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Stereocontrolled Sequential Functionalization in Acyclic Systems by Exploiting Internal 1,2-Asymmetric Induction – Generation of Symmetry-Related Polyamino Alcohol Motifs

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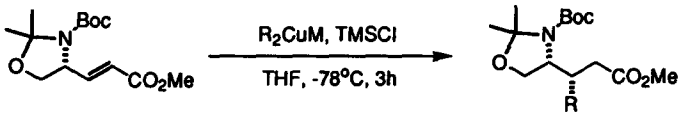
Abstract: Treatment of acyclic γ-ureido α,β-unsaturated esters with lithium dialkyl or diaryl cuprates leads to the corresponding β,γ-substituted esters with high *syn*-stereoselectivity. The potassium enolates of these compounds react with trisyl azide or the Davis oxaziridine reagent to give all *syn*-orientated α-azido esters, or α-hydroxy esters. Mitsunobu inversion with azide ion produces diastereomeric compounds. The products are excellent examples of functionalized diamines and amino alcohols which can also be made in an iterative manner.

The amino alcohol unit is an important functional feature in the design of a number of enzyme inhibitors.[1] Although methods of synthesis in this area are well known,[2] the issue of stereochemical control and the specific deployment of amino, hydroxy and alkyl groups in acyclic chains is not a trivial one. Thus, amino, diamino, hydroxy and related groups that have recurring alternating and symmetry-related patterns are of interest not only as possible subunits of natural or unnatural molecules, but as scaffolds for the attachment of pharmacologically relevant motifs in conjunction with combinatorial methods of drug discovery.[3]

In the preceding Letter,[4] we demonstrated the feasibility of a stereocontrolled conjugate addition of lithium dimethylcuprate to γ-ether substituted α,β-unsaturated esters.[5] The potassium enolates of the resulting *anti*-orientated products could be further functionalized with electrophiles to give *anti-syn* disposed propionate-type triads, as well as other products depending on the nature of the electrophile. In our original work,[5] we had also shown that of conjugate addition lithium dimethylcuprate to γ-N-Boc α,β-unsaturated acyclic esters led to the C-methyl products having a *syn*-relationship to the resident amine group (1,2-asymmetric induction).[6]

We now wish to report on the generality of this observation as seen in Table 1. Thus, ethyl, butyl vinyl, 2-propenyl and phenyl substituents can be introduced in good to excellent yields and with a high degree of stereocontrol. The *syn*-relationship of the newly introduced group relative to the resident functionality was established by chemical means as well as by X-ray crystal structure analysis of derivatives. A rationale for the observed stereochemical pattern has been previously given.[5]

Table 1



Entry	R	M	Yield [a]	Syn/Anti [b]	$[\alpha]_D$ [c]
1	Methyl	Li	97%	>50:1	-16.3
2	Ethyl	MgBr	70%	>50:1	-20.8
3	Butyl	Li	90%	>50:1 [d]	-10.5
4	Vinyl	MgBr	80%	>50:1	-12.4
5	2-Propenyl	Li	75%	>14:1 [d]	+5.7
6	Phenyl	MgBr	80%	>8:1	+36.0

a. Yield of isolated product after flash chromatography; b. Ratio determined by ^{1}H-NMR of crude product before chromatography; c. Optical rotation was measured at 25°C in $CHCl_3$; d. X-ray structure

It was of interest to study the reactivity of, and the stereochemical outcome from the reaction of enolates derived from the products shown in Table 1 with oxygen and nitrogen electrophiles. For the purposes of generating "aminopropionate" triads, we chose to study the β-methyl analog (Scheme 1).

