CHAPTER 8

EXPERIMENTAL SECTION RELATING TO CHAPTER 4

8.1. Attempts without piperidinyl N-protection

8.1.1. tert-Butyl (3S)-2-oxopiperidin-3-ylcarbamate [(S)-212]

This compound was prepared according to a known procedure.\textsuperscript{119} A mixture of L-ornithine hydrochloride (1.77 g, 10.5 mmol) and HMDS (22 cm\textsuperscript{3}, 0.10 mol) in dry CH\textsubscript{3}CN (44 cm\textsuperscript{3}) was heated under reflux for 48 h. After cooling to rt, MeOH (90 cm\textsuperscript{3}) was added and the solution was evaporated at rt \textit{in vacuo}, followed by thorough drying under high vacuum. The residual viscous, orange-coloured oil [(S)-205] was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (40 cm\textsuperscript{3}), after which Boc\textsubscript{2}O (3.98 g, 18.2 mmol) was added. The reaction mixture was stirred for 3 days at rt and filtered through celite, followed by washing with water (30 cm\textsuperscript{3}) and brine (30 cm\textsuperscript{3}). After drying (Na\textsubscript{2}SO\textsubscript{4}), the CH\textsubscript{2}Cl\textsubscript{2} layer was concentrated under reduced pressure. Column chromatography (CH\textsubscript{2}Cl\textsubscript{2} followed by CH\textsubscript{2}Cl\textsubscript{2}:MeOH, 9:1) of the residue yielded (S)-212 as a viscous colourless oil (1.65 g, 73%), \(R_f\) 0.55 (CHCl\textsubscript{3}:MeOH, 9:1); [\(\alpha\)]\textsubscript{D}\textsuperscript{24} +54.4 (c 2.85, CHCl\textsubscript{3}) {lit., (R)-212; [\(\alpha\)]\textsubscript{D}\textsuperscript{24} –57.4 (c 1.07, CHCl\textsubscript{3})}; \(\delta\)\textsubscript{H} (400 MHz; CDCl\textsubscript{3}) 6.59 (1H, br s, 1 \(\times\) NH), 5.51 (1H, br s, 1 \(\times\) NH), 4.03 (1H, m, O=CC\textsubscript{H}), 3.32 (2H, m, NCH\textsubscript{2}), 2.46 (1H, m, 0.5 \(\times\) CH\textsubscript{2}), 1.91 (2H, m, 1 \(\times\) CH\textsubscript{2}), 1.56–1.66 (1H, m, 0.5 \(\times\) CH\textsubscript{2}), 1.45 (9H, s, (CH\textsubscript{3})\textsubscript{3}). Spectroscopic data agree with those reported elsewhere.\textsuperscript{121}

8.1.2. tert-Butyl (3S)-2-thioxopiperidin-3-ylcarbamate (204)

Method A:

A mixture of tert-butyl (3S)-2-oxopiperidin-3-ylcarbamate (540 mg, 2.52 mmol) (S)-212 and Lawesson’s reagent (510 mg, 1.26 mmol) in freshly distilled benzene (6 cm\textsuperscript{3}) was heated under reflux for 2 h. After evaporation of the solvent \textit{in vacuo}, the residue was
purified by column chromatography (CH$_2$Cl$_2$ followed by EtOAc:hexane, 1:1) to yield 204 as a colourless solid (478 mg, 82%), mp 153–154 °C (from EtOAc–hexane); R$_f$ 0.72 (EtOAc); [α]$_D^{20}$ –2.2 (c 0.891, CHCl$_3$); $\nu_{\text{max}}$(CH$_3$Cl)/cm$^{-1}$ 3291 (m, br, N–H str), 2971 (m, CH$_3$ asym str), 2925 (m, CH$_2$ asym str), 2854 (w, CH$_2$ sym str), 1697 (s, br, C=O), 1541 (s, C=S), 1489 (s); δ$_{1H}$ (400 MHz; CDCl$_3$) 8.65 (1H, br s, S=CNH), 5.93 (1H, br s, Boc NH), 4.16 (1H, quintet, $J$ 5.6, S=CH), 3.82 (2H, m, NCH$_2$), 2.45–2.51 (1H, m, 0.5 × CH$_2$), 1.94–2.05 (2H, m, 1 × CH$_2$), 1.52 and 1.55 (1H, detectable signals of overlapping m, 0.5 × CH$_2$), 1.47 (9H, s, (CH$_3$)$_3$); δ$_C$ (75 MHz; CDCl$_3$) 203.5 (C=S), 155.5 (C=O), 79.8 (C(CH$_3$)$_3$), 55.3 (S=CH), 43.6 (NCH$_2$), 28.4 (C(CH$_3$)$_3$), 27.1 (CH$_2$), 20.4 (CH$_2$); m/z (EI) 230 (40%, M$^+$), 174 (97, M$^+$–C(CH$_3$)$_2$CH$_2$), 157 (32, M$^+$–OC(CH$_3$)$_3$), 141 (20), 130 (31), 113 (49, 2-thiopiperidonium ion), 97 (25), 87 (10), 70 (25, CH$_2$CHCH$_2$CHNH$_2^+$), 57 (100, C(CH$_3$)$_3^+$), 41 (40, +CH$_2$CHCH$_2$) (Found: M$^+$, 230.1085. C$_{10}$H$_{18}$N$_2$O$_2$S requires 230.1089). 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 4.2.2.).

