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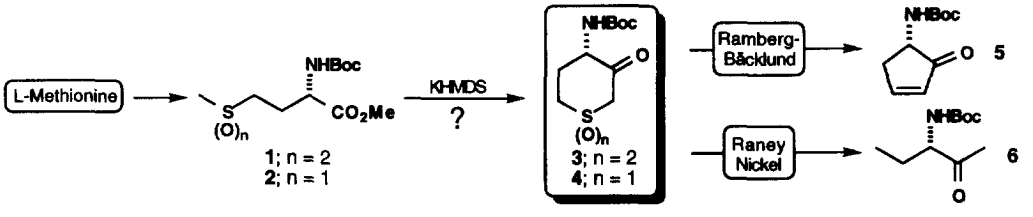
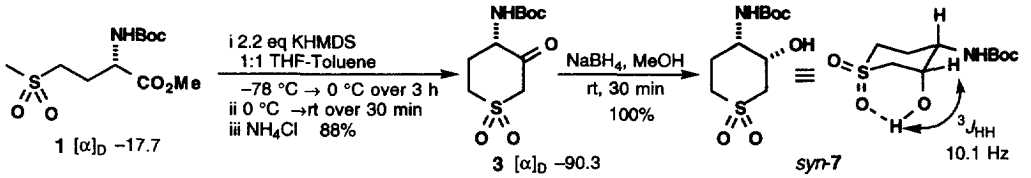
Abstract: Sulfones and sulfoxides synthesised from methionine and homocysteine thiolactone have been cyclised to amino ketones using potassium bis(trimethylsilyl)amide. Ramberg-Bäcklund chemistry on one of the sulfones gave an amino cyclopentenone whereas acyclic α-amino ketones and *anti*-amino alcohols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

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

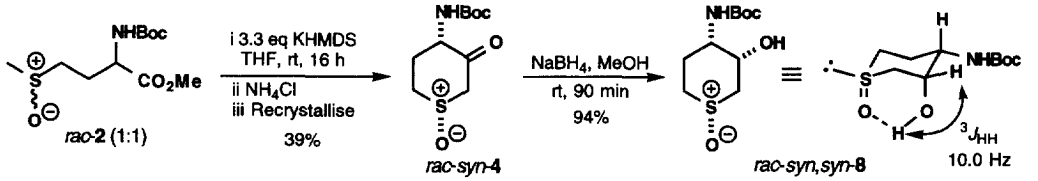


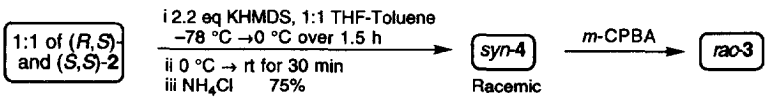
Our published route[2] to amino cyclopentanes utilised the potassium bis(trimethylsilyl)amide (KHMDS) mediated cyclisation of a glutamic acid derived phenylsulfone to a cyclic ketone. With this type of reaction in mind, we wondered whether it would be possible to cyclise the methionine-derived sulfone **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[6,7] should afford acyclic amino ketone **6** whereas the use of the Ramberg-Bäcklund reaction[4] 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 α-amino ketones and *anti*-amino alcohols as well as a substituted cyclopentenone are described.

Sulfone **1**[8] was obtained in 76% yield by Oxone® oxidation of known[9] *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[10] was observed; we have noted a similar effect before.[1] Stereoselective reduction[11] with sodium borohydride afforded *syn*-**7**[12] and subsequent conversion to its Mosher's ester[13] 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[14] on *syn,syn*-**8** which was the only product observed when *syn*-**4** was reduced with sodium borohydride.[15] It is interesting to note that *syn*-**7** and *syn,syn*-**8** have $^3J_{HH}$ (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.

