Synthesis and Antibacterial Activity of Bicyclic Lactam–Lactones

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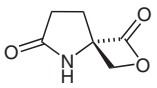
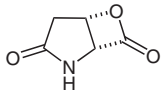
Abstract: The synthesis of a lactam–lactone bicyclic system containing a pyroglutamate subunit proceeds to give the fused lactone system, which is favoured over the spirocyclic lactone alternative. These systems display no or weak antibacterial activity against the test organisms *S. aureus* and *E. coli*.

Key words: heterocycles, natural products, cyclisation, antibiotics, lactams

Spirocyclic and fused lactone–lactam systems **1** and **2** (Figure 1) have been of recent interest, both as a result of their occurrence in the salinosporamide,[1] cinnabarimide[2] and oxazolomycin[3] natural products, and of their conformationally well-defined structures, providing useful templates for drug design (e.g. MI-219 which possesses p53:MDM2 inhibitory activity[4]). Methodology is now well established to access spirocyclic[5] and fused β-lactone–lactam systems,[1,6] and given the ease with which it is possible to prepare highly functionalised tetramates using some of our recently reported methodology,[7] it was of interest to examine the possibility of direct lactone formation in a highly functional pyroglutamate nucleus; we have already made use of modified tetramates for the preparation of mimics of oxazolomycin.[8]



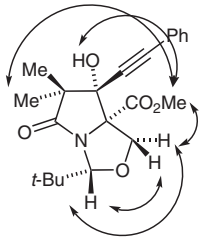
2-oxa-5-azaspiro[3.4]octane-1,6-dione (**1**)



6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione (**2**)

Figure 1

We recently reported that pyroglutamate **3a** (Scheme 1) is readily available by kinetically controlled *endo*-delivery of a dithiane anion to the parent tetramate,[7] and this outcome is different from that obtained by direct aldol cyclisation.[9] It was found that similar *endo*-phenylacetylide delivery also generates the pyroglutaminol **3b** in good yield (92%), the stereochemistry of which was established by NOE analysis (Figure 2) and confirmed by single crystal X-ray analysis (Figure 3).[10] Similar highly chemoselective acetylide additions have been reported.[11] Deprotection of the oxazolidine ring of each of **3a**,**b** using Corey–Reichard conditions[12] gave alcohols **4a**,**c** in excellent yields, and the stereochemistry of **4c** was established by single crystal X-ray crystallography (Figure 3).[10] Ester hydrolysis (LiOH, THF, H_2O, MeOH) of **4a** to give acid **4b**, which could be easily isolated by acid-base extraction in highly pure form, was followed by β-lactone formation using tosyl chloride–pyridine conditions. Although two possible modes of cyclisation were possible, only fused bicyclic product **5a** and not the alternative spirocyclic product was obtained, although their calculated enthalpies are similar at –115.1 kcal/mol and –118.4 kcal/mol, respectively (Spartan), and after optimisation, yields were up to 80%.[13] That β-lactone formation had been achieved was clearly indicated from IR and ^{13}C NMR analysis (ν = 1835 cm^{-1} and δ = 167.5 ppm), but unequivocal assignment of selectivity was possible only with successful characterisation of lactone **5a** by single crystal X-ray analysis (Figure 3).[10] It was found that lactam **5a** could be readily acylated by reaction with acetyl chloride and triethylamine to give **5b** in 75% yield or methylated using neat methyl iodide and caesium carbonate to give the *N*-methyl derivative **5c** in quantitative yield, confirmed by IR absorptions at 1810, 1716 and 1689 cm^{-1}. The preference for the formation of the fused β-lactone product in this case is likely to be due to the conformational constraint which places the reacting carboxylic acid and alcohol functions in close proximity.