Method B:

A suspension of P$_4$S$_{10}$ (2.16 g, 9.72 mmol, 1.3 eq.) and anhydrous Na$_2$CO$_3$ (1.03 g, 9.72 mmol, 1.3 eq.) in dry THF (40 cm$^3$) was stirred at rt for 20 min, when a yellow solution was obtained. A solution of crude (S)-212 [prepared from L-ornithine hydrochloride (1.26 g, 7.47 mmol) according to the method given above] in THF (10 cm$^3$) was added dropwise to the P$_4$S$_{10}$ solution at rt. After stirring for 14 h at rt, aq. Na$_3$PO$_4$ solution (33 cm$^3$) was added carefully to the reaction mixture, followed by EtOAc (25 cm$^3$) and hexane (25 cm$^3$). The aqueous phase was extracted with EtOAc (15 cm$^3$) and the combined organic extracts were dried (MgSO$_4$) and filtered through celite. After evaporating the filtrate in vacuo, the residual oil was purified by column chromatography, as shown above, to obtain 204 as a colourless solid (1.39 g, 81%), the characterization data of which agree with those given above.
8.1.3. 3-{(Z)-3-[(S)-3-(tert-Butoxycarbonylamino)piperidin-2-ylidene]-2-oxopropyl}quinazolin-4(3H)-one (220)

A mixture of 3-(3-bromo-2-oxopropyl)quinazolin-4(3H)-one 105 (0.57 g, 2.0 mmol) and tert-butyl (S)-2-thioxopiperidin-3-ylcarbamate 204 (0.47 g, 2.0 mmol) in dry THF (40 cm³) was stirred at rt o.n. After evaporating the solvent in vacuo, dry CH₃CN (40 cm³), PPh₃ (1.06 g, 4.04 mmol) and 1-methylpiperidine (0.50 cm³, 4.1 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 CH₂Cl₂ (25 cm³) and filtered through celite. After evaporation of CH₂Cl₂ in vacuo, the residue was subjected to column chromatography (EtOAc, followed by EtOAc:MeOH, 19:1 to 4:1) to yield putative compound 220 as a pink, very viscous oil (0.51 g, 64%) which could not be crystallized, ν(max(film))/cm⁻¹ 3399 (m, vbr, N⁻H str), 2976 (w, CH₃ asym str), 2931 (w, CH₂ asym str), 1676 (s, br, 3 × C=O), 1612 (s, sh, Ar C=C str), 1564 (w), 1508 (w, Ar C=C str), 1474 (w, Ar C=C str); δ₁H (300 MHz; CDCl₃) 8.77 (1H, s, 1 × NH), 8.35 (1H, s, H-2), 8.17 (1H, d, J 7.9, H-5), 7.63–7.73 (2H, m, H-7 and H-8), 7.45 (1H, d, J 7.1, H-6), 5.78 (1H, d, J 16.0, 0.5 × NCH₂C=O), 5.66 (1H, d, J 15.8, 0.5 × NCH₂C=O), 5.30 (1H, m, CHNH₂Boc), 4.86 (1H, m, 0.5 × ring NCH₂ or C=CH₂), 4.66 (1H, m, 0.5 × ring NCH₂ or C=CH₂), ca. 3.5 (2H, br s, 1 × NH and 0.5 × ring NCH₂), 2.47 (2H, m, 1 × ring CH₂), 2.33 (2H, m, 1 × ring CH₂), 1.44 (9H, s, C(CH₃)₃); m/z (FABMS) M⁺ absent; major signals: 463 (31), 452 (6), 303 (29), 289 (13), 279 (9), 154 (100), 136 (79), 120 (15), 107 (29).

8.1.4. Attempted hydrogenation of 220

PtO₂ (Adams catalyst, 10 mg) was pre-hydrogenated in MeOH (1 cm³) by stirring under H₂ gas (1 atm) for 10 min. A solution of putative 3-{(Z)-3-[(S)-3-(tert-Butoxycarbonylamino)piperidin-2-ylidene]-2-oxopropyl}quinazolin-4(3H)-one 220 (0.10 g, 0.25 mmol) in MeOH (4 cm³) was subsequently transferred into the reaction flask, followed by glacial AcOH (ca. 0.3 cm³). The mixture was stirred under H₂ (2 atm) for 4 h and then stirred under H₂ (1 atm) for an additional 18 h. After filtering
the reaction mixture through celite and evaporation of the solvent in vacuo to dryness, the residue was subjected to column chromatography (EtOAc followed by EtOAc:MeOH, 9:1). Five products (deduced from TLC spots) were isolated from the column, none of which could be properly identified. The major product (ca. 50 mg) contained, by \(^1\)H NMR, the quinazolinone moiety, the Boc protecting group and possibly the piperidinyl moiety. However, no peaks corresponding to the central dimethylene ketone portion of the desired molecule were observed. We concluded that decomposition had occurred and this synthetic route was consequently discontinued.

