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A Concise Synthesis of Aza-Dipeptide Isosteres.

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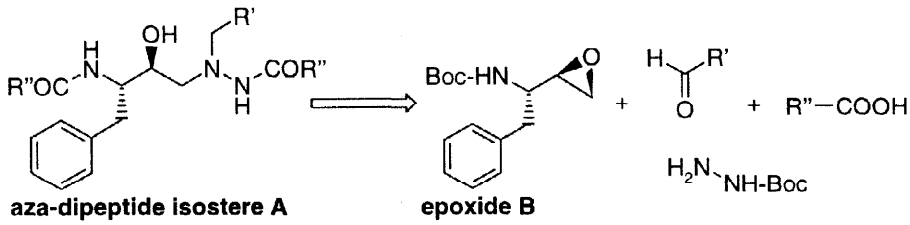
Abstract

Aza-dipeptide isosteres as potent HIV-protease inhibitors containing a (hydroxyethyl)-hydrazine moiety are synthesised in >98% diastereomeric and enantiomeric purity starting from *(L)*-phenylalanine aldehyde.

Keywords: cyanohydrins; hydrazides; hydrogenation; rearrangement.

We have recently reported a series of aza-dipeptide analogues as HIV-protease inhibitors with an excellent antiviral and pharmacokinetic profile [1]. These compounds contain a (hydroxyethyl)-hydrazine moiety **(A)** with an *(S)*-configured hydroxyl group as a transition state replacement for a scissile dipeptide bond. As shown in Scheme 1 they are readily accessible from an aldehyde, Boc-protected hydrazine and N-Boc-2(*S*)-amino-1-phenyl-3(*R*)-3,4-epoxybutane **(B)**, followed by removal of the Boc protecting groups and simultaneous acylation of the amine and hydrazine nitrogen atoms.

Scheme 1



aza-dipeptide isostere A **epoxide B**

A number of stereoselective syntheses for (2*S*,3*R*)-epoxide **(B)** as a versatile key intermediate have been described in recent literature [2], starting from either achiral olefins [3], or using chiral precursors [4], especially *(L)*-phenylalanine. Although applicable on a laboratory scale with chromatographic purification these latter methods seemed less practical for larger scale synthesis of the pure (2*S*,3*R*)-enantiomer: Direct conversion of the aldehyde derived from Boc-(*L*)-phenylalanine using one-step methylene transfer with dimethyloxosulfonium and dimethylsulfonium methylides [5], or Wittig olefination followed by epoxidation with peracids [6] proceeded with a 5 to 6:1 *threo* selectivity; however, it led to a considerable loss of optical purity (66-76% ee) due to racemisation of the starting aldehyde. The silyl-Wittig modification, although fully preserving the optical purity, required a four-step sequence and re-introduction of the Boc protecting group [7].

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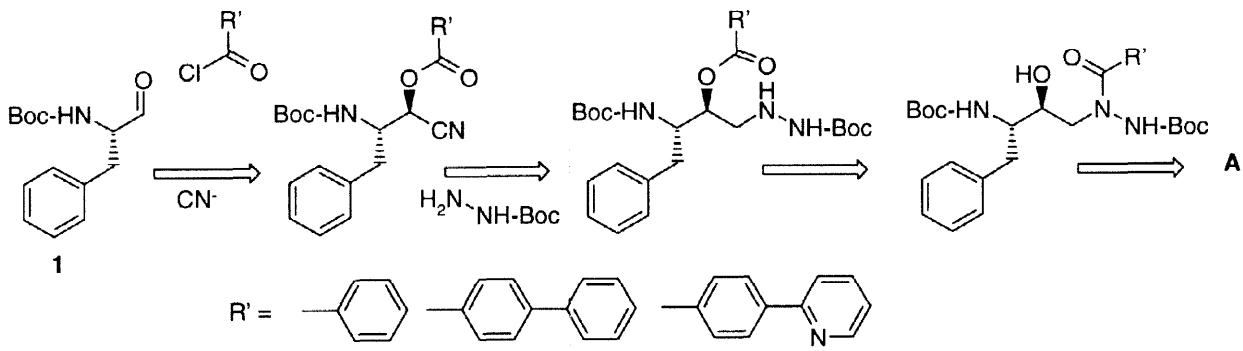
Concept

Once the inhibitors with the best overall profile were chosen for further pre-clinical evaluation we sought to develop an alternative synthesis of *bis*-Boc protected (hydroxyethyl)-hydrazine dipeptide isostere (**A**) carrying the selected substituents R' = phenyl, 4-biphenyl and 4-(2-pyridyl)-phenyl. Our synthetic concept shown in Scheme 2, circumventing the use of epoxide (**B**) was supported by the following experimental evidence: Cyanide addition to Boc-phenylalaninal **1** occurs with *threo* selectivity in the presence of an acylating agent. No face selectivity is observed under equilibrium conditions, suggesting that the kinetically favoured addition product is trapped by acylation [8]. Alkyl nitriles can be reductively transformed into hydrazones and finally hydrazines by hydrogenation with Raney Nickel in the presence of acetic acid and a monoacylated hydrazine [9]. Our initial investigations revealed that the intermediate 3-acyloxy-hydrazide as a reduction product underwent a facile [O→N] acyl transfer even under basic work-up conditions which offered the possibility to introduce the required final benzyl substituent as an acyl protecting and directing group in the inital cyanohydrin forming step.

