–C_2H_5OH), 161 (6), 136 (14, $H_2NCHArOCH_3^+$), 121 (100, $CH_2ArOCH_3^+$), 107 (6, $PhCH_2NH_2^+$), 91 (8, tropylium ion), 78 (11, $C_6H_6^+$, aromatics), 43 (5, $C_3H_7^+$, alkanes) (Found: M^+, 235.1223. $C_{13}H_{17}NO_3$ requires 235.1208). This compound was also characterized by single crystal X-ray diffraction (see Section 5.3.5.).

9.3.2.3. Attempted amide deprotection of (3*S*)-3-hydroxy-1-(4-methoxybenzyl) piperidin-2-one (294)

Trial A

This deprotection method was based on a known procedure [128]. To a solution of (3*S*)-3-hydroxy-1-(4-methoxybenzyl)piperidin-2-one **294** (0.30 g, 1.3 mmol) in CH_3CN:H_2O (10:1, 8 cm^3) was added portionwise over several minutes and with mechanical stirring CAN (3.5 g, 6.4 mmol). The mixture was stirred for 2 h, after which MeOH (10 cm^3) was added and the precipitate was removed by filtration through celite. The residue was triturated for 30 min in EtOAc:MeOH (30 cm^3, 5:1) and left to complete precipitation in the fridge overnight. After filtering and drying the precipitate, *ca*. 0.2 g of a colourless solid material was obtained. The ^{1}H NMR spectrum, recorded in $CDCl_3$, indicated that a mixture of undesired products was obtained by co-precipitation. Mostly aromatic signals were observed in this crude ^{1}H NMR spectrum.

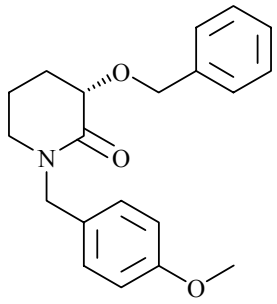
Trial B

A second known PMB-deprotection protocol [129] was attempted. A solution of (3*S*)-3-hydroxy-1-(4-methoxybenzyl)piperidin-2-one **294** (0.23 g, 0.98 mmol) in EtOAc:AcOH (9:1, 10 cm^3) was hydrogenated over $PdCl_2$ (175 mg) under H_2 gas (1 atm) for 18.5 h. After filtering through celite, the filtrate was evaporated *in vacuo* and the crude product was subjected to column chromatography (EtOAc) to yield only starting material (0.20 g).

Trial C

A third PMB-deprotection protocol [161] was attempted. The starting material **294** recovered from Trial B was refluxed in TFA (2 cm^3) for 1 h and evaporated *in vacuo*. Column chromatography (CH_2Cl_2:MeOH, 4:1) afforded an orange-coloured oil (0.11 g) as the only quantifiable product. It was deduced from the high polarity of the compound and from the ^1H NMR spectrum in $CDCl_3$ that the trifluoroacetate salt [**294**(H^+)·CF_3COO^-] of the starting material was isolated, δ_H (300 MHz; $CDCl_3$) 10.76 (1H, vbr s, CHO*H*), 7.19 (2H, d, *J* 8.2, 2 × *m*-H_{arom}), 6.87 (2H, *J* 7.9, 2 × *o*-H_{arom}), 4.56 (2H, br s, NCH_2Ar), 3.79 (4H, s and overlapping m, OCH_3 and C*H*OH), 3.26 (1H, br s, 0.5 × ring NCH_2), 2.58 (1H, br s, 0.5 × ring NCH_2), 1.78 (4H, m, 2 × CH_2).

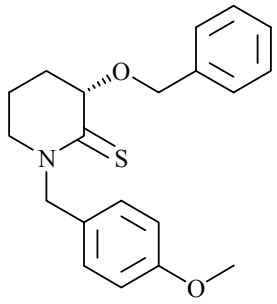
9.3.2.4. (3*S*)-3-Benzyloxy-1-(4-methoxybenzyl)piperidin-2-one (295)



