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A Memory of Chirality Approach to the Stereoselective Synthesis of 4-Hydroxy-α-methylprolines

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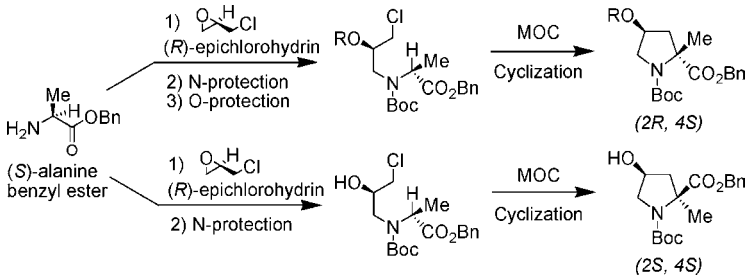
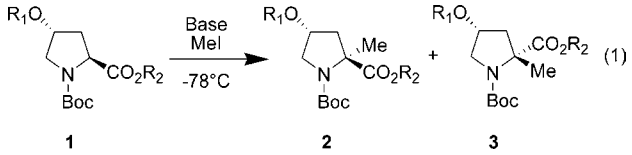
ABSTRACT

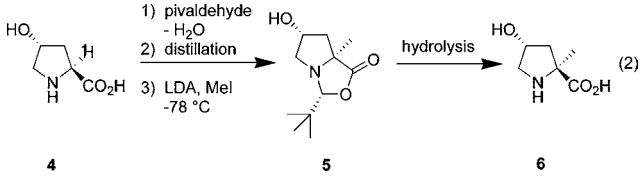


To extend the memory of chirality (MOC) methodology to structurally more diverse compounds, the synthesis of 4-hydroxy-α-methylprolines was undertaken. Yield and selectivity were very good, with an unexpected reversal in selectivity observed for the cyclization of one adduct with an unprotected hydroxyl.

Incorporation of α-alkyl-α-amino acids into synthetic peptides and proteins can have a significant impact on structure.[1] These conformationally restricted building blocks play an important role as peptide conformation modifiers and as enzyme inhibitors. The constraining effects exerted by these nonproteinogenic building blocks are even more pronounced when placed in a cyclic system such as α-methylproline.[2] The diastereomers of 4-hydroxy-α-methylproline (**2** and **3**, and their enantiomers) are structurally interesting variants that have been underutilized due in part to the challenge of stereoselective synthesis. While some of the four diastereomers have been synthesized, most reported approaches[3−7] to these targets rely on alkylation of a protected 4-hydroxyproline substrate followed by separation of the isomeric products (eq 1).



One stereoselective synthesis has been reported; Seebach found that pivaldehyde *N*,*O*-acetal alkylation (eq 2) cleanly afforded trans-isomer **6** (ds >95%) after hydrolysis. However, this route is limited by the availability of the *trans*-4-hydroxyproline,[8−10] and does not allow access to the *cis* isomers.



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Memory of chirality (MOC)[11−13] is a potentially powerful strategy for the stereospecific construction of quaternary centers. Kawabata and co-workers recently described an MOC route to cyclic α-substituted amino acids (see Figure 1),[14] a novel and operationally uncomplicated approach to

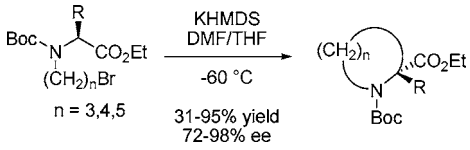


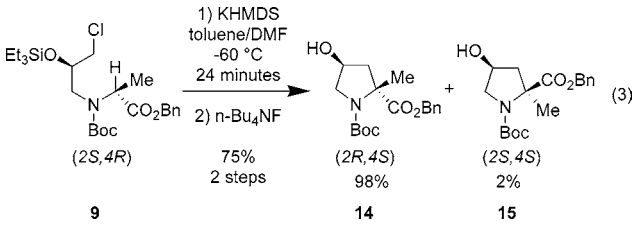
Figure 1. Kawabata's MOC approach to cyclic amino acids with a quaternary stereocenter.

this synthetic problem. In an effort to extend this methodology to functionally more complex cyclic α-alkyl amino acids, we undertook a study targeting the stereoselective synthesis of 4-hydroxy-α-methylproline diastereomers.