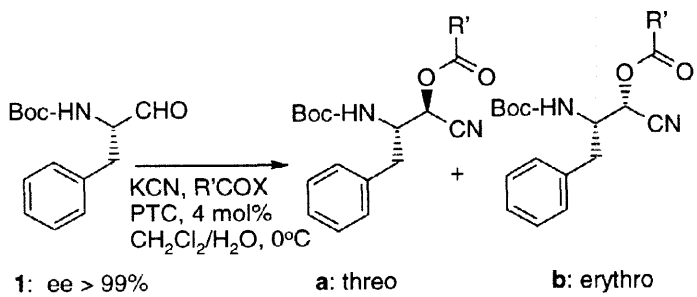
Scheme 2



Results

Cyanide addition to aldehyde **1** [10] in the presence of the appropriate acid chloride (entries **2** and **3**) or mixed anhydride using isobutyl chloroformate (entry **4**) occurred with up to 83:17 *threo* selectivity, whereby the nature of the phase transfer catalyst (4 mol %, 1.2 eq R'COX, 1.2 eq KCN in CH_2Cl_2/H_2O) had little influence on selectivity but on the yield of **2**, **3**, and **4**. With our intention to avoid column chromatography during the whole sequence wherever possible, cyanohydrins **2** and **3** were carried forward as diastereomeric mixtures whereas pure **4a** could be crystallised.

Scheme 3

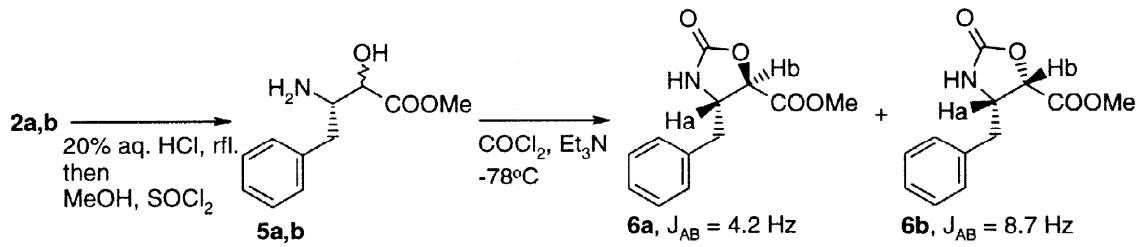


cpd	R'	PTC	yield	threo:erythro
2a,b	Ph	BCNC[1]	54%	83 : 17
3a,b	Ph-Ph	-	45%	77 : 23
3a,b	Ph-Ph	BCNC	97%	81 : 19
4a,b[2]	Ph-py	$N^+BnEt_3Cl^-$	70%	80 : 20

[1] BCNC: N-Benzyl cinchoninium chloride.
[2] Diastereomerically pure crystalline **4a** was obtained in 39% yield.