Scheme 1

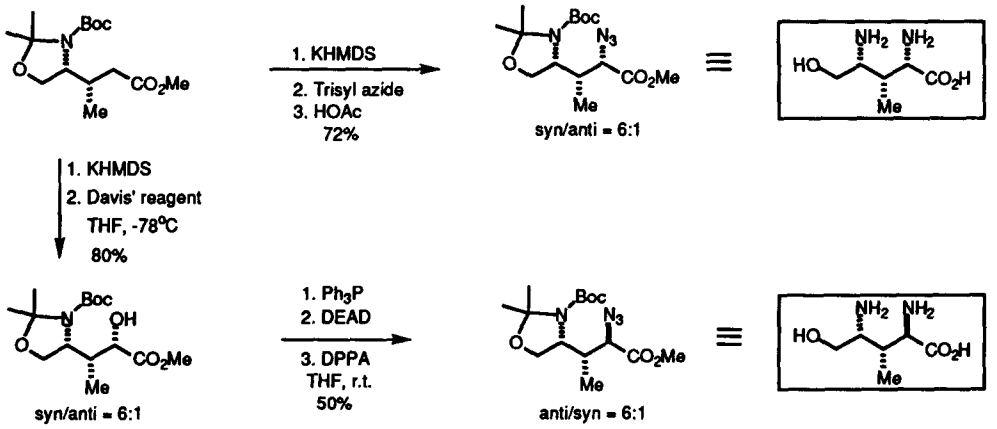
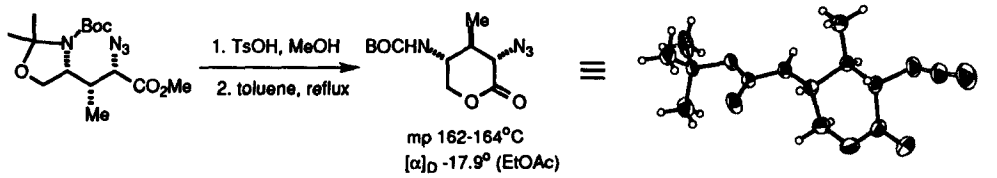


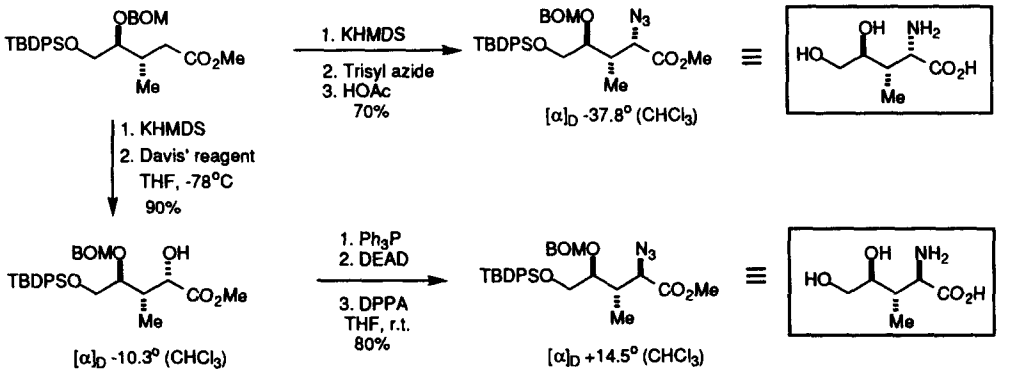
Figure 1



Treatment of the potassium enolate with trisyl azide[7] led to a mixture of the *syn-syn* and *syn-anti* products in a ratio of 6:1.[8] The stereochemical identity of the major product was secured by a single crystal X-ray analysis of the corresponding lactam (Figure 1). The stereochemical outcome of the azidation reaction can be rationalized based on a transition state proposed in the preceding Letter[4] for hydroxylation in related acyclic potassium enolates. Treatment of the potassium enolate with the Davis oxaziridine reagent,[9] led to a high yield of the corresponding α-hydroxylated ester as a mixture of *syn-syn* and *syn-anti* isomers (6:1 respectively). Mitsunobu inversion[10] with diphenylphosphoryl azide afforded the *syn-anti* azido diastereomer.[11]

An alternative synthesis of diastereomeric 1,3-amino alcohol motifs that are related to the all *syn*-isomer is presented in Scheme 2. Thus the readily available γ-alkoxy β-C-methylated ester[5] can be directly "azidated" via its potassium enolate to provide the *syn*-α-azido ester in high yield and excellent stereoselectivity. The diastereomeric *anti-anti* isomer can be easily obtained by a Mitsunobu protocol.

