

# Intramolecular aldol ring closures of cysteine derivatives leading to densely functionalised pyroglutamates

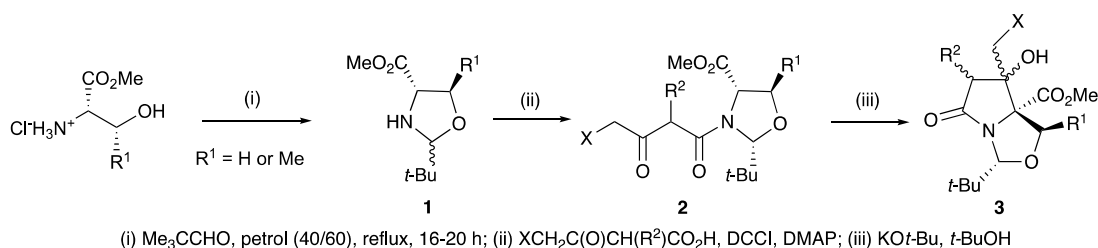
Hadia Almahli, Niamh C. Jimenez and Mark G. Moloney\*

The Department of Chemistry, Chemistry Research Laboratory, The University of Oxford, 12 Mansfield Road, Oxford OX1 3TA, United Kingdom and Oxford Suzhou Centre for Advanced Research, Building A, 388 Ruo Shui Road, Suzhou Industrial Park, Jiangsu, 215123, P.R. China.

mark.moloney@chem.ox.ac.uk

**Abstract:** The synthesis of densely functionalised pyroglutamates derived from cysteine by an aldol cyclisation strategy has been achieved.

We have reported that malonyloxazolidines and malonylthiazolidines derived from serine and threonine, or cysteine respectively, are suitable for highly chemoselective Dieckmann ring closures,<sup>1,2,3</sup> and that the serine- and threonine-derived oxazolidine systems **1** are, moreover, suitable for diastereoselective aldol ring closures after conversion to their ketoamide derivatives **2**,<sup>4-6</sup> giving highly functionalised pyroglutamates **3** (Scheme 1)<sup>7</sup> which are closely related to the lactam moiety of oxazolomycin.<sup>8,9</sup> Related aldol ring closures have been reported<sup>10</sup> and it has been suggested that such processes are biomimetic.<sup>11</sup> Of interest to us was the possibility that a similar ring closure might also be applicable to cysteine-derived systems, even though these aldol reactions may be reversible<sup>12</sup> and the five-membered ring containing the large sulfur atom might be expected to influence the outcome of such a reaction; moreover, of interest was whether the reaction might be extended to thiazolidines other than those derived from pivaldehyde, since such systems exhibited unexpected behaviour in related Dieckmann cyclisations.<sup>1</sup> This report details our results in that regard.



(i) Me<sub>3</sub>CCHO, petrol (40/60), reflux, 16-20 h; (ii) XCH<sub>2</sub>C(O)CH(R<sup>2</sup>)CO<sub>2</sub>H, DCCl, DMAP; (iii) KO<sup>t</sup>-Bu, *t*-BuOH

Scheme 1

The starting thiazolidines **4a-e** were obtained by reflux of cysteine with the respective

aldehyde under reported conditions (Scheme 2 and Table 1);<sup>1</sup> these were obtained in good to excellent yield, as a mixture of inseparable diastereomers usually favouring the *cis*- isomer; a similar outcome had been observed earlier with analogous cysteine derivatives.<sup>1</sup>