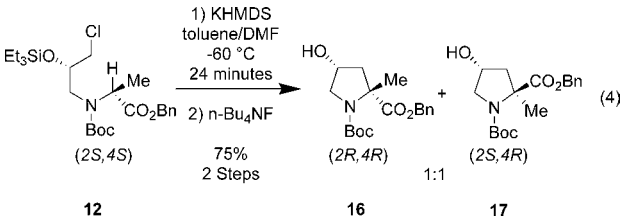
Our approach to the synthesis of 4-hydroxy-α-methylproline builds on the observation that epichlorohydrin reacts stereospecifically with carboxy-protected alanine to give the corresponding chiral chlorohydrin.[15] Installation of protecting groups and cyclization under standard conditions should lead to the desired 4-hydroxy-α-methylproline. By judicious choice of commercially available optically active starting materials it should be possible to construct any of the four stereoisomers. To demonstrate proof of principle we chose to react the naturally occurring (*S*)-alanine benzyl ester with (*R*)- and (*S*)-epichlorohydrin (Scheme 1).

As expected, when optically active starting materials were used, a single chlorohydrin diastereomer was formed. We protected the nitrogen as the *tert*-butylcarbamate[14,16] and the hydroxyl as the TES (triethylsilyl) ether in preparation for cyclization. Reaction of the (2*S*,4*R*)-chlorohydrin **9** under standard conditions[14] followed by deprotection of the hydroxyl led to the expected (2*R*,4*S*) isomer as the major product with excellent diastereoselectivity[17] (eq 3).

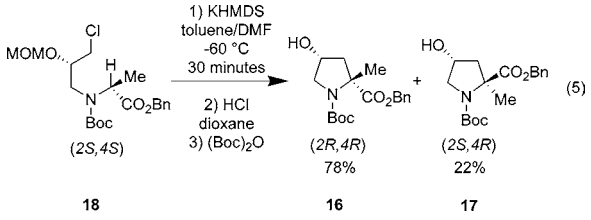
On the other hand, we were surprised to discover in the (*S*)-chlorohydrin series that cyclization gave a 1:1 mixture



(eq 4) of the diastereomeric products. Inspection of models suggests that crowding in the transition state may be occurring, disfavoring the expected (2*R*,4*R*) product.

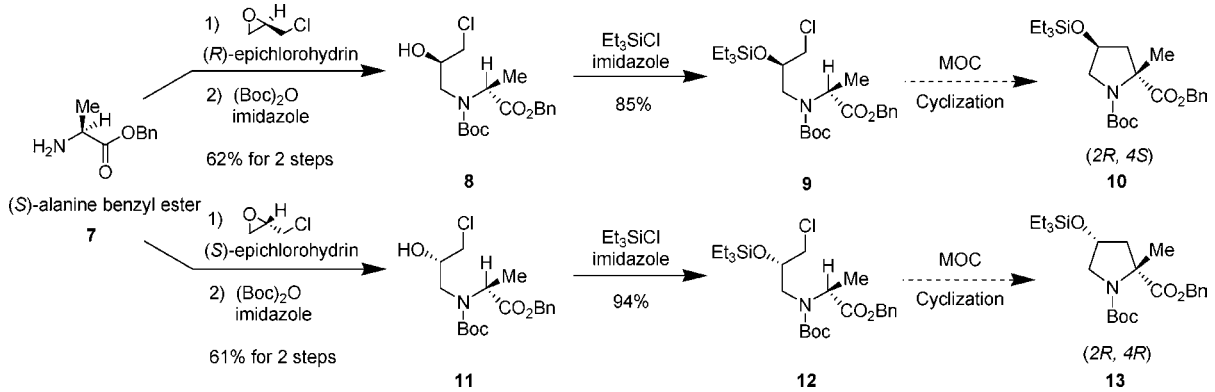


We reasoned that a smaller alcohol protecting group might decrease steric congestion and tilt the balance in favor of the expected diastereomer. To test this theory we made the corresponding MOM ether and carried out the cyclization under identical conditions (eq 5). We were gratified to see a small but noticeable increase in the selective formation of the (2*R*,4*R*) diastereomer with the sterically less demanding protecting group, supporting our hypothesis.