3b

Figure 2

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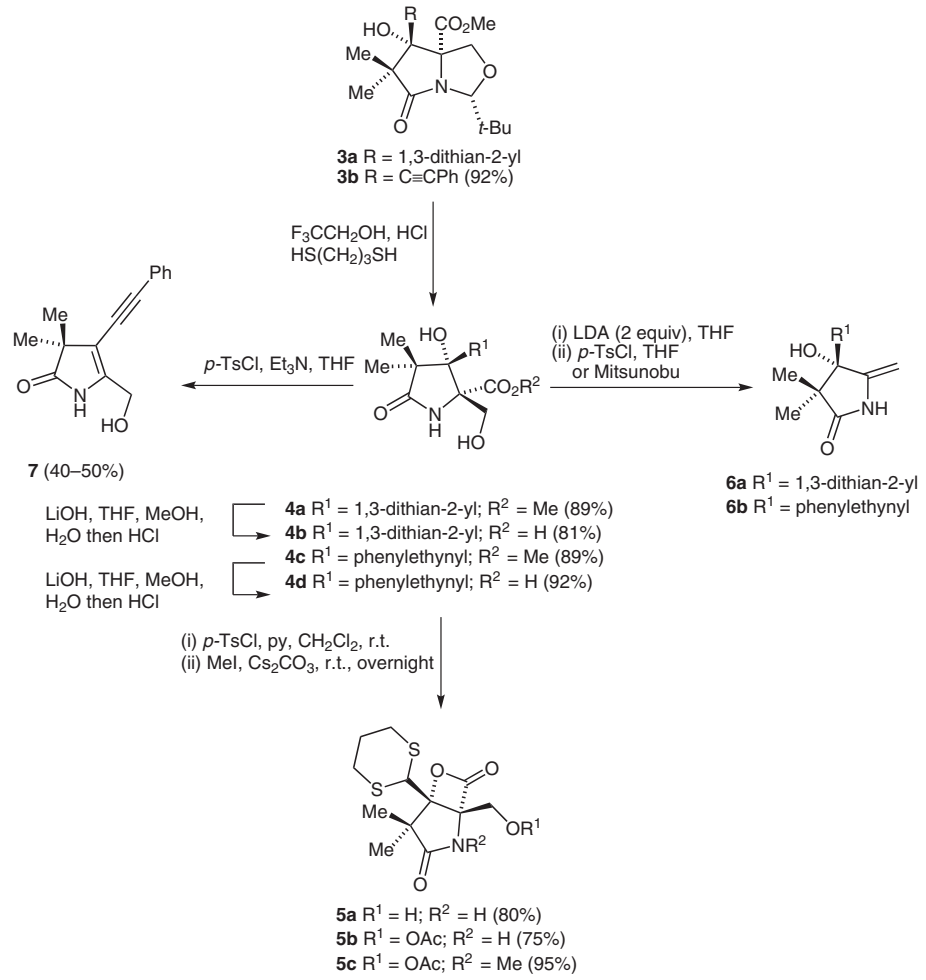

Scheme 1

However, of interest was that application of this sequence to the corresponding phenylethynyl derivative **4c** gave no isolable lactone products; thus hydrolysis of ester **4c** and subjection of the product **4d** to the tosyl chloride–pyridine conditions gave only enyne **7** in yields of 40–50%, possibly arising from transient formation of the desired fused β-lactone followed by collapse with loss of carbon dioxide, although another route is by direct decarboxylation–elimination of the expected tosyloxy intermediate, without β-lactone formation. In an attempt to force the desired cyclisation, double deprotonation of **4b** and **4d** with two equivalents of LDA followed by reaction with one equivalent of TsCl gave not the desired product, but the enamides **6a** and **6b**, respectively. An attempted cyclisation of **4b** by intramolecular Mitsunobu reaction (Ph_3P, DEAD or DIAD) gave alkene **6a**; however, application of this sequence to **4d** gave only a complex mixture of products. Neither **6a** nor **6b** were stable nor could they be isolated

