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Equilibration in bicyclic pyroglutamates by ring opening-reclosure

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ABSTRACT

Enantiopure bicyclic tetramates, readily obtained by Dieckmann ring closure on oxazolidine-derived templates, can be further converted to hydroxypyroglutamates by kinetically controlled nucleophilic additions, and some of these products are capable of equilibration via a facile retro-aldol/aldol reclosure.

The synthesis of highly functionalised lactams has assumed considerable recent importance as a result of the recognition of the potential roles of the potent 20S proteasome inhibitors omuralide, lactacystin and salinosporamide in diverse disease therapies.[1] Of significance is the fact that the bicyclic motif common to these natural products occurs more widely, for example, in the cinnabarimides[2] and the oxazolomycins.[3] Our interest in methodology providing access to enantiopure tetramate systems has led to the development of a sequence based upon Dieckmann or aldol ring closure,[4–7] critical to the success of which has been the application of Seebach's Self Regeneration of Stereocentres concept.[8] We report here that further elaboration of these systems by reaction of the tetramate C-6 carbonyl group with dithiane anions, chosen for their potential for further elaboration to analogues of lactacystin and oxazolomycin, is possible in a reaction which is controlled by the inherent steric and stereoelectronic bias of the bicyclic structure, but that an unexpected rearrangement capable of compromising the stereochemical or the skeletal integrity of the product can occur.

Dieckmann ring closure of malonamide **1** using our reported procedure[5] gave the resulting potassium tetramate salt product, which was not isolated, but reacted immediately with an excess of methyl iodide, generating the *gem*-dimethyl product **2** in 68% yield along with some of the enol ether **3** (17%); the introduction of the *gem*-dimethyl function serves to remove synthetic complications which arise from the presence of the highly acidic α-position of an unsubstituted tetramic acid.[9] Addition of the lithium salt of 1,3-dithiane to the C-6 carbonyl group proceeded diastereoselectively, by a kinetically controlled addition of the nucleophile *anti* to the nitrogen lone pair to the more hindered *endo*-face, giving lactam **4** in 49% yield. Interestingly, this reaction was also accompanied by some lactam ring opening to give product **5** in 24% yield; the structures of both of these products were confirmed by single crystal X-ray analysis (Fig. 1).[10] Significantly, it was found that lactam **4** efficiently epimerised to the thermodynamically preferred lactam **6** (stereochemistry confirmed by both NOE (Scheme 1) and X-ray analysis[10] (Fig. 1)) under mildly basic conditions (Et_3N and THF) by a retro-aldol/aldol reclosure process (Scheme 2, path a). Of interest was that the *endo*-located methyl substituent in **4** and **6** was approximately 0.3–0.4 ppm. upfield of the corresponding *exo*-located methyl in the ^1H NMR spectrum, which is likely to be diagnostic since it was observed in all of the lactam compounds prepared subsequently. The dithiane unit of **4** was easily deprotected under standard methylating conditions (MeI, $CaCO_3$, CH_3CN and H_2O), although this did not give the expected [3.3.0]-bicyclic system **7**, but the ring expanded [4.3.0]-bicyclic system **8**, most likely resulting from a similar spontaneous retro-aldol reaction of the starting **4**, leading to formation of a reactive α-ketoaldehyde intermediate, followed by immediate ring closure onto the aldehyde group, as shown in Scheme 2 (path b). Protection of the hydroxyl group of product **8** as the TMS ether gave crystalline lactam **9**, whose structure and stereochemistry was confirmed by X-ray analysis (Fig. 1),[10] and which allowed unequivocal assignment of the structure of **8**. Attempts to protect the hydroxyl group of lactam **4** with *p*-methoxybenzyl chloride, phenylsulfenyl chloride, or allyl bromide and thereby prevent the retro-aldolisation were unsuccessful, due to the hindered nature of this tertiary hydroxyl group.

In order to confirm that kinetic *endo*-addition to the bicyclic tetramate system was indeed preferred, reaction with hydride sources was examined, for which reversible reaction was not possible. Addition of the smaller hydride nucleophile (as sodium borohydride or lithium aluminium hydride) to **2** gave alcohol **10** (Scheme 3) in excellent yield, arising from *endo*-addition of the hydride *anti*- to the nitrogen lone pair in a stereoelectronically controlled process. The structure and stereochemistry of lactam **10** was unequivocally assigned by single crystal X-ray analysis (Fig. 1).[10] On the other hand, diisobutylaluminium hydride gave the product of lactam reduction, again by reduction *anti* to the nitrogen lone pair, to give the stable hemiaminal ether **11**; the stereochemistry of this compound was confirmed by NOE analysis, giving key enhancements as shown (Scheme 3).