The smallest C4 group would of course be the unprotected alcohol. However, reaction of this substrate could be complicated by cyclization to the epoxide (Figure 2). The

Scheme 1. Proposed MOC approach to (*2R*) diastereomers of 4-hydroxy-α-methylproline



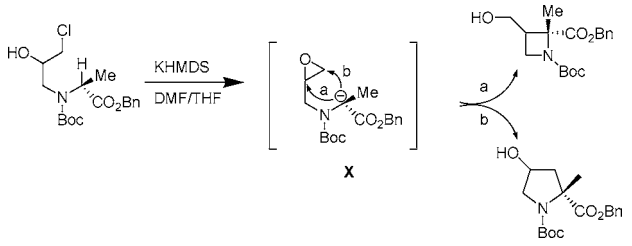
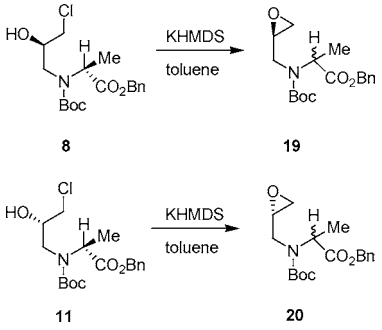


Figure 2. Possible cyclizations of the unprotected chlorohydrin.

resulting epoxyenolate (**X**) could then undergo either exo closure to the azetidine (path a) or endo to the pyrrolidine (path b).[18]

When the two unprotected chlorohydrins were exposed to excess KHMDS in toluene at −60 °C, the epoxides were the only identifiable products (Scheme 2). The proton and

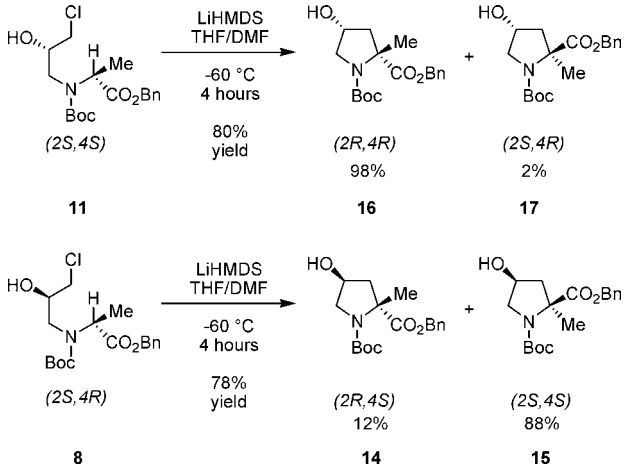
Scheme 2. KHMDS Treatment of Unprotected Hydroxy Compounds



carbon NMR spectra of compounds **19** and **20** are virtually indistinguishable, suggesting that scrambling occurred at C2.

Interestingly, when the base was switched to LiHMDS (1 M in THF) and the chlorohydrin substrate dissolved in a coordinating solvent (DMF) only the α-methylproline products were observed (Scheme 3). And while the TES protected

Scheme 3. Cyclization of Unprotected Hydroxy Substrates with LiHMDS

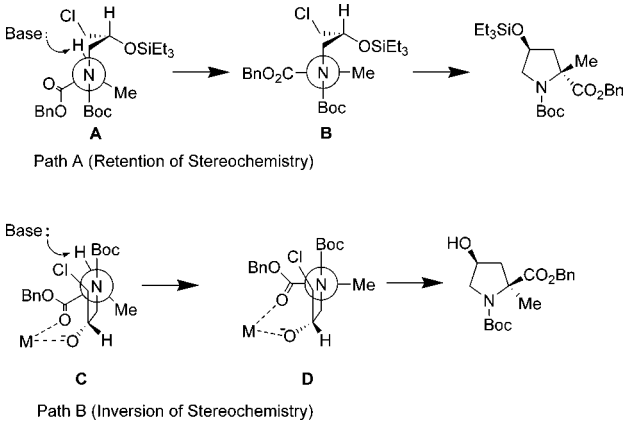


(2*S*,4*S*) diastereomer **12** gave a 1:1 mixture of products **16** and **17** (eq 4), the unprotected hydroxyl compound **11** gave almost exclusively the expected (2*R*,4*R*) product **16**. Surprisingly, when the (2*S*,4*R*) isomer **8** was cyclized, the major product was not the expected (2*R*,4*S*) isomer, but rather the (2*S*,4*S*), where the carboxylate bearing stereocenter has been inverted.

During the course of the reaction we observed (by HPLC) what appeared to be the epoxide, but it is not clear if this is a true intermediate, or an artifact of our sample preparation and analysis. When authentic epoxide was treated with LiHMDS in THF, even in the presence of excess LiCl, no reaction was observed.