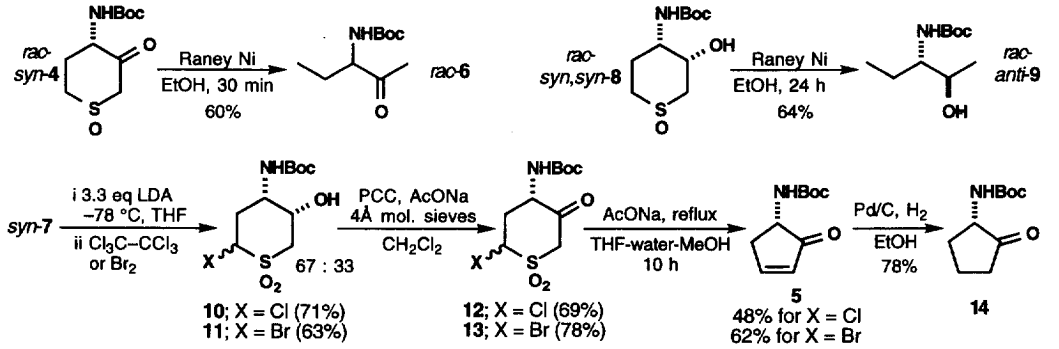




In an attempt to improve the yield of the sulfoxide cyclisation reaction, we repeated the reaction of **2** with only 2.2 equivalents of KHMDS and obtained a single product, *syn*-**4**, in 75% yield. Because this yield is greater than 50%, we suggest that a 1:1 mixture of *syn*- and *anti*-**4** is initially produced but subsequent epimerisation α to nitrogen occurs to give thermodynamically favoured[16] *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 β-hydroxy sulfoxides required long reaction times and elevated temperatures for

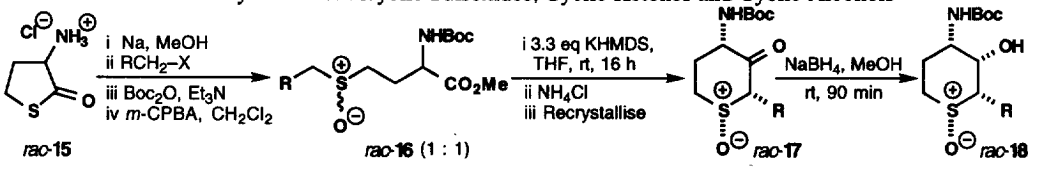
desulfurisation.[6] In contrast, we did not encounter any such problems. Even keto sulfoxide *syn*-**4** was successfully desulfurised to give **6** provided that the conditions used for the reduction were controlled.



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[10]) 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 $CHCl_3$). This material was converted into the known cyclopentanone **14** which had $[\alpha]_D$ +5.2 (*c* 0.05 in $CHCl_3$), lit.[17] $[\alpha]_D$ +125 (*c* 0.2 in $CHCl_3$). 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.

Table: Synthesis of Acyclic Sulfoxides, Cyclic Ketones and Cyclic Alcohols

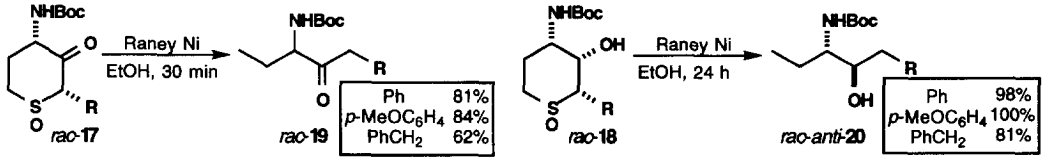


	Sulfoxides **16**		Cyclic Ketones **17**			Alcohols **18**	
R	Product	% Yield[a]	Product	Ratio	% Yield[b]	Product	% Yield[c]
Ph	**16a**	63	**17a**	50:50	63 (23)	**18a**	96
p-$MeOC_6H_4$	**16b**	73	**17b**	60:40	71 (39)	**18b**	96
p-BrC_6H_4	**16c**	60	**17c**	50:50	71 (38[d])	**18c**	–[e]
$PhCH_2$	**16d**	60	**17d**	50:50	79 (39)	**18d**	85

[a] Yield of 1:1 diastereomeric mixture over four steps; [b] Yield of unpurified mixture (recrystallised yield of pure **17**); [c] From pure **17**; [d] 1:1 mixture; [e] 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[19] 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 $^3J_{HH}$ (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 α-amino ketone **19b** and an excellent quantitative yield of α-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 α-amino ketones and alcohols containing unnatural amino acid side chains.[20]

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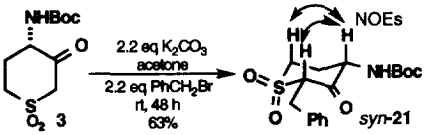

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