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## Amino Acid Derived Thiane Oxide and Dioxide Systems as Disposable Templates: Synthesis of α-Amino Ketones, *anti*-Amino Alcohols and an Amino Cyclopentenone

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Abstract: Sulfones and sulfoxides synthesised from methionine and homocysteine thiolactone have been cyclised to amino ketones using potassium bis(trimethylsilyl)amide. Ramberg-Bäcklund chemistry on one of the sulfones gave an amino cyclopentenone whereas acyclic  $\alpha$ -amino ketones and *anti*-amino alcohols were obtained by Raney nickel desulfurisation of the sulfoxides. Copyright © 1996 Elsevier Science Ltd

For some time now, we<sup>1,2</sup> and others<sup>3</sup> have been exploring the synthetic potential of sulfones derived from  $\alpha$ -amino acids. For example, we used a novel Ramberg-Bäcklund reaction<sup>4</sup> on a methionine-derived  $\alpha$ chlorosulfone to complete a synthesis of enantiomerically pure allylglycine in protected form<sup>1</sup> and, more recently, we synthesised some amino cyclopentanes using sulfones derived from glutamic acid.<sup>2</sup> In related work, *trans*-carbovir was prepared using a Ramberg-Bäcklund reaction on a cyclic amino sulfone.<sup>5</sup> By combining different aspects of each one of our earlier studies, we now wish to report that novel amino acidderived thiane oxide and dioxide systems can be prepared and used as two-directional disposable templates.<sup>6</sup>



Our published route<sup>2</sup> to amino cyclopentanes utilised the potassium bis(trimethylsilyl)amide (KHMDS) mediated cyclisation of a glutamic acid derived phenylsulfone to a cyclic ketone. With this type of reaction in mind, we wondered whether it would be possible to cyclise the methionine-derived sulfone 1 or sulfoxides 2 to the corresponding ketones 3 and 4 respectively. If successful, we imagined that ketones 3 and 4 would be very useful and versatile synthetic intermediates: simple Raney nickel desulfurisation<sup>6,7</sup> should afford acyclic amino ketone 6 whereas the use of the Ramberg-Bäcklund reaction<sup>4</sup> might allow us to synthesise cyclopentenone 5. We now report that this approach does indeed work: starting from methionine and homocysteine thiolactone, syntheses of acyclic  $\alpha$ -amino ketones and *anti*-amino alcohols as well as a substituted cyclopentenone are described.

Sulfone 1<sup>8</sup> was obtained in 76% yield by Oxone<sup>®</sup> oxidation of known<sup>9</sup> *N*-Boc protected L-methionine methyl ester. After a detailed investigation, we were able to find racemisation-free cyclisation conditions: treatment of sulfone 1 with 2.2 equivalents of KHMDS at -78 °C followed by slow warming to 0 °C over 2-3 hours and to room temperature over 30 minutes afforded a 91% crude yield of ketone 3 which had  $[\alpha]_D$  -90.3 (c 0.3 in acetone) and  $[\alpha]_D$  -91.5 (c 0.3 in acetone) after recrystallisation. If the reaction mixture was allowed to warm to room temperature for any longer than 30 minutes, racemisation<sup>10</sup> was observed; we have noted a similar effect before.<sup>1</sup> Stereoselective reduction<sup>11</sup> with sodium borohydride afforded syn-7<sup>12</sup> and subsequent conversion to its Mosher's ester<sup>13</sup> indicated that it (and therefore ketone 3) had ≥90% ee.



As a result of this success with the sulfone, attention was switched to the corresponding sulfoxides. We decided to begin our study with *racemic N*-Boc protected methionine methyl ester: an inseparable mixture of diastereomeric sulfoxides 2 (1:1; 92% yield) was obtained by *m*-CPBA oxidation. Initially, we carried out the cyclisation reaction of 2 with 3.3 equivalents of KHMDS and a 39% yield of *syn-4* was isolated after recrystallisation. Its stereochemistry was elucidated by X-ray crystallography<sup>14</sup> on *syn,syn-8* which was the only product observed when *syn-4* was reduced with sodium borohydride.<sup>15</sup> It is interesting to note that *syn-7* and *syn,syn-8* have <sup>3</sup>J<sub>HH</sub> (OH) = 10.0 and 10.1 Hz respectively; presumably, this is because hydrogen bonding between the axial S=O and O-H bonds fixes the conformation as shown.



