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Epoxyalcohol route to hydroxyethylene dipeptide isosteres: a new synthesis of the diaminoalcohol core of HIV-protease inhibitor ABT-538 (Ritonavir)

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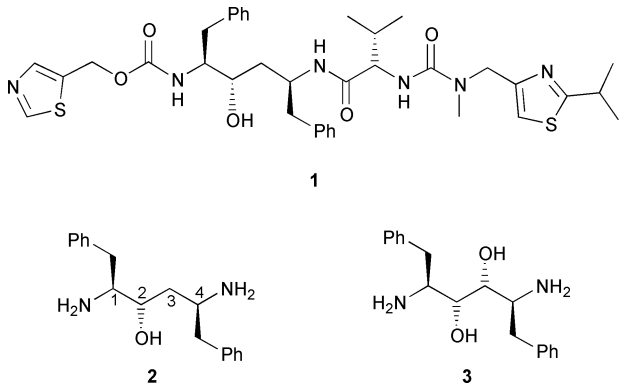
A stereoselective synthesis of the diaminoalcohol core of Ritonavir illustrates a novel approach to hydroxyethylene dipeptide isosteres, based on the regioselective reduction of amino acid-derived epoxyalcohols.

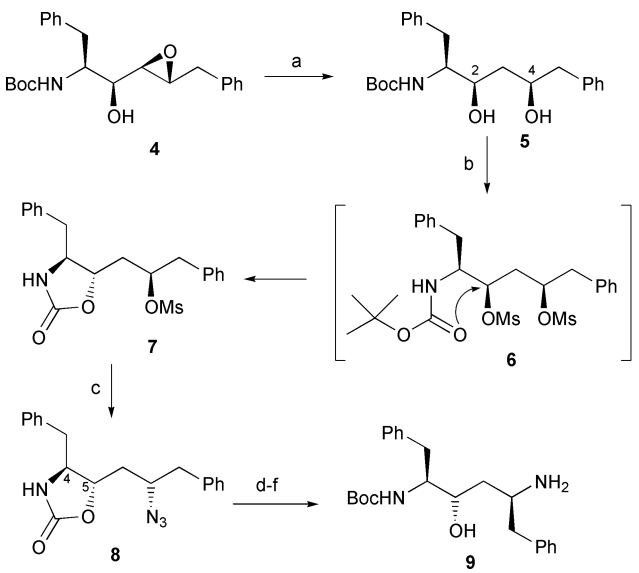
Ritonavir (**1**), approved in 1996,[1] is a potent and clinically effective peptidomimetic inhibitor of the protease of HIV, with high oral bioavailability.[2] The structure of Ritonavir was designed to target the enzyme's active site and is based on the hydroxyethylene dipeptide isostere **2**.[2a] In the original synthesis of the inhibitor,[3] the diaminoalcohol **2** was obtained from the corresponding diaminodiol **3** by a multi-step deoxygenation



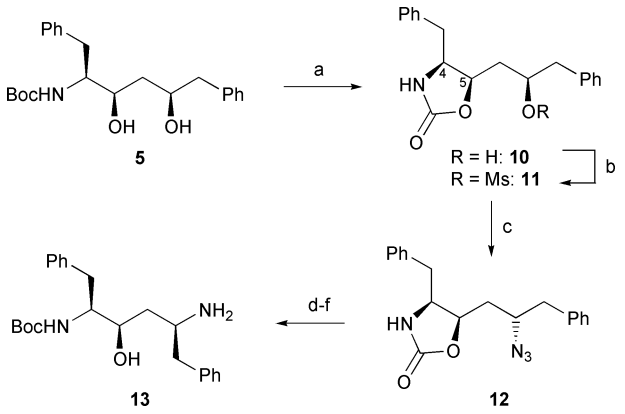
approach.[4] The core **2** was then statistically monoacylated to introduce the first side chain while the second flanking residue was introduced in the final step. This strategy has some drawbacks: loss of **2** through undesired bis-acylation, impossibility of introducing different residues on the isostere's C1 and C4, which originate from the Cα of the same aminoacid *via* the reductive dimerization of the corresponding aminoaldehyde,[4] and a less than optimal stereocontrol in the synthesis of **3**. Several approaches have been proposed to overcome these limitations, based on aminoacids as precursors from the chiral pool[5] or on enantioselective synthetic strategies.[6] In this communication we describe a short and efficient synthesis of the monoprotected Ritonavir core **9** which utilizes the amino-acid derived epoxyalcohol **4** as key intermediate (Scheme 1).