To a solution of 3-hydroxy-1-(4-methoxybenzyl)piperidin-2-one **294** (234 mg, 0.995 mmol) at 0 ºC in THF (10 cm^3) was added NaH (60% mineral oil suspension, 42 mg, 1.1 mmol). After stirring for 10 min, freshly distilled benzyl bromide (0.12 cm^3, 1.0 mmol) was added dropwise at 0 ºC. The reaction was warmed to rt and stirred for a further 18.5 h. After quenching with EtOH (0.2 cm^3), the solvent was evaporated *in vacuo* and the residue was dissolved in CH_2Cl_2 (20 cm^3) and washed with water (20 cm^3). After extraction of the aqueous layer with CH_2Cl_2 (2 × 10 cm^3), the combined organic extracts were washed with brine (20 cm^3), dried ($MgSO_4$) and evaporated *in vacuo*. Column chromatography (hexane:EtOAc, 4:1) afforded **295** as a viscous colourless oil (197 mg, 61%), R_f 0.52 (EtOAc:hexane, 1:1); $[\alpha]_D^{15}$ –11.4 (*c* 2.54, $CHCl_3$); ν_{max}(film)/cm^{-1} 3030 and 3002 (w, Ar–H str), 2936 (m, CH_2 asym str), 2866 and 2836 (w, CH_2 sym str), 1645 (s, lactam C=O), 1611 (m), 1585 (w, Ar C=C str), 1512 (s, sh, Ar C=C str), 1491 (m, sh, Ar C=C str), 1456 (m, C=C str), 1245 (s, C–O–C asym str); δ_H (300 MHz; $CDCl_3$) 7.24–7.42 (5H, m, 5 × Bn H_{arom}), 7.19 (2H, d, *J* 8.6, 2 × *m*-H_{arom}), 6.84 (2H, *J* 8.6, 2 × *o*-H_{arom}), 5.01 (1H, d, *J* 12.0, 0.5 × OCH_2), 4.79 (1H, d, *J* 12.0, 0.5 × OCH_2), 4.55 (1H, d, *J* 14.4, 0.5 × NCH_2Ar), 4.49 (1H, d, *J* 14.4, 0.5 × NCH_2Ar), 3.93 (1H, t, *J* 5.5, O=CC*H*), 3.78 (3H, s, OCH_3), 3.16 (2H, m, ring NCH_2), 1.92–2.02 (3H, m, 1.5 × ring CH_2), 1.63–1.71 (1H, m, 0.5 × ring CH_2); δ_C (75 MHz; $CDCl_3$) 169.2 (*C*=O), 158.9 (H_3COC_{arom}), 138.5 (Bn quaternary C_{arom}), 129.4 (2 × PMB *m*-C_{arom}), 129.1 (PMB *p*-C_{arom}), 128.2 (2 × Bn C_{arom}), 127.8 (2 × Bn C_{arom}), 127.5 (Bn *p*-C_{arom}), 113.9 (2 × PMB *o*-C_{arom}), 74.5 (O=C*C*), 72.7 (O*C*H_2), 55.2 (O*C*H_3), 49.3 (N*C*H_2Ar), 46.6 (ring N*C*H_2), 28.2 (ring *C*H_2), 19.2 (ring *C*H_2); *m/z* (EI) 325 (1%, M^+), 219 (40, M+1$^+$–OBn), 206 (12, M+1$^+$–

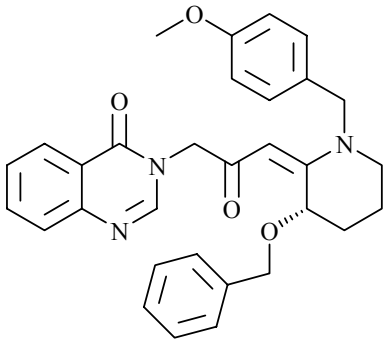
HCOBn), 189 (12), 149 (4), 136 (14, $H_2NCHArOCH_3^+$), 121 (100, $CH_2ArOCH_3^+$), 91 (41, tropylium ion), 77 (10, phenonium ion), 43 (10, $C_3H_7^+$, alkanes), 29 (4, $C_2H_5^+$) (Found: M^+, 325.1697. $C_{20}H_{23}NO_3$ requires 325.1678).

9.3.2.5. (3*S*)-3-Benzylthioxy-1-(4-methoxybenzyl)piperidin-2-one (296)



