Tetrahedron Letters, Vol.32, No.16, pp 1897-1898, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

STEREOSELECTIVE SYNTHESIS OF N-BOC-O-BENZYL-(4S,5S)-5-AMINO-4-HYDROXY-6-PHENYLHEXANOIC ACID, THE HYDROXYETHYLENE ISOSTERIC MOIETY OF POTENT HIV-1 PROTEASE INHIBITOR

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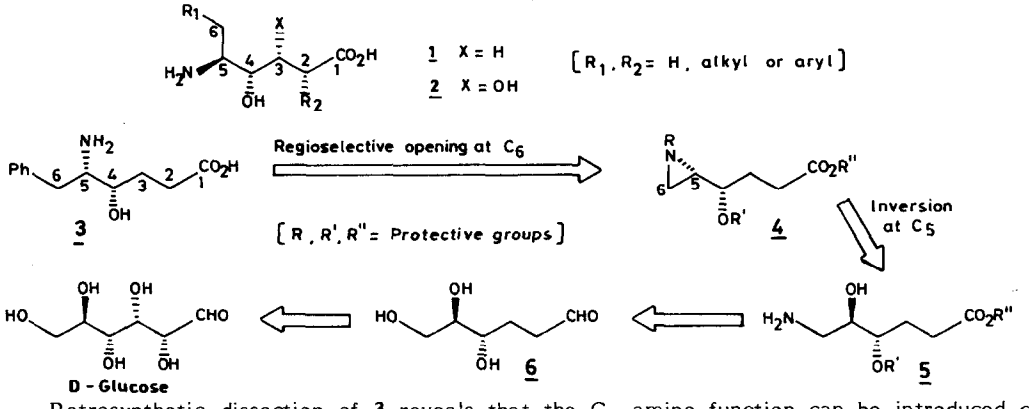
Abstract N-Boc-O-benzyl-(4S,5S)-5-amino-4-hydroxy-6-phenylhexanoic acid is synthesized in a highly stereoselective way involving, as a key step, regioselective opening of carbohydrate-based aziridine ring.

Potent inhibitors of aspartic protease such as HIV-1 protease, porcine pepsin and human renin have been designed in which the scissile dipeptide of an oligopeptide substrate is replaced by nonhydrolyzable synthetic hydroxyethylene **1** (ψ[CH(OH)CH_2]) or dihydroxyethylene **2** (ψ[CH(OH)-CH(OH)]) isosteres which act as transition-state analogues and mimic the tetrahedral intermediate formed during the enzyme-catalyzed hydrolysis of the peptide bond.[1] These peptidomimetic analogues have, so far, been synthesized only from amino acids.[2] We report here a highly stereoselective synthesis of N-Boc-O-benzyl-(4S,5S)-5-amino-4-hydroxy-6-phenylhexanoic acid **3** (Boc-Phe ψ[CH(OBn)CH_2]Gly), the hydroxyethylene isosteric moiety of potent inhibitor of HIV-1 protease[3], starting from a carbohydrate precursor, which will allow the synthesis of this useful class of analogues in multigram quantities for biological studies.



Retrosynthetic dissection of **3** reveals that the C_5 amino function can be introduced conveniently by regioselective organocuprate opening of a suitably functionalized terminal aziridine ring **4**[4] derived easily from vicinal amino alcohol **5**. In other words, conversion of C_6-hydroxyl of 2,3-dideoxy-D-glucose **6** to amino group followed by its migration to 5-position with inversion of configuration in a two-step process sums up our overall strategy.

