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Functionalisation of Pyrrolidin-2-ones at C4 and C5

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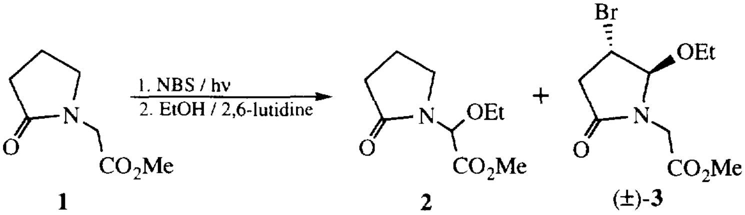
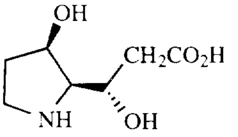
Abstract: Treatment of pyrrolidin-2-ones with *N*-bromosuccinimide affords the corresponding 4,5-dibromo-γ-lactams. The introduced bromo substituents may be selectively displaced in ionic and radical reactions. The synthetic utility of this procedure is illustrated in regioselective elaborations of the dibromides, including the generation of a bicyclic tetrahydrofuropyrrolidinone system.

A variety of methods have been reported for the direct functionalisation of pyrrolidin-2-ones at C5.[1-7] Anodic oxidation of *N*-alkylpyrrolidinones occurs regioselectively at endocyclic carbon adjacent to nitrogen, to give the corresponding 5-hydroxypyrrolidinones and imides,[2] and *N*-unsubstituted pyrrolidinones are similarly oxidised.[3,4] Photochemical oxidation of pyrrolidin-2-ones to their corresponding imides has also been reported.[5,6] Alternatively, free radical benzoyloxylation has been used for the introduction of the synthetically versatile acyloxy group at C5.[7] More recently, we have described reactions with *N*-bromosuccinimide as methodology for functionalisation of *N*-substituted γ-lactams at exocyclic carbon adjacent to nitrogen.[8] For example, the reaction of the pyrrolidinone **1** with *N*-bromosuccinimide, followed by treatment with ethanol, gave mainly the exocyclic substitution product **2** (*Scheme 1*). As part of that study, endocyclic substitution of pyrrolidinones at C4 and C5 was observed as a minor reaction pathway and, in the reaction of the pyrrolidinone **1**, the 4,5-disubstituted γ-lactam **3** was obtained.



Scheme 1

Substituted pyrrolidinones have found widespread use in the synthesis of alkaloids[9-13] and the generation of 4,5-disubstituted pyrrolidinones is of potential interest in this area. Detoxinine (**4**)[14] and retronecine (**5**)[15] are examples of alkaloids bearing a disubstituted pyrrolidine ring. Accordingly, we have examined the



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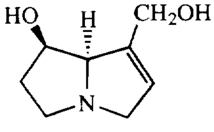


5

processes involved in the formation of the 4,5-disubstituted γ-lactam **3** in more detail, and exploited the procedure to develop methodology for the direct endocyclic functionalisation of pyrrolidinones at C4 and C5.

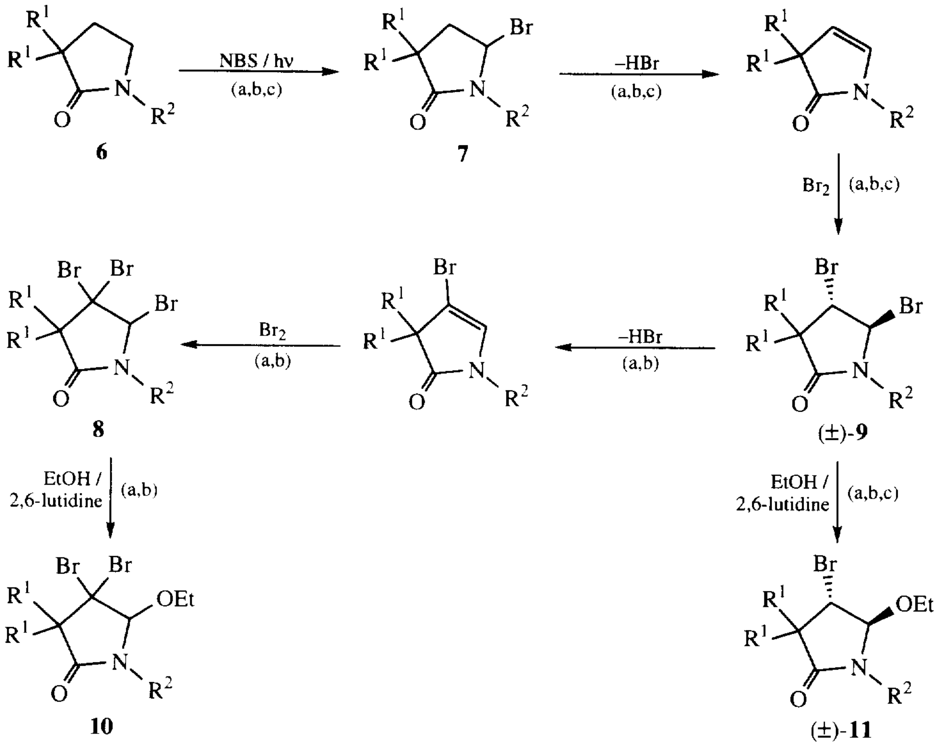
RESULTS AND DISCUSSION

The major reaction of the pyrrolidinone **1** to give the exocyclic substitution product **2** is facilitated by the methoxycarbonyl substituent activating the exocyclic position to hydrogen atom abstraction. Accordingly, we anticipated that in the absence of activating substituents at the exocyclic position, the balance of exo- and endocyclic functionalisation would be altered. We therefore chose to investigate reactions of the *N*-methylpyrrolidinones **6a** and **6b** with *N*-bromosuccinimide. The trimethylpyrrolidinone **6a** was chosen for initial investigation as it was reasoned that the methyl substituents at C3 would block that position to possible side reactions.

