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SYNTHESIS OF 8-MEMBERED CYCLIC SULFAMIDES: NOVEL HIV-1 PROTEASE INHIBITORS

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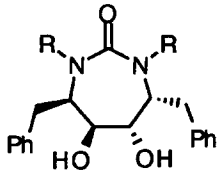
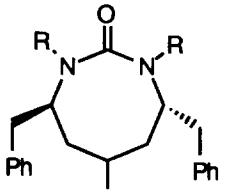
Summary: One pot synthesis of pseudo C2 symmetric (2S,6S)-2,6-dihydroxy-1,7-diphenylhept-4-one in high enantiomeric purity has been developed and the intermediate was used for the synthesis of 8-membered cyclic sulfamides.

Inhibition of HIV-1 protease has been intensely investigated worldwide for finding effective therapies for the treatment of AIDS.[1-4] HIV-1 protease is an ideal target since functional protease is essential for the maturation of fully infectious virus particles. The enzyme is virally encoded and structurally differs from mammalian aspartyl proteases. It consists of a symmetrical dimer in which each monomer is composed of 99 amino acid residues. The active site consists of two aspartic acid residues contributed by each monomer unit.[1-4] Protein X-ray crystallography studies of the substrate based inhibitor and HIV-1 complex revealed the presence of a unique water molecule which is hydrogen bonded to the two carbonyls of the inhibitor and the flap residues of the enzyme.[5] We previously described successful incorporation of the structural water molecule in the cyclic urea (**1**) class of HIV-1 protease inhibitors.[6] In an effort to examine the effect of the ring size and other cyclic scaffolds on the inhibitory activity of the cyclic series of HIV-1 protease inhibitors, synthesis of 8-membered cyclic urea (**2**) and cyclic sulfamide (**3**) was undertaken. In this communication, we report a highly stereoselective synthesis of pseudo C2 symmetric 2,6-dihydroxy-4-keto derivative in very high enantiomeric purity and its utilization for the synthesis of 8-membered cyclic sulfamides.



1, DMP323



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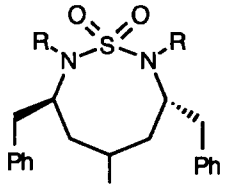
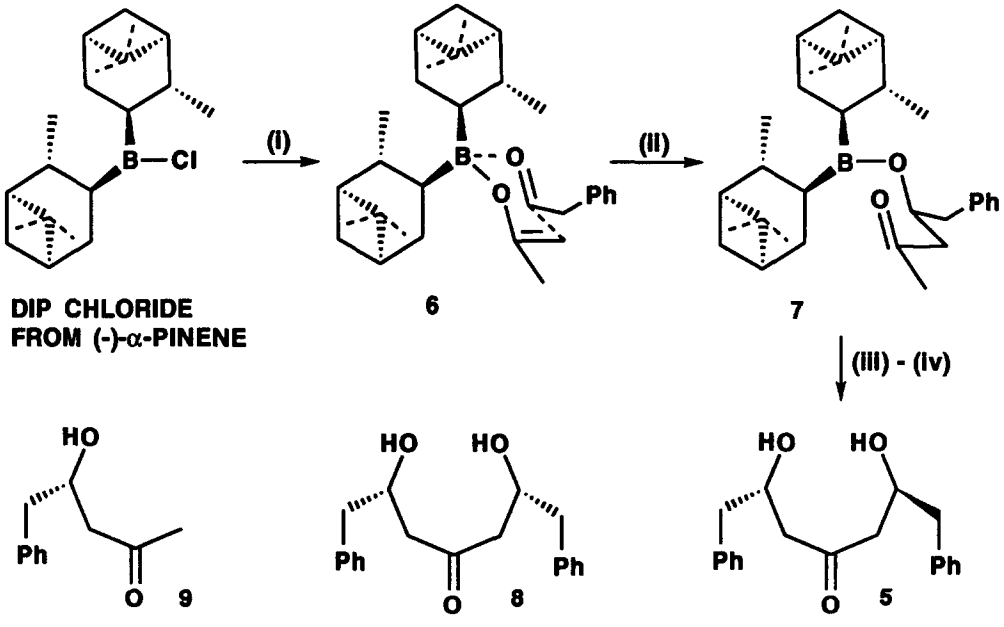