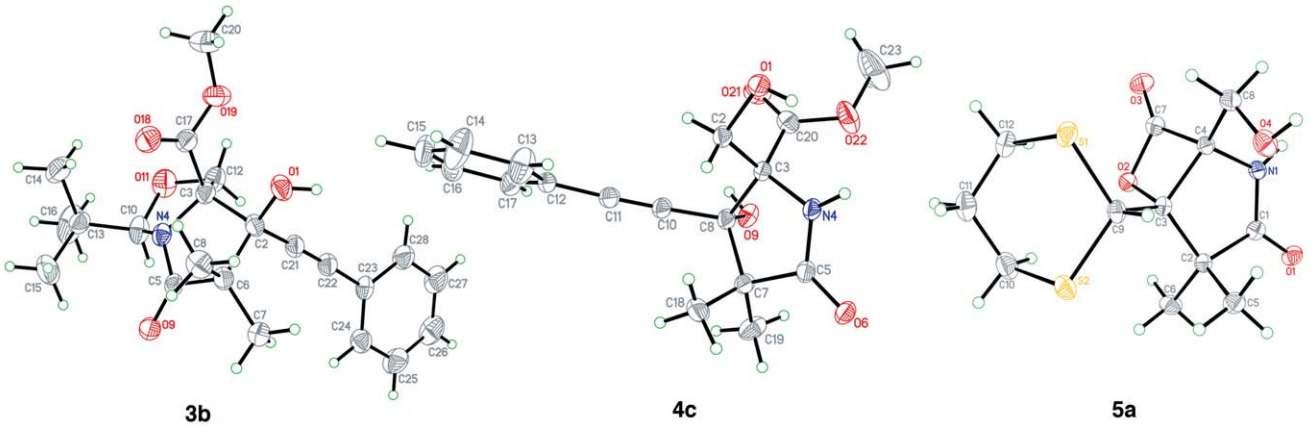

Figure 3 Thermal ellipsoid plots (ORTEP-3) at 40% probability level for compounds **3b**, **4c** and **5a**

Table 1 Cheminformatic and Bioactivity Data for Selected Compounds

Compound	cLogP[a]	PSA[a]	%PSA[a]	MSA[a]	CMR[a]	Polarisability[a]	Bioactivity[b]	
							S. aureus	*E. coli*
4a	0.32	95.9	20.4	469.5	79.5	32.0	inactive	inactive
4b	0.16	106.9	24.7	433.6	74.7	30.6	inactive	–
4c	1.1	95.9	20.9	458.6	81.3	32.7	inactive	weakly active
4d	0.9	106.9	25.3	422.2	76.5	30.6	inactive	–
5a	0.85	75.6	18.6	407.4	73.0	29.5	inactive	weakly active
5b	1.31	81.7	17.3	470.8	82.2	33.3	inactive	inactive

[a] cLogP, polar surface area parameter (PSA), calculated molecular refractivity (CMR) and molecular surface area (MSA) were calculated using Marvin;[15] %PSA = (PSA/MSA) × 100%.
[b] Inhibition by hole-plate bioassay using 100 μL of a 4 mg/mL solution (DMSO).

in pure form, and evidence for their formation came from NMR spectroscopic (methylene resonances in the region δ = 5.5–6.5 ppm) and mass spectrometric data.

Calculation of some cheminformatic parameters,[14] including polarisability, calculated molecular refractivity (CMR), cLogP, polar surface area (PSA), molecular surface area (MSA) and molecular volume, was made using Marvin (www.chemaxon.org, accessed via chemicalize.org),[15] and the relevant data are included in Table 1. The cLogP values (0.32–1.3) confirm the hydrophilic character of all compounds and the van der Waals molecular surface area (MSA) is in the range of 405–470, as would be expected from their common structural skeleton. The CMR, polarisability and %PSA parameters are in the range of 73–83, 30–34, and 17–25%, respectively, consistent with a tightly defined library. No compounds exhibited activity against *S. aureus*, and only **4c** and **5a** were weakly active against *E. coli*. We recently reported two different tetramate libraries which exhibited activity against *E. coli* possessing cLogP and %PSA values of 2.3 ± 0.9 and 16.5 ± 3.0, and –0.6 ± 0.6 and 26.2 ± 4.1 respectively.[16] Of interest is that the weakly active compounds **4c** and **5a** lie outside both of these ranges, and this may account for their low activity; noteworthy is the lack of activity of **5b**, and this suggests that the β-lactone itself is insufficient for the introduction of antibacterial activity in these systems. This observation is consistent with our recently reported results in which we demonstrated that although simple tetramates do not exhibit antibacterial activity,[8] larger conjugates do, probably since they possess better cell membrane permeability.