A mixture of (3*S*)-3-benzyloxy-1-(4-methoxybenzyl)piperidin-2-one **295** (170 mg, 0.522 mmol) and Lawesson's reagent (106 mg, 0.262 mmol) in benzene (8 cm^3) was refluxed for 4 h. After evaporating the solvent *in vacuo*, the residue was purified by column chromatography (hexane:EtOAc, 4:1) to yield **296** as shiny colourless crystals (174 mg, 98%), mp 76.5–78.5 ºC (from EtOAc-hexane, 1:4); R_f 0.51 (hexane:EtOAc, 7:3); $[\alpha]_D^{15}$ –3.9 (*c* 2.85, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3030 and 3001 (w, Ar–H str), 2949 (m, br, CH_3 and CH_2 asym str), 2868 and 2835 (w, CH_2 sym str), 1612 (w, sh, C=S), 1584 (w, sh, Ar C=C str), 1512 (s, sh, Ar C=C str), 1454 (m, C=C str), 1248 (m, C–O–C asym str); δ_H (300 MHz; $CDCl_3$) 7.25–7.38 (5H, m, 5 × Bn H_{arom}), 7.26 (2H, overlapping d, *J* 8.4, 2 × *m*-H_{arom}), 6.85 (2H, *J* 8.6, 2 × *o*-H_{arom}), 5.30 (1H, d, *J* 14.2, 0.5 × OCH_2), 5.11 (1H, d, *J* 14.2, 0.5 × OCH_2), 4.98 (1H, d, *J* 11.8, 0.5 × NCH_2Ar), 4.77 (1H, d, *J* 11.8, 0.5 × NCH_2Ar), 4.54 (1H, t, *J* 3.3, S=CC*H*), 3.80 (3H, s, OCH_3), 3.60 (1H, quintet, *J* 6.5, 0.5 × ring NCH_2), 3.26 (1H, quintet, *J* 6.5, 0.5 × ring NCH_2), 1.98–2.11 (2H, m, ring CH_2), 1.81–1.93 (1H, m, 0.5 × ring CH_2), 1.64–1.75 (1H, m, 0.5 × ring CH_2); δ_C (75 MHz; $CDCl_3$) 198.6 (*C*=S), 159.3 (H_3COC_{arom}), 138.4 (quaternary C_{arom}), 134.1 (quaternary C_{arom}), 129.3, 128.3, 127.9, 127.6, 114.1, 81.6 (S=C*C*), 72.1 (O*C*H_2), 56.7 (O*C*H_3), 55.3 (N*C*H_2Ar), 48.3 (ring N*C*H_2), 25.8 (ring *C*H_2), 18.4 (ring *C*H_2); *m/z* (EI) 341 (0.4%, M^+), 235 (57, M+1–$PhOCH_3$), 202 (4), 153 (5), 127 (9), 121 (100, $CH_2ArOCH_3^+$), 91 (28, tropylium ion), 77 (11, phenonium ion), 65 (6) (Found: M^+, 341.1437. $C_{20}H_{23}NO_2S$ requires 341.1449). This compound was also characterized by single crystal X-ray diffraction (see Section 5.3.6.).

9.3.2.6. {3-(*E*)-3-[(3*S*)-Benzyloxy-1-(4-methoxybenzyl)piperidin-2-ylidene]2-oxopropyl} quinazolin-4(3*H*)-one (297)



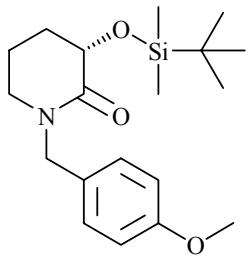
To a solution of (3*S*)-3-benzylthioxy-1-(4-methoxybenzyl) piperidin-2-one **296** (0.15 g, 0.44 mmol) in dry THF (15 cm^3) was added 3-(3-bromo-2-oxopropyl)quinazolin-4(3*H*)-one **105** (125 mg, 0.445 mmol). The mixture was left stirring at rt for 42.5 h followed by refluxing for 1.5 h. After evaporation of the solvent *in vacuo*, the residue was dissolved in CH_3CN (10 cm^3) and PPh_3 (0.14 g, 0.53 mmol) and NEt_3 (0.070 cm^3, 0.50 mmol) were sequentially added at 0 ºC. After warming to rt, the reaction was stirred for 22 h. Evaporation of the solvent *in vacuo* was followed by column chromatography (hexane:EtOAc, 7:3 and EtOAc) to yield putative **297** as a very viscous colourless oil (138 mg, 62% of crude product) which could not be purified further by repeated column chromatography (EtOAc:hexane, 7:3), nor be induced to crystallize, R_f 0.52 (EtOAc); ^1H and ^{13}C NMR spectra were too complex to interpret conclusively, although many of the expected signals were observed (see Section 5.3.4.).

In a trial experiment, attempted *O*-Bn and/or *N*-PMB deprotection of this crude product failed (see the next section). For this reason, this compound was not re-synthesized nor characterized and the route was discontinued owing to time constraints.

9.3.2.7. Attempted reduction and/or deprotection of 297

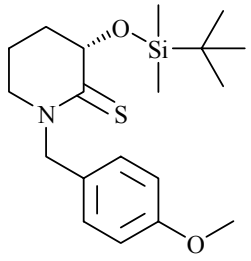
A solution of the above product (88 mg, max. 0.17 mmol) in EtOAc (5 cm^3) was hydrogenated over Pd/C (10%, 15 mg) under H_2 gas (1 atm) for 22 h. Filtering through celite, evaporation and column chromatography yielded starting material (*ca*. 70 mg) as the only isolable material. The experiment was repeated on the recovered starting material by using EtOH (95%, 1.5 cm^3) as the solvent and pre-hydrogenated Pd/C (10%, 12 mg). Stirring under H_2 gas (1 atm) was continued for 18h. After work-up and column chromatography as before, only starting material was recovered.

