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STEREOSELECTIVE SYNTHESIS OF NON SYMMETRIC DIHYDROXYETHYLENE DIPEPTIDE ISOSTERES VIA EPOXYALCOHOLS DERIVED FROM α-AMINO ACIDS

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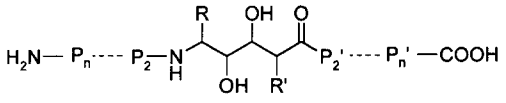
Abstract: (*1R,2R,3S,4S*)-4-Amino-3-hydroxy-1,2-epoxybutanes, accessible in four steps from L-aminoesters, react regio- and stereoselectively with diethyl aluminum cyanide to give (*1R,2S,3S,4S*)-4-amino-2,3-dihydroxynitriles. Hydrolysis yields hydroxylactones equivalent to 2,3-dihydroxy-4-aminoacids. The sequence provides a novel approach to dihydroxyethylene isosteres potentially useful for new HIV-protease inhibitors.

Keywords: Amino acids and derivs; isosteres; stereospecificity; enzyme inhibitors

Extensive efforts to discover new drugs against AIDS has led to the development of effective aspartic protease inhibitors[1] based on pseudopeptides of general structure P_n—P_2—P_1—P_1'—P_2'—P_n' where the core unit P_1—P_1' is a dipeptide isostere containing a non scissile bond, while the P_n—P_2 and P_2'—P_n' residues are responsible for non covalent interactions with subsites on the protein. Among the many peptide bond replacements that have been proposed, dihydroxyethylene isosteres $P_1\Psi$[CH(OH)CH(OH)]P_1' have shown excellent activity against HIV-1 protease.[2,3] In general, dihydroxyethylene isosteres can be based either on the "non symmetrical" dihydroxy-δ-aminoacid structure as in **1**[2] or on the diaminodiol structure as in **2**,[3,4] While inhibitors of the latter class are accessible by the pinacol coupling of aminoaldehydes[5] and other methods[6] and have been subject of extensive investigations, inhibitors of type **1** have been much less studied, one reason probably being the more demanding synthetic approach.[3]



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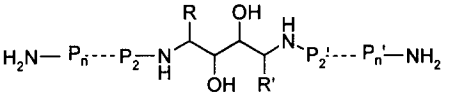

2

As part of a project on the design and modular synthesis of novel pseudopeptide inhibitors of HIV-1 protease, we have recently described a stereoselective synthesis of all-*S* diaminodiols **4** (Scheme 1), which utilizes readily available L-aminoesters as starting materials.[7] These are first converted, in several steps, into epoxyalcohols **3**, with complete control of the stereoselectivity over the three new chiral centers: ring opening by ammonia or diethyl aluminium azide[8] leads then to the mono-protected product **4**. With this methodology in

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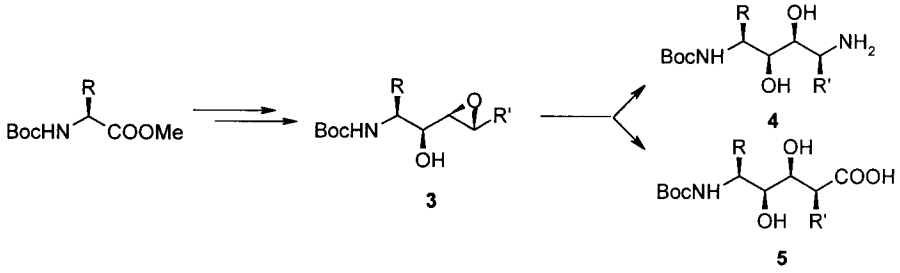
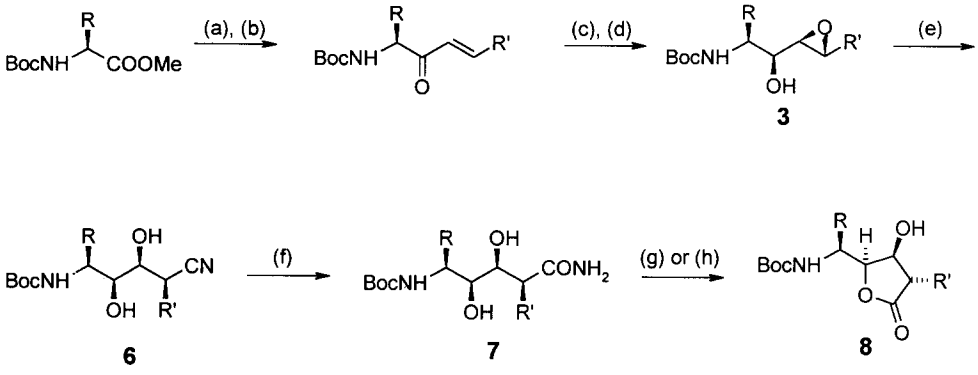
hand we have been able to synthesize a variety of diaminodiols **4** and, from these, pseudopeptides **2** with identical or non-identical R,R' and P_n-P_2, P_n'-P_2' groups that show promising activity against HIV-PR.[9] In this communication we will show that this versatile approach can be extended to the synthesis of the corresponding all-*S* dihydroxy-δ-aminoacids **5**, precursors of inhibitors **1** (Scheme 1).