**Table 1:** Yields of thiazolidines **4a-e**.

| Compound  | R <sup>1</sup>  | $\delta_{\text{H}}$ (ppm) for H-2 |      | Ratio ( <i>cis</i> -: <i>trans</i> -) | Yield (%) |
|-----------|---|-----------------------------------|------|---------------------------------------|-----------|
| <b>4a</b> | <i>t</i> -Bu  | 4.45                              | 4.52 | 1:0.4                                 | 89        |
| <b>4b</b> | <i>i</i> -Pr  | 4.35                              | 4.43 | 2.5:1                                 | 80        |
| <b>4c</b> | Ph  | 5.57                              | 5.82 | 1:0.7                                 | 100       |
| <b>4d</b> | <i>o</i> -FC <sub>6</sub> H <sub>4</sub>                | 5.79                              | 6.01 | 1:1                                   | 61        |
| <b>4e</b> | <i>o</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> | 5.86                              | 6.10 | 1:0.53                                | 17        |

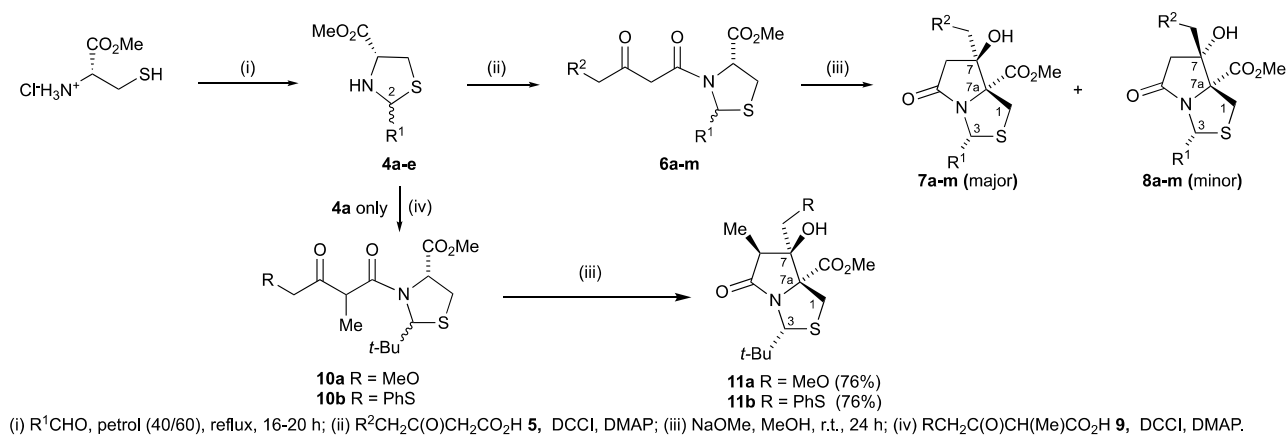
Initial preparation of the required side chain  $\beta$ -ketoacids from Meldrum's acid, by acylation and then acid-catalysed collapse, using literature methodology, gave ketoacids **5** (Scheme 2);<sup>5,6</sup> coupling of these with thiazolidines **4a-e** gave acetoacetylthiazolidines **6a-m** in good yield (Scheme 2 and Table 2). These compounds existed as rotamers in several cases as evidenced by broad signals in the <sup>1</sup>H NMR spectrum, as keto-enol mixtures, and as a mixture of diastereomers, leading to complex NMR spectra, but were nonetheless used directly for further reaction; as has been observed previously, the diastereomeric ratio of the starting thiazolidines **4a-e** is not necessarily translated into that for the acetoacetylthiazolidines **6a-m** due to equilibration during the acylation process.<sup>1</sup> When subjected to base treatment (NaOMe),<sup>4</sup> the acetoacetylthiazolidines **6a-m** gave the corresponding aldol adducts usually as diastereomeric mixtures of **7a-m** and **8a-m** in good overall yield (Scheme 2 and Table 2);<sup>13</sup> however, as has been shown previously in a related system,<sup>1</sup> *cis*- and *trans*-acetoacetylthiazolidines **6a-m** are not separated, and since their aldol closure leads to enantiomers of each of the products **7** and **8**, the overall process proceeds with some loss of enantiomeric integrity. The stereochemistry of the newly created stereogenic centre for the major diastereomer was established as 7*R* (that is, hydroxyl group *endo*) by NOE analysis (Figure 1), and the stereochemistry of the others was assumed by the similarity of chemical shift values of H-6<sub>exo</sub> and H-6<sub>endo</sub> with this NOE-assigned structure ( $\delta_{\text{H-6}}$  3.04 and 2.45 for **7a**). This was similar to reported chemical shifts of the H-6 protons for the serine (H-6<sub>endo</sub> ( $\delta$ 3.2) and H-6<sub>exo</sub> ( $\delta$ 2.5)<sup>3</sup>) and threonine (H-6<sub>exo</sub> ( $\delta$ 3.1) and H-6<sub>endo</sub> ( $\delta$ 2.4)<sup>6</sup>). This earlier work had shown those chemical shifts were conserved in similar diastereomers, generally regardless of substitution, and in the systems reported here, the chemical shift values for H-1 and H-6 were also conserved across multiple substitution patterns, with the differences of chemical shift of each geminal set being smaller for the