1,3,3-Trimethylpyrrolidin-2-one (**6a**) was treated with two mole equivalents of *N*-bromosuccinimide, in carbon tetrachloride at reflux under nitrogen for 10 minutes, with reaction initiated by irradiation with a 300 W mercury lamp. The products of reaction were converted to stable derivatives, for isolation and characterisation, through treatment with two mole equivalents of ethanol and one mole equivalent of 2,6-lutidine. This afforded, after chromatography of the product mixture on silica, the 4-bromo-5-ethoxypyrrolidinone **11a** and the 4,4-dibromo-5-ethoxypyrrolidinone **10a**, in yields of 9 and 14%, respectively. Similar treatment of *N*-methylpyrrolidin-2-one (**6b**) afforded the 4-bromo-5-ethoxypyrrolidinone **11b** and the 4,4-dibromo-5-ethoxypyrrolidinone **10b**, in yields of 9 and 11%, respectively. As comparable yields of products were obtained in these reactions, in the presence and absence of methyl substituents at C3, reaction of 1,3,3-trimethylpyrrolidin-2-one (**6b**) was not investigated further. In each case, no products attributable to bromination of the *N*-methyl substituent were observed.

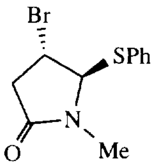
Production of the 4-bromo-5-ethoxylactams **11a** and **11b** and the 4,4-dibromo-5-ethoxylactams **10a** and **10b** may be attributed to initial free radical bromination to give the bromides **7a** and **7b**, which undergo ionic reactions as shown in *Scheme 2* to give the *trans*-dibromides **9a** and **9b** and the tribromides **8a** and **8b**. Indeed, ^{1}H NMR spectroscopic analysis of the crude products of the reaction of *N*-methylpyrrolidin-2-one (**6b**) with *N*-bromosuccinimide indicated formation of a major amount of the *trans*-dibromide **9b** and the tribromide **8b** in an approximately 5:2 ratio.

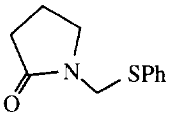
To maximise the ratio of production of the dibromide **9b** to the tribromide **8b**, from the pyrrolidinone **6b**, AIBN was added to the reaction mixture to increase the efficiency of the radical reaction, and the reaction time was reduced in order to limit subsequent ionic reactions. Coincidentally, conversion of the products of bromination of **6b** to their corresponding phenylthioethers was investigated. Thus, *N*-methylpyrrolidin-2-one (**6b**) was treated with *N*-bromosuccinimide in the presence of a catalytic amount of AIBN, for only 5 minutes, and the product mixture was treated with thiophenol. This reaction afforded the 4-bromo-5-phenylthio-γ-lactam **12**, in 25% yield, and the *N*-phenylthiomethyl-γ-lactam **13**, resulting from exocyclic substitution, in 3% yield.



a: $R^1 = R^2 = Me$
b: $R^1 = H$, $R^2 = Me$
c: $R^1 = H$, $R^2 = p$-MeOPh

Scheme 2


(±)-**12**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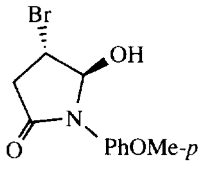
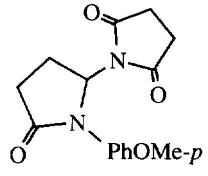
Despite the modest product yields obtained in this reaction, given the ready availability of *N*-methylpyrrolidin-2-one (**6b**), the above reactions illustrate the accessibility of 4,5-difunctionalised γ-lactams through this procedure. In addition, the above examples demonstrate selective substitution of the C5 bromine.

The *N*-(*p*-methoxyphenyl)-substituted pyrrolidinone **6c** was next investigated. Reaction of the lactam **6c** with a slight molar excess of *N*-bromosuccinimide in the presence of a catalytic amount of AIBN for 5 minutes, followed by treatment with ethanol, afforded, after chromatography, the 4-bromo-5-ethoxypyrrolidinone **11c**, in 38% yield. In addition, 33% of the starting material **6c** was recovered unreacted, and the alcohol **14** and the 5-succinimidopyrrolidinone **15** were obtained as minor products, in yields of 14 and 7%, respectively. The *p*-methoxyphenyl substituent has previously been reported to be amenable to removal from nitrogen of functionalised β-lactams,[16] through oxidative dearylation with ceric ammonium nitrate,[17] so elaboration of the lactam **6c** should provide a route to functionalised *N*-unsubstituted pyrrolidinones.



