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# Stereoselective oxygenation of bicyclic lactams

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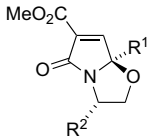
**Abstract**—Stereoselective syntheses of the epoxy and diol derivatives of a bicyclic lactam derived from pyroglutamic acid are reported, and their reactivity is discussed.


Pyrrolidines are widely occurring structural sub-units in natural products, and recently hydroxylated examples have begun to emerge as an important structural subtype with diverse biological activity. Examples include pramanicin, an antibiotic and antifungal agent,[1] epolactaene, a nerve growth factor,[2] anisomycin, an antiprotozoal and antifungal agent,[3] plakoridine, a cytoxic agent[4] and polyhydroxylated pyrrolidine and pyrrolizidine alkaloids such as the broussonetines[5] and radicamines,[6] which are highly effective competitive glycosidase inhibitors. Aside from the obvious route for the synthesis of these compounds from carbohydrate precursors, one possibility is the introduction of oxygen functionality onto a pre-existing lactam ring. Barratt et al. in their synthesis of pramanicin achieved this indirectly by introduction and subsequent interconversion of silicon functionality.[7] Meyers et al. have demonstrated that direct epoxidation of chiral unsaturated lactams of type **1** using NMO in excellent yield is possible provided that the alkene is also activated with an ester function (Fig. 1).[8] Although the epoxidation[9,10] of unactivated lactam **2a** to give **3a** has also been previously reported, carefully optimised reaction conditions were required for successful conversion.[11] Surprisingly, no investigation of similar reactions of the activated system **2b** have been made, although conjugate addition of carbon[12,13] and nitrogen[14,15] nucleophiles have been described, and this communication reports our findings in this regard.




**1** $R^1$= Ph, Me; $R^2$=Ph, iPr

**Figure 1.**

Application of the Herdeis conditions (*t*-BuOOH/$n$Bu$_4$NF/$K_2CO_3$/DMF)[10] to the activated lactam **2b** gave only a 20% yield of the expected product **3b**, and examination of a large number of alternative conditions to improve the yield (e.g., NMO,[8] alkaline hydrogen peroxide,[16] hydrogen peroxide–Triton B,[17] and hydrogen peroxide–*t*-BuLi[18]) were unsuccessful (Scheme 1). Frustrated by this lack of success, a series of experiments was conducted in which lactam **2b** was treated with hydrogen peroxide in dichloromethane, and buffered at pH 3, 5, 7 and 9, with vigorous stirring for 24 h; at pH 9 (sodium tetraborate–HCl), it was found that yields of epoxide **3b** of up to 70% were readily obtained.[19] At lower pH, the epoxidation reaction was markedly slower and at pH 3 the sole product was dimer **4**. These results were surprising, since we had found earlier that enone **2b** rapidly dimerised on storage[20] or under basic conditions[14] to give dimer **4**. The stereostructure of **3b** was initially established by NOE analysis (which exhibited clear enhancement in the series H-2 → H-4$_{endo}$ → H-6, indicating their *cis*-, *endo*-relationship, see Fig. 2) and later confirmed by X-ray analysis.[21] This compound was readily deprotected to give pyroglutaminol **5** in quantitative yield.

Investigation of the ring opening chemistry of epoxide **3b** indicated an unexpected lack of reactivity under acidic,[22–24] nucleophilic (PhSeNa, AcOH, EtOH)[25] or