3

R = 4-hydroxymethylbenzyl

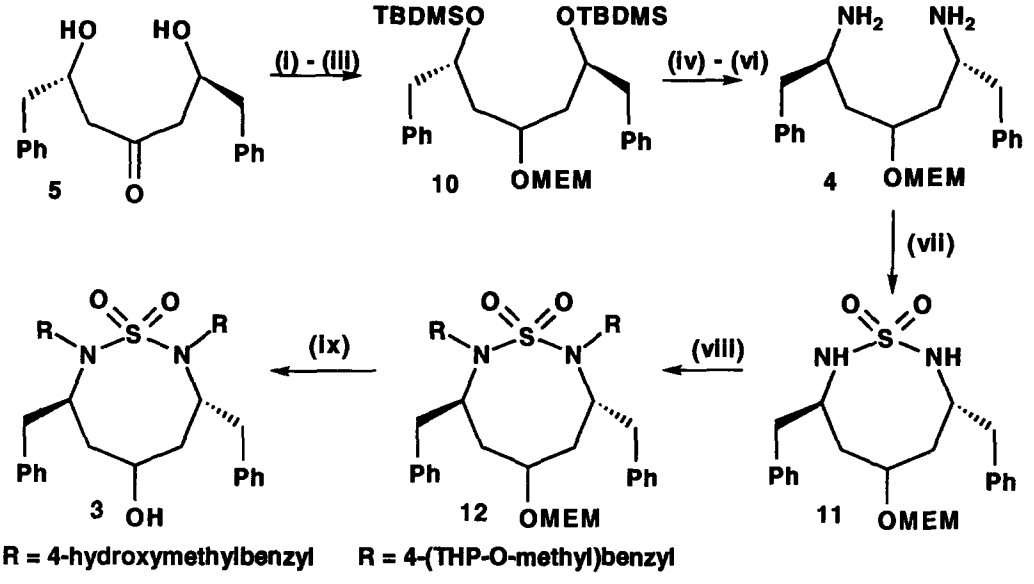
Retrosynthetic analysis indicated that we needed *(2R,6R)*-2,6-diamino-1,7-diphenyl-4-hydroxyheptane derivative (**4**) which we thought could be obtained from *(2S,6S)*-2,6-dihydroxy-1,7-diphenylhept-4-one (**5**). We envisioned that a boron aldol reaction using enol diisopinocampheylborinate[7] may provide (**5**) in one pot. Thus aldol condensation of acetone derived enol diisopinocampheylborinate (**6**) with phenacetaldehyde provided boron aldol adduct (**7**) which was subsequently converted *in situ* into enol diisopinocampheylborinate derivative and condensed with an additional equivalent of phenacetaldehyde. Oxidative workup provided *(2S,6S)*-2,6-dihydroxy-1,7-diphenylhept-4-one (**5**) in very high enantiomeric purity (**Scheme 1**). The desired *(S,S)* diol (**5**; 35% yield) was separated from meso (S,R) diol (**8**; 11% yield) and mono aldol product (**9**; 27% yield) by careful column chromatography. It should be pointed out that the minor enantiomer formed during the first aldol is transformed into meso diol in the subsequent aldol reaction which makes the separation of (**8**) from diastereomeric (**5**) readily possible. Although diol (**5**) is obtained only in 35% yield, the synthesis is attractive considering the fact that it can be synthesized in one pot from commercially available reagents (e. g. acetone, phenacetaldehyde and (+)-DIP Chloride). In addition, this protocol could be used for the synthesis of other *pseudo* C2 symmetric or mixed 2,6-dihydroxy-4-ketone derivatives in either enantiomeric form since both the enantiomers of DIP Chloride are commercially available.