8.2. Attempts using \(N\)-(4-methoxybenzyl) as a piperidinyl \(N\)-protecting group

8.2.1. \(\text{tert-Butyl (3S)-1-(4-methoxybenzyl)-2-oxopiperidin-3-ylcarbamate (223)}\)

This compound was prepared by modifying an existing procedure, which was used for the preparation of 1-(4-methoxybenzyl)piperidin-2-one 222. To a suspension of NaH (60\%, 212 mg, 5.30 mmol) in dry THF (5.5 cm\(^3\)) at \(-78\) °C was added 4-methoxybenzyl alcohol (0.62 cm\(^3\), 5.0 mmol) in THF (5.5 cm\(^3\)). The solution was stirred for 20 min, after which a solution of \(p\)-toluenesulfonyl chloride (0.95 g, 5.0 mmol) in THF (5.5 cm\(^3\)) was added. The slurry was stirred for another hour at \(-78\) °C, after which a suspension of \(\text{tert-butyl (3S)-2-oxopiperidin-3-ylcarbamate (S)-212}\) (1.01 g, 4.71 mmol) and NaH (60\%, 210 mg, 5.25 mmol) in THF (10 cm\(^3\)), prepared and kept at 0 °C, was added dropwise to the above slurry. The reaction was warmed to rt and left stirring for 14 h. After pouring the orange coloured reaction mixture into water (40 cm\(^3\)), it was extracted with CH\(_2\)Cl\(_2\) (4 \(\times\) 25 cm\(^3\)). The combined organic extracts were washed successively with saturated NaHCO\(_3\) (30 cm\(^3\)), H\(_2\)O (2 \(\times\) 30 cm\(^3\)) and brine (2 \(\times\) 30 cm\(^3\)), dried (MgSO\(_4\)) and evaporated in vacuo to afford a residual oil which was purified by column chromatography (EtOAc:hexane, 1:1) to yield 223 as a colourless solid (1.12 g, 71\%), mp 80.5–82 °C (from EtOAc–hexane); \(R_f\) 0.33 (EtOAc:hexane, 1:1); \(\lbrack\alpha\rbrack_d^{20}\) 14.4 (c 0.680, CHCl\(_3\)); \(v_{\text{max}}\) (CH\(_3\)Cl)/cm\(^{-1}\) 3326 (m, br, N–H str), 2974 (m, CH\(_3\) asym str), 2934 (m, CH\(_2\) asym str), 2870 (w, CH\(_2\) sym str), 2837 (w), 1713 (s, Boc C=O), 1648
(s, lactam C=O), 1613 (m, sh, Ar C=C str), 1586 (w, Ar C=C str), 1513 (s, sh, Ar C=C str), 1489 (m, Ar C=C str), 1465 (m, Ar C=C str); $\delta$H (300 MHz; CDCl3) 7.17 (2H, d, $J$ 8.6, 2 × m-Harom), 6.85 (2H, J 8.6, 2 × o-Harom), 5.56 (1H, br s, NH), 4.55 (1H, d, $J$ 14.4, 0.5 × NCH2Ar), 4.47 (1H, d, $J$ 14.4, 0.5 × NCH2Ar), 4.02–4.10 (1H, m, O=CH), 3.80 (3H, s, OCH3), 3.21 (2H, dd, $J$ 12.2 and 6.4, ring NC=H2), 2.44–2.53 (1H, m, 0.5 × CH2), 1.84 (2H, m, 1 × ring CH2), 1.51–1.65 (1H, m, 0.5 ×CH2CH), 1.46 (9H, s, (CH3)3); $\delta$C (75 MHz; CDCl3) 169.6 (lactam C=O), 159.1 (Boc C=O), 156.0 (ipso-Carom), 129.5 (m-Carom), 128.9 (p-Carom), 114.0 (o-Carom), 79.5 (C(CH3)3), 55.2 (OCH3), 52.0 (O=CCH), 50.0 (NCH2Ar), 46.3 (ring NCH2), 28.4 (C(CH3)3), 27.8 (ring CH2), 19.3 (ring CH2); m/z (EI) 334 (17%, M+), 278 (43, M+–C(CH3)2CH2), 261 (12, M+–OC(CH3)3), 249 (4, M+–COC(CH3)3), 217 (52, M+–H2NC(O)OC(CH3)3), 205 (6, M+–HCHNC(O)OC(CH3)3), 189 (94), 162 (5), 136 (16), 121 (100, CH2Ar+), 113 (7), 91 (5, tropylium ion), 78 (8), 70 (12), 57 (48, C(CH3)3+), 41 (15, C3H5), 30 (8) (Found: M+, 334.1893. C18H26N2O4 requires 334.1893).