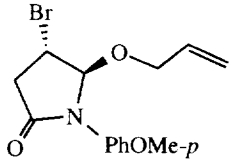
(±)-**14**



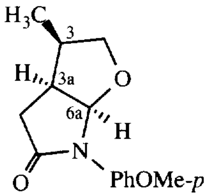
15

This procedure for functionalisation of pyrrolidinones at C4 and C5, and for differential elaboration of the introduced functionality has potential in the synthesis of bicyclic pyrrolidinones. Accordingly, 1-(*p*-methoxyphenyl)pyrrolidin-2-one (**6c**) was treated with a slight molar excess of *N*-bromosuccinimide followed by allyl alcohol. Chromatography of the crude product mixture afforded the 5-allyloxy-4-bromo-pyrrolidinone **16** in 29% yield. In addition, 48% of the pyrrolidinone **6c** was recovered unreacted and the alcohol **14** was obtained in 8% yield. The yield of the allyl ether **16** from the pyrrolidinone **6c**, *via* this procedure, was improved to 47% when the reaction was conducted with five mole equivalents of *N*-bromosuccinimide. The alcohol **14** was also obtained, in 9% yield, and 31% of the starting material **6c** was recovered. In each case above, production of a minor amount of the 5-succinimidopyrrolidinone **15** was also detected.

Cyclisation of the 5-allyloxy-4-bromopyrrolidinone **16** was achieved by treatment with tri-*n*-butyltin hydride according to the method reported by Hart and co-workers[12,13] for the intramolecular cyclisation of related systems. Thus a dilute solution of tri-*n*-butyltin hydride and a catalytic amount of AIBN in benzene was added dropwise to a solution of the bromide **16** in benzene, heated at reflux under nitrogen. Chromatography of the crude product mixture afforded the tetrahydrofuropyrrolidinone **17**, in 38% yield, resulting from 1,5-*exo* cyclization.[18,19] No products resulting from simple reduction of the bromide **16** were detected.



(±)-**16**



(±)-**17**

Both ^1H and ^{13}C n.m.r. analyses of the tetrahydrofuropyrrolidinone **17** indicated it to be a single diastereomer. A high degree of stereoselectivity is exhibited in the free radical cyclisation of related systems,[13,20–22] whereby the major diastereomer obtained is invariably that in which the three substituents of the newly formed 5-membered ring are in an all-*cis* geometry. The stereochemical preference may be rationalised as due to reaction *via* a transition state geometry that affords maximal overlap between the semioccupied *p*-orbital of the radical centre and the π*-orbital of the alkenyl moiety.[18,21,22] On this basis, the single diastereomer of **17** obtained was assigned as that with the all-*cis* geometry, namely the (3*SR*,3a*RS*,6a*SR*)-diastereomer.

Synthesis of the tetrahydrofuropyrrolidinone **17** from **6c**, whilst exemplifying the viability of the free radical bromination procedure for the synthesis of bicyclic pyrrolidinones, moreover highlights the provision of the free radical bromination procedure for selective elaboration of functionality thus introduced at both C4 and C5 of a pyrrolidinone system. In summary, the procedure described in this paper provides an effective method for the synthesis of 4,5-difunctionalised pyrrolidinones and bears scope for application to the synthesis of pyrrolidine and pyrrolizidine alkaloids.

EXPERIMENTAL

General. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi 270-30 spectrophotometer as nujol mulls between sodium chloride plates, or as liquid films or solutions as indicated. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were recorded on either a Bruker AC-P 300 or CXP 300 spectrometer as dilute solutions in deuterochloroform, using tetramethylsilane as internal standard. Electron impact mass spectra and high resolution mass spectra were recorded on an AEI MS-3010 spectrometer, using an ionising voltage of 70 eV. Elemental analyses were performed by Canadian Microanalytical Service Ltd., New Westminster, British Columbia, Canada.

Flash column chromatography was carried out using Matrex™ silica gel (pore size 60 Å, particle size 50 µm, No. 84072). Squat column[23] and preparative thin layer chromatographies were carried out using Merck silica gel 60$_{\mathrm{PF-254}}$ (Art. 7749). Preparative thin layer chromatographies were carried out on a Chromatotron 7924T (Harrison Research, Palo Alto/ TC Research, Norwich). All organic extracts were dried over anhydrous magnesium sulphate. Light petroleum refers to the fraction with b.p. 66 – 69°C. A WOTAN Ultra-Vitalux® 300 W sunlamp was used as the light source in reactions of *N*-bromosuccinimide. *N*-Bromosuccinimide was recrystallised from water and dried under reduced pressure before use.

1,3,3-Trimethylpyrrolidin-2-one (**6a**) was prepared according to the method reported by Gasman and Fox.[24] 1-Methylpyrrolidin-2-one (**6b**) was purchased from Merck (Art. 806072) and used without further purification.

N-(p-Methoxyphenyl)-4-chlorobutyramide. 4-Chlorobutyryl chloride (30 g, 213 mmol) was dissolved in dichloromethane (200 ml) and a solution of freshly recrystallised *p*-anisidine (28.8 g, 266 mmol) in dichloromethane (100 ml) was added dropwise with stirring. After the addition was complete the solution was stirred at room temperature for a further 4 hr. The solution was then washed with water (3 × 100 ml), dried, and evaporated under reduced pressure to give an oil that solidified on standing. The residual solid was recrystallised from ethyl acetate / light petroleum to give *N*-(*p*-methoxyphenyl)-4-chlorobutyramide as a white crystalline solid (23.8 g, 54%): m.p. 85°C; IR (nujol) 3308, 1662, 1620, 1518, 1240, 1024, 840 cm^{-1}; ^{1}H NMR δ 2.13 (2H, tt, *J* 7.2, 6.2 Hz, C*H*$_2$CH$_2$Cl), 2.48 (2H, t, *J* 7.2 Hz, CH$_2$Cl), 3.59 (2H, t, *J* 6.2 Hz, C*H*$_2$CONH), 3.76 (3H, s, OCH$_3$), 6.80 (2H, m, ArH), 7.38 (2H, m, ArH), 8.06 (1H, broad, NH); ^{13}C NMR δ 169.84, 156.40, 130.70, 121.80, 114.07, 55.44, 44.50, 33.89, 27.94; HRMS calcd for $C_{11}H_{14}{}^{35}ClNO_2$ *m/z* 227.0713 (M$^+$), found 227.0757. Anal. Calcd for $C_{11}H_{14}ClNO_2$: C, 58.01; H, 6.20; N, 6.15. Found: C, 58.31; H, 5.87; N, 6.14.