As suggested by Kawabata,[14] we believe that where retention of configuration is observed (Scheme 4, path A), deprotonation and cyclization occur from the shown con-

Scheme 4. Possible Mechanism for Stereoselective Cyclizations



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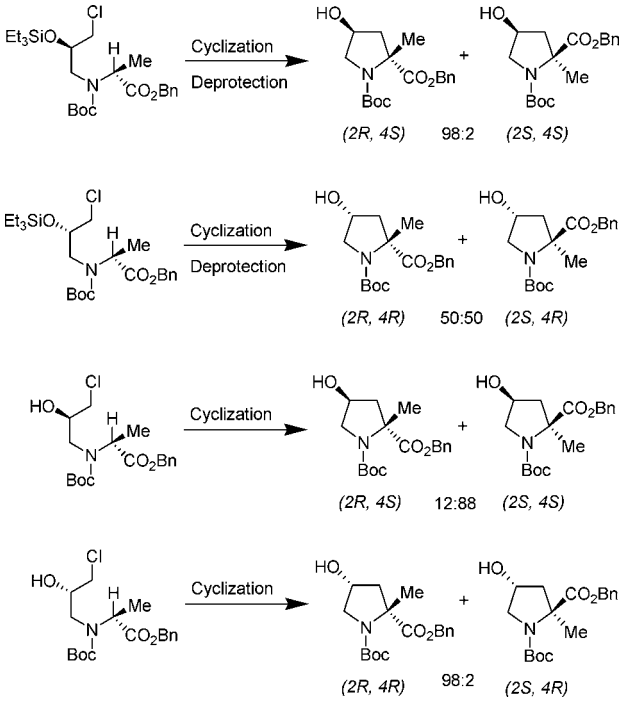
Scheme 5. Summary of Cyclizations



former **A**, with base approaching opposite to the sterically more demanding Boc group. Cyclization is rapid relative to racemization of the enolate. However, in the case of the unprotected alcohol **8** we believe that the alkoxide forms a complex (**C**) that locks the Boc group into a syn relationship to the proton. Additional base then deprotonates to give the enolate, which cyclizes to the cis product.[19]

In conclusion, we have demonstrated a straightforward method for the synthesis of the four diastereomers of 4-hydroxy-α-methylproline. Using memory of chirality methodology, cyclization of the protected (2*S*,4*R*) compound **9** gave the trans product **14** with excellent selectivity. Omission of the hydroxy protecting group for the (2*S*,4*S*) compound **11** led to the technically more challenging cis diastereomer **16**. Unexpectedly, cyclization of the unprotected (2*S*,4*R*) isomer **8** gave predominately the cis diastereomer **15**, via inversion of the carboxylate stereocenter. The (2*S*,4*S*) and (2*S*,4*R*) 4-hydroxy-α-methylproline diastereomers are accessible starting with (*R*)-alanine.

Acknowledgment. Many thanks to our colleagues in Abbott Structural Chemistry for all their help: Rodger Henry for the X-ray analysis on **21**, Ian Marsden for help interpreting the NMR data, and Paul West for HRMS analysis.

Supporting Information Available: Experimental procedures and analytical data for compounds **8**, **9**, **11**, **12**, **14**, **15**, and **18**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The NMR of the major product compares favorably with that previously reported.[4] The *trans* stereochemistry of the major product (**14**) was confirmed by removal of the benzyl ester and single-crystal X-ray analysis of the resultant *N*-boc-4-hydroxy-α-methylproline (**21**).

(18) Metal−halogen exchange induced cyclization of ω-iodopentyl epoxides led predominately to the cyclobutylmethanol. Addition of certain Lewis acids reverses selectivity to the cyclopentanol. See: Cooke, M. P.; Houpis, I. N. *Tetrahedron Lett.* **1985**, *26*, 3643−3646. Reaction of ω-bromopentyl epoxides with activated copper in the presence of trialkyl or triaryl phosphines leads predominately to the cyclopentanols. See: Wu, T.-C.; Rieke, R. D. *Tetrahedron Lett.* **1988**, *29*, 6753−6756. See also: Stork, G.; Cohen, J. F. *J. Am. Chem. Soc.* **1974**, *96*, 5270−5272.

(19) During the review process an alternate mechanism was proposed in which the asymmetric alkylation results from kinetic resolution of racemic enolates by the alkoxide derived from the chiral chlorohydrin. We thank the referee for this suggestion.