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TANDEM ALDOLIZATION/LACTONIZATION/DYOTROPIC REARRANGEMENT OF α-AMINO-ALDEHYDES

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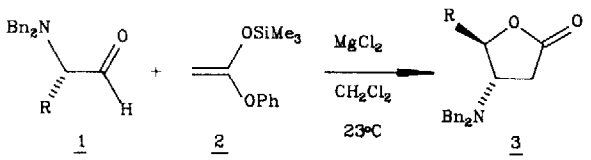
Abstract: N,N-Dibenzyl-protected α-amino-aldehydes 1 undergo non-chelation-controlled aldol additions of 1-phenoxy-1-trimethylsiloxyethylene 2 followed by β-lactone formation and dyotropic rearrangement, all three reactions being catalyzed by $MgCl_2$. The products, 4-substituted 3-amino-γ-lactones 3, are stereochemically pure (de and ee > 99 %).

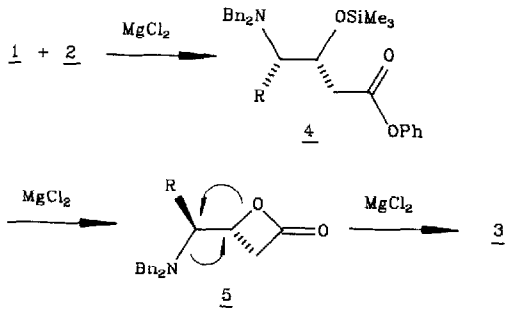
We have previously shown that α-N,N-dibenzylamino aldehydes 1, prepared from the corresponding amino acids, undergo non-chelation-controlled additions of RMgX, RLi, Li-enolates and Me_3SiCN/ZnX_2[1]. All of the presently known examples constitute effective "protective group tuning", since singly protected analogs (BOC, 9-phenyl-9-fluorenyl, etc) generally deliver mixtures of adducts[2]. Indeed, aldehydes 1 have since been employed by several other groups in similar reactions[3]. In some cases reversal of diastereoselectivity has been achieved using strongly Lewis acidic reagents[1]. In this communication we report some unexpected results obtained upon reacting the aldehydes 1 with the O-silylketene ketal 2 in the presence of $MgCl_2$:



1 2 3

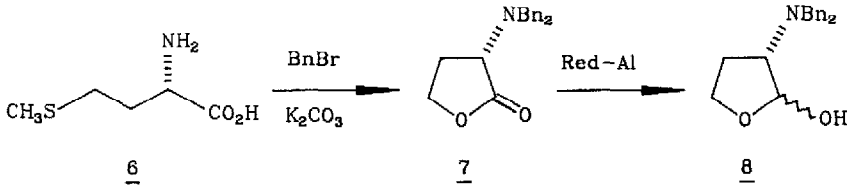
a) R = CH_3	a) 42%
b) R = $PhCH_2$	b) 49%
c) R = $(CH_3)_2CH$	c) 55%
d) R = $(CH_3)_2CHCH_2$	d) 53%

In hope of performing a group transfer Mukaiyama-type aldol addition, we reacted 2 (which is known not to rearrange to the unreactive C-silylated isomer)[4] with 1 in the presence of $MgCl_2$. The main products turned out not to be the expected aldol adducts 4 (or their chelation-controlled diastereomers), but the 3-amino γ-lactones 3. We interpret this interesting transformation as a process involving three tandem $MgCl_2$-mediated reactions: 1) Non-chelation-controlled aldol addition to 4; 2) Lactonization to 5; and 3) Stereospecific dyotropic rearrangement [5] to the final diastereo- and enantiomerically pure products 3. MgX_2-catalyzed dyotropic rearrangements of β-lactones have been previously described by Mulzer[6] in other situations and applied by Black[7].

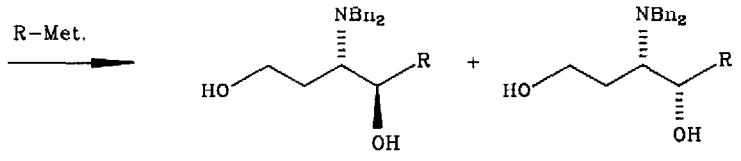


Conversion of 1 to 3 amounts to > 75 %, the yields of analytically pure products following chromatography being 40-55 %[8]. The major side products are the aldol adducts 4 (10 - 20 %), but the diastereomers of 4 could not be detected. Isolated 4a undergoes $MgCl_2$-mediated transformation to 3a. The assignment of the relative configuration in 3 was made on the basis of NOE experiments (trans arrangement of the substituents at the chiral centers of the lactone ring). The absolute configuration was ascertained as follows, which also supports the above conclusion regarding the relative configuration: Protection and lactonization of L-methionine 6[9] afforded the α-amino lactone 7, which was reduced to the lactol 8. Addition of two equivalents of CH_3MgI (or $CH_3Ti(OiPr)_3$[10]) or PhMgBr yielded the amino diols 9 stereoselectively[11]. This stereoselectivity is expected on the basis of non-chelation-control in the reaction of the intermediate α-amino aldehyde[1], a conclusion which was corroborated by an X-ray analysis of adduct 9b[12]. Finally, lactone 3a was reacted with $LiAlH_4$, affording a single product 9a ($[\alpha]_D^{24}$ = 1.0; c = 0.13, CH_3OH) which was enantiomerically pure as shown by control experiments. Accordingly, this diol was doubly esterified using the+"Mosher-Chloride"[13], which provided a single diastereomer (NMR, HPLC). This esterification was also performed on 9a

obtained from 6, a process which led to the same diester[14]. Since the absolute configuration of L-methionine is as shown in 6, the relative and absolute configurations of 3 are established unequivocally.



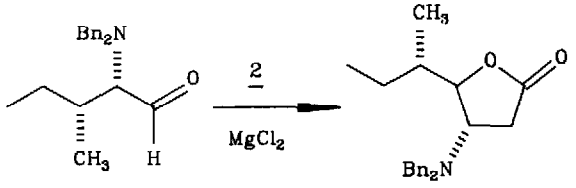
6 7 8



9 10

CH_3MgI	a) R = CH_3	95	:	5 (72%)
$CH_3Ti(OiPr)_3$	a) R = CH_3	>98	:	<2 (71%)
PhMgBr	b) R = Ph	92	:	8 (74%)

In a final experiment, we treated the amino aldehyde 1e derived from L-isoleucine with 2. In the crude product we detected 3e as the only γ-lactone (75 %) present, which was isolated in pure form (40 %). The results show that no epimerization in the aldehyde 1e occurs, in line with the observed absence of racemization of 1a-d during formation or reaction.



1e 3e

3-Amino γ-lactones are of interest as unusual natural[15] and non-proteinogenic amino acid derivatives and as precursors for amino sugars such as ristosamine[16].

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