9.3.2.8. 3-(*tert*-Butyldimethylsilyloxy)-1-(4-methoxybenzyl)piperidin-2-one (299)



This compound was prepared based on a known procedure [163]. To a solution of (3*S*)-3-hydroxy-1-(4-methoxybenzyl)piperidin-2-one **294** (0.30 g, 1.3 mmol) in CH_2Cl_2 (15 cm^3) was added imidazole (90 mg, 1.3 mmol) and TBDMSCl (95%, 0.21 g, 1.3 mmol). The mixture was stirred at rt for 0.5 h followed by heating under reflux for 2 h. After cooling down to rt, more CH_2Cl_2 (20 cm^3) was added and the solution was washed with saturated aq. $NaHCO_3$ (20 cm^3) followed by saturated NaCl (10 cm^3). The organic layer was dried ($MgSO_4$), evaporated *in vacuo* and purified by column chromatography (hexane:EtOAc, 9:1) to afford **299** as a colourless oil (342 mg, 75%), R_f 0.36 (hexane:EtOAc, 4:1); $[\alpha]_D^{20}$ –7.5 (*c* 0.671, $CHCl_3$); ν_{max}(film)/cm^{-1} 2952 (m, CH_3 asym str), 2930 (m, CH_2 asym str), 2855 (m, CH_2 sym str), 1655 (s, C=O), 1612 (w), 1513 (s, sh, Ar C=C str), 1491 (w, sh, Ar C=C str), 1462 and 1443 (w, Ar C=C str), 1248 (s, C–O–C asym str); δ_H (300 MHz; $CDCl_3$) 7.18 (2H, d, *J* 8.6, 2 × *m*-H_{arom}), 6.84 (2H, *J* 8.7, 2 × *o*-H_{arom}), 4.53 (1H, d, *J* 14.4, 0.5 × NCH_2Ar), 4.45 (1H, *J* 14.4, 0.5 × NCH_2Ar), 4.16 (1H, dd, *J* 6.7 and 4.5, O=CC*H*), 3.79 (3H, s, OCH_3), 3.13 (2H, m, ring NCH_2), 1.81–2.00 (3H, m, 1.5 × ring CH_2), 1.61–1.70 (1H, m, 0.5 × ring CH_2), 0.92 (9H, s, C(CH_3)$_3$), 0.19 (3H, s, 1 × SiCH_3), 0.17 (3H, s, 1 × SiCH_3); δ_C (75 MHz; $CDCl_3$) 170.0 (*C*=O), 158.9 (*ipso*-C_{arom}), 129.4 (*m*-C_{arom}), 129.3 (*p*-C_{arom}), 113.9 (*o*-C_{arom}), 69.6 (O=C*C*H), 55.2 (O*C*H_3), 49.4 (N*C*H_2Ar), 46.8 (ring N*C*H_2), 30.9 (*C*H_2CO), 25.8 (C(*C*H_3)$_3$), 19.1 (ring *C*H_2), 18.3 (*C*(CH$_3$)$_3$), -4.5 (1 × Si*C*H_3), -5.4 (1 × Si*C*H_3); *m/z* (EI) 350 (1%, M+1$^+$), 334 (5, M+1$^+$–O), 292 (76, M$^+$–C(CH$_3$)$_3$), 189 (4), 143 (9), 121 (100, $CH_2ArOCH_3^+$), 91 (4, tropylium ion), 73 (9) (Found: M$^+$, 349.2061. $C_{19}H_{31}NO_3Si$ requires 349.2073; Found: M$^+$–C(CH$_3$)$_3$, 292.1370. $C_{15}H_{22}NO_3Si$ requires 292.1369.)