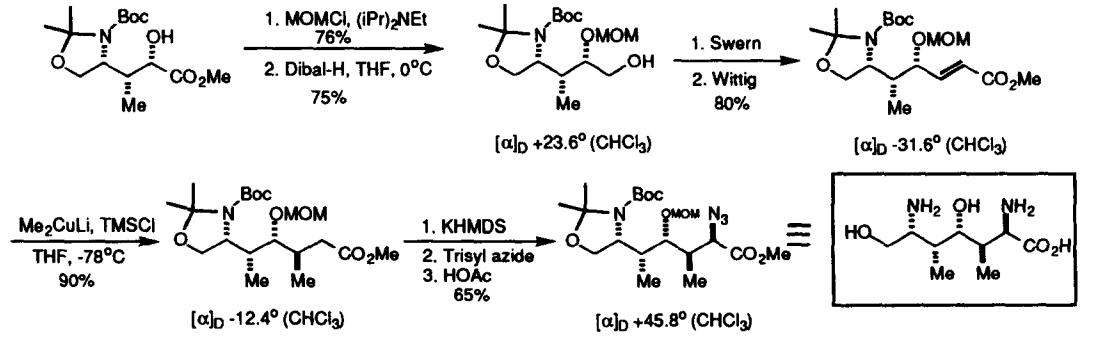
Scheme 2



The diamino acids shown in Schemes 1 and 2 are interesting pseudo symmetrical amino and amino alcohol variants of nature's ubiquitous polypropionate triads.

In an effort to extend the conjugate addition-electrophilic hydroxylation or azidation to an iterative process, we adopted the protocol shown in Scheme 3. Thus the 6:1 mixture of hydroxylated products was protected as the MOM ether and the ester group was reduced to the primary alcohol. Separation of the major *syn-syn* isomer, oxidation and Wittig extension afforded an α,β-unsaturated γ-alkoxy template for a second

Scheme 3



conjugate addition reaction. Treatment with lithium dimethylcuprate afforded the β-C-methyl adduct in excellent yield as a single compound. As expected, delivery of the cuprate occurred in a non-chelation mode to produce an *anti*-orientation relative to the resident OMOM group (1,2-induction).[5,6a] Treatment of the potassium enolate with trisyl azide followed by normal acidic quench gave the corresponding α-azido ester as a single isomer after chromatography. This corresponds to a seven-carbon pseudo C_2 symmetrical diamino alcohol motif with differently functionalized end groups.

We have presented methods that allow the elaboration of 1,3-diamines, 1,5-diamines, and related amino alcohol derivatives[12] from a single chiral progenitor by a series of iterative asymmetric 1,2-inductions. In addition to their interest as unnatural α-amino acid derivatives, they are also differentially derivatized acyclic chains with stereochemically tunable functionality, that can be utilized as cyclic lactone and lactam templates or scaffolds for chemical diversification.

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References and Notes

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8. For a typical procedure: at -78°C, KHMDS (1.2eq, 0.5 M in toluene) was added to a solution of ester (1 eq) in THF, the resulting solution was stirred for 30 min, then treated with trisyl azide (1.5 eq) in THF. The reaction was continued for 20 min at -78°C and then quenched by adding glacial acetic acid (6 eq) with immediate warming to 30°C in a water bath. After stirring for 2h, the white slurry was diluted with EtOAc, washed with 5% $NaHCO_3$, satd. NaCl, and dried over Na_2SO_4. The product was purified by flash chromatography.
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