The epoxyalcohol **4** was obtained from phenylalanine, in four steps and 40% overall yield, as described previously.[7] 2,3-Epoxyalcohols are regioselectively converted into the corresponding 1,3-diols by Red-Al;[8] accordingly, when the epoxyalcohol **4** was treated with this reagent (3 equiv.) in THF at 50 °C for 24 h, attack of hydride took place selectively to give the Boc-protected aminodiol **5** {$[\alpha]_D^{25} = -18$ (*c* 0.2, MeOH)} in 60% yield after chromatography. In order to convert this compound into the required diaminoalcohol **9**, it is necessary to: i) selectively activate the hydroxy group on C4 towards displacement by a suitable precursor of the aminogroup and ii) invert the configuration of C2 which is opposite to that of **9**. Differentiation of the two secondary hydroxy groups, selective activation and inversion of the configuration of C2 were obtained in a single step by treating the diol with 3 equiv. of methanesulfonyl chloride and 6 equiv. diisopropylethylamine (DIPEA) in 1,2-dichloroethane, at 80 °C for 6 h. The dimesylate **6** initially obtained spontaneously cyclizes *via* S_N2 attack of the carbonyl oxygen of Boc on the neighbouring sulfonate ester to give the inverted oxazolidinone **7**. Displacement of the second mesylate was obtained by treating crude **7** with 1.5 equiv. NaN_3 in DMSO for 18 h at 50 °C, in the presence of 1 equiv. of 18-crown-6, affording the azide **8** {$[\alpha]_D^{25} = -35$ (*c* 0.2, MeOH)} in which all the stereocenters have the correct configuration (50% for the two steps). The stereochemistry of the oxazolidinone **8** was established from NOE experiments. These show a 3% enhancement between the ring H4 and H5, consistent with a *trans* relationship between these protons, while in the *cis*-oxazolidinone **12** (Scheme 2) a 11% enhancement is detected between the same protons. The Boc-protected amino group was then restored by treatment of **8** with equimolar amounts of Boc_2O and NaH in THF, at 25 °C for 12 h, followed by hydrolysis of the resulting N-Boc heterocycle with Cs_2CO_3 in MeOH–water at 25 °C for 2 h.[9] Finally, hydrogenation of the azide, in MeOH over 10% Pd/C, gave the monoprotected (*S*,*S*,*S*) hydroxyethylene dipeptide isostere **9** {$[\alpha]_D^{25} = -19$ (*c* 0.2, MeOH)} in 20% overall yield from the epoxyalcohol **4**.

The synthetic approach shown here can be expanded to obtain the epimeric Phe-Phe dipeptide isostere **13** with the opposite configuration at the alcoholic carbon (Scheme 2). In this case the diol **5** is treated with sodium hydride in THF at 25 °C for 12 h to give, in 85% yield, the *cis*-oxazolidinone **10** arising from a normal acyl transfer cyclization[10] {$[\alpha]_D^{25} = -42$ (*c* 0.2, MeOH)}. The NOE enhancement between the ring



Scheme 1 *Reagents and conditions*: (a) Red-Al, THF, 50 °C, 60%; (b) MsCl, DIPEA, 80 °C; (c) NaN_3, DMSO, 18-crown-6, 50 °C, 50%, 2 steps; (d) NaH, Boc_2O, THF; (e) Cs_2CO_3, MeOH–H_2O, 67%, 2 steps; (f) 1 atm H_2, 10% Pd/C, MeOH, 100%.



Scheme 2 *Reagents and conditions*: (a) NaH, THF, 25 °C, 85%; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C; (c) NaN_3, DMSO, 18-crown-6, 50 °C, 75%, 2 steps; (d) NaH, Boc_2O, THF; (e) Cs_2CO_3, MeOH–H_2O, 58%, 2 steps; (f) 1 atm H_2, 10% Pd/C, MeOH, 100%.

protons (11%) is consistent with the *cis* stereochemistry of the ring substituents. With the first hydroxy group thus protected, the second OH can be activated as mesylate, in CH_2Cl_2 at 0 °C,[11] and the resulting oxazolidinone **11** is then converted into the selectively protected (*S*,*R*,*S*) isostere **13** {$[\alpha]_D^{25}$ = +1.0 (*c* 2, MeOH)} by the same sequence of reactions seen before for the synthesis of **9** (Scheme 2). The overall yield of **13** is 22%, from the epoxyalcohol **4**.

We have thus described a novel approach to the synthesis of the (*S*,*S*,*S*) dipeptide isostere of Ritonavir **9** and its (*S*,*R*,*S*) epimer **13**, based on the regioselective ring opening of an epoxyalcohol with aluminium hydride. This strategy leads to a mono-protected diaminoalcohol from which peptidomimetic protease inhibitors can be directly obtained by coupling with different peptide, or non-peptide, residues. The approach is not limited to isosteres with identical side chains, and it should thus be possible to extend this methodology to the synthesis of a repertoire of isosteres with different residues, starting from the corresponding, readily available epoxyalcohols.[7] The synthesis of dihydroxyethylene dipeptide isosteres from the same epoxyaminoalcohols **4** has been described previously;[7,12] the present extension to the synthesis of monohydroxyethylene isosteres further demonstrates the synthetic utility of these intermediates.

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