major isomer ( $\Delta\delta$ 0.5 and 0.1 respectively) than for the minor isomer ( $\Delta\delta$ 0.8 and 0.5 respectively). The yields of these aldol reactions were often significantly better than that obtained in our earlier work with serine<sup>5,7</sup> and threonine;<sup>6</sup> the 7*R* diastereoselectivity, however, was poorer than this earlier work, presumably arising from the need to accommodate the larger sulfur in the bicyclic system. Of interest is that enantioselective aldol reactions of malonic acid half thioesters with aldehydes have recently been reported.<sup>14</sup>

**Table 2:** Yields of products **6-8**.

| Compound<br><b>6, 7 or 8</b> | R <sup>1</sup>  | R <sup>2</sup>                     | <b>6</b>                  |  | <b>7 and 8</b> |   | $\delta_{\text{H}}$ for H-3 |       |
|------------------------------|---|------------------------------------|---------------------------|--|----------------|---|-----------------------------|-------|
|                              |   |                                    | Yield<br>(%) <sup>a</sup> | <i>cis</i> -:<br><i>trans</i> -<br>ratio | Yield<br>(%)   | 7 <i>R</i> - <b>7</b> :<br>7 <i>S</i> - <b>8</b><br>ratio | major                       | minor |
| <b>a</b>                     | <i>t</i> -Bu  | H                                  | 48                        | 1:1                                      | 88             | 1:0.4   | 5.11                        | 5.07  |
| <b>b</b>                     | <i>t</i> -Bu  | MeO                                | 44                        | 1:2                                      | 69             | 1:0.3   | 5.05                        | 4.97  |
| <b>c</b>                     | <i>t</i> -Bu  | CH <sub>2</sub> =CHCH <sub>2</sub> | 78                        | 1:1                                      | 99             | 1:0 <sup>a</sup>  | 5.11                        | -     |
| <b>d</b>                     | <i>t</i> -Bu  | p-BrC <sub>6</sub> H <sub>4</sub>  | 73                        | 1:1                                      | 100            | 1:0 <sup>a</sup>  | 5.08                        | -     |
| <b>e</b>                     | <i>i</i> -Pr  | MeO                                | 48                        | 1:1                                      | 41             | 1:0.3   | 4.86                        | 4.79  |
| <b>f</b>                     | Ph  | H                                  | 49                        | 1:0.6                                    | 52             | 1:0.3   | 6.17                        | 6.24  |
| <b>g</b>                     | Ph  | p-BrC <sub>6</sub> H <sub>4</sub>  | 81                        | 2:3                                      | 48             | 1:0 <sup>a</sup>  | 5.99                        | -     |
| <b>h</b>                     | <i>o</i> -FC <sub>6</sub> H <sub>4</sub>                | H                                  | 71                        | 1:1                                      | 96             | 1:0.2   | 6.36                        | 6.29  |
| <b>i</b>                     | <i>o</i> -FC <sub>6</sub> H <sub>4</sub>                | MeO                                | 26                        | 4:1                                      | 76             | 1:0.4   | 6.28                        | 6.25  |
| <b>j</b>                     | <i>o</i> -FC <sub>6</sub> H <sub>4</sub>                | CH <sub>2</sub> =CHCH <sub>2</sub> | 52                        | 2:3                                      | 71             | 1:0 <sup>a</sup>  | 6.33                        | -     |
| <b>k</b>                     | <i>o</i> -FC <sub>6</sub> H <sub>4</sub>                | p-BrC <sub>6</sub> H <sub>4</sub>  | 50                        | 7:3                                      | 80             | 1:0 <sup>a</sup>  | 6.43                        | -     |
| <b>l</b>                     | <i>o</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> | H                                  | 46                        | 0:1                                      | 79             | 1:0.2   | 6.22                        | 6.26  |
| <b>m</b>                     | <i>o</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> | CH <sub>2</sub> =CHCH <sub>2</sub> | 47                        | 0:1                                      | 82             | 1:0 <sup>a</sup>  | 6.20                        | -     |