Our synthesis started with ethyl-2,3-dideoxy-α-D-glucopyranoside **7**[5] (Scheme 1). Standard methods were followed to get 6-azido-4-benzyloxy derivative **8**.[6] Opening of pyranoside ring with

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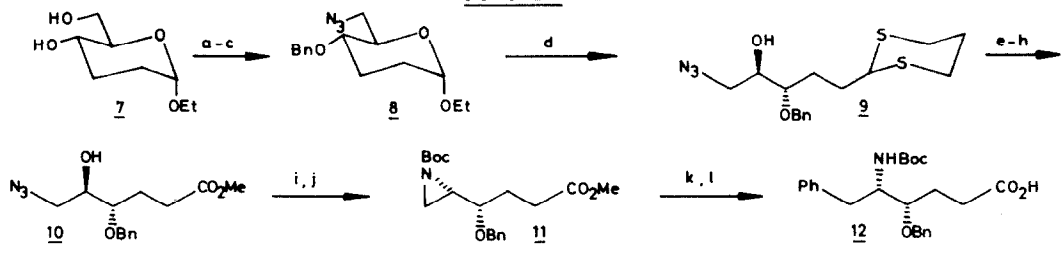
propane-1,3-dithiol followed by functional group manipulations gave the azidoalcohol **10**[6] which was converted to the required aziridine intermediate **11**[6] either by one-step or two-step process. Opening of aziridine ring was carried out regioselectively using PhMgBr in presence of $CuBr.SMe_2$. Finally, treatment with base gave the target amino acid in N-Boc-O-benzyl-protected form **12**,[7] ready to be coupled with subsequent amino acids.

SCHEME-1



a) TsCl (1.1 eq), Py, rt, 12 h, 80%; b) NaN_3 (4 eq), DMF, 65°, 4 h, 95%; c) NaH (1.1 eq), BnBr (1.1 eq), TBAI (0.1 eq), THF, 0°, rt, 2 h, 100%; d) $HS(CH_2)_3SH$ (1.2 eq), $BF_3.Et_2O$ (1 eq), CH_2Cl_2, rt, 45 mins, 80%; e) Ac_2O, Py, 12 h, 100%; f) HgO (2 eq), $BF_3.Et_2O$ (2 eq), 85% aq.THF, rt, 20 mins, 93%; g) PDC (2.3 eq), DMF, rt, 4 h, then CH_2N_2, 60%; h) K_2CO_3, MeOH, 1 h, 100%; i) Ph_3P, C_6H_6, 1 h, reflux, followed by $(Boc)_2O$, rt, 2 h, or step i followed by j) Ph_3P, DEAD, rt, 1 h, 80% overall; k) PhMgBr (1 eq), $CuBr.Me_2S$ (0.2 eq), toluene, -30°, 1 h, 70%; l) aq.1(N)LiOH, THF, rt, 6 h.

In conclusion, an efficient methodology for the construction of very useful hydroxyethylene isostere amino acid analogues is developed starting from, for the first time, a carbohydrate precursor. This strategy can also be employed for the synthesis of dihydroxyethylene isosteres **2**. Further work is under progress.

Acknowledgement. We thank Dr A V Rama Rao, Director, for his keen interest and encouragement.

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5. **6** was prepared in three steps from tri-O-acetyl-D-glucal : L. Stamatatos, P. Sinay, J.-R. Pougny, Tetrahedron, **40**, 1713 (1984).
6. Satisfactory NMR, IR and Mass spectra were obtained for this compound.
7. ^1H NMR of N-Boc-O-benzyl-(4S,5S)-5-amino-4-hydroxy-6-phenylhexanoic acid methyl ester (200 MHz, $CDCl_3$) : δ 7.1-7.4 (m, 10H, aromatic), 4.87 (d, J = 8.3 Hz, 1H, NH), 4.62 and 4.45 (doublets, J = 11.2 Hz, 2H, OCH_2Ph), 3.84 (m, 1H, CH-NHBoc), 3.57 (s, 3H, $COOCH_3$), 3.36 (m, 1H, CH-OBn), 2.82 (d, J = 7.5 Hz, 2H, $PhCH_2$), 2.4-2.2 (m, 2H, CH_2COOMe), 2.1-1.7 (m, 2H, CH_2), 1.37 (s, 9H, $(CH_3)_3C$-); $[\alpha]_D^{25}$ + 3.75 (c 0.4, $CHCl_3$); m.p. 63°C.

(Received in UK 14 February 1991)