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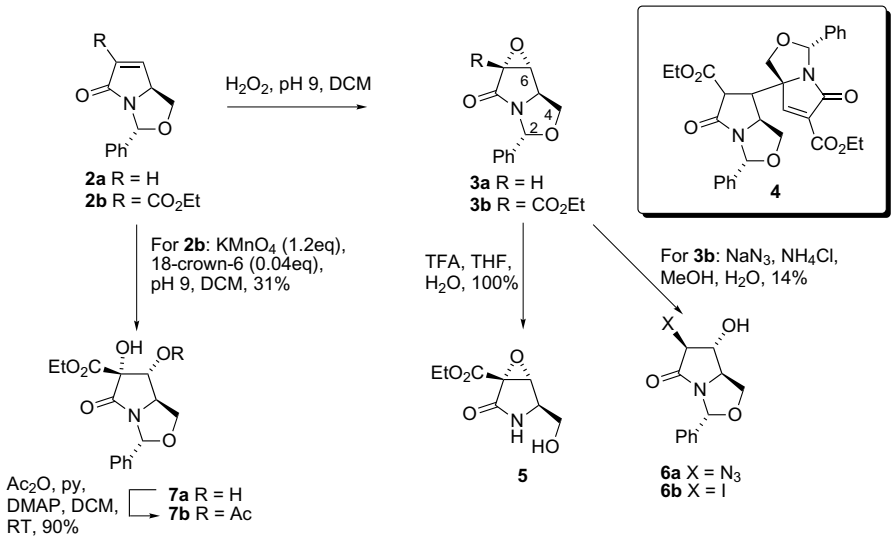


**Scheme 1.**

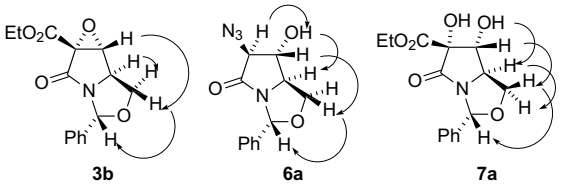


**Figure 2.**

reductive ($SmI_2$[9,10] or $LiAlH_4$[26]) conditions, but sodium azide/methanol/water gave the *trans*-azido alcohol **6a** in low yield (14%), whose stereochemistry was confirmed by NOE studies (Fig. 2); this material was the same as that obtained from reaction of epoxide **3a** under previously reported identical reaction conditions.[10] Similar lack of reactivity of epoxides of this type has been previously reported: the nucleophilic opening of the epoxide **3a** is difficult, and apart from the azide opening outlined above, could only be achieved with NaI/NaOAc/HOAc to give iodide **6b**.[10] The formation of epoxides in the reactions of related bicyclic piperidinones has also been reported by Amat et al. who also found that the epoxide exhibited low reactivity to nucleophilic opening.[27]

Attention was then turned towards the synthesis of dihydroxylated lactam **7a**. There is literature precedent for the *cis*-dihydroxylation of lactam **2a** using osmium tetroxide under standard conditions.[11] However, these conditions failed with lactam **2b**, and it was desirable to identify suitable reagents that could be used with the same conditions that had proved so successful for the epoxidation reaction (DCM buffered at pH 9). One such reagent is potassium permanganate,[28] and application of this reagent in conjunction with 18-crown-6 ether yielded the required dihydroxylated product **7a** in 30% yield.[29] The stereochemistry was initially established by NOE analysis in dry $d_6$-DMSO, which enabled resolution of the C(6) and C(7) hydroxyl groups (Fig. 2) and confirmed by X-ray analysis of the white crystals obtained after purification by column chromatography.[21] The diol **7a** was successfully acetylated with acetic anhydride to give the monoacetylated product **7b**,[29] as evidenced by a significant downfield shift of C(6)H (to $\delta$ 5.17 from $\delta$ 4.34 in the starting material) but oxidation of **7a** to the corresponding ketone proved not to be possible under several conditions (Swern, PCC and $RuCl_3/NaIO_4$), perhaps due to steric hindrance at this position.

Thus, diastereocontrolled oxygenation of the ring of bicyclic lactams derived from pyroglutamic acid has proved to be possible, leading to highly functionalised derivatives, although these products have displayed unexpected reactivity.