8.2.2. tert-Butyl (3S)-1-(4-methoxybenzyl)-2-thioxopiperidin-3-ylcarbamate (224)

A mixture of tert-butyl (S)-1-(4-methoxybenzyl)-2-oxopiperidin-3-ylcarbamate 223 (1.05 g, 3.14 mmol), P2S5 (0.50 g, 2.2 mmol) and HMDO (1.20 cm3) in CH2Cl2 (7 cm3) was stirred at rt for 3 days. At 0 ºC, saturated K2CO3 (15 cm3) and acetone (4 cm3) were added and the mixture was stirred for another 20 min at 0 ºC. After adding CH2Cl2 (50 cm3) and H2O (40 cm3), the layers were separated and the aqueous layer was extracted with CH2Cl2 (2 × 30 cm3). The combined organic phases were dried (MgSO4) and evaporated. Column chromatography (hexane:EtOAc, 3:2) yielded 224 as a colourless solid (0.44 g, 40%), mp 109–110.5 ºC (from EtOAc–hexane); Rf 0.60 (EtOAc:hexane, 1:1); [\(\alpha\)]D20 –14.5 (c 0.927, CHCl3); $\nu_{max}$(CHCl3)/cm–1 3318 (m, br, N–H str), 2974 (m, CH3 sym str), 2933 (m, CH2 asym str), 2873 (w, CH2 sym str), 2836 (w), 1709 (s, C=O), 1612 (m, sh, Ar C=C str), 1585 (w, Ar C=C str), 1513 (s, sh, Ar C=C str), 1486 (s, Ar C=C str), 1465 and 1454 (m, Ar C=C str), 1250 (s), 1172 (s); $\delta$H (300 MHz; CDCl3) 7.25 (2H, d, $J$ 9.0, 2 × m-Harom), 6.86 (2H, J 8.7, 2 × o-Harom), 6.38 (1H, br s, NH), 5.29 (1H, d, $J$ 14.3, 0.5 × NCH2Ar), 5.17 (1H, d, $J$ 14.3, 0.5 × NCH2Ar), 4.31 (1H, quintet, $J$ 5.8,
S=C(H)C), 3.80 (3H, s, OCH₃), 3.43 (2H, dd, J 8.2 and 4.9, ring NCH₂), 2.44–2.55 (1H, m, 0.5 × CH₂CH), 1.82–1.93 (1H, m, 0.5 × ring CH₂), 1.47 (9H, s, (CH₃)₃), 1.32–1.43 (1H, detectable signals of overlapping m, 0.5 × CH₂CH); δ (75 MHz; CDCl₃) 201.0 (C=S), 159.4 (C=O), 155.3 (ipso-C arom), 129.3 (m-C arom), 127.3 (p-C arom), 114.2 (o-C arom), 79.6 (C(CH₃)₃), 57.5 (OCH₃), 55.8 (S=C(H)C), 55.3 (NCH₂Ar), 47.6 (ring NCH₂), 28.4 (C(CH₃)₃), 26.9 (ring CH₂), 19.8 (ring CH₂); m/z (HREI) 350 (60%, M⁺), 294 (37, M⁺–C(CH₃)₂CH₂), 277 (23, M⁺–OC(CH₃)₃), 261 (10), 233 (76, H₂NC(O)OC(CH₃)₃⁺), 205 (10), 200 (30), 198 (11), 153 (24), 148 (6), 136 (12), 129 (6), 121 (100, CH₂Ar⁺), 97 (5), 91 (10, tropylion ion), 78 (16), 70 (19), 57 (41, C(CH₃)₃⁺), 41 (12, C₃H₅⁺), 29 (6, C₂H₅⁺) (Found: M⁺, 350.1666. C₁₈H₂₆N₂O₃S requires 350.1664).

8.2.3. 3-{[(E)-3-[(3S)-3-(tert-Butoxycarbonylamino)-1-(4-methoxybenzyl)piperidin-2-ylidene]2-oxopropyl}quinazolin-4(3H)-one (221)