<sup>a</sup> Single diastereomer isolated only



Scheme 2

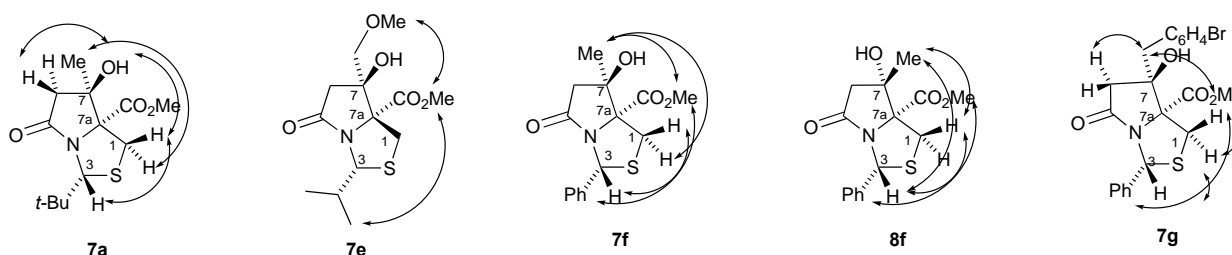


Figure 1

An examination of more substituted systems was made, and to this end, malonamides **10a-b** were prepared from the corresponding carboxylic acid **9**<sup>6</sup> and thiazolidine **4a**, by DCC coupling (Scheme 2). Aldol reaction using base (NaOMe) gave the corresponding pyroglutamates **11a-b** in good yield as single diastereomers, whose stereochemistry was assigned on the basis of the chemical shift information outlined above; thus, the H-1 geminal set showed a difference of  $\Delta\delta 0.5$  and  $0.1$ , corresponding to the *7R* (*endo*-hydroxyl) configuration, in keeping with that observed in the simpler systems, and in close correspondence to equivalent reported analogues in the serine<sup>4, 5</sup> and threonine<sup>6</sup> series.

Assay of these compounds against a small panel of Gram positive (Methicillin resistant *Staphylococcus aureus*, *Streptococcus pneumonia*) and Gram negative (*Escherichia coli* (EC 34), *Klebsiella pneumonia* (KL 18) and *Pseudomonas aeruginosa* (PS 23)) bacteria mostly showed no activity, confirming earlier results that simple lactam systems do not display such activity and which only becomes observable with further suitable ring substitution.<sup>15</sup> The exception was **6p**, which showed good activity against both of Methicillin resistant *Staphylococcus aureus* and *Streptococcus pneumonia* with an MIC of  $3.9\mu\text{g/mL}$ .

In conclusion, we have shown that aldol reactions may be achieved in sterically encumbered thiazolidine substrates derived from cysteine, and that these may proceed in a diastereoselective manner, at least in some cases. This outcome offers the prospect of the construction of sulfur-

containing mimics of the oxazolomycin group of natural products.<sup>9, 16</sup>

## Acknowledgements

A.H. gratefully acknowledges the award of a Council for At-Risk Academics (CARA) Fellowship and Christ Church College, University of Oxford, and N.J. funding from EPSRC SBM CDT.