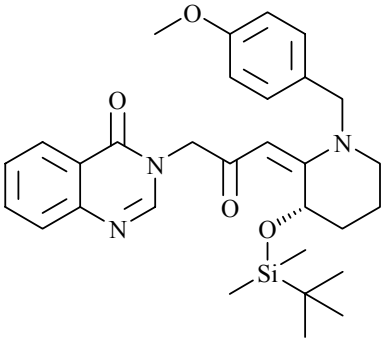
9.3.2.9. 3-(*tert*-Butyldimethylsilyloxy)-1-(4-methoxybenzyl)piperidine-2-thione (300)



A mixture of 3-(*tert*-butyldimethylsilyloxy)-1-(4-methoxybenzyl)piperidin-2-one **299** (93 mg, 0.27 mmol) and Lawesson's reagent (54 mg, 0.13 mmol) in benzene (4 cm^3) was refluxed for 30 min. After evaporation of the solvent *in vacuo*, the residue was purified by column chromatography (hexane:EtOAc, 19:1) to afford **300** as a colourless oil (82 mg, 83%), R_f 0.70 (hexane:EtOAc, 4:1); $[\alpha]_D^{20}$ –26.4 (*c* 0.607, $CHCl_3$); ν_{max}(film)/cm^{-1} 2952 (m, CH_3 asym str), 2929 (m, CH_2 asym str), 2854 (w, CH_2 sym str), 1646 (w), 1613 (w), 1513 (s, sh, Ar C=C str), 1461 and 1440 (w, Ar C=C str), 1249 (s, C–O–C asym str); δ_H (300 MHz; $CDCl_3$) 7.24 (2H, d, *J* 8.6, 2 × *m*-H_{arom}), 6.85

(2H, *J* 8.7, 2 × *o*-H_{arom}), 5.38 (1H, d, *J* 14.3, 0.5 × NCH_2Ar), 4.96 (1H, *J* 14.3, 0.5 × NCH_2Ar), 4.74 (1H, t, *J* 3.4, S=CC*H*), 3.79 (3H, s, OCH_3), 3.55 (1H, quintet, *J* 6.4, 0.5 × ring NCH_2), 3.24 (1H, quintet, *J* 6.7, 0.5 × ring NCH_2), 1.99–2.11 (1H, m, 0.5 × ring CH_2), 1.81–1.88 (2H, m, 1 × ring CH_2), 1.65–1.75 (1H, m, 0.5 × ring CH_2); 0.89 (9H, s, C(CH_3)$_3$), 0.21 (3H, s, 1 × SiCH_3), 0.19 (3H, s, 1 × SiCH_3); δ_C (75 MHz; $CDCl_3$) 200.7 (*C*=S), 159.2 (*ipso*-C_{arom}), 129.1 (*m*-C_{arom}), 127.6 (*p*-C_{arom}), 114.0 (*o*-C_{arom}), 75.9 (S=C*C*H), 56.6 (O*C*H_3), 55.3 (N*C*H_2Ar), 48.3 (ring N*C*H_2), 27.7 (*C*H_2CO), 25.8 (C(*C*H_3)$_3$), 18.1 (*C*(CH$_3$)$_3$), 17.8 (ring *C*H_2), -4.1 (1 × Si*C*H_3), -5.1 (1 × Si*C*H_3); *m/z* (EI) 365 (10%, M^+), 308 (62, M^+–C(CH$_3$)$_3$), 251 (14, M+1$^+$–(CH$_3$)$_2$SiC(CH$_3$)$_3$), 233 (16, M^+–$H_2OSi(CH_3)_2C(CH_3)_3^+$), 218 (6), 200 (6), 189 (9), 121 (100, $CH_2ArOCH_3^+$), 83 (14), 73 (11) (Found: M^+, 365.1853. $C_{19}H_{31}NO_2SSi$ requires 365.1845.)

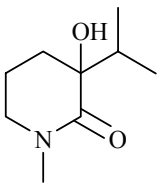
9.3.2.10. Attempted preparation of 3-{(*E*)-3-[(3-(*tert*-butyldimethylsilyloxy)-1-(4-methoxybenzyl))piperidin-2-ylidene]2-oxopropyl}quinazolin-4(3*H*)-one (<u>301</u>)



To a solution of 3-(*tert*-butyldimethylsilyloxy)-1-(4-methoxybenzyl)piperidine-2-thione **300** (60 mg, 0.16 mmol) in dry THF (15 cm^3) was added 3-(3-bromo-2-oxopropyl)quinazolin-4(3*H*)-one (46 mg, 0.16 mmol). The mixture was left stirring at rt for 7 days. After evaporation of the solvent *in vacuo*, the residue was dissolved in CH_3CN (5 cm^3) and PPh_3 (50 mg, 0.19 mmol) and NEt_3 (0.026 cm^3, 0.19 mmol) were sequentially added at 0 ºC. After warming to rt, the reaction was stirred for 1 h. Evaporation of the solvent *in vacuo* was followed by column chromatography (EtOAc, followed by CH_2Cl_2:MeOH, 19:1) to yield several unidentifiable products. The experimental route was consequently discontinued.