A mixture of 3-(3-bromo-2-oxopropyl)quinazolin-4(3H)-one 105 (255 mg, 0.907 mmol) and tert-butyldimethylsilyl chloride (224) (320 mg, 0.913 mmol) in dry THF (18 cm³) was stirred at rt for 18 h. After evaporating the solvent in vacuo, dry CH₃CN (18 cm³), PPh₃ (333 mg, 1.27 mmol) and freshly distilled NEt₃ (0.18 cm³, 1.3 mmol) were sequentially added to the remaining residue at 0 ºC. After warming to rt, stirring was continued for 30 min. The solvent was evaporated in vacuo, after which the residue was purified by column chromatography (EtOAc, followed by CH₂Cl₂:MeOH, 19:1) to yield 221 as a colourless solid (245 mg, 52%), mp 164–166 ºC (from EtOAc); Rf 0.38 (CH₂Cl₂:MeOH, 19:1); [α]D²⁰ 5.49 (c 0.182, CHCl₃); νmax(CHCl₃)/cm⁻¹ 3002 (w), 2976 (m, CH₃ asym str), 2936 (m, CH₂ asym str), 2838 (w, CH₂ sym str), 1738 (s), 1714 (s, Boc C=O), 1677 (s, enaminone and quinazolinone C=O), 1611 (s, sh, Ar C=C str), 1584 (w, sh, Ar C=C str), 1547 (m), 1515 (s, sh, Ar C=C str), 1474 (m, sh, Ar C=C str), 1252 (s); δH (300 MHz; CDCl₃) 8.25 (1H, d, J 7.9, H-5), 7.91 (1H, s, H-2), 7.67–7.76 (2H, m, H-7 and H-8), 7.46 (1H, dt, J 7.3 and 1.2, H-6), 7.07 (2H, d, J 8.4, 2 × PMB m-Harom), 6.79 (2H, J 8.5, 2 × PMB o-Harom), 5.88 (1H, br s, NH), 5.06 (1H, s, NC=CH), 4.98 (1H, m, CHNHBoc), 4.67 (1H, d, J 16.0, 0.5× NCH₂C=O),
4.56 (1H, d, $J = 15.9$, $0.5 \times \text{NCH}_2\text{Ar}$), 4.52 (1H, d, $J = 15.9$, $0.5 \times \text{NCH}_2\text{C}=\text{O}$), 4.34 (1H, d, $J = 16.2$, $0.5 \times \text{NCH}_2\text{Ar}$), 3.78 (3H, s, OCH$_3$), 3.63 (1H, m, $0.5 \times \text{ring NCH}_2$), 3.22 (1H, br quintet, $J = 5.9$, $0.5 \times \text{ring NCH}_2$), 3.17 (1H, m, $0.5 \times \text{ring NCH}_2$), 1.40 (9H, s, (C$_3$H$_3$)$_3$); $\delta_c$ (75 MHz; CDCl$_3$) 185.1 (enaminone C=O), 165.1 (NC=CH), 160.9 (quinazolinone C=O), 158.9 (Boc C=O), 156.3 (PMB ipso-C$_{arom}$), 148.3 (C-8a), 147.2 (C-2), 134.0 (C-7), 127.6, 127.4, 126.9, 126.7, 126.2, 122.1 (C-4a), 114.3 (PMB o-C$_{arom}$), 89.8 (NC=CH), 79.3 (C(CH$_3$)$_3$), 56.5 (NCH$_2$C=O), 55.2 (OCH$_3$), 54.0 (NCH$_2$Ar), 50.9 (ring NCH$_2$), 47.3 (CHNHBoc), 28.4 (C(CH$_3$)$_3$), 25.6 (ring CHCH$_2$), 20.6 (ring NCH$_2$CH$_2$); $m/z$ (EI) 518 (17%, M$^+$), 500 (28), 445 (10), 418 (34), 400 (100), 372 (23), 359 (57), 316 (10), 303 (72), 279 (77), 259 (78), 254 (85), 242 (15), 214 (13), 187 (12), 151 (14), 146 (67), 133 (47), 121 (80, CH$_2$Ar$^+$), 118 (22), 106 (17), 91 (36), 77 (45), 66 (19), 57 (86, C(CH$_3$)$_3^+$), 51 (13), 41 (60, C$_3$H$_5^+$) (Found: M$^+$, 518.2529. C$_{29}$H$_{34}$N$_4$O$_5$ requires 518.2529).

8.2.4. Attempted hydrogenation of 3-{[(E)-3-[(3S)-3-(tert-butoxycarbonylamino)-1-(4-methoxybenzyl) piperidin-2-ylidene]2-oxopropyl}quinazolin-4(3H)-one (221)

A solution of 3-[(E)-3-[(3S)-3-(tert-butoxycarbonylamino)-1-(4-methoxybenzyl) piperidin-2-ylidene]2-oxopropyl]quinazolin-4(3H)-one 221 (0.20 g, 0.39 mmol) in glacial AcOH (5 cm$^3$) was stirred over pre-hydrogenated PtO$_2$ (Adam’s catalyst, 20 mg) under H$_2$ gas (1 atm) for 72 h. After filtering the reaction mixture through celite, saturated aq. K$_2$CO$_3$ (10 cm$^3$) was added to the filtrate. Extraction using CH$_2$Cl$_2$ (2 × 10 cm$^3$) was followed by washing the combined organic extracts with saturated NaCl (10 cm$^3$). After drying (MgSO$_4$) and evaporation of CH$_2$Cl$_2$ in vacuo, the residue was purified by gradient column chromatography (CH$_2$Cl$_2$:MeOH, 99:1 to 9:1) to yield three products. Only the first least polar product was characterizable (experimental data to follow) and isolated as a yellow oil (51 mg, 25% based on the structure given below), which decomposed slowly on storage to a greenish colour. It is thought to possibly possess the structure of the following isoxazine (see also Section 4.3.2): tert-Butyl 5-(4-methoxybenzyl)-5,6,7,8-tetrahydro-3-[[4-oxoquinazolin-3(4H)-yl]-methyl]pyrido[3,2-c][1,2]oxazine-1-carboxylate 226;
262