## References

1. Panduwawala, T. D.; Iqbal, S.; Tirfoin, R.; Moloney, M. G. *Org. Biomol. Chem.* **2016**, 14, 4464-4478.
2. Anwar, M.; Moloney, M. G. *Chem Biol Drug Des* **2013**, 81, 645-649; Anwar, M.; Cowley, A. R.; Moloney, M. G. *Tetrahedron: Asymmetry* **2010**, 21, 1758-1770; Anwar, M.; Moloney, M. G. *Tetrahedron Lett.* **2007**, 48, 7259-7262.
3. Andrews, M. D.; Brewster, A. G.; Crapnell, K. M.; Ibbett, A. J.; Jones, T.; Moloney, M. G.; Prout, K.; Watkin, D. J. *Chem. Soc., Perkin Trans. 1* **1998**, (2), 223-235.
4. Andrews, M. D.; Brewster, A. G.; Moloney, M. G. *Synlett* **1996**, 612-614.
5. Angelov, P.; Chau, Y. K. S.; Fryer, P. J.; Moloney, M. G.; Thompson, A. L.; Trippier, P. C. *Org. Biomol. Chem.* **2012**, 10, 3472-3485.
6. Heaviside, E. A.; Moloney, M. G.; Thompson, A. L. *RSC Adv.* **2014**, 4, 16233-16249.
7. Andrews, M. D.; Brewster, A. G.; Moloney, M. G. *J. Chem. Soc., Perkin Trans. 1* **2002**, (1), 80-90.
8. Ishihara, J.; Hatakeyama, S. *The Chemical Record* **2014**, 14, 663-677.
9. Moloney, M. G.; Trippier, P. C.; Yaqoob, M.; Wang, Z. *Curr. Drug Discovery Technol.* **2004**, 1, 181-199.
10. Satoh, N.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2011**, 13, 3028-3031; Nguyen, H.; Ma, G.; Gladysheva, T.; Fremgen, T.; Romo, D. *J. Org. Chem.* **2011**, 76, 2-12; Nguyen, H.; Maz, G.; Romo, D. *Chem. Commun.* **2010**, 46, 4803-4805.
11. Ma, G.; Nguyen, H.; Romo, D. *Org. Lett.* **2007**, 9, 2143-2146.
12. Moloney, M. G.; Yaqoob, M. *Tetrahedron Lett.* **2008**, 49, 6202-6204.
13. Method for aldol cyclisation: To a solution of *N*-acylated thiazolidine (1.0 eq.) in methanol was added sodium methoxide (1.05 eq.) and the resulting mixture was stirred at rt for 15-24 h. Subsequently, the mixture was partitioned between Et<sub>2</sub>O and 1M HCl. The Et<sub>2</sub>O layer was washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated in vacuo to furnish the crude pyroglutamates. **Methyl (3*R*,7*R*,7*aR*)-3-(*tert*-butyl)-7-hydroxy-7-methyl-5-oxodihydro-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-7*a*(5*H*)-carboxylate (7*a* and 8*a*).** yellow oil;  $\nu_{\max}/\text{cm}^{-1}$  2958, 1739, 1688, 1616, 1366, 1260, 1108, 1022; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta_{\text{H}}$  major 5.11 (s, 1H, H-3), 3.80 (s, 3H, CO<sub>2</sub>Me), 3.62 (d, J 12.1 Hz, 1H, H-1), 3.55 (d, J 12.1 Hz, 1H, H-1), 3.04 (d, J 16.3 Hz, 1H, H-6), 2.45 (d, J 16.3 Hz, 1H, H-6), 1.27 (s, 3H, H-9), 0.93 (s, 9H, *t*-Bu); minor 5.07 (s, 1H, H-3), 3.82 (s, 3H, CO<sub>2</sub>Me), 3.69 (d, J 12.9 Hz, 1H, H-1), 3.27 (d, J 12.9 Hz, 1H, H-1), 3.23 (d, J 15.7 Hz, 1H, H-6), 2.42 (d, J 15.6 Hz, 1H, H-6), 1.51 (s, 3H, H-9), 0.93 (s, 9H, *t*-Bu); <sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>):  $\delta_{\text{C}}$  major 175.3 (C-5), 172.0 (CO<sub>2</sub>Me), 85.0 (C-7*a*), 79.6 (C-7), 73.1 (C-3), 53.1 (CO<sub>2</sub>Me), 47.2 (C-6), 38.3 (C-10), 33.4 (C-1), 26.4 (*t*-Bu), 21.8 (C-9); minor 173.6 (C-5), 172.4 (CO<sub>2</sub>Me), 84.2 (C-7*a*), 78.7 (C-7), 72.2 (C-3), 53.0 (CO<sub>2</sub>Me), 46.7 (C-6), 38.3 (C-10), 33.8 (C-1), 26.4 (*t*-Bu), 24.04 (C-9); HRMS (ESI<sup>+</sup>) C<sub>13</sub>H<sub>22</sub>NO<sub>4</sub>S<sup>+</sup> (M+H<sup>+</sup>) requires 288.12641, found 288.12650. **Methyl (3*R*,7*S*,7*aR*)-3-(*tert*-butyl)-7-hydroxy-6-methyl-5-oxo-7-((phenylthio)methyl)-hexahydropyrrolo[1,2-*c*]thiazole-7*a*(5*H*)-carboxylate (11*b*).** yellow oil (0.19 g, 76%).  $[\alpha]_{\text{D}}^{23} = -19.8$  (c 1.0 in CHCl<sub>3</sub>);  $\nu_{\max}/\text{cm}^{-1}$  3358, 2930, 2854, 1713, 1583;  $\delta_{\text{H}}$  (500 MHz, CDCl<sub>3</sub>) 7.19-7.23 (5H, m, ArH), 5.11 (1H, s, C(3)H), 3.79 (3H, s, OCH<sub>3</sub>), 3.75 (1H, d, J 16.2, C(1)H<sub>A</sub>H<sub>B</sub>), 3.65 (1H, d, J 16.2, C(1)H<sub>A</sub>H<sub>B</sub>), 3.22 (1H, d, J 16.2, CH<sub>A</sub>H<sub>B</sub>), 3.10 (1H, q, J 7.2, C(6)H), 3.07 (1H, d, J 16.2, CH<sub>A</sub>H<sub>B</sub>),