*1-(*p*-Methoxyphenyl)pyrrolidin-2-one (6c).* A solution of *N*-(*p*-methoxyphenyl)-4-chlorobutyramide (2.28 g, 10 mmol) in dichloromethane (200 ml) was added dropwise over 6 hr, to a stirred suspension of powdered potassium hydroxide (672 mg, 12 mmol) and tetra-*n*-butylammonium chloride (556 mg, 2 mmol) in dichloromethane (200 ml). After the addition was complete, stirring was continued for 30 min. The precipitate was filtered off and washed with dichloromethane (2 × 50 ml). The combined filtrates were dried and concentrated under reduced pressure to give an oil that was chromatographed on a squat column, gradient eluting with light petroleum and ethyl acetate. The resulting solid was recrystallised from ethyl acetate / light petroleum to give 1-(*p*-methoxyphenyl)pyrrolidin-2-one (**6c**) as fine transparent leaves (1.19 g, 63%): m.p. 108°C; IR (nujol) 1682, 1612, 1514, 1252, 1032, 830 cm^{-1}; ^{1}H NMR δ 2.12 (2H, tt, *J* 8.1, 7.0 Hz, C4-H_2), 2.56 (2H, t, *J* 8.1 Hz, C3-H_2), 3.78 (3H, s, OCH_3), 3.80 (2H, t, *J* 7.0 Hz, C5-H_2), 6.89 (2H, m, ArH), 7.48 (2H, m, ArH); ^{13}C NMR δ 173.90, 156.49, 132.53, 121.79, 113.96, 55.41, 49.15, 32.42, 17.98; HRMS calcd for $C_{11}H_{13}NO_2$ *m/z* 191.0946 (M$^+$), found 191.1005. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.09; H, 6.93; N, 7.35.

trans-*4-Bromo-5-ethoxy-1,3,3-trimethylpyrrolidin-2-one (11a) and 4,4-dibromo-5-ethoxy-1,3,3-trimethylpyrrolidin-2-one (10a).* A mixture of 1,3,3-trimethylpyrrolidin-2-one (**6a**) (252 mg, 1.98 mmol) and *N*-bromosuccinimide (705 mg, 3.96 mmol) in carbon tetrachloride (40 ml) was heated at reflux under nitrogen, whilst irradiating with a 300 W mercury lamp, for 10 min. The reaction mixture was cooled to room temperature, dry ethanol (240 µl, 4.09 mmol) and 2,6-lutidine (230 µl, 1.97 mmol) were added and the mixture was stirred under nitrogen for 3 hr. The reaction mixture was filtered and evaporated under reduced pressure and the resultant residue was taken up in ethyl acetate and washed successively with 0.01 M hydrochloric acid, brine, saturated aqueous sodium bicarbonate and brine. The organic layer was dried and concentrated under reduced pressure and flash column chromatography of the residue, eluting with a mixture of light petroleum and ethyl acetate (2:5), then afforded two products, **11a** and **10a**.

trans-4-Bromo-5-ethoxy-1,3,3-trimethylpyrrolidin-2-one (**11a**) as an oil (46 mg, 9%): IR (liquid film) 2972, 1708, 1276, 1064, 760 cm^{-1}; ^{1}H NMR δ 1.22 (3H, s, C3-CH_3), 1.28 (3H, s, C3-CH_3), 1.29 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 2.87 (3H, s, NCH_3), 3.74 (1H, dq, *J* 9.4, 7.0 Hz, $OCHHCH_3$), 3.80 (1H, dq, *J* 9.4, 7.0 Hz, $CHHCH_3$), 3.98 (1H, d, *J* 3.8 Hz, C4-H), 4.89 (1H, d, *J* 3.8 Hz, C5-H); ^{13}C NMR δ 175.55, 95.57, 65.61, 57.92, 44.84, 27.13, 24.19, 23.95, 15.47; MS *m/z* (relative intensity) 251 (M$^+$, 6), 249 (M$^+$, 6), 206 ([M – OEt]$^+$, 66), 204 ([M – OEt]$^+$, 67), 192 (11), 190 (11), 170 ([M – Br]$^+$, 21), 149 (13.5), 147 (14), 113 (100), 85 (81). HRMS calcd for $C_9H_{16}{}^{79}BrNO_2$ *m/z* 249.0364 (M$^+$), found 249.0355.

