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STEREOCONTROLLED SYNTHESIS OF HIV-1 PROTEASE INHIBITORS WITH C_2-AXIS OF SYMMETRY

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Summary: An efficient and stereocontrolled synthesis of various C_2-symmetric HIV-1 protease inhibitors is described, starting from commercially available and inexpensive D-mannitol.

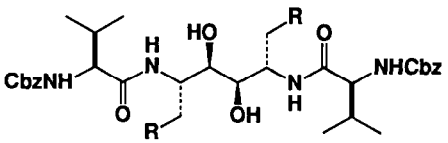
Acquired immunodeficiency syndrome (AIDS), a degenerative disease of the immune system, is one of the most challenging problems in medical history. Soon after the discovery of human immunodeficiency virus (HIV),[1] the etiological agent for AIDS, there has been an intense effort to find compounds for AIDS chemotherapy. Because the HIV-1 encoded protease is responsible for proteolytic processing of the *gag* and *gag-pol* polyproteins to form mature virion proteins,[2] inhibition of this enzyme is recognized to be one of the therapeutic strategies for the treatment of AIDS.[3] Consequently, we[4] and others have discovered a number of potent and selective HIV protease inhibitors, which include various nonhydrolyzable hydroxyethylene and hydroxyethylamine isosteres.[5] More recently, Erickson et. al.[6a] and Kempf et. al.[6b] have reported a new class of C_2-symmetric inhibitors which were designed based on the symmetric disposition of the enzyme structure.[7] During the course of our investigation in this area, we required an efficient, flexible and enantioselective synthesis of a range of symmetric inhibitors which were not limited to amino acid derived substitutents. In this letter, we report an efficient and stereocontrolled synthesis of inhibitors **1** and **2** which promises to be of general applicability for the synthesis of other symmetric compounds.

The starting material which is appropriately functionalized for the synthesis of such analogues is the commercially available and enantiomerically pure D-mannitol. It has a twofold axis of symmetry with the C3 and C4 hydroxy stereochemistry perfectly set for inhibitors **1** and **2**. Thus, D-mannitol **3** was transformed into 3,4-O-isopropylidene-D-mannitol **4** on a multigram scale according to the procedure reported by Wiggins.[8]

Tetraol **4** was then converted to the desired bis-epoxide **5** in the following two step sequence: (1) reaction of **4** with 2-acetoxyisobutyryl chloride[9] (3 equiv) in chloroform at 23°C for 3 h and (2) treatment of the resulting crude 1,6-dichloro-2,5-diacetate derivative with sodium methoxide (5 equiv) in dry tetrahydrofuran at 23°C for 4 h to provide the bis-epoxide **5** in 68% yield after silica gel chromatography. Ring opening of the bis-epoxide **5** with phenylmagnesium bromide (4 equiv) in the presence of cuprous iodide (2 equiv) at -40°C to 0°C for 3 h afforded the symmetric diol **6** in 82% yield after flash chromatography over silica gel. Reaction of **5** with benzylmagnesium chloride and cuprous iodide under similar reaction conditions resulted in **7** in 92% isolated yield.

