A novel and facile synthesis of C₂-symmetric HIV - Protease inhibitors

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A facile synthesis of C₂-symmetric HIV protease inhibitors 7 and 10 is described via a novel dichloromethylation of oxazolidinone 1 and its conversion to allyl amine 3.

The inhibition of HIV protease by peptidomimetic structures incorporating a hydroxyethylamine (HEA) isostere offers a promising area of therapeutic intervention against acquired immunodeficiency syndrome (AIDS). As studies of several HEA based HIV protease inhibitors especially possessing C₂-symmetry have advanced from the laboratory to preclinical and clinical stages, the need for efficient syntheses has gained crucial importance. The key building block for such molecules comes from a substituted allyl amine. Limited methods are available in the literature to make such precursors in optically pure form. The reported methods suffer from drawbacks such as racemisation as it involves the use of configurationally labile N-protected α-aminoaldehydes and usage of toxic reagents. We report here an elegant synthesis of allyl amine 3, starting with readily accessible oxazolidinone 1 in two steps (dichloromethylation and reductive elimination) and its conversion to the target C₂-symmetric molecules 7 and 10 (Scheme I).

The oxazolidinone 1 on treatment with CCl₄-P₃O underwent Wittig type of dichloromethylation to give 5-dichloromethylenoxazolidine 2 in excellent yield. The structure of 2 was established on the basis of spectral data. In IR spectrum of 1, two characteristic peaks appeared at 1680 cm⁻¹ and 1808 cm⁻¹ representing the carbonyl stretches of CO-NH and CO-O functionalities respectively, whereas the IR spectrum of 2 showed only one peak at 1680 cm⁻¹ which corresponded to CO-NH stretch. In mass spectrum of 2, the abundance of M, M+2, M+4 peaks are in the ratio of 10:6.5:1 clearly indicating the presence of two chlorine atoms. In H NMR spectra of 2, two sets of signals for each proton are appeared due to the existence of two envelope conformers. Reaction of 2 with metallic sodium in refluxing THF and subsequent quenching with methanol effected the reductive dehalogenation, ring opening and elimination of formaldehyde in a single step to give the desired allyl amine 3 of high optical purity (>99%). Formation of 3 is evident from 'H NMR spectra showing important characteristic signals at δ 5.05 (d, 1H, J=8.8 Hz), 5.15 (d, 1H, J=14.0 Hz), 5.80 (ddd, 1H, J=6.3 Hz) indicating the terminal olefin functionality. Optical purity of 3 was determined by ¹9F NMR spectrum of the corresponding (R)-Mosher amide.

**Synthesis of 3-N-BOC-amino-1-[3-N-BOC-amino-2-hydroxy-4-phenyl-(2S, 3S)-butyramino]-4-phenyl (2S, 3S)-butan-2-ol 7 and its (2R, 3S) isomer 10.** Allyl amine 3 on treatment with 6N HCl followed by BOC₂O in the presence of Na₂CO₃ gave (3S)-3-N-tert-butoxycarbonylamino-4-phenyl-1-butene 4 as a solid [mp 67 °C, [α]D⁰ +36.9° (c1, CHCl₃)], lit. mp 66-67 °C, [α]D⁰ +36.7° (c 0.9 chloroform). MCPBA oxidation of 4 afforded the threo-amino epoxide 5. The reaction of epoxide 5 with 0.5 eq. of benzylic amine in DMF gave the diol 6. Pd/C catalysed hydrogenolysis of 6 gave the aminodiol 7 [mp 141 °C, [α]D⁰ -42.9° (c1, CH₂OH)]; lit. mp 140-141 °C, [α]D⁰ -42.4° (c0.29, CH₂OH)]. The diol 6 was subjected to Mitsunobu reaction for carbonyl inversion to achieve the desired isomer 10. However, this reaction let to some unidentified products. This difficulty was circumvented by taking N-Cbz diol 8.
which was smoothly converted, to 9 under Mitsunobu conditions. Saponification of 9 followed by Pd/C catalysed hydrogenolysis gave the target aminodiol 10 as a solid [mp 179-180 °C, $[\alpha]_D^{25} = -7.18$ ($c$ 0.4, CH$_2$OH)]; lit. mp 178-180 °C, $[\alpha]_D^{25} = -7.1$ ($c$ 0.1, CH$_2$OH)] as shown in Scheme I. All the compounds were fully characterized by spectroscopic data, specific rotations were found to be in good agreement with the assigned structures with high optical purities and also with literature data.

In conclusion, we report a novel, facile and simple synthesis of potential C$_2$-symmetric HIV protease inhibitors. The present methodology enables the synthesis of analogous series of compounds with ease. Further work is in progress and will be reported in due course.

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References


8 Spectroscopic data of 2 (Two conformers in a ratio of 1:1)—$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 1.60, 1.90 (2s, 3H, CH$_3$CO), 2.90-3.30 (m, 2H, CH$_2$Ph), 4.00, 5.00, 4.60, 5.60 (4d, 2H, $J=6.1$ Hz, H-2), 4.70-4.85, 5.10-5.25 (2m, 1H, H-4), 7.00-7.30 (m, 5H, Ph); EIMS: $m/z$ 285 (M$^+$); Anal. Calcd for C$_{13}$H$_{13}$Cl$_2$NO$_2$: C, 54.54; H, 4.57; N, 4.89. Found: C, 54.89; H, 4.81; N, 4.67%.


10 Spectroscopic data of 3 — $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 1.95 (s, 3H, CH$_3$CO), 2.85 (d, 2H, $J=13.4$ Hz, CH$_2$Ph), 4.70-4.88 (m, 1H, CH-NAc), 5.05 (d, 1H, $J=8.8$ Hz, CH$_2$=CH), 5.15 (d, 1H, $J=14$ Hz, CH$_2$=CH), 5.35-5.5 (br s, 1H, NH), 5.8 (ddd, 1H, $J=6.3$ Hz, CH=CH$_2$), 7.12-7.40 (m, 5H, Ph); EIMS: $m/z$ 89 (M$^+$, -CH$_2$Ph); Anal. Calcd. for C$_{12}$H$_{15}$NO (189.25) : C, 76.15; H, 7.98; N, 7.40. Found: C, 76.12; H, 7.92; N, 7.36%.


Mitsunobu O, Synthesis, 1981, 1