Scheme 1

(i) CH_3COCH_3/ Et_3N/ 0° C/ 0.5h (ii) -78° C/ $PhCH_2CHO$/ -78° C/1h then warm to 0° C (iii) (+)-DIP Chloride/ Et_3N/ 0° C/ 0.5h then -78° C/ $PhCH_2CHO$/ -78° C/1h then warm to 0° C (iv) pH 7 buffer/ 30% H_2O_2/ 25° C/ 18h.

Synthesis of (*2R,6R*)-2,6-diamino-1,7-diphenyl-4-hydroxyheptane derivative (**4**) from (**5**) is achieved as shown in **Scheme 2**. Thus, protection[8] of diol (**5**) with *tert*-butyldimethylsilyl (TBDMS) group, reduction of the keto derivative with sodium borohydride to the secondary alcohol, followed by protection of the hydroxyl with methoxyethoxymethyl (MEM) provided a differentially protected triol derivative (**10**). Removal of the TBDMS groups with tetrabutylammonium fluoride (TBAF) furnished a diol derivative which was then subjected to a Mitsunobu[9] reaction to provide the bis azide in excellent yield. Reduction of the bis azide under palladium catalyzed hydrogenation conditions provided the desired intermediate (**4**). The diamino derivative thus obtained was now ready for cyclization to either 8-membered cyclic urea or 8-membered cyclic sulfamide. Cyclization of diamino derivative (**4**) to 8-membered cyclic urea (**2**, R = H) with carbonyldiimidazole proceeded only in <10% yield under a variety of reaction conditions including high dilution techniques. Synthesis of 8-membered cyclic urea analogs was not pursued further in view of the very poor yields of the key intermediate (**2**, R = H).



Scheme 2

(i) TBDMSCl/ Imidazole/ DMF/ 25° C/ 18h; 92% (ii) NaBH4/ Methanol/ 25° C/ 1h; 90% (iii) MEMCl/ diisopropylethylamine in CH_2Cl_2/ reflux/ 18h; 79% (iv) TBAF/ THF/ 25° C/ 18h; 95% (v) Triphenylphosphine/ Diethyl azodicarboxylate/ Diphenylphosphoryl azide/ THF/ 0° C then at 25° C; 78% (vi) 20% $Pd(OH)_2$ on carbon/ H_2/ ethanol/ 25° C/ 18h; 91% (vii) $NH_2SO_2NH_2$/ pyridine/ reflux/ 18h; 65% (viii) 4-(tetrahydropyranyloxymethyl)benzyl chloride/ NaH/ DMF/ 25° C/ 18h; 90% (ix) 2N HCl in 1:1 CH_3OH: Dioxane/ 25° C/ 18h; 85%

However, cyclization of (**4**) to (**11**) with sulfamide ($H_2NSO_2NH_2$) in refluxing pyridine proceeded in good yields (65%, unoptimized).[10] The cyclic sulfamide (**11**) was alkylated with various alkylating agents using sodium hydride (NaH) as base and dimethylformamide (DMF) as solvent (**Scheme 2**). Deprotection of the MEM group with anhydrous 2M hydrogen chloride in 1:1 methanol-dioxane mixture provided target inhibitors (**Table 1**).[11,12] Unfortunately, 8-membered cyclic sulfamides are much less potent (>1000 fold less potent) inhibitors of HIV-1 protease as compared to the corresponding 7-membered cyclic ureas.[6]

Table 1

	3; R	**Isolated yield 11**	**Ki (μM)**
3	4-hydroxymethylbenzyl	61	2.1
13	cyclopropylmethyl	71	1.5
14	3-hydroxybenzyl	63	1.0

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11. All intermediates and final compounds were characterized by 1H and 13C NMR and HRMS.
12. Compounds **3**, **13**, & **14** were analyzed on HPLC using chiral columns under variety of conditions but none of them showed any presence of S,S enantiomers.

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