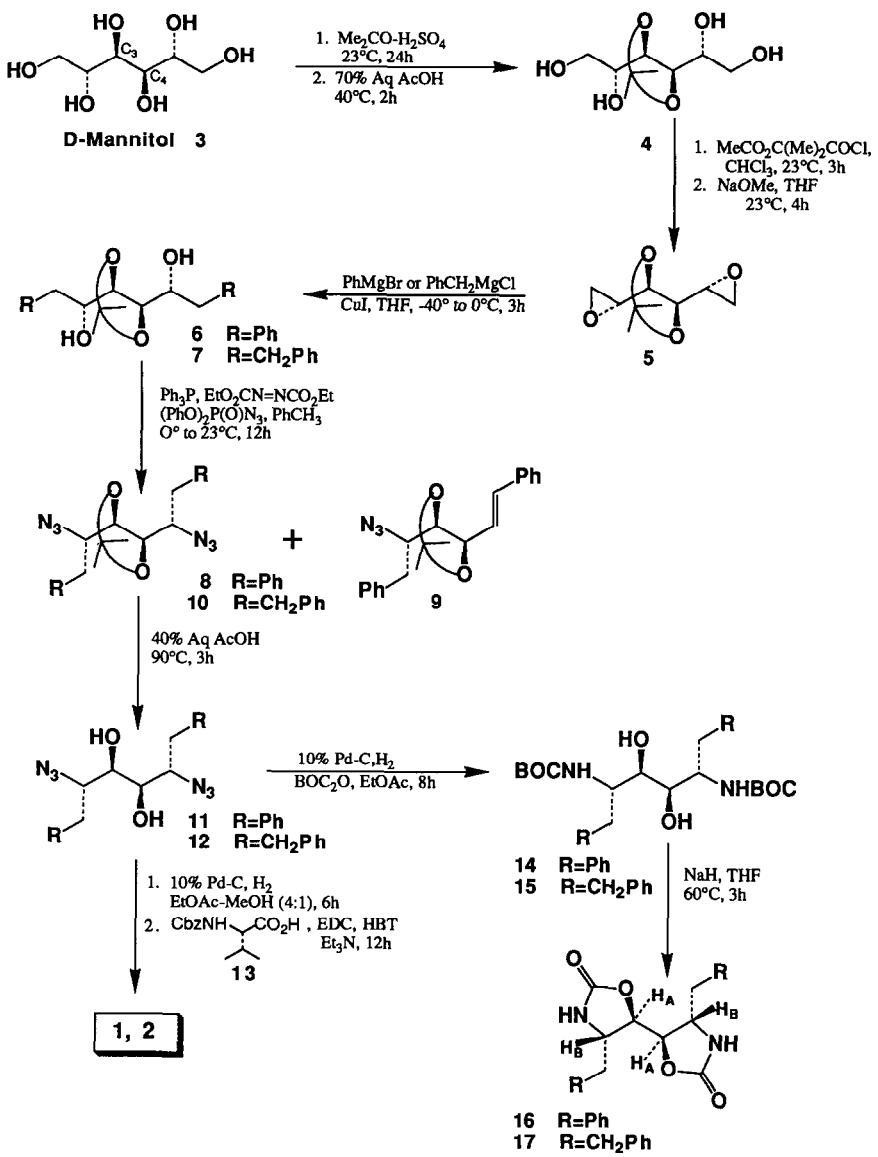
Conversion of diol **7** to the corresponding diazide **10** was readily achieved by a Mitsunobu reaction.[10] Thus, reaction of **7** with triphenylphosphine (2 equiv), diethyl azodicarboxylate (2 equiv) and diphenylphosphoryl azide (2 equiv) in toluene at 0°C to 23°C for 12h furnished the diazide **10** in 92% isolated yield. Removal of the isopropylidene group was effected by heating the diazide **10** with 40% aqueous acetic acid at 90°C for 3 h (91% yield). Reaction of diol **6** under the azidation conditions mentioned above, provided an inseparable mixture (1:1 by ^{1}H-NMR) of diazide **8** and undesired monoazide **9**, arising from competing E_2-reaction. Lower reaction temperature and longer time (-18°C for 72 h) afforded only slight improvement of the mixture ratio (3:2). Additionally, formation of the mesylate of **6** with mesyl chloride in pyridine and subsequent displacement of the mesylate with sodium azide or, tetramethylguanidinium azide in DMF (80°- 90°C) resulted in lower yield of **8**. However, desired diazidodiol **11** was obtained in 45% yield (from **6**) after removal of the isopropylidene group (40% aq AcOH, 90°C, 3h). Catalytic hydrogenation of **11** with 10% palladium on charcoal under atmospheric pressure in 4:1 ethyl acetate-methanol afforded the corresponding diamine in quantitative yield. Using a standard peptide coupling procedure, carbobenzyloxy-L-valine **13** was reacted with the diamine in the presence of N-ethyl-N'-(dimethylaminopropyl)carbodiimide hydrochloride (1.2 equiv), triethylamine (3 equiv) and 1-hydroxybenzotriazole hydrate (1.2 equiv) in DMF to afford **1** (white solid, m.p. 229-231°C) in 82% yield after chromatography (Rf 0.35, 5% methanol in chloroform). Similarly, catalytic hydrogenation of **12** followed by coupling of **13** provided **2** (white solid, m.p. 215- 217°C) in 87% yield.

Furthermore, catalytic hydrogenation[11] of **11** and **12** with 10% palladium on charcoal in the presence of di-*tert*-butyl dicarbonate furnished the bis-carbamate **14** (92%, m.p. 200-201°C) and **15** (90%, m.p. 174-176°C). The C_2 and C_5 stereochemistry of **14** and **15** was confirmed by its conversion to the corresponding bis-oxazolidinone **16** and **17**. Thus, exposure of these bis-carbamates to sodium hydride (5 equiv) in THF at 60°C for 3 h resulted in **16** (84%) and **17** (88%) after chromatography.[12] Bis-oxazolidinone **16** and **17** exhibited ^{1}H NMR coupling constant of J_{AB}=5.4 Hz and J_{AB}=5.2 Hz respectively which are consistent with the values reported by Kempf et. al.[6b]



1 R=Ph
2 R=PhCH$_2$

Scheme 1:



In conclusion, an efficient and stereocontrolled synthetic route to symmetric protease inhibitors **1** and **2** has been developed. Synthesis of a number of other symmetric inhibitors and their biological evaluation is currently under investigation.

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12. All new compounds gave satisfactory spectroscopic and analytical results.

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