9.3.3. Towards the piperidinyl *N*-methyl derivative of febrifugine

9.3.3.1. 3-Hydroxy-3-isopropyl-1-methylpiperidin-2-one (<u>312</u>)

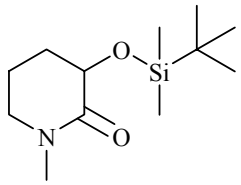


This compound was prepared based on a known procedure [156]. To a solution of diisopropylamine (6.2 cm^3, 44 mmol) in THF (30 cm^3) was added *n*-BuLi (1.6 M solution in hexane, 27.5 cm^3, 44.0 mmol) at –70 ºC. After 20 min, a solution of 1-

methylpiperidin-2-one (99%, 2.0 cm^3, 17 mmol) in THF (75 cm^3) at 0 ºC was added dropwise and under N_2 over 5 min to the first mixture at –70 ºC. After stirring the reaction mixture for 30 min, the reaction was warmed to 0 ºC and O_2 gas was bubbled through continuously for 20 min. After quenching with MeOH (0.5 cm^3) the solvent was evaporated *in vacuo*. Saturated aq. Na_2SO_3 (180 cm^3) and acetone (5 cm^3) were added to the residue and the mixture was stirred vigorously for 15 min, diluted with water (120 cm^3) and extracted with CH_2Cl_2 (100 cm^3 followed by 3 × 80 cm^3). The combined organic extracts were washed with saturated NaCl (100 cm^3), dried (Na_2SO_4) and purified by column chromatography (EtOAc:hexane, 1:1) to yield **312** as a pale yellow oil (1.22g, 42%) *, R_f 0.49 (EtOAc); ν_{max}(film)/cm^{-1} 3354 (m, br, O–H str), 2970 (m, CH_3 asym str), 2937 (m, CH_2 asym str), 2872 (m, CH_2 sym str), 1613 (s, lactam C=O); δ_H (300 MHz; $CDCl_3$) 6.46 (1H, s, O*H*), 3.38 (1H, td, *J* 12.0 and 4.5, 0.5 × NCH_2), 3.22–3.29 (1H, m, 0.5 × NCH_2), 2.95 (3H, s, NCH_3), 2.41 (1H, dd, *J* 12.1 and 6.2, 0.5× OCCH_2), 1.90–2.07 [2H, m, 0.5 × OCCH_2 and CH(CH_3)$_2$], 1.77 (1H, *ca*. dddd, *J ca.* 25.1, 13.2, 5.6 and 2.9, 0.5 × NCH_2CH_2), 1.43 (1H, ddd, *J* 25.3, 12.8 and 3.1, 0.5 × NCH_2CH_2), 1.18 [6H, d, *J* 9.0, CH(CH_3)$_2$]; δ_C (75 MHz; $CDCl_3$) 173.3 (*C*=O), 72.4 (O=C*C*), 51.1 (N*C*H_2), 50.1 (OC*C*H_2), 34.8 (N*C*H_3), 28.1, 24.6, 24.4, 22.4; *m/z* (EI) 171 (1%, M^+), 156 (49, M^+–CH_3), 125 (5), 114 (18), 113 (100), 98 (19), 70 (9), 59 (18, $C_2H_5CH{=}OH^+$), 43 (21, $C_3H_7^+$), 28 (36, CO^+ and $C_2H_4^+$) (Found: M^+–CH_3, 156.1007. $C_8H_{14}NO_2$ requires 156.1025).

* None of the desired compound, 3-hydroxy-1-methylpiperidin-2-one, was isolated.

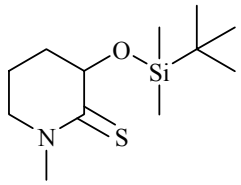
9.3.3.2. 3-(*tert*-Butyldimethylsilyloxy)-1-methylpiperidin-2-one (311)



To a solution of HMDS (5.72 cm^3, 27.1 mmol) in THF (20 cm^3) was added BuLi (1.6 M solution in hexane, 16.5 cm^3, 26.4 mmol) at 0 ºC. After stirring for 20 min, a solution of 1-methylpiperidin-2-one (2.0 cm^3, 17.6 mmol) in THF (80 cm^3) at 0 ºC was added dropwise to the first mixture. After stirring for a further 30 min at 0 ºC, O_2 gas was bubbled through for 10 min after which the reaction was quenched using saturated NH_4Cl (1 cm^3), warmed to rt and evaporated *in vacuo*. Saturated Na_2SO_3 (100 cm^3) and acetone (2 cm^3) were added to the residue and the resulting mixture was stirred vigorously for 10 min. Extraction with CH_2Cl_2 (3 × 50 cm^3), followed by drying ($MgSO_4$) and evaporation *in vacuo* of the combined organic extracts, afforded an inseparable mixture of 3-hydroxy-1-methylpiperidin-2-one and 1-methylpiperidin-2-one. After dissolving this mixture in CH_2Cl_2 (100 cm^3), imidazole (0.77 g, 11.3 mmol) and TBDMSCl (1.80 g, 11.9 mmol) were added to the solution. The reaction mixture was refluxed for 1 h, cooled down and filtered through celite. After evaporation of the solvent *in*