We have shown that the fused 6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione but not the alternative spirocyclic system can be obtained by a selective lactonisation process from a highly functional pyroglutamate precursor, and that the cyclisation is dependent on the nature of the lactam ring substituents. Moreover, such compounds are not strongly antibacterial against the test organisms *S. aureus* and *E. coli*; this behaviour appears to be similar to that of other simple tetramates[16] and spirocyclic pyroglutamates,[17,18] which we have also shown not to exhibit significant bioactivity.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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References and Notes

(1) Moore, B. S.; Gulder, T. A. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 9346.
(2) Stadler, M.; Bitzer, J.; Mayer-Bartschmid, A.; Müller, H.; Benet-Buchholz, J.; Gantner, F.; Tichy, H.-V.; Reinemer, P.; Bacon, K. B. *J. Nat. Prod.* **2007**, *70*, 246.
(3) Moloney, M. G.; Trippier, P. C.; Yaqoob, M.; Wang, Z. *Curr. Drug Discovery Technol.* **2004**, *1*, 181.
(4) Zinzalla, G.; Thurston, D. E. *Future Med. Chem.* **2009**, *1*, 65.
(5) (a) Mondal, D.; Bera, S. *Synthesis* **2010**, 3301. (b) Yamada, T.; Sakaguchi, K.; Shinada, T.; Ohfune, Y.; Soloshonok, V. A. *Tetrahedron: Asymmetry* **2008**, *19*, 2789. (c) Donohoe, T. J.; Chiu, J. Y. K.; Thomas, R. E. *Org. Lett.* **2007**, *9*, 421. (d) Mohapatra, D. K.; Mondal, D.; Gonnade, R. G.; Chorghade, M. S.; Gurjar, M. K. *Tetrahedron Lett.* **2006**, *47*, 6031. (e) Papillon, J. P. N.; Taylor, R. J. K. *Org. Lett.* **2000**, *2*, 1987.
(6) (a) Borissenko, L.; Groll, M. *Chem. Rev.* **2007**, *107*, 687. (b) Nguyen, H.; Ma, G.; Gladysheva, T.; Fremgen, T.; Romo, D. *J. Org. Chem.* **2011**, *76*, 2.
(7) Moloney, M. G.; Yaqoob, M. *Tetrahedron Lett.* **2008**, *49*, 6202.
(8) Bagwell, C. L.; Moloney, M. G.; Yaqoob, M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2090.
(9) Andrews, M. D.; Brewster, A. G.; Moloney, M. G. *Synlett* **1996**, 612.

(10) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre (**3b**: CCDC 827286, **4c**: CCDC 827287, **5a**: CCDC 682703) and copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.
(11) Cordero-Vargas, A.; Perez-Martin, I.; Quiclet-Sire, B.; Zard, S. Z. *Org. Biomol. Chem.* **2004**, *2*, 3018.
(12) Corey, E. J.; Reichard, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 10677.
(13) Calculated by using semi-empirical AM1 and PM3 at ground state in Spartan 02.
(14) Hann, M. M.; Leach, A. R.; Harper, G. *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 856.
(15) Marvin 5.2.1(2009) was used for drawing, displaying and characterising chemical structures, substructures and reactions. Calculator plugins were used for structure property prediction and calculation, Marvin 5.2.5.1(2009) by ChemAxon (http://www.chemaxon.com).
(16) Holloway, C. A.; Matthews, C. J.; Jeong, Y.-C.; Moloney, M. G.; Roberts, C. F.; Yaqoob, M. *Chem. Biol. Drug. Des.* **2011**, *78*, 229.
(17) Jeong, Y.-C.; Moloney, M. G. *Synlett* **2009**, 2487.
(18) Hill, T.; Kocis, P.; Moloney, M. G. *Tetrahedron Lett.* **2006**, *47*, 1461.