\[ R_f \] 0.47 (CH\(_2\)Cl\(_2\):MeOH, 19:1); \( \nu_{\text{max}}(\text{CHCl}_3)/\text{cm}^{-1} \)
3058 (w, Ar–H str), 3006 (w), 2974 (m, CH\(_3\) asym str),
2935 (m, CH\(_2\) asym str), 2872 and 2838 (w,
CH\(_2\) sym str), 1716 (s), 1681 (s, br, enaminone C=O
and conjugated Boc C=O), 1612 (s, sh, Ar C=C str),
1547 (m), 1514 (m, sh, Ar C=C str), 1475 (m, sh,
Ar C=C str), 1438 (m, sh, Ar C=C str); \( \delta \)H (300 MHz; CDCl\(_3\)) 8.33 (1H, d,
\( J \) 7.7, H-5), 8.14 (1H, s, H-2), 7.69–7.78 (2H, m, H-7 and H-8), 7.49 (1H, dt?, \( J \) 7.3 and 1.6, H-6),
7.17 (2H, d, \( J \) 8.6, 2 \( \times \) PMB m-H\(_{\text{arom}}\)), 6.79 (2H, d, \( J \) 8.6, 2 \( \times \) PMB o-H\(_{\text{arom}}\)), 5.94 (1H,
s, NC=CH), 5.37 (2H, s, NCH\(_2\)Ar\(^*\)), 3.97 (2H, s, NCH\(_2\)C=O\(^*\)), 3.76 (3H, s, OCH\(_3\)),
2.76–2.80 (4H, m, 2 \( \times \) ring NCH\(_2\) and 2 \( \times \) ring NCCH\(_2\)), 1.84–1.89 (2H, m, ring
NCH\(_2\)CH\(_2\)), 1.53 (9H, s, (CH\(_3\))\(_3\)); \( \delta \)C (75 MHz; CDCl\(_3\)) 161.0 (quinazolinone C=O),
158.7 (Boc C=O), 150.1 (PMB ipso-C\(_{\text{arom}}\)), 148.1 (C-8a), 146.6 (C-2), 135.2
(quaternary C), 134.0 (C-7), 130.4 (quaternary C), 129.4, 127.4, 127.0, 126.8, 125.9
(quaternary C), 122.2 (C-4a), 115.1 (quaternary C), 113.6 (PMB o-C\(_{\text{arom}}\)), 107.1
(NC=CH), 83.9 (C(CH\(_3\))\(_3\)), 56.8 (NCH\(_2\)C=O\(^*\)), 55.2 (OCH\(_3\)), 47.8 (ring NCH\(_2\)), 44.3
(NCH\(_2\)Ar\(^*\)), 28.1 (C(CH\(_3\))\(_3\)), 24.1 (ring NCCH\(_2\)), 22.4 (ring NCH\(_2\)CH\(_2\)) [\(^*\) These \(^1\)H
and \(^{13}\)C signals are interchangeable]; \( m/z \) (HREI) 516 (64%, M\(^+\)), 415 (12), 400 (14),
396 (41), 357 (10), 341 (5), 313 (15), 301 (33), 286 (19), 275 (44), 257 (21), 255 (6),
228 (9), 204 (14), 176 (5), 160 (9), 146 (55), 121 (100), 118 (16), 102 (10), 91 (24),
77 (31), 63 (10), 57 (39), 44 (25), 41 (37) (Found: M\(^+\), 516.2379. C\(_{29}\)H\(_{32}\)N\(_4\)O\(_5\) requires
516.2373).

8.3. Attempts using \( N\)-(2-methylnaphthyl) as a piperidinyl \( N\)-protecting group

8.3.1. \( \text{tert-Butyl (3S)-1-[(naphthalen-3-yl)methyl]-2-oxopiperidin-3-yl} \)carbamate
\( (229) \)

