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A General Stereocontrolled Synthesis of Hydroxyethylene Dipeptide Isosteres

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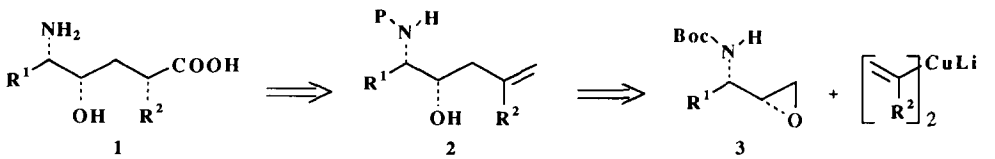
Abstract: Hydroxyethylene dipeptide isosteres were synthesized by stereocontrolled hydroboration of homoallylic alcohols derived from *syn* protected aminoepoxides followed by chemoselective oxidation of the resulting primary alcohols.

The design and synthesis of transition-state mimics for the hydrolysis of peptide bonds has attracted considerable interest. One such transition-state mimic is the "hydroxy" peptide bond isostere which may serve as a mimic of the tetrahedral intermediate for hydrolysis. The hydroxyethylene isostere **1** has yielded potent inhibitors of the aspartic protease renin or HIV-1 protease when used to remplace the scissile peptide bond in substrate analogs [1].

Many new syntheses of hydroxyethylene dipeptide isosteres have been recently described [2]. However, most of them utilize an intermediate aminoaldehyde derived from essential aminoacids and are applicable only to a limited choice of R^1, R^2 side chains or fail to provide adequate steric control.

In order to avoid the use of these rather unstable aminoaldehydes, we thought that it would be perhaps possible to elaborate the required *syn* aminoalcohol system by modification of stereochemically defined aminoepoxides [3].

We wish to report here a flexible and efficient route based on the stereoselective hydroboration of homoallylic alcohols **2** obtained by condensation of protected *syn* epoxyamines **3** with divinylcuprates.

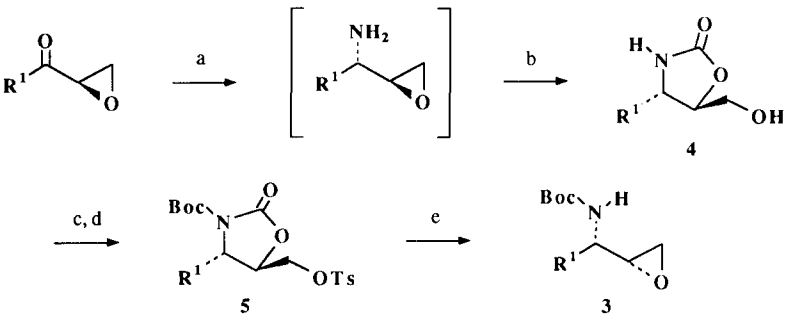


1 2 3

We have previously shown that the reductive amination of optically active epoxyketones [4] by tetramethylammonium triacetoxyborohydride allowed the access to *anti* epoxyamines [5]. However, due to the fact that the most active hydroxyethylene pseudodipeptides generally present an "all-*syn*" configuration, these epoxyamines did not allow the access to such compounds and it was necessary to effect an inversion of configuration in order to obtain the appropriate homoallylic alcohols.

In our early studies related to the synthesis of 3-amino 2-hydroxyacids [6], we had observed, in analogy to a result described by Cardillo [7], that the reaction of the unprotected epoxyamines resulting from the sodium cyanoborohydride aminating reduction with the carbonated form of Amberlyst A 26 afforded the *trans* oxazolidinones **4**. This reaction was conducted in one step without isolation of the free epoxyamine and was the result of an intramolecular epoxide opening with inversion of configuration [8].

At first, we attempted to carry out the direct coupling of the tosylate **5** with vinylic cuprates. However, whatever the conditions, this reaction failed to give any product.