4,4-Dibromo-5-ethoxy-1,3,3-trimethylpyrrolidin-2-one (**10a**) as an oil (91 mg, 14%): IR (liquid film) 2976, 1714, 1294, 1064, 770 cm^{-1}; ^{1}H NMR δ 1.30 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 1.38 (3H, s, C3-CH_3), 1.42 (3H, s, C3-CH_3), 2.92 (3H, s, NCH_3), 3.81 (1H, dq, *J* 9.4, 7.0 Hz, $OCHHCH_3$), 4.11 (1H, dq, *J* 9.4, 7.0 Hz, $OCHHCH_3$), 5.02 (1H, s, C5-H); ^{13}C NMR δ 173.52, 98.55, 75.70, 68.39, 51.81, 26.91, 24.54, 24.08, 15.15; MS *m/z* (relative intensity) 331 (M$^+$, 9), 329 (M$^+$, 18), 327 (M$^+$, 9), 286 ([M – OEt]$^+$, 21), 284 ([M – OEt]$^+$, 42), 282 ([M – OEt]$^+$, 21), 250 ([M – Br]$^+$, 5), 248 ([M – Br]$^+$, 5), 206 (31), 204 (32), 165 (98), 163 (100). HRMS calcd for $C_9H_{15}{}^{79}Br_2NO_2$ *m/z* 326.9470 (M$^+$) found 326.9461.

Treatment of 1-methylpyrrolidin-2-one (6b) with N*-bromosuccinimide.* A mixture of 1-methylpyrrolidin-2-one (**6b**) (230 mg, 2.32 mmol) and *N*-bromosuccinimide (826 mg, 4.64 mmol) in carbon tetrachloride

(20 ml) was heated at reflux under nitrogen, whilst irradiating with a 300 W mercury lamp, for 10 min. The cooled reaction mixture was filtered through glass wool and concentrated under reduced pressure to give an oil containing an approximately 5:2 mixture of *trans*-4,5-dibromo-1-methylpyrrolidin-2-one (**9b**) and 1-methyl-4,4,5-tribromopyrrolidin-2-one (**8b**) as judged by ^{1}H NMR spectroscopic analysis. No discrete products were isolated from this reaction mixture.

trans-4,5-Dibromo-1-methylpyrrolidin-2-one (**9b**): ^{1}H NMR δ 2.90 (3H, s, $\mathrm{NCH_3}$), 3.08 (1H, d, *J* 18.5 Hz, C3-H), 3.29 (1H, dd, *J* 18.5, 5.9 Hz, C3-H'), 4.87 (1H, d, *J* 5.9 Hz, C4-H), 6.12 (1H, s, C5-H).

1-Methyl-4,4,5-tribromopyrrolidin-2-one (**8b**): ^{1}H NMR δ 2.95 (3H, s, $\mathrm{NCH_3}$), 3.39 (1H, d, *J* 17.5 Hz, C3-H), 3.47 (1H, d, *J* 17.5 Hz, C3-H'), 6.34 (1H, s, C5-H).

trans-*4-Bromo-5-ethoxy-1-methylpyrrolidin-2-one (**11b**) and 4,4-dibromo-5-ethoxy-1-methylpyrrolidin-2-one (**10b**).* A mixture of 1-methylpyrrolidin-2-one (**6b**) (169 mg, 1.71 mmol) and *N*-bromosuccinimide (607 mg, 3.41 mmol) in carbon tetrachloride (20 ml) was heated at reflux under nitrogen, whilst irradiating with a 300 W mercury lamp, for 10 min. The reaction mixture was cooled to room temperature, dry ethanol (200 µl, 3.41 mmol) and 2,6-lutidine (200 µl, 1.72 mmol) were added and the mixture was stirred under nitrogen for 3 hr. Upon workup, as above for the similar treatment of the pyrrolidinone **6a**, the residue obtained was purified by preparative thin layer chromatography, eluting with a mixture of light petroleum and ethyl acetate (50:50), affording two products, **11b** and **10b**.

trans-4-Bromo-5-ethoxy-1-methylpyrrolidin-2-one (**11b**) as an oil (34 mg, 9%): IR (liquid film) 2976, 1712, 1262, 1068, 708 cm^{-1}; ^{1}H NMR δ 1.26 (3H, t, *J* 7.0 Hz, $\mathrm{OCH_2C}\mathit{H}_3$), 2.65 (1H, dd, *J* 17.9, 1.4 Hz, C3-H), 2.92 (3H, s, $\mathrm{NCH_3}$), 3.21 (1H, dd, *J* 17.9, 6.8 Hz, C3-H'), 3.63 (1H, dq, *J* 9.2, 7.0 Hz, $\mathrm{OC}\mathit{H}\mathrm{HCH_3}$), 3.68 (1H, dq, *J* 9.2, 7.0 Hz, $\mathrm{OCH}\mathit{H}\mathrm{CH_3}$), 4.24 (1H, ddd, *J* 6.8, 1.4, 0.9 Hz, C4-H), 4.97 (1H, d, *J* 0.9 Hz, C5-H); ^{13}C NMR δ 171.29, 97.90, 63.93, 41.64, 39.54, 27.50, 14.98; MS *m/z* (relative intensity) 223 (M$^+$, 9), 221 (M$^+$, 9), 178 ([M – OEt]$^+$, 98), 176 ([M – OEt]$^+$, 100), 150 (28), 148 (29), 142 ([M – Br]$^+$, 11); HRMS calcd for $\mathrm{C_7H_{12}{}^{79}BrNO_2}$ *m/z* 221.0051 (M$^+$), found: 221.0058.