## Acknowledgements

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19. Procedure for (2*R*,5*R*,6*R*,7*R*)-6,7-epoxy-7-ethoxycarbonyl-8-oxo-2-phenyl-1-aza-3-oxabicyclo[3.3.0]octane **3b**: To a solution of enone **2b** (1.90 g, 7.0 mmol) in DCM (200 mL) were added pH 9 buffer solution (200 mL) and hydrogen peroxide (4.00 g, 35 mmol, 35% aq), and the biphasic mixture was stirred rapidly for 16 h. The organic layer was separated, dried ($MgSO_4$), filtered and concentrated in vacuo. The crude was purified by flash column chromatography eluting with EtOAc–petrol (1:1) to yield the title compound as white crystals (1.39 g, 69%). $R_f = 0.34$ (petrol–EtOAc (1:1)); $[\alpha]_D^{22} = +20.9$ ($c = 1.0$ in $CHCl_3$); mp 138–140 °C; $\nu_{max}/cm^{-1}$ (film) 1751 (br, 2×C=O); $\delta_H$ (400 MHz, DMSO-$d_6$) 1.25 (3H, t, *J* 7.1, C$H_3$CH$_2$), 3.57 (1H, dd, *J* 8.5, 1.0, C(4)$H_{endo}$), 4.19–4.25 (1H, m, C(4)$H_{exo}$), 4.25–4.29 (2H, m, CH$_3$ C$H_2$), 4.30–4.35 (1H, m, C(5)*H*), 4.83 (1H, s, C(6)*H*), 6.14 (1H, s, C(2)*H*), 7.33–7.44 (5H, m, Ar*H*); $\delta_C$ (100.6 MHz, DMSO-$d_6$) 14.76 (OCH$_2$*C*H$_3$), 58.78 (*C*(7)), 59.44 (*C*(5)), 62.87 (O*C*H$_2$CH$_3$), 63.91 (*C*(6)), 66.61 (*C*(4)), 88.71 (*C*(2)), 126.83, 129.35, 129.64, 139.26 (Ar*C*), 163.51, 171.26 (*C*=O); *m/z* (APCI$^+$) 290 ([M+H]$^+$, 100%); HRMS (ES$^+$) 290.1023, $C_{15}H_{16}NO_5$ requires 290.1028.
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21. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated Mo K$_\alpha$ radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package.[31] The structure was solved using the direct-methods program SIR92,[32] which located all nonhydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite.[33]
Crystal data and data collection parameters for compound **3b**: $C_{15}H_{15}NO_5$, $T = 298$ K, $M = 289.29$, orthorhombic, $a = 6.3547(1)$, $b = 7.7537(2)$, $c = 28.1695(6)$ Å, $V = 1388.0$ Å$^3$. Space group $P\ 2_1\ 2_1\ 2_1$, $Z = 4$, $D_x = 1.384$ mg m$^{-3}$, $\mu = 0.105$ mm$^{-1}$. The compound was crystallised from EtOAc–petrol. Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-232469. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or email: deposit@ccdc.cam.ac.uk].
Crystal data and data collection parameters for compound **7a**: $C_{15}H_{17}NO_6$, $T = 150$ K, $M = 307.30$, orthorhombic, $a = 5.8907(2)$, $b = 10.4767(4)$, $c = 23.5621(8)$ Å, $V = 1454.1$ Å$^3$. Space group $P\ 2_1\ 2_1\ 2_1$, $Z = 4$, $D_x = 1.404$ mg m$^{-3}$, $\mu = 0.109$ mm$^{-1}$. The compound was crystallised from EtOH. Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC232468. Copies of the data can be obtained,free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or email: deposit@ccdc.cam.ac.uk].
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29. Procedure for (2*R*,5*R*,6*R*,7*R*)-7-ethoxycarbonyl-8-oxo-2-phenyl-6,7-dihydroxy-1-aza-3-oxabicyclo[3.3.0]octane **7a**: To enone **2b** (245 mg, 0.90 mmol) in DCM (20 mL) was added pH 9 buffer solution (20 mL), potassium permanganate (221 mg, 1.08 mmol) and 18-crown-6 ether (12 mg, 0.04 mmol), and the biphasic mixture was stirred rapidly at room temperature for 3 h. Sodium sulfite solution was added (satd aq 5.0 mL), and the mixture was neutralised with citric acid solution (5% aq). The dark brown mixture was then allowed to stand, with occasional stirring, until all the precipitate had dissolved, leaving a colourless mixture (1–3 days). The whole mixture was extracted with DCM (3×30 mL) and EtOAc (3×30 mL), the organics were combined, dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash column chromatography eluting with EtOAc–Petrol (1:1) to yield the title compound as white crystals (110 mg, 31%). $R_f = 0.19$ (EtOAc–Petrol (1:1); $[\alpha]_D^{22} = +127$ ($c = 1.0$ in $CHCl_3$); mp 109–113 °C; $\nu_{max}/cm^{-1}$ (film) 3400 (br w, OH), 1750 (br s, 2×C=O); $\delta_H$ (500 MHz, DMSO-$d_6$) 1.21 (3H, t, *J* 4.0, OC$H_3$CH$_2$), 3.84–3.88 (1H, m, C(4)$H_{endo}$), 4.03–4.07 (1H, m, C(5)*H*), 4.18–4.22 (1H, m, OCH$_3$C$H_2$), 4.23–4.29 (1H, C(4)$H_{exo}$), 4.32–4.36 (1H, m, C(6)*H*), 5.92 (1H, d, *J* 6.4, C(6)O*H*), 6.17 (1H, s, C(2)*H*), 6.65 (1H, s, C(7)O*H*), 7.36–7.45 (5H, m, Ar*H*); $\delta_C$ (125.7 MHz, DMSO-$d_6$) 15.0 (O*C*H$_3$CH$_2$), 62.1 (OCH$_3$*C*H$_2$), 63.6 (*C*(5)), 70.2 (*C*(4)), 77.3 (*C*(6)), 84.9 (*C*(2)), 86.9 (*C*(7)), 127.1, 129.3, 129.7, 130.1 (Ar*C*), 171.1, 172.7 (*C*=O); *m/z* (APCI$^+$) 308 ([M+H]$^+$, 100%); HRMS (EI$^+$) 308.1136, $C_{15}H_{18}NO_6$ ([M+H]$^+$) requires 308.1134. Procedure for (2*R*,5*R*,6*R*,7*R*)-6-acetoxy-7-ethoxycarbonyl-8-oxo-2-phenyl-7-hydroxy-1-aza-3-oxa-bicyclo[3.3.0] octane **7b**: Diol **7a** (30 mg, 0.098 mmol) was stirred overnight with DCM (10 mL), acetic anhydride (9.2 μL, 0.098 mmol), pyridine (15.8 μL, 0.196 mmol) and DMAP (11.9 mg, 0.98 mmol). The reaction mixture was washed with pH 5 buffer solution, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash column chromatography eluting with EtOAc–petrol (1:1) to yield the title compound as a colourless oil. $R_f = 0.25$ (petrol–EtOAc

