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Application of the asymmetric aminohydroxylation reaction for the syntheses of HIV-protease inhibitor, hydroxyethylene dipeptide isostere and γ-amino acid derivative

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Abstract—An enantioselective synthesis of lactone **1**, a precursor to the (2*R*,4*S*,5*S*) hydroxyethylene dipeptide isostere and amino acid AHPPA **2** has been accomplished from the common intermediate **5** employing Sharpless asymmetric aminohydroxylation as the key step.

The last two decades have witnessed a considerable upsurge of interest in the use of enzyme inhibitors as therapeutic agents.[1] The advent of acquired immunodeficiency syndrome (AIDS) and the discovery of its causative agent, human immunodeficiency virus (HIV-1),[2] has given an impetus to the development of efficient inhibitors of viral enzymes, in particular of the transcriptase and more recently of the proteinase (HIV-PR).[3]

Consequently numerous potent and selective HIV protease inhibitors have been designed based upon the transition state mimetic concept, incorporating hydroxyethylene and hydroxyethylamine dipeptide isosteres as the scissile site.[4] In view of this, a highly enantioselective synthesis of the isostere unit is still desirable.

The development of new approaches to the stereo controlled synthesis of γ-amino β-hydroxy acids has been a subject of immense interest within the context of biologically active peptide mimics.[5] The two well known examples are AHPPA (4-amino-3-hydroxy-5-phenylpentanoic acid) **2** and statin. They are the key constituents of microbially produced aspartic peptidase inhibitor, pepstatin.[6] AHPPA has also been employed for the design of HIV protease inhibitors.[7] While the majority of the earlier syntheses of isosteres and AHPPA use optically active amino acids as chiral pool material,[8,9] reports in which all the stereogenic centres are constructed by asymmetric synthesis are rather scarce.[10] As part of our research programme aimed at developing enantioselective syntheses of naturally occurring amino alcohols,[11] the Sharpless asymmetric aminohydroxylation (AA)[12] was envisioned as a powerful tool, offering considerable opportunities for synthetic manipulations. We have now developed a new and enantioselective synthesis of lactone **1** and AHPPA **2** utilising Sharpless asymmetric aminohydroxylation as the key step (Fig. 1).

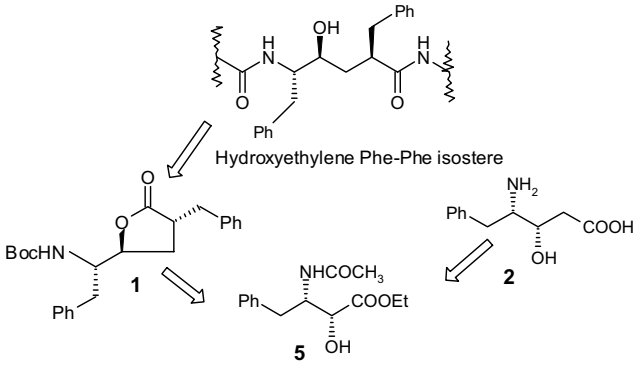

Figure 1.

Keywords: HIV-protease inhibitor; Hydroxyethylene dipeptide isostere; γ-Amino acid derivative; Sharpless asymmetric aminohydroxylation.