In an attempt to improve the yield of the sulfoxide cyclisation reaction, we repeated the reaction of 2 with only 2.2 equivalents of KHMDS and obtained a single product, syn-4, in 75% yield. Because this yield is greater than 50%, we suggest that a 1:1 mixture of syn- and anti-4 is initially produced but subsequent epimerisation  $\alpha$  to nitrogen occurs to give thermodynamically favoured<sup>16</sup> syn-4. This was confirmed by commencing our synthetic sequence with (S)-methionine and using the cyclisation conditions that we had had optimised for preventing racemisation in the sulfone series: a 1:1 mixture of (R,S)- and (S,S)-2 gave the same 75% isolated yield of sulfoxide syn-4 only, which was shown to be racemic (by oxidation to sulfone rac-3).

All attempts at carrying out Raney nickel desulfurisation with cyclic sulfone syn-7 were unsuccessful. In contrast, the corresponding sulfoxide, syn,syn-8, was smoothly desulfurised when treated with Raney nickel at room temperature giving acyclic ketone anti-9 in a good 64% yield. Simpkins has previously noted that some related  $\beta$ -hydroxy sulfoxides required long reaction times and elevated temperatures for desulfurisation.<sup>6</sup> In contrast, we did not encounter any such problems. Even keto sulfoxide syn-4 was successfully desulfurised to give 6 provided that the conditions used for the reduction were controlled.



Using a Ramberg-Bäcklund approach, we have been able to make use of the cyclic sulfones in a different way although this was not as straightforward as we had hoped. Initially, sulfone *syn*-7 (prepared from ketone 1 of ~50% ee<sup>10</sup>) was halogenated after addition of 3 equivalents of LDA. Attempted Ramberg-Bäcklund reactions with 10 and 11 gave non-reproducible yields of the corresponding cyclopentenol. Therefore, we oxidised to ketones 12 and 13 and carried out Ramberg-Bäcklund reactions with a refluxing solution of sodium acetate. Sulfone 13 gave a better yield (62%) but cyclopentenone 5 generated in this way only had  $[\alpha]_D$  +4.3 (c 0.1 in CHCl<sub>3</sub>). This material was converted into the known cyclopentanone 14 which had  $[\alpha]_D$  +5.2 (c 0.05 in CHCl<sub>3</sub>), lit.<sup>17</sup>  $[\alpha]_D$  +125 (c 0.2 in CHCl<sub>3</sub>). Although racemisation has occurred in this sequence (presumably during the Ramberg-Bäcklund reaction), we have demonstrated that it is possible to use Ramberg-Bäcklund chemistry with amino acid derived cyclic sulfones.

We have also used the sulfoxide chemistry to prepare a range of racemic acyclic ketones and *anti*amino alcohols. For this, we required a synthesis of substituted methionine sulfoxides 16 and we chose to prepare them from racemic homocysteine thiolactone  $15^{18}$  via reductive ring opening, alkylation, N-Boc protection and m-CPBA oxidation; the yields for this four step method are recorded in the Table.



<sup>a</sup> Yield of 1:1 diastereomeric mixture over four steps; <sup>b</sup> Yield of unpurified mixture (recrystallised yield of pure 17); <sup>c</sup> From pure 17; <sup>d</sup> 1:1 mixture; <sup>e</sup> Reaction not attempted.

These sulfoxides were cyclised using 3.3 equivalents of KHMDS to generate essentially 1:1 mixtures of cyclic ketones 17 (see Table) which were shown to be a mixture of diastereoisomers at sulfur by oxidation

to a single diastereoisomer of the corresponding sulfone. For 17d, we had already made the ketosulfone using a different route<sup>19</sup> and had established its stereochemistry using NOEs. Thus, we assigned a *cis* relationship between the NHBoc and R groups in cyclic sulfoxides 17. In most cases, recrystallisation gave single diastereoisomers of 17 which we believe have the same stereochemistry at sulfur found in *syn*-4: alcohols 18 obtained after reduction with sodium borohydride had  ${}^{3}J_{\rm HH}$  (OH) ~ 10 Hz. Cyclic sulfoxides 17 and 18 have been desulfurised. For example, treatment of 17b and 18b with Raney nickel generated a very good 84% yield of  $\alpha$ -amino ketone 19b and an excellent quantitative yield of  $\alpha$ -amino alcohol 20b.



In summary, we have demonstrated that cyclic sulfoxides and sulfones dervied from methionine and homocysteine thiolactone are useful synthetic intermediates. One of the cyclic sulfones was converted into a cyclopentenone but, more importantly, the sulfoxides undergo facile desulfurisation to give acyclic  $\alpha$ -amino ketones and alcohols containing unnatural amino acid side chains.<sup>20</sup>

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