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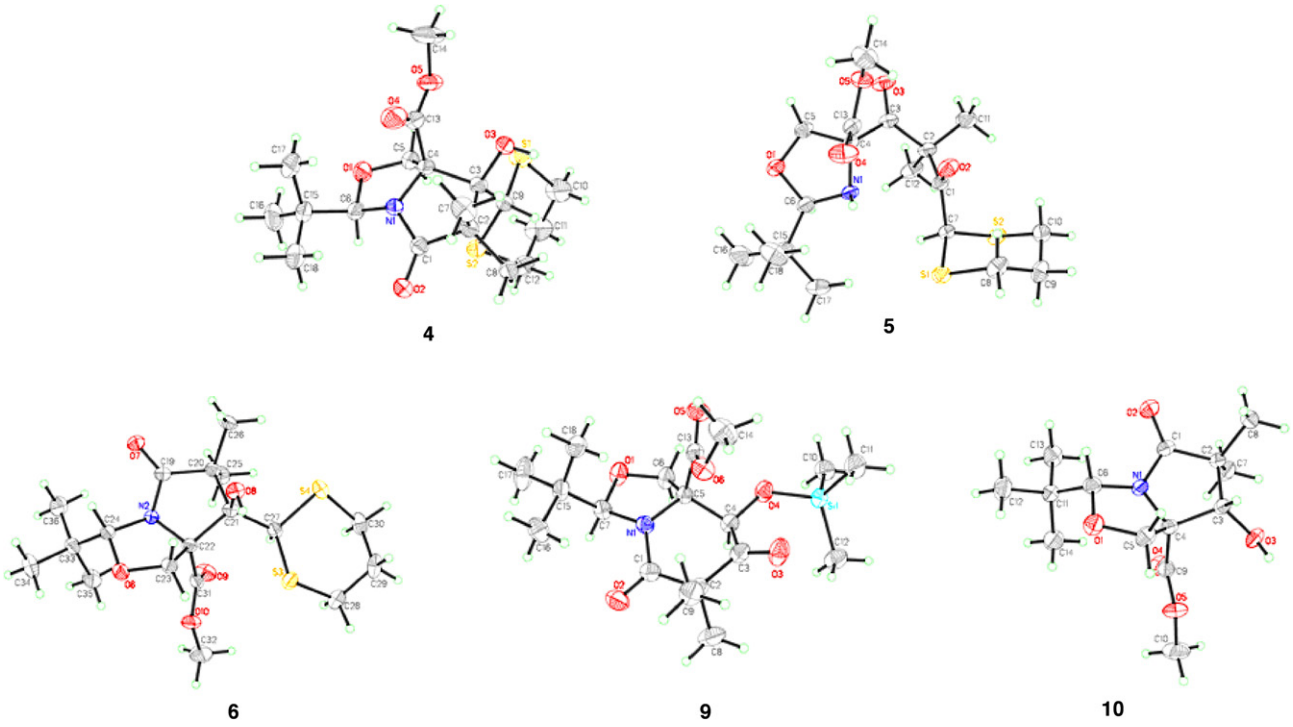
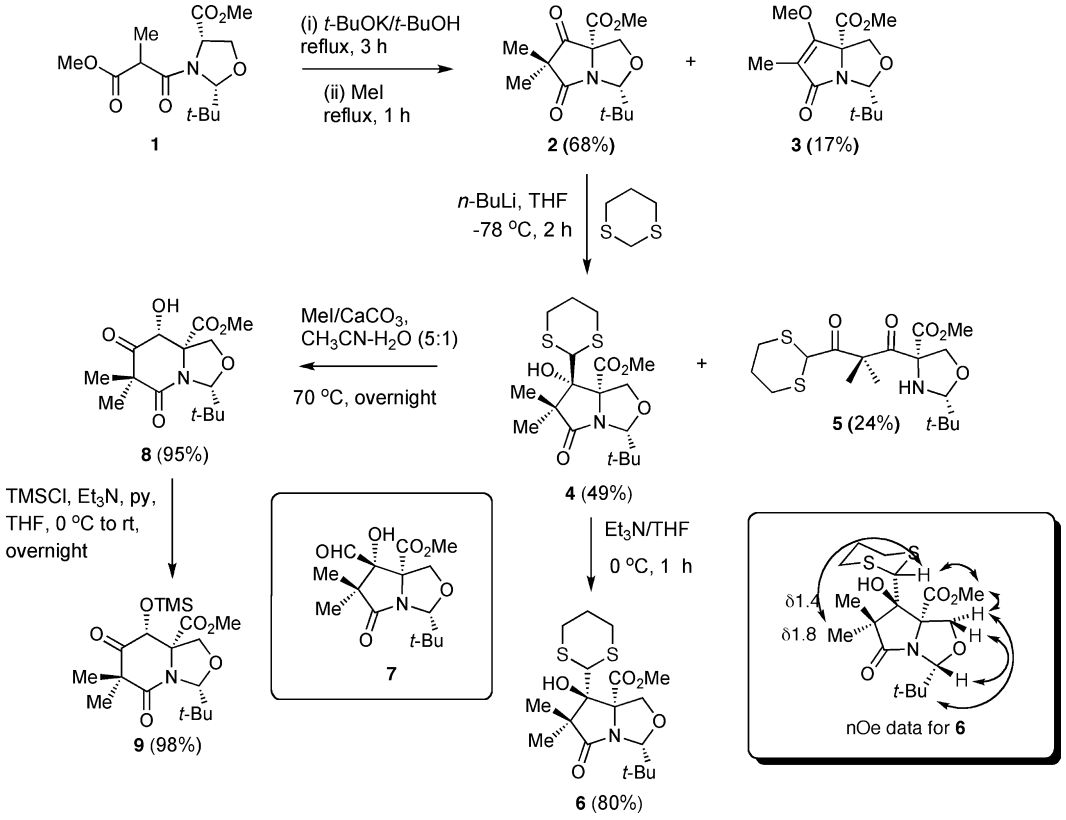
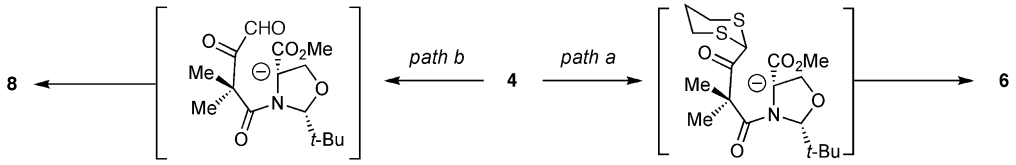