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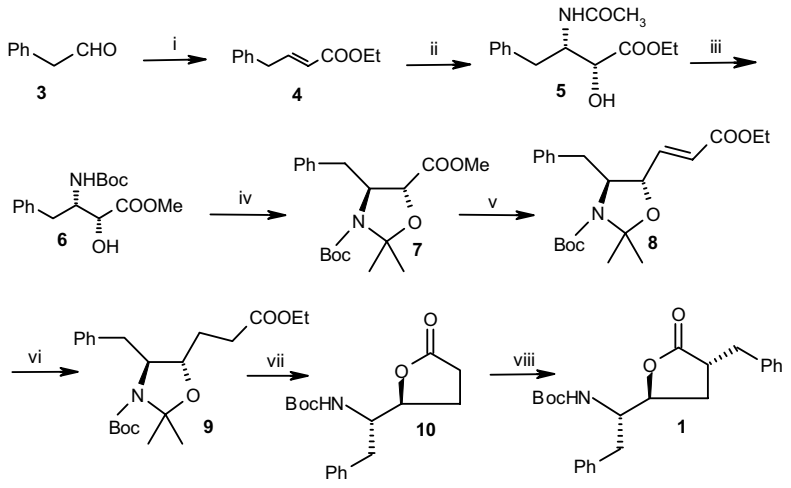
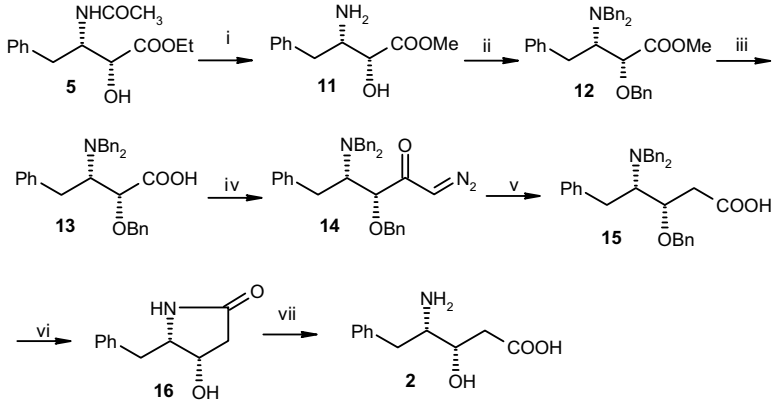


Scheme 1. Reagents and conditions: (i) $Ph_3P{=}CHCO_2Et$, THF, 0 °C to rt, 85%; (ii) $(DHQ)_2PHAL$, $K_2[OsO_2(OH)_2]$, LiOH, *N*-bromoacetamide, *t*-butanol–H_2O (1:1), 0 °C to rt, 64%; (iii) 0.5 M HCl in MeOH, reflux, then Boc_2O, Et_3N, DCM, 0 °C to rt, 87%; (iv) 2,2-DMP, *p*-TSA, DCM, rt, 89%; (v) (a) DIBAL-H, DCM, −78 °C to rt, 76%, (b) $Ph_3P{=}CHCO_2Et$, THF, 0 °C to rt, 60%; (vi) H_2, 10% Pd–C, EtOAc–MeOH, 90%; (vii) AcOH, PhMe, reflux; 67%; (viii) LiHMDS, BnBr, THF, −78 °C, 79%.

The synthesis (Scheme 1) of lactone **1** started from phenyl acetaldehyde **3**, a readily available starting material. Thus, treatment of **3** with (ethoxycarbonylmethylene)triphenylphosphorane in THF under reflux gave the Wittig product **4** in 85% yield. In the next, Sharpless aminohydroxylation step, it was envisioned that *N*-bromoacetamide would be the best nitrogen source of all those available at present[12b] for an easy chromatographic separation of the product and subsequent synthetic manipulation. Thus the asymmetric amino hydroxylation of the olefin **4** with potassium osmate (4 mol%) as oxidant in *tert*-butanol–water (1:1) in the presence of $(DHQ)_2PHAL$ (5 mol%) as chiral ligand and freshly prepared *N*-bromoacetamide[13] as the nitrogen source, afforded the desired amino alcohol **5**[14] in 10:1 regioisomeric ratio and 64% yield with 89% ee, $[\alpha]_D^{20}$ −56.08 (*c* 0.8, $CHCl_3$).[15]

Further, in order to achieve the synthesis of target compound **1** from **5**, we required a suitable amino protecting group for further synthetic manipulation. To this end the amide **5** was subjected to hydrolysis using 0.5 M HCl in methanol under reflux to furnish free amine with concomitant transesterification to the methyl ester. The successive conversion of amine into the Boc protected amino alcohol **6** followed by further protection as acetonide using 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid afforded **7** in 89% yield. Reduction with DIBAL-H to the corresponding aldehyde and subsequent Wittig reaction with (ethoxycarbonylmethylene)triphenylphosphorane afforded the olefin **8** in good yield. The olefin reduction by hydrogenation using 10% Pd–C gave **9** in 90% yield, which on acetonide deprotection using acetic acid followed by reflux in toluene underwent smooth lactonisation to furnish **10** in 67% yield. The lactone **10** was alkylated with benzyl bromide using LiHMDS as a base to furnish the desired compound **1** in excellent yield, $[\alpha]_D^{20}$ −41.7 (*c* 0.32, $CHCl_3$), lit.[8b] $[\alpha]_D^{20}$ −40.0 (*c* 0.10, $CHCl_3$) along with a small amount (5%) of *cis*-alkylated product. This step completes the formal synthesis of the isostere since transformation of **1** to the isostere has been reported previously.[8b]