(1:1)); $[\alpha]_D^{22} = +2.9$ ($c = 0.025$ in $CHCl_3$); $\nu_{max}/cm^{-1}$ (film) 3400 (br s, OH), 1610 (br s, 2×C=O); $\delta_H$ (400 MHz, DMSO-$d_6$) 1.23 (3H, t, $J$ 7.0, $OCH_2$ $CH_3$), 2.06 (3H, s, $COCH_3$), 4.82–4.91 (1H, m, C(4)$H_{endo}$), 4.17–4.22 (2H, m, $OCH_2$ $CH_3$), 4.30–4.35 (2H, m, C(5)*H*, C(4)$H_{exo}$), 5.17 (1H, d, $J$ 5.5, C(6)*H*), 6.16 (1H, s, C(2)*H*), 7.07 (1H, s, O*H*), 7.34–7.42 (5H, m, Ar*H*); $\delta_C$ (100.6 MHz, DMSO-$d_6$) 14.76 ($OCH_2CH_3$), 21.22 ($COCH_3$), 61.64 (*C*(5)), 62.29 ($OCH_2CH_3$), 70.63 (*C*(4)), 76.38 (*C*(6)), 83.59 (*C*(7)), 87.24 (*C*(2)), 127.22, 129.40, 138.63 (Ar*C*), 169.80, 170.72, 170.90 (C=O); *m*/*z* ($APCI^+$) 350 ($[M+H]^+$, 35%); HRMS ($EI^+$) 350.1240, $C_{17}H_{20}NO_7$ ($[M+H]^+$) requires 350.1240.

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