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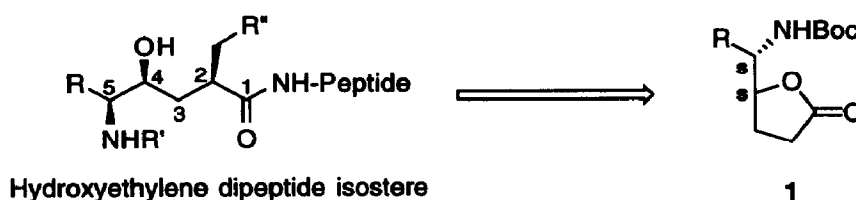
Diastereoselective Synthesis of the Key Lactone Intermediate for the Preparation of Hydroxyethylene Dipeptide Isosteres

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Abstract: An efficient and highly stereoselective route for preparing hydroxyethylene dipeptide isosteres from α -N,N-dibenzylamino ketones has been developed.

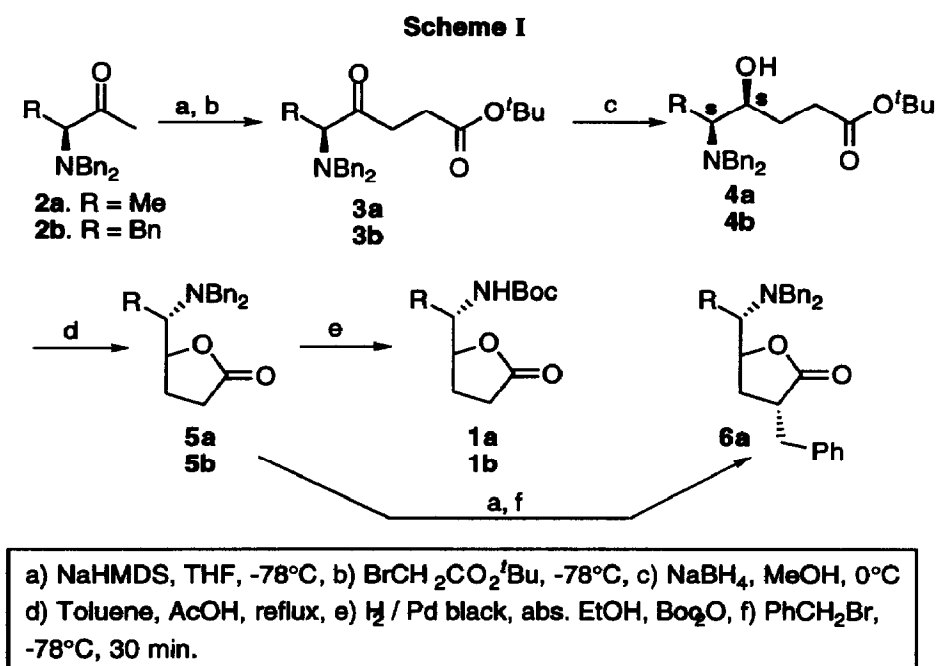
In the last few years hydroxyethylene dipeptide isosteres ("peptide mimics") have generated considerable interest in the scientific community due to their potential therapeutic value as inhibitors of both HIV-protease and renin.¹ These peptidomimetics consist of amino alcohol functionality which almost invariably exhibit the (4*S*,5*S*) stereochemistry. They also typically possess a substituent at the C₂ position with the indicated absolute configuration (*Note:* the R, S-designation may change depending upon the substituent priority).



Many of the reported synthetic approaches to these isosteres make use of the lactone **1** as a key intermediate which is then further elaborated *via* a diastereoselective alkylation of the enolate and a subsequent ring opening.² Several groups have synthesized **1** from an α -amino aldehydes by reactions with: (a) homoenolate equivalents,^{2a} (b) lithium ethyl propiolate,^{2b} or (c) allylic organometallic reagents.^{2c} Alternatively, α -amino aldehydes have been converted to **1** *via* the intermediacy of the corresponding α -amino epoxides.^{2d} In addition, approaches involving the synthesis of **1** from carbohydrate precursors, such as D-mannose,³ or γ -ketoesters derived from N-Cbz phenylalanine,^{4a} N-benzyl-N-Boc phenylalanine^{4b} and N-phthalimido phenylalanine^{4c} have been reported. However, virtually all of them suffer from at least one disadvantage (low chemical efficiency, poor diastereoselectivity, expensive starting materials, *etc.*) which makes them unattractive for scale-up. An exception to this is the elegant synthesis reported by the Merck group which was carried out on a multigram scale. Perhaps the only small disadvantage of this approach is that the starting α -amino aldehyde is sensitive towards racemization under a variety of experimental conditions.⁵ Our goal was to develop a general synthetic route which was efficient, selective and

which employed configurationally-stable starting materials. Herein, we report a novel synthetic route to these hydroxyethylene dipeptide isosteres starting from α -amino ketones that satisfies the above-mentioned criteria.