Scheme 2 summarises the synthesis of (3*S*,4*S*)-4-amino-3-hydroxy-5-phenylpentanoic acid (AHPPA) from the



Scheme 2. Reagents and conditions: (i) 0.5 M HCl in MeOH, reflux, 87%; (ii) BnBr, K_2CO_3, DCM, 91%; (iii) LiOH, MeOH–H_2O (3:1), 76%; (iv) Et_3N, $ClCO_2Et$, THF, CH_2N_2, 50%; (v) Ag_2O, THF–H_2O, 60%; (vi) H_2, 10% Pd–C, EtOAc, rt, 85%; (vii) concd HCl, 80 °C, 73%.

common intermediate **5**. The cleavage of the *N*-acetyl group of **5** to the free amine was accomplished using 0.5 M HCl in methanol under reflux with concomitant transesterification to afford **11** in excellent yield. *N*- and *O*-benzylation of **11** was followed by base hydrolysis of the ester to the corresponding acid **13** in good yield. For one carbon homologation of the acid **13** to **15**, we attempted the following sequence. Acid **13** was first converted into a mixed anhydride and subsequently treated with excess of diazomethane to furnish the diazo compound **14**[16] in moderate yield. Further treatment with silver oxide resulted in the desired acid **15** via Wolff rearrangement. Debenzylation of **15** led to the formation of the lactam **16**, which on ring opening with concd HCl furnished the target compound **2** in 73% yield {$[\alpha]_D^{20}$ −22.3 (*c* 0.36, H_2O), lit.[17] $[\alpha]_D^{20}$ −24.0 (*c* 0.44, H_2O)}. The physical and spectroscopic data were in full agreement with the literature.[17]

In conclusion, enantioselective syntheses of lactone **1** and AHPPA **2** have been accomplished from a common intermediate **5** for the first time utilising Sharpless catalytic aminohydroxylation as the key step. A short reaction sequence and high overall yield of the target compounds render our strategy a good alternative to the known methods.

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14. During the column purification of **5**, the corresponding dihydroxy compound (12%) was also isolated as side product.
15. The regioisomeric ratio of **5** was determined based on ^{1}H NMR spectra and the enantiomeric excess (ee) was calculated using Mosher analysis by converting ester **7** into the the corresponding alcohol and then derivatising it as the Mosher ester. The ee was found to be 89%. Spectral data **5**: $[\alpha]_D^{20}$ −56.08 (*c* 0.8, $CHCl_3$) IR ($CHCl_3$, cm^{-1}): 3390–3360, 2983, 2361, 1738, 1657; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26–1.28 (t, $J = 7.2$ Hz, 3H), 2.12 (s, 3H), 2.85–2.97 (m, 2H), 4.17–4.22 (q, $J = 6.8$ Hz, 2H), 4.35–4.39 (m, 1H), 4.72–4.74 (dd, $J = 9.1$, $J = 1.9$ Hz, 1H), 6.48–6.50 (d, $J = 9.1$ Hz, 1H), 7.22–7.34 (m, 5H), ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.01, 22.89, 37.87, 40.44, 52.83, 55.88, 61.56, 62.05, 72.73, 126.69, 128.49, 137.28, 170.94. GC–MS: 266 (M+1).
16. Spectral data **14**: $[\alpha]_D^{20}$ −2.87 (*c* 1.60, $CHCl_3$) IR (neat, cm^{-1}): 2964, 2361, 2106, 1813, 1749, 1680; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.9–3.04 (t, $J = 11.5$ Hz, 1H), 3.20–3.26 (m, 1H), 3.57–3.59 (d, $J = 12.8$ Hz, 2H), 4.13–4.16 (d, $J = 13.3$ Hz, 2H), 4.22–4.31 (m, 2H), 4.74–4.77 (m, 2H), 5.36 (s, 1H), 7.2–7.44 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.24, 55.17, 64.67, 126.53, 127.09, 128.13, 128.56, 128.68, 128.82, 128.99, 129.25, 139.88; GC–MS: 490 (M+1).
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