This compound was prepared based on a known procedure \(^99\).
To a solution of \( \text{tert-butyl (3S)-2-oxopiperidin-3-yl} \)carbamate
\( (S)-212 \) (1.71 g, 7.98 mmol) in dry THF (80 cm\(^3\)) was added
NaH (60%, 385 mg, 9.63 mmol) at 0 ºC. After stirring for 30
min, 2-(bromomethyl)naphthalene (95 %, 1.82 g, 8.23 mmol) was added, the reaction was warmed to rt and stirring was continued for 18 h. MeOH (9 cm³) and ice (18 g) were added and the resulting mixture was extracted with CH₂Cl₂ (90 cm³). The organic layer was washed with saturated aq. NaHCO₃ (2 × 70 cm³), dried (MgSO₄) and evaporated in vacuo. Column chromatography (hexane:EtOAc, 4:1 to 1:1) of the residue yielded 229 as a colourless solid (1.92 g, 68%), mp 114-115 ºC (from EtOAc:hexane, 1:5); Rf 0.62 (EtOAc:hexane, 1:1); [α]D²⁰ –4.31 (c 0.928, CHCl₃); νmax(CHCl₃)/cm⁻¹ 3327 (w, br, N–H str), 2925 (m, CH₂ asym str), 2855 (w, CH₂ sym str), 1712 (s, boc C=O), 1648 (s, lactam C=O), 1508 (m, Ar C=C str), 1489 (m, Ar C=C str), 1465 (m, Ar C=C str), 1447 (m, Ar C=C str); δh (300 MHz; CDCl₃) 7.79–7.82 (3H, m, 3 × H_arom), 7.67 (1H, s, H-1 of NAP), 7.46–7.49 (2H, m, 2 × H_arom), 7.37 (1H, d, J 8.5, 1 × H_arom), 5.59 (1H, br s, NH), 4.80 (1H, d, J 14.6, 0.5 × NCH₂Ar), 4.69 (1H, d, J 14.6, 0.5 × NCH₂Ar), 4.12 (1H, m, O=CCH), 3.22–3.28 (2H, m, ring NC(CH₃)₂), 2.50 (1H, m, 0.5 × CH₂CH), 1.82–1.86 (2H, m, 1 × ring CH₂), 1.62 (1H, m, 0.5 × CH₂CH), 1.47 (9H, s, (CH₃)₃); δc (75 MHz; CDCl₃) 169.8 (lactam C=O), 156.0 (Boc C=O), 134.3, 133.2, 132.8, 128.6, 127.7, 127.0, 126.9, 126.3, 126.0, 125.9, 79.6 (C(CH₃)₃), 52.0 (O=CCH), 50.7 (NCH₂Ar), 46.5 (ring NCH₂), 28.4 (C(CH₃)₃), 27.8 (ring CH₂), 20.7 (ring CH₂); m/z (EI) 354 (17%, M⁺), 298 (69, M⁺–C(CH₃)₂CH₂), 281 (15, M⁺–OC(CH₃)₂), 237 (38, M⁺–H₂NC(O)OC(CH₃)₃), 209 (95), 156 (10), 141 (100, NAP⁺), 115 (17), 70 (11), 57 (49, C(CH₃)₃⁺), 41 (13, C₃H₇⁺), 30 (8) (Found: M⁺, 354.1946. C₂₁H₂₆N₂O₃ requires 354.1943).

8.3.2. tert-Butyl (3S)-1-[(naphthalen-3-yl)methyl]-2-oxopiperidin-3-ylcarbamate (230)

A mixture of tert-butyl (3S)-1-[(naphthalen-3-yl)methyl]-2-oxopiperidin-3-ylcarbamate 229 (415 mg, 1.17 mmol) and Lawesson’s reagent (237 mg, 0.586 mmol) in benzene (15 cm³) was refluxed for 15 h. After evaporation of the solvent in vacuo, the residue was purified by column chromatography (hexane:EtOAc, 4:1) to yield 230 as a colourless solid (0.42 g, 97%), mp 108-109 ºC (from EtOAc-hexane); Rf 0.39 (hexane:EtOAc, 7:3); [α]D²⁰ –0.99 (c 1.01, CHCl₃); νmax(CHCl₃)/cm⁻¹ 3327 (m, br, N–H str), 3054 (w, Ar–H), 2975 (m, CH₃ asym str), 2931 (CH₂ asym str), 2873 (w, CH₂ sym str), 1708 (s, C=O and C=S),
1487 (s, Ar C=C str), 1453 (s, sh, Ar C=C str); δ_H (300 MHz; CDCl3) 7.80–7.84 (3H, m, 3 × H_arom), 7.71 (1H, s, H-1 of NAP), 7.45–7.52 (2H, m, 2 × H_arom), 7.43 (1H, dd, J 8.5 and 1.6, 1 × H_arom), 6.41 (1H, br s, NH), 5.50 (1H, d, J 14.5, 0.5 × NCH2Ar), 5.42 (1H, d, J 14.5, 0.5 × NCH2Ar), 4.28 (1H, quintet, J 5.7, O=CCH), 3.47 (2H, dd, J 14.5, 0.5 × NC2H), 2.46–2.57 (1H, m, 0.5 × C2H), 1.81–1.95 (1H, m, 0.5 × ring CH2), 1.60–1.74 (1H, m, 0.5 × ring CH2), 1.49 (9H, s, (CH3)3), 1.37–1.45 (1H, discernible overlapping m, 1 × C2H), δ_C (75 MHz; CDCl3) 201.5 (C=S), 155.3 (C=O), 133.2, 133.0, 132.7, 128.8, 127.7 (2 × C_arom), 126.9, 126.4, 126.2, 125.6, 79.6 (C(CH3)3), 58.2 (NCH2Ar), 55.9 (O=CCH), 47.8 (ring NCH2), 28.4 (C(CH3)3), 26.9 (ring CH2), 19.8 (ring CH2); m/z (EI) 370 (62%, M+), 314 (47, M+–C(CH3)2CH2), 297 (20, M+–OC(CH3)3), 281 (11), 269 (8), 253 (80), 220 (51), 209 (5), 173 (15), 168 (7), 156 (7, NAPNH+), 141 (100, NAP+), 129 (12), 115 (26), 95 (13), 83 (20), 70 (22), 57 (48, C3H7+), 43 (11, C3H7+), 29 (13, C2H5+). (Found: M+, 370.1709. C21H26N2O2S requires 370.1715).