Figure 1. Thermal ellipsoid plots (ORTEP-3[4]) at 40% probablility level for compounds **4**–**6** and **9**.

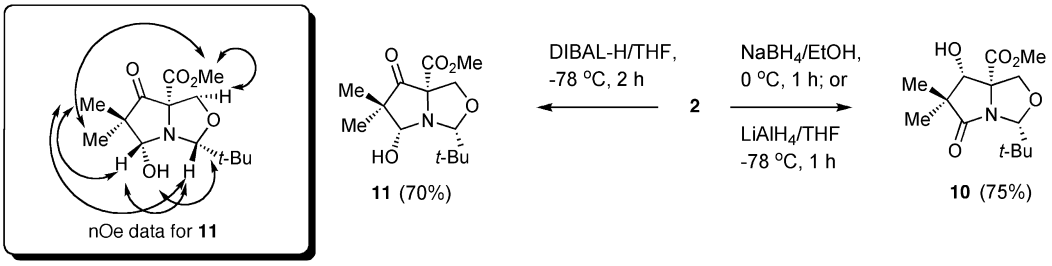


Scheme 1.

We have shown that bicyclic tetramate systems react by kinetically controlled additions in which the incoming nucleophile enters *anti* to the nitrogen lone pair, but that product equilibration, leading to epimerised [3.3.0] systems or ring-expanded [4.3.0] systems, is possible in those cases leading to the formation of reactive carbonyl intermediates.



Scheme 2.



Scheme 3.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.08.021.

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9. Moloney, M. G.; Yaqoob, M. *Synlett* **2004**, 1631–1633.
10. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 682698 (4), 682699 (5), 682700 (6), 682701 (9), 682702 (10). 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 e-mail: deposit@ccdc.cam.ac.uk).