- 1.07 (3H, d, CH<sub>3</sub>), 0.93 (9H, s, *t*-Bu);  $\delta_C$  (126 MHz, CDCl<sub>3</sub>) 176.7 C(O)), 172.1 (CO<sub>2</sub>Me), 126.8-129.4 (C(aromatic)), 83.50 (C(7a)), 83.31 (C(3)), 72.85 (C(7)), 53.43 (OMe), 51.46 (OMe), 46.49 (C(6)), 41.11 (CH<sub>2</sub>), 38.40 (C(3)), 34.32 (C(CH<sub>3</sub>)<sub>3</sub>), 26.64 (C(CH<sub>3</sub>)<sub>3</sub>), 14.41 (CH<sub>3</sub>); HRMS (ESI) C<sub>20</sub>H<sub>28</sub>NO<sub>4</sub>S<sub>2</sub> (M<sup>+</sup>) requires 410.14543, found: 410.14539.
14. Wang, Y.; Huang, G.; Hu, S.; Jin, K.; Wu, Y.; Chen, F. *Tetrahedron* **2017**, 73, (34), 5055-5062.
15. Jeong, Y.-C.; Moloney, M. G. *Synlett*. **2009**, 2487-2491
16. Eto, K.; Yoshino, M.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2011**, 13, (19), 5398-5401.