8.3.3. 3-{(E)-3-[(3S)-3-(tert-Butoxycarbonylamino)-1-((naphthalen-3-yl)methyl)piperidin-2-ylidene]2-oxopropyl}quinazolin-4(3H)-one (231)

A mixture of 3-(3-bromo-2-oxopropyl)quinazolin-4(3H)-one 105 (296 mg, 1.05 mmol) and tert-butyl (3S)-1-[(naphthalen-3-yl)methyl]-2-oxopiperidin-3-ylcarbamate 230 (390 mg, 1.05 mmol) in dry THF (20 cm³) was stirred at rt for 7 days. After evaporating the solvent in vacuo, dry CH3CN (15 cm³) and PPh3 (0.33 g, 1.3 mmol) were added to the residue. After cooling to 0 °C, a solution freshly distilled NEt3 (0.18 cm³, 1.3 mmol) in CH3CN (5 cm³) was added dropwise to the above solution. The mixture was warmed to rt and stirred for 2 h, after which it was filtered through celite and evaporated in vacuo. Repeated column chromatography (CH2Cl2:MeOH, 99:1) of the residue yielded a viscous colourless oil (265 mg, < 47%) containing trace impurities evident from NMR spectroscopy (note the additional peaks in 13C NMR spectrum), Rf 0.46 (CH2Cl2:MeOH, 19:1); v_max(film)/cm⁻¹ 3321 (w, br, N–H str), 3056 (w, Ar–H str), 3007 (w, Ar–H str), 2975 (m, CH3 asym str), 2932 (w, CH2 asym str), 2864 (w, CH2 sym str), 1681 (s, br, 3 × C=O), 1612 (s, sh, Ar C=C str), 1547 (s), 1509 (m, sh, Ar C=C str), 1475 (m, sh, Ar
C=C str); δH (300 MHz; CDCl3) 8.28 (1H, d, J 7.9, H-5), 7.87 (1H, s, H-2), 7.38–7.84 (9H, m, 9 × H arom), 7.26 (1H, d, J 7.3, 1 × H arom), 5.98 (1H, br s, NH), 5.12 (1H, s, NC=CH), 5.01 (1H, br s, CHNBoc), 4.81 (1H, d, J 16.6, 0.5 × NCH2C=O), 4.65 (1H, d, J 16.1, 0.5 × NCH2Ar), 4.56 (1H, d, J 16.6, 0.5 × NCH2C=O), 4.47 (1H, d, J 16.0, 0.5 × NCH2Ar), 3.73 (1H, m, 0.5 × ring NCH2), 3.30 (1H, br quintet, J 6.0, 0.5 × ring NCH2), 2.31 (1H, m, 0.5 × ring CH2), 2.08 (1H, m, 0.5 × ring CH2), 1.76 (2H, br m, 1 × ring CH2), 1.43 (9H, s, (CH3)3); δC (75 MHz; CDCl3) 185.3 (enaminone C=O), 165.4 (NC=CH), 160.9 (quinazolinone C=O), 156.3 (Boc C=O), 148.1 (C-8a), 147.14, 147.07, 133.9, 133.4, 132.7, 132.1, 132.0, 131.9, 131.7, 128.8, 128.5, 128.4, 127.8, 127.7, 127.3, 126.8, 126.6, 126.3, 126.0, 124.9, 124.2, 122.0 (C-4a), 89.9 (NC=CH), 79.4 (C(CH3)3), 57.3 (NCH2C=O), 54.0 (NCH2Ar), 51.1 (ring NCH2), 47.4 (CHNBoc), 31.7 (ring CH2), 28.4 (C(CH3)3), 25.9 (ring CH2); m/z (El) 538 (0.1%, M+), 520 (2, M+–H2O), 420 (14, M+–NHC(O)O(CH3)3–H2), 298 (7), 277 (100), 246 (12), 201 (25), 183 (19), 146 (86, 4(3H)quinazolinone+) 141 (93, Nap+), 135 (32, CH2N(CH2)3CHCCCO3), 118 (31), 91 (18, tropylium ion), 77 (25, phenonium ion), 41 (56, C3H5+), 28 (9, C2H4+ and CO+). No accurate molecular ion peak was found in the high-resolution mass spectrum run of this compound.

### 8.3.4. Attempted hydrogenation of 231

A solution of 231 (0.21 g, 0.39 mmol) in glacial AcOH (3 cm³) was stirred over PtO2 (Adams catalyst, 20 mg) and under H2 gas (1 atm) for 51 h. After neutralizing the AcOH using saturated aq. K2CO3 (5 cm³), the solution was extracted with EtOAc (3 × 30 cm³). The combined organic extracts were dried (MgSO4) and evaporated in vacuo to yield an orange oil which was subjected to column chromatography (CH2Cl2:MeOH, 49:1). Two almost inseparable fractions (spots on Tlc), Rf ca. 0.5 (CH2Cl2:MeOH, 19:1), were isolated. From the ¹H NMR spectra obtained, it was found that both fractions were mixtures of unidentifiable products, and that decomposition of the s.m. had occurred. This synthetic route was consequently discontinued.