4,4-Dibromo-5-ethoxy-1-methylpyrrolidin-2-one (**10b**) as an oil (54 mg, 11%): IR (liquid film) 2976, 1710, 1282, 1072, 752 cm^{-1}; ^{1}H NMR δ 1.32 (3H, t, *J* 7.0 Hz, $\mathrm{OCH_2C}\mathit{H}_3$), 2.93 (3H, s, $\mathrm{NCH_3}$), 3.36 (1H, d, *J* 17.6 Hz, C3-H), 3.51 (1H, d, *J* 17.6 Hz, C3-H'), 3.80 (1H, dq, *J* 9.3, 7.0 Hz, $\mathrm{OC}\mathit{H}\mathrm{HCH_3}$), 4.07 (1H, dq, *J* 9.3, 7.0 Hz, $\mathrm{OCH}\mathit{H}\mathrm{CH_3}$), 5.02 (1H, s, C5-H); ^{13}C NMR δ 168.8, 99.19, 67.16, 57.33, 52.29, 27.64, 14.89; MS *m/z* (relative intensity) 303 (M$^+$, 18.5), 301 (M$^+$, 37.5), 299 (M$^+$, 19), 258 ([M – OEt]$^+$, 49.5), 256 ([M – OEt]$^+$, 100), 254 ([M – OEt]$^+$, 50.5), 230 (9), 228 (18), 226 (9), 222 ([M – Br]$^+$, 7), 220 ([M – Br]$^+$, 7); HRMS calcd for $\mathrm{C_7H_{11}{}^{79}Br_2NO_2}$ *m/z* 298.9157 (M$^+$), found 298.9153.

trans-*4-Bromo-1-methyl-5-phenylthiopyrrolidin-2-one (**12**) and 1-phenylthiomethylpyrrolidin-2-one (**13**).* A mixture of 1-methylpyrrolidin-2-one (**6b**) (195 mg, 1.97 mmol), *N*-bromosuccinimide (740 mg, 4.16 mmol) and a catalytic amount of AIBN in carbon tetrachloride (35 ml) was heated at reflux under nitrogen, whilst irradiating with a 300 W mercury lamp, for 5 min. The reaction mixture was immediately cooled to room temperature, thiophenol (410 µl, 3.99 mmol) and 2,6-lutidine (460 µl, 3.95 mmol) were added and the mixture was stirred at room temperature under nitrogen for 2 hr. The residue obtained upon workup was purified by preparative thin layer chromatography, eluting with a mixture of light petroleum and ethyl acetate (50:50) and afforded two products, **12** and **13**.

trans-4-Bromo-1-methyl-5-phenylthiopyrrolidin-2-one (**12**) as an oil (139 mg, 25%): IR (liquid film)

3054, 2934, 1722, 1584, 1476 cm^{-1}; ^{1}H NMR δ 2.38 (1H, dd, *J* 18.4, 6.5 Hz, C3-H), 2.51 (1H, dd, *J* 18.4, 1.2 Hz, C3-H'), 3.06 (3H, s, NCH_3), 4.53 (1H, ddd, *J* 6.5, 1.2, 1.1 Hz, C4-H), 4.98 (1H, d, *J* 1.1 Hz, C5-H), 7.23 - 7.51 (5H, m, ArH); ^{13}C NMR δ 171.08, 134.55, 134.15, 129.60, 129.36, 77.27, 44.63, 40.20, 28.20; MS *m/z* (relative intensity) 287 (M$^+$, 3), 285 (M$^+$, 3), 205 ([M – HBr]$^+$, 45), 177 ([M – PhSH]$^+$, 98), 175 ([M – PhSH]$^+$, 100), 149 (50), 147 (51), 108 (71); HRMS calcd for $C_{11}H_{12}{}^{79}BrNOS$ *m/z* 284.9823 (M$^+$), found 284.9811.

1-Phenylthiomethylpyrrolidin-2-one (**13**) as an oil (10.4 mg, 3%): IR (liquid film) 3054, 2926, 1696, 1584, 1488 cm^{-1}; ^{1}H NMR δ 1.96 (2H, tt, *J* 8.1, 7.1 Hz, C4-H_2), 2.30 (2H, t, *J* 8.1 Hz, C3-H_2), 3.44 (2H, t, *J* 7.1 Hz, C5-H_2), 4.77 (2H, s, NCH_2S), 7.27 (3H, m, ArH), 7.44 (2H, m, ArH); ^{13}C NMR δ 174.85, 133.51, 130.87, 129.01, 127.16, 46.65, 45.86, 30.80, 17.54; MS *m/z* (relative intensity) 207 (M$^+$, 14), 98 ([M – PhS]$^+$, 100), 70 (23); HRMS calcd for $C_{11}H_{13}NOS$ *m/z* 207.0718 (M$^+$), found 207.0721. Anal. Calcd for $C_{11}H_{13}NOS$: C, 63.74; H, 6.32; N, 6.75. Found: C, 63.66; H, 6.52; N, 7.02.

trans-*4-Bromo-5-ethoxy-1-(*p*-methoxyphenyl)pyrrolidin-2-one (11c).* A mixture of 1-(*p*-methoxyphenyl)-pyrrolidin-2-one (**6c**) (92.3 mg, 0.48 mmol), *N*-bromosuccinimide (100 mg, 0.56 mmol) and a catalytic amount of AIBN in carbon tetrachloride and dichloromethane (8:1, 18 ml) was heated at reflux under nitrogen, whilst irradiating with a 300 W mercury lamp, for 5 min. The reaction mixture was cooled to room temperature, dry ethanol (60 µl, 1.02 mmol) and 2,6-lutidine (120 µl, 1.03 mmol) were added and the mixture was stirred at room temperature under nitrogen for 2 hr. The residue obtained upon workup was purified by preparative thin layer chromatography, eluting with ethyl acetate, to give *trans*-4-bromo-5-ethoxy-1-(*p*-methoxyphenyl)pyrrolidin-2-one (**11c**), the alcohol **14**, the 5-succinimidopyrrolidinone **15** and unreacted starting material **6c** (30 mg, 33%).