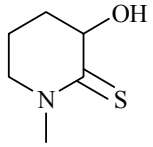
vacuo, the residue was purified by column chromatography (hexane:EtOAc, 7:3) to yield **311** as a colourless oil (305 mg, 7% over 2 steps), R_f 0.60 (EtOAc); ν_{max}(film)/cm^{-1} 2942 (m, CH_2 asym str), 2871 (m, CH_2 sym str), 1627 (s, lactam C=O); δ_H (300 MHz; $CDCl_3$) 4.07 (1H, dd, *J* 7.2 and 4.6, O=CC*H*), 3.19–3.28 (2H, m, NCH_2), 2.89 (3H, s, NCH_3), 1.73–1.99 (4H, m, 2 × CH_2), 0.89 (9H, s, C(CH_3)$_3$), 0.15 (3H, s, 1 × Si(CH_3)$_2$), 0.13 (3H, s, 1 × Si(CH_3)$_2$); δ_C (75 MHz; $CDCl_3$) 170.3 (*C*=O), 69.4 (O=C*C*), 49.9 (N*C*H$_2$), 34.6 (N*C*H$_3$), 31.1 (*C*H$_2$), 25.8 (C(*C*H$_3$)$_3$), 19.4 (*C*H$_2$), 18.3 (*C*(CH$_3$)$_3$), –4.52 (s, 1 × Si(*C*H$_3$)$_2$), –5.52 (s, 1 × Si(*C*H$_3$)$_2$); *m/z* (EI) 244 (2%, M+1$^+$), 202 (46, M$^+$–C$_3$H$_5$), 185 (5, M$^+$–C$_3$H$_8$N), 167 (12), 156 (32), 142 (35), 129 (83, M+1$^+$–Si(CH$_3$)$_2$C(CH$_3$)$_3$, 113 (92), 100 (49, M$^+$– COSi(CH$_3$)$_2$C(CH$_3$)$_3$), 83 (36), 72 (73), 57 (30, C(CH$_3$)$_3^+$), 55 (33, C$_4$H$_7^+$), 44 (100, CH$_2$=NHCH$_3^+$), 27 (29, C$_2$H$_3^+$) (Found: M+1$^+$–Si(CH$_3$)$_2$C(CH$_3$)$_3$, 129.0769. C$_6$H$_{11}$NO$_2$ requires 128.0790).

9.3.3.3. 3-(*tert*-Butyldimethylsilyloxy)-1-methylpiperidin-2-thione (313)



A mixture of 3-(*tert*-butyldimethylsilyloxy)-1-methylpiperidin-2-one **311** (0.25 g, 1.0 mmol), P_2S_5 (85 mg), HMDO (0.40 cm^3) and CH_2Cl_2 (5 cm^3) was stirred at rt for 17 h. After the addition of aq. saturated Na_2CO_3 (2 cm^3), H_2O (5 cm^3) was added and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by column chromatography (hexane:EtOAc, 9:1) to afford **313** as a yellow oil (88 mg, 34%), R_f 0.57 (hexane:EtOAc, 7:3); ν_{max}(film)/cm^{-1} 2952 (s, CH_3 asym str), 2929 (s, CH_2 asym str), 2855 (m, CH_2 sym str), 1527 (s, C=S); δ_H (300 MHz; $CDCl_3$) 4.60 (1H, m, S=CC*H*), 3.57–3.65 (1H, m, 1 × NCH_2), 3.40 (3H, s, NCH_3), 3.30–3.40 (1H, m, 0.5 × NCH_2), 2.14–2.27 (1H, 0.5 × CH_2), 1.73–1.90 (3H, m, 1.5 × CH_2), 0.89 (9H, s, C(CH_3)$_3$), 0.185 (3H, s, 1 × Si(CH_3)$_2$), 0.180 (3H, s, 1 × Si(CH_3)$_2$); δ_C (75 MHz; $CDCl_3$) 75.0 (S=C*C*), 52.2 (N*C*H$_2$), 43.4 (N*C*H$_3$), 28.3 (*C*H$_2$), 25.8 (C(*C*H$_3$)$_3$), 18.2 (*C*(CH$_3$)$_3$), 17.6 (*C*H$_2$), –4.04 (s, 1 × Si(*C*H$_3$)$_2$), –5.20 (s, 1 × Si(*C*H$_3$)$_2$); *m/z* (EI) 260 (4%, M+1$^+$), 244 (6), 202 (100, M$^+$–C(CH$_3$)$_3$), 128 (26, M$^+$–OSi(CH$_3$)$_2$C(CH$_3$)$_3$), 112 (44, C$_5$H$_6$NS$^+$), 84 (10, C$_5$H$_{10}$N$^+$), 75 (8), 73 (8), 57 (9, C$_4$H$_9^+$), 55 (8, C$_4$H$_7^+$), 41 (6, C$_3$H$_5^+$), 29 (5, C$_2$H$_5^+$) (Found: M$^+$, 259.1473. C$_9$H$_{20}$NO$_2$Si requires 259.1426).