Reetz and coworkers have demonstrated that the keto group of α -*N,N*-dibenzyl amino ketones, which are readily synthesized from α -(*L*)-amino acids, can be reduced with excellent diastereoselectivity to the corresponding vicinal amino alcohol possessing (*S,S*)-stereochemistry.^{6a,b} In a seemingly unrelated study, we have recently reported that lithium enolates of these ketones undergo aldol reactions with a variety of aldehydes in highly diastereoselective manner.⁷ Our synthesis of **1**, which is outlined in Scheme I, conceptually links these two findings.



The α -amino ketones **2a,b** were synthesized from *L*-alanine and *L*-phenylalanine, respectively, using a minor modification of Reetz's procedure.^{6a} These ketones were converted into their corresponding γ -keto esters **3a,b** in high yield by sequential treatment with sodium hexamethyldisilazide, followed by *t*-butyl bromoacetate. The use of lithium enolates gave slightly lower yields and the use of ethyl bromoacetate resulted in a complex mixture of products. The NaBH₄ reduction of these γ -keto esters proceeded smoothly to give **4a,b** in 93% yield with excellent diastereoselectivity (only one diastereomer was observed by ¹H and ¹³C NMR analysis of the crude product). The absolute configuration at the newly formed center was tentatively assigned to be (*S*) based on the literature precedents.⁴ **4a,b** were converted into their corresponding lactones **5a,b** using a standard, acid-catalyzed protocol.⁸ In order to obtain a rigorous proof of the absolute

stereochemistry, **5b** was converted into its *t*-Boc protected derivative **1b** by a one pot debenzylation, protection sequence.⁹ The lactone **1b** exhibited the same physical and spectral characteristics as the authentic sample.¹⁰

Lactone **1a** was alkylated via its sodium enolate (NaHMDS / THF, followed by addition of benzyl bromide at -78°C, 30 min) to produce **6a** in 81% yield. Again, only one diastereomer was detected by ¹H and ¹³C NMR (> 95% d.e.). This material can then be converted into the desired isostere by a ring opening reaction which employs one of the well-established amidation protocols (e. g., the Weinreb procedure).¹¹

Thus, we have developed an efficient and highly stereoselective route for preparing hydroxyethylene dipeptide isosteres from α -N,N-dibenzylamino ketones. The salient features of this route include: (1) the relatively few number of steps required, (2) the use of configurationally-stable α -N,N-dibenzylamino ketones as starting materials and (3) excellent diastereoselectivity and chemical efficiency.¹²

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8. The physical characteristics of the two lactone intermediates are as follows:
5a: White solid., m.p. 61-62°C, ¹H NMR (300.15 MHz, CDCl₃) δ 1.11 (d, J= 6.6 Hz, 3H), 1.85-

2.15 (m, 2H), 2.44-2.50 (m, 2H), 2.86 (pentet, $J = 6.9$ Hz, 1H), 3.71 (AB_q, $\delta_A = 3.87$, $\delta_B = 3.56$, $J_{AB} = 13.8$ Hz, 4H), 4.49 (pentet, $J = 7.2$ Hz, 1H), 7.10-7.41 (m, 10H); ¹³C NMR (75.5 MHz) 10.9, 25.6, 28.7, 54.3(2C), 55.8, 83.1, 126.8(2C), 128.2(4C), 128.7(4C), 139.9(2C), 177.1; Mass Spectrum (low res.) 310 (M+1, 20%), 224 (MeCHNBn₂, 40%), 91 (NBn₂, 100%); HRMS for C₂₀H₂₄O₂N: 310.1807 (Calc'd 310.1801); E.A. Found C 77.54, H 7.55, N 4.49; Calc'd C 77.64, H 7.49, N 4.53.

5b: White solid., m.p. 165-166°C, ¹H NMR (300.15 MHz, CDCl₃) δ 1.41-1.82 (m, 2H), 2.22-2.57 (m, 2H), 2.83-3.13 (m, 3H), 3.81 (AB_q, $\delta_A = 4.01$, $\delta_B = 3.60$, $J_{AB} = 13.5$ Hz, 4H), 4.49 (m, 1H), 7.13-7.28 (m, 15H); ¹³C NMR (75.5 MHz) 24.4, 28.8, 31.8, 55.3, 61.3, 81.2, 126.2, 126.9(2C), 128.3(3C), 128.4(2C), 128.8(4C), 129.4, 139.2, 139.5(2C), 177.0; Mass Spectrum (low res.) 386 (M+1, 30%), 300 (BnCHNBn₂, 38%), 91 (NBn₂, 100%); HRMS for C₂₆H₂₇O₂N: 385.2037 (Calc'd 385.2035); E.A. Found C 80.75, H 7.22, N 3.63; Calc'd C 81.00, H 7.06, N 3.61.

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10. We would like to thank Dr. David Askin and Dr. Ichiro Shinkai (Merck, Sharp and Dohme Research Laboratories) for providing us with an authentic sample of this material.
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12. Just prior to submission of this manuscript, we became aware of an approach which utilizes N,N-dibenzyl phenylalanine derivatives in a fashion which is complementary to our procedure. See: Diederich, A. M.; Ryckman, D. M. *Tetrahedron Lett.* **1993**, *34*, 6169.

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