Scheme 1

Epoxyalcohols **3a-e** (Scheme 2) were obtained in enantiomerically pure form as described previously.[7] Ring opening of **3** by cyanide was the chosen route for the introduction of the carboxylate group. We have recently shown that ring opening of unprotected 2,3-epoxyalcohols can be efficiently carried out, under mild conditions, with diethylaluminum cyanide (Nagata's reagent)[10] and demonstrated a marked preference for attack at C-3 with complete inversion of configuration.[11] Accordingly, epoxides **3**, when treated with one equivalent of this reagent, in toluene at room temperature for 24 hours, gave exclusively the required regioisomers **6** as single stereoisomers in 60-70% yield.[12]



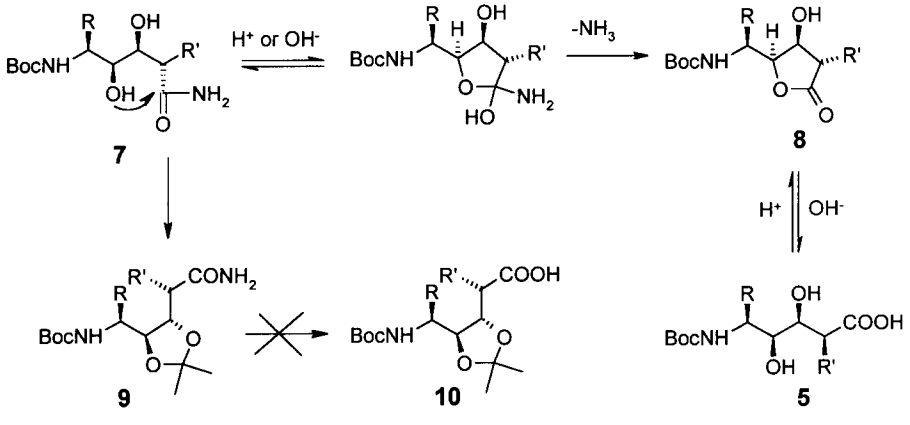
R,R' = a: *s*-Bu, CH_2*c*-Hex c: CH_2Ph, *i*-Pr e: CH_2Ph, CH_2*c*-Hex
b: *i*-Pr, CH_2*c*-Hex d: CH_2Ph, CH_2Ph

Reagents: (a) 6 eqv.$LiCH_2P(O)(OMe)_2$,THF, -78 °C, 2 h. (b) R'CHO, K_2CO_3, EtOH, 25 °C, 0.5-4 h. (c) $NaBH_4$, MeOH, 0 °C. (d) *m*-CPBA, CH_2Cl_2, 25 °C. (e) Et_2AlCN, toluene, 25 °C, 24 h. (f) H_2O_2, cat. K_2CO_3, DMSO, 25 °C 2-15 h. (g) Na_2O_2, 1:1 EtOH-H_2O, 50 °C, 4 h. (h) pH 2, H_2O-dioxan, 25 °C, 24 h.