9.3.3.4. 3-Hydroxy-1-methylpiperidin-2-thione (<u>314</u>)



To a solution of 3-(*tert*-butyldimethylsilyloxy)-1-methylpiperidine-2-thione **313** (75 mg, 0.29 mmol) in CH_2Cl_2:MeOH (2:1, 3 cm^3) was added a catalytic amount of *p*-toluenesulfonic acid monohydrate (10 mg). The mixture was stirred at rt for 2h, but the reaction did not proceed satisfactorily under these conditions. After evaporation of the solvent *in vacuo*, the residue was dissolved in MeOH (2 cm^3) and additional $TsOH.H_2O$ (30 mg) was added. After refluxing for 20 min, the solvent was evaporated *in vacuo* and the residue was directly purified by column chromatography (hexane:EtOAc, 3:2) to afford **314** as a yellow oil (18 mg, 43%), R_f 0.23 (EtOAc:hexane, 1:1); ν_{max}(film)/cm^{-1} 3297 (m, br, OH str), 2951 (m, br, CH_3 asym str), 2871 (m, CH_2 sym str), 1539 (s, C=S); δ_H (300 MHz; $CDCl_3$) 4.62 (1H, br s, O*H*), 4.04 (1H, dd, *J* 5.9, S=CC*H*), 3.52 (2H, m, NCH_2), 3.47 (3H, s, NCH_3), 2.27–2.36 (1H, 0.5 × CH_2), 1.94–2.04 (2H, m, 1 × CH_2), 1.56-1.70 (1H, m, 0.5 × CH_2); δ_C (75 MHz; $CDCl_3$) 71.2 (S=C*C*), 52.7 (NCH_2), 43.8 (NCH_3), 27.1 (*C*H_2), 19.5 (*C*H_2); *m/z* (EI) 145 (99.8%, M^+), 146 (100, M+1$^+$), 127 (41, M^+–H_2O), 116 (14, M^+–C_2H_5), 112 (14, M^+–HS), 100 (12), 94 (6), 88 (17), 83 (29, $C_5H_9N^+$), 74 (37), 55 (44, $C_4H_7^+$), 44 (49, $CH_2NH{=}CH_3^+$), 27 (17, $C_2H_3^+$) (Found: M^+, 145.0568. $C_6H_{11}NOS$ requires 145.0561).

9.3.3.5. Sulfide contraction reaction between <u>314</u> and <u>105</u>

To a solution of 3-hydroxy-1-methylpiperidine-2-thione **314** (8 mg, 0.06 mmol) in THF (2 cm^3) was added 3-(3-bromo-2-oxopropyl)quinazolin-4(3*H*)-one **105** (15 mg, 0.05 mmol). The mixture was stirred for 15 h at rt. At this stage, thiolactam was still present by TLC. After adding an additional amount of the bromide (10 mg, 0.04 mmol), the mixture was refluxed for 2h, followed by evaporation of the solvent *in vacuo*. The residue was suspended in CH_3CN (5 cm^3) and PPh_3 (30 mg, 0.11 mmol) followed by NEt_3 (15 µl, 0.11 mmol) were added at 0 ºC. After warming to rt, the orange-coloured solution was stirred for another 1 h. After evaporation of the solvent *in vacuo*, the residue was purified by column chromatography (EtOAc) to elute the PPh_3 products together with excess bromide s.m. Elution using CH_2Cl_2:MeOH (19:1) yielded a colourless solid as the only isolable product of the reaction, R_f 0.35 (CH_2Cl_2:MeOH, 9:1). ^{1}H NMR in $CDCl_3$ revealed mostly aromatic signals with trace amounts of aliphatic impurities. This product could not be accurately characterized owing to the small scale of the experiment, nor could this experimental route be repeated because of time constraints (see also Section 5.3.7).