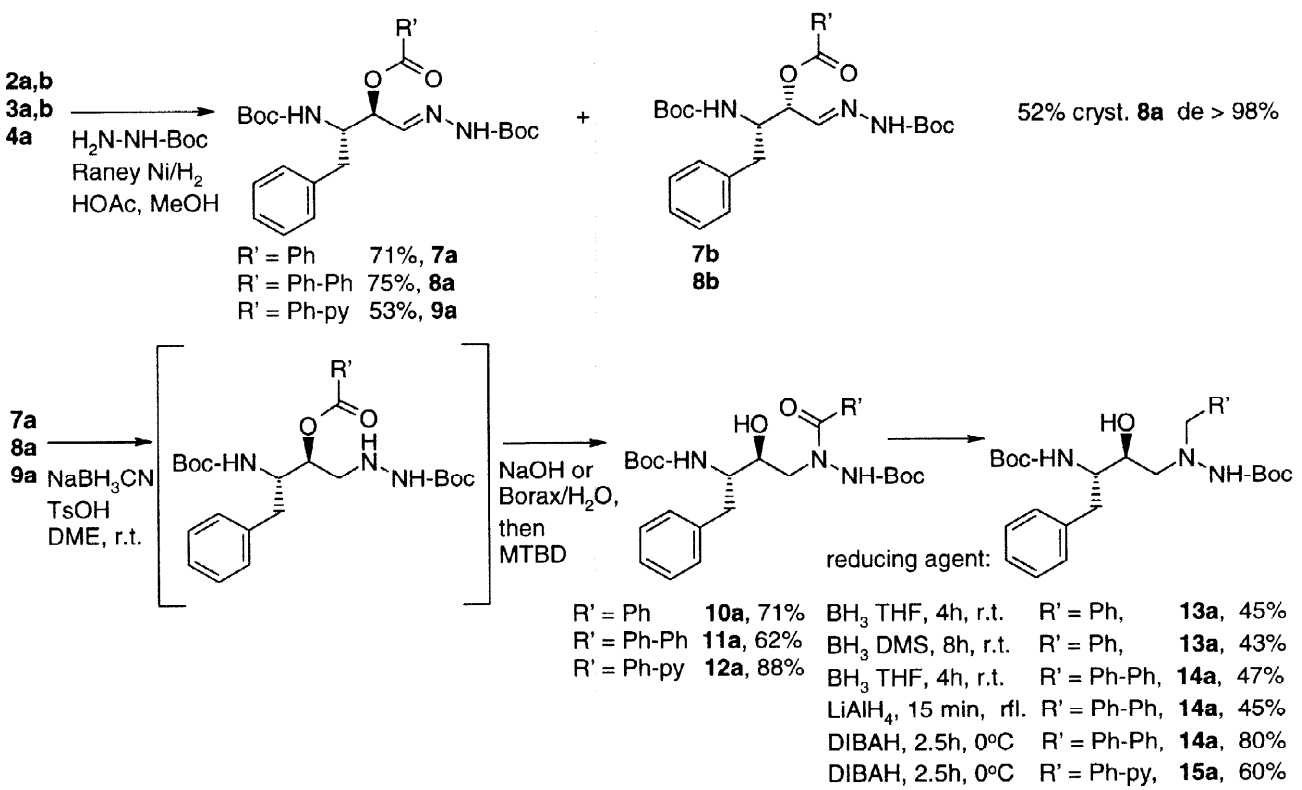
Enantio-**1** derived from *(D)*-phenylalanine was used to prepare cyanohydrins *enantio*-**2a** and *enantio*-**2b** under identical conditions as a control. Baseline separation of all four possible isomers by chiral HPLC[3] allowed the conclusion that the optical integrity of **1** could be fully retained. The *threo* configuration of the predominant isomer was determined by hydrolysis of the mixture of **2a,b** to the norstatin esters **5a,b**, followed by cyclisation into the corresponding oxazolidinones **6a** and **6b** and comparison of their ^{1}H-NMR coupling constants[4].

Scheme 4



Cyanohydrins **2a,b**, **3a,b** and **4a** were readily reduced with Raney nickel (1 bar H_2, r.t.) and HOAc (1 - 3 eq) in MeOH in the presence of Boc-hydrazine (1 eq) to form the hydrazones **7a,b**, **8a,b** as diastereomeric mixtures and **9a**. Pure *threo* hydrazones **8a** (de > 98%, Mp: 178-180°C) and **9a** (de > 98%, Mp: 195-196°C) could be isolated by crystallisation in up to 53% yield.

Scheme 5



[3] Chiralpak AD, hexane:isopropanol 9:1, retention time: (2S,3R) 23.6 min; (2S,3S) 17.9 min; (2R,3S) 13.8 min; (2R,3R) 9.3 min.

[4] The coupling constant J_{AB} of 4.2Hz in the major isomer is consistent with the expected *threo* configuration, while a coupling constant J_{AB} of 8.7Hz in the minor isomer indicates *erythro* configuration as described for related oxazolidinones [6].

Even under forcing conditions (Raney Nickel, 5% Pt/C catalyst, 80°C, 100 bar H_2) further hydrogenation of the hydrazones was not complete. Instead, the pure diastereomers **7a**, **8a** and **9a** were subjected to reduction using $NaBH_3CN$ (1.1 eq) and TsOH (1.1 eq) in DME [11]. Under the basic work-up conditions of the resulting acyloxy hydrazide borate complexes partial [O→N] acyl transfer occurred, which was pushed to completion under the influence of 1N aq. NaOH in DME (16h, r.t.) The use of anhydrous conditions for the rearrangement step (7-methyl-1,5,7-triazabicyclo[4,4,0]dec-5-ene (MTBD), DME, 1.5h, 80°C) reduced the degree of ester hydrolysis as a competitive side reaction and improved the yield.

The choice of conditions suitable for the reduction of the amides **10a**, **11a** and **12a** was limited by the reactivity of the benzylic hydrazine generated as well as by the stability of the Boc protecting groups [12]. Indeed, benzylic dealkylation of the tertiary hydrazide moiety was observed as the major side reaction during the reduction using borane (4h, 0°C to r.t.) or $LiAlH_4$ in refluxing THF (15 min). The use of DIBAH (1M in CH_2Cl_2, 6 eq, 2.5h, 0°C) gave a good yield of **14a** (Mp: 185-186°C) and **15a** (Mp: 184°C) which were isolated as crystalline solids. Simultaneous removal of the Boc protecting groups followed by acylation of the primary amine and hydrazine functions led to the final inhibitors.

Conclusion

Aza-dipeptide isosteres as a new class of potent HIV-protease inhibitors containing a (hydroxyethyl)-hydrazine moiety are obtained in high diastereomeric and enantiomeric purity starting from *(L)*-phenylaninal **1**. The synthetic route, which centres around an [O→N] acyl transfer, involves a sequence of simple transformations without chromatographic separations, hence making it suitable for larger scale preparation.

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