Scheme 2

Conversion of the nitriles **6** to acids proved more difficult than expected. Direct hydrolysis failed on both free diols **6** and the corresponding acetonides; equally unsuccessful was the attempted reduction of the nitrile to aldehyde with diisobutylaluminum hydride. However, nitriles **6** could be hydrated under the oxidative conditions described by Katritzky[13] to give the corresponding amides **7** in 70-90 % yield (Scheme 2).[12] The reaction is sensitive to the steric hindrance of the R' group, and reaction times range from 2 hours for **6e** (R' = CH_2-*c*Hex) to 15 hours for **6a** (R' = *i*-Pr). Amides **7**, on the contrary, were very prone to hydrolysis; this was carried out either in aqueous dioxan at pH = 2, or in aqueous ethanol, in the presence of Na_2O_2.[14] In the acidic medium lactones **8** (60%)[12] were isolated, while hydroxyacids **5** were the products from the basic hydrolysis; these however, rapidly cyclize to lactones during work-up.

In an attempt to obtain the protected dihydroxyaminoacids **10**, amides **7** were protected as acetonides **9** (Scheme 3). However, while hydrolysis of unprotected amides **7** is fast both in acidic and basic medium, the protected amides **9** failed to react under similar conditions. This suggests an intramolecular mechanism for the hydrolysis (Scheme 3), with partecipation by the OH group which would lead directly to lactones **8**, in agreement with observations that amide hydrolysis can be accelerated by a factor of up to 10^{10} by intramolecular assistance.[15]



Scheme 3

This novel, stereoselective approach to 2,3-dihydroxy-1,4-aminoacids further demonstrates the utility of epoxides **3** as pivotal intermediates in the synthesis of both "non symmetric" (**5**) and "symmetric" (**4**) dihydroxyethylene dipeptide isosteres (Scheme 1). The application of this strategy to the synthesis of pseudopeptide inhibitors **1** of HIV-1 protease is currently underway.

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12. Selected spectral data. **6d**: ^{1}H nmr ($CDCl_3$, 400MHz): δ 1.28 (s, 9H), 2.35 (d, 1H, J=11.3 Hz), 2.75 (m, 1H), 2.93 (m, 1H), 3.07 (dd, 1H, J= 9.8, 3.9 Hz), 3.16 (m, 2H), 3.42 (m, 1H), 3.55 (m, 1H), 3.67 (m, 1H), 4.41 (d, 1H, J= 8.3 Hz), 4.62 (d, NH, J=4.4 Hz), 7.09-7.24 (m, 10 H). ^{13}C nmr ($CDCl_3$,100.1MHz): δ 28.1, 33.8, 35.5, 36.8, 53.0, 68.4, 73.3, 81.0, 119.8, 126.8, 127.0, 128.6, 128.8, 129.2, 129.6, 136.5, 136.8, 157.6. **7d**: ^{1}H nmr ($CDCl_3$, 400MHz): δ 1.28 (s, 9H), 2.58-2.90 (m, 3H), 3.13 (m, 2H), 3.33 (m, 1H), 3.76 (m, 2H), 4.86 (d, NH, J= 9.2 Hz), 5.66 (m, 1H), 6.14 (m, 1H), 7.10-7.32 (m, 10H). ^{13}C nmr ($CDCl_3$, 100.1MHz): δ 28.1, 35.3, 36.9, 51.7, 53.4, 70.4, 72.8, 80.1, 126.0, 126.3, 126.9, 128.2, 128.3, 128.6, 128.7, 128.9, 129.1, 137.8, 156.2, 175.8. **8d**: ^{1}H nmr ($CDCl_3$, 400MHz): δ 1.27 (s, 9H), 2.81 (m, 1H), 2.91-3.02 (m, 4H), 3.54 (m, 2H), 4.2 (m, 1H), 4.42 (d, NH, J=8.6 Hz), 7.08-7.25 (m, 10H). ^{13}C nmr ($CDCl_3$, 100.1MHz): δ 28.6, 32.9, 35.9, 46.9, 50.6, 70.1, 80.4, 81.2, 127.2, 127.6, 129.0, 129.4, 130.3, 131.4, 136.2, 136.5, 156.1, 176.5.
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