Conditions: a) $AcONH_4$, $NaBH_3CN$ b) Amberlyst A26-Na_2CO_3 c) TosCl, pyridine
d) Boc_2O, cat. DMAP, CH_2Cl_2 e) Cs_2CO_3, MeOH

We envisaged then to prepare the desired alcohols **6** by reaction of vinylic cuprates with an epoxide. To perform such a strategy, the tosylate **5** derived from the oxazolidinone **4** was reacted with cesium carbonate in methanol. Thus, we succeeded, in a one-pot reaction, to open the oxazolidinones **5** and to cyclize *in situ* the intermediate N-protected cesium alkoxides into the *syn* epoxides **3** [9]. The reaction of these epoxides with divinylcuprates at - 30° C allowed the access to the corresponding homoallylic alcohols in very good yields (80-90%).

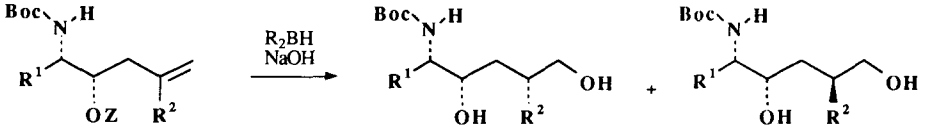
We studied next the hydroboration of these alcohols. Some years ago, it has been shown by Evans and coll. that the hydroboration of 2,4-dialkyl alk-1-enes afforded mainly the isomer where the middle group was *syn* to the alkyl group bound to the double bond [10]. This reaction was recently extended to compounds with a protected hydroxy function in the 4 position and applied to the synthesis of dipeptide isosteres [11].

We wanted to know if such an hydroboration would be possible with unprotected homoallylic alcohols (Scheme 2). Thus, we submitted several homoallylic alcohols (under free and acetate-protected form) to

Table 1 Hydroboration of Homoallylic Alcohols **6**

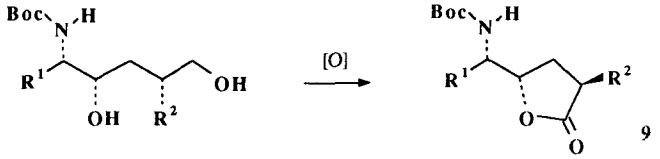
	R^1	R^2	Z	R_2BH	Yield%	7/8
1	*i*-Bu	Me	H	9-BBN	71	70/30
2	Bn	Me	H	9-BBN	66	68/32
3	C_6H_{11}-CH_2	Me	H	9-BBN	75	65/35
4	*i*-Bu	*i*-Bu	H	9-BBN	25	-
5	Bn	Bn	H	BH_3	0	-
6	*i*-Bu	*i*-Bu	Ac	BH_3	51	68/32
7	Bn	Bn	Ac	BH_3	51	65/35

various hydroborating agents. Our results are summarized in Table 1. In general, the reaction of free alcohols gives satisfactory yields when the R^2 substituent is small enough (entries 1, 2 and 3). In contrast, with more hindered substituents, the reaction is very sluggish and it is necessary to protect the secondary hydroxyl function to observe the hydroboration. It should be noted that the diastereomeric ratio was not very different for the free and the protected alcohols.



6 **7** **8**

As anticipated, in all cases, this reaction afforded mainly the *syn* diols. The configuration was determined after selective oxidation of the primary alcohol with Ley's reagent [12]. The resulting hydroxyacids



9

a R^1 *i*Bu, R^2 Me b R^1 Bn, R^2 Me
c R^1 C_6H_{11}-CH_2, R^2 Me d R^1 *i*Bu, R^2 *i*Bu
e R^1 Bn, R^2 Bn

Conditions: N-morpholine oxide, cat. *n*-$Prop_4RuO_4$ (3%);
4 Å molecular sieves; CH_2Cl_2 (Yield:46-60%)

were isolated as γ-lactones **9** which are the protected forms of the hydroxyethylene dipeptide isosteres[13].

Work is in progress to improve the above reported synthetic scheme and to enhance the diastereoselectivity of the hydroboration by appropriate modification of the hydroxyl protecting groups.

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9. *Syn* epoxides **3** ($[\alpha]_D^{20}$ (c, $CHCl_3$)-yields from **5**): R^1 = *i*Bu -14.7 (c 1.9)-(55%); R^1 = Bn +1.7 (c 2.1)-(50%); $R^1 = C_6H_{11}\text{-}CH_2$ -14.0 (c 2.0)-(48%).
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