trans-4-Bromo-5-ethoxy-1-(*p*-methoxyphenyl)pyrrolidin-2-one (**11c**) as an oil which solidified on standing (58.1 mg, 38%): m.p. 53°C; b.p. 105°C/0.02mm (block); IR (liquid film) 2972, 1722, 1610, 1514, 1250, 1066, 700 cm^{-1}; ^{1}H NMR δ 1.19 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 2.82 (1H, dd, *J* 18.2, 1.0 Hz, C3-H), 3.42 (1H, dd, *J* 18.2, 6.4 Hz, C3-H'), 3.54 (1H, dq, *J* 9.3, 7.0 Hz, OC*H*HCH$_3$), 3.59 (1H, dq, *J* 9.3, 7.0 Hz, OCH*H*CH$_3$), 3.81 (3H, s, OCH_3), 4.35 (1H, ddd, *J* 6.4, 1.0, 0.9 Hz, C4-H), 5.27 (1H, d, *J* 0.9 Hz, C5-H), 6.93 (2H, m, ArH), 7.34 (2H, m, ArH); ^{13}C NMR δ 171.29, 158.30, 129.35, 125.98, 114.34, 98.37, 64.52, 55.40, 42.57, 40.18, 15.20; MS *m/z* (relative intensity) 315 (M$^+$, 84), 313 (M$^+$, 86), 269 ([M – EtOH]$^+$, 42), 267 ([M – EtOH]$^+$, 43), 234 ([M – Br]$^+$, 14), 203 (36), 199 (100); HRMS calcd for $C_{13}H_{16}{}^{79}BrNO_3$ *m/z* 313.0314 (M$^+$), found 313.0306.

trans-4-Bromo-5-hydroxy-1-(*p*-methoxyphenyl)pyrrolidin-2-one (**14**) as an oil (19.7 mg, 14%): IR ($CDCl_3$) 3400, 1704, 1610, 1514, 1254, 1034 cm^{-1}; ^{1}H NMR δ 1.77 (1H, broad, OH), 2.74 (1H, dd, *J* 18.4, 1.4 Hz, C3-H), 3.36 (1H, dd, *J* 18.4, 6.5 Hz, C3-H'), 3.89 (3H, s, OCH_3), 4.23 (1H, ddd, *J* 6.5, 1.4, 1.2 Hz, C4-H), 5.51 (1H, d, *J* 1.2 Hz, C5-H), 6.90 (2H, m, ArH), 7.32 (2H, m, ArH); ^{13}C NMR δ 171.95, 158.39, 129.02, 125.91, 114.40, 92.41, 55.45, 44.70, 40.85; MS *m/z* (relative intensity) 287 (M$^+$, 54), 285 (M$^+$, 55), 269 ([M – H_2O]$^+$, 98), 267 ([M – H_2O]$^+$, 100), 254 (29.5), 252 (30), 205 ([M – HBr]$^+$, 23), 160 (61); HRMS calcd for $C_{11}H_{12}{}^{79}BrNO_3$ *m/z* 285.0001 (M$^+$), found 284.9992.

1-(*p*-Methoxyphenyl)-5-(1-succinimido)pyrrolidin-2-one (**15**) as a white crystalline solid (9.7 mg, 7%): m.p. 77°C; IR (CH_2Cl_2) 2960, 1780, 1712, 1610, 1514 cm^{-1}; ^{1}H NMR δ 2.23 (1H, m), 2.62 (2H, m), 2.55 (4H, s), 3.05 (1H, m), 3.78 (3H, s, OCH_3), 6.20 (1H, dd, *J* 8.9, 2.2 Hz, C5-H), 6.87 (2H, m, ArH), 7.22 (2H, m, ArH); ^{13}C NMR δ 176.09, 174.62, 158.03, 128.24, 125.83, 114.41, 65.85, 55.34, 30.58, 27.74, 22.57; MS *m/z* (relative intensity) 288 (M$^+$, 100), 233 (33), 190 ([M – $C_4H_4NO_2$]$^+$, 38), 134

(52), 123 (53); HRMS calcd for $C_{15}H_{16}N_2O_4$ *m/z* 288.1110 (M^+), found 288.1113.

trans-*5-Allyloxy-4-bromo-1-(*p*-methoxyphenyl)pyrrolidin-2-one (**16**).* A mixture of 1-(*p*-methoxyphenyl)pyrrolidin-2-one (**6c**) (371 mg, 1.94 mmol), *N*-bromosuccinimide (380 mg, 2.13 mmol) and a catalytic amount of AIBN in carbon tetrachloride and dichloromethane (6:1, 55 ml) was heated at reflux under nitrogen, whilst irradiating with a 300 W mercury lamp, for 10 min. The reaction mixture was then cooled to room temperature, allyl alcohol (3 ml, excess) and 2,6-lutidine (450 µl, 3.86 mmol) were added and the mixture was stirred at room temperature under nitrogen overnight. Upon workup, preparative thin layer chromatography of the residue, eluting with a mixture of ethyl acetate and light petroleum (50:50), afforded *trans*-5-allyloxy-4-bromo-1-(*p*-methoxyphenyl)pyrrolidin-2-one (**16**) (181 mg, 29%), the alcohol **14** (46 mg, 8%), unreacted starting material **6c** (177 mg, 48%) and a minor amount of the 5-succinimidopyrrolidinone **15**.

A greater yield of **16** was obtained from **6c** when the pyrrolidinone **6c** was treated with excess *N*-bromosuccinimide. Thus, 1-(*p*-methoxyphenyl)pyrrolidin-2-one (**6c**) (108 mg, 0.56 mmol), was treated with *N*-bromosuccinimide (502 mg, 2.82 mmol) in the presence of a catalytic amount of AIBN in carbon tetrachloride and dichloromethane (6:1, 35 ml) as described above. The reaction mixture was then cooled to room temperature, allyl alcohol (1 ml, excess) and 2,6-lutidine (130 µl, 1.12 mmol) were added and the mixture was stirred at room temperature under nitrogen for 4.5 hr. Upon workup, chromatography of the residue, as before, afforded *trans*-5-allyloxy-4-bromo-1-(*p*-methoxyphenyl)pyrrolidin-2-one (**16**) (87.3 mg, 47%), the alcohol **14** (14 mg, 9%), unreacted starting material **6c** (33.8 mg, 31%) and a minor amount of the 5-succinimidopyrrolidinone **15**.

trans-5-Allyloxy-4-bromo-1-(*p*-methoxyphenyl)pyrrolidin-2-one (**16**) as an oil: IR ($CDCl_3$) 3020, 1714, 1612, 1512, 1224 cm^{-1}; ^1H NMR δ 2.82 (1H, dd, *J* 18.2, 0.9 Hz, C3-H), 3.43 (1H, dd, *J* 18.2, 6.3 Hz, C3-H'), 3.81 (3H, s, OCH_3), 4.00 (1H, dddd, *J* 12.8, 5.7, 1.5, 1.3 Hz, C*H*HCH=CH_2), 4.04 (1H, dddd, *J* 12.8, 5.7, 1.5, 1.3 Hz CH*H*CH=CH_2), 4.37 (1H, ddd, *J* 6.3, 0.9, 0.8 Hz, C4-H), 5.20 (1H, ddt, *J* 10.5, 1.4, 1.3 Hz, CH=C*H*H), 5.22 (1H, dtd, *J* 17.1, 1.5, 1.4 Hz, CH=CH*H*), 5.33 (1H, d, *J* 0.8 Hz, C5-H), 5.81 (1H, ddt, *J* 17.1, 10.5, 5.7 Hz, C*H*=CH_2), 6.94 (2H, m, ArH), 7.33 (2H, m, ArH); ^{13}C NMR δ 171.36, 158.31, 132.90, 129.53, 126.12, 118.29, 114.28, 97.67, 69.64, 55.32, 42.45, 40.02; MS *m/z* (relative intensity) 327 (M^+, 13.5), 325 (M^+, 14), 270 ($[M - C_3H_5O]^+$, 17.5), 268 ($[M - C_3H_5O]^+$, 18), 245 (M – HBr],$^+$ 10), 189 (100); HRMS calcd for $C_{14}H_{16}{}^{79}BrNO_3$ *m/z* 325.0314 (M^+), found 325.0299.

*(3*SR*,3a*RS*,6a*SR*)-6-(*p*-Methoxyphenyl)-3-methyl-5-oxotetrahydrofuro[2,3-*b*]pyrrolidine (**17**).* A solution of tri-*n*-butyltin hydride (475 µl, 1.77 mmol) and a catalytic amount of AIBN in dry benzene (15 ml) was added dropwise with stirring, over 2.5 hr to a solution of *trans*-5-allyloxy-4-bromo-1-(*p*-methoxyphenyl)-2-oxopyrrolidine (**16**) (384 mg, 1.18 mmol) in dry benzene (20 ml) heated at reflux. After the addition was complete the reaction mixture was further heated at reflux under nitrogen, overnight. The reaction mixture was then evaporated under reduced pressure and preparative thin layer chromatography of the resultant residue, gradient eluting with a mixture of light petroleum and ethyl acetate gave an oil which solidified on standing. Subsequent recrystallisation from dichloromethane / light petroleum afforded (3*SR*,3a*RS*,6a*SR*)-6-(*p*-methoxyphenyl)-3-methyl-5-oxotetrahydrofuro[2,3-*b*]pyrrolidine (**17**) as a white crystalline solid (111 mg, 38%): m.p. 95°C; IR (CH_2Cl_2) 2960, 1700, 1612, 1514, 1036 cm^{-1}; ^1H NMR δ 1.06 (3H, d, *J* 6.9 Hz, CCH_3), 2.49 (1H, dddq, *J* 11.3, 8.0, 6.9, 6.8 Hz, C3-H), 2.53 (1H, dd, *J* 18.2, 10.0 Hz, C4-H), 2.62 (1H, dd, *J* 18.2, 6.4 Hz, C4-H'), 3.02 (1H, dddd, *J* 10.0, 8.0, 6.4, 6.2 Hz, C3a-H), 3.44 (1H, dd, *J* 11.3, 8.8 Hz, C2-H), 3.80 (3H, s, OCH_3), 3.98 (1H, dd, *J* 8.8, 6.8 Hz, C2-H'), 5.78 (1H, d, *J* 6.2 Hz,

C6a-H), 6.91 (2H, m, ArH), 7.48 (2H, m, ArH); ^{13}C NMR δ 173.43, 157.58, 130.62, 124.71, 114.10, 95.91, 71.50, 55.36, 38.58, 36.01, 30.12, 10.97; HRMS calcd for $C_{14}H_{17}NO_3$ *m/z* 247